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Gold-Catalyzed Stereocontrolled Oxacyclization/[4+2]-Cycloaddition Cascade of Ketone-Allene Substrates

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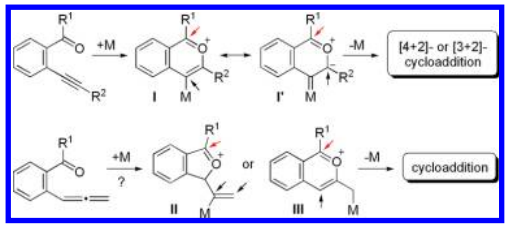
Abstract: We report the first success on the Au-catalyzed tandem oxacyclization/[4+2]-cycloaddition cascade using ketone-allene substrates to give highly substituted oxacyclics with excellent stereocontrol. In contrast to oxo-alkyne substrates, the resulting cycloadducts are isolable and efficiently produced from a reasonable scope of enol ethers.

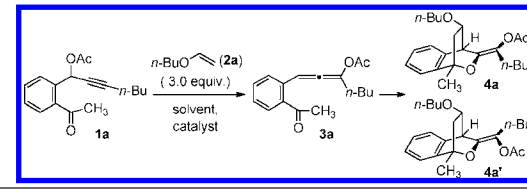
Metal-catalyzed cycloaddition/annulation reactions are important tools to access complex molecular frameworks.[1] The Au- and Pt-catalyzed activation of alkynes enables the generation of unusual intermediates to react with dipolarophiles in a cycloaddition fashion.[2] Such reactions have attained considerable success only on oxo-alkyne substrates.[1a,b] In the presence of Au or Pt catalysts, 2-oxo-1-alkynylbenzenes form metal-containing benzopyriliums (**I**) or carbonyl ylides (**I′**) that react with dipolarophiles to give hypothetic [4+2]- or [3+2]-cycloaddition intermediates.[3,4] Generation of 1,n-dipole species remains unexplored for oxo-allene substrates. This approach is mechanistically appealing because of the uncertain workability of oxonium-vinylmetal (**II**) or benzopyrilium (**III**) as 1,n-dipoles (n = 4, 5). Species **II** is kinetically favored by the Pt or Au-π-allene bonding,[5] but its participation is absent in this work.

Scheme 1



We prepared alkynyl acetate **1a** readily from 2′-bromoacetophenone. This substrate works as a precursor to generate ketone-allene **3a** via a catalytic 1,3-acyloxy shift.[6] As shown in Table 1, treatment of compound **1a** with *n*-butyl vinyl ether (**2a**, 3 equiv) with $PtCl_2$/CO or $AuCl_3$ in hot dichloroethane (50−80 °C) gave an exclusive recovery of unreacted **1a**. The use of $PPh_3AuCl/AgSbF_6$ (3 mol %) in dichloromethane (DCM) produced ketone-allene **3a** in 83% yield, but with no tractable amount of cycloadducts **4a/4a′**. We were pleased to discover that ClAuP(*t*-Bu)$_2$(*o*-biphenyl)/$AgSbF_6$ (3 mol %) enabled the desired cyclization/cycloaddition cascade to give **4a** (29%) and **4a′** (56%) as a diastereomeric mixture, separable on a silica column. The stereoselectivity is greatly enhanced with ClAuP(*t*-Bu)$_2$(*o*-biphenyl)/$AgNTf_2$, giving only **4a′** in 79% yield (entry 5); within a brief time (1 h), we obtained ketone-allene **3a** in 40% yield in addition to the desired **4a′** (46%, entry 6). The intermediacy of ketone-allene **3a** was confirmed by a complete conversion to **4a′** with the same gold catalyst (entry 7). Control experiments indicate that ClAuP(*t*-Bu)$_2$(*o*-biphenyl) and $AgNTf_2$ alone were catalytically inactive (entries 8−9). An altered chemoselectivity was observed for IPrAuCl/$AgNTf_2$ (IPr = 1,3-bis(diisopropyl-phenyl)imidazol-2-ylidene) that preferably gave **4a** as the major product (entry 10). Characterization of the structure of product **4a′** relies on an X-ray diffraction study of its analogue **4b′** (Table 2, entry 1).

Table 1. Screening of Catalytic Activity over Various Metal Catalysts



entry	substrate[a]	catalyst (mol %)	condition	product (yield)[b]
1	**1a**	$AuCl_3$ (5)	DCE (80 °C, 24 h)	**1a** (85%)
2	**1a**	$PtCl_2$/CO (5)	DCE (50 °C, 20 h)	**1a** (46%)[c]
3	**1a**	Ph_3PAuCl (3)/ $AgSbF_6$ (3)	DCM (30 °C, 8 h)	**3a** (83%)
4	**1a**	AuCIL (3)/ $AgSbF_6$ (3)	DCM (30 °C, 2 h)	**4a** (29%), **4a′** (56%)
5	**1a**	**AuCIL (3)/ $AgNTf_2$ (3)**	**DCM (30 °C, 2.5 h)**	**4a (trace), 4a′** (79%)
6	**1a**	AuCIL (3)/ $AgNTf_2$ (3)	DCM (30 °C, 1 h)	**3a** (40%), **4a′** (46%)
7	**3a**	AuCIL (3)/ $AgNTf_2$ (3)	DCM (30 °C, 2 h)	**4a** (trace), **4a′** (86%)
8	**1a**	AuCIL (5)	DCM (30 °C, 20 h)	**1a** (94%)
9	**1a**	$AgNTf_2$ (5)	DCM (30 °C, 20 h)	**1a** (62%), **3a** (17%)
10	**1a**	IPrAuCl (3)/ $AgNTf_2$ (3)	DCM (30 °C, 2 h)	**4a** (48%), **4a′** (22%)

[a] L = P(*t*-Bu)$_2$(*o*-biphenyl), [substrate] = 0.1 M, DCM = dichloromethane, DCE = 1,2-dichloroethane. [b] Isolated yields were reported after purification from a silica gel column. [c] Decomposition of starting **1a** was observed in entry 2.

We prepared ketone substrates **1b**−**1e** bearing altered R^1 and R^2 substituents to examine the scope of this catalysis, as depicted in Table 2. Herein, the aldehyde substrates are not studied due to the intrinsic instability of 2-allenyl benzaldehyde intermediates.[7] This reaction works well with both ethyl- and *n*-butyl vinyl ether (**2a**−**2b**), and it is also efficient with alterations of the R^1 (Me, *n*-Bu, *i*-Bu) and R^2 alkyls (Me, *n*-Pr) of substrates **1a**−**1e**. In entries 2, 4, and 5, due to the poor diastereoselectivity or chromatographic inseparable property, the cycloadducts **4b/4b′** and **4c/4c′** were subject to deacylation with NaOMe in MeOH to give ketone derivatives **5b**, **6b**, and **6c** with high dr values (8.5−10.0:1). For

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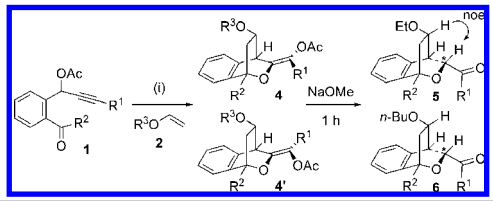
Table 2. Au(I)-Catalyzed Oxacyclization/Cycloaddition Cascade with Vinyl Ethers



entry	substrates[a]	enol ether	time (step i)	products (yield)[b]
1	$R^1 = R^2 =$ Me (**1b**)	$R^3 =$ Et (**2b**)	1.5 h	**4b** (46%), **4b′** (42%)
2	**1b**	**2b**	1.5 h	**5b** (85%, dr = 9:1)[c]
3	$R^1 = n$-Bu, $R^2 =$ Me (**1a**)	$R^3 = n$-Bu (**2a**)	2 h	**4a′** (79%, dr > 20:1)
4	$R^1 =$ Me, $R^2 =$ Me (**1b**)	**2a**	2 h	**6b** (83%, dr = 10:1)[c]
5	$R^1 =$ Me, $R^2 = n$-Pr (**1c**)	**2a**	2 h	**6c** (76%, dr = 8.5:1)[c]
6	$R^1 = n$-Bu, $R^2 = n$-Pr (**1d**)	**2a**	2 h	**4d′** (69%, dr > 20:1)
7	$R^1 = i$-Bu, $R^2 =$ Me (**1e**)	**2a**	3 h	**4e′** (61%, dr > 20:1)[d]

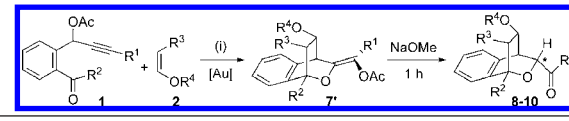
[a] ClAuP(t-Bu)$_2$(o-biphenyl)/AgNTf$_2$ (3 mol %), [substrate] = 0.1 M, DCM, enol ethers (3 equiv). [b] Isolated yields were reported after purification from a silica gel column. [c] The configuration at the *C carbon is responsible for the occurrence of two diastereomers. [d] Messy mixture was obtained for portion of **1e.**

substrates **1a** and **1d**−**1e** bearing a bulky R^1 ($R^1 = n$-Bu or i-Bu), the same reactions gave compounds **4a′** and **4d′**−**4e′** with excellent dr values (>20:1), due to a large steric interaction of the other isomers **4**. The structure of representative compound **4b′** is determined by an X-ray diffraction study.[8]

The scope of this new synthetic method is substantially expanded with its compatibility with substituted enol ethers including 1-ethoxypro-1-ene (**2c**, $Z/E = 1.8$, 3 equiv) and cyclic enol ethers **2d**−**2e**, as illustrated in Table 3. These enol ethers proceeded with excellent diastereoselectivity that we did not obtain any epimers bearing mutual *trans*-R^3 and OR^4 substituents. For starting ketones **1a**−**1c** and 1-ethoxypro-1-ene (entries 1−3), their cycloadducts **8a**−**8c** were obtained as one single diastereomer with its structure carefully determined by ^{1}H-NOE, suggesting that *cis*-enol ether **2c** is more active than its *trans* isomer. Indeed, the reaction of **2c** ($Z/E = 0.5$, 3 equiv) with ketone **1a** gave cycloadduct **8a** in diminished yield (31%) together with ketone-allene **3a** (61%). This new tandem cascade also works with 3,4-dihydro-2*H*-pyran (**2d**) that reacts with ketones **1a**−**1f** smoothly (entries 5−10), giving satisfactory yields (58−82%) of the expected cycloadducts **7a′**, **7d′**−**7f′** or the deacylation products **9b**−**9c**. 2,3-Dihydrofuran is also applicable to this catalysis, and it reacts with ketone **1b** to deliver compound **10b** in 53% yield (dr = 6.5:1).

We also prepared new substrates **1g**−**1l** to examine the effects of their phenyl substituents; their reactions with 3,4-dihydro-2*H*-pyran are described in Table 4. Good yields (72−87%) were obtained for cycloadducts **7g′**−**7h′** and **7k′**−**7l′** bearing fluoro and methoxy substituents because these π-donor groups stabilize proposed benzopyriliums **III** (*vide infra*). Hypothetic [4+2]-cycloadditions of free benzopyriliums[3f−h] and their metal-containing analogues[3] are restricted to unsubstituted benzenes and methoxy derivatives. The workability with substrates **1i** and **1j** bearing electron-deficient benzenes highlights the high reactivity of our new benzopyrilium (**III**).

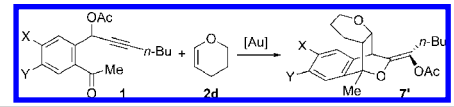
Table 3. Au(I)-Catalyzed Oxacyclization/Cycloaddition Cascade with Substituted Enol Ethers



entry	substrates[a]	alkene	t (step i)	products[b]
1	$R^1 = n$-Bu, $R^2 =$ Me (**1a**)	$R^3 =$ Me, $R^4 =$ Et (**2c**, $Z/E = 1.8$)	4 h	**8a** (76%, dr > 20:1)[c]
2	$R^1 = R^2 =$ Me (**1b**)	**2c**	4 h	**8b** (82%, dr = 7.3:1)[c]
3	$R^1 =$ Me, $R^2 = n$-Pr (**1c**)	**2c**	4 h	**8c** (81%, dr > 15:1)[c]
4	$R^1 = n$-Bu, $R^2 =$ Me (**1a**)	**2c** ($Z/E = 0.5$)	4 h	**8a** (31%, dr > 20:1)[c,d]
5	$R^1 = n$-Bu, $R^2 =$ Me (**1a**)	R^3, $R^4 =$ -$(CH_2)_3$- (**2d**)	1 h	**7a′** (82%, dr > 20:1)
6	$R^1 = R^2 =$ Me (**1b**)	**2d**	2 h	**9b** (72%, dr = 10:1)[c]
7	$R^1 =$ Me, $R^2 = n$-Pr (**1c**)	**2d**	1 h	**9c** (64%, dr = 7.5:1)[c]
8	$R^1 = n$-Bu, $R^2 = n$-Pr (**1d**)	**2d**	2 h	**7d′** (75%, dr > 20:1)
9	$R^1 = i$-Bu, $R^2 =$ Me (**1e**)	**2d**	3 h	**7e′** (63%, dr > 20:1)[e]
10	$R^1 =$ Ph, $R^2 =$ Me (**1f**)	**2d**	5 h	**7f′** (58%, dr > 20:1)[e]
11	$R^1 = R^2 =$ Me (**1b**)	R^3, $R^4 =$ -$(CH_2)_2$- (**2e**)	2 h	**10b** (53%, dr = 6.5:1)[c,e]

[a] ClAuP(t-Bu)$_2$(o-biphenyl)/AgNTf$_2$ (3 mol %), [substrate] = 0.1 M, DCM, enol ethers (3 equiv). [b] Isolated yields were given after purification from a silica gel column. [c] The configuration at the *C carbon is responsible for the occurrence of two diastereomers. [d] Ketone-allene **3a** was obtained in 61%. [e] Messy mixture was obtained for portion of **1b**, **1e**, or **1f.**

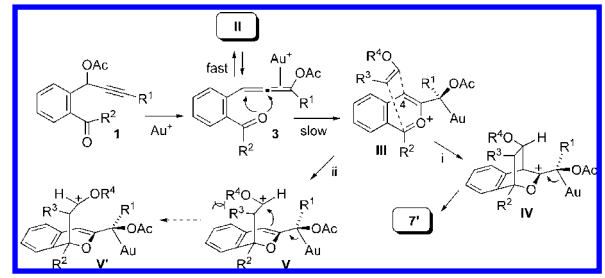
Table 4. Au(I)-Catalyzed Oxacyclization/Cycloaddition Cascade of Substituted Aromatic Substrates



entry	substrates[a]	t [h]	products (yield)[b]
1	X = H, Y = F (**1g**)	6	**7g′** (78%, dr >20:1)
2	X = F, Y = H (**1h**)	8	**7h′** (72%, dr >20:1)
3	X = H, Y = Cl (**1i**)	6	**7i′** (42%, dr >20:1)
4	X = Cl, Y = H (**1j**)	6	**7j′** (47%, dr >20:1)
5	X = H, Y = OMe (**1k**)	2	**7k′** (87%, dr >20:1)
6	X = OMe, Y = H (**1l**)	2	**7l′** (85%, dr >20:1)

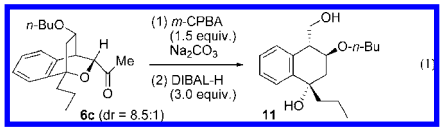
[a] ClAuP(t-Bu)$_2$(o-biphenyl)/AgNTf$_2$ (3 mol %), [substrate] = 0.1 M, DCM, enol ethers (3 equiv.). [b] Isolated yields were given after purification from a silica gel column.

Scheme 2



Structural analysis of resulting cycloadducts asserts the intermediacy of benzopyrilium (**III**), although gold-π-allene species **3** has cationic character located mainly at the C(1)- and C(3)-carbons.[5] We hypothesize a fast equilibrium between ketone-allene (**3**) and intermediate (**II**), but the cycloadducts expected from species (**II**) fail to proceed. Here, we propose a concerted mechanism (i) for

the [4+2]-cycloadditions of the new benzopyrilium (**III**). As shown in Scheme 2, *cis*-substituted enol ether approaches the pyrilium core of species **III** with its R^3 and OR^4 lying away from the bulky gold-containing substituent. We envisage that the allylic gold fragment of benzopyrilium **III** raises the HOMO energy level at the C(4)-carbon, facilitating this concerted process.[2b,9] The stepwise pathway (ii) involving cationic intermediates **V** and **V′** is opposed by our observation that no epimers resulted from the conformer **V′** which is actually favored by steric interactions of the *cis*-R^3 and OR^4 substituents of species **V**. Species (**III**) is more useful than reported benzopyriliums[3] in synthetic utility, because of its isolable and stereocontrolled [4+2]-cycloadducts.



Equation 1 shows the use of this catalysis for a stereoselective synthesis of a highly oxygenated molecule. A sequential treatment of compound **6c** with *m*-CPBA (1.5 equiv), followed by the DIBAL-H cleavage of resulting acetal, gave triol derivative **11** (65%) as a single diastereomer.

In summary, we report the first success on the Au-catalyzed tandem oxacyclization/[4+2]-cycloaddition cascade using ketone-allene substrates to give highly substituted oxacyclics with excellent stereocontrol. Control experiments reveal the involvement of benzopyrilium intermediates (**III**) that is active for [4+2]-cycloaddition reactions.[9] In contrast to oxo-alkyne substrates,[3] the resulting cycloadducts are isolable and efficiently produced from a reasonable scope of enol ethers. Efforts to realize the asymmetric version of this catalysis is under current investigation.

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Supporting Information Available: Experimental procedures, characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) Selected examples: (a) Shapiro, N. D.; Shi, Y.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 11654. (b) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 9244. (c) Li, G.; Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 6944. (d) Zhang, G.; Huang, X.; Li, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 1814. (e) Liu, F.; Yu, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5505.

(3) [4+2]-Cycloadducts from benzopyrilium (**I**) are kinetically unstable and easily rearranged to naphthalene derivatives; only allylic alcohols[3e] allow the interception. See selected examples: (a) Asao, N. *Synlett* **2006**, 1645. (b) Asao, N.; Kasahara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3504. (c) Asao, N.; Akiwa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458. (d) Dyker, G.; Hildebrandt, D.; Liu, J.; Merz, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4399. (e) Hsu, Y.-C.; Ting, C.-M.; Liu, R.-S. *J. Am. Chem. Soc.* **2009**, *131*, 2090. (f) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *Adv. Synth. Catal.* **2005**, *347*, 526. (g) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *Org. Lett.* **2003**, *5*, 4121. (h) Hu, Z.-L.; Qian, W.-J.; Wang, S.; Wang, S.; Yao, Z.-J. *Org. Lett.* **2009**, *11*, 4676.

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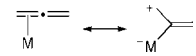

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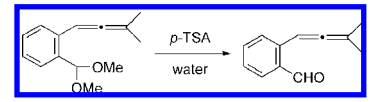

(8) The X-ray crystallographic data of compound **4b′** are provided in the Supporting Information.

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