Pure Appl. Chem., Vol. 84, No. 8, pp. 1749–1757, 2012.
http://dx.doi.org/10.1351/PAC-CON-11-09-13

Access to molecular complexity via gold- and platinum-catalyzed cascade reactions*

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Abstract: We report recent progress on Au- and Pt-catalyzed cascade reactions to access complicated molecular frameworks. Reported reactions include new cyclization/cycloaddition cascades on carbonyl and epoxide substrates tethered with an allene, alkene, and alkyne. Such substrates enable Au-catalyzed cascade reactions comprising an initial cyclization to form reactive 1,*n*-dipole that undergoes subsequent cycloadditions with suitable dipolarophiles.

Keywords: alkynes; cascade reactions; electrophilic activation; gold catalysis; catalysis; molecular complexity; platinum catalysis; tandem reactions.

INTRODUCTION

Traditional metal-catalyzed reactions [1] typically produce one chemical bond that is unsuitable to access compounds with molecular complexity. Metal-catalyzed tandem reactions can generate several chemical bonds in a single operation. Au and Pt catalysis is emerging as a rapidly growing field, especially in the electrophilic activation of alkynes, allenes, and alkenes [2,3], but Au is also a soft Lewis acid, providing an effective activation of O- and N-containing electrophiles such as aldehydes, ketones, imines, and epoxides [4]. Au catalysts are beneficial in the design of new catalysis because of their less oxophilicity to facilitate regeneration of the catalyst.

Organizing a summary of Au- and Pt-catalyzed cascade reactions needs caution because of diverse reaction paths. In many instances, products from cascade reactions are too complicated to attract a general readership; forming too many bonds in a one-pot operation also leads to a loss of focus and confusion. To give a topic with scientific merit, we emphasize a cyclization/cycloaddition cascade involving an initial cyclization to generate a reactive 1,*n*-dipole that subsequently undergoes cycloaddition with a suitable dipolarophile. We envisage that such a three-bond forming-process meets the reaction simplicity, and will become attractive to general readers. A protocol is illustrated in Scheme 1, involving substrates bearing donor (alkene, carbonyl, and epoxide), tethered with an acceptor including metal-coordinated allene, carbonyl, and alkyne; reported instances of this specific protocol are increasing rapidly, which reflects its importance.

Pure Appl. Chem. **84**, 1673–1784 (2012). A collection of invited papers based on presentations at the 16th International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-16), Shanghai, China, 24–28 July 2011.
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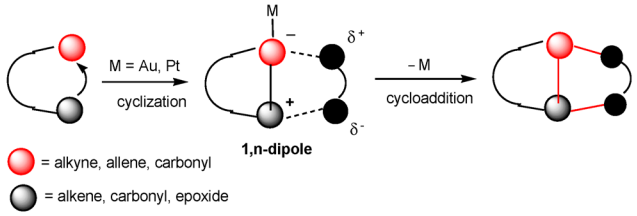
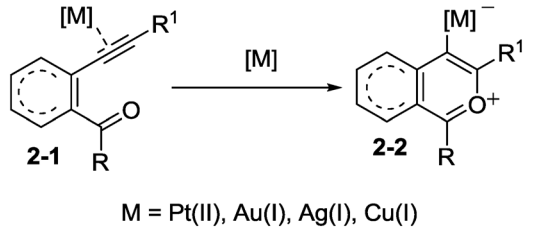


Scheme 1 General protocols for cyclization/cycloaddition cascades.

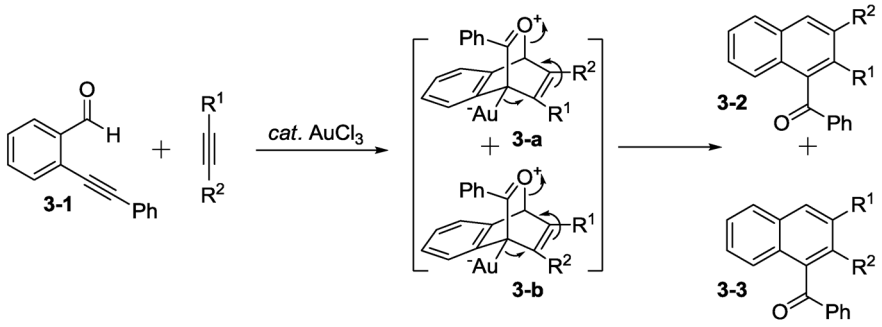
OXOALKYNES

Oxoalkyne substrates (**2-1**) undergo cycloadditions with various dipolarophiles including alkyne, alkene, enol ether, or carbonyl compounds. Metal-containing benzopyrylium intermediates (**2-2**) are generated through an attack of carbonyl group onto the metal-alkyne, as depicted in Scheme 2; these intermediates are capable of reacting with these dipolarophiles to yield various cycloadducts.



Scheme 2 Formation of metal-containing benzopyrylium-type intermediates.

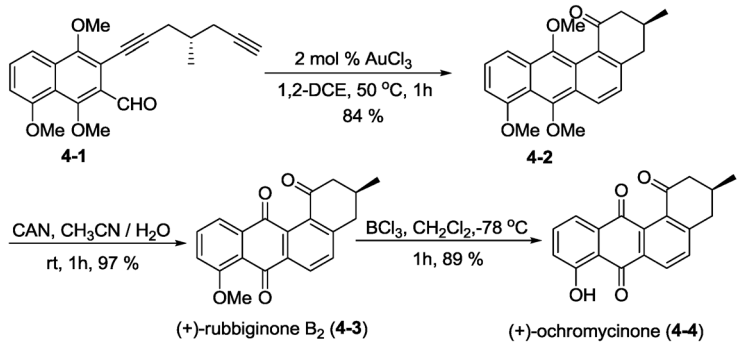
In 2002, Yamamoto et al. [5,6] published seminal papers on $AuCl_3$-catalyzed formal [4 + 2] cycloaddition of *o*-alkynylbenzaldehyde with alkyne via a Au-containing benzopyrylium intermediate, as depicted in Scheme 3. This reaction gave a regioisomeric mixture of highly substituted naphthalene derivatives; the product distribution was sensitive to the alkynyl substituents. As shown in Scheme 3, large R^1 substituents (propyl or phenyl) gave compounds **3-2** as the major regioisomers in which the bulky R^1 group was adjacent to the benzoyl group (entries 1–2). A reverse product distribution was observed for a trimethylsilyl-substituted alkyne that gave **3-3** predominantly (entry 3). In the case of internal alkynes (R^1 = phenyl and R^2 = Me_3Si or CH_3) compounds **3-2** were produced exclusively (entries 4–5).



entry	R^1	R^2	product ratio (**3-2**:**3-3**)
1	C_3H_7	H	92:8
2	Ph	H	99:<1
3	Me_3Si	H	16:84
4	Ph	Me_3Si	99:<1
5	Ph	CH_3	99:<1

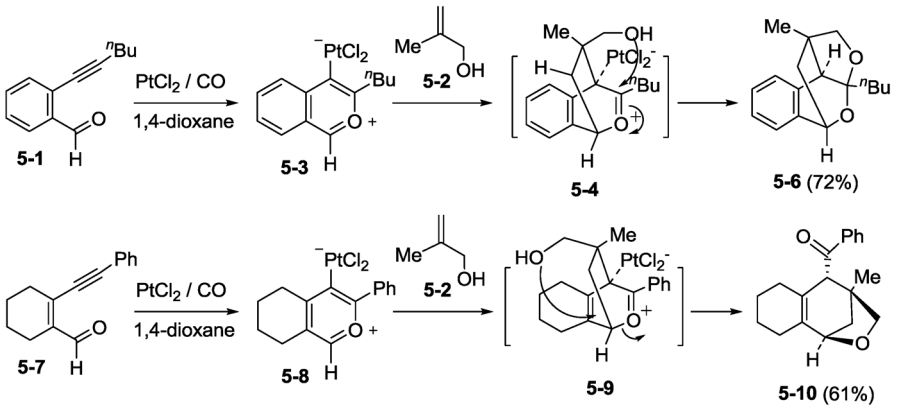
Scheme 3 Benzannulation through a formal intermolecular [4 + 2] cycloaddition.

An intramolecular version of this [4 + 2] benzannulation was applicable to the synthesis of (+)-rubiginone B2 (**4-3**) and (+)-ochromycinone (**4-4**) [7], members of the angucyclinone family of natural products (Scheme 4). Treatment of oxoalkyne **4-1** with $AuCl_3$ initiated an efficient intramolecular benzannulation to allow a rapid construction of the 3,4-dihydrotetraphen-1(2*H*)-one framework, and a subsequent oxidation afforded (+)-rubiginone B2 (**4-3**). The BCl_3-mediated demethylation of species **4-3** led to (+)-ochromycinone (**4-4**), another member of the same natural product series.



Scheme 4 Synthesis of (+)-rubiginone B2 and (+)-ochromycinone.

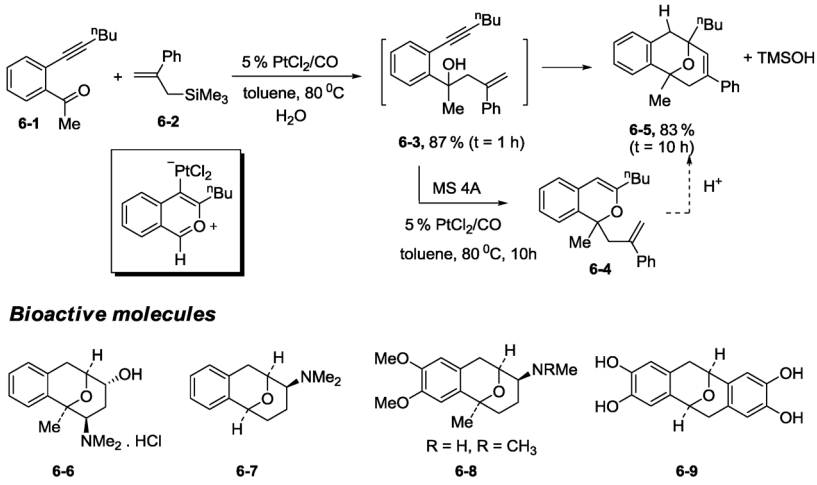
We achieved new oxacyclic compounds via Pt-catalyzed [4 + 2] annulation of enynals **5-1** with allylic alcohols [8]. Pt-containing benzopyrylium **5-3** (or pyrilium **5-8**) intermediates are capable of reacting with 2-substituted allylic alcohols to yield various oxacyclic compounds **5-6** or **5-10** depending on enynals of the types (Scheme 5). Tetracyclic ketal **5-6** species are obtained stereoselectively from 2-(hex-1-ynyl)benzaldehyde **5-1**, whereas tricyclic oxacyclic compounds **5-10** are produced exclusively



Scheme 5 Pt-catalyzed streocontrolled [4 + 2] cycloadditions and annulations of enynals with allylic alcohols.

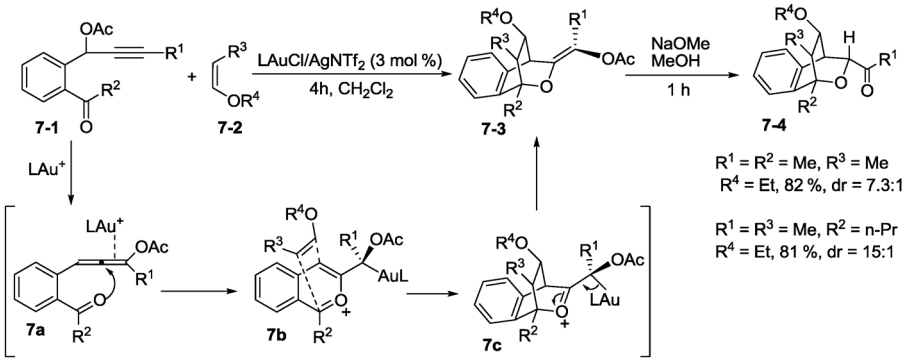
from non-benzenoid substrates **5-7**. These cycloadditions have emerged as powerful tools for the efficient synthesis of complex oxacyclic molecules.

Scheme 6 shows a new Pt-catalyzed synthesis of 9-oxabicyclo[3.3.1]nona-2,6-dienes from readily available 2-alkynyl-1-carbonylbenzene, allylsilane, and water in which the carbocyclization does not involve benzopyrilium species [9]. This is a tandem allylation/annulation sequence involving three consecutive steps: (i) $PtCl_2$-catalyzed allylation of the carbonyl group, and (ii) intramolecular hydroalkoxylation of alkyne, producing 1*H*-isochromene **6-4.** The final ene-oxonium annulation relies on Brønsted acid to give 9-oxabicyclo[3.3.1]nona-2,6-dienes **6-5**. This oxatricyclic is synthetically interesting because bioactive molecules **6-6** to **6-9** possess the same framework, which showed biological effects in the central nervous system [10], as well as HIV-1 inhibitory activities [11].



Scheme 6 Pt-catalyzed annulation of 2-alkynyl-1-carbonylbenzene with allylsilane.

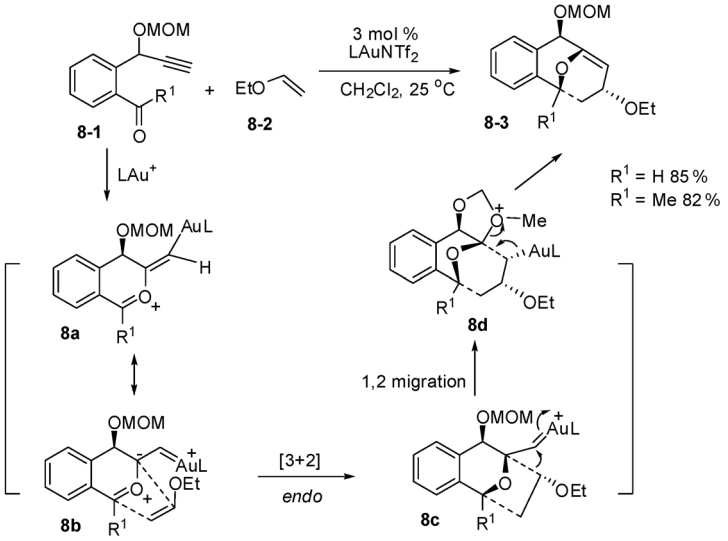
Scheme 7 depicts a Au-catalyzed oxacyclization/[4 + 2] cycloaddition cascade for oxoalkyne substrates **7-1** and an enol ether [12]. The cationic Au complex catalyzed an initial 1,3-acyloxy shift of starting **7-1** to generate initial oxoallene **7a**, which subsequently formed benzopyrilium of new type **7b** via a 6-*endo-dig*-cyclization. Such a benzopyrilium intermediate reacted well with enol ethers to give



Scheme 7 Au-catalyzed tandem oxacyclization/[4 + 2]-cycloaddition.

isolable [4 + 2] cycloadduct **7-3** as a mixture of two diastereomers. Further base-catalyzed hydrolysis of these oxocyclic products gave oxabicyclo ketone **7-4** in high diastereoselectivity (dr > 10:1).

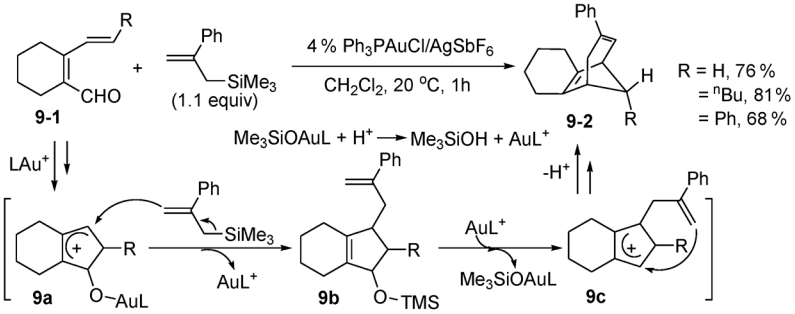
Scheme 8 reveals a highly stereoselective Au-catalyzed synthesis of 9-oxabicyclo[3.3.1]nona-4,7-dienes from the reaction of 1-oxo-4-oxy-5-ynes (**8-1**) with enol ethers; the success of this catalysis relied on the generation of *s-trans*-methylene(vinyl)oxoniums (**8a**) that function as 1,4 dipoles [13]. Notably, oxacyclic products **8-3** have *anti*-Bredt structures, and are formed with high stereocontrol. Although the overall transformation can be visualized as a formal [4 + 2] cycloaddition, the origin of high diastereoselectivity arises from a prior [3 + 2] cycloaddition of enol ethers with *s-trans*-2-oxadienum (**8b**), followed by a 1,2-alkyl migration, as depicted in Scheme 8.



Scheme 8 Synthesis of 9-oxabicyclo[3.3.1]nona-4,7-dienes via a formal [4 + 2] cycloaddition.

OXODIENES

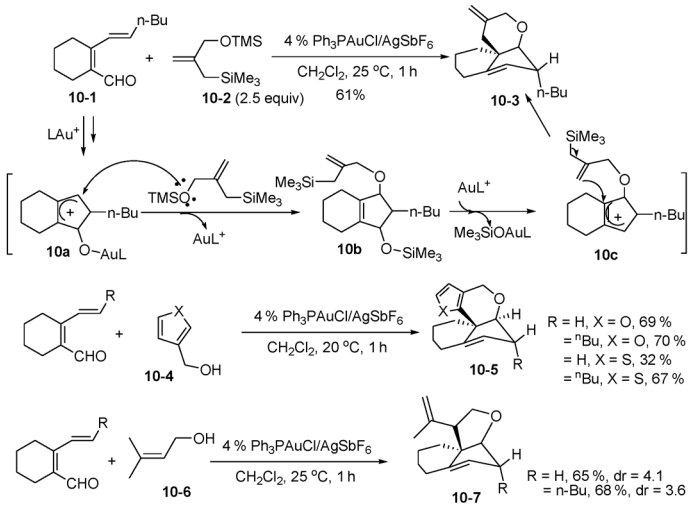
2,4-Dien-1-als have been thoroughly investigated for various Au-catalyzed cyclization/cycloaddition modes, accessing diversified carbo- and heterocyclic compounds [14]. A new [4 + 3] annulation of *cis*-2,4-dien-1-als **9-1** with allylsilanes was developed for the stereoselective synthesis of tricyclic



Scheme 9 Catalytic cyclization/[4 + 3] annulation of *cis*-2,4-dien-1-al with allylsilane.

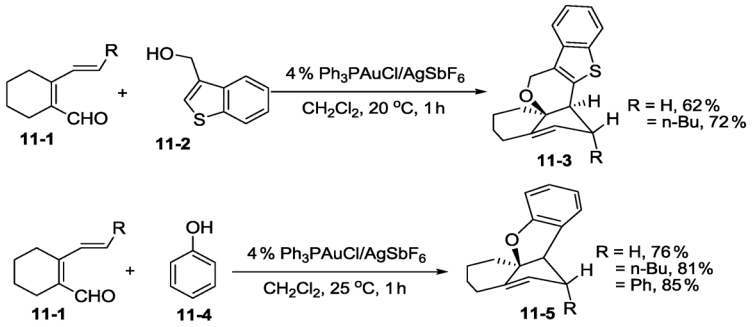
molecular framework **9-2**. Here, Au(I)-initiated 5-*exo* cyclization of dienal **9-1** gave an allylic cation **9a** that underwent a subsequent nucleophilic attack of allylsilane to give intermediate **9b**. The ionization/intramolecular nucleophilic attack delivered the final [4 + 3]-annulated product **9-2** (Scheme 9).

The preceding cascade reaction implicates dication equivalents for dienals **9-1**; this concept stimulates new reactions. For examples, 2-silyloxymethylallylsilane (**10-2**) reacted smoothly with *cis*-2,4-dien-1-als **10-1**, giving oxabicyclo compound **10-3**. Here, the initial nucleophilic attack on allylic cation intermediate **10a** took place to generate intermediate **10b**, as shown in Scheme 10. Species **10b** underwent a subsequent ionization, followed by an intramolecular allylation to furnish the final [4 + 2] annulation product **10-3**. 3-Hydroxymethyl heteroarenes **10-4** were also suitable to this Au catalysis via [4 + 2]-annulations with 2,4-dien-1-als. For furan and thiophene bearing a 3-hydroxymethyl substituent, tricyclic pyran derivatives **10-5** were obtained as formal [4 + 2] cycloadducts (Scheme 10) while allylic alcohols underwent distinct [3 + 2] cycloadditions to furnish oxatricyclic product **10-7**.



Scheme 10 Au-catalyzed [4 + 2] and [3 + 2] annulation of *cis*-2,4-dien-1-als with 3-hydroxymethyl heteroarenes and allylic alcohols.

In the presence of PPh_3AuSbF_6, phenol and (benzo[*b*]thiophen-3-yl)methanol reacted smoothly with 2,4-dien-1-als in stereoselective [3 + 2] and [4 + 2] cycloaddition fashions. Resulting oxatricyclic

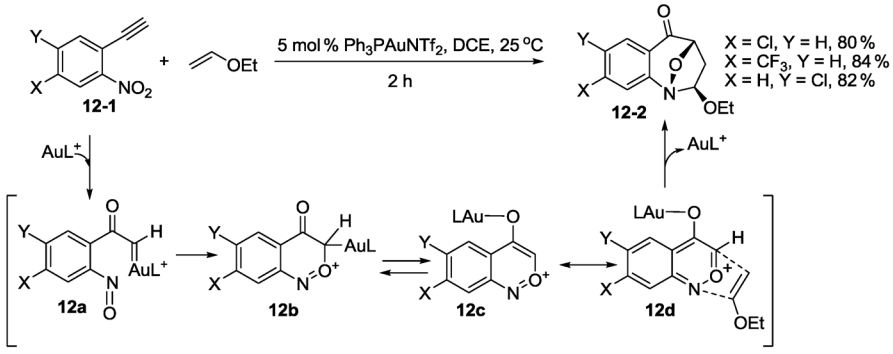


Scheme 11 Distinct regioselectivities for the annulation with phenol and (benzo[*b*]thiophen-3-yl)methanol.

products **11-3** and **11-5**, as shown in Scheme 11, have an O- and C-linkage to the central cyclopentene ring, opposite to those observed for **10-5** and **10-7**.

NITROALKYNE

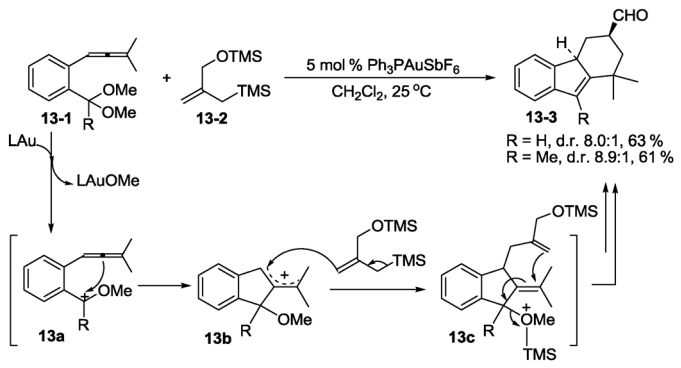
The synthesis of complex azabicyclic framework **12-2** from readily available nitroalkyne **12-1** and electron-rich alkene is reported from our laboratory (Scheme 12) [15]. This catalytic transformation involved a formal [2 + 2 + 1] cycloaddition among α-carbonyl carbenoid intermediate **12a**, a tethered nitroso functionality and external olefins, as represented by species **12a**. Here, α-carbonyl carbenoid species **12-a** presumably arose from a Au-catalyzed redox process. This carbenoid species underwent an intramolecular cyclization to give oxonium species **12b**. Keto-enol equilibrium gave rise to enolate **12c**, which is represented also in its resonance form **12d**. A [3 + 2] cycloaddition of species **12d** with an olefin in a concerted *exo*-addition mode delivered observed compound **12-2**.



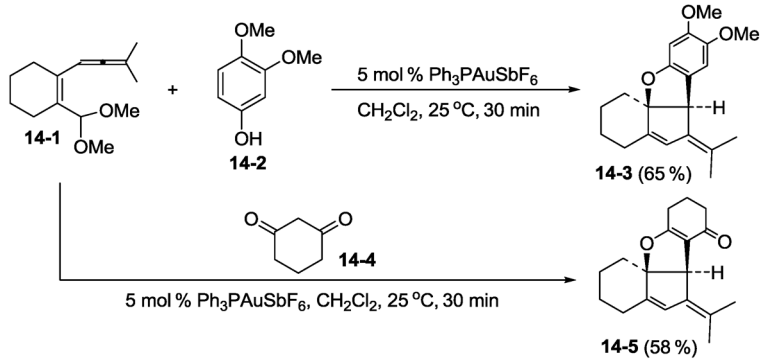
Scheme 12 Au-catalyzed [2 + 2 + 1] cascade of nitroalkynes.

ALLENYL ACETALS

We developed also a carbocyclization/[3 + 3] annulation cascade for allenyl acetals and -ketals. Treatment of these substrates with 2-substituted allylsilane and Au catalysts enabled a rapid construction of complex carbocyclic framework with good stereocontrol [16]. The value of this novel annulation protocol is reflected by its access to the framework of naturally occurring dichronal B and taiwaniaquinol [17]. As shown in Scheme 13, the mechanism involves a Prins cyclization of cationic intermediate **13a**, resulting in an allylic carbocation **13b** that undergoes allylation with silane **13-2**, sub-



Scheme 13 Au-catalyzed dealkoxylative carbocyclization/[3 + 3] annulation cascade.



Scheme 14 Au-catalyzed [3 + 2] annulation cascade of allene-acetal.

sequently delivering aldehyde **13-3** through a hydride migration. The same reactions of aliphatic substrates **14-1** with phenols or 1,3-diketones led to distinct [3 + 2] annulation, enabling a facile construction of oxacyclic compounds (Scheme 14).

CONCLUSION

Herein, we provide an overview of Au-catalyzed cyclization/cycloaddition cascades. We envisage that such a three-bond formation process meets the simplicity of reaction patterns to attract general readership. Generation of reactive 1,*n*-dipoles in this cascade sequence is of scientific interest. We endeavored to summarize our recent development in this area. Au-catalyzed tandem cycloadditions emerge as a powerful tool to access complicated molecular architecture. Although recent reports have focused mainly on oxoalkynes, other substrates remain less explored.

ACKNOWLEDGMENTS

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

REFERENCES

1. M. Beller, C. Bolm. *Transition Metals for Organic Synthesis*, 2nd ed., Wiley-VCH, Weinheim (2004).

2. (a) N. T. Patil, Y. Yamamoto. *Chem. Rev*. **108**, 3395 (2008); (b) A. S. K. Hashmi. *Chem. Rev.* **107**, 3180 (2007); (c) J. Li, C. Brouwer, C. He. *Chem. Rev.* **108**, 3239 (2008); (d) E. J. Jiménez-Núñez, A. M. Echavarren. *Chem. Rev.* **108**, 3326 (2008); (e) A. Arcadi. *Chem. Rev.* **108**, 3266 (2008); (f) D. J. Gorin, B. D. Sherry, F. D. Toste. *Chem. Rev.* **108**, 3351 (2008); (g) A. R. Chianese, S. J. Lee, M. R. Gagné. *Angew. Chem., Int. Ed.* **46**, 4042 (2007); (h) D. J. Gorin, F. D. Toste. *Nature* **446**, 395 (2007); (i) E. Jiménez-Núñez, A. M. Echavarren. *Chem. Commun*. 333 (2007); (j) A. S. K. Hashmi. *Chem. Rev.* **107**, 3180 (2007); (k) L. Zhang, J. Sun, S. A. Kozmin. *Adv. Synth. Catal.* **348**, 2271 (2006); (l) A. Fürstner, P. W. Davies. *Angew. Chem., Int. Ed.* **46**, 3410 (2007); (m) V. Michelet, P. Y. Toullec, J.-P. Genêt. *Angew. Chem., Int. Ed.* **47**, 4268 (2008); (n) B. Crone, S. F. Kirsh. *Chem.—Eur. J.* **14**, 3514 (2008); (o) C. Hahn. *Chem.—Eur. J.* **10**, 5888 (2004); (p) S. M. Abu Sohel, R.-S. Liu. *Chem. Soc. Rev*. **38**, 2269 (2009).
3. (a) A. Fürstner. *Chem. Soc. Rev*. **38**, 3208 (2009); (b) E. Soriano, J. Marco-Contelles. *Acc. Chem. Res*. **42**, 1026 (2009); (c) S. I. Lee, N. Chatani. *Chem. Commun*. 371 (2009); (d) S. F. Kirsch. *Synthesis* 3183 (2008); (e) J. Muzart. *Tetrahedron* **64**, 5815 (2008); (f) R. A. Widenhoefer. *Chem.—Eur. J.* **14**, 5382 (2008); (g) A. S. K. Hashmi. *Angew. Chem., Int. Ed.* **47**, 6754 (2008); (h) N. Bongers, N. Krause. *Angew. Chem., Int. Ed.* **47**, 2178 (2008); (i) A. S. K. Hashmi. *Angew. Chem., Int. Ed.* **44**, 6990 (2005); (j) A. M. Echavarren, C. Nevado. *Chem. Soc. Rev*. **33**, 431 (2004); (k) S. T. Diver, A. J. Giessert. *Chem. Rev.* **104**, 1317 (2004); (l) T. C. Boorman, I. Larrosa. *Chem. Soc. Rev*. **40**, 1910 (2011); (m) M. Bandini. *Chem. Soc. Rev*. **40**, 1358 (2011); (n) N. Krause, C. Winter. *Chem. Rev.* **111**, 1994 (2011); (o) B. Alcaide, P. Almendros, J. M. Alonso. *Org. Biomol. Chem.* **9**, 4405 (2011); (p) M. Rudolph, A. S. K. Hashmi. *Chem. Commun.* **47**, 6536 (2011).
4. A. Das, S. M. A. Sohel, R.-S. Liu. *Org. Biomol. Chem.* **8**, 960 (2010).
5. N. Asao, K. Takahashi, S. Lee, T. Kasahara, Y. Yamamoto. *J. Am. Chem. Soc*. **124**, 12650 (2002).
6. N. Asao, T. Nogami, S. Lee, Y. Yamamoto. *J. Am. Chem. Soc*. **125**, 10921 (2003).
7. K. Sato, N. Asao, Y. Yamamoto. *J. Org. Chem.* **70**, 8977 (2005).
8. Y.-C. Hsu, C.-M. Ting, R.-S. Liu. *J. Am. Chem. Soc.* **131**, 2090 (2009).
9. S. Bhunia, K.-C. Wang, R.-S. Liu. *Angew. Chem., Int. Ed.* **47**, 5063 (2008).
10. (a) B. Wünsch, M. Zott, G. Höfner. *Arch. Pharm*. **325**, 733 (1992); (b) B. Wünsch, M. Zott, G. Höfner. *Arch. Pharm*. **326**, 823 (1993); (c) C. Ketterer, S. Grimme, E. Weckert, B. Wünsch. *Tetrahedron: Asymmetry* **17**, 3046 (2006).
11. (a) C. Maurin, F. Bailly, P. Cortelle. *Curr. Med. Chem*. **10**, 1795 (2003); (b) R. Dupont, L. Jeanson, J.-F. Mouscadet, P. Cotelle. *Bioorg. Med. Chem. Lett*. **11**, 3175 (2001); (c) R. Dupont, P. Cotelle. *Tetrahedron Lett*. **39**, 8457 (1998).
12. T.-M. Teng, R.-S. Liu. *J. Am. Chem. Soc.* **132**, 9298 (2010).
13. T.-M. Teng, A. Das, D. B. Huple, R.-S. Liu. *J. Am. Chem. Soc.* **132**, 12565 (2010).
14. (a) C.-C. Lin, T.-M. Teng, A. Odedra, R.-S. Liu. *J. Am. Chem. Soc.* **129**, 3798 (2007); (b) C.-C. Lin, T.-M. Teng, C.-C. Tsai, H.-Y. Liao, R.-S. Liu. *J. Am. Chem. Soc.* **130**, 16417 (2008).
15. A. M. Jadhav, S. Bhunia, H.-Y. Liao, R.-S. Liu. *J. Am. Chem. Soc.* **133**, 1769 (2011).
16. T.-M. Teng, M.-S. Lin, D. Vasu, S. Bhunia, T.-A. Liu, R.-S. Liu. *Chem.—Eur. J.* **16**, 4744 (2010).
17. Occurrence: (a) W.-H. Lin, J.-M. Fang, Y.-S. Cheng. *Phytochemistry* **40**, 871 (1995); (b) W.-H. Lin, J.-M. Fang, Y.-S. Cheng. *Phytochemistry* **42**, 1657 (1996); (c) K. Kawazoe, M. Yamamoto, Y. Takaishi, G. Honda, T. Fujita, E. Sezik, E. Yesilada. *Phytochemistry* **50**, 493 (1999); (d) C.-I. Chang, S.-C. Chien, S.-M. Lee, Y.-H. Kuo. *Chem. Pharm. Bull.* **51**, 1420 (2003); (e) C.-I. Chang, J.-Y. Chang, C.-C. Kuo, W.-Y. Pan, Y.-H. Kuo. *Planta Med.* **71**, 72 (2005); Total synthesis: (f) G. Liang, Y. Xu, I. B. Seiple, D. Trauner. *J. Am. Chem. Soc.* **128**, 11022 (2006); (g) M. Banerjee, R. Mukhopadhyay, B. Achari, A. K. Banerjee. *J. Org. Chem.* **71**, 2787 (2006); (h) S. Tang, Y. Xu, J. He, Y. He, J. Zheng, X. Pan, X. She. *Org. Lett.* **10**, 1855 (2008).

