

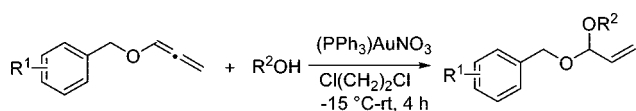
Gold-Catalyzed Hydroalkoxylation of Alkoxyallenes

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Received November 11, 2008



We report synthesis of allylic acetals via gold-catalyzed hydroalkoxylation of alkoxyallenes with alcohols containing primary and secondary alcohols in good to excellent yields under mild condition.

The hydroalkoxylation of alkoxyallenes represents one of the most effective and atom-economical methods to prepare allylic acetals which are invaluable precursors for synthesis of natural products and other potentially biologically relevant substances.¹ In 1997, Alper et al.² reported the first example of a palladium-mediated hydroalkoxylation of alkoxyallenes and later further developed by Rutjes.³ But, it is worthy to note that other transition metals have not been used in this hydroalkoxylation, besides the palladium complex. On the other hand, Au salts are power soft Lewis acids and readily activate unsaturated C—C bonds toward attacks by a variety of nucleophiles for the formation of carbon—carbon and carbon—heteroatom bonds.^{4–6} A variety of structural motifs have been efficiently accessed under exceedingly mild reaction condition. Recently, Hashmi et al. have also reported

the hydroalkoxylation of enol ether substructures.⁷ As part of our ongoing studies on metal-catalyzed atom-economical reactions, we have been interested in the use of gold for simple and highly efficient transformations.⁸ As a continuation of our studies on gold-catalyzed addition, in this paper, we wish to develop a gold(I) complex catalyzed hydroalkoxylation of alkoxyallenes to synthesize allylic acetals in mild condition.⁹

Our initial explorations focused on the reaction of 3,4-dimethoxybenzyloxyallene (**1a**) (0.2 mmol) with phenylmethanol (**2a**) (0.4 mmol) in the presence of a catalytic amount of (Ph₃P)AuNO₃¹⁰ (2 mol %) in dichloroethane (1.5 mL) at –15 °C to room temperature for 4 h, which proceeded efficiently to form allylic acetal **3a** in 67% yield (Table 1, entry 1). Efficient hydroalkoxylation was realized with significantly lower catalyst loading (Table 1, entry 2). Investigation of starting material stoichiometries revealed that a slight excess of allene (1.5–2 equiv) was necessary to drive the alcohol to full conversion (Table 1, entries 4–6).¹¹ The yields of the acetals depended upon their sensitivity to decomposition during workup. Adding a small amount of triethylamine after reaction completion allowed the acetals to be isolated in high yields (Table 1, entry 6). Different solvents were screened, and dichloroethane was found to be the best one (Table 1, entries 7–9). The reaction did not proceed in the absence of the Au catalyst (Table 1, entry 10).

To assess the scope of this process, we have examined the hydroalkoxylation of several alkoxyallenes with alcohols under the optimized condition indicated in entry 6 of Table 1. The results are summarized in Table 2. In alcohols, secondary alcohols can serve as good substrates to afford the allylic acetals (Table 2, entries 2 and 3). Benzyl alcohols with not only an electron-donating alkoxy group but also an electron-withdrawing chloro group on the

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- (11) 3,4-Dimethoxybenzyloxy allene was found to decompose to 3,4-dimethoxyphenol under the reaction condition.

TABLE 1. Au (I)-Catalyzed Hydroalkoxylation of Alkoxyallenes^a

entry	[Au] (mol %)	solvent	ratio 1a:2a	time (h)	temp (°C)	yield (%)
1	2	(CH ₂ Cl) ₂	1:2	4	-15 to rt	67
2	1	(CH ₂ Cl) ₂	1:2	4	-15 to rt	63
3	2	(CH ₂ Cl) ₂	1:2	3	-15 to 50	63
4	2	(CH ₂ Cl) ₂	1.5:1	3	-15 to rt	80
5	2	(CH ₂ Cl) ₂	2:1	3	-15 to rt	80
6	2	(CH ₂ Cl) ₂	1.5:1	3	-15 to rt	90 ^b
7	2	CH ₂ Cl ₂	1:2	4	-15 to rt	57
8	2	toluene	1:2	4	-15 to rt	52
9	2	THF	1:2	4	-15 to rt	50
10		(CH ₂ Cl) ₂	1:2	3	-15 to rt	0

^a The reactions were performed with 0.2–0.4 mmol of allene **1a**, 0.2–0.4 mmol of **2a**, and (Ph₃P)AuNO₃ in 1.5 mL of solvent; entries 1–3 and 7–10 with 0.2 mmol of **1a** and 0.4 mmol of **2a**; entries 4 and 6 with 0.3 mmol of **1a** and 0.2 mmol of **2a**; entry 5 with 0.4 mmol of **1a** and 0.2 mmol of **2a**. ^b Adding a small amount of triethylamine after reaction completion.

TABLE 2. Gold-Catalyzed Hydroalkoxylation of Allene^a

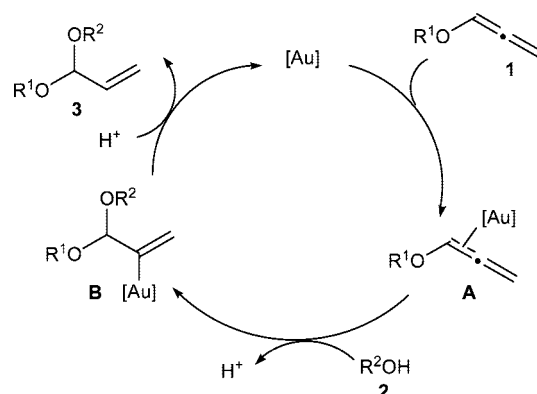
entry	1	R ¹	R ²	3	yield (%)
1	1a	3,4-(MeO) ₂ C ₆ H ₃	Me	3b	90
2	1a	3,4-(MeO) ₂ C ₆ H ₃	ⁱ Pr	3c	75
3	1a	3,4-(MeO) ₂ C ₆ H ₃	C ₆ H ₄ (Me)CH	3d	75
4	1a	3,4-(MeO) ₂ C ₆ H ₃	4-MeOC ₆ H ₄ CH ₂	3e	85
5	1a	3,4-(MeO) ₂ C ₆ H ₃	3,4-(MeO) ₂ C ₆ H ₃ CH ₂	3f	95
6	1a	3,4-(MeO) ₂ C ₆ H ₃	4-ClC ₆ H ₄ CH ₂	3g	99
7	1a	3,4-(MeO) ₂ C ₆ H ₃	(E)-C ₆ H ₅ CHCHCH ₂	3h	99
8	1b	4-MeOC ₆ H ₃	3,4-(MeO) ₂ C ₆ H ₃ CH ₂	3e	69
9	1c	C ₆ H ₅	3,4-(MeO) ₂ C ₆ H ₃ CH ₂	3a	90
10	1c	C ₆ H ₅	Bn	3i	98
11	1d	4-ClC ₆ H ₅	3,4-(MeO) ₂ C ₆ H ₃ CH ₂	3g	79
12	1d	4-ClC ₆ H ₅	4-MeOC ₆ H ₄ CH ₂	3j	60
13	1d	4-ClC ₆ H ₅	4-ClC ₆ H ₄ CH ₂	3k	99

^a All reactions were performed with allene (0.3 mmol), alcohol (0.2 mmol), and (Ph₃P)AuNO₃ (2 mol %) in dichloroethane (1.5 mL) at -15 °C to rt for 3 h.

benzene ring gave good yields of the corresponding allylic acetals (Table 2, entries 4–6). Under the same reaction condition (*E*)-3-phenylprop-2-en-1-ol was also converted into the expected adduct product (Table 2, entry 7). Furthermore, allenes **1c** and **1d** bearing aromatic groups of various electron density also worked well and reacted with alcohols to afford products with good yields (Table 2, entries 8–13).

The proposed mechanism of the gold-catalyzed hydroalkoxylation of alkoxyallenes is shown in Scheme 1. The gold cation coordinated with the more electron-rich oxygen-substituted double bond of allene to form an Au- π -alkyne complex **A**. The alcohol as the nucleophile attacks to the gold cation-chelated C=C bond to form a vinylgold species **B**. Then, the organogold intermediate **B** liberates the adducts **3** and the gold catalyst by protodemetalation. In summary, we have developed gold-catalyzed hydroalkoxylation of alkoxyallenes with different alcohols to provide allylic acetals. This reaction took place under mild conditions with good yields and may be used in the synthesis of strongly functionalized building blocks, potentially biologically active substances, and natural products.

SCHEME 1. Proposed Mechanism for Hydroalkoxylation of Alkoxyallene



Experimental Section

General Procedure. To a reactor containing allene (0.3 mmol), PPh₃AuNO₃ (2.1 mg, 0.004 mmol, 2 mol %), and 1,2-dichloroethane (1.5 mL) was added alcohol (0.2 mmol) at -15 °C. The mixture was then sealed and stirred at rt. After 3 h, a small amount of triethylamine was added to terminate the reaction. The solution was concentrated and the residue was purified by flash chromatography to give the pure product.

4-((1-(Benzyloxy)allyloxy)methyl)-1,2-dimethoxybenzene (3a**):** colorless oil; *R_f* 0.44 (petroleum–ethyl acetate = 5:1); ¹H NMR (500 MHz, CDCl₃) δ 7.36–7.28 (m, 5H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.86 (s, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 5.95 (ddd, *J* = 17.5, 10.5, 5.0 Hz, 1H), 5.50 (d, *J* = 17.5 Hz, 1H), 5.37 (d, *J* = 10.5 Hz, 1H), 5.12 (d, *J* = 5.0 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.61 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 149.0, 148.6, 138.1, 135.0, 130.6, 128.4, 127.7, 127.6, 120.4, 118.9, 111.3, 111.0, 100.3, 67.2, 67.2, 55.9, 55.8; IR (KBr, cm⁻¹) 2930, 1026, 939, 807; HRMS (EI) calcd for C₁₉H₂₂O₄ 314.1518, found 314.1543.

1,2-Dimethoxy-4-((1-methoxyallyloxy)methyl)benzene (3b**):** colorless oil; *R_f* 0.30 (petroleum–ethyl acetate = 5:1); ¹H NMR (500 MHz, CDCl₃) δ 6.90 (d, *J* = 8.0 Hz, 1H), 6.85 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 5.87 (ddd, *J* = 17.5, 10.5, 5.0 Hz, 1H), 5.45 (dt, *J* = 17.5, 1.5 Hz, 1H), 5.34 (dt, *J* = 10.5, 1.5 Hz, 1H), 4.93 (dt, *J* = 5.0, 1.5 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.36 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 149.0, 148.6, 134.8, 130.6, 120.4, 118.9, 111.2, 110.9, 101.5, 67.2, 55.9, 55.8, 52.7; IR (KBr, cm⁻¹) 2936, 1029, 938, 808; HRMS (EI) calcd for C₁₃H₁₈O₄ 238.1205, found 238.1209.

4-((1-Isopropoxyallyloxy)methyl)-1,2-dimethoxybenzene (3c**):** colorless oil; *R_f* 0.5 (petroleum–ethyl acetate = 5:1); ¹H NMR (500 MHz, CDCl₃) δ 6.91–6.82 (m, 3H), 5.91 (ddd, *J* = 17.0, 10.5, 5.0 Hz, 1H), 5.49 (dt, *J* = 17.0, 1.5 Hz, 1H), 5.37 (dt, *J* = 10.5, 1.5 Hz, 1H), 5.03 (dt, *J* = 5.0, 1.5 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 3.96–3.91 (m, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 1.24 (d, *J* = 6.0 Hz, 3H), 1.17 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 149.0, 148.5, 135.9, 130.9, 120.2, 118.1, 111.1, 111.0, 99.6, 68.5, 66.5, 55.9, 55.8, 23.2, 22.4; IR (KBr, cm⁻¹) 2970, 1029, 934, 806; HRMS (EI) calcd for C₁₅H₂₂O₄ 266.1518, found 266.1527.

Acknowledgement. This work was partially supported by the Natural Science Foundation of China (Nos. 20672099 and 20572094).

Supporting Information Available: Experimental procedures, compound characterization, and copies of ¹H and ¹³C NMR spectra for all isolated products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO802513A