Gold-Catalyzed Hydrophenoxylation of Propargylic alcohols and amines: Synthesis of Phenyl Enol Ethers

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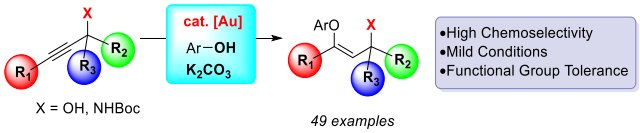
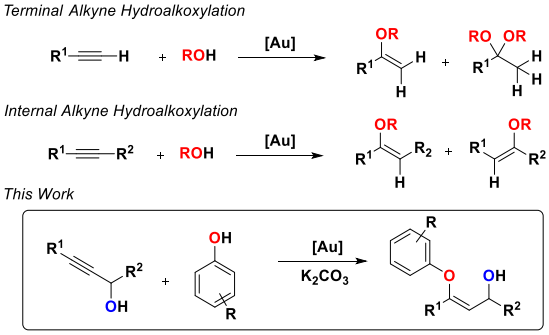


A practical method for the synthesis of phenyl enol ethers is reported. The combination of a gold(I) catalyst and potassium carbonate selectively mediates the addition of phenols to propargylic alcohols/amines in a chemo-, regio- and stereoselective fashion in high yield. The resulting enol ethers are formed exclusively with a *Z*-configuration and can be obtained from a wide array of phenols and propargylic alcohols or amines with the reaction showing excellent functional group tolerance.

The discovery of new synthetic methods for the formation of C-O bonds has drawn considerable attention in synthetic organic chemistry.[1–4] A straightforward approach consists of the addition of alcohols to unsaturated bonds, particularly alkynes,[5,6] in an intramolecular[7–10] or intermolecular[11–14] fashion. Compared to the well-developed hydroamination of alkynes,[15] hydroalkoxylation reactions are far less developed, probably due to the lower nucleophilicity of alcohols compared to amines. The addition of alcohols to alkynes yields enol ethers, although acetal products have also been observed[16] as double addition of the alcohol is possible. These additions usually have a high activation barrier which is overcome by the use of harsh conditions or through metal catalysis. Many methods have been reported over the years with a wide array of metal catalysts including Cu,[17] Rh,[18] Ru,[19] Ir,[20] Pt[21] or Au.[22]

Over the past decade Au catalysis has become considered as the most effective approach to achieve hydration,[23] hydroamination[15] or hydroalkoxylation[6] of alkynes efficiently with a wide range of substrates. Gold-catalyzed intramolecular hydroalkoxylation of alkynes has proved to be a very useful method for the synthesis of various heterocycles[24–26] and natural products,[27] and although more challenging, the intermolecular version of this reaction has been described for primary[13] and secondary[22] alcohols and to a lesser extent, with phenols.[28-30] In these reactions, internal alkynes usually show considerably lower reactivity in comparison to terminal alkynes,[6] but the nature of the alcohol species has a more significant impact on the feasibility of the reaction, with the addition of primary and secondary alcohols to alkynes being relatively well-known, even at mild temperatures. Reports of the addition of tertiary alcohols and phenols are much rarer, and usually involve harsher conditions. Furthermore, simple gold phenolates which could potentially be formed in the reactions have been reported to be unstable, potentially leading to catalyst decomposition.[31] An added problem when dealing with internal alkynes is the regioselectivity of the reaction. Alcohol additions to terminal alkynes generally occur at the internal carbon to give ketals or enol ether products, but internal alkynes usually give mixtures of regioisomers, especially when the two substituents have similar electronic properties. With intramolecular reactions the regioselectivity of the reaction can usually be controlled, as the kinetically faster ring formation will usually determine the selectivity.

Scheme 1. Alkoxylation of Alkynes

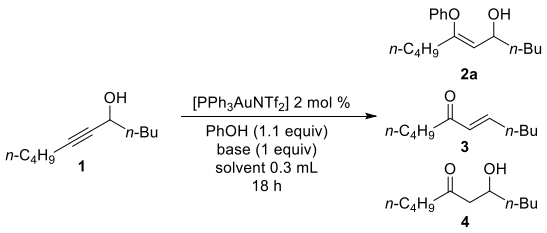


Propargylic alcohols are very versatile and readily available starting materials, where the presence of the alcohol group adjacent to the alkyne gives a distinctive reactivity which differs significantly from simple internal alkynes. Numerous methods to access useful building blocks from propargylic alcohols have been described in the literature. Our group and others have reported the gold-catalyzed transformation of propargylic alcohols into enones,[32] bromo/fluoro enones,[33,34] heterocycles[35,36] or geminal dihalides.[37] Recently we described how propargylic alcohols activated by the Gagosz catalyst[38] could undergo regioselective hydroamination with anilines

under mild conditions.[39] We demonstrated that the OH played a key role in significantly increasing the reactivity of the triple bond, and directing the attack of the aniline regioselectively to form the 3-hydroxyimine.

Inspired by these results, we decided to explore the hydrophenoxylation of propargylic alcohols, with a view to improving the regioselectivity of previously reported alcohol additions to internal alkynes. Hydrophenoxylation of alkynes has seldom been reported,[28-30] and although gold catalysts can mediate the reaction, harsh conditions are usually required and the reactions typically lack selectivity. We hereby report a method for the hydrophenoxylation of propargylic alcohols to yield phenyl enol ethers with high chemo- and regio- selectivity under mild conditions. The robustness of the reaction is demonstrated by a broad substrate scope both in terms of phenols and propargylic alcohols. The reaction can also be extended to Boc-protected propargylic amine substrates.

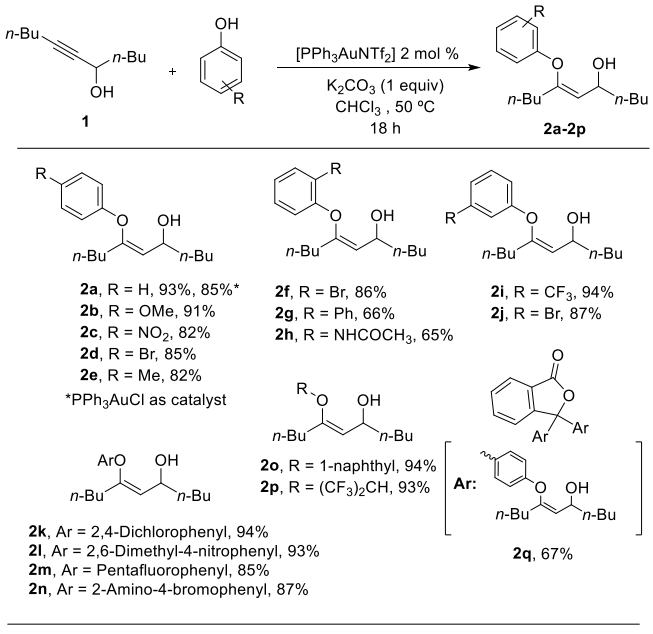
Table 1. Optimization of the Reaction Conditions



entry	base	solv.	temp. (°C)	conv.	sel. (2a:3:4)
1	--	$CHCl_3$	rt	40	5:70:25
2	Cs_2CO_3	$CHCl_3$	rt	0	--
3	NaOAc	$CHCl_3$	rt	58	67:32:1
4	Na_2CO_3	$CHCl_3$	rt	24	91:8:1
5	K_2CO_3	$CHCl_3$	rt	27	98:1:1
6	K_2CO_3	$CHCl_3$	50	99	98:1:1
7	Na_2CO_3	$CHCl_3$	50	82	98:1:1
8	K_2CO_3	PhMe	50	72	98:1:1
9	K_2CO_3	$PhCF_3$	50	85	98:1:1
10	K_2CO_3	C_6H_5F	50	78	98:1:1

To investigate this reaction we chose the propargylic alcohol **1**, derived from the addition of 1-hexyne to valeraldehyde. In our previous work, we have observed that addition of 4-nitrophenol to the reaction of a propargylic alcohol with a gold catalyst promotes the formation of 3-hydroxyketone over Meyer-Schuster rearrangement to the enone.[40] However, little or no addition of the phenol to the alkyne was observed in these reactions. Our first attempts at phenol addition in this study were not successful, and mixing phenol, **1** and gold catalyst in chloroform at room temperature gave only trace amounts of the addition product **2a**, together with the corresponding enone **3** and 3-hydroxyketone **4** after 18 hours. Previously reported phenoxylation reactions of alkynes have employed a stoichiometric amount of base[28-29] to partially deprotonate the phenol and increase its nucleophilicity. To our delight, upon the addition of sodium acetate the selectivity of the reaction towards the addition product **2a** increased significantly (Table 1, entry 3). Sodium acetate proved to lead to non-selective reactions, producing significant amounts of enone side-product **3**. Optimization of the base and reaction parameters led us to identify K_2CO_3 and 50 ºC as the ideal conditions. The optimization was carried out in $CHCl_3$ but alternative non-chlorinated solvents can also be used including toluene, fluorobenzene or trifluorotoluene. We also examined a range of gold catalysts to explore the effect of ligands and counteranions[41] on the reaction. Comparable results were obtained with different non-coordinating counterions, and remarkably the reaction even proceeded effectively with a chloride counterion although the isolated yield of product was lower. A range of phosphine ligands were similarly effective in the reaction, whilst a gold complex bearing an NHC ligand was slightly less reactive. (See supporting information). As PPh_3AuNTf_2 is available commercially and gave the highest isolated yield of product, this was used in further reactions. The phenyl enol ethers were formed exclusively as the *Z*-isomer (NOE data for compound **2c**, see supporting information), confirming that the gold catalyst promotes *trans* addition of the phenol across the alkyne.

Scheme 2. Enol Ether Scope with Phenols



Once optimal conditions were identified, we set out to determine the scope of the reaction. First we focused on screening phenols using substrate **1** as the propargylic alcohol (Scheme 2). We examined the compatibility of the reaction with functionalized phenols and found that it tolerated a wide range of substituents on the phenol including electron-donating (Me, NH_2, OMe) or electron-withdrawing (NO_2, CF_3, F, Cl, Br and Ph) groups. The reaction doesn't seem to be significantly affected by sterics as it proceeded smoothly with hindered phenols containing Cl or Me at the *ortho* positions (**2f**, **2g**, **2h**

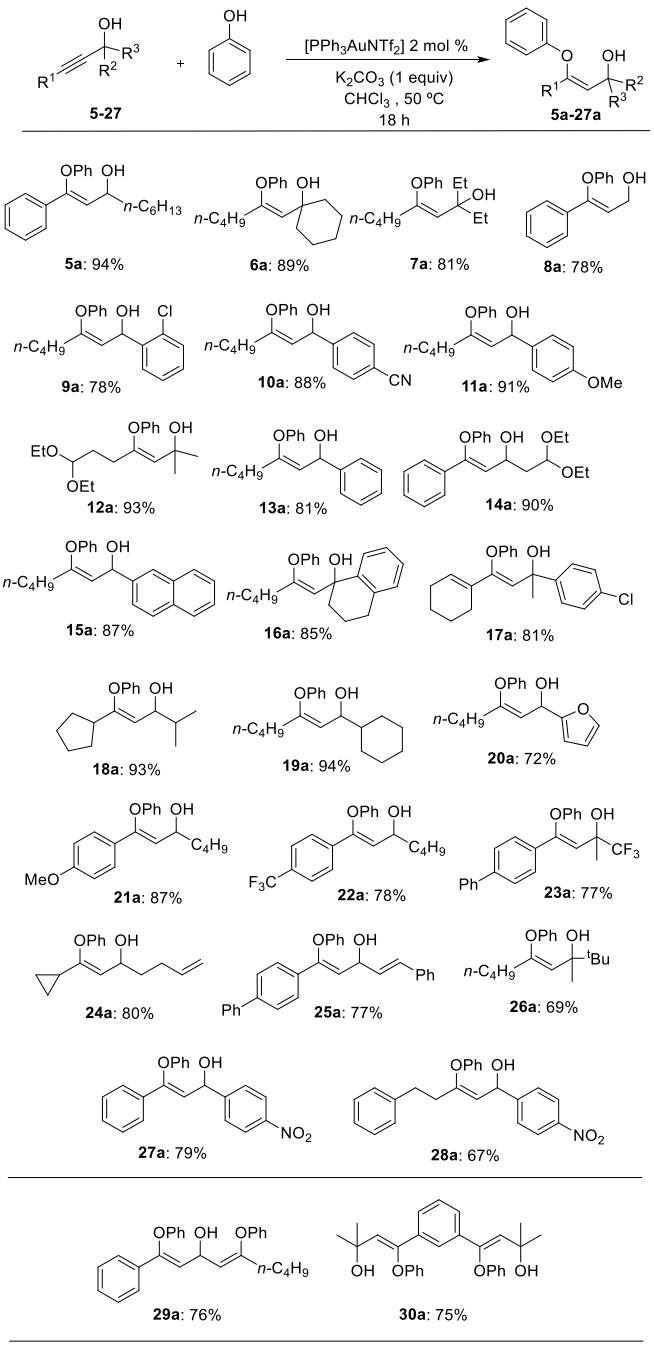
and **2k**), and even when both *ortho* positions are substituted (**2l**). To our surprise, under the reaction conditions a phenol reacts preferentially to an adjacent aniline (**2n**) which we have shown can attack propargylic alcohols under similar reaction conditions in the absence of base.[39] This result illustrates the higher reactivity of deprotonated phenols, and supports previous proposals that the gold catalyst can have a dual role in alkyne phenoxylations, activating both the alkyne and the phenol.[29,30] Gold phenolates are reported in the literature[31] and have been proposed as the nucleophilic species which attacks the electrophilic gold-alkyne complex.[29] Hexafluoroisopropanol, which has a comparable acidity to phenol, can also undergo the reaction (**2p**), but typical alcohols (MeOH, etc) were unreactive, even with the addition of stronger bases such as *tert*-butoxides or hydrides.

After determining the tolerance of the reaction conditions to a broad range of phenols, a variety of propargylic alcohols were examined. As can be observed in Scheme 3 a broad range of propargylic alcohols can be transformed into the corresponding phenyl enol ethers. Primary (**8a**), secondary (**5a**, **14a**, **18a**, **19a**, **21a** and **22a**) and tertiary (**6a**, **7a**, **12a**, **16a** and **23a**) propargylic alcohols can be employed, including benzylic (**9a**, **10a**, **11a**, **13a**, **15a**, **17a** and **20a**) alcohols, and all smoothly undergo the addition reaction in high yield and with excellent selectivity. Aromatic rings on the alcohol can include electron-withdrawing groups (**10a**, **15a**, **17a**, **27a** or **28a**) or electron-donating groups (**11a**). Again the reaction shows tolerance of steric hindrance with substrates bearing cyclic alkylic chains (**6a**, **16a** and **17a**), isopropyl (**18a**) or *tert* butyl groups (**26a**) all giving good yields. Other functional groups such as diethyl acetals (**12a**, **14a**) furan rings (**20a**), trifluoromethyl groups (**23a**) or alkenes (**17a, 24a** and **25a**) are also well tolerated.

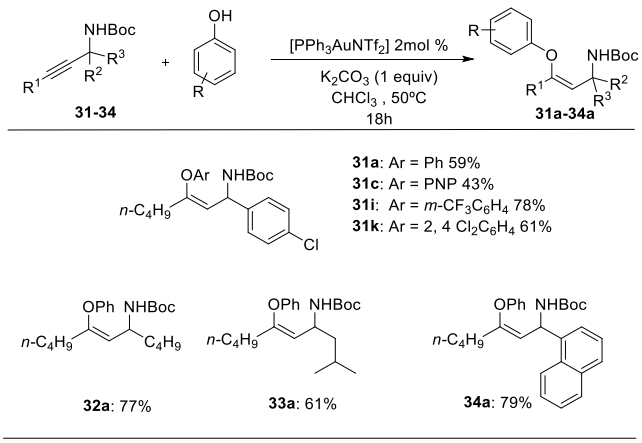
Double addition reactions are also possible using this methodology. Molecules with two phenols, such as phenolphthalein (Scheme 2, **2q**) react with two equivalents of propargylic alcohol forming the double addition product in moderate yield. Double addition reactions can also be achieved in molecules with two alkyne moieties, including two different alkynes linked to the same alcohol group (Scheme 3, **29a**), and a molecule containing two identical propargylic alcohol moieties (**30a**). These systems open up the possibility of forming molecules containing multiple enol ethers which could be of interest in coatings applications, where polyvinyl ethers are important starting materials.

Following the successful phenoxylation of propargylic alcohols, we decided to explore the reaction with analogous propargylic amines, which could also have the potential to undergo regioselective additions guided by hydrogen bonding.[42] As alkylic amines are known to bond strongly to gold centers and prevent alkyne activation, we examined propargylic amines bearing electron-withdrawing groups to reduce nitrogen nucleophilicity. Sulfonamides proved to be unreactive and underwent deprotonation in the presence of K_2CO_3 and did not react further. Gratifyingly we found that a range of Boc-protected propargylic amines[43] underwent the phenol addition reaction with complete selectivity and in moderate to good yields (Scheme 4).

Scheme 3. Scope with Respect to the Propargylic Alcohols



Scheme 4. Hydrophenoxylation of Propargylic Amines



In conclusion we report a chemo- stereo- and regioselective method for the hydrophenoxylation of propargylic alcohols/amines to yield phenyl enol ethers in high yields. The method is very robust, tolerating a significant range of electronically/sterically diverse phenols, as well as propargylic alcohols and propargylic amines with a wide array of substitution patterns and functionalities. This is the first report describing the hydrophenoxylation of propargylic alcohols and propargylic amines, and further supports the role of adjacent hydrogen bonding groups in increasing the reactivity of alkynes towards gold-catalysed addition of nucleophiles in a stereoselective and regioselective fashion.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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