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Sequential O–H/C–H Bond Insertion of Phenols Initiated by the Gold(I)-Catalyzed Cyclization of 1-Bromo-1,5-enynes

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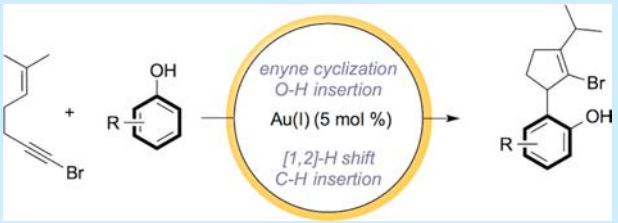
Supporting Information

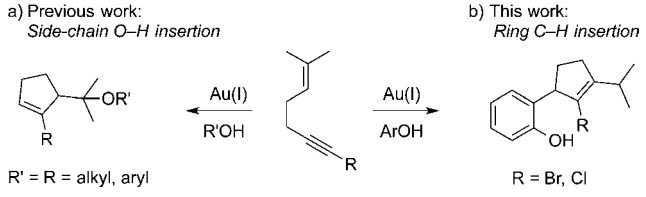
ABSTRACT: The development of a sequential O–H/C–H bond functionalization of phenols initiated by the cationic gold(I)-catalyzed cyclization of 1-bromo-1,5-enynes to produce (2-bromocyclopent-2-en-1-yl)phenols is reported. This unprecedented domino transformation efficiently proceeds under mild conditions (5 mol % of $(t\text{-Bu})_3PAuNTf_2$, CH_2Cl_2, 0–23 °C) via an intermediate aryl alkyl ether which collapses at ambient temperature to undergo a 1,2-hydride shift followed by C–H insertion of the phenol.



Reactions involving the cyclization of 1,*n*-enynes are highly valuable as they can generate molecular complexity under mild conditions in one synthetic operation.[1] Within this general reaction class, chemical processes based on the gold(I)-catalyzed cyclization of 1,5- and 1,6-enynes have emerged as a reliable and efficient strategy for the synthesis of functionalized cycloalkane derivatives.[2] Although the overall reaction mechanism of these transformations is strongly dependent upon the exact experimental conditions and reaction partners, a few intermediates were proposed to play a key-role.[3]

The way these transient structures interact with an external nucleophile has a profound influence on the reaction pathway and the substitution pattern of the products.[2c,4] Carbon (arenes, heteroarenes, 1,3-dicarbonyls)[4d] and oxygen (H_2O, ROH, RCOOH) nucleophiles[4e−h] typically attack the putative enyne–cyclization intermediates to give products carrying the former nucleophile in their side-chain (Scheme 1a, Nu = R′OH, R′ = R = alkyl, aryl).[3d]

Scheme 1. Gold(I)-Promoted Cyclization of 1,5-Enynes in the Presence of External Oxygen Nucleophiles



Herein, we describe a mild experimental procedure for the realization of an unexplored reaction pathway[4d] that is operative for 1-halo-1,5-enynes in the presence of phenols (Scheme 1b, Nu = ArOH, R = Br, Cl). This strategy constitutes a facile entry to synthetically useful (2-halocyclopent-2-en-1-yl)phenols whose underlying (cyclopentyl)phenol structural motif can be found in several biologically active molecules (Figure 1).[5]

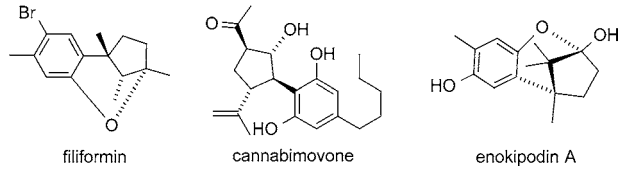


Figure 1. Selected natural products containing the (cyclopentyl)phenol structural motif.

As part of our efforts to study the gold(I)-catalyzed addition of phenols to 1-bromoalkynes for the synthesis of aryl bromoenol ethers, we discovered that Nolan's $[(IPr)Au(OH)]$ $HBF_4{\cdot}OEt_2$ catalyst[6] (5 mol %) promotes the cycloisomerization of 1-bromo-6-methylhept-5-en-1-yne **1a** followed by C–H insertion of *p*-cresol to provide **2a** (37%) and traces of the bis-alkylated phenol **3a** (Table 1, entry 1). Careful reaction monitoring revealed that both products had only formed after concentration of the yellow reaction solution at 50 °C to give the product mixture as a red-orange residue. The expected *trans*-addition of *p*-cresol across the alkyne, to give the bromo enol ether, was not observed. Excited by this unexpected result, we evaluated a series of different catalytic systems to optimize the transformation of enyne **1a** to **2a**. We found that the electronic nature of the spectator ligand (phosphine, phosphite, or *N*-heterocyclic carbene ligand) had little effect on the reactivity of the catalyst (entries 2–4).[7] However, exchange of the counterion led to a dramatic change in reaction yield (entries 1 and 5–7).[8] It was interesting to note that the catalytic system containing either the triflate or triflimide anion showed similar efficiency, whereas a sharp drop was observed for hexafluoroantimonate. Chloride failed to catalyze the transformation at all. Finally, by increasing the amount of phenol to 5 equiv, the byproduct **3a** could be further diminished to give **2a** in 76% yield (entry 8). The recently

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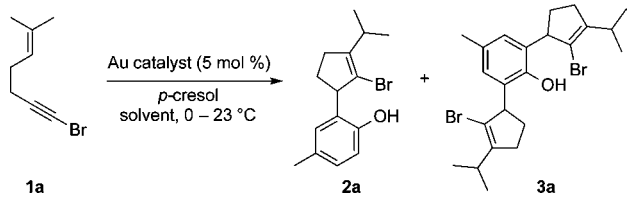
Table 1. Gold(I)-Catalyzed Cycloisomerization of 1-Bromo-1,5-enyne 1a in the Presence of *p*-Cresol. Optimization of Reaction Parameters[a]



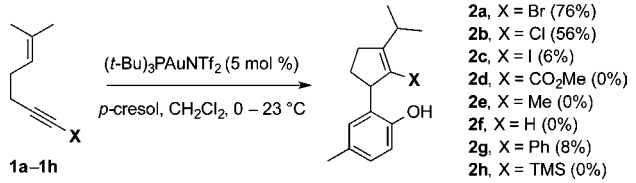
entry[a]	catalyst	solvent	yield **2a**/**3a** (%)
1	(IPr)Au(OH), HBF_4·OEt_2	toluene	37/6[b]
2	IPrAuNTf$_2$	CH_2Cl_2	62/5
3	(2,4-*t*-BuPhO)$_3$PAuNTf$_2$	CH_2Cl_2	64/4
4	(*t*-Bu)$_3$PAuNTf$_2$	CH_2Cl_2	66/4
5	(*t*-Bu)$_3$PAuCl	CH_2Cl_2	0
6	(*t*-Bu)$_3$PAuCl, $AgSbF_6$	CH_2Cl_2	39/4
7	(*t*-Bu)$_3$PAuCl, AgOTf	CH_2Cl_2	65
8	**(*t*-Bu)$_3$PAuNTf$_2$**	CH_2Cl_2	**76**[c]
9	InI_3, $AgSbF_6$	CH_2Cl_2	43/4

[a]Reaction conditions: **1** (0.25 mmol), *p*-cresol (0.38 mmol), catalyst (5 mol %), CH_2Cl_2 (1 mL), 23 °C. Yields of **2a**/**3a** were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [b]**1** (0.49 mmol), *p*-cresol (0.54 mmol), catalyst (5 mol %), toluene (1.8 mL), 50 °C. [c]*p*-Cresol (5 equiv), isolated yield. IPr = (2,6-diisopropylphenyl)-1,3-imidazol-2-ylidene; NTf_2 = bis[(trifluoromethane)sulfonyl]amide].

described yneophile diodoindium(II) cation[9] promoted this reaction as well but showed significantly lower conversion (entry 9). For a full analysis of reaction conditions, promoters, and control experiments, see Table 1 in the Supporting Information.

After having performed these initial experiments, we speculated that the 1-bromo substituent might exert a unique steric and electronic effect on this transformation. To prove this hypothesis, several substrates differing in the alkyne substitution were prepared (Scheme 2).

Scheme 2. Influence of the Alkyne Substituent on the Overall Reaction Sequence

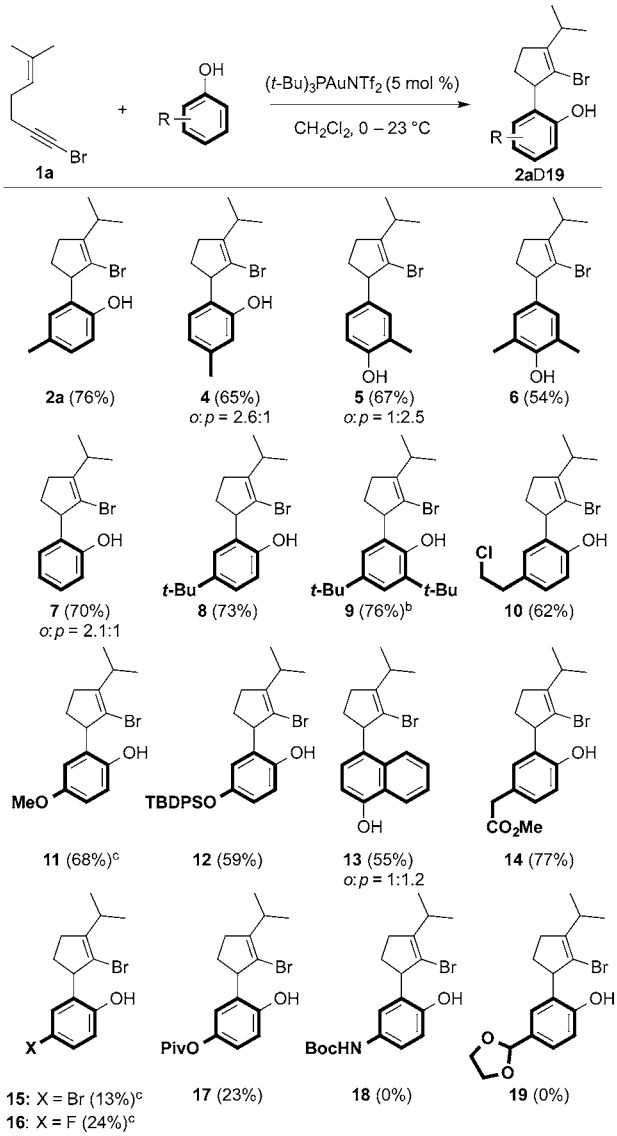


2a, X = Br (76%)
2b, X = Cl (56%)
2c, X = I (6%)
2d, X = CO_2Me (0%)
2e, X = Me (0%)
2f, X = H (0%)
2g, X = Ph (8%)
2h, X = TMS (0%)

The unique behavior of **1a** was immediately evident, as product formation for nonhalogenated substrates could only be observed for **2g** (X = Ph, 8%). Exchange for chlorine decreased the yield to 56%, whereas only a 6% yield was obtained for 1-iodoalkyne **1c**, which was unstable under the reaction conditions.[10] The reactions of **1d**–**g** led to the formation of side products (see Supporting Information for details), and for **1h** decomposition occurred.

Having established the optimized reaction conditions, the substrate scope was investigated with a panel of phenols. As shown in Scheme 3, electron-rich phenols react smoothly to give **2a** and **4**–**13** in good yields. Although exclusive chemoselectivity was observed for the C–H bond, the site-selectivity was less predictable. For **5** and **13**, the *para* position was favored, and for **4** and **7** the *ortho* products were predominantly formed. This ratio was also not altered when the catalyst (2,4-*t*-BuPhO)$_3$PAuNTf$_2$, previously reported for the gold(I)-catalyzed site-specific C–H bond functionalization of phenols,[11] was used. When *para*-substituted phenols were employed, the *ortho* C–H functionalization products could be isolated in yields up to 76%.

Scheme 3. Substrate Scope and Functional-Group Tolerance[a]



[a]Reaction conditions according to entry 8 of Table 1. Yields of the isolated product. Average of two runs. [b]*p*-Fluorophenol (1.05 equiv) was added prior to the addition of 2,4-di-*tert*-butylphenol. [c]*p*-Methoxyphenol, *p*-fluorophenol, and *p*-bromophenol were used in excess (10 equiv).

Substrates containing functional groups such as halides (**10**), alkyl ethers (**11**), silyl ethers (**12**), and esters (**14**, **17**) were also tolerated under the reaction conditions. Unfortunately, the less electron-rich compounds **15**–**17** were formed in low yields even in the presence of a large excess of phenol (10 equiv).[12] For **16**, the O–H insertion product according to the pathway shown in Scheme 1a could be isolated in 75% yield (see the Supporting Information for details). However, the low reactivity of *p*-fluorophenol in the consecutive C–H insertion step made the overall transformation inefficient.

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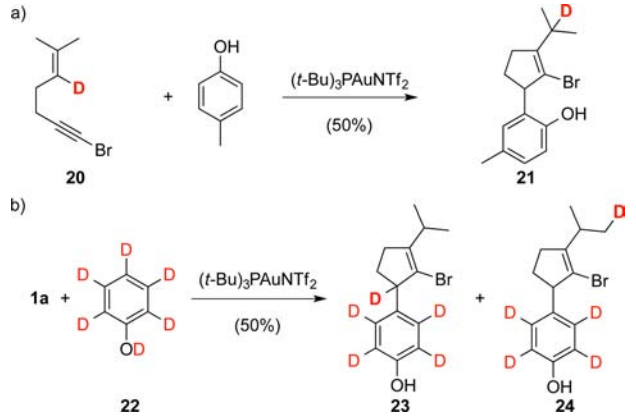
For sterically hindered phenols, which reacted sluggishly with **1a**, we could take advantage of this observation. Addition of 2,4-di-*tert*-butylphenol (5 equiv) to the aforementioned O−H insertion product in the presence of catalyst gave **9** in good yield.[13] The electron-poor substrates *p*-(trifluoromethyl)phenol, methyl *p*-hydroxybenzoate, and *p*-hydroxyacetophenone were unreactive under the reaction conditions, and for substrates containing nitrogen (**18**) or acid-labile groups (**19**), no C−H insertion could be observed.

To obtain a more detailed insight into the reaction mechanisms, the deuterium-labeled 1-bromo-1,5-enyne **20** was exposed to the standard reaction conditions (Scheme 4a).

Scheme 4. Mechanistic Investigations



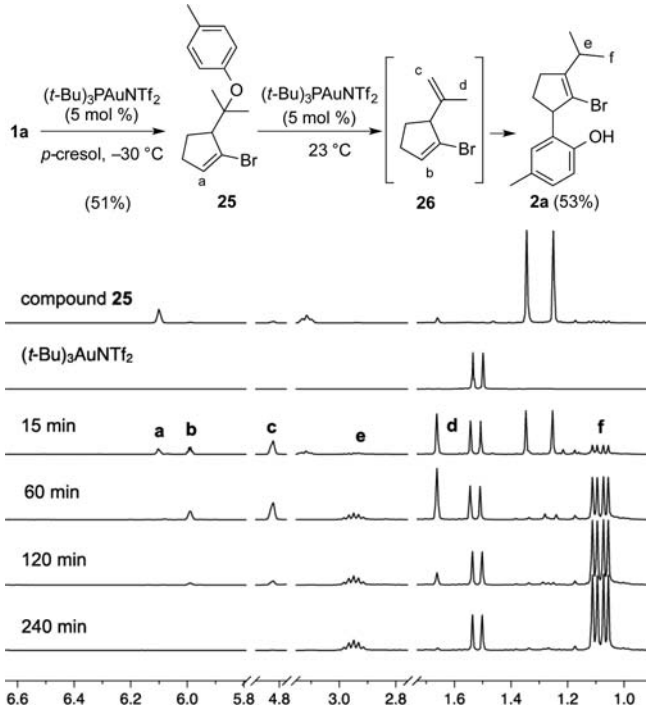
Isolation of **21** confirmed that deuterium underwent a [1,2]-shift prior to C−H insertion. The HR-MS and ^{2}H NMR analysis of the product mixture obtained from the reaction of **1a** with phenol-d_6 revealed that incorporation of deuterium has occurred as depicted for **23** and **24** (Scheme 4b). These results are consistent with a reaction pathway that includes a protodeauration step after enyne cyclization and the occurrence of a transient isopropyl cation. The latter would be in equilibrium with an isopropenyl group which, in the presence of traces of $DNTf_2$, accounts for the formation of **24**.[14]

Further evidence for the pathway leading to **24** was obtained from a time-resolved ^{1}H NMR experiment (Scheme 5). Lowering the reaction temperature to −30 °C led to the formation of aryl alkyl ether **25** as a single compound. Rapid purification by flash column chromatography on silica gel gave **25** in 51% yield. When a solution of **25** in dichloromethane-d_2 was treated with gold(I) complex (*t*-Bu)$_3$PAuNTf$_2$ at 23 °C, clean formation of **26** and **2a** could be observed within 15 min.

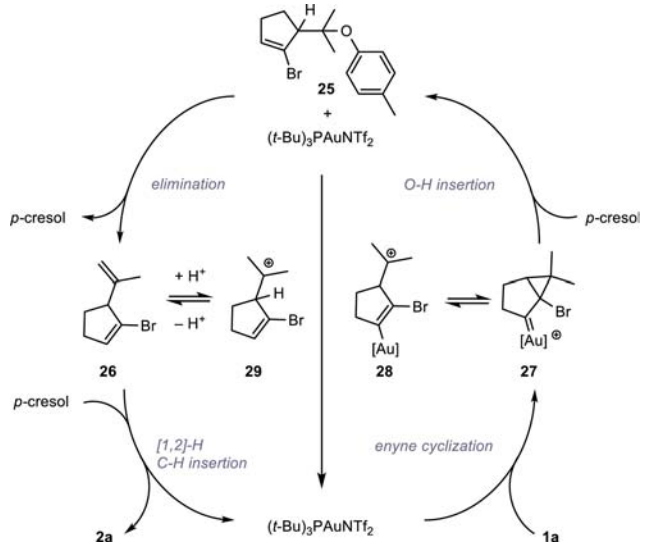
A proposed reaction mechanism that is consistent with the experimental data and literature[3,4g,h] is provided in Scheme 6. Site-selective addition of *p*-cresol to the gold-stabilized carbocation[15] **27** or **28**,[16] obtained via the enyne−cycloisomerization of **1a** produces the aryl alkyl ether **25**.[17] Monitoring the reaction via ^{1}H and ^{31}P NMR revealed that the catalyst was fully regenerated after the formation of **25** at low temperature (−30 °C). The unstable alkyl aryl ether collapses under the reactions conditions at ambient temperature with concomitant expulsion of *p*-cresol to give **26** which, in the presence of traces of acid, is in equilibrium with **29**.

The subsequent [1,2]-hydride shift of **29** should be favored due to the formation of a tertiary allylic cation (not shown) which could be further stabilized by the adjacent bromine substituent. Addition of *p*-cresol (C−H insertion step) to the allylic system

Scheme 5. Synthesis of Aryl Ether 25 and Monitoring Its Conversion to 2a via ^{1}H NMR Spectroscopy (CD_2Cl_2, 400 MHz)



Scheme 6. Proposed Catalytic Cycle



leads to **2a**. In a separate experiment, it was found that the overall rearrangement from **25** to **2a** can be promoted in the presence of catalytic amounts of $HNTf_2$ (5 mol %, 51% yield).[14,18] This explains why the overall reaction outcome is dominated by the counterion and not the ligand on the gold(I) catalyst.

The site-selectivity is controlled by the substrate structure. The unique feature that only 1-halo-1,5-enynes **1a** and **1b** efficiently undergo this transformation is noteworthy, too.[19] However, the exact role of the halogen substituent is still unclear.

In summary, we have developed a domino transformation which converts 1-halo-1,5-enynes in the presence of phenols to 2-(halocyclopent-2-en-1-yl)phenols which are valuable precursors for the elaboration of more complex structures. This

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carbon−carbon bond-forming reaction is catalyzed by cationic gold(I) complexes, proceeds via a sequential O−H/C−H functionalization of phenols, and extends the product range typically observed for simple 1,5-enynes. An application of this method for the synthesis of bioactive molecules is currently underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, compound characterization data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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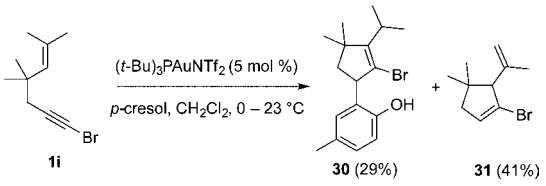

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