Communication

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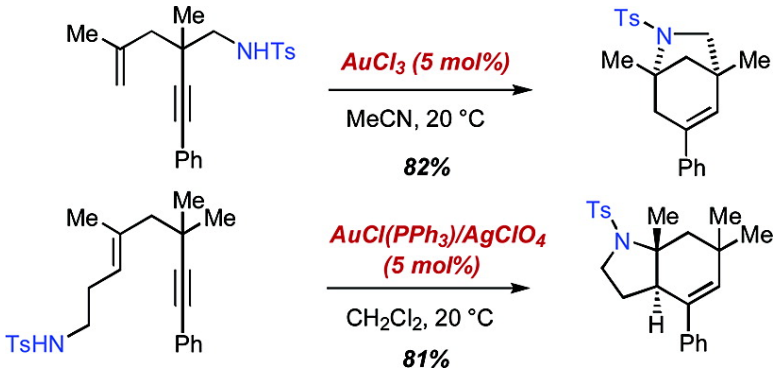

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Gold-Catalyzed Assembly of Heterobicyclic Systems

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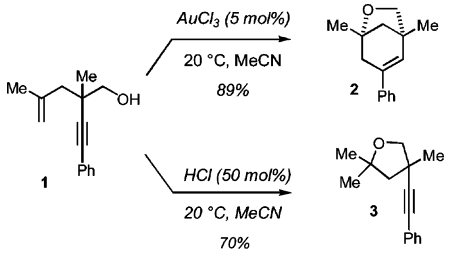
Gold-based chemoselective alkyne activation is emerging as an attractive strategy for the development of an arsenal of new catalytic processes.[1] Due to the exceptional alkynophilicity of gold, such reactions generally proceed under exceedingly mild conditions enabling the formation of new carbon−carbon and carbon−heteroatom bonds with high turnover efficiency.[2,3] In this communication, we describe an efficient gold-catalyzed synthesis of heterobicyclic alkenes as a result of the *6-endo-dig* carbocyclizations of 1,5-enynes with a concomitant intramolecular formation of either C−O or C−N bonds. The most notable aspect of this process is a mild and chemoselective metal-based alkyne activation, which enables rapid assembly of a range of heterobicyclic products with high efficiency and excellent diastereoselectivity.

In the course of our investigation of gold-catalyzed cycloisomerization of 1,5-enynes,[4] we discovered that treatment of enyne **1** with either a Au(I) or Au(III) catalytic promoter afforded a new product that was identified as 6-oxabicyclo[3.2.1]octene **2** (Scheme 1).[5−7] The optimized protocol entailed a brief exposure of alcohol

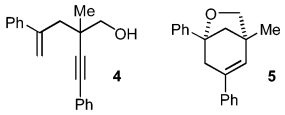
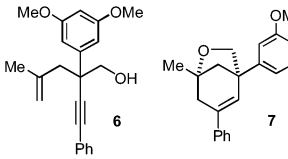
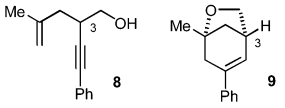
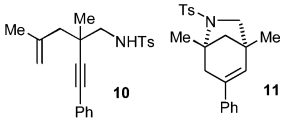
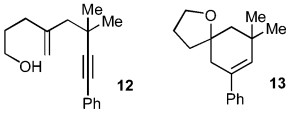
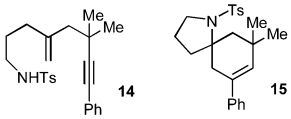
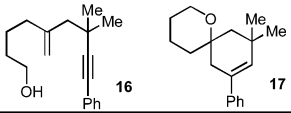
Scheme 1



1 to a catalytic amount of $AuCl_3$ in MeCN, which furnished alkene **2** in 89% yield. The use of $Au(PPh_3)Cl$ in combination with $AgClO_4$ proved to be equally effective. To rule out a possible involvement of the conjugate Brønsted acid in the alkyne activation,[8] alcohol **1** was treated with a substoichiometric amount of HCl in the absence of $AuCl_3$. The observed reaction was significantly slower and afforded exclusively tetrahydrofuran **3**. The outcome of this experiment demonstrated unambiguously that gold-based catalysis was uniquely responsible for chemoselective alkyne activation.

Our investigation of the generality and scope of the reaction is summarized in Table 1. Subjection of enynes **4** and **6** to the general protocol utilizing $AuCl_3$ efficiently afforded the expected bicyclic products **5** and **7**, respectively, indicating that aryl substitution of the enyne was well tolerated (entries 1 and 2). To probe the requirement of the quaternary center at the C(3), we subjected alcohol **8** to the standard protocol (entry 3). While the efficiency of the reaction utilizing $AuCl_3$ was moderate, the use of $Au(PPh_3)$-Cl and $AgClO_4$ afforded the oxabicyclic alkene **9** in 89% yield. Treatment of sulfonamide **10** with $AuCl_3$ resulted in efficient assembly of azabicyclo[3.2.1]octene **11** (entry 4). This finding is particularly noteworthy as it provides the first example of efficient interception of a cationic intermediate formed in a gold-catalyzed process by a sulfonamide-based nucleophile.[9] When alcohol **12**

Table 1. Gold-Catalyzed Synthesis of Heterobicyclic Alkenes

Entry	Alkyne	Product	Catalyst	Yield, %[c]
1	 **4**	**5**	$AuCl_3$[a]	90
2	 **6**	**7**	$AuCl_3$[a]	92
3	 **8**	**9**	$Au(PPh_3)Cl$[b] $AgClO_4$	89
4	 **10**	**11**	$AuCl_3$[a]	82
5	 **12**	**13**	$Au(PPh_3)Cl$[b] $AgClO_4$	86
6	 **14**	**15**	$Au(PPh_3)Cl$[b] $AgClO_4$	87
7	 **16**	**17**	$Au(PPh_3)Cl$[b] $AgClO_4$	96

[a] Method A: Enyne (0.1 mmol) was dissolved in MeCN (2 mL) and treated with $AuCl_3$ (5 μmol). The resulting solution was stirred at 20 °C for 1 h and treated with Et_3N (50 μL). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel. [b] Method B: Enyne (0.1 mmol) was dissolved in CH_2Cl_2 (2 mL) and treated with $[Au(PPh_3)]ClO_4$ (5 μmol) generated from $Au(PPh_3)Cl$ and $AgClO_4$. The resulting solution was stirred at 20 °C for 1 h. The product was obtained similarly as described above. [c] Refers to isolated yields of spectroscopically pure products that were fully characterized by NMR, IR, and MS.

(entry 5) was treated with $[Au(PPh_3)]ClO_4$, oxaspiro[5.4]decene **13** was obtained in 86% yield. Cyclization of the corresponding sulfonamide **14** efficiently afforded azaspiro[5.4]decene **15** (entry 6). Finally, enyne **16** armed with a chain-extended alcohol efficiently furnished the spirocyclic ether **17** (entry 7).

To examine the formation of fused heterobicycloalkenes, alcohol **18**, containing trisubstituted *E*-alkene, was treated with 10 mol % of $AuCl_3$ to successfully afford a strained *trans*-oxabicyclo[4.3.0]-nonene **19**[10] with excellent diastereoselectivity (eq 1).[11] Additional studies demonstrated the diastereospecific nature of this double cyclization allowing to access either the cis- or trans-fused bicyclic

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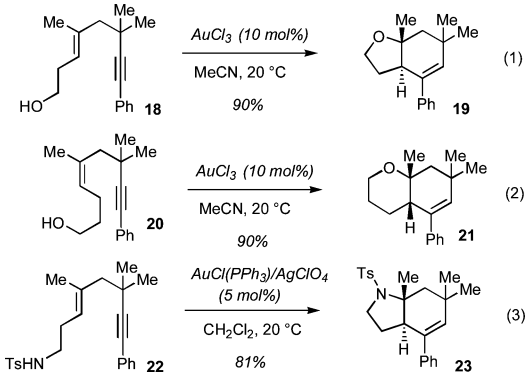
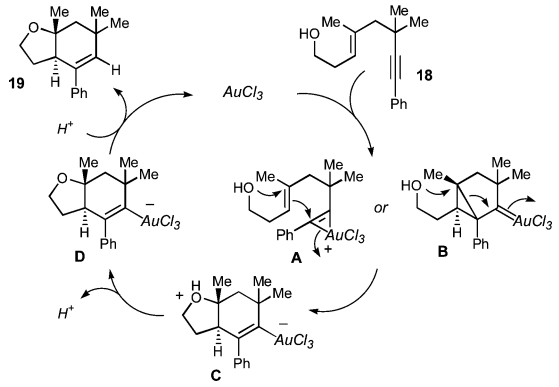
ethers.[12] Double cyclization of one-carbon extended trisubstituted *Z*-alkene **20** (eq 2) afforded exclusively *cis*-oxabicyclo[4.4.0]decene **21** (dr > 97:3). Finally, subjection of sulfonamide **22** to [Au(PPh_3)]-ClO_4 furnished *trans*-oxabicyclo[4.3.0]nonene **23** with excellent efficiency and diastereoselectivity (eq 3).



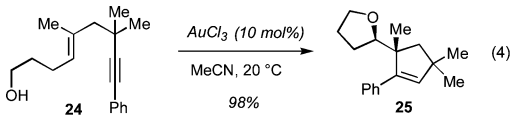
The diastereospecific course of the double cyclization can be viewed as either a concerted process **A** or a stepwise route involving nucleophilic opening of the cyclopropyl gold carbene intermediate **B** (Scheme 2). Release of the proton from **C** followed by

Scheme 2



protodemetalation of the alkenyl gold complex **D** affords the observed bicyclic ether. While gold carbenes of type **B** have been implicated as reactive intermediates in 5-*exo-dig*,[2f] 6-*exo-dig*,[6] and 6-*endo-dig* cyclizations,[2k,l,4] our results strongly indicate that the double cyclization is a highly concerted process, which results in anti addition of the alkyne and the nucleophile to the alkene. Indeed, successful cyclization of sulfonamide **10** (Table 1, entry 4) indicates significant carbocationic character at the C(5), which is more consistent with a concerted reaction manifold. Furthermore, the cyclization of alcohol **8** (Table 1, entry 3) proceeded without any observed formation of an alternative [3.1.0] bicyclic alkene[2k,l] as a result of hydride migration and elimination from the gold carbene intermediate of type **B**.

Interestingly, subjection of trisubstituted *E*-alkene **24** (eq 4) to 10 mol % of $AuCl_3$ afforded unexpectedly tetrahydrofuran **25** as an exclusive anti-Markovnikov reaction product (dr > 97:3).[13] The outcome of this experiment can be rationalized by a strained nature of the alternative *trans*-oxabicyclo[4.4.0]decene product, changing the reaction course to the 5-*endo-dig* cyclization.



In summary, we have developed an efficient gold-catalyzed double cyclization of simple 1,5-enynes armed with either oxygen- or nitrogen-based nucleophiles. This mild catalytic process provides an efficient access to oxa- and azabicyclic alkenes containing bridged, fused, and spirocyclic architectures. Furthermore, the assembly of fused oxabicycloalkenes proceeds diastereospecifically, strongly suggesting a concerted nature of this double cyclization.

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Supporting Information Available: Full characterization of new compounds and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Semiempirical calculations revealed that *trans*-oxabicyclo[4.3.0]nonene **19** was 7.7 kcal/mol higher in energy compared to the corresponding cis-fused bicyclic ether.

(11) Bicyclic ether **19** was produced as a 9:1 mixture of trans:cis diastereomers corresponding to the 9:1 mixture *E:Z* geometrical isomers of alkene **18**.

(12) Subjection of the 2:1 mixture *E:Z* geometrical isomers of alkene **18** to $AuCl_3$ (10 mol %) afforded a 2:1 mixture of trans:cis-fused bicyclic ethers **19**, which were separated and fully characterized. See Supporting Information for details.

(13) The structure of **25** was verified by X-ray crystallography. See Supporting Information for details.

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