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An Au-Catalyzed Cyclialkylation of Electron-Rich Arenes with Epoxides To Prepare 3-Chromanols

Zhangjie Shi and Chuan He*

Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637

Received December 25, 2003; E-mail: chuanhe@uchicago.edu

3-Chromanol is a structural motif found in many natural products and pharmaceutical agents (Figure 1A). For example, this group is the core structure of catechin, epicatechin, and tupichinols, which all bear electron-rich substituents on the phenyl ring.[1] Methods to efficiently construct this core structure in a regio- and stereocontrolled manner are limited. We have discovered a unique gold(III)-catalyzed process that can access this core structure through direct cyclialkylation of electron-rich arenes with the tethered epoxides (Figure 1B). The endo addition products were obtained exclusively, and the reaction is stereospecific.

Reacting anhydrous gold(III) chloride with aromatic groups to form arylgold(III) complexes regiospecifically at room temperature has been demonstrated a long time ago.[2] Recently, it was found that $AuCl_3$ can catalyze a 1,4-addition of electron-rich aromatic rings to methyl vinyl ketone in acetonitrile.[3] It was proposed that the gold(III) species may be engaged in a direct C−H functionalization to form arylgold(III) species in this reaction. This species then attacks methyl vinyl ketone in a manner like a Michael addition. Hydroarylation of electron-deficient alkynes was also discovered.[4] However, a different mechanism with gold(III) merely working as a Lewis acid that activates the alkyne groups was proposed. None of these two mechanisms have been confirmed through mechanistic studies. At the beginning of initiating this program, we hypothesized that if an arylgold(III) intermediate could form from an auration step, this species might be able to add to other functional groups such as epoxides in an S_N2 manner.

We tested this idea with (phenoxymethyl)oxiranes, materials that are either commercially available or can be readily synthesized.[5] To our delight, we discovered that treating these substrates with $AuCl_3$/3AgOTf (2.5 mol % based on gold) in dichloroethane yielded endo addition product 3-chromanols (Table 1). The observation of this endo addition cyclization is unique. Previously, metalation of *o*-bromo-substituted (phenoxymethyl)oxiranes with butyllithium or activated copper species at low temperature via bromine-metal exchange was reported. Subsequent cyclization of the tethered epoxide gave mostly *exo* addition five-membered ring products.[6] The reaction catalyzed by the gold described here does not require a bromo group at the ortho-position,[6a,b] nor does it need a directing group for metalation.[6c] It produces the endo addition product exclusively, which represents an excellent method for preparation of various 3-chromanol-type structures efficiently.

The reactions were completed in 4 h at 50 °C for electron-rich arene substrates. For less electron-rich substrates, higher temperature and longer reaction time were required (entries 1, 3, and 9 in Table 1). The reaction also tolerated halide substituents on the electron-rich ring, which is useful for further functionalization of the ring (entry 9 in Table 1). Gold(III) catalyst was absolutely required for the reaction. $AuCl_3$ alone gave low yields of products (10−20%). The yields increased dramatically in the presence of 3 equiv (based on gold) of AgOTf. The exact role of the silver salt is not clear. It might help to remove the chloride anion from $AuCl_3$ to generate more electrophilic gold(III) species. AgOTf alone did not catalyze these reactions under the same conditions.

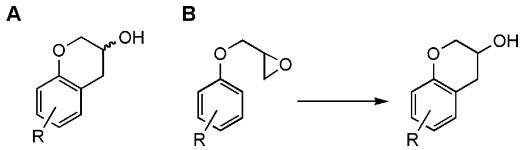
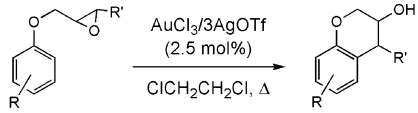
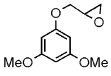
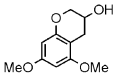
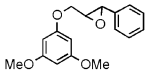
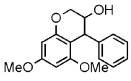
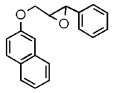
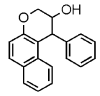
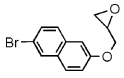
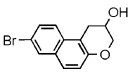


Figure 1. (A) 3-Chromanol core structure. (B) Strategy for preparing 3-chromanol via a cyclialkylation reaction.

Table 1. Gold(III)-Catalyzed Intramolecular Cyclialkylation[a]



Entry	Substrate	Product	Temperature	Yield
1			83 °C	65% (84%)[b]
2			50 °C	68%
3			83 °C	58% (87%)[b]
4			83 °C	65%[c]
5			50 °C	83%
6			50 °C	76%[d]
7			50 °C	76%
8			50 °C	85%[d]
9			83 °C	69%

[a] Reactions were typically conducted with 0.5 mmol of (phenoxymethyl)oxiranes and 2.5 mol % of $AuCl_3$/3AgOTf in 3 mL of dichloroethane. The isolated yields are reported here. Reactions were typically run for 4 h. [b] An increased catalyst loading of 5 mol % of $AuCl_3$/3AgOTf was used, and the reaction was run for 48 h (a portion of starting material was recovered, and the reaction completion percentage is reported in the parentheses). [c] The reaction was run for 48 h. [d] Exclusive trans product was obtained.

10.1021/ja031953a CCC: $27.50

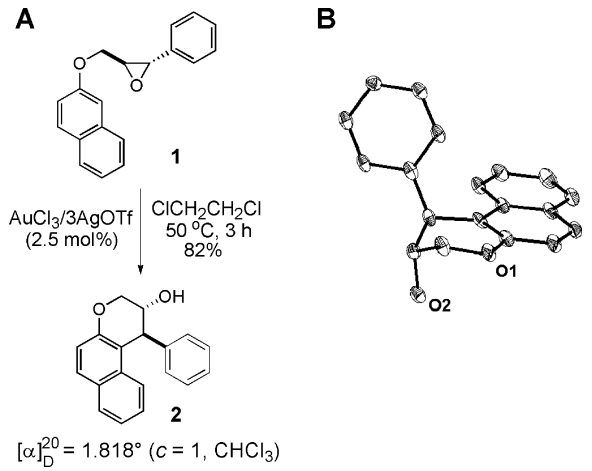


Figure 2. (A) Gold-catalyzed cyclization of **1** to form **2** stereospecifically. (B) ORTEP diagram of **2** showing the 40% probability thermal ellipsoids for all non-hydrogen atoms.

Previously, cyclialkylation of arylalkyl epoxides was investigated.[7] Among Lewis acids that were tested, it was found that 2 equiv of $SnCl_4$ can induce the cyclization of arylalkyl epoxides in CH_2Cl_2. It was proposed that this reaction goes through a Friedel−Crafts-type mechanism. We tested the same conditions with a (phenoxymethyl)oxirane substrate (entry 7 in Table 1). Only a small amount of the cyclized product was obtained. With longer reaction time (refluxing for 24 h), ∼30% of the product could be obtained with ∼30% of starting material recovered. A large excess amount of toxic tin reagents was used for this reaction. Other Lewis acids such as 20% BF_3•Et_2O and triflic acid (15% and 30%) were also tested under various conditions. No desired cyclized product was obtained in all cases. These controls showed the unique activity of gold catalyst in mediating this reaction.

The reaction showed high diastereoselectivity with trans products obtained exclusively for entries 6 and 8 in Table 1. Substrate **1** (Figure 2A) was employed as a probe to examine the stereoselectivity of the reaction. Product **2** was produced and crystallized in high yield (82% isolated yield) with inversion of configuration of the carbon atom linked to the aryl ring. The stereochemistry was confirmed by structural analysis of single crystals of **2** (Figure 2B). This result showed that the cyclization reaction is stereospecific. The stereochemistry of the starting epoxide substrate is relatively easy to control;[8] thus, this method offers a good way to access 3-chromanols stereospecifically.

We also performed an intermolecular reaction by treating trimethoxybenzene with 3 equiv of propylene oxide in the presence of 5 mol % $AuCl_3$/3AgOTf in dichloroethane at 83 °C. Product 1-(2,4,6-trimethoxyphenyl)-2-propanol was obtained in 52% isolated yield after 24 h (Figure 3). It is known that Lewis acid-catalyzed Friedel−Crafts-type alkylation of benzene with propylene oxide gave 2-phenyl-1-propanol product, presumably through generation of a partial secondary carbon cation which attacks the benzene ring.[9a] Other works with propylene oxide or styrene oxide also showed alkylation of aromatic rings with the internal carbon atom of the epoxides under typical Friedel−Crafts conditions.[9b−g] We observed the addition of the trimethoxybenzene to the less hindered

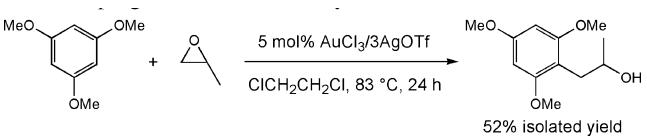


Figure 3. Intermolecular addition of trimethoxybenzene to propylene oxide afforded 1-(2,4,6-trimethoxyphenyl)-2-propanol.

epoxide primary carbon atom, which seems to be a unique feature associated with the catalytic system described here and suggests that the reaction goes through an S_N2 type mechanism.

In summary, we report a gold(III)-catalyzed cyclialkylation of electron-rich arenes with tethered epoxides. This reaction is stereospecific and can be used to synthesize 3-chromanol-type structures efficiently. The reaction could go through two different types of mechanisms: (i) an auration step followed by an attack of the arylgold(III) to the tethered epoxide in an S_N2 manner; or (ii) a concerted Lewis acid mechanism with gold(III) purely activating the epoxides group. Efforts to understand the reaction mechanism and explore synthetic utilities of the reactions reported here are in progress in our laboratory.

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Supporting Information Available: Experimental details (PDF); X-ray file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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