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Gold(I)-Catalyzed Intermolecular Addition of Phenols and Carboxylic Acids to Olefins

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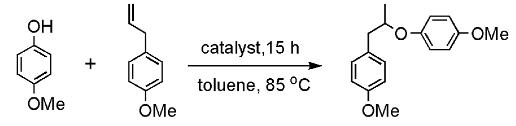
Gold-catalyzed reactions have emerged as important synthetic methods.[1] Cationic gold(I) and gold(III) show exceptional activities to activate alkynes toward addition by a variety of functional groups both intra- and intermolecularly. This chemistry is also very valuable in constructing complex molecules.[1,2] Despite the successes with alkynes, reactions involving nucleophilic addition to olefins catalyzed by gold are very limited.[3,4] Recently, an interesting gold(III)-mediated addition of β-diketone to alkenes was shown, but the role of gold(III) was thought to mainly activate the nucleophile and the alkene scope is limited to styrene and norbornylene.[4] To this date, there has not been a report of gold-catalyzed formation of carbon−heteroatom bonds through activation of inert olefins. Such reactions have been traditionally mediated by acids or stoichiometic amounts of toxic reagents.[5] Platinum,[6] ruthenium,[7] and palladium[8] have been shown to catalyze some of these reactions, but efficient intermolecular addition of various nucleophiles to inactivated olefins under mild conditions has yet to be achieved. In the case of palladium-catalyzed reactions, β-hydride elimination often occurs to afford unsaturated products.[8]

We report here that simple olefins can be activated by $Ph_3PAuOTf$.[9] Intermolecular additions of phenols and carboxylic acids to alkenes can be catalyzed by this catalyst under relatively mild conditions. A reaction between *p*-methoxyphenol (1 mmol) and 4-allylanisole (4 mmol) was used to investigate activity of different catalysts (eq 1). Triflic acid, $ZnOTf_2$, AgOTf, and $AuCl_3$/3AgOTf all failed to give the desired product in good yields (Table 1). A combination of 2 mol % of Ph_3PAuCl and AgOTf gave a good yield of the Markovnikov product (entry 5, Table 1). If AgCl precipitates were filtered after mixing the same equivalents of Ph_3PAuCl and AgOTf, the filtrate still exhibited the same catalytic activity (entry 6, Table 1). Different solvents were screened, and toluene was found to be the best solvent for this reaction.

Table 1. Effect of Catalysts on an Intermolecular Addition Reaction



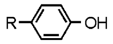
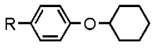
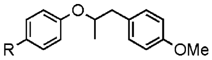
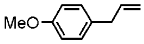
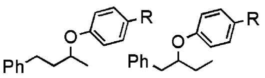
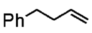
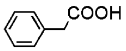
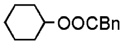
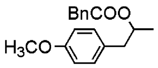
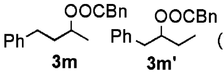
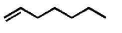
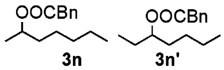
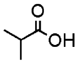
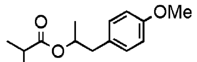
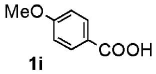
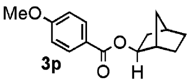
(1)

entry	catalyst	yield[a]
1	15% HOTf	0%
2	5% $ZnOTf_2$	0%
3	5% AgOTf	trace
4	5% $AuCl_3$/15% AgOTf	<5%
5	2% Ph_3PAuCl/2% AgOTf	84%
6	2% $Ph_3PAuOTf$	78%

[a] Yield based on the phenol and determined by crude ^1H NMR using an internal standard.

Both electron-rich and electron-deficient phenols serve as good substrates (Table 2). Different olefins including inactivated ones work well in this reaction. Good yields can be obtained for all cases reported. Although excess amounts of olefins were used (4 equiv), usually 2 equiv of olefins could be recovered after the reaction. Carboxylic acids can also be added to alkenes to give esters under the same reaction conditions (Table 2), but a higher catalyst loading (5 mol %) is required for the completion of the reactions. A sterically bulky acid was employed, which still afforded a reasonable yield of the product (entry 15, Table 2).

Table 2. Intermolecular Addition of Phenols and Carboxylic Acids to Olefins[h]

Entry	Nucleophile	Olefin	Product	Yield[a]
				
1	**1a** R = MeO	 **2a**	**3a** R = MeO	78%
2	**1b** R = *tert*-Butyl		**3b** R = *tert*-Butyl	70%[b]
3	**1c** R = CO_2Me		**3c** R = CO_2Me	68%
4	**1d** R = NO_2		**3d** R = NO_2	71%[c]
				
5	**1a**	 **2b**	**3e** R = MeO	58%
6	**1c**		**3f** R = CO_2Me	80%
7	**1d**		**3g** R = NO_2	81%[c]
				
8	**1a**	 **2c**	**3h** R = MeO **3h'**	71%[d]
9	**1e** R = Br		**3i** R = Br **3i'**	85% (7:1)[b]
10	**1f** R = H		**3j** R = H **3j'**	80% (15:1)[b]
11	 **1 g** BnCOOH	**2a**	**3k** 	84%[c]
12	**1g**	**2b**	**3l** 	95%[c]
13	**1g**	**2c**	 **3m** **3m'**	78% (10:1)[c,e]
14	**1g**	 **2d**	 **3n** **3n'**	75% (5.5 : 1)[c]
15	 **1h**	**2b**	 **3o**	46%[c,f]
16	 **1i**	 **2e**	 **3p**	>95%[c,g]

[a] The isolated yields are reported. [b] NMR yield with an internal standard. [c] With 5 mol % of the catalyst. [d] Isolated yield for **3h**. [e] 5 mol % $Ph_3PAuSbF_6$ was used. [f] Conversion is 55% based on the alkene. [g] 1:1 ratio of acid and nobornylene were used. [h] Reactions were conducted with 1 mmol of nucleophiles, 4 mmol of olefins, and 2 mol % (for phenols) or 5 mol % (for carboxylic acids) of Ph_3PAuCl/AgOTf in 2 mL of toluene at 85 °C.

We are exploring the scope of this gold(I)-based activity. Our data indicate that an intramolecular cyclization of a γ-hydroxyl

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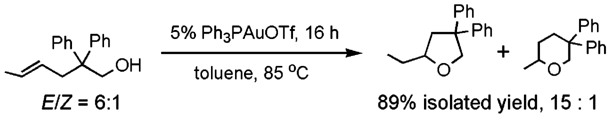
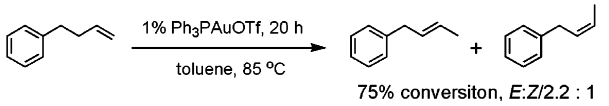
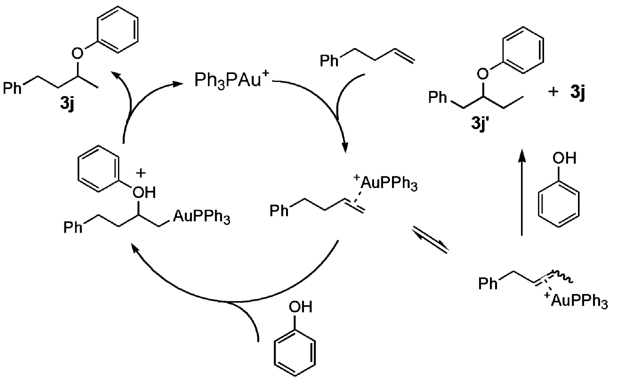
Scheme 1. Intramolecular Addition of Alcohol to Olefin



Scheme 2. Terminal Olefin Migration Catalyzed by Au(I)



Scheme 3 Proposed Catalytic Mechanism



alkene can be mediated by gold(I) under the same conditions (Scheme 1). The product yield is comparable to that reported recently with a platinum-based system.[6a] This type of intramolecular addition of a hydroxyl group to an alkene was suggested as a potential step in a gold(III)-catalyzed tandem reaction previously;[3a] however, this has never been demonstrated experimentally. Preliminary results also indicate that acidic alcohols serve as good nucleophiles to add intermolecularly into olefins.

While investigating these reactions, we discovered that migration of double bonds occurred in some cases (entries 8−10, 13, and 14 in Table 2). To confirm the observation, we took 4-phenyl-1-butene and heated it at 85 °C for 20 h in the presence of 1 mol % of Ph_3PAuOTf without any nucleophiles in toluene. Seventy-five percent of the alkene was converted to 4-phenyl-2-butene in a 2.2:1/*E*:*Z* ratio (Scheme 2). Further migration to the conjugated system was not observed; the same phenomenon was also discovered with a ruthenium-based system.[10]

The reaction mechanism is proposed in Scheme 3. We believe the cationic gold(I) binds and activates alkene for a nucleophilic addition by the phenols or carboxylic acids,[11] a reaction similar to the Wacker process catalyzed by palladium(II).[12] A subsequent proton-transfer step affords the final product and regenerates gold(I) catalyst. The gold catalyst also promotes migration of double bonds, which gives rise to formation of small amounts of side products for some substrates (Scheme 3). The mechanism of the double bond migration mediated by gold(I) is unclear at this moment.

In summary, we report here the gold(I)-catalyzed intermolecular addition of phenols and carboxylic acids to olefins. The reaction is simple and runs under relatively mild conditions. To our knowledge, this is the first example of a gold(I)-mediated activation of inert alkenes toward nucleophilic addition. Experimental results support a proposed mechanism with the gold(I) directly activating the olefin. This study may open a new direction for alkene functionalization.

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

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