CHEMISTRY
A EUROPEAN JOURNAL

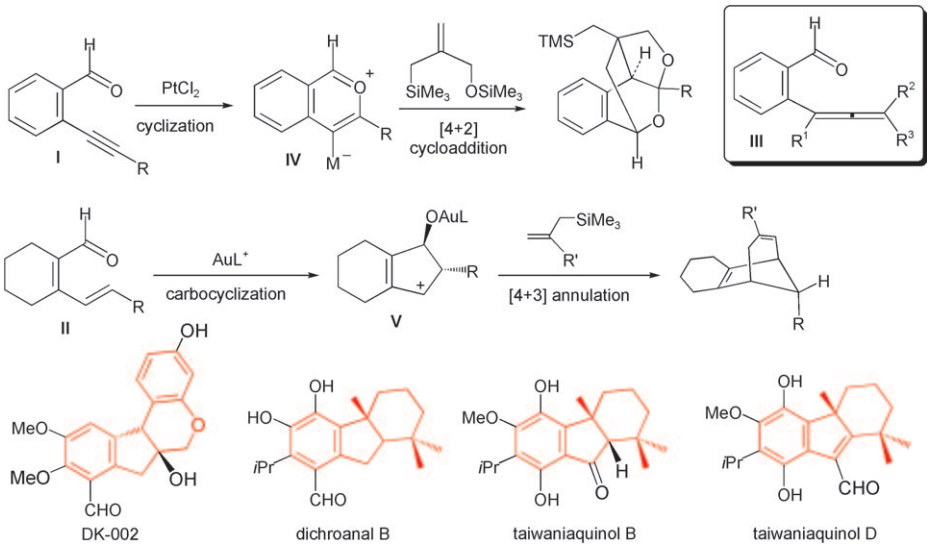
DOI: 10.1002/chem.201000041

Gold-Catalyzed Dealkoxylative Carbocyclization/[3+3] Annulation Cascade of Acetal–Allene or Ketal–Allene Substrates

Tse-Min Teng, Ming-Shiun Lin, Dhananjayan Vasu, Sabyasachi Bhunia, Ting-An Liu, and Rai-Shung Liu*[a]

Transition-metal catalyzed cyclization/annulation cascade is a powerful tool to access complex polycyclic skeletons.[1] Such reactions have been studied on oxo–alkyne substrates (**I**)[1–3] with a representative example depicted in Scheme 1.[4] In contrast, the tandem cyclization/annulation cascade remained less studied for oxo–alkene and oxo–allene substrates (**II**–**III**). We reported[5] gold-catalyzed deoxygenative Nazarov[6] cyclization/annulation reactions of *cis*-2,4-dien-1-als that serve as the first cyclization/annulation cascade reaction for oxo–alkene substrates **II**. The success of this process relies on sequential generation of an allylic cation such as species **V**, to enable a [4+3] annulation with allylsilane. Herein, we report the first success of this catalytic cascade on acetal–allene or ketal–allene substrates through an initial Prins[7] cyclization. The use of this new catalysis is its potential access to the central cores of bioactive or natural products DK-002,[8] dichroanal B and taiwaniaquinol A–D.[9]

We prepared substrate **1a** bearing an acetal functionality because its aldehyde form was too unstable to isolate. Treatment of acetal **1a** with allylsilane (2.2 equiv) and PPh_3AuSbF_6 (5 mol%) in CH_2Cl_2 (25 °C, 3 min) delivered double-addition product **2** (*trans*/*cis* 10:1)[10,11] in 78% yield (Scheme 2). We also examined this dealkoxylative carbocyclization in CH_2Cl_2 (25 °C) over commonly acidic catalysts (5 mol%), which provided the desired compound **2** with the following optimized time and yields:



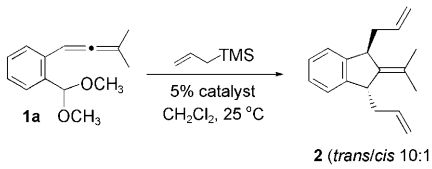
Scheme 1. Metal-catalyzed tandem cyclization/annulation cascade of oxo–alkyne and oxo–alkene substrates.

$AuCl_3$ (1 h, 70%), AuCl (1 h, 22%), $AgSbF_6$ (2 h, 14%), AgOTf (4 h, 34%), $Cu(OTf)_2$ (4 h, 54%), $FeCl_3$ (1 h, 43%), $In(OTf)_3$ (30 min, 19%), $PtCl_2$/CO (3 h, 3%), $BF_3{\cdot}OEt_2$ (0 °C, 30 min, 35%), TMSOTf (0 °C, 20 min, 17%), *p*-TSA (5 h, 17%) and HOTf (3 h, 5%); all these catalysts led to complete consumption of starting material **1a**. As expected the reaction failed with the use of *p*-TSA and HOTf because of protonation of allylsilane.[10]

The dication equivalent of acetal **1a** enables one-pot construction of complicated carbocyclic or heterocyclic species

[a] T.-M. Teng, M.-S. Lin, D. Vasu, S. Bhunia, Dr. T.-A. Liu, Prof. Dr. R.-S. Liu
Department of Chemistry, National Tsing-Hua University
Hsinchu, 30043, Taiwan (ROC)
Fax: (+886) 3-5711082
E-mail: rsliu@mx.nthu.edu.tw

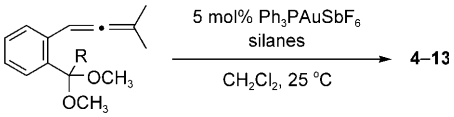
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201000041.



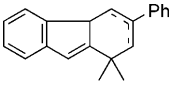
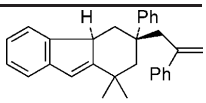
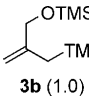
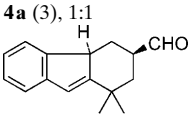
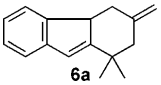
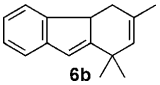
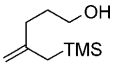
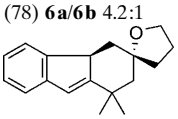
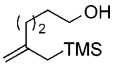
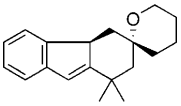
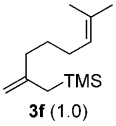
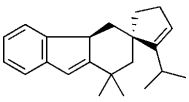
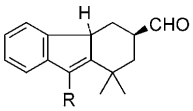
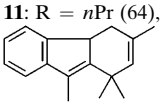
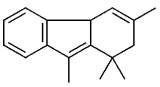
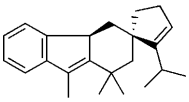
Scheme 2. Gold-catalyzed double-addition reaction of **1a** with allyltrimethylsilane.

4–13, through a dealkoxylative carbocyclization/[3+3]-annulation cascade with suitable 2-substituted allylsilanes **3a–3f**. Notably, these products bear 1,1-dimethylfluorene skeletons that are the central core structure of naturally occurring compounds such as dichroanal B and taiwaniaquinol A–D (see Scheme 1).[9] A summary of the results is provided in Table 1. Treatment of **1a** with 2-phenylallylsilane (**3a**; 1 equiv) and PPh_3AuSbF_6 (5 mol%) in CH_2Cl_2 (25°C) gave tricyclic compounds **4a** (isomeric ratio 1:1) and **4b** in 76 and 9% yield, respectively (entry 1). Herein, an increased amount of silane **3a** (2 equiv) led to a significant formation of **4b** in 82% yield (entry 2), of which the structure was determined with ^1H NOE spectroscopy. The use of 2-siloxymethyl- or 2-silylmethylallylsilane (**3b** or **3c**) produced carbocyclic species **5** (d.r. 8.0:1) and **6** (**a**/**b** 4.2:1) in 63 and 78% yield, respectively (entries 3–4). This new gold catalysis is applicable even to the stereoselective synthesis of tetracyclic furan and pyran species **7** and **8**, which were obtained in 50 and 36% yield, respectively (entries 5–6). Gold-catalyzed annulation of acetal **1a** with silane **3f** led to formation of complex carbocyclic compound **9** in 61% yield with d.r. 3.1:1 (entry 7). This gold catalysis can be extended to the annulation of ketal species **1b** and **1c** with silanes **3b**, **3c** and **3f** to give aldehydes **10–11**, tricyclic product **12** and spiro compound **13** in good yields (> 61% yield, entries 8–11). A good ratio **12a**/**12b** 7.1:1 was obtained for compound **12** after treatment of the crude products with *p*-TSA (10 mol%) in hot THF (60°C, 3 h). Simultaneous generation of three new cyclic rings with stereocontrol reflects the versatility of this approach to access molecular complexity of products.

Table 1. Carbocyclization/[3+3]-annulation cascade of acetal–allenes and ketal–allenes with allylsilanes.

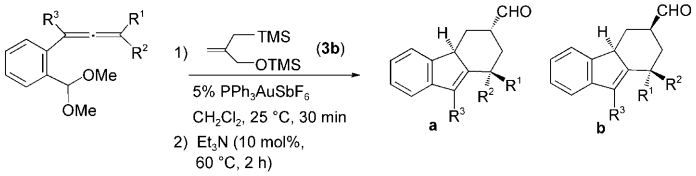


1a: R = H, **1b**: R = Me, **1c**: *n*Pr

Entry	Substrate[a]	Silane (equiv)	*t* [min]	Product (Yield [%])[b]	
1	**1a**	 **3a** (1.0)	5	 **4a** (76), 1:1	 **4b** (9), d.r. >20:1
2	**1a**	**3a** (2.0)	20	**4a** (3), 1:1	**4b** (82), d.r. >20:1
3	**1a**	 **3b** (1.0)	10	 **5** (63), d.r. 8.0:1[c,d]	
4	**1a**	 **3c** (1.0)	10	 **6a** (78) **6a**/**6b** 4.2:1	 **6b**
5	**1a**	 **3d** (1.0)	240	 **7** (50), d.r. >20:1[d]	
6	**1a**	 **3e** (1.0)	240	 **8** (36) d.r. 4.2:1[d]	
7	**1a**	 **3f** (1.0)	15	 **9** (61), d.r. = 3.1:1[d]	
8	**1b**	**3b** (1.0)	30	 **10**: R = Me (61), d.r. 8.9:1[c,d]	
9	**1c**	**3b** (1.0)	30	**11**: R = *n*Pr (64), d.r. 11.1:1[c]	
10	**1b**	**3c** (1.0)	10	 **12a** (81) **12a**/**12b** 7.1:1[e]	 **12b**
11	**1b**	**3f** (1.0)	20	 **13** (69), d.r. 1.8:1[d]	

[a] [substrate] = 0.02 M. [b] Product yields are given after purification from a silica column. [c] d.r. values are obtained after treatment of the crude product with triethylamine in CH_2Cl_2 at 25°C for 16 h. [d] This structure represents stereochemistry of the major diastereomer. [e] *p*-TSA treatment in hot THF (60°C, 3 h).

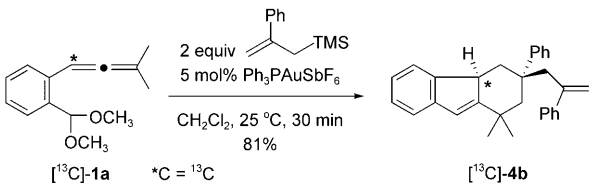
We also prepared acetals **1d–f** by varying their allenyl substituents. As depicted in Scheme 3, gold-catalyzed [3+3] annulations of these substrates with silane **3b** proceeded smoothly to give corresponding tricyclic aldehydes **14a–b**, **15b** and **10** in moderate to good yields; their structures were determined by ^{1}H NOE spectroscopy. For trisubstituted allene **1f**, its annulation product **10** was also obtained alternatively from ketal **1b** following the same gold catalytic reaction (Table 1, entry 8).



Scheme 3. Gold-catalyzed cyclization of various acetals with silane **3b**.

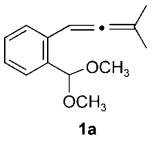
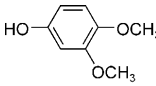
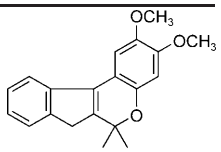
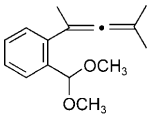
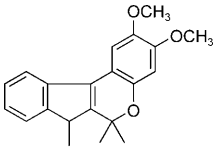
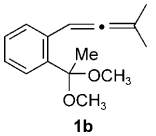
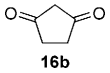
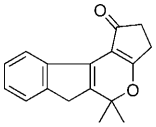
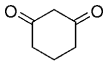
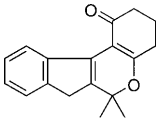
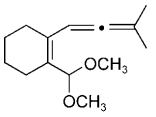
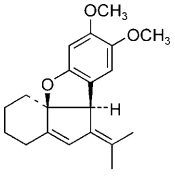
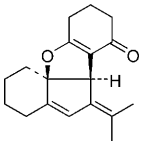
The additional utility of this catalysis is highlighted by the availability of new complicated oxacyclic skeletons using phenol derivative **16a** or enolizable ketones **16b–c**; the results are shown in Table 2. Unlike preceding carbocyclic compounds, these oxacyclic compounds worked well with various Lewis and Brønsted acids.[12] [3+3] Annulation of acetal **1a** with phenol **16a** afforded desired compound **17** in 91% yield (entry 1). Notably, the annulation reaction of acetal **1f** and ketal **1b** with phenol **16a** gave one identical product **18** (entries 2–3). For **1a**, the annulation with cyclic 1,3-diketones **16b–c** gave oxacyclic ketones **19** and **20** in 46 and 61% yield, respectively (entries 4–5). This catalysis is applicable to nonaromatic substrate **1g** that gave distinct oxacyclic skeletons **21** and **22**, via its [3+2] annulations with phenol **16a** and 1,3-diketone **16c**, respectively (entries 6–7); the molecular structure of compound **21** was confirmed by X-ray diffraction study.[13]

Equation (1) shows a ^{13}C-labeling experiment to clarify the reaction mechanism. We prepared [^{13}C]-**1a** with a 10% ^{13}C content at its allenyl =CH carbon. Gold-catalyzed annulation of this species with 2-phenylallylsilane gave resulting [^{13}C]-**4b** with the ^{13}C enrichment only occurring at the indenyl C(3)–H carbon. This information unambiguously excludes two possible pathways, including a) a direct allylation of acetal in the initial step, and b) gold π-allene activated a transfer of methoxy to the allenyl *C*H carbon.[14,15]



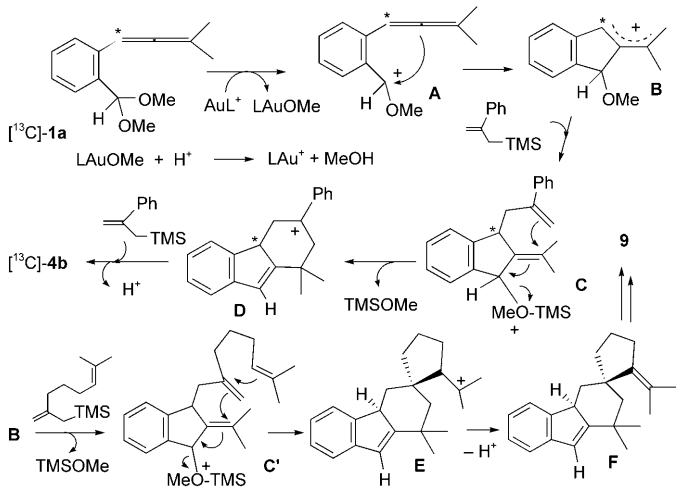
(1)

Table 2. Carbocyclization/annulation cascade of acetal–allenes and ketals–allenes with phenol and 1,3-diketones.

Entry	Substrate[a]	Nucleophile	*t* [min]	Product (Yield [%])[b]
1	 **1a**	 **16a**	10	 **17** (91)
2	 **1f**	**16a**	15	 **18** (92)
3	 **1b**	**16a**	15	**18** (90)
4	**1a**	 **16b**	40	 **19** (46)
5	**1a**	 **16c**	40	 **20** (61)
6	 **1g**	**16a**	30	 **21** (65)
7	**1g**	**16c**	30	 **22** (58)

[a] [Substrate] = 0.02 M. [b] Product yields are given after purification from a silica gel column.

Scheme 4 depicts a plausible mechanism involving an initial Prins cyclization of acetal **1a** by PPh_3AuSbF_6 to give oxonium species **A**. A subsequent carbocyclization of this species generates allylic cation **B**, which reacts with 2-phenylallylsilane **3a** to give allylation product **C** with its methoxy group stabilizing trimethysilyl group. We envisage the oxonium functionality of species **C** triggers intramolecular cyclization to generate tertiary cation **D**, inducing a second allylation to deliver observed product **4b**. This mechanism also rationalizes the formation of tetracyclic species **F**, via sequential formation of two carbocyclic rings of initial intermediate **C′**, ultimately giving tertiary cation **E** and species **F**.



Scheme 4. A plausible formation mechanism of compound **4b** and spiro product **9**.

A subsequent Brønsted acid-catalyzed isomerization of species **F** gives observed product **9**. This proposed mechanism also rationalizes the aldehyde products **5** and **10**, produced from the annulations of acetals **1a** and **1f** with 2-siloxymethylallylsilane **3b**.[16]

In summary, we report the first success to implement a catalytic tandem carbocyclization/annulation cascade on acetal–allene or ketal–allene substrates.[17] Annulation of these substrates with 2-substituted allylsilanes, phenol and enolizable ketones enables a rapid construction of carbocyclic and oxacyclic frameworks with good stereocontrol for most cases. The value of this annulation is also highlighted by its potential access to the central core structures of bioactive or natural products DK-002,[8] dichroanal B and taiwaniaquinol A–D.[9] The use of this method for synthesis of natural compounds is under future investigation.

Experimental Section

A solution of $ClAuPPh_3$ (7.4 mg, 0.015 mmol) and $AgSbF_6$ (5.1 mg, 0.015 mmol) in CH_2Cl_2 (13 mL) was stirred at 25 °C for 10 min before addition of acetal **1a** (66 mg, 0.30 mmol) and silane **3b** (65 mg, 0.30 mmol) in CH_2Cl_2 (2 mL) with syringe pump during 30 min. The mixture was kept stirring for 10 min before the solution was filtered over a short silica bed. The solvent was evaporated under reduced pressure and the crude product was eluted through a silica gel column. The two diastereomeric products were then treated with Et_3N in CH_2Cl_2 at room temperature for 16 h to afford aldehyde product **5** (43 mg, 0.19 mmol, 63%, d.r. 8.0:1).

Acknowledgements

The authors thank National Science Council, Taiwan for support this work.

Keywords: allenes · annulation · carbocyclization · cascade reactions · gold

[1] a) N. T. Patil, Y. Yamamoto, *ARKIVOC* **2007**, *5*, 6; b) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395; c) S. M. Abu Sohel, R.-S. Liu, *Chem. Soc. Rev.* **2009**, *38*, 2269.

[2] For [3+2] cycloadditions, see selected examples: a) H. Kusama, H. Funami, M. Shido, Y. Hara, J. Takaya, N. Iwasawa, *J. Am. Chem. Soc.* **2005**, *127*, 2709; b) A. B. Beeler, S. Su, C. A. Singleton, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2007**, *129*, 1413; c) C.-H. Oh, J.-H. Lee, S.-J. Lee, J.-I. Kim, C.-S. Hong, *Angew. Chem.* **2008**, *120*, 7615; *Angew. Chem. Int. Ed.* **2008**, *47*, 7505; d) S. Bhunia, K.-C. Wang, R.-S. Liu, *Angew. Chem.* **2008**, *120*, 5141; *Angew. Chem. Int. Ed.* **2008**, *47*, 5063; e) S. Shin, A.-K. Gupta, C.-Y. Rhim, C.-H. Oh, *Chem. Commun.* **2005**, 4429.

[3] For [4+2] cycloadditions, see selected examples: a) N. Asao, T. Nogami, S. Lee, Y. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 10921; b) N. Asao, T. Kasahara, Y. Yamamoto, *Angew. Chem.* **2003**, *115*, 3628; *Angew. Chem. Int. Ed.* **2003**, *42*, 3504; c) N. Asao, H. Akiwa, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 7458; d) N. Iwasawa, M. Shido, K. Maeyama, H. Kuasama, *J. Am. Chem. Soc.* **2000**, *122*, 10226.

[4] Y.-C. Hsu, C.-M. Ting, R.-S. Liu, *J. Am. Chem. Soc.* **2009**, *131*, 2090.

[5] a) C.-C. Lin, T.-M. Teng, A. Odedra, R.-S. Liu, *J. Am. Chem. Soc.* **2007**, *129*, 3798; b) C.-C. Lin, T.-M. Teng, C.-C. Tsai, H.-Y. Liao, R.-S. Liu, *J. Am. Chem. Soc.* **2008**, *130*, 16417.

[6] a) K. L. Habermas, S. E. Denmark, T. K. Jones, *Org. React.* **1994**, *45*, 1; b) A. J. Frontier, C. Collison, *Tetrahedron* **2005**, *61*, 7577; c) M. A. Tius, *Eur. J. Org. Chem.* **2005**, 2193; d) E. G. Occhiato, C. Prandi, A. Ferrali, A. Guarna, P. Venturello, *J. Org. Chem.* **2003**, *68*, 9728; e) G. X. Liang, S. N. Gradl, D. Trauner, *Org. Lett.* **2003**, *5*, 4931; f) C. Bee, E. Leclerc, M. A. Tius, *Org. Lett.* **2003**, *5*, 4927.

[7] a) M. J. Cloninger, L. E. Overman, *J. Am. Chem. Soc.* **1999**, *121*, 1092; b) D. J. Kopecky, S. D. Rychnovsky, *J. Am. Chem. Soc.* **2001**, *123*, 8420; c) J. D. Elsworth, C. L. Willis, *Chem. Commun.* **2008**, 1587; d) P. O. Miranda, D. D. Díaz, J. I. Padrón, J. Bermejo, V. S. Martín, *Org. Lett.* **2003**, *5*, 1979; e) C. Shin, S. N. Chavre, A. N. Pae, J. H. Cha, H. Y. Koh, M. H. Chang, J. H. Choi, Y. S. Cho, *Org. Lett.* **2005**, *7*, 3283; f) E. Jiménez-Núñez, C. K. Claverie, C. Nieto-Oberhuber, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 5578; *Angew. Chem. Int. Ed.* **2006**, *45*, 5452; g) C. E. Davis, R. M. Coates, *Angew. Chem.* **2002**, *114*, 509; *Angew. Chem. Int. Ed.* **2002**, *41*, 491.

[8] C.-K. Moon, *Life Sci.* **2006**, *78*, 1091.

[9] Occurence: a) W.-H. Lin, J.-M. Fang, Y.-S. Cheng, *Phytochemistry* **1995**, *40*, 871; b) W.-H. Lin, J.-M. Fang, Y.-S. Cheng, *Phytochemistry* **1996**, *42*, 1657; c) K. Kawazoe, M. Yamamoto, Y. Takaishi, G. Honda, T. Fujita, E. Sezik, E. Yesilada, *Phytochemistry* **1999**, *50*, 493; d) C.-I. Chang, S.-C. Chien, S.-M. Lee, Y.-H. Kuo, *Chem. Pharm. Bull.* **2003**, *51*, 1420; e) C.-I. Chang, J.-Y. Chang, C.-C. Kuo, W.-Y. Pan, Y.-H. Kuo, *Planta Med.* **2005**, *71*, 72; Total synthesis: f) G. Liang, Y. Xu, I. B. Seiple, D. Trauner, *J. Am. Chem. Soc.* **2006**, *128*, 11022; g) M. Banerjee, R. Mukhopadhyay, B. Achari, A. K. Banerjee, *J. Org. Chem.* **2006**, *71*, 2787; h) S. Tang, Y. Xu, J. He, Y. He, J. Zheng, X. Pan, X. She, *Org. Lett.* **2008**, *10*, 1855.

[10] Treatment of PPh_3AuSbF_6 with $allylSiMe_3$ under running conditions did not generate $PPh_3Au(allyl)$ species, see: Y.-C. Hsu, S. Datta, C.-M. Ting, R.-S. Liu, *Org. Lett.* **2008**, *10*, 521.

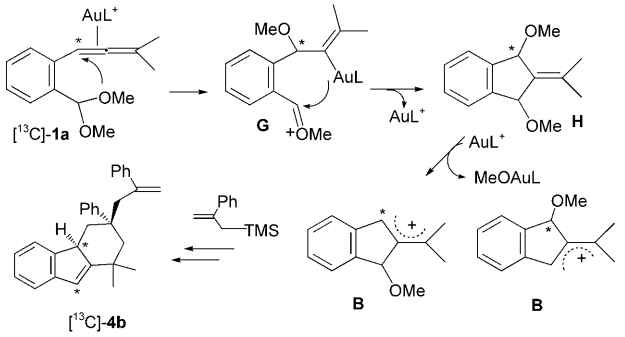
[11] The major diastereomer of compound **2** was assigned to be the *trans* isomer because it was separated into two components on a chiral column (OD-H, hexane).

[12] Production of oxacyclic compounds **17** and **20** are efficient for common acid catalysts; see Supporting Information (Tables S1 and S2 in the Supporting Information).

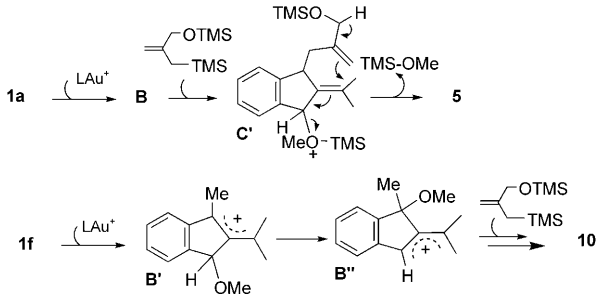
[13] CCDC-727899 (**21**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] Gold–π-allene complex may induce an intramolecular methoxy attack to give gold–alkenyl oxonium species **G** according to gold π-alkyne chemistry.[15] This process also generate hypothetic intermediate **B** through ionization of intermediate **H**. Nevertheless, this path-

way is expected to give desired product [^{13}C]-**4b** with ^{13}C occurring at its indenyl C(1) and C(3) carbons. .



hyde **5**. For acetal–allene **1f**, the initial allyl cation **B′** is proposed to be inactive toward allylation to avoid formation of a tertiary carbon. This species likely undergoes a 1,4-methoxy transfer to give cation **B″** that is more active for the allylation. .



[15] a) P. Dubé, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 12062; b) A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 15024; c) A. Fürstner, H. Szillat, F. Stelzer, *J. Am. Chem. Soc.* **2000**, *122*, 6785.

[16] For the formation of aldehyde **5** from substrate **1a**, we propose that the first allylation product **C′** is subject to ionization that is triggered by a cyclization/Pinacol rearrangement cascade to give desired alde-

[17] Carbocyclization of oxo–allene substrates has one precedent; see J. Montgomery, M. Song, *Org. Lett.* **2002**, *4*, 4009.

Received: January 8, 2010
Published online: March 22, 2010

