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Enhancement of Reaction Efficiency by Functionalized Alcohols on Gold(I)-Catalyzed Intermolecular Hydroalkoxylation of Unactivated Olefins

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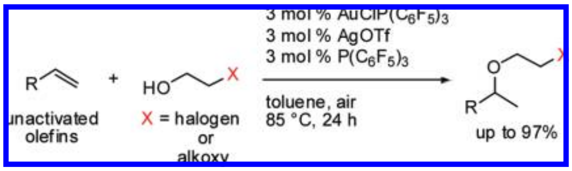
ABSTRACT



Intermolecular hydroalkoxylation of unactivated olefins catalyzed by the combination of gold(I) and electron deficient phosphine ligands has been developed. Although pairings of unactivated olefins and common aliphatic alcohols gave unsatisfactory results in gold catalyzed hydroalkoxylations, the use of alcohol substrates bearing coordination functionalities such as halogen or alkoxy groups showed great improvement of reactivity.

Nucleophilic addition reactions to carbon−carbon multiple bonds are one of the most important transformations of unsaturated organic compounds.[1] Among them, hydroalkoxylation is a quite straightforward method to access ether products from unsaturated hydrocarbons. Many methodologies have been developed by means of metal catalysts (e.g., Pd,[2] Pt,[3] and others[4]) or acid catalysts (Brønsted acid[5] or Lewis superacid[6]) to activate C−C multiple bonds. Recently Au catalysts are drawing great attention because of their moderate activity for this purpose.[7] While the Au-catalyzed hydroalkoxylation of alkynes[8] and allenes[9] is relatively well-developed, the hydroalkoxylation of olefins, regardless of

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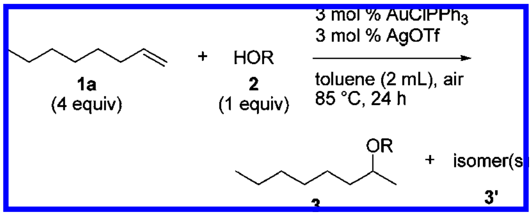
intermolecular or intramolecular fashion, is still a challenging field triggered by the first report made by He in 2005[10a] and there are only few subsequent reports.[10b,c] Here we report on enhancement of reaction efficiency of intermolecular hydroalkoxylation of olefins by employing the alcohol substrates bearing coordination functionalities such as halogen or alkoxy groups. This reaction resulted in desired ether products in moderate to excellent yields even using unactivated olefins. To the best of our knowledge, it is the first report on devising alcohol substrates to enhance reaction efficiency for intermolecular hydroalkoxylation.

The initial screening was done with $AuClPPh_3$/AgOTf catalyst system which was employed in the first gold-catalyzed intermolecular hydroalkoxylation of olefins reported by He.[10a] As expected from previous reports, a combination of unactivated olefin (**1a**) and common alcohol (**2a**) produced only trace amount of ether (Table 1, entry 1). The incorporation of chlorine atom on the terminal carbon of alcohol gave the adduct in moderate yield (Table 1, entry 2). Along with a major C-2 adduct, small amount of regioisomers were observed due to olefin isomerization ability of the gold catalyst.[10a] A similar result was obtained in the case of bromine atom, but it was more meaningful (Table 1, entry 3). An alkoxy group was revealed to have a same effect (Table 1, entries 4 and 5). These results may indicate the reactivity improvement effect was caused by the change of the acidity of alcohol substrates because of electronegativity of the incorporated atoms.

Table 1. Intermolecular Addition of Various Alcohols to 1-Octene[a]

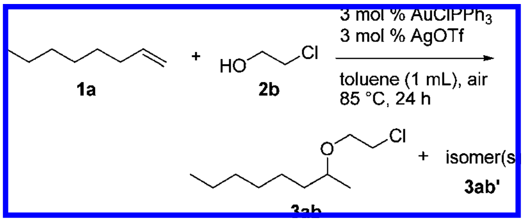


entry	alcohol	product	yield[b,c] (%)
1	CH_3CH_2OH (**2a**)	**3aa**	trace
2	$ClCH_2CH_2OH$ (**2b**)	**3ab**	21[e]
3	$BrCH_2CH_2OH$ (**2c**)	**3ac**	62[f]
4[d]	$CH_3OCH_2CH_2OH$ (**2d**)	**3ad**	27[g]
5[d]	$CH_3OCH_2CH_2OCH_2CH_2OH$ (**2e**)	**3ae**	34[h]

[a] The reactions were carried out on 1 mmol scale. [b] GC yield. [c] The 3-adduct was mainly obtained as **3′**, and only a trace amount of 4-adduct was found in each entries. [d] The reaction was carried out at 120 °C. [e] Contained 1% of **3ab′**. [f] Contained 8% of **3ac′**. [g] Contained 1% of **3ad′**. [h] Contained 1% of **3ae′**.

The optimal material ratio was sought by changing the reaction conditions (Table 2). When the reaction was conducted with equimolar of **1a** and **2b**, the yield of the product was poor (Table 2, entry 1) and a raised temperature offered only slight improvement (Table 2, entry 2). The less amount of **1a** than **2b** depressed reaction efficiency (Table 2, entry 3). On the other hand, using an excess amount of **1a** to **2b** lead increase of the yield (Table 2, entries 4−6).

Table 2. Optimization of the Reaction Conditions[a]



entry	olefin (equiv)	alcohol (equiv)	temp (°C)	yield[b,c] (%)
1	1	1	85	19[d]
2	1	1	120	26[e]
3	1	2	85	8[f]
4	2	1	85	52[g]
5	4	1	85	49[h]
6	5	1	85	54[i]

[a] The reactions were carried out on a 1 mmol scale. [b] GC yield based on alcohol except entry 3. [c] The 3-adduct was mainly obtained as **3ab′**, and only a trace amount of 4-adduct was found in each entry. [d] Contained 1% of **3ab′**. [e] Contained 1% of **3ab′**. [f] Contained a trace amount of **3ab′**. [g] Contained 9% of **3ab′**. [h] Contained 4% of **3ab′**. [i] Contained 4% of **3ab′**.

The efficiency of the reaction was greatly affected by nature of the phosphine ligand, particularly extent of electron deficiency. Compared to PPh_3, the formation of the desired ether product was increased along with lowering the electron density. Although there are few reports on the ligand effect for gold-catalyzed hydroalkoxylation of olefins, similar trends were observed on the gold-catalyzed hydroalkoxylation of allenes[9f] and platinum-catalyzed intramolecular hydroalkoxylation.[3] It is explained by the relationship between electron deficiency and Lewis acidity, and could be recognized as one evidence for the involvement of the multiple bond activation by the metal catalyst in the reaction course. Interestingly, further increase of the yield was observed by the addition of 1 equivalent of $P(C_6F_5)_3$ (Table 3, entry 4). The role of the additional phosphine is unclear, but the fact PPh_3 or $P(C_6F_5)_3$ itself did not show any catalytic activity for this reaction (data not shown) indicated some sort of contributions to stabilization of gold complex. The regioselectivity was indeed different from that of phosphine-catalyzed hydroalkoxylation.[11]

The substrate scope was examined with several unactivated olefins **1a**−**c** and alcohols **2b**−**e** (Table 4). Moderate to good yields were obtained in most of the combinations. Alcohols bearing alkoxy group **2d** and **2e** were not relatively effective than halogenated alcohols **2b** and **2c**. In some cases, changing

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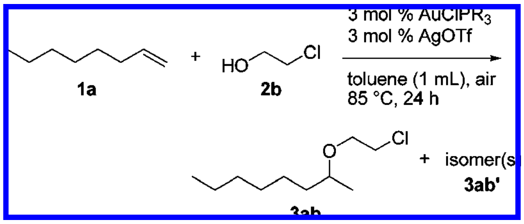
[11] Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696.

Table 3. Effect of Phosphine Ligands[a]

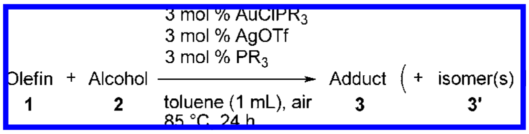


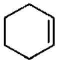
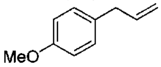
entry	gold catalyst	yield[b,c] (%)
1	$AuClPPh_3$	54[d]
2	$AuClP(4\text{-}CF_3C_6H_4)_3$	56[e]
3	$AuClP(C_6F_5)_3$	79[f]
4	$AuClP(C_6F_5)_3 + P(C_6F_5)_3$	92[g]

[a] The reactions were carried out on a 1 mmol scale. [b] GC yield. [c] The 3-adduct was mainly obtained, and only a trace amount of 4-adduct was found in each entry. [d] Contained 4% of **3ab′**. [e] Contained 3% of **3ab′**. [f] Contained 12% of **3ab′**. [g] Contained 8% of **3ab′**.

the added phosphine to electron deficient one greatly improved the yields (Table 4, entries 2,7, and 8).

Table 4. Hydroalkoxylation Reactions under the Optimized Condition Using PPh_3 or $P(C_6F_5)_3$[a]

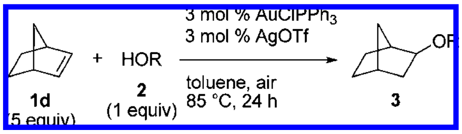


entry	olefin	alcohol	product	yield (%)[b]	
				R = Ph	R = C_6F_5
1	 **(1b)**	**2b**	**3bb**	58	74
2	 **(1c)**	**2b**	**3cb**	24	80
3	**1a**	**2c**	**3ac**	85[d]	97[e]
4	**1b**	**2c**	**3bc**	68	66
5	**1c**	**2c**	**3cc**	46	71
6[c]	**1a**	**2d**	**3ad**	52[f]	66[g]
7[c]	**1b**	**2d**	**3bd**	26	68
8	**1c**	**2d**	**3cd**	18	84
9[c]	**1a**	**2e**	**3ae**	34[h]	9[i]
10[c]	**1b**	**2e**	**3be**	50	31
11	**1c**	**2e**	**3ce**	11	51

[a] The reactions were carried out on a 1 mmol scale. [b] GC yield. [c] The reaction was carried out at 120 °C. [d] Contained 21% of **3ac′**. [e] Contained 17% of **3ac′**. [f] Contained 2% of **3ad′**. [g] Contained 6% of **3ad′**. [h] Contained 1% of **3ae′**. [i] Contained trace amount of **3ae′**.

Norbornene (**1d**) has a reactive double bond due to its rigid bicyclostructure. As expected, all reactions conducted with **1d** and several alcohols gave excellent yields (Table 5). Nucleophilic additions to norbornenes tend to produce *exo* adduct, this trend was also observed in the case of the gold-catalyzed hydroalkoxylation. Stereochemistry of the products was determined by comparison of ^1H NMR chemical shift of C-1 proton between the alcohol adducts and reported or synthesized norborneol derivatives (see Supporting Information for detailed stereochemistry determination).

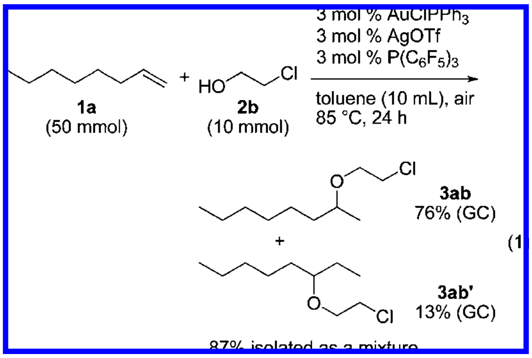
Table 5. Hydroalkoxylation Reactions of Norbornene[a]



entry	alcohol	product	yield[b] (%)
1	$ClCH_2CH_2OH$ (**2b**)	**3db**	92
2	$CH_3OCH_2CH_2OH$ (**2d**)	**3dd**	93
3	$ClCH_2CH_2CH_2OH$ (**2f**)	**3df**	97
4	$CH_3OCH_2CH_2CH_2OH$ (**2g**)	**3dg**	92

[a] The reactions were carried out on a 1 mmol scale. [b] Isolated yield.

A large scale reaction was attempted with 10 mmol of alcohol (**2b**) and 50 mmol of olefin (**1a**) (ten times larger than other entries) under the same condition. As shown in eq 1, 76% of major and 13% of minor adducts were found on GC analysis, and 87% of the products were isolated as a mixture of isomers. Though the product ratio was slightly changed, it was revealed this catalyst system was practical even for large scale reaction.



The detailed reaction mechanism is still unclear, but some experimental results lead to several presumptions. The reaction conducted under the condition of Table 1 with 1-octene (**1a**) and 2,2,2-trifluoroethanol, having less coordinating fluorine atoms than chlorine or bromine atom, proceeded in slightly lower yield than Cl or Br case (*ca.* 8% for F_3 vs 20% for Cl, 54% for Br). This result may indicate coordinating functionalities were actually playing different

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(12) (a) Gimeno, M. C.; Laguna, A. *Chem. Rev.* **1997**, *97*, 511. (b) Carvajal, M. A.; Novoa, J. J.; Alvarez, S. *J. Am. Chem. Soc.* **2004**, *126*, 1465.

role from induction of chelate effect. Indeed it is generally believed Au(I) takes a linear two-coordination mode,[12] so the intermediate is hard to be stabilized by chelation with 2-functionalized ethanols. However it does not mean to negate a formation of four coordinated Au(I) intermediate since Au(I) is able to take three- or four-coordination modes under several situation.[12,13] The other possibility may be explained by acidity of the hydroxyl group. The functionalized alcohols used in this study have acidities as pK_a around 14−15[14] because of electron-withdrawing nature of substituents. On the other hand both of ethanol and phenol, having more weaker ($pK_a = 16$) or stronger ($pK_a = 10$) acidity, gave only trace amount of the ether products. The moderate acidity might be necessary to proceed the reaction efficiently.

Equilibrium experiments were also performed. When a 1:1 mixture of 1-octene (**1a**) and 2-chloroethanol (**2b**) was treated with $AuClPPh_3$ and AgOTf, *ca.* 50% of the ether products and *ca.* 50% of octenes (presumably formed by isomerization[10a] (Table S1) and/or addition−elimination process) were found by GC analysis at the reaction period of 6 days, and this ratio did not practically change up to 8 days (Table S2). A reversal pathway was also investigated with **3ab** under the same condition and a similar product ratio was obtained at the time of 7 days (Table S3). On the other hand, similar procedures using the combination of **1a** and methanol, or 2-methoxyoctane did not form any alcohol adducts or eliminated products. This result indicated there were no appropriate mechanisms for gold-catalyzed hydroalkoxylation using methanol.

In conclusion, a gold-catalyzed intermolecular hydroalkoxylation of unactivated olefins has been developed. A significant improvement of reaction efficiency was observed by employing alcohol substrates bearing coordination functionalities. In addition, the catalyst system with electron deficient phosphines were also found to effectively catalyze the objective reaction. The studies on detailed mechanism of the reaction are underway.

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

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