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Gold(I)-catalyzed benzannulation of 3-hydroxy-1,5-enynes: an efficient synthesis of substituted tetrahydronaphthalenes and related compounds

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Abstract

We report a novel gold(I)-catalyzed benzannulation of 3-hydroxy-1,5-enynes to prepare tetrahydronaphthalenes. The reaction is catalyzed by 2.5 mol % Ph_3PAuCl and 2.5 mol % AgOTf in dichloromethane. We discovered that this process can be also catalyzed by 1 mol % Ph_3PAuCl and 1 mol % TfOH. To the best of our knowledge, this constitutes the first report of an active gold catalyst generated from $Au(PPh_3)Cl$ and triflic acid. This mild process is compatible with a variety of functional groups and proves to be an effective method to synthesize various *meta*-substituted aromatic rings in good yields.

1. Introduction

Substituted aromatic compounds have a fundamental importance in organic chemistry. They are found in natural products, medicinally important molecules, as well as in materials. Although there are many methods to functionalize aromatic rings, one must also consider a benzannulation reaction as an efficient approach to access these substituted aromatic compounds. Various strategies have been developed for acyclic precursors to be transformed into aromatic rings. Generally, these methods have the advantages that the substituted aromatic compounds are accessed in few steps and with high regioselectivity. Examples of benzannulation reactions include the Dötz reaction of Fisher carbene complexes, acid-promoted benzannulation, anionic cyclization, [4+2] cycloaddition, and metal-catalyzed carbocyclization.[1]

Taking into account the peculiar reactivity of gold salts to activate alkynes, allenes, and alkenes,[2] one can imagine the use of gold complexes to catalyze benzannulation and related reactions. For instance, Hashmi and co-workers described a selective synthesis of substituted phenols using 2 mol % $AuCl_3$ in acetonitrile.[3] Subsequently, Asao and co-workers have developed a gold-catalyzed [4+2]-benzannulation between enynals and carbonyl compounds.[4] From this point, the number of reports on gold-catalyzed benzannulation reactions has increased dramatically. It was shown that the cycloisomerization of aromatic enynes gave an access to substituted phenanthrenes,[5] naphthalenes,[6] or styrenes.[7] Toste and co-workers provided a new approach to form substituted naphthalenes via a metal-catalyzed tandem [3,3]-sigmatropic rearrangement/formal Myers–Saito cyclization.[8] Liu and co-workers disclosed the synthesis of various arenes using an intramolecular [3+2]-cycloaddition of arenyne-yne substrates.[9]

1,2,3,4-Tetrahydronaphthalenes and related derivatives are found to be key fragments of medicinally important molecules. Selected examples are shown in Figure 1. Methionine aminopeptidase-2 reversible inhibitor **1**, glucocorticoid receptor agonist **2**, α_{1A}-adronoceptor selective agonist **3**, serotonin 5-HT_7 receptor agonist **4**, and thromboxane receptor antagonist **5** are just a few of the biologically active compounds that were identified.[10] Numerous syntheses to obtain this important class of molecules have been developed. One of the most common ways to access these molecules is hydrogenation of naphthalenes.[11] Alternatively, the cyclohexane ring

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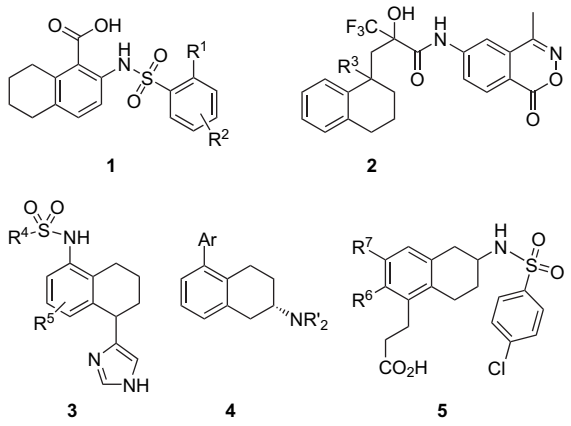
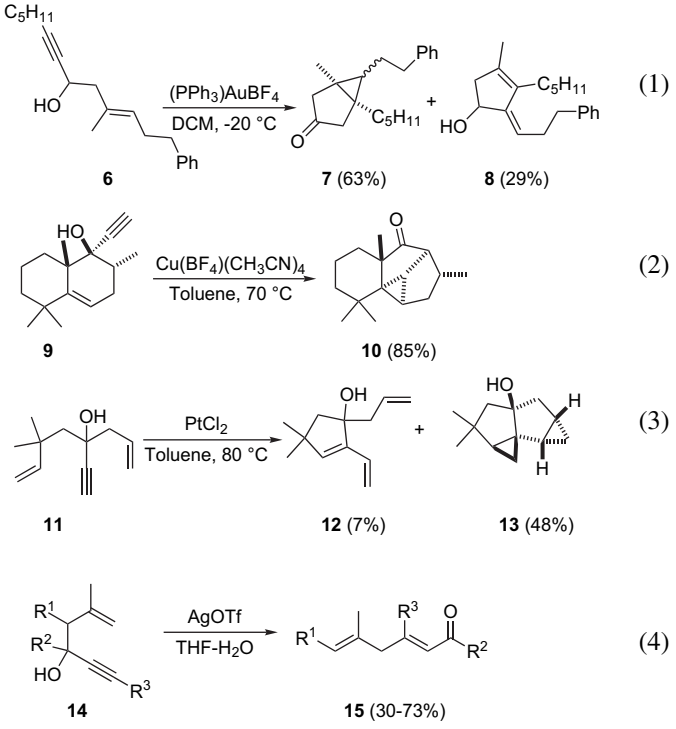


Figure 1. Examples of biologically active tetrahydronaphthalenes.

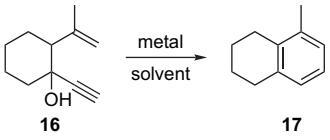
can be generated via a Friedel–Crafts alkylation.[12] Another frequent approach is the use of [4+2] cycloadditions to form the aromatic ring of the tetrahydronaphthalenes.[13] These approaches are limited due to the regioselectivity problems, the restricted scope and/or low yields. Thus, gold-catalyzed benzannulation of hydroxy-enynes represents an attractive alternative for de novo synthesis of the tetrahydronaphthalene framework.

It has been demonstrated that 3-hydroxy-1,5-enynes undergo cycloisomerization when they were treated with Cu, Pt, or Au salts.[14] Typically, the products generated were either metathesis-type or polycyclic compounds. For example, Gagosz has shown that enyne **6** rearranged to give bicyclic compound **7** and cyclopentenol **8** (Eq. 1, Scheme 1).[14c] In 2006, Fehr and co-workers reported that ring expansion of hydroxy-enyne **9** to polycyclic compound **10** occurred in 85% yield (Eq. 2).[14b] Also, Malacria and co-workers established that polycyclic compound **13** was the major product when dienyne **11** was treated with $PtCl_2$ (Eq. 3).[14h]



Scheme 1. Metal-catalyzed rearrangement of hydroxy-enynes.

3-Hydroxy-1,5-enynes were also shown to rearrange via the oxy-Cope reaction in the presence of soft Lewis acid. Goré and co-workers reported Ag(I)-mediated sigmatropic rearrangement of 3-hydroxy-1,5-enynes to provide the desired enone (Eq. 4).[15] However, they disclosed that treatment of alcohol **16** with a stoichiometric amount of AgOTf in THF–H_2O gave a complex mixture of products (Scheme 2). The only product that they were able to isolate in 15% yield and characterize was tetrahydronaphthalene **17**.[15a] Therefore, we decide to explore a catalytic version of this unusual benzannulation.[16]



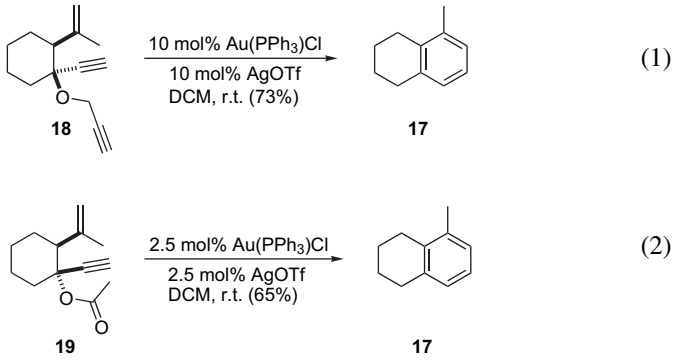
Scheme 2. Metal-mediated benzannulation.

2. Results and discussion

Propargylic alcohol **16** and related compounds were readily prepared in 2–3 steps from commercially available cycloalkene oxide.[16] Exposure of alcohol **16** as a cis and trans mixture (1:1) to 1 mol % $Au(PPh_3)Cl$ and 1 mol % AgOTf in dichloromethane at room temperature for 18 h gave **17** in 72% yield (Scheme 2).[17] Other soft Lewis acids such as AuCl, $AuCl_3$, AgOTf, and $PdCl_2(PhCN)_2$ gave low conversions and low yields.[18] After an optimization of the reaction conditions, we found that the combination of 2.5 mol % $Au(PPh_3)Cl$ and AgOTf in dichloromethane (23 °C, 18 h) led to the desired product **17** in 84% yield. It is important to note that the reduction of the catalyst loading to 0.1 mol % $Au(PPh_3)Cl$ and AgOTf led to a significant loss in yield (58%) along with longer reaction time (96 h).

To gain more insight into the reaction mechanism, compounds **18** and **19** were treated with a catalytic amount of $Au(PPh_3)Cl$ and AgOTf (Scheme 3). In both cases, only tetrahydronaphthalene **17** was isolated in 73% and 65% yield, respectively. Surprisingly, acetate **19** did not form any products resulting from a gold-catalyzed propargylic acetate rearrangement (carbene formation). Based on these results, we proposed the following mechanism illustrated in Scheme 4.

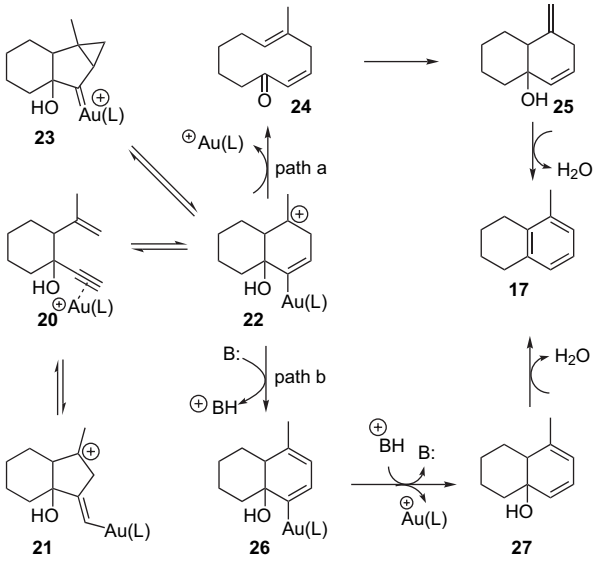
The combination of the pre-catalysts $Au(PPh_3)Cl$ and AgOTf produces a cationic gold species, which can coordinate to the alkyne in a reversible manner. This enables the nucleophilic attack of the alkene onto the alkyne via a 5-*exo*-dig[19] or 6-*endo*-dig[6b,7,14b,20] mode to afford **21** and **22**, respectively. Intermediate **22** could be in equilibrium with **23**. Examples of polycyclic products arising from a 1,2-hydride shift of intermediates analogous to **23** have been demonstrated recently.[14a,c,f] However, in the present case, the formation of such polycyclic products is not possible due to the tertiary alcohol. From intermediate **22**, two possible pathways are considered.



Scheme 3. Benzannulation of enynes.

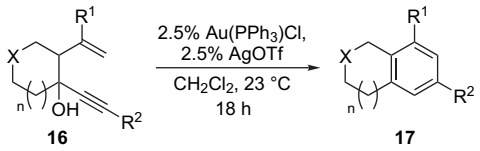
The first scenario (pathway a) could be a ring expansion of **22** to give the formal oxy-Cope product **24**.[14c] At this point, **24** could undergo a transannular ene reaction to give **25**, which upon loss of water followed by aromatization would give **17**. Alternatively, intermediate **22** could undergo a subsequent deprotonation, protonation, and aromatization sequence to afford tetrahydronaphthalene **17** (pathway b). To determine which pathway, A or B, is involved in the reaction mechanism, we treated alcohol **25**[21] with 2.5 mol % $Au(PPh_3)Cl$ and AgOTf in dichloromethane at room temperature. After stirring for 3 h, **25** was slowly converted to **17**.[22] One might propose that pathway A could be involved in the reaction mechanism. However, we did not detect any products in the crude reaction mixture resulting from an oxy-Cope reaction when **18** and **19** were treated a catalytic amount of Au(I) and Ag(I) (Eqs.1 and 2, Scheme 3). The slow conversion of **25** to **17** combined by the absence of any oxy-Cope products during the benzannulation process suggests that the reaction would proceed through pathway B. Having established the reaction mechanism and found the optimal reaction conditions, the scope of the reaction was then examined (Tables 1 and 2).

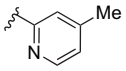
A cursory inspection of the results illustrated in the Table 1 revealed that the ring size and the substitution at R^1 influence



Scheme 4. Proposed mechanism for Au(I)-catalyzed benzannulation.

Table 1
Au(I)-catalyzed cyclization of 3-hydroxy-1,5-enynes



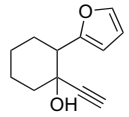
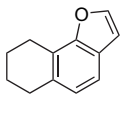
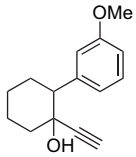
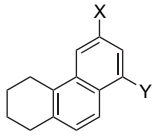
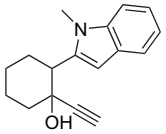
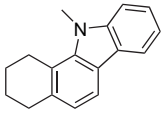
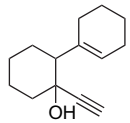
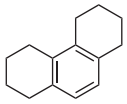
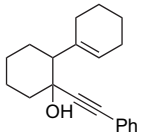
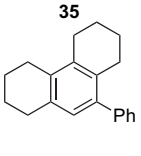
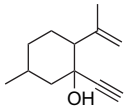
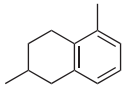
Entry	R^1	R^2	*n*	X	Yield[a] %
1	Me	H	0	CH_2	**17a**, 28
2	H	H	1	CH_2	**17b**, 10
3	Ph	H	1	CH_2	**17c**, 84
4	Me	Me	1	CH_2	**17d**, 77
5	Me	Ph	1	CH_2	**17e**, 86
6	Me	4-$NO_2C_6H_4$	1	CH_2	**17f**, 73
7	Me	4-$NHAcC_6H_4$	1	CH_2	**17g**, 66
8	Me		1	CH_2	**17h**, 75[b]
9	OEt	H	1	CH_2	**17i**, 12[c]
10	Me	H	2	CH_2	**17j**, 51
11	Me	Ph	2	CH_2	**17k**, 65
12	Me	H	1	NTs	**17l**, 49
13	Me	Ph	1	NTs	**17m**,67
14	Me	H	1	O	**17n**, 51

[a] Isolated yield after column chromatography.
[b] PTSA (1.5 equiv) was added and 10 mol % of Au(I) and Ag(I) were used.
[c] Beside the desired product, only decomposition was only observed.

the reaction yield. A low yield of 28% was observed when the reaction was performed on substrate having five-membered ring (Table 1, entry 1). When R^1 is a hydrogen, the desired product **17b** was obtained in 10% yield (Table 1, entry 2). One might assume that the stability of the carbocation in **22** affects the process. Thus, the substituents R^1 were chosen in function of their ability to stabilize the carbocation. Although enol ether **16i** does satisfy this criterion, the benzannulation gave the desired product **17i** in only 12% yield (Table 1, entry 9). In contrast, substrates bearing a phenyl (Table 1, entry 3) or a methyl (Table 1, entries 4–6) substituent on the alkene gave the desired benzannulation product in good yields. Also, electron rich aromatic ring system such as furan **28**, aryl **30**, and indole **32** proceeded in 57, 76, and 81% yield, respectively (Table 2, entries 1–3). Satisfyingly, the reaction proceeded in good yields with substrates having an internal alkyne (Table 1, entries 4–8 and 11). This generated *meta*-substituted aromatic rings, which are rather difficult to obtain via cross-coupling reactions. However, benzannulation of the pyridine derivative **16h** did not occur under the typical reaction conditions as only starting material was recovered. One might propose that the pyridine group could bind on the gold complex thereby inhibiting the benzannulation. Addition of 1.5 equiv of PTSA was proved to be necessary to obtain **17h** (Table 1, entry 8).

Lastly, we investigated substitution on the cyclohexane ring. Protected piperidines **16l** and **16m** were treated under the benzannulation conditions to give the corresponding tetrahydroisoquinolines **17l** and **17m** in 49 and 67% yield, respectively (Table 1, entries 12–13). The method can be extended to a cyclic ether **17n** (Table 1, entry 14) and methyl-substituted

Table 2
Au(I)-catalyzed cyclization of 3-hydroxy-1,5-enynes[a]

Entry	Substrate	Product	Yield[b] %
1	 **28**	 **29**	57
2	 **30**	 **31A** X = OMe, Y = H (1.5) **31B** X = H, Y = OMe (1)	76
3	 **32**	 **33**	81
4	 **34**	 **35**	70
5	 **36**	 **37**	81
6	 **38**	 **39**	74

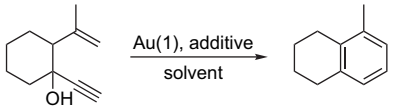
[a] The reaction conditions are 2.5 mol % of each AgOTf and Au(PPh$_3$)Cl in dichloromethane at 23 °C for 18 h.
[b] Isolated yield after column chromatography.

cyclohexane **38** (Table 2, entry 6). Thus, the gold-catalyzed benzannulation can be utilized to generate many different tetrahydronaphthalene scaffolds.

As previously mentioned above, the reaction with pyridine substrate **17h** only proceeded in the presence of an excess of acid. This result suggests that acid might play a role in the other benzannulation reactions. One might assume that a trace of triflic acid could be present in the typical reaction conditions due to the presence of silver triflate. From a mechanistic point of view, one might propose that elimination of water could be assisted with acid (**27**→**17**, Scheme 4). Alternatively, one might suggest that the elimination of water could occur initially to generate a diene-yne intermediate, which undergoes a gold-catalyzed benzannulation.

To clarify the role of the protic acid, hydroxy-enyne **16** was treated with 2.5 mol % each of Au(PPh$_3$)Cl and AgOTf in the presence of a hindered base such as 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 1.05 equiv) (Table 3, entry 1). After 18 h, only starting material was recovered. However, a low

Table 3
Investigation into the reactive species



16 **17**

Entry	Catalyst[a]	Additive (equiv)	Conv.[b] (%)
1	Au(PPh$_3$)Cl, AgOTf	DTBMP (1.05)	0
2	Au(PPh$_3$)Cl, AgOTf	DTBMP (0.05)	31–50
3	TfOH[c]	—	0
4	Au(PPh$_3$)Cl, AgOTf	4 Å Mol. sieves	>95
5	Au(PPh$_3$)Cl, TfOH	—	95
6	AuCl, TfOH	—	29

[a] Reactions were done with 2.5 mol % of each species in DCM at 23 °C for 18 h.
[b] Determined by ^{1}H NMR.
[c] TfOH of 5 mol % was used.

conversion was observed when the reaction was carried out in the presence of 5 mol % DTBMP (entry 2). Recently, Hartwig reported examples of reaction catalyzed by metal triflates, which are the result from simple protic acid catalysis.[23] In our case, exposure of alcohol **16** to 5 mol % TfOH, PTSA, or chloroacetic acid did not give any desired product **17**. Only starting material was recovered, thus it was possible to rule out simple Brønsted acid catalyzed benzannulation or formation of a diene-yne intermediate.[24]

To explore the effect of water in the reaction, hydroxy-enyne **16** was treated with the standard conditions but molecular sieves were added. The conversion was greater than 95%, thus it is possible to exclude the role of water in the mechanism other than a leaving group. In order to further investigate the reactive species, hydroxy-enyne **16** was treated with 2.5 mol % of each Au(PPh$_3$)Cl and TfOH. Surprisingly, tetrahydronaphthalene **17** was obtained in 95% conversion. In contrast, 2.5 mol % of each AuCl and TfOH only gave 29% conversion to the desired tetrahydronaphthalene. It is important to note that Au(PPh$_3$)Cl alone did not catalyze the reaction whereas AuCl alone gave a 22% conversion. To the best of our knowledge, this is first report of an active catalyst generated from Au(PPh$_3$)Cl and triflic acid. To study this novel catalytic system, we investigated different sources of protic acid.

Weak organic acids (acetic acid, tartaric acid, trichloroacetic acid, trifluoroacetic acid, phenyl phosphonic acid, and mineral acids (HBr, HCl, H_3PO_4, and H_2SO_4) did not catalyze the reaction. Nonetheless, PTSA and CSA in combination with Au(PPh$_3$)Cl did promote the benzannulation with good conversion. However, the results were not reproducible. It was later found that reactions performed with freshly recrystallized PTSA or CSA did not produce the desired product. Only starting material was recovered. One might propose that the commercial acids were contaminated with a stronger acid, which was responsible for the catalysis. This suggests an active catalyst can only be generated when Au(PPh$_3$)Cl is in the presence of a very strong acid.

We also studied the use of Lewis acids as potential activators of Au(PPh$_3$)Cl. Hydroxy-enyne **16** was submitted to

conditions consisting of 5 mol % $Au(PPh_3)Cl$ and 5 mol % $BF_3{-}OEt_2$ or TMSOTf. In both cases, the benzannulation occurred in 83% and 80% conversion, respectively. However, we must take into consideration the possible presence of protic acids in the reaction mixture. To avoid background reactions created by the presence of protic acids, the reactions were performed by pre-mixing the Lewis acid (5 mol %), $Au(PPh_3)Cl$ (5 mol %), and DTBMP (20 mol %) followed by the addition of substrate **16**. Four Lewis acids were tested under these conditions ($BF_3{-}OEt_2$, TMSOTf, $MgBr_2{-}OEt_2$, and $SnCl_4$). In all cases, we recovered only starting material. These results show that $Au(PPh_3)Cl$ can only be activated by a strong protic acid. Undoubtedly, triflic acid was the best acid to use in combination with $Au(PPh_3)Cl$ since it gave the best conversion (95%). We found that an increase of the triflic acid loading while keeping constant $Au(PPh_3)Cl$ at 2.5 mol % was detrimental to the reaction. This resulted in low conversions to tetrahydronaphthalene **17**. Thus, a 1:1 ratio of triflic acid to Au(I) revealed to be optimal.

Next, we carried out the benzannulation reactions in various solvents at room temperature for 18 h. Reactions ran in toluene, methanol, THF, diethyl ether, acetonitrile, water, and a dichloromethane/water combination showed very low conversions. Changing the solvent for dichloroethane and heating to reflux proved to be successful as a 100% conversion was observed (Table 4, entry 1). Gratifyingly, we were able to decrease the catalyst loading to 1 mol % without affecting the conversion (entry 2). A quantitative conversion was observed when the reaction was performed using 1 mol % of AuCl, TfOH, and PPh_3 (entry 3). Unexpectedly, treating substrate **16** with $Au(PPh_3)Cl$ in dichloroethane at 80 °C did give the desired product in 43% conversion (entry 4). In contrast, only starting material was recovered when hydroxy-enyne **16** was treated with $Au(PPh_3)Cl$ in dichloroethane at room temperature. Also, it was noticed that no desired product was observed when the substrate was heated alone or in the presence of triflic acid (entries 5 and 6).[25] Having established the optimal reaction conditions, we investigated the scope of this Au(I)/TfOH-catalyzed benzannulation using selected hydroxy-enynes (Table 5).

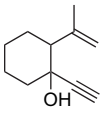
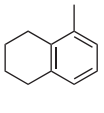
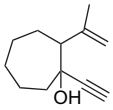
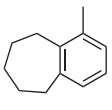
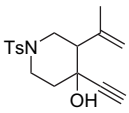
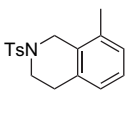
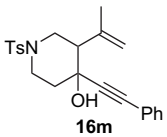
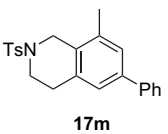
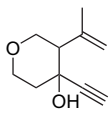
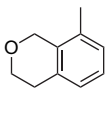
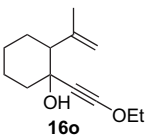
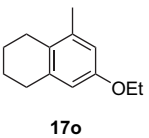
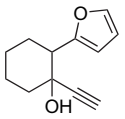
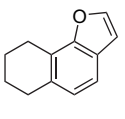
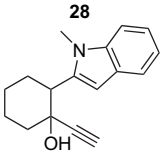
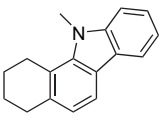
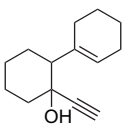
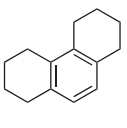
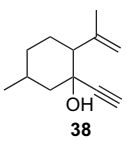
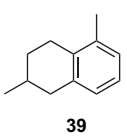
Cyclization of six and seven-membered hydroxy-enynes **16**, **16j**, and **38** gave the corresponding aromatic compounds **17**, **17j**, and **39** in 50, 68, and 82% yield, respectively (entries 1–2 and 10). *N*-Tosyl-piperidine **16l** and **16m** and tetrahydropyran **16n** were easily transformed to the corresponding tetrahydroisoquinolines **17l**, **17m**, and isochromane **17n** in good yields (entries 3–5). To our delight, the highly acid sensitive ynol ether **16o** was converted to the corresponding phenol ether **17o** in 51% yield (entry 10).[26] Under these conditions, electron rich aromatics **28** and **32** gave the desired

Table 4
Optimization of the catalyst system

Entry	Catalyst[a]	Loading (mol %)	Conv.[b] (%)
1	$Au(PPh_3)Cl$, TfOH	2.5	100
2	$Au(PPh_3)Cl$, TfOH	1	100
3	AuCl, TfOH, PPh_3	1	100
4	$Au(PPh_3)Cl$	1	43
5	TfOH	1	0
6	None	—	0

[a] Reactions were done in DCE at 80 °C for 18 h.
[b] Determined by GC.

Table 5
$Au(PPh_3)Cl$/TfOH-catalyzed benzannulation[a]

Entry	Substrate	Product	Yield[b] %
1	 **16**	 **17**	50
2	 **16j**	 **17j**	68
3	 **16l**	 **17l**	67
4	 **16m**	 **17m**	56
5	 **16n**	 **17n**	62
6	 **16o**	 **17o**	51
7	 **28**	 **29**	64
8	 **32**	 **33**	76
9	 **34**	 **35**	82
10	 **38**	 **39**	82

[a] The reaction conditions are 1 mol % of each TfOH and $Au(PPh_3)Cl$ in dichloroethane at 80 °C for 18 h.
[b] Isolated yield after column chromatography.

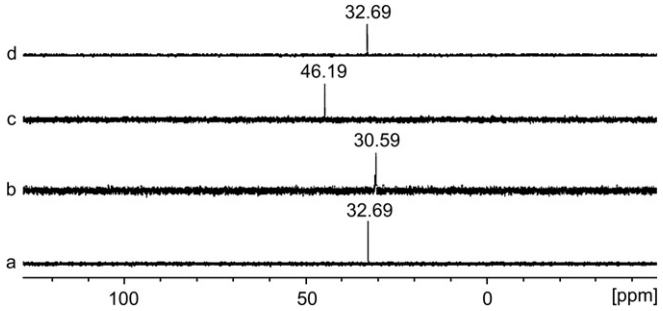


Figure 2. ^{31}P NMR study at 23 °C in $CDCl_3$ (PPh_3 used as a standard at −6.0 ppm). (a) $Au(PPh_3)Cl$; (b) $Au(PPh_3)Cl$ (2.5 mol %) and AgOTf (2.5 mol %) after 16 h; (c) $Au(PPh_3)Cl$ (2.5 mol %), AgOTf (2.5 mol %), and alcohol **16** (59% conversion); (d) $Au(PPh_3)Cl$ (5 mol %), TfOH (5 mol %), and alcohol **16** (37% conversion).

tetrahydronaphthalenes **29** and **33** in 64 and 76% yield, respectively (entries 6 and 7). Benzannulation of cyclic olefin **34** occurred smoothly providing **35** in 82% yield (entry 8). With the exception of substrates **16** and **16n**, the yields were higher when the benzannulation was catalyzed with $Au(PPh_3)Cl$ and TfOH in comparison with $Au(PPh_3)Cl$ and AgOTf. Overall, we have shown that 1 mol % $Au(PPh_3)Cl$ and triflic acid generated an effective catalyst system for benzannulation of 3-hydroxy-1,5-enyne. Since neither species catalyzed the benzannulation reaction on their own (at room temperature), an active catalyst must be generated when these two species are in contact. Teles and co-workers reported that a cationic gold complex is generated by protonolysis of $Au(PPh_3)Me$ and methanesulfonic acid.[27] By analogy, one might suggest that protonolysis of $Au(PPh_3)Cl$ by triflic acid might give the cationic gold catalyst, $Au(PPh_3)OTf$.

^{31}P NMR studies were performed to gain insight into the reactive species (Fig. 2). Different Au(I) complexes were detected when $Au(PPh_3)Cl$ and AgOTf were mixed alone to form $Au(PPh_3)OTf$ (spectrum b) or in the presence of substrate **16** (spectrum c). In the latter case, the complex generated could be such as $[Au(PPh_3)-Ar]^+$ (Ar=tetrahydronaphthalene) since the benzannulation occurred in the NMR tube. In contrast, Au(I) cationic species were not identified when $Au(PPh_3)Cl$ and TfOH were combined in the presence of the substrate **16** (spectrum d). In fact, the chemical shift of the single peak (32.7 ppm) correspond to that of $Au(PPh_3)Cl$ (spectrum a). Based on the NMR data, one might suggest that a more reactive Au catalyst, in the case of $Au(PPh_3)Cl$ and TfOH, is generated and its concentration is below the limits of detection.

3. Conclusion

In summary, we disclosed a gold-catalyzed benzannulation of 3-hydroxy-1,5-enynes. The reaction conditions were compatible with a variety of functional groups proving to be an effective method to generate substituted tetrahydronaphthalenes. In the course of the study, we discovered that the combination of 1 mol % $Au(PPh_3)Cl$ and TfOH in dichloroethane emerged as a novel and effective catalyst for the benzannulation process. In general, the tetrahydronaphthalenes were obtained in higher yields. Application of this novel catalyst system toward the development of new tandem reactions and further investigations into the nature of the catalyst are on going and will be reported in due course.

4. Experimental

4.1. General

All reactions were performed under argon atmosphere in flame-dried glassware equipped with a magnetic stir bar and a rubber septum, unless otherwise indicated. All solvents were freshly distilled prior to use; diethyl ether and THF over sodium and benzophenone; acetonitrile and DCM over calcium hydride. Triflic acid was distilled over triflic anhydride and kept under argon in the refrigerator. All other commercial reagents were used without purification, unless otherwise noted.

Reactions were monitored by thin layer chromatography (TLC) analysis of aliquots using glass sheets pre-coated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck). Thin layer chromatography plates were viewed under UV light and stained with phosphomolybdic acid or *p*-anisaldehyde staining solution. Column chromatographies were carried out with silica gel 60 (230–400 mesh, Merck). ^{1}H and ^{13}C NMR spectra were recorded in deuterated solvents, on Bruker Avance 300, 400, and 500 MHz spectrometers. IR spectra were recorded with a Bomem Michaelson 100 FTIR spectrometer. HRMS were obtained on a Kratos Analytical Concept instrument (University of Ottawa Mass Spectrum Centre). Melting points were recorded on a Gallenkamp melting point machine apparatus P 1106G.

The spectroscopic data of following compounds have been previously described:[16] **16a–k**, **17a–k**, **28–31**, and **34–37**.

4.1.1. 1-Ethynyl-2-isopropenyl-1-prop-2-ynyloxy-cyclohexane (*18*)

To a solution of (±)-[1*S*,2*S*]-1-ethynyl-2-isopropenyl-cyclohexanol[16] (2.55 g, 15.5 mmol) and propargyl bromide (5.16 mL, 46.0 mmol) in THF/DMF (9:3 mL) was added sodium hydride 60% in oil (1.86 g, 46.0 mmol) slowly at room temperature. The reaction was followed by TLC and quenched with NH_4Cl (satd aq) upon completion. The mixture was extracted with diethyl ether (3×) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% ethyl acetate in hexanes) afforded **18** (2.57 g, 81%) as a yellow oil. IR (neat, cm^{-1}) 3303 (s), 3073 (m), 2934 (s), 2858 (s), 1641 (m), 1448 (m), 1376 (m), 1143 (m), 1094 (s), 1063 (s), 892 (s); ^{1}H NMR ($CDCl_3$) δ 4.81 (d, J=1.2 Hz, 2H), 4.24 (dd, J_{AB}=15.2 Hz, J_{Ax}=2.5 Hz, 1H), 4.13 (dd, J_{AB}=15.2 Hz, J_{Bx}=2.5 Hz, 1H), 2.48 (s, 1H), 2.34 (t, J=2.5 Hz, 1H), 2.25–2.12 (m, 2H), 1.86 (qd, J=12.4, 3.7 Hz, 1H), 1.78 (s, 3H), 1.75–1.67 (m, 1H), 1.60–1.38 (m, 4H), 1.33–1.16 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 146.6 (C), 113.5 (CH_2), 84.2 (C), 80.9 (C), 75.9 (C), 74.9 (CH), 73.1 (CH), 54.3 (CH), 51.9 (CH_2), 35.8 (CH_2), 26.2

(CH_2), 25.7 (CH_2), 22.1 (CH_3), 20.6 (CH_2); HRMS (EI) *m/z* calcd for $C_{14}H_{18}O$ (M^+) 202.1358, found 202.1348.

4.1.2. Acetic acid 1-ethynyl-2-isopropenyl-cyclohexyl ester (**19**)

To a solution of (±)-[1*S*,2*R*]-1-ethynyl-2-isopropenyl-cyclohexanol[16] (0.600 g,3.66 mmol) in DCM (45.0 mL) was added 4-DMAP (223 mg,1.83 mmol) followed by triethylamine (0.713 mL, 5.12 mmol) and acetic anhydride (0.420 mL, 4.39 mmol). The following solution was stirred at room temperature for 3 h. The solution was quenched with water. The mixture was extracted with DCM (3×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (5% ethyl acetate in hexanes) afforded ester **19** (465 mg, 62%) as a colorless oil. IR (neat, cm^{-1}) 2934 (s), 2115 (m), 1733 (m), 1240 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.88 (s, 1H), 4.87 (s, 1H), 2.73–2.69 (m, 1H), 2.65 (s, 1H), 2.43–2.38 (dd, *J*=12.5, 9.5 Hz, 1H), 1.98 (s, 3H), 1.85 (s, 3H), 1.78–1.61 (m, 6H), 1.27–1.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.1 (C), 145.3 (C), 113.6 (CH_2), 81.1 (C), 79.8 (C), 77.3 (CH), 52.7 (CH), 37.4 (CH_2), 29.3 (CH_2), 25.6 (CH_2), 23.5 (CH_2), 23.5 (CH_3), 22.1 (CH_3); HRMS (EI) *m/z* calcd for $C_{11}H_{14}$ ($M-C_2H_4O_2^+$) 146.1096, found 146.1107.

4.1.3. 4-Ethynyl-3-(prop-1-en-2-yl)-1-tosylpiperidin-4-ol (**16l**)

To a solution of 3-isopropenyl-1-(toluene-4-sulfonyl)-piperidin-4-one[28] (0.910 g, 3.10 mmol) in THF (2 mL) at 0 °C was added dropwise ethynylmagnesium bromide (15.4 mL, 7.72 mmol). The solution was warmed to room temperature and stirred for 3 h. The mixture was cooled to 0 °C and quenched with NH_4Cl (satd aq). The mixture was extracted with ether (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% ethyl acetate in hexane) afforded compound **16l** as a mixture of diastereoisomers as a beige solid (0.497 g, 50%).

4.1.3.1. Major (±)-[3S,4S]. IR (neat, cm^{-1}) 3495 (br), 3279 (br), 2926 (w), 2867 (w), 1340 (m), 1168 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.62 (d, *J*=8.0 Hz, 2H), 7.31 (d, *J*=8.0 Hz, 2H), 5.03 (s, 1H), 4.68 (s, 1H), 3.63–3.58 (m, 1H), 3.55–3.51 (ddd, *J*=10.9, 2.0, 3.3 Hz, 1H), 2.59–2.38 (m, 4H), 2.44 (s, 1H), 2.42 (s, 3H), 2.41 (br s, 1H), 2.09 (dd, *J*=3.1, 3.1 Hz, 1H), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.2 (C), 143.7 (C), 133.2 (C), 129.8 (2×CH), 127.6 (2×CH), 113.8 (CH_2), 86.2 (C), 72.6 (CH), 64.6 (C), 50.4 (CH), 45.2 (CH_2), 41.1 (CH_2), 37.9 (CH_2), 26.3 (CH_3), 21.6 (CH_3); HRMS (EI) *m/z* calcd for $C_{17}H_{21}NO_3S$ (M^+) 319.1242, found 319.1234; mp=143.0–148.5 °C.

4.1.3.2. Minor (±)-[3S,4R]. IR (neat, cm^{-1}) 3490 (br), 3274 (s), 2926 (m), 2866 (w), 1340 (s), 1167 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, *J*=8.3 Hz, 2H), 7.31 (d, *J*=8.0 Hz, 2H), 5.04 (t, *J*=1.5 Hz, 1H), 4.95 (s, 1H), 3.86–3.80 (m, 1H), 3.78–3.74 (m, 1H), 2.71 (ddd, *J*=12.5, 12.5, 2.6 Hz, 1H), 2.63 (dd, *J*=11.9, 11.9 Hz, 1H), 2.58 (br, 1H), 2.42 (s, 3H), 2.39 (dd, *J*=11.8, 3.7 Hz, 2H), 2.04–1.99 (m, 1H), 1.83 (dd, *J*=12.7, 4.4 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.6 (C), 141.3 (C), 134.0 (C), 129.8 (2×CH), 127.5 (2×CH), 116.6 (CH_2), 83.5 (C), 76.3 (CH), 68.9 (C), 53.2 (CH), 47.2 (CH_2), 44.0 (CH_2), 39.0 (CH_2), 22.1 (CH_3), 21.6 (CH_3); HRMS (EI) *m/z* calcd for $C_{17}H_{21}NO_3S$ (M^+) 319.1242, found 319.1240; mp=116.0–126.0 °C.

4.1.4. 3-Isopropenyl-4-phenylethynyl-1-(toluene-4-sulfonyl)-piperidin-4-ol (**16m**)

$PdCl_2(PPh_3)_2$ (30.6 mg, 0.05 mmol) and CuI (8.3 mg, 0.05 mmol) were weighed in the glovebox under argon. A solution of [3*S*,4*S*]-**16l** (0.280 g, 1.00 mmol) in acetonitrile (13.4 mL) was transferred via cannula. Following the addition of the iodobenzene (108 mg, 1.11 mmol), the resulting solution was degassed with argon for 10 min. Then, freshly distilled diisopropylethylamine (0.760 mL, 5.00 mmol) was added and the mixture was stirred at room temperature. Upon completion, the reaction mixture was concentrated and loaded directly onto a silica gel column for purification (10% ethyl acetate in hexanes) to give **16m** (181 mg, 48%) as a yellow solid.

IR (neat, cm^{-1}) 3496 (br), 2932 (m), 2870 (m), 1595 (w), 1345 (s), 1210 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, *J*=8.3 Hz, 2H), 7.29–7.26 (m, 2H), 7.24–7.23 (m, 5H), 4.99 (s, 1H), 4.67 (s, 1H), 3.59–3.56 (m, 1H), 3.53–3.49 (m, 1H), 2.57–2.49 (m, 3H), 2.36 (s, 3H), 2.20–2.06 (m, 3H), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.3 (C), 143.6 (C), 133.3 (C), 131.6 (2×CH), 129.8 (CH×2), 128.7 (CH), 128.4 (2×CH), 127.7 (2×CH), 122.2 (C), 113.8 (CH_2), 91.5 (C), 84.3 (C), 65.1 (C), 50.8 (CH), 45.4 (CH_2), 41.3 (CH_2), 38.0 (CH_2), 26.3 (CH_3), 21.6 (CH_3); HRMS (EI) *m/z* calcd for $C_{23}H_{25}NO_3S$ (M^+) 395.1555, found 395.1575; mp=155.8–156.7 °C.

4.1.5. 3-(3-Methyl-but-2-enyloxy)-propan-1-ol (**16nA**)

1,3-Propanediol (0.110 g, 1.43 mmol) was dissolved in DMF (2 mL) and the mixture was stirred at 0 °C for 15 min. At that point, NaH (30.0 mg, 1.24 mmol) was added and the resulting solution was stirred for 15 min before 1-bromo-3-methyl-but-2-ene (0.070 mL, 0.590 mmol) was added. The solution was stirred until the reaction was complete by TLC. The reaction was quenched with NH_4Cl, extracted 3× with Et_2O, and the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash column chromatography (30–60% ethyl acetate in hexanes) gave **16nA** (60.0 mg, 71%) as a colorless oil.

IR (neat, cm^{-1}) 3402 (s), 2930 (s), 2867 (s), 1085 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.33–5.29 (m, 1H), 3.94 (d, *J*=6.9 Hz, 2H), 3.75 (t, *J*=5.7 Hz, 2H), 3.59 (t, *J*=5.8 Hz, 2H), 2.14 (br, 1H), 1.81 (dddd, *J*=5.8, 5.8, 5.8, 5.8 Hz, 2H), 1.72 (s, 3H), 1.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.2 (C), 120.9 (CH), 69.4 (CH_2), 67.6 (CH_2), 62.3 (CH_2), 32.1 (CH_2), 25.8 (CH_3), 18.0 (CH_3); HRMS (EI) *m/z* calcd for $C_8H_{16}O_2$ (M^+) 144.1150, found 144.1151.

*4.1.6. 3-(3-Methyl-but-2-enyloxy)-propionaldehyde (**16nB**)*

DMSO (1.94 mL, 27.3 mmol) was slowly added to a solution of oxalyl chloride (1.19 mL, 13.7 mmol) in DCM (34 mL) at −78 °C. After stirring for 20 min, **16nA** in DCM (16 mL) was added and the mixture was stirred for another 90 min. Triethylamine (7.90 mL, 56.9 mmol) was added and the solution was again stirred at 0 °C for another hour before being quenched with NH_4Cl (satd aq). The mixture was extracted with ether (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (30% ethyl acetate in hexane) gave **16nB** (0.820 g, 51%) as a yellow oil.

IR (neat, cm^{-1}) 2863 (s), 1725 (s), 1085 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.74 (s, 1H), 5.30−5.26 (m, 1H), 3.93 (d, J=6.9 Hz, 2H), 3.71 (t, J=6.1, 6.1 Hz, 2H), 2.62 (td, J=1.7, 6.2 Hz, 2H), 1.70 (s, 3H), 1.63 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.3 (CH), 137.5 (C), 120.7 (CH), 67.6 (CH_2), 63.6 (CH_2), 44.0 (CH_2), 25.8 (CH_3), 18.0 (CH_3); HRMS (EI) *m/z* calcd for $C_7H_{11}O_2$ $(M-Me)^+$ 127.0754, found 127.0761.

*4.1.7. 3-Isopropenyl-tetrahydro-pyran-4-one (**16nC**)*

To a suspension of molecular sieves (0.41 g) in DCM (8.1 mL) was added **16nB** (0.580 g, 4.23 mmol). The mixture was cooled to −78 °C and tin tetrachloride (0.410 mL, 0.423 mmol) was added dropwise. The solution was stirred at −60 °C for 1 h before it was quenched with NH_4Cl. The solution was allowed to stir overnight at room temperature. The mixture was filtered through Celite and the resulting solution was extracted with DCM 3×. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated.

DMSO (0.430 mL, 6.13 mmol) was slowly added to a solution of oxalyl chloride (0.270 mL, 3.06 mmol) in DCM (8.0 mL) at −78 °C. After stirring for 20 min, the alcohol in DCM (4.0 mL) was added and the mixture was stirred for another 90 min. Triethylamine (1.78 mL, 12.8 mmol) was added and the solution was again stirred at 0 °C for another hour before being quenched with NH_4Cl (satd aq). The mixture was extracted with ether (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (25% ethyl acetate in hexanes) gave **16nC** (0.100 g, 27%) as a colorless liquid.

IR (neat, cm^{-1}) 2968 (s), 2856 (s), 1718 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.99 (s, 1H), 4.85 (s, 1H), 4.10−4.06 (m, 2H), 3.87−3.79 (m, 2H), 3.13 (dd, J=8.5, 6.0 Hz, 1H), 2.53−2.49 (m, 2H), 1.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.1 (C), 139.9 (C), 114.8 (CH_2), 71.4 (CH_2), 68.3 (CH_2), 58.8 (CH), 41.9 (CH_2), 22.0 (CH_3); HRMS (EI) *m/z* calcd for $C_8H_{12}O_2$ (M^+) 140.0837, found 140.0840.

*4.1.8. 4-Ethynyl-3-isopropenyl-tetrahydro-pyran-4-ol (**16n**)*

To a solution of **16nC** (0.100 g, 0.703 mmol) in THF (7 mL) at 0 °C was added dropwise ethynylmagnesium bromide (3.50 mL, 1.76 mmol). The solution was warmed to room temperature and stirred for 3 h. The mixture was cooled to 0 °C and quenched with NH_4Cl (satd aq). The mixture was extracted with ether (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (20% ethyl acetate in hexanes) afforded compound **16n** as a mixture of diastereoisomers as colorless oils (0.822 g, 70%).

4.1.8.1. Major (±)-[3S,4S]. IR (neat, cm^{-1}) 3351 (br), 3231 (s), 2961 (m), 2864 (m), 1113 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.04−5.03 (t, J=1.4 Hz, 1H), 4.75 (s, 1H), 3.73−3.70 (m, 2H), 3.61−3.56 (m, 2H), 2.52−2.48 (dd, J=9.8, 6.1 Hz, 1H), 2.44 (s, 1H), 2.35 (br, 1H), 2.04−1.93 (m, 2H), 1.96 (dd, J=1.4, 1.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.8 (C), 113.7 (CH_2), 87.0 (C), 71.9 (CH), 66.2 (CH_2), 64.7 (C), 62.7 (CH_2), 51.1 (CH), 38.6 (CH_2), 26.5 (CH_3); HRMS (EI) *m/z* calcd for $C_{10}H_{13}O_2$ $(M-H)^+$ 165.0921, found 165.0919.

4.1.8.2. Minor (±)-[3S,4R]. IR (neat, cm^{-1}) 3381 (br), 2962 (s), 2869 (m), 1640 (w), 1107 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.03−5.02 (t, J=1.6 Hz, 1H), 4.96 (s, 1H), 3.99−3.94 (m, 1H), 3.85 (dd, J=11.5, 4.0 Hz, 1H), 3.75−3.69 (ddd, J=7.6, 7.6, 2.3 Hz, 1H), 3.64−3.58 (dd, J=11.5 Hz, 1H), 2.61 (br, 1H), 2.56 (s, 1H), 2.40−2.36 (dd, J=11.5, 4.0 Hz, 1H), 1.99−1.94 (m, 1H), 1.87 (dd, J=12.4, 4.6 Hz, 1H), 1.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.3 (C), 115.9 (CH_2), 84.5 (C), 75.6 (CH), 68.9 (C), 68.6 (CH_2), 65.8 (CH_2), 54.6 (CH), 40.6 (CH_2), 22.5 (CH_3); HRMS (EI) *m/z* calcd for $C_{10}H_{13}O_2$ $(M-H)^+$ 165.0921, found 165.0919.

*4.1.9. 1-Ethoxyethynyl-2-isopropylcyclohexanol (**16o**)*

A solution of ethoxyethynyl ether (40% in hexanes, 2.17 mmol, 380 mg) in THF was cooled to −78 °C and *n*-BuLi (1.86 M in hexanes, 1.08 mmol, 0.58 mL) was added. After stirring for 40 min, a solution of (±)-2-isopropenylcycloxenone (99.9 mg, 0.72 mmol) in THF (7 mL) was added at −78 °C. After stirring for 5 h, the reaction quenched with NH_4Cl (satd aq). The mixture was extracted with ether (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% ethyl acetate in hexanes) afforded compound **16o** as a mixture of diastereoisomers as colorless oils (78.8 mg, 53%).

4.1.9.1. Major (±)-[1S,2S]. IR (neat, cm^{-1}) 3445 (br), 2931 (s), 2858 (m), 2258 (s), 1603 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.93−4.86 (m, 1H), 4.87−4.86 (m, 1H), 4.06 (q, J=7 Hz, 2H), 2.54 (s, 1H), 2.09 (dd, J=10.7, 4.2 Hz, 1H), 2.00−1.96 (m, 1H), 1.85 (s, 3H), 1.75−1.58 (m, 5H), 1.45 (ddd, J=12, 12, 4 Hz, 1H), 1.35 (t, J=7 Hz, 3H), 1.22−1.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.1 (C), 114.3 (CH_2), 94.7 (C), 74.1 (C), 69.9 (C), 56.3 (CH), 41.2 (CH_2), 39.7 (CH_2), 28.5 (CH_2), 25.6 (CH_2), 23.9 (CH_2), 21.0 (CH_3), 14.3 (CH_3); HRMS (EI) *m/z* calcd for $C_{13}H_{20}O_2$ (M^+) 208.1463, found 208.1475.

*4.1.10. 2-Chloro-1-(1-methyl-1H-indol-2-yl)-cyclohexanol (**32A**)*

1-Methylindole (1.46 mL, 11.4 mmol) was dissolved in THF (6.8 mL) and the resulting mixture was cooled to 0 °C

before *n*-BuLi (7.63 mL, 15.2 mmol) was added. The ice bath was then removed and the solution stirred for 2 h at room temperature. The mixture was cooled to −78 °C before 2-chlorocyclohexanone (1.10 mL, 9.50 mmol) dissolved in THF (3.4 mL) was slowly cannulated. The reaction was then stirred at room temperature until completed by TLC. The reaction was quenched with the addition of NH_4Cl, followed by the addition of water to dissolve the precipitate. The mixture was extracted with ether (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% ethyl acetate in hexanes) gave **32A** (0.840 g, 33%) as a yellow oil.

IR (neat, cm^{-1}) 3530 (m), 2940 (s), 2861 (m), 1720 (m), 1467 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, J=7.8 Hz, 1H), 7.32 (d, J=8.2 Hz, 1H), 7.24−7.20 (m, 1H), 7.12−7.08 (m, 1H), 6.45 (s, 1H), 4.73 (dd, J=6.9, 6.9 Hz, 1H), 4.00 (s, 3H), 2.66 (br, 1H), 2.47−2.44 (m, 1H), 2.19−2.16 (m, 2H), 1.87−1.76 (m, 2H), 1.64−1.57 (m, 2H), 1.46−1.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 142.5 (C), 138.4 (C), 126.9 (C), 121.7 (CH), 120.6 (CH), 119.7 (CH), 109.1 (CH), 99.6 (CH), 73.7 (C), 66.7 (CH), 38.5 (CH_2), 32.6 (CH_2), 32.1 (CH_3), 25.7 (CH_2), 20.7 (CH_2); HRMS (EI) *m/z* calcd for $C_{17}H_{17}N$ (M^+) 263.1077, found 263.1084.

4.1.11. 1-Ethynyl-2-(1-methyl-1H-indol-2-yl)-cyclohexanol (*32*)

To a solution of cyclohexanol **32A** (46.0 mg, 0.178 mmol) in THF (1 mL) was added dropwise ethynylmagnesium bromide (1.17 mL, 0.582 mmol). The reaction was heated to reflux and stirred until completion by TLC (3 h), at which point it was cooled to room temperature and quenched with NH_4Cl (satd aq). The mixture was extracted with diethyl ether (3×) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (10% ethyl acetate in hexanes) gave **32** as a mixture of diastereoisomers (27.3 mg, 61%) as yellow oils.

4.1.11.1. Major (±)-[1S,2S]. IR (neat, cm^{-1}) 3527 (br), 3285 (s), 2938 (s), 2856 (m), 1465 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.67 (dt, J=7.8, 0.8 Hz, 1H), 7.41−7.38 (m, 1H), 7.31−7.26 (m, 1H), 7.20−7.16 (m, 1H), 6.50 (s, 1H), 3.87 (s, 3H), 3.28−3.24 (dd, J=12.6, 3.7 Hz, 1H), 3.14 (s, 1H), 2.59 (s, 1H), 2.39−2.33 (m, 1H), 2.33 (s, 1H), 2.17−1.44 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.1 (C), 137.5 (C), 127.7 (C), 121.4 (CH), 120.2 (CH), 119.6 (CH), 109.5 (CH), 99.6 (CH), 88.2 (C), 71.7 (CH), 66.8 (C), 43.7 (CH), 38.8 (CH_2), 30.6 (CH_3), 27.9 (CH_2), 25.8 (CH_2), 20.3 (CH_2); HRMS (EI) *m/z* calcd for $C_{17}H_{19}NO$ (M^+) 253.1467, found 253.1465.

4.1.11.2. Minor (±)-[1R,2S]. IR (neat, cm^{-1}) 3424 (m), 3285 (m), 2936 (s), 2859 (m), 1468 (m), 1317 (m), 1231 (w); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, J=7.8 Hz, 1H), 7.36 (d, J=8.2 Hz, 1H), 7.24 (td, J=1.2, 7.0, 7.0 Hz, 1H), 7.16−7.12 (m, 1H), 6.70 (s, 1H), 3.79 (s, 3H), 3.01 (dd, J=3.3, 12.1 Hz, 1H), 2.65 (s, 1H), 2.44 (s, 1H), 2.26−2.22 (m, 1H), 2.10−1.73 (m, 6H), 1.50−1.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 140.5 (C), 137.2 (C), 127.7 (C), 121.0 (CH), 120.3 (CH), 119.4 (CH), 109.3 (CH), 100.3 (CH), 84.8 (C), 76.1 (CH), 73.6 (C), 46.4 (CH), 40.6 (CH_2), 31.1 (CH_2), 30.1 (CH_3), 26.0 (CH_2), 25.6 (CH_2); HRMS (EI) *m/z* calcd for $C_{17}H_{19}NO$ (M^+) 253.1467, found 253.1474.

4.1.12. 1-Ethynyl-2-isopropenyl-5-methyl-cyclohexanol (*38*)

To a solution of (+)-isopulegone[29] (1.00 g, 6.57 mmol) in THF (1 mL) was added dropwise ethynylmagnesium bromide (1.17 mL, 0.582 mmol). The reaction was stirred until completion by TLC (3 h) before being quenched with NH_4Cl (satd aq). The mixture was extracted with diethyl ether (3×) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (5% ethyl acetate in hexanes) gave **38** as a mixture of diastereoisomers (0.940 g, 80%) as colorless oils.

4.1.12.1. Major (±)-[1S,2S,5R]. IR (neat, cm^{-1}) 3549 (br), 3309 (s), 2951 (s), 1727 (m), 1638 (w), 1455 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.97 (t, J=1.6 Hz, 1H), 4.81 (s, 1H), 2.37 (s, 1H), 2.15−2.08 (m, 3H), 1.94 (s, 3H), 1.76−1.63 (m, 3H), 1.46−1.41 (m, 1H), 1.32 (dd, J=12.3, 13.7 Hz, 1H), 0.93−0.88 (m, 1H), 0.84 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.9 (C), 112.4 (CH_2), 88.6 (C), 71.2 (CH), 67.4 (C), 52.2 (CH), 48.0 (CH_2), 34.5 (CH_2), 26.8 (CH_2), 26.6 (CH), 25.9 (CH_3), 21.8 (CH_3); HRMS (EI) *m/z* calcd for $C_{12}H_{18}O$ (M^+) 178.1358, found 178.1345.

4.1.12.2. Minor (±)-[1R,2S,5R]. IR (neat, cm^{-1}) 3459 (br), 3307 (s), 2928 (s), 1633 (w), 1455 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.95 (t, J=0.7 Hz, 1H), 4.88 (s, 1H), 2.43 (s, 1H), 2.10−2.00 (m, 2H), 1.95−1.60 (m, 5H), 1.84 (s, 3H), 1.17 (dd, J=12.3, 12.3 Hz, 1H), 0.92 (d, J=5.2 Hz, 3H), 0.95−0.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.4 (C), 115.2 (CH_2), 86.3 (C), 74.2 (CH), 69.6 (C), 55.7 (CH), 48.7 (CH_2), 34.4 (CH_2), 30.3 (CH), 28.0 (CH_2), 21.9 (CH_3), 21.0 (CH_3); HRMS (EI) *m/z* calcd for $C_{12}H_{18}O$ (M^+) 178.1358, found 178.1345.

4.2. General procedures for gold(I)-catalyzed benzannulation of 3-hydroxy-1,5-enynes

Procedure A: AgOTf (2.5 mol %) and $Au(PPh_3)Cl$ (2.5 mol %) were weighed in the glovebox. Then, a solution of the substrate in dichloromethane (0.1 M based on the alcohol) was cannulated. The resulting dark solution was stirred for 15−18 h until completion by TLC. The reaction mixture was filtered through Celite and evaporated in vacuo. Purification by flash chromatography yielded the desired benzannulation products.

Procedure B: $Au(PPh_3)Cl$ (1.0 mol %) was weighed in the glovebox. Then, a solution of TfOH (1.0 mol %) (0.01 M in ether) was added to the flame-dried flask. Subsequently, the substrate in dichloroethane (0.1 M based on the alcohol) was cannulated. The resulting dark solution was refluxed for 15−18 h until completion by TLC. The reaction mixture was cooled to room temperature and quenched with $NaHCO_3$. The mixture was extracted with DCM (3×) and the combined

organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography yielded the desired benzannulated products.

4.2.1. 5-Methyl-1,2,3,4-tetrahydro-naphthalene (**17**)

Procedure B: purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **17** (16.9 mg, 48%) as a yellow oil. Characterization is available through the literature.[16]

4.2.2. 1-Methyl-6,7,8,9-tetrahydro-5H-benzocycloheptene (**17j**)

Procedure B: purification by flash chromatography (5% ethyl acetate/hexanes) afforded benzannulated product **17j** (12.0 mg, 68%) as a yellow oil. Characterization is available through the literature.[16]

4.2.3. 1,2,3,4-Tetrahydro-8-methyl-2-tosylisoquinoline (**17l**)

Procedure A: purification by flash chromatography (10% ethyl acetate/hexanes) afforded benzannulated product **17l** (16.2 mg, 67%) as a white solid.

Procedure B: purification by flash chromatography (10% ethyl acetate/hexanes) afforded benzannulated product **17l** (51.4 mg, 55%) as a white solid.

Mixture of atropisomers: IR (neat, cm^{-1}) 2922 (w), 2852 (w), 1597 (w), 1461 (w), 1335 (m), 1165 (s), 1094 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (dd, J=9.1, 8.4 Hz, 4H), 7.31 (dd, J=5.8, 2.1 Hz, 4H), 7.06–6.87 (m, 6H), 4.18 (s, 2H), 4.13 (s, 2H), 3.31 (ddd, J=7.1, 5.8, 1.2 Hz, 4H), 2.95–2.83 (m, 4H), 2.41 (s, 6H), 2.25 (s, 2.7H), 2.16 (s, 3.3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.7 (C), 143.6 (C), 136.3 (C), 134.6 (C), 133.3 (2×C), 133.0 (C), 132.9 (C), 130.1 (C), 129.7 (2×CH), 129.7 (2×CH), 129.3 (CH), 128.6 (C), 127.9 (CH), 127.8 (2×CH), 127.7 (2×CH), 127.2 (CH), 126.5 (CH), 126.4 (CH), 126.2 (CH), 47.4 (CH_2), 45.8 (CH_2), 43.8 (CH_2), 43.3 (CH_2), 29.4 (CH_2), 28.9 (CH_2), 21.5 (2×CH_3), 21.0 (CH_3), 18.6 (CH_3); HRMS (EI) m/z calcd for $C_{17}H_{19}NO_2S$ (M^+) 301.1137, found 301.1142; mp=119.0–123.4 °C.

4.2.4. 8-Methyl-6-phenyl-2-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-isoquinoline (**17m**)

Procedure A: purification by flash chromatography (10% ethyl acetate/hexanes) afforded tetrahydronaphthalene **17m** (18.2 mg, 67%) as a beige solid.

Procedure B: purification by flash chromatography (10% ethyl acetate/hexanes) afforded tetrahydronaphthalene **17m** (20.0 mg, 56%) as a beige solid.

IR (neat, cm^{-1}) 2910 (m), 2830 (w), 1605 (w), 1450 (w), 1340 (m), 1164 (s), 1098 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.75–7.73 (m, 2H), 7.52–7.50 (m, 2H), 7.41–7.37 (m, 2H), 7.33–7.30 (m, 3H), 7.21 (s, 1H), 7.14 (s, 1H), 4.16 (s, 2H), 3.35 (dd, J=5.8, 5.8 Hz, 2H), 2.98 (dd, J=5.7, 5.7 Hz, 2H), 2.41 (s, 3H), 2.23 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.7 (C), 140.7 (C), 139.5 (C), 135.1 (C), 133.5 (C), 133.4 (C), 129.8 (2×CH), 129.3 (C), 128.7 (2×CH), 127.7 (2×CH), 127.3 (CH), 127.0 (2×CH), 126.8 (CH), 125.2 (CH), 45.7 (CH_2), 43.4 (CH_2), 29.5 (CH_2), 21.5 (CH_3), 18.8 (CH_3); HRMS (EI) m/z calcd for $C_{23}H_{23}NO_2S$ (M^+) 377.1450, found 377.1442; mp=52.7–55.1 °C.

4.2.5. 8-Methyl-isochromane (**17n**)

Procedure A: purification by flash chromatography (10% ethyl acetate/hexanes) afforded tetrahydronaphthalene **17n** (5.0 mg, 51%) as a beige solid.

Procedure B: purification by flash chromatography (10% ethyl acetate/hexanes) afforded tetrahydronaphthalene **17n** (12.7 mg, 62%) as a beige solid.

IR (neat, cm^{-1}) 2927 (br), 2855 (m), 1725 (m), 1264 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.08 (dd, J=7.5, 7.5 Hz, 1H), 6.98–6.95 (m, 2H), 4.71 (s, 2H), 3.93 (t, J=5.6 Hz, 2H), 2.85 (t, J=5.6 Hz, 2H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.5 (C), 133.2 (C), 133.1 (C), 127.6 (CH), 126.6 (CH), 126.1 (CH), 66.5 (CH_2), 64.9 (CH_2), 28.7 (CH_2), 17.8 (CH_3); HRMS (EI) m/z calcd for $C_{10}H_{12}O$ (M^+) 148.0888, found 148.0883.

4.2.6. 7-Ethoxy-5-methyl-1,2,3,4-tetrahydronaphthalene (**17o**)

Procedure B: purification by flash chromatography (10% ethyl acetate/hexanes) afforded tetrahydronaphthalene **17o** (5.7 mg, 51%) as a colorless oil.

IR (neat, cm^{-1}) 2925 (br), 2857 (m), 1607 (m), 1477 (m); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.55 (br s, 1H), 6.45 (br s, 1H), 3.97 (q, J=7 Hz, 2H), 2.70 (dd, J=5.6 Hz, 2H), 2.52 (dd, J=5.6 Hz, 2H), 2.15 (s, 3H), 1.83–1.67 (m, 4H), 1.35 (t, J=7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.1 (C), 128.2 (C), 114.5 (CH), 112.3 (CH), 63.6 (CH_2), 30.9 (CH_2), 26.4 (CH_2), 24.0 (CH_2), 23.4 (CH_2), 20.1 (CH_3), 15.3 (CH_3); HRMS (EI) m/z calcd for $C_{13}H_{18}O$ (M^+) 190.1358, found 190.1353.

4.2.7. 6,7,8,9-Tetrahydro-naphtho[1,2-b]furan (**29**)

Procedure B: purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **29** (15.5 mg, 64%) as an orange oil. Characterization is available through the literature.[16]

4.2.8. 11-Methyl-2,3,4,11-tetrahydro-1H-benzo[a]carbazole (**33**)

Procedure A: purification by flash chromatography (10% ethyl acetate/hexanes) afforded tetrahydronaphthalene **33** (12.2 mg, 81%) as a white solid.

Procedure B: purification by flash chromatography (10% ethyl acetate/hexanes) afforded tetrahydronaphthalene **33** (21.6 mg, 76%) as a white solid.

IR (neat, cm^{-1}) 2919 (m), 2857 (w), 1467 (s), 1403 (s), 745 (s); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, J=7.7 Hz, 1H), 7.86 (d, J=7.9 Hz, 1H), 7.48–7.36 (m, 2H), 7.22 (t, J=7.7 Hz, 1H), 6.98 (t, J=8.0 Hz, 1H), 4.15 (s, 3H), 3.43 (t, J=5.6 Hz, 2H), 3.02 (t, J=6.1 Hz, 2H), 1.99–1.85 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.9 (C), 140.0 (C), 135.4 (C), 124.9 (CH), 123.1 (C), 121.4 (CH), 121.3 (C), 120.6 (C), 119.5 (CH), 118.8 (CH), 117.5 (CH), 108.6 (CH), 33.2 (CH_3), 30.7 (CH_2), 26.9 (CH_2), 23.6 (CH_2), 22.8 (CH_2);

HRMS (EI) *m/z* calcd for $C_{17}H_{17}N$ (M^+) 235.1361, found 235.1361; mp=149.3–150.2 °C.

*4.2.9. 1,2,3,4,5,6,7,8-Octahydro-phenanthrene (**35**)*

Procedure B: purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **35** (37.9 mg, 49%) as a yellow oil. Characterization is available through the literature.[16]

*4.2.10. 2,5-Dimethyl-1,2,3,4-tetrahydro-naphthalene (**39**)*

Procedure A: purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **39** (72.6 mg, 74%) as a yellow oil.

Procedure B: purification by flash chromatography (5% ethyl acetate/hexanes) afforded tetrahydronaphthalene **39** (67.5 mg, 82%) as a yellow oil.

IR (neat, cm^{-1}) 2917 (s), 1587 (m), 1455 (s), 764 (s); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.04–6.92 (m, 3H), 2.83–2.73 (m, 2H), 2.63–2.54 (m, 1H), 2.43 (dd, J=16.3, 10.8 Hz, 1H), 2.22 (s, 3H), 1.98–1.92 (m, 1H), 1.84–1.80 (m, 1H), 1.45–1.35 (m, 1H), 1.05 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 136.9 (C), 136.4 (C), 135.2 (C), 127.0 (CH), 126.9 (CH), 125.2 (CH), 38.8 (CH_2), 31.7 (CH_2), 28.8 (CH), 27.8 (CH_2), 21.9 (CH_3), 19.6 (CH_3); HRMS (EI) *m/z* calcd for $C_{12}H_{16}$ (M^+) 160.1252, found 160.1277.

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