Direct Functionalization of Arenes by Primary Alcohol Sulfonate Esters Catalyzed by Gold(III)

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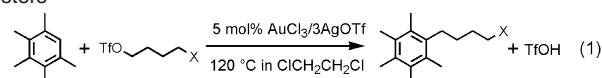Received May 26, 2004; E-mail: chuanhe@uchicago.edu

Organic transformations catalyzed by gold have been a focus of attention recently.[1] Gold(I) and gold(III) show unique activity in mediating reactions involving alkynes. In contrast, gold-catalyzed arene functionalization has been less developed. Such processes could provide efficient ways to construct C−C bonds from simple arene substrates. We and others have recently reported functionalization of arenes with gold.[1b,1h,1j,2a] Our group also discovered a gold-catalyzed alkylation of arenes by epoxides.[2b] We report here a unique reaction for functionalizing arenes with primary alcohol triflate or methanesulfonate esters and studies revealing mechanistic aspects of the reaction.

Alkylation of aromatic groups is typically achieved with Friedel−Crafts reactions.[3] Most of these reactions are run under harsh conditions with either high concentrations of acids or large amounts of strong Lewis acids, which can hardly be tolerated by many functional groups. Thus, direct functionalization of aromatic C−H under mild conditions holds great promise in synthetic chemistry.[4] Encouraged by our recent success with gold(III)-catalyzed arene functionalization,[2] we explored reactions between arenes and primary alcohol triflate and methanesulfonate esters. Such reactions could give linear products with the primary carbon linked to the arene (eq 1). We found that a reaction between 0.5 mmol of pentamethylbenzene and 1.0 mmol of *n*-butyl triflate catalyzed by 5 mol % AuCl$_3$/3AgOTf at 120 °C in dicholoethane gave a linear product in 72% isolated yield (Table 1, entry 1). No other side product was observed from the reaction. The presence of both gold and silver is required for the reaction.

With a chloro-substituted triflate ester, the linear product could still be obtained with the chloride group intact in a reasonable yield (Table 1, entry 6). This result shows the potential functional group tolerance of the reaction. Primary alcohol methanesulfonates could also be employed as the substrate. For instance, 2-phenethyl methanesulfonate, despite the presence of a benzylic carbon, reacted with pentamethylbenzene to give the linear product (Table 1, entry 7).

To our surprise, when mesitylene was employed as the arene substrate, approximately equal amounts of linear and branched products were generated (Table 1, entry 3). When *p*-xylene was tested, more branched product was observed. The branched product was produced predominantly with benzene (Table 1), but ∼5 mol % of the linear product was also observed. It appears that there are two mechanisms operating here. For electron-rich arenes, a gold(III)-mediated reaction, which seems to go through an S$_N$2 type mechanism, gives linear products. With benzene or other less-electron-rich arenes, a Friedel−Crafts pathway may take place to give the branched products. This second pathway could be catalyzed by metal ions and/or the acid generated from the auration reaction. A control reaction was run between 1.0 mmol of pentamethylbenzene and 2.0 mmol of *n*-butyl triflate in the presence of 0.15 mmol of triflic acid. The branched product (30%) together with ∼50% pentamethylbenzene was observed after 2 days. The exact mechanism that leads to the branched products needs further investigation.

Table 1. Functionalization of Arenes with Primary Sulfonate Esters[a]


Entry	Arene	Ester	Product 1, yield[b]	Product 2, yield[b]
1		OTf	90%(72%)	---
2[c]		OTf	70%	< 5%
3		OTf	40%	50%
4		OTf	10%	80%
5		OTf	5%	90%
6[d,e]		Cl-OTf	75%(54%)	---
7[d,f]		Ph-OMs	(92%)	---

[a] All reactions were conducted at 120 °C in ClCH$_2$CH$_2$Cl with 0.5 mmol of arene, 1 mmol of sulfonate ester, and 5 mol % AuCl$_3$/3Ag(OTf) for 48 h (entries 1 and 7 need only 20 h). [b] Yields were determined by GC; isolated yields are also shown for entries 1, 6, and 7 in parentheses. [c] An additional product (∼20%) with two linear alkyl groups attached to the arene was also observed. [d] No second product was observed. [e] 10 mol % catalyst and 4 equiv of the ester were used. [f] Ms stands for methanesulfonate.

To study the mechanism, we prepared a dichlorophenylgold-(III) complex[5] and treated it with 2 equiv of AgOTf and 2 equiv of *n*-butyl triflate; 30% of the linear product was obtained after 2 days. The yield of the linear product increased to 70% after 7 days of reaction.[6] *Importantly, branched product was not observed during this reaction. The phenylgold(III) species, once formed, does lead to the linear product upon reacting with n-butyl triflate, but in a slow rate.*

To further probe the reaction mechanism, we ran the reaction between pentamethylbenzene and *n*-butyl triflate with 20 mol % catalyst for 1 h. The reaction was stopped by adding saturated aqueous NaCl solution. Approximately 65% of the starting material was observed together with ∼12% of the linear product **1** on the basis of gas chromatography/mass spectrometry (GC/MS) analysis (Scheme 1 and Supporting Information Figure S2). Importantly, ∼20% of the chloro-substituted pentamethylbenzene (**2**) was also observed. This product comes from the arylgold(III) species upon treatment with aqueous NaCl solution, as implicated from previous studies.[5] We also confirmed that treating isolated arylgold(III) complexes with saturated aqueous NaCl solution gave high yields of the chloro-substituted arenes. Thus, the results indicate that

Scheme 1
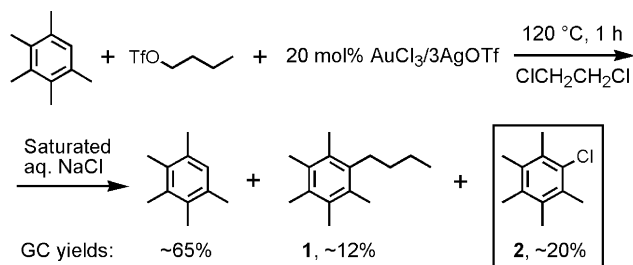
almost all gold(III) is in the arylgold(III) form during the course of the reaction.

The method described here can be used to construct cyclic structures, as shown in Table 2. Various chromans can be prepared in good to excellent yields. Benzopyranones can also be obtained in good yields from the substrates shown in entries 11–14 (Table 2). The ester bond in the product can be hydrolyzed (eq 2), and this provides a good method for accessing a group of important structures[7] with modification at the ortho-position of phenols. It should

be noted that the reaction is sensitive to steric hindrance. For instance, with a secondary methanesulfonate ester (Table 2, entry 3), the product was obtained in a very poor yield under the same reaction conditions. This result further argues against a pure Lewis acid mechanism. Previously, it was shown that scandium(III) triflate can catalyze the alkylation of aromatic compounds with methanesulfonates derived from secondary alcohols through a Friedel–Crafts process, which is quite different from the reaction described here.[8]

In summary, we report a gold(III)-catalyzed functionalization of aromatic C–H with primary alcohol triflate or methanesulfonate esters to construct C–C bonds. Linear substituted arene products were prepared. We also showed that chromans and benzopyranones can be synthesized in good yields with the use of this method. Mechanistic studies indicate the involvement of the arylgold(III) species as the reaction intermediate. This intermediate then reacts with the sulfonate ester to give the final product.

Supporting Information Available: Experimental details and Supporting Information Figures S1 and S2. This material is available free of charge via the Internet at http://pubs.acs.org.

Table 2. Gold-Catalyzed Intramolecular Cyclialkylation[a]

[a] All reactions were conducted with 0.5 mmol of substrate and 5 mol % AuCl₃/3Ag(OTf) at 120 °C in ClCH₂CH₂Cl for 48 h. [b] Isolated yields are reported. [c] GC yield, most starting material was recovered.

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(6) Isolated dichlorophenylgold(III) (0.2 mmol) was reacted with 0.4 mmol of AgOTf and 0.4 mmol of *n*-butyl triflate at 120 °C in dichloroethane. The reaction was monitored by GC/MS. The product yield was determined by GC peak intensity after comparing to that of the standard compound (Supporting Information Figure S1).
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