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Gold-Catalyzed Synthesis of Substituted Tetrahydronaphthalenes

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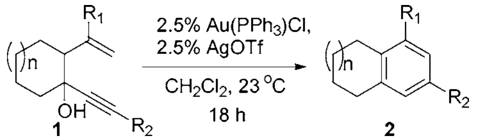
ABSTRACT



We report a gold-catalyzed benzannulation of 3-hydroxy-1,5-enynes to generate tetrahydronaphthalenes. This mild process proves to be an effective method to synthesize various metasubstituted aromatic rings in good yields.

1,2,3,4-Tetrahydronaphthalenes and related derivatives are an important class of molecules which often comprise key fragments of medicinally important molecules.[1] Typically, tetrahydronaphthalenes are obtained by hydrogenation of naphthalenes or by Friedel−Crafts alkylations.[2] These approaches are plagued by regioselectivity problems and low yields. Owing to the importance of substituted aromatic compounds in organic and medicinal chemistry, the development of efficient methods to prepare aromatic rings is of paramount importance. Transition-metal-catalyzed benzannulation of enynes represents an attractive alternative for de novo synthesis of tetrahydronaphthalene frameworks. Catalysis by Au salts/complexes provides a mild and efficient method to activate alkynes, allenes, and alkenes. As a consequence, numerous accounts of gold-catalyzed carbon−carbon bond-forming reactions have been reported.[3] More specifically, cycloisomerization of 1,5-enynes and 1,6-enynes has been investigated and reported as a method to access various synthons.[4] Yet, only a few examples of Au- and Ag-catalyzed benzannulations have been described.[5] Herein, we present a new efficient catalytic method to access tetrahydronaphthalenes from 3-hydroxy-1,5-enynes.

Hydroxy-enynes are known to undergo cycloisomerization upon treatment with Cu, Pt, or Au salts.[6] Typically, the products observed were either metathesis-type or polycyclic compounds. In 1984, Gore et al. reported Ag(I)-mediated

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(1) Selected examples: (a) Cimetiere, B.; Dubuffet, T.; Landras, C.; Descombes, J.-J.; Simonet, S.; Verbeuren, T. J.; Lavielle, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1381. (b) Stutz, A.; Georgopoulos, A.; Granitzer, W.; Petranyi, G.; Berneyt, D. *J. Med. Chem.* **1986**, *29*, 112. (c) Dumas, M.; Dumas, J. P.; Bardou, M.; Rochette, L.; Advenier, C.; Giudicelli, J. F. *Eur. J. Pharmacol.* **1998**, *348*, 223.

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(3) Recent reviews on gold-catalyzed reactions: (a) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem*. **2005**, *3*, 387. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990. (c) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51. (d) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431.

(4) Cycloisomerization of enynes. For recent reviews, see: Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed*. **2006**, *45*, 200. Other recent papers: (a) Lopez, S.; Herrero-Gomez, E.; Perez-Galan, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6029.

(5) (a) Shibata, T.; Ueno, Y.; Kanda, K. *Synlett* **2006**, *3*, 411. (b) Asao, N. *Synlett* **2006**, *11*, 1645. (c) Zhao, J.; Hughes, C. O.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 7436. (d) Lin, M.-Y.; Das, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2006**, *128*, 9340. (e) Hashmi, A. S. K.; Weyrauch, J. P.; Kurpejovic, E.; Frost, T. M.; Miehlich, B.; Frey, W.; Bats, J. W. *Chem.−Eur. J.* **2006**, *12*, 5806. (f) Dankwardt, J. W. *Tetrahedron Lett.* **2001**, *42*, 5809.

(6) (a) PtCl$_2$: Harrack, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouriès, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656. (b) Cu(BF$_4$)(CH$_3$CN)$_4$ or PtCl$_2$: Fehr, C.; Farris, I.; Sommer, H. *Org. Lett.* **2006**, *8*, 1839. (c) Au salts: Gagosz, F. *Org. Lett.* **2005**, *7*, 4129. (d) PtCl$_2$ and Au salts: Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. (e) Pt, Cu, and Au salts: Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2901. (f) Pt and Au salts: Fürstner, A.; Hannen, P. *Chem.−Eur. J.* **2006**, *12*, 3006. (g) Au salts: Marion, N.; de Frémont, P.; Lemière, G.; Stevens, E. D.; Fensterbank, L.; Malacria, M.; Nolan, S. P. *Chem. Commun.* **2006**, *19*, 2048. (h) Pt salts: Mainetti, E.; Mouriès, V.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132. (i) Pt salts: Blaszykowski, C.; Harrak, Y.; Goncüalves, M.-H.; Cloarec, J.-M.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 3771.

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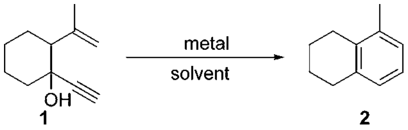
oxy-Cope reaction of various 3-hydroxy-1,5-enynes to give the desired enone.[7] However, they found that the treatment of alcohol **1** with a stoichiometric amount of AgOTf in THF−H_2O gave a complex mixture of products from which tetrahydronaphthalene **2** was isolated in 15% yield.[7a] Therefore, we investigated a catalytic version of this unusual benzannulation. To our delight, subjection of **1** to 1 mol % of Au(PPh_3)Cl and 1 mol % of AgOTf in dichloromethane gave **2** in 72% yield. To optimize the reaction conditions, other catalyst systems were explored (Table 1).

Table 1. Au- and Ag(I)-Catalyzed Tetrahydronaphthalene Synthesis



entry	catalyst^a	yield^b (%)
1	5% Au(PPh_3)Cl, 5% $AgBF_4$	42
2	5% Au(PPh_3)Cl, 5% $AgSbF_6$	22
3	2.5% $AuCl_3$	22^c
4	2.5% Au(PPh_3)Cl	0
5	2.5% AgOTf	48^c
6	2.5% AgOTf, 2.5% PPh_3	45^c
7	2.5% Au(PPh_3)Cl, 2.5% AgOTf	84

^{a} Reactions run in DCM, 23 °C, 18 h. ^{b} Isolated yield. ^{c} NMR conversion.

Treatment of alcohol **1** with 5% of Au(PPh_3)Cl and 5% of $AgBF_4$ (entry 1) gave **2** in 42% yield. Changing the silver salt to $AgSbF_6$ gave the desired product in 22% yield (entry 2). A catalytic amount of $AuCl_3$ also catalyzed the benzannulation, albeit in low conversion (entry 3). A control experiment employing 2.5% of Au(PPh_3)Cl only (entry 4) did not give any desired tetrahydronaphthalene **2**. However, 2.5% of AgOTf (entry 5) or 2.5% of AgOTf and 2.5% of PPh_3 (entry 6) did promote the reaction, although with a 48 and 45% yield, respectively, after 18 h. The best catalyst system was a combination of Au(PPh_3)Cl and AgOTf. The use of 2.5 mol % of both catalysts led to the desired product in 84% yield. A reduction of catalyst loading to 0.1 mol % of Au(PPh_3)Cl and AgOTf, however, led to a significant loss in yield (58%), and a longer reaction time (96 h) was observed.

We proposed the following mechanism depicted in Scheme 1. Cyclization of the Au(I) complex **3** can either occur in a 5-exo dig manner giving **4** or in a 6-endo dig fashion to give **5** which exists in equilibrium with compound **6**. It is known that acyclic 3-hydroxy-1,5-enynes react via an intermediate analogous to **6** followed by a 1,2-hydride shift to generate polycyclic compounds.[6b,c] In this case, a 1,2-hydride shift is not possible due to the tertiary alcohol. On the other hand, a ring expansion of **5** (or **4**) to give the corresponding oxy-Cope product **8** could be envisaged. However, no oxy-Cope or ring expansion products were observed from the reaction mixture as only tetrahydronaphthalene **2** was isolated. This enyne cycloisomerization has a unique mechanism because an aromatic compound was generated instead of a metathesis, a polycyclic, or an oxy-Cope product. Having the optimal reaction conditions (entry 7, Table 1) in our hands, we thus examined the scope of the reaction (Table 2).

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

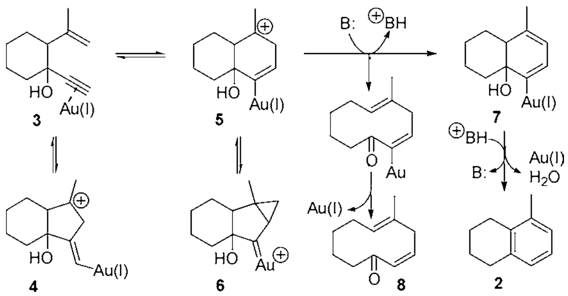
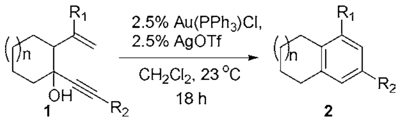
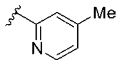


Table 2. Au(I)-Catalyzed Cyclization of 3-Hydroxy-1,5-enynes



entry	R_1	R_2	n	yield %^{a}
1	Me	H	0	**2a**, 28
2	H	H	1	**2b**, 10
3	Ph	H	1	**2c**, 84
4	Me	Me	1	**2d**, 77
5	Me	Ph	1	**2e**, 86
6	Me	4-$NO_2C_6H_4$	1	**2f**, 73
7	Me	4-$NHAcC_6H_4$	1	**2g**, 66
8	Me		1	**2h,** 75^b
9	OEt	H	1	**2i**, 12
10	Me	H	2	**2j**, 51
11	Me	Ph	2	**2k**, 65

^{a} Isolated yield after column chromatography. ^{b} 1.5 equiv of PTSA was added and 10% of Au and Ag was used.

At first glance, we observed that the ring size affected the yield of the reaction. Lower yields were observed when the reaction was performed with 3-hydroxy-1,5-enynes having five- and seven-membered rings (entries 1, 10, and 11). It was noticed that the substituents at R_1 play an important role in the reaction. When R_1 was a hydrogen, the desired product **2b** was isolated in 10% yield (entry 2). One might assume that the stability of the carbocation in **5** could favor the process. To our surprise, benzannulation of enol ether **1i** provided the desired product **2i** in only 12% yield (entry 9).[8] In contrast, Au(I)-catalyzed benzannulation

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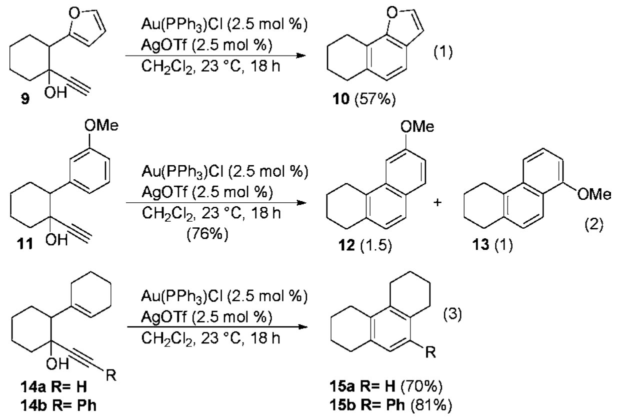
(7) (a) Bluthe, N.; Malacria, M.; Gore, J. *Tetrahedron Lett.* **1984**, *25*, 2873. (b) Bluthe, N.; Malacria, M.; Gore, J. *Tetrahedron* **1986**, *42*, 1333.

of an electron-rich aromatic ring system such as furan **9** and aryl **11** proceeded in 57 and 76% yields, respectively (eqs 2 and 3, Scheme 2). On the other hand, the reaction proceeded in good yields with substrates having an internal alkyne (entries 4−7 and 11) and cyclic olefin (eq 4). This provided metasubstituted aromatic rings which are difficult to obtain via cross-coupling reactions. Conversely, the cyclization of the pyridine derivative **1h** did not occur under the typical reaction conditions and only starting material was recovered. It was found that the addition of 1.5 equiv of PTSA was necessary to obtain **2h** in 75% yield (entry 8).

Scheme 2

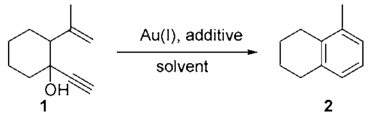


Because the reaction with substrate **1h** only proceeded when in the presence of an excess of acid, we were curious to determine if the Bronsted acid plays a role in the other benzannulations. One might propose that elimination of water could be facilitated in the presence of acid (**7**→**2**, Scheme 1). Alternatively, one might suggest that the elimination of water could occur to form a diene-yne intermediate which undergoes a Au(I) benzannulation. To verify this, the reaction was performed in the presence of 1.05 equiv of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (Table 3, run 1). In this case, only starting material was recovered.

However, a low conversion was observed when the reaction was performed in the presence of 5 mol % of DTBMP (run 2). On the other hand, exposure of alcohol **1** to 5 mol % of TfOH, PTSA, or chloroacetic acid did not give any desired product **2**. Only starting material was recovered, thereby ruling out simple Bronsted acid catalyzed benzannulation or formation of a diene-yne intermediate.[9]

To further study the exact nature of the catalyst, a series of experiments with different gold complexes were conducted. A catalyst system generated from 2.5 mol % of Au(PPh$_3$)Cl and 2.5 mol % of TfOH gave a conversion of 79% after 18 h (run 3). Catalyst systems generated from Au(PPh$_3$)Cl and PTSA (run 6), trichloroacetic acid (run 7), or TFA (run 8) gave conversions of 34, 38, and 0%, respectively. A comparison between AuCl and TfOH (run 4) and AuCl alone (run 5) indicated that the phosphine ligand might have a role in the catalysis. ^{31}P NMR studies revealed that Au(I) cationic species were not detected when Au(PPh$_3$)Cl and TfOH were mixed in the presence of the substrate **1** (spectra d, Figure 1). In fact, the chemical shift (32.69 ppm) is identical to that of Au(PPh$_3$)Cl alone (spectra a). However, different Au(I) complexes were generated when Au(PPh$_3$)Cl and AgOTf were mixed alone to form Au(PPh$_3$)OTf (spectra b) or in the presence of substrate **1** (spectra c). In the latter case, one might propose the existence of a cationic gold species such as [Au(PPh$_3$)-Ar]$^+$ (Ar = tetrahydronaphthalene).

Table 3. Investigation into the Reactive Species



run	catalyst[a]	additive (equiv)	conversion[b] (%)
1	2.5% Au(PPh$_3$)Cl, 2.5% AgOTf	DTBMP (1.05)	0
2	2.5% Au(PPh$_3$)Cl, 2.5% AgOTf	DTBMP (0.05)	31−50
3	2.5% Au(PPh$_3$)Cl, 2.5% TfOH	−	79
4	2.5% AuCl, 2.5% TfOH	−	29
5	2.5% AuCl	−	22
6	2.5% Au(PPh$_3$)Cl, 2.5% PTSA	−	34
7	2.5% Au(PPh$_3$)Cl, 2.5% TCA	−	38
8	2.5% Au(PPh$_3$)Cl, 2.5% TFA	−	0

[a] Reactions run in DCM at 23 °C for 18 h. [b] Determined by ^{1}H NMR.

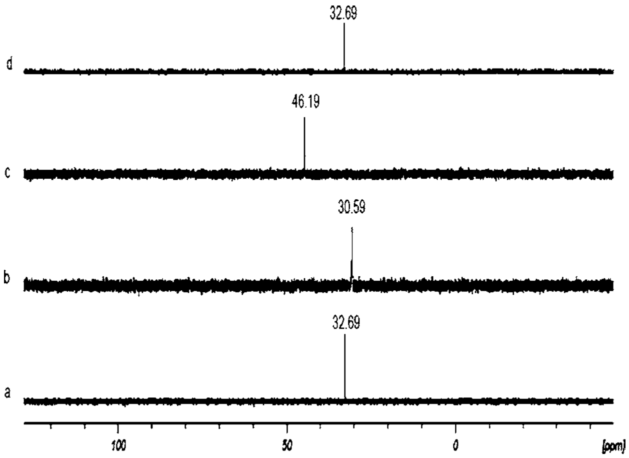


Figure 1. ^{31}P NMR study at 23 °C in CDCl$_3$ (PPh$_3$ used as a standard at −6.0 ppm). (a) Au(PPh$_3$)Cl; (b) Au(PPh$_3$)Cl (2.5 mol %) and AgOTf (2.5 mol %) after 16 h; (c) Au(PPh$_3$)Cl (2.5 mol %), AgOTf (2.5 mol %), and alcohol **1** (59% conversion); (d) Au(PPh$_3$)Cl (5 mol %), TfOH (5 mol %), and alcohol **1** (37% conversion).

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(8) Besides the desired product **2i**, only degradation products were observed by ^{1}H NMR.

(9) Exposure of **1** and **1e** to 1 equiv of TfOH and PTSA, respectively, in DCM at room temperature gave a myriad of compounds from which no tetrahydronaphthalenes, **2**, **2e**, or diene-yne products were observed by ^{1}H NMR of the crude mixture. Compound **2** was exposed to TfOH (1 equiv) for 2.5 h at 23 °C, and no degradation products were observed.

On the basis of this, we suggest that in the case of the benzannulation of **1** catalyzed by gold and acid the active catalyst may exist as an equilibrium with Au(PPh_3)Cl and TfOH. To the best of our knowledge, there are no reports of an active catalyst generated from Au(PPh_3)Cl and an acid.[10] Further investigations on the exact nature of the active catalyst are ongoing and will be reported in due course.

In summary, we reported a gold-catalyzed benzannulation of 3-hydroxy-1,5-enynes to generate tetrahydronaphthalenes. This process has proven to be an effective method to synthesize various metasubstituted aromatic rings.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) It was reported that cationic gold species are generated when Au(PPh_3)Me is treated with an acid. See: Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415.