Tetrahedron Letters 49 (2008) 4908–4911

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Gold-catalyzed intermolecular hydroalkoxylation of allenes; difference in mechanism between hydroalkoxylation and hydroamination

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ARTICLE INFO

Article history:
Received 28 April 2008
Revised 30 May 2008
Accepted 30 May 2008
Available online 5 June 2008

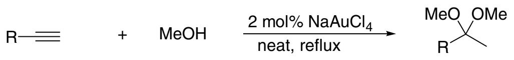
Keywords:
Alcohol
Allene
Chirality transfer
Gold catalysis
Hydroalkoxylation
Allylic ether
Silver triflate
Gold chloride

ABSTRACT

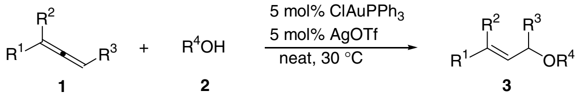
A wide range of alcohols **2** react with various allenes **1** in the presence of $ClAuPPh_3/AgOTf$ catalyst at ambient temperature without solvent to produce allylic ethers **3**. Contrary to the hydroamination, which proceeds through high chiral-face selectivity for chiral allenes to give the corresponding chiral allylic amines, transfer of chirality is not observed in the hydroalkoxylation, suggesting that the mechanism of the gold-catalyzed hydroalkoxylation is different from that of hydroamination.

Inter- or intramolecular hydroalkoxylation, the formal addition of alcohols to carbon–carbon multiple bonds, is a direct and efficient procedure for the synthesis of various ethers and oxygen-containing heterocycles.[1] The nucleophilic addition of alcohols under basic conditions has been studied widely[2] but the use of transition metal catalysts is more favorable for the hydroalkoxylation than the use of bases, primarily due to their effectiveness and the milder conditions.[3] In general, the intermolecular addition of alcohols is more difficult than the intramolecular process.[4] Accordingly, it has been considered that the use of strong Lewis acidic transition metal catalysts is needed for intermolecular hydroalkoxylation.[3]

The gold-catalyzed hydration reaction was reported in 1976.[5–7] Later, a synthetically useful protocol appeared for hydration of alkynes with $NaAuCl_4$ and cationic phosphine–gold as catalyst under almost neutral conditions to give carbonyl compounds.[8] The gold-catalyzed hydroalkoxylation, the addition of alcohols, was first reported in 1991 by Utimoto and co-workers (Eq. 1).[9] They reported the direct transformation of alkynes into dimethyl acetal by the addition of two equivalents of MeOH. In 1997, Teles et al. used $MeAuPPh_3$ and $MeSO_3H$, as precursors for the in situ generated Au cationic catalyst, in the addition of alcohols to differently substituted alkynes under acidic conditions.[8c,10] However, most of these additions could not be stopped at the stage of the first addition, that is, during formation of the dialkyl acetals. For the addition to the cumulated double bond of allenes, only one example was reported; the gold-catalyzed reaction of gaseous allene ($CH_2{=}C{=}CH_2$) with MeOH gave the corresponding dimethyl acetal, $(MeO)_2C(CH_3)_2$.[10a]



(1)



(2)

Herein, we report that the intermolecular hydroalkoxylation of allenes **1** with various alcohols **2** takes place readily without solvent using cationic gold(I) as the catalyst to give the corresponding allylic ethers **3** in high yields (Eq. 2). It should be noted that mono-addition takes place at the terminal carbon of the allenes, which is different from the addition at the central carbon observed previously,[10a] and dialkyl acetals are not produced at all. Although the gold-catalyzed intermolecular hydroamination of chiral allenes with aromatic amines took place with high chiral-face selectivity, and complete chirality transfer from chiral allenes to allylamines was realized with very high efficiency (Eq. 3),[11a] the corresponding hydroalkoxylation with alcohols proceeded without chirality transfer, resulting in the formation of racemic allylic ethers (Eq. 4). This dramatic change depending on the nucleophiles suggests that the

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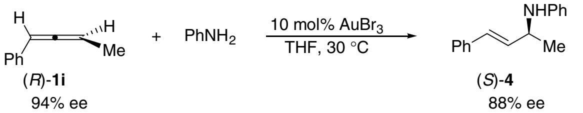
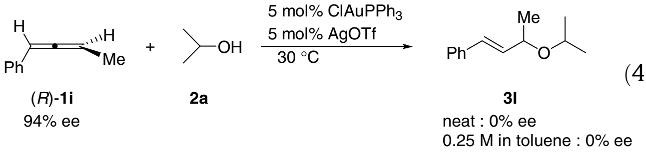
doi:10.1016/j.tetlet.2008.05.152

mechanism of the gold-catalyzed hydroalkoxylation is different from that of hydroamination.



(3)



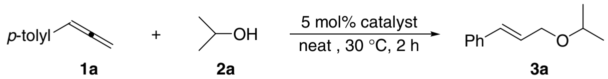
(4)

Initially, the catalytic activity of Lewis acidic transition metals was investigated in the reaction of *p*-tolylallene (**1a**) with isopropyl alcohol (**2a**) (Table 1). In the absence of a catalyst, no reaction occurred at 30 °C or even at 50 °C (entry 1). The use of gold catalysts, such as AuCl, AuI, AuCl(CO), $AuBr_3$, and $ClAuPPh_3$ was not effective at all (entries 2–4, 6, and 8). Gold(III) salts such as $AuCl_3$ and $NaAuCl_4\cdot 2H_2O$, produced **3a** in low yields (entries 5 and 7). Other catalysts, such as Ag(I), Cu(I), Cu(II), and H^+, did not promote the hydroalkoxylation at all (entries 10–13). Although very reactive gold catalysts were needed for hydroamination,[11b] the hydroalkoxylation proceeded with a very high yield using commercially available $ClAuPPh_3$ in the presence of AgOTf (entry 9). The reaction at higher temperatures gave lower yields of **3a**; 84% yield at 50 °C and 45% yield at 80 °C.

The scope and limitations of the hydroalkoxylation with various alcohols under the optimized conditions are summarized in Table 2. Primary, secondary, and tertiary alcohols proved to be good substrates for the hydroalkoxylation (entries 1–5). Benzyl alcohol **2f** and its derivative **2g** showed high reactivity affording the corresponding allylic ethers in good to high yields (entries 6 and 7). Allyl alcohol **2h** gave the corresponding product in a good yield (entry 8), however, propargyl alcohol **2i** gave a complex mixture of products (entry 9).[12] Phenol **2j** also produced a complex mixture of products (entry 10).[12,13] In the case of the diol, ethylene glycol **2k**, the reaction proceeded well to give nearly a 1:1 mixture of the products **3k** and **3k′**. Mono-hydroalkoxylation gave **3k** and further hydroalkoxylation of **3k** produced **3k′** (double-hydroalkoxylation, entry 11).

The scope and limitations of the reaction with respect to various allenes are summarized in Table 3. Aryl allenes proved to be good substrates for the hydroalkoxylation, except for the highly reactive *p*-anisyl allene,[12] which gave a complex mixture of products (entries 1–4 and 9–10). Aliphatic allenes gave the corresponding products in moderate yields (entries 5–8). We also investigated the reactivities of disubstituted allenes. The 1,3-disubstituted allene **1i** showed reactivity comparable with the monosubstituted allene **1b** (entry 9) without producing a regioisomer. The aliphatic 1,3-disubstituted allene **1k** gave the corresponding product in a high yield unlike monosubstituted aliphatic allenes (entry 11 vs entries 5–7). The 1,1-disubstituted allene **1j** gave the corresponding

Table 1
Effect of catalyst[a]

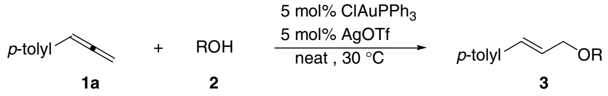


Entry	Catalyst	Yield[b] (%)
1	none	0
2	AuCl	0
3	AuI	0
4	ClAu(CO)	0
5	$AuCl_3$	20
6	$AuBr_3$	0
7	$NaAuCl_4\cdot 2H_2O$	11
8	$ClAuPPh_3$	0
9	$ClAuPPh_3$/AgOTf	97
10	AgOTf	0
11	2[CuOTf]·toluene	0
12	$Cu(OTf)_2$	0
13	TfOH	0

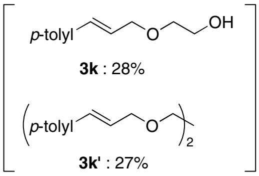
[a] To a mixture of **2a** (0.75 mmol) and catalyst (5 mol %) was added **1a** (0.50 mmol) and the mixture was stirred at 30 °C for 2 h.

[b] Yields were determined by ^1H NMR with dibromomethane as an internal standard.

Table 2
Gold-catalyzed intermolecular hydroalkoxylation of allene **1a** with alcohols **2**[a]



Entry	2	R	Time (h)	3	Yield[b] (%)
1	**2a**	*i*-Pr	2	**3a**	98
2	**2b**	Me	0.5	**3b**	98
3	**2c**	*n*-Bu	1	**3c**	98
4	**2d**	Cy	1.25	**3d**	98
5	**2e**	*t*-Bu	5	**3e**	84
6	**2f**	Bn	0.3	**3f**	69
7	**2g**	PhCH(Me)–	1	**3g**	86
8	**2h**	Allyl	1	**3h**	71
9	**2i**	Propargyl	0.5	**3i**	0[c]
10	**2j**	Ph	0.5	**3j**	0[c]
11	**2k**	$-CH_2CH_2OH$	7	**3k**/**3k′**	28[d]/27[e]



[a] To a mixture of **2** (0.75 mmol) and catalyst (5 mol %) was added **1a** (0.50 mmol) and the mixture was stirred at 30 °C.

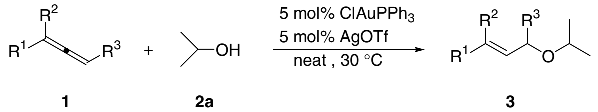
[b] Isolated yield.

[c] A complex mixture of products was formed.

[d] Monohydroalkoxylation product.

[e] Dihydroalkoxylation product.

Table 3
Gold-catalyzed intermolecular hydroalkoxylation of allenes **1** with *i*-PrOH (**2a**)[a]



Entry	1	R^1	R^2	R^3	Time (h)	3	Yield[b] (%)
1	**1a**	*p*-Tolyl	H	H	2	**3A**	98
2	**1b**	Ph	H	H	2.5	**3B**	96
3	**1c**	*p*-Anisyl	H	H	0.1	**3C**	0[c]
4	**1d**	*p*-F-C_6H_4	H	H	5	**3D**	99
5	**1e**	Bn	H	H	1	**3E**	57
6	**1f**	*n*-Oct	H	H	2.5	**3F**	62
7	**1g**	Cy	H	H	2	**3G**	42
8	**1h**	*t*-Bu	H	H	12	**3H**	38[d]
9	**1i**	Ph	H	Me	2	**3I**	93
10	**1j**	Ph	Me	H	6	**3J**	65
11	**1k**	*n*-Pent	H	*n*-Pent	2.5	**3K**	97
12	**1l**	*n*-Pent	*n*-Pent	H	6	**3L**	13

[a] To a mixture of **2a** (0.75 mmol) and catalyst (5 mol %) was added **1** (0.50 mmol) and the mixture was stirred at 30 °C.

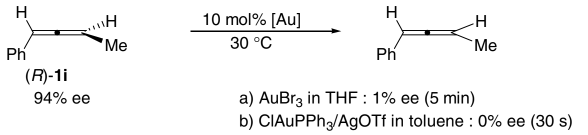
[b] Isolated yield.

[c] A complex mixture of products was formed.

[d] Yields were determined by ^1H NMR with dibromomethane as an internal standard.

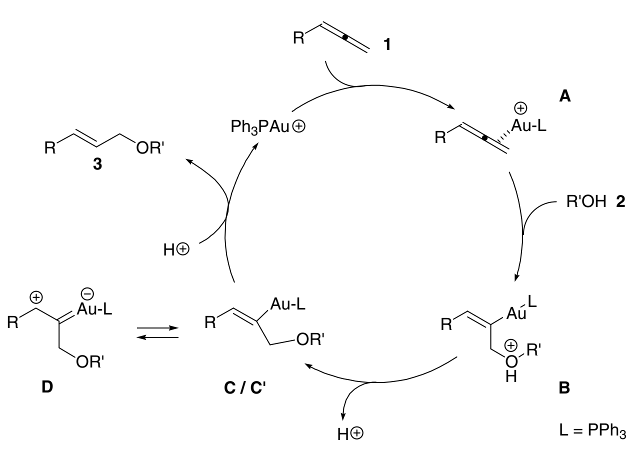
product as a single stereoisomer in moderate yield (entry 10). In our previous work on hydroamination, this allene gave the product as a stereoisomeric mixture. The structure of the product **3J** was determined as *E* by NOE experiments. The aliphatic 1,1-disubstituted allene **1l** gave the corresponding product in extremely low yield (entry 12). It should be noted that all four potential selectivity problems of substituted allenes (positional selectivity, chemoselectivity, regioselectivity, and stereoselectivity) have been solved in the reactions of **1i**–**k**, and selective formation of **3I**–**K** was realized (entries 9–11).[14]

The chirality transfer was also examined using the chiral allene **1i** (Eq. 4). Surprisingly, the allene chirality was not transferred onto the product at all. The experiment was also examined in dilute toluene, however, only a racemic product was obtained. No chirality transfer suggests that the mechanism of the hydroalkoxylation is different from that of hydroamination. In the hydroamination, a highly nucleophilic amine reacts first with a gold complex, resulting in the formation of an amine–gold complex which then reacts with the allenes.[11a] Formation of the amine–gold complex was strongly supported from the fact that, in the absence of an amine, rapid racemization of the allene occurred (Eq. 5);[11c,15] however, in the presence of an amine, highly efficient chirality transfer was accomplished. In the case of hydroalkoxylation, alcohols are in general less nucleophilic than amines and thus a gold complex must react first with the allene (*R*)-**1i** prior to the addition of alcohols. The fact that no chirality transfer took place also suggested the formation of a gold–allene complex.



(5)

A plausible mechanism, though speculative, is shown in Scheme 1 The cationic gold species was generated in situ from $ClAuPPh_3$ by halogen precipitation as the silver salt. The catalytic cycle is initiated most probably by coordination of the allene to gold to afford the intermediate **A**. The addition of an alcohol takes place through **B** to give the gold–vinyl intermediate **C**, which produces allylic ether **3** and Ph_3PAu^+ upon protonation of the carbon–metal bond. The formation of *E* allylic ethers can be explained alternatively by the generation of a π-allylic gold cation followed by alcohol attack, however, as far as we know, this type of gold species is not known. We think that the intervention of species **B** is more probable from the study of the gas-phase reaction and its theoretical investigation.[10b,16] The stereochemistry of the intermediates **B** is speculated based on the hydroamination observations; attack of gold takes place from the less hindered side of the allene double bond. One explanation for the observation of the *E*-isomers **3** is that the isomerization may take place through the intermediate **D**.



Scheme 1. Proposed mechanism for the gold-catalyzed intermolecular hydroalkoxylation of allenes **1** with alcohols **2**.

In conclusion, we have developed a gold-catalyzed intermolecular hydroalkoxylation of allenes, which proceeds smoothly at room temperature without solvent. Investigation of the chirality transfer of the hydroalkoxylation led to the important finding that an oxygen nucleophile reacts differently to a nitrogen nucleophile in the gold-catalyzed addition to allenes.[17]

General procedure for hydroalkoxylation of an allene. To a suspension of $ClAuPPh_3$ (12.4 mg, 0.025 mmol) and AgOTf (6.4 mg, 0.025 mmol) in *i*-PrOH (**2a**, 57 μl, 0.75 mmol; neat conditions) was added *p*-tolylallene (**1a**, 64.9 mg, 0.50 mmol) and the mixture was stirred at 30 °C under an Ar atmosphere. After the reaction was complete (2 h), the reaction mixture was filtered through a short silica gel pad with ether as the eluent. The product was purified by column chromatography (silica gel, pentane) to give **3a** in 98% yield (93.4 mg).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.152.

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