Organic LETTERS

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Fused Catechol Ethers from Gold(I)-Catalyzed Intramolecular Reaction of Propargyl Ethers with Acetals

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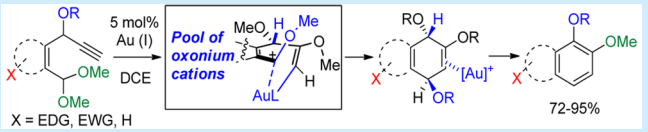
Supporting Information

ABSTRACT: Selective gold(I)-catalyzed rearrangement of aromatic methoxypropynyl acetals leads to fused catechol ethers (1,2-dialkoxynapthalenes) in excellent yields. Furthermore, this process extends to the analogous heterocyclic and aliphatic substrates. Alkyne activation triggers nucleophilic addition of the acetal oxygen that leads to an equilibrating mixture of oxonium ions of similar stability. This mixture is "kinetically self-sorted" via a highly exothermic cyclization. Selective formation of 1,2-dialkoxy naphthalenes originates from chemoselective aromatization of the cyclic intermediate via 1,4-elimination of methanol.



Alkynes have the same redox state as carbonyl compounds and, thus, offer a "back door" entry into the rich field of carbonyl chemistry. However, despite the high energy (thermodynamic "metastability") of the alkyne moiety, their π-bonds are relatively strong and unreactive.[1] The notable alkynophilicity of electron-deficient gold species is frequently used for overcoming this kinetic hurdle. In this scenario, the "carbonyl chemistry of alkynes" is unlocked via nucleophilic addition of heteroatoms that converts alkynes into enols, enamines, and their equivalents.[2] Furthermore, the combination of the carbon-rich character of alkynes and the variety of available stereoelectronic approaches to control cyclizations[3] opens attractive routes for the preparation of functionalized conjugated molecules and materials.[4]

Several Au-catalyzed cycloisomerizations of acetylene acetals reported in the literature illustrate the diversity of this chemistry (Figure 1).[5] Toste and co-workers reported synthesis of indenyl

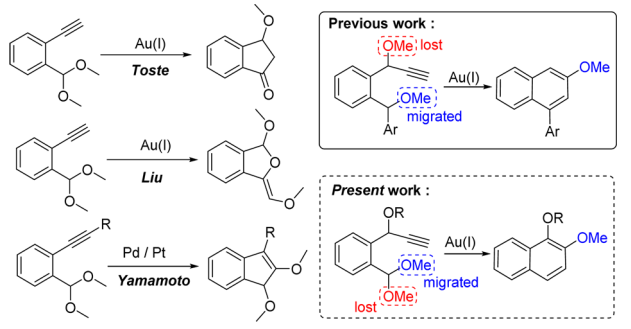


Figure 1. (Left) The earlier metal-catalyzed reactions of conjugated acetylenic acetals. (Right) Two approaches to substituted naphthalenes from propargylic ethers developed in our lab.

ethers by intramolecular carboalkoxylation of alkynes.[5a] Liu et al. disclosed a transformation of allenyl acetals into 5-alkylidene-cyclopent-2-en-1-ones.[5b] Synthesis of highly substituted piperidines has been developed by the Rhee group,[5c] whereas Zhang et al. reported carboalkoxylation with efficient chirality transfer from enantioenriched benzylic ethers and N,O-acetals.[5e,f] Pd- and Pt-catalyzed cycloisomerizations of *o*-alkynylbenzaldehyde acetals and thioacetals to functionalized indenes were described by Yamamoto.[5i] Recently, we reported Au-catalyzed cycloisomerization of aryl propargyl ethers that opened synthetic access to substituted biaryls with a functionalized naphthalene core.[6] There have been several examples of Au-assisted formation of aromatic cores.[7]

In this work, we report the synthesis of fused catechol ethers via a room-temperature gold-catalyzed cycloisomerization reaction. Fused catechols can be found in a number of biologically active natural products and pharmaceuticals.[8]

Since the known synthetic routes to 1,2-dialkoxy-substituted fused polyaromatics generally start with the preassembled 1,2-dialkoxybenzenes and concentrate on the assembly of the second ring, such approaches are limited in scope (Figure S2).[9] Herein, we describe a new strategy that will directly produce the 1,2-dialkoxy substituted ring at a cyclic scaffold via a high-yielding transformation at ambient temperature. This strategy allows efficient preparation of a variety of such compounds via a unified synthetic approach.

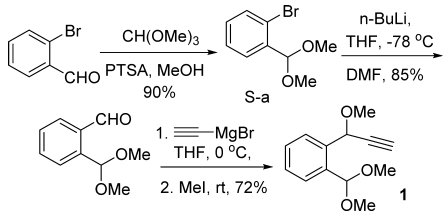
The substrates **1** were prepared in good yields from 2-bromobenzaldehydes. The first step included formation of acetals via treatment with trimethoxyorthoformate. The acetals were transformed into the requisite propagylic substrates **1** in two additional steps shown in Scheme 1. Ortho formylation was followed by reaction with ethynyl magnesium bromide with the in situ addition of methyl iodide to produce the library of *o*-methoxyprop-2-ynyl acetal benzenes in 70−85% yields. The scope of prepared substrates is shown in Table 2.

Next, we investigated the influence of Lewis acids in the transformation of *o*-methoxypropynyl acetal benzene **1a** into 1,2-dimethoxynapthalene **2a**. The screening was carried out in

Received: December 22, 2015

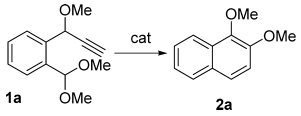
DOI: 10.1021/acs.orglett.5b03522
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of Acetylenic Acetals



dichloroethane (DCE) at room temperature using 5 mol % catalyst. All triflates, PPh_3AuOTf, LAuOTf (L = P(*t*-Bu)$_2$(*o*-biphenyl), and IPrAuOTf provided the 1,2-dimethoxynapthalene **2a** in good yields. Decrease in the nucleophilic nature of an anion (PPh_3AuX with X = SbF_6, NTf_2, Table 1, entries 4 and 5) had only a minor effect on the reaction time and yield of **2a**. Use of dichloromethane and toluene as solvents slightly decreased the yield of **2a** and increased the reaction time (entries 6 and 7, respectively). The reaction was slower when 2 mol % catalyst was used, but the yield remained acceptable (90%). The activation of the Au−Cl bond with cationic Ag salts was essential, since no reaction was observed with LAuCl alone. As expected, $AgNTf_2$ was inefficient if the Au salts were absent (Table 1, entries 9 and 10). PPh_3AuNTf_2 gave the best results, providing **2a** in 91% yield (entry 5). In most cases, reaction mixtures were very clean and pure products can be obtained via simple filtration through silica plug followed by evaporation of the solvent.

Table 1. Screening of Catalysts and Solvents



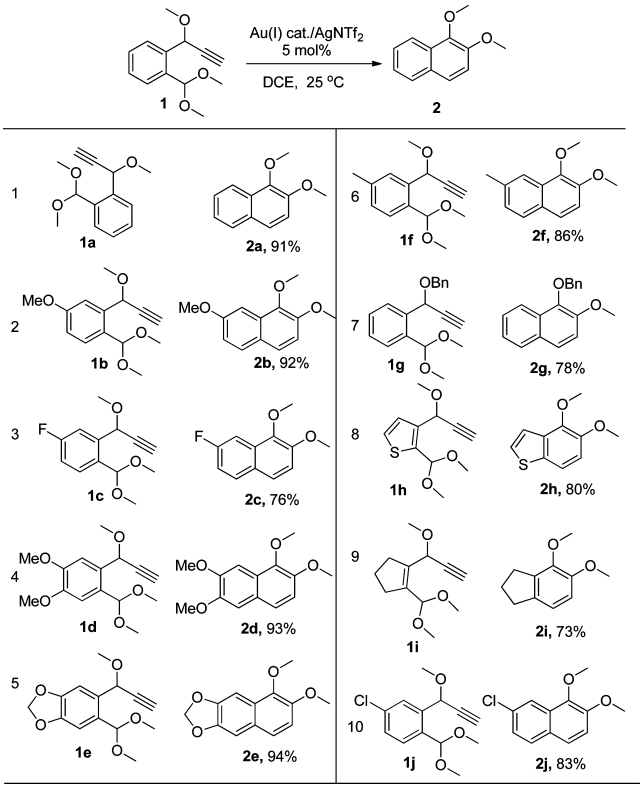
entry	catalyst (mol %)[a,b]	conditions	yield[c]
1	LAuCl/AgOTf (5)	DCE, 25 min, rt	78%
2	$PPh_3AuCl/AgOTf$ (5)	DCE, 30 min, rt	74%
3	IPrAuCl/AgOTf (5)	DCE, 25 min, rt	75%
4	$PPh_3AuCl/AgSbF_6$ (5)	DCE, 25 min, rt	84%
5	$PPh_3AuCl/AgNTf_2$ (5)	DCE, 20 min, rt	91%
6	$PPh_3AuCl/AgNTf_2$ (5)	DCM, 35 min, rt	64%
7	$PPh_3AuCl/AgNTf_2$ (5)	Toluene, 40 min, rt	85%
8	$PPh_3AuCl/AgNTf_2$ (2)	DCE, 45 min, rt	90%
9	$AgNTf_2$ (10)	DCE, 2 h, rt	nd[d]
10	PPh_3AuCl (5)	DCE, 1 h, rt	nd

[a]IPr = 1,3-bis(diisopropylphenyl)imidazole-2-ylidine, L = P(*t*-Bu)2-(*o*-biphenyl), Tf = trifluoromethane sulfonyl. [b]Substrate 0.1 M solution. [c]Yields reported after passed over small silica plug. [d]nd = no desired product (only acetal deprotection observed).

With these optimized reaction conditions in hand, we investigated the substrate scope. The gold-catalyzed cycloisomerization of additional *o*-propargyl ether acetals **1a**−**1j** under the optimized conditions (Table 2) illustrates that this process is fully compatible with alkoxy and halogen substituents at the aryl ring. The reaction also tolerates heteroaromatics (**2h**) and works well with partially saturated cyclic substrates (**2i**). These results highlight the scope and selectivity of this method.

We have also varied the alkoxy groups at the propargylic position by comparing the methoxy, ethoxy, and benzyloxy substituents. All of these alkoxy groups are compatible with this reaction cascade. Furthermore, the rearrangement of substrates

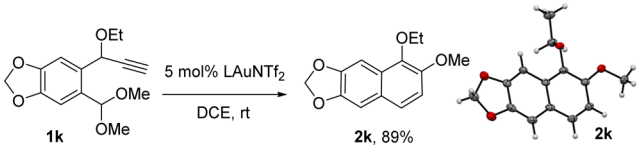
Table 2. Substrate Scope[a]



[a]Isolated yields after filtration through a small silica plug.

1g, **1k** revealed that the propargylic ether group remains a bystander whereas each of the alkoxy groups from the acetal participates in the reaction cascade; one of them migrates whereas the other one is eliminated in the aromatization process.[10] The structures of the final products were confirmed with the combination of NMR spectroscopy techniques, and, in the case of compound **2k** (Scheme 2), with X-ray crystallography.[11]

Scheme 2. Control Experiments Illustrate the OR Moiety Transposition and ORTEP Representation of the Product



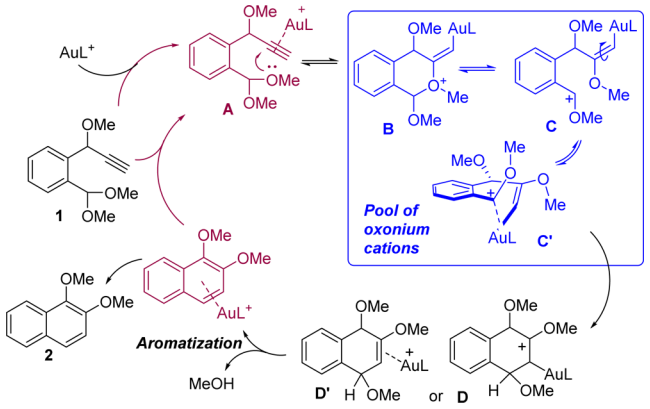
Computational Analysis. We used the hybrid PBE0[12] DFT functional, reported to give a good description of gold complexes.[13] The 6-311+G(d,p) Gaussian basis set was employed for C, P, O, and H atoms, while the Def2-TZVP[14] basis set, including Effective Core Potential (ECP), was used for Au atoms. Further details are provided in the Supporting Information (SI).

The intramolecular nucleophilic addition of the acetal at the activated Au−alkyne complex leads to the regioselective transformation of the alkyne into an activated enol ether/oxonium intermediate **B**. According to our computational data, this step and the following formation of the benzylic carbocation **C** are slightly endergonic (Scheme 3).

The relatively low barriers for the intercoversion of oxonium ions of similar energies suggest that this situation can be treated

DOI: 10.1021/acs.orglett.5b03522
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Proposed Mechanism



as a "pool of equilibrating cations",[15] self-sorted via their relative reactivity. One can consider such a system as an example of Dynamic Covalent Chemistry (DCC)[16−18] in Au-catalyzed transformations. In this scenario, the system can take advantage of the "error-checking" in DCC where fast equilibration allows covalent bonds to form, break, and reform reversibly before converging on *one* of many possible products.[19]

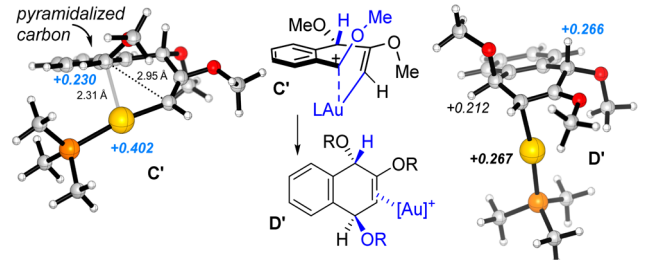
The pre-equilibration steps lead to the transfer of one of the acetal OR groups that accomplishes two goals: (1) transform the alkyne into an enol ether and (2) convert an acetal in an activated electrophile (the oxonium ion). The favorable combination of two appropriately positioned reaction partners of complementary polarities results in a fast and irreversible cyclization via the C−C bond formation. The latter step provides kinetic self-sorting to the pool of dynamically interconverting species via conversion of one of the pool components into a much more stable six-membered cyclic intermediate **D**.

The key cation that undergoes an irreversible ring closure depleting and self-sorting the pool arises from an unusual directing element, coordination of the cationic center at the Au end of the Au−C σ-bond (Scheme 4). This interaction is too strong to be accurately estimated by the NBO perturbation analysis, but this dynamically formed Au−C contact is comparable in magnitude to a chemical bond.[20] Note that the carbon at this point is both pyramidalized and depleted of most of its cationic character. In a highly exothermic and irreversible step, this species "slips" over from Au- to C-coordination via a very low (0.2 kcal/mol) transition state that provides the six-membered ring of the product (Scheme 5).

The central part of the cascade that converts the heterocyclic cation **B** into its carbocyclic isomer **D** corresponds to a Au-catalyzed version of Petasis−Ferrier rearrangement.[21] Selective elimination of methanol[22] from the cyclic carbocation yields the target 1,2-dimethoxy naphthalenes upon aromatization. This step involves selective cleavage of the more acidic C1−H bond communicating stereoelectronically with the cationic Au catalyst through the alkene π-system. The Au-catalyst transfer from the product to the alkyne moiety of a new starting material is exergonic by 2 kcal/mol, and thus, the catalytic cycle restarts.

In summary, we have developed an efficient approach for the synthesis of fused catechol ethers via Au(I)-catalyzed intramolecular reaction of propargyl ethers and acetals under mild conditions. Both alkoxy groups of acetal functionality serve a distinct mechanistic purpose: one acts as an internal nucleophile, whereas the other one enables a facile elimination pathway needed for the final aromatization step.

Scheme 4. Calculated Geometry of C′ and D′ with the NBO Charges and Key Stereodefining Groups (Shown in Blue)



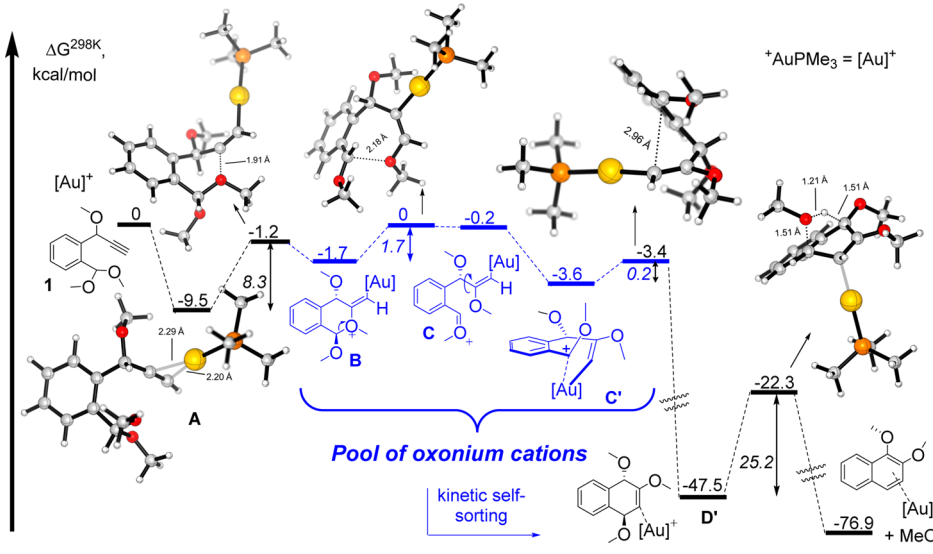
■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03522.

Full synthetic procedures, ^{1}H NMR, ^{13}C NMR, X-ray structure, computational details (PDF)

Scheme 5. Calculated Gibbs Energy Surface for the Proposed Reaction Mechanism



DOI: 10.1021/acs.orglett.5b03522
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful to the National Science Foundation (CHE-1465142) for support of this research. We are also grateful to Mr. Mark Silver for X-ray crystallographic analysis, undergraduate students C. G. Michas and Ana Phelan for their assistance in several experiments, and FSU Research Computing Center for the allocation of computational resources.

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(22) For the IRC analysis of this highly asynchronous TS, see SI.

DOI: 10.1021/acs.orglett.5b03522
Org. Lett. XXXX, XXX, XXX−XXX