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Gold(III)-Catalyzed Nucleophilic Substitution of Propargylic Alcohols

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The substitution of propargylic alcohols, compared to allylic substitution, is a relatively underscored reaction. These reactions have been traditionally carried out using the Nicholas reaction, with, however, some limitations (several steps and a stoichiometric amount of $[Co_2(CO)_8]$ are necessary).[1] More recently, Toste[2] and Nishibayashi/Uemura[3] have described efficient rhenium (5% (dppm)Re(O)Cl_3, $MeNO_2$, 65 °C) and diruthenium (5% $[Cp^*RuCl(SR)]_2$, $ClCH_2CH_2Cl$, 60 °C, R_3═H) catalyzed reactions. In the past few years, gold (Au(I) and Au(III)) homogeneous catalysis has emerged as an efficient tool to activate triple bonds for the addition of various nucleophiles.[4,5] We anticipated that, through coordination to π-bond, gold catalysts may also act as propargylic alcohol-activating agents in propargylic substitutions (Scheme 1).[6]

To test this hypothesis, the reactivity of 1-phenyloct-2-yn-1-ol **1a** (R_1 = Ph, R_2 = H, R_3 = *n*-pentyl) with allyltrimethylsilane has been tested in the presence of various gold catalysts (Scheme 2, Table 1) at room temperature. Gratifyingly, the reaction proved to be efficient with various Au(III) catalysts (5%) (Table 1, entries 1−4). Best results were observed with $NaAuCl_4 \cdot 2H_2O$ (Table 1, entry 1) and allowed us to reduce the amount of catalyst to 1%, leading to **2a** in 2 h and 71% yield (Table 1, entry 9). In the presence of Au(I) catalysts (Table 1, entries 5 and 6), more disappointing results were obtained. Finally, no reaction occurred under the same reaction conditions in the presence of $PtCl_2$ and $PdCl_2(PhCN)_2$ catalysts. Toste has recently described the gold(I)-catalyzed isomerization of 1,5-enynes to bicyclo[3,1,0]hexenes.[5d] Such post-transformation of 1,5-enyne **2a** to **3a** was only observed with $HAuCl_4 \cdot 3H_2O$ (Table 1, entry 4), however, to a small extent (11%).

Starting from these initial experiments, we set out to define the scope of the Au(III)-catalyzed propargylic substitution. Variations on the substrate have then been first examined (Scheme 1, Table 2).

The reaction could be carried out with electron-rich (entries 1 and 2) and moderately electron-poor aromatic substrates (entry 3). No reaction was, however, observed using a *p*-nitro substituent (entry 4). Starting from a cinnamyl derivative (entry 5), an inseparable 2:2:1 mixture of $\alpha/\gamma E/\gamma Z$ isomers was obtained.

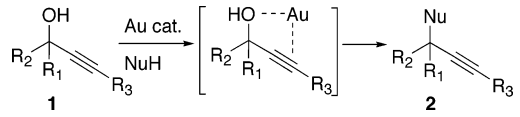
Modifications on the alkynyl part are also allowed in these reactions (entries 6−8) since silyl and aryl substituents are well tolerated, whereas once again, no reaction occurred with an electron-withdrawing group (entry 8). Finally, nonbenzylic and tertiary propargylic alcohols (Table 2, entries 9 and 10) can also act as efficient substrates in these reactions.

The Au(III)-catalyzed reaction was next tested for a diverse collection of nucleophiles, as illustrated in Table 3. Using alcohols (Table 3, entries 1−3), the corresponding propargylic ethers were obtained in good yields. In the presence of ethanol (Scheme 3 and Table 3, entries 4 and 5) and 5% of $NaAuCl_4 \cdot 2H_2O$, the rearranged unsaturated ketones[7] are obtained in good yields. However, starting from **1a** with only 1% of catalyst, the reaction can be stopped at the ether stage (**2o**) obtained in 60% yield.

In the presence of electron-rich aromatic compounds, Friedel−Crafts arylation occurs to give the arylated compounds in good yields (Table 3, entries 6−8). Finally, thiols (Table 3, entries 9−11) could also act as efficient nucleophiles to give the corresponding sulfides in modest to good yields. From a mechanistic point of view, starting from an enantiomerically enriched propargylic alcohol **1h** (96% ee),[8] the corresponding allylated compound **2h** was obtained in a racemic form. Such an experiment, consistent with previously observed pitfalls (Table 2, entries 4 and 8), suggests a mechanism through the formation of a carbonium intermediate.[9,10]

In conclusion, we have developed an efficient gold-catalyzed propargylic substitution with various C-, O-, and S-nucleophiles, where gold simultaneously acts as a Lewis acid and as a transition

Scheme 1



Scheme 2. Gold-Catalyzed Allylation of **1a**

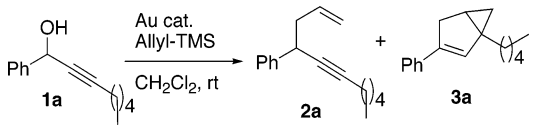


Table 1. Gold-Catalyzed Substitution of **1a** with Allyltrimethylsilane

entry	gold cat. (%)	time (H)	**2a** isolated yield (%)
1	$NaAuCl_4 \cdot 2H_2O$ (5)	12	82
2	$AuBr_3$ (5)	12	68
3	$AuCl_3$ (5)	12	65
4	$HAuCl_4 \cdot 3H_2O$ (5)	12	60[a]
5	AuCl	12	30
6	Ph_3PAuCl	12	NR
7	$PdCl_2(PhCN)_2$ (5)	12	NR
8	$PtCl_2$ (5)	12	NR
9	$NaAuCl_4 \cdot 2H_2O$ (1)	2	71

[a] Bicyclic **3a** (11%) was isolated in this reaction.

Table 2. Gold-Catalyzed Substitution of Various Propargylic Alcohols **1** with Allyltrimethylsilane Nu═Allyl[a]

entry	R_1; R_2; R_3	product	isolated yield (%)
1	2-naphthyl; H; *n*-pentyl	**2b**	83
2	(2,3-diOMe)C_6H_3; H; *n*-pentyl	**2c**	85
3	3-Br−C_6H_4; H; *n*-pentyl	**2d**	72
4	4-NO_2−C_6H_4; H; *n*-pentyl	**2e**	NR
5	cinnamyl; H; *n*-pentyl	**2f**	66[b]
6	Ph; H; TMS	**2g**	71
7	Ph; H; Ph	**2h**	97
8	Ph; H; CO_2Et	**2i**	NR
9	Ph; Me; *n*-pentyl	**2j**	33
10	Me; Me; Ph	**2k**	59

[a] Reactions carried out at room temperature, in DCM, in the presence of $NaAuCl_4 \cdot 2H_2O$ (5%). [b] An inseparable 2:2:1 mixture of α:γ(E):γ(Z) isomers is obtained.

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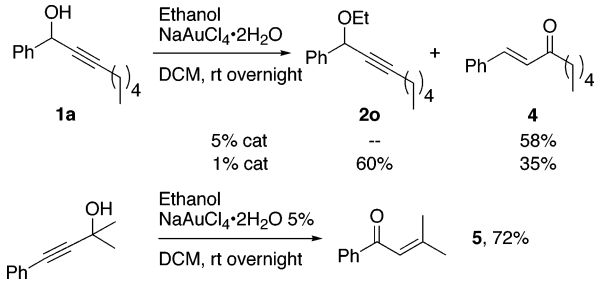
Table 3. Gold-Catalyzed Substitution of Propargylic Alcohols **1** with Various Nucleophiles[a]

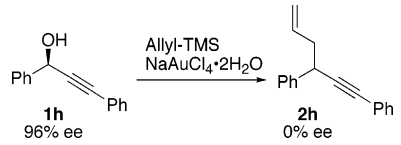
entry	R_1; R_2; R_3	Nu–H	product	isolated yield (%)
1	Ph; H; *n*-pentyl	butanol	**2l**	88
2	Ph; H; TMS	3-buten-1-ol	**2m**	75
3	Me; Me; Ph	$HO(CH_2)_3Cl$	**2n**	79
4	Ph; H; *n*-pentyl	ethanol	**2o/4**	see text Scheme 3
5	Me; Me; Ph	ethanol	**5**	72
6	Ph; H; TMS	(1,3-diOMe)C_6H_4[b]	**2p**	75
7	Ph; H; TMS	methoxybenzene[c]	**2q**	65[d]
8	Ph; H; Ph	furan	**2r**	46
9	Ph; H; *n*-pentyl	$HSCH_2COOEt$	**2s**	66
10	Ph; H; Ph	PhSH	**2t**	50
11	Ph; H; Ph	Boc(L)-CysOEt	**2u**	35[e]

[a] Reactions carried out at room temperature, in DCM, in the presence of $NaAuCl_4 \cdot 2H_2O$ (5%). [b] 5 equiv of nucleophile have been used. [c] 1.1 equiv of nucleophile have been used. [d] Obtained as a 10:1 mixture of para/others isomers. [e] Obtained as 1:1 mixture of the two diastereoisomers.

Scheme 3



Scheme 4



metal.[6c] The reaction proceeds under very mild conditions (dichloromethane, room temperature) with a commercially available catalyst, with water as the only byproduct. Further developments on this methodology are currently going on in our laboratories.

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Supporting Information Available: Experimental details and characterization for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) (a) However, no Ritter reaction could be observed in the presence of acetonitrile. (b) In the presence of electron-rich aromatic nucleophiles (Table 3, entries 6−8), an alternative mechanism first involving the direct metalation of the arene (and H^+ release) can be envisioned (see ref 5u).

(10) One referee has suggested that HCl (from the reaction of water with the gold complex) might be the actual catalyst. Although such a mechanism cannot totally be excluded in some particular cases, no reaction occurred in a model reaction with **1a** and butanol (see Table 3, entry 1) in the presence of 10% (and up to a stoichiometric amount) of HCl.

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