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Gold-Catalyzed Synthesis of Carbon-Bridged Medium-Sized Rings

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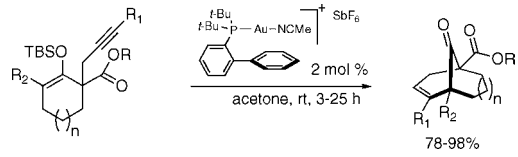
ABSTRACT



Bicyclo[*m.n.*1]alkenone frameworks possessing quaternary carbon centers adjacent to a bridged ketone are frequently found in bioactive natural products. Although several methods have been developed to construct such frameworks, most of them are specific to a particular scaffold. Herein, we report a mild and highly efficient method to generate carbon-bridged frameworks of various sizes using phosphino gold(I) catalysts.

Highly oxygenated and densely substituted bicyclo[*m.n.*1]-alkanone cores are commonly found in nature as structural frameworks of bioactive natural products.[1] Most of these compounds bear quaternary carbon centers adjacent to the bridged ketone. These comprise enaimeone A (**1**),[2] hyperforin (**2**)[3] (isolated from *Hyperycum perforatum*, known as St. John's wort), and penostastin (**3**)[4] (Figure 1).

Owing to the promising biological properties and challenging structures of these molecules, considerable research efforts have been devoted to develop efficient methods to construct carbon bridged-medium sized rings.[5] However, most of them are specific for a particular framework.

To address this issue, transition-metal-promoted cyclizations of enol ethers with alkynes represent an attractive and efficient strategy to generate fused-carbocyclic rings.[6,7] However, reports of their use in the synthesis of bicyclo-[*m.n.*1]alkenone rings are rare and substrate specific.[8] Taking advantage of the affinity of phosphino gold(I) salts for triple bonds,[9] we envisioned a Au(I)-catalyzed 6-*endo-dig* cyclization of cyclic silyl enol ether **4** to synthesize bicyclic bridgehead ketone **7** (Scheme 1). A cursory inspection of

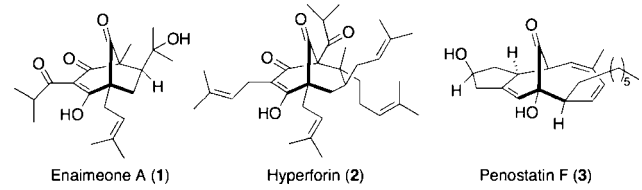


Figure 1. Structure of enaimeone (**1**), hyperforin (**2**), and penostatin F (**3**).

(1) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963.
(2) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *Helv. Chim. Acta* **2001**, *84*, 3380.
(3) (a) For isolation of hyperforin, see: Gurevich, A. I.; Dobrynin, V. N.; Kolosov, M. N.; Popravko, S. A.; Riabova, I. D. *Antibiotiki* **1971**, *16*, 510. (b) Bystrov, N. S.; Chernov, B. K.; Dobrynin, V. N.; Kolosov, M. N. *Tetrahedron Lett.* **1975**, 2791. (c) For synthetic studies, see: Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2009**, *50*, 3519. (d) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2008**, *49*, 1417. (e) Shimizu, Y.; Kuramochi, A.; Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2007**, *48*, 4173. (f) Nicolaou, K. C.; Carenzi, G. E. A.; Jeso, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 3895.
(4) (a) For isolation of penostatin F, see: Numata, A.; Iwamoto, C.; Minoura, K.; Hagishita, S.; Nomoto, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 449. For synthetic studies, see: (b) Barriault, L.; Ang, P. A. J.; Lavigne, R. M. A. *Org. Lett.* **2004**, *6*, 1317.
(5) (a) For a review on the synthesis of bicyclo[3.3.1]nonanes, see: Butkus, E. *Synlett* **2001**, 1827. (b) For a review on the synthesis of the bicyclo[4.3.1]decenone skeleton of phomoidrides, see: Spiegel, D. A.; Njardason, J. T.; McDonald, I. M.; Wood, J. L. *Chem. Rev.* **2003**, *103*, 2691. (c) For a review on the synthesis of the bicyclo[5.3.1]undecene framework of Taxol, see: Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemp. Org. Synth.* **1994**, *1*, 47. (d) Sheehan, S. M.; Lalic, G.; Chen, J. S.; Shair, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2714. (e) Lavigne, R. M. A.; Riou, M.; Girardin, M.; Morency, L.; Barriault, L. *Org. Lett.* **2005**, *7*, 5921.

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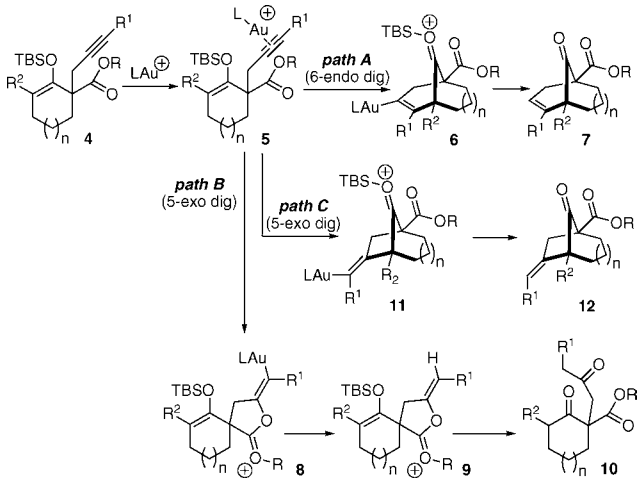
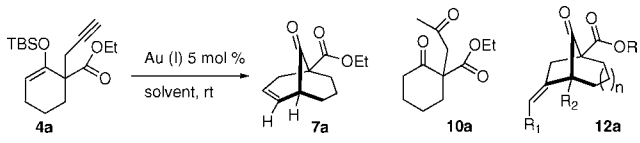
Scheme 1. Proposed Mechanism for the Au(I)-Catalyzed Cyclization

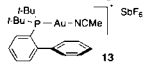


the mechanism reveals that the Au(I)-catalyzed cyclization can proceed via three distinct pathways. In path A, a 6-*endo-dig* cyclization of **4** gives intermediate **6** which after protonation leads to the desired product **7**. Conversely, Au(I) complex **5** can undergo competitive 5-*exo-dig* cyclization to afford intermediate **8** (path B) and **11** (path C) which upon protonation and hydrolysis provide the hydration product **10** and the bicyclic ketone **12**, respectively.

Keeping this in mind, we examined various cationic phosphinogold(I) complexes. Treatment of silyl enol ether **4a**[10] with 5 mol % of $Ph_3PAuCl/AgBF_4$ in DCM at room temperature gave the bridged ketone **7a** as the major product in low conversion (30%) (Table 1, run 1). The minor product

Table 1. Optimization



run	catalyst	solvent	time (h)	convn (**7a**:**10a**:**12a**)[a]
1	$Ph_3PAuCl/AgBF_4$	DCM	7	30% (8:1:0)
2	$Et_3PAuCl/AgBF_4$	DCM	7	76% (30:1:0)
3	$Et_3PAuCl/AgSbF_6$	DCM	6	78% (14:1:0)
4	$Et_3PAuCl/AgOTf$	DCM	6	100% (2.5:1:0)
5		DCE	4	100% (1:5:0)
6		MeCN	4	100% (4.5:1:0)
7		toluene	4	88% (37:1:0)
8		acetone	3	100% (30:1:0)[b,c]

[a] Determined by ^{1}H NMR. [b] 2 mol % of catalyst was used. [c] Isolated yield = 90%.

ketone **10a** results from a cyclization via path B. The replacement of triphenylphosphine by triethylphosphine dramatically improved the chemoselectivity (30:1) and the conversion (76%) (run 2). On the other hand, the replacement of the counterion by SbF_6^- and OTf^- proved to be detrimental to the selectivity despite a slight improvement of the conversion (runs 3 and 4). Surprisingly, the air stable Echavarren catalyst **13**,[11] gave mainly the hydration product **10a** in dichloroethane (run 5). In contrast, high chemoselectivity was achieved when toluene was used as solvent (run 7). Additional experimentation demonstrated that 2 mol % of **13** in acetone was optimal for this process (run 8).[12]

Having established the reaction conditions, the scope of this Au(I)-catalyzed 6-*endo-dig* cyclization was then examined (Table 2).[13] Enol ethers **4b**, **4c**,and **4d** were readily converted to ketones **7b**, **7c**, and **7d** in 85, 80, and 98% yields, respectively. Thus, the frameworks of the three natural products depicted in Figure 1 are rapidly and efficiently synthesized using this new approach. The method tolerates substitution, as evidenced by the cyclization of substrates **4e**−**h**, which give the desired ketones **7e**−**h** exclusively and in high yields. It worth noting is that bicyclo[3.3.1]nonenones **7g** and **7h** bear the two bridgehead quaternary carbon centers present in **2** and related natural polycyclic polyprenylated acetylphloroglucin compounds.

Next, we looked at the Au(I)-catalyzed carbocyclization of substrates possessing a tetrasubstituted enol ether and an internal alkyne. Compounds **4i**−**l** were treated under the standard conditions to provide the corresponding bicyclo-[3.3.1]nonenones **7i**−**l** in 78−92% yield. These results confirmed that alkyl and/or aryl substitutions at R_1 and R_2 in **4** do not impair the regio- and chemoselectivity of the reaction.

In the context of its application to the total synthesis of natural polycyclic polyprenylated acetylphloroglucins, we further probed the scope of this transformation.

(6) (a) Drouin, J.; Boaventura, M. A.; Conia, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1726. (b) Drouin, J.; Boaventura, M. A. *Tetrahedron Lett.* **1987**, *28*, 3923. (c) Huang, H.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 2773. (d) Iwasawa, N.; Maeyama, K.; Kusama, H. *Org. Lett.* **2001**, *3*, 3871. (e) Iwasawa, N.; Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Lee., P. H. *Org. Lett.* **2002**, *4*, 4463. (f) Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2003**, *9*, 2627. (g) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2764.

(7) For Au(I)-catalyzed cyclization, see: (a) Dankwardt, J. K. *Tetrahedron Lett.* **2001**, *42*, 5809. (b) Suhre, M. H.; Reif, M.; Kirsch, S. F. *Org. Lett.* **2005**, *7*, 3925. (c) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991. (d) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7671. (e) Lee, K.; Lee, P. H. *Adv. Synth. Catal.* **2007**, *349*, 2092.

(8) For terminal alkynes, 10 mol % $W(CO)_5$(THF) is required, see: (a) Iwasawa, N.; Maeyama, K. *J. Am. Chem. Soc.* **1998**, *120*, 1928. For substituted alkynes, a stoichiometric amount of $W(CO)_5$(THF) is required, see: (b) Iwasawa, N.; Miura, T. *J. Am. Chem. Soc.* **2002**, *124*, 518. (c) For $EtAlCl_2$-mediated cyclization, see: Imamura, K.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4081.

(9) Recent reviews on gold catalysis: (a) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (b) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (c) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (d) Jimenez-Núnez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (e) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395.

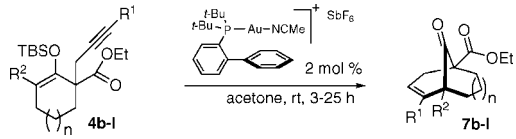
(10) The preparation of silyl enol ethers **4a**−**l** is described in the Supporting Information.

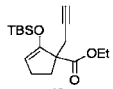
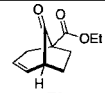
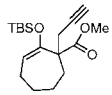
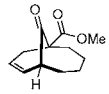
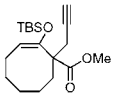
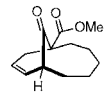
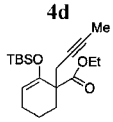
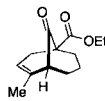
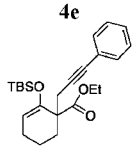
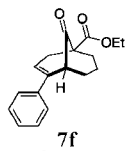
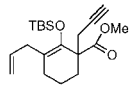
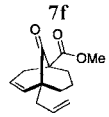
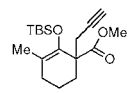
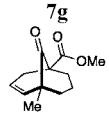
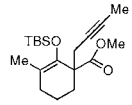
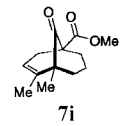
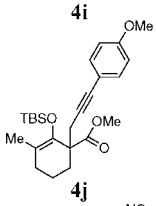
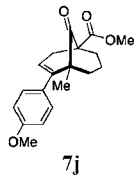
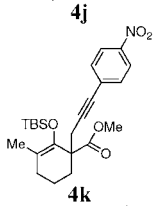
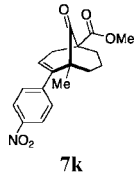
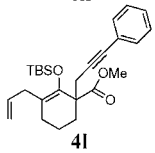
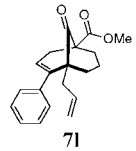
(11) Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.

(12) All reaction vessels were treated in a KOH/*i*-PrOH bath prior to use.

(13) In all runs, no products from path B or C were observed by ^{1}H NMR of the crude reaction mixture.

Table 2. Gold(I)-Catalyzed 6-Endo Cyclization

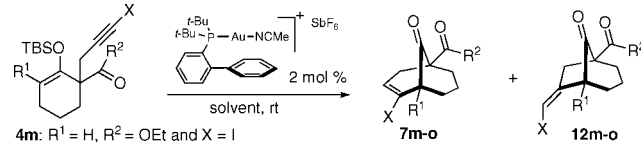


run	substrate	product	time (h)	yield (%)
1	 **4b**	 **7b**	12	85
2	 **4c**	 **7c**	25	80[a]
3	 **4d**	 **7d**	2	98
4	 **4e**	 **7e**	6	91
5	 **4f**	 **7f**	7	88
6	 **4g**	 **7g**	4	87
7	 **4h**	 **7h**	6	91
8	 **4i**	 **7i**	20 35	78 92[a]
9	 **4j**	 **7j**	15	88
10	 **4k**	 **7k**	20	83
11	 **4l**	 **7l**	15	92

[a] Reaction performed in acetonitrile.

Halogenated alkynes **4m** and **4n** were subjected to the optimized reaction conditions (Table 3). Much to our surprise, mixtures of 6-*endo* **7m**,**n** and 5-*exo* **12m**,**n** (cyclization via path C) were obtained (entries 1 and 2). To improve the reaction selectivity, other solvents were investigated. It was found that the cyclization in benzene gave also a mixture of **7m**,**n** and **12m**,**n** (ratio ≈ 3:1) (entries 3 and 4), whereas in MeOH, the formation of the 5-*exo* products **12m**,**n** were slightly favored (entries 5 and 6). The best results were obtained in chloroform (entries 7 and 9) to give mainly the desired bicyclo[3.3.1]nonenone **7m** and **7n** in 92% and 85% yield, respectively. Interestingly, Au(I)-catalyzed cyclization of bromoalkyne **4o** afforded the corresponding bicyclic-bridged ketone **7o** in 93% yield as the sole isomer (entry 9).

Table 3. Au(I)-Catalyzed Cyclized of Halogenated Alkynes



4m: R^1 = H, R^2 = OEt and X = I
4n: R^1 = Me, R^2 = OMe and X = I
4o: R^1 = Me, R^2 = OMe and X = Br

entry	substrate	solvent	ratio **7**:**12**[a]	yield (%)
1	**4m**	acetone	1.2:1	88
2	**4n**	acetone	2.1:1	91
3	**4m**	benzene	2.6:1	83
4	**4n**	benzene	2.9:1	88
5	**4m**	MeOH	1:2.3	73
6	**4n**	MeOH	1:1.2	68
7	**4m**	$CHCl_3$	10.3:1	92
8	**4n**	$CHCl_3$	12.5:1	85
9	**4o**	acetone	>95:5	93

[a] Determined by ^{1}H NMR.

In summary, we have developed a mild and efficient method to generate bicyclo[*m*.3.1]alkenones using phosphino gold(I) catalysts. The attractive feature of this method resides in ability to construct carbon bridged-medium rings of various sizes as well as the installment of quaternary carbon centers adjacent to the bridgehead ketone. Applications of this method to the synthesis of hyperforin (**2**) and related compounds are underway and will be reported in due course.

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Supporting Information Available: Experimental details and analytical data for all new compounds and ORTEP view of **7k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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