Gold-Catalyzed Direct Amination of Allylic Alcohols

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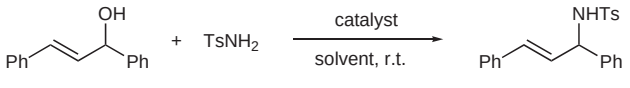
Abstract: An efficient and direct synthesis of allylic amines from allylic alcohols was developed by utilization of gold complexes as catalysts under mild reaction conditions. $AuCl_3$ proved to be a better catalyst than a cationic gold(I) complex of $AuCl(PPh_3)$/AgOTf.

Key words: gold catalysis, allylic alcohols, amination, nucleophilic substitution, synthetic methods

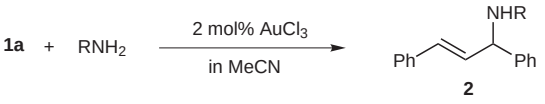
Transition-metal-catalyzed carbon–carbon bond or carbon–heteroatom bond-formation reactions which can provide a significant amplification of molecular complexity from simple building blocks occupy an important place in organic synthesis.[1] In this regard, metal-catalyzed nucleophilic substitution of allylic substrates represents a powerful method for producing useful synthetic intermediates which have been widely applied in natural product synthesis.[2] Most of the studies focused on the Pd-catalyzed allylation using allylic carboxylates,[3] carbonates,[4] phosphates,[5] halides[6] and related compounds[7] as substrates. However, there have been only limited reports on the allylic transformation utilization of allylic alcohols directly.[8–18] This is apparently due to the poor leaving ability of the hydroxy group compared to the groups mentioned above. From both an economical and an environmental point of view, conversion of allylic alcohols directly into allylation products is highly desirable. Several successful approaches for metal-catalyzed (mainly Pd) direct substitution of allylic alcohols have been developed. In most cases, additives such as $Ti(O\textit{i}\text{-}Pr)_4$,[9] Et_3B,[10] Ph_3B,[11] $SnCl_2$,[12] As_2O_3,[13] CO_2[14] etc. were employed for in situ activation of the OH group. In a recent work reported by Ozawa and Yoshifuji,[15] η^3-allyl palladium complexes bearing unique phosphorus ligands, diphosphinidenecyclobutenes, have been demonstrated to catalyze the direct allylation in the absence of activating agents. More recently, $InCl_3$[16] and Brønsted acid such as *p*-toluenesulfonic acid monohydrate[17] have emerged as useful catalysts for nucleophilic substitution of allylic alcohols. Nevertheless, the search of highly efficient catalysts for direct cleavage of the C–O bond in allylic alcohols still remains as a challenging objective.[18] On the other hand, it was reported that Au(III) salts and Au(I) complexes displayed considerable catalytic activity under moderate conditions.[19] In the course of our studies on gold-catalyzed processes[20] and zirconium-mediated allylic alcohol formation reactions,[21,22] we found that gold could efficiently catalyze nucleophilic substitutions of allylic alcohols. Herein, we would like to report gold-catalyzed[23,24] direct amination of allylic alcohols, which offers a straightforward route to substituted allylic amines.

We began our investigation with the reaction of 1,3-diphenylprop-2-en-1-ol (**1a**) and *p*-toluenesulfonamide (Scheme 1). Treatment of a mixture of **1a** and two equivalents of $TsNH_2$ with 2 mol% $AuCl_3$ in anhydrous MeCN afforded the corresponding allyl sulfonamide **2a** smoothly in 87% isolated yield after stirring 30 minutes at room temperature. Reducing the amount of $TsNH_2$ to one equivalent resulted in a lower yield (67%) of **2a** after three hours. It is worth noting that no other additive was needed for this reaction. The cationic gold(I) complex $AuCl(PPh_3)$/AgOTf also showed good catalytic activity in THF to afford 76% of **2a**, however, a prolonged reaction time (12 h) was required.



Scheme 1 Gold-catalyzed direct substitution of **1a** with $TsNH_2$

Table 1 $AuCl_3$-Catalyzed Amination of **1a** with Various Amines[26]



Entry	RNH_2	Temp (°C)	Time (h)	Product	Yield (%)[a]
1	*p*-$FC_6H_4NH_2$	50	24	**2b**	79
2	*p*-$ClC_6H_4NH_2$	50	3	**2c**	92
3	*p*-$IC_6H_4NH_2$	50	3	**2d**	84
4	*p*-$NO_2C_6H_4NH_2$	r.t.	0.5	**2e**	92
5	*p*-$MeC_6H_4NH_2$	50	24	**2f**	29

[a] Isolated yield.

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In order to test the scope of nucleophiles, we examined the substitution reactions of **1a** with a variety of amines under the optimized reaction conditions. The results are summarized in Table 1. Treatment of **1a** with *p*-$FC_6H_4NH_2$ resulted in the formation of allyl amine **2b** in 79% yield (Table 1, entry 1). Other halide functionalities, such as chloro or iodo, on the aromatic ring of the amine were also well tolerated during the reaction, affording the corresponding products **2c** and **2d** in 92% and 84% yields, respectively (entries 2 and 3).

The most reactive substrate was *p*-$NO_2C_6H_4NH_2$ containing a strong electron-withdrawing group on the aromatic ring, which provided substitution product **2e** in 92% yield within 30 minutes (entry 4). In contrast to this result, electron-donating group (Me) on the aromatic ring resulted in a lower yield (29%) of **2f**, even after stirring at 50 °C for 24 hours (entry 5). This result suggested that a facile coordination of electron-rich amine to the metal center might occur, which tended to inhibition of the catalysis.

The present method could be applied successfully to various types of cyclic and acyclic allylic alcohols to provide the allylic amines in 58–96% yields (Table 2). The reaction of 1-phenylbut-2-en-1-ol (**1b**) with $TsNH_2$ afforded the corresponding amide **2g** in 90% yields with high regioselectivity (Table 2, entry 1), in which the new C–N bond was formed selectively at the C-3 position of the starting material. Interestingly, its regioisomer **1c** gave rise to the same product in slightly lower yield of 82% (entry 2). These experimental results suggested that the same allylic cation was generated as the reactive intermediate for both allylic alcohols. When 1,5-diphenylpenta-1,4-dien-3-ol (**1e**) was employed, a stereodefined (2*E*,4*E*)-2,4-pentadienyl aryl amine product **2i** was selectively formed in 96% yield (entry 4). The trisubstituted olefins **1f** and **1g**, which were easily prepared through a zirconium-mediated alkyne–aldehyde coupling reaction,[22] also reacted with $TsNH_2$ smoothly to generate **2j** and **2k** in 66% and 80% yields, respectively, in high regio- and stereoselectivity (entries 5, 6). However, in these cases, at least 4 equivalents of the amine nucleophile were required for achieving a clean transformation. The *E*-configuration of C=C bond in these products was determined by ^1H–^1H NOESY NMR spectral analysis. The reaction also proceeded well with cyclic allylic alcohol **1h**, furnishing **2l** in 84% yield (entry 7). A phenyl-substituted tertiary alcohol **1i** gave **2m** in 89% yield as a single regioisomer (entry 8). This result indicated that the sulfonamide selectively attacked the less hindered terminus of allylic moiety. Similarly, an alkyl-substituted tertiary alcohol **1j** afforded **2n** in 75% yield with high regioselectivity (entry 9). The use of alcohols **1l**–**o** resulted in the formation of a mixture of two regioisomers in 58–76% yields (entries 11–14). The two regioisomers in products **2p** and **2r** could be easily separated by column chromatography. It should be noted that while the current catalyst is quite effective for some secondary and tertiary allylic alcohols, the substrate of non-1-en-3-ol which may form less stable carbon cations and the primary alcohols such as 2-propen-1-ol and (2*E*)-3-phenyl-2-propen-1-ol do not react with amine at all under similar reaction conditions. Although the mechanism of the reaction presented here is not clear yet, a plausible reaction pathway is considered as follows: The initial cleavage of a C–O bond in allylic alcohol, which is probably induced by the coordination of OH group to $AuCl_3$, affords an allylic cation intermediate. Subsequent nucleophilic attack of an amine give the desired allyl amines. The similar reaction mechanism was also suggested by other related studies.[25]

Table 2 $AuCl_3$-Catalyzed Direct Amination of Allylic Alcohol **1b**–**o**

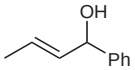
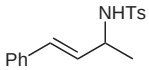
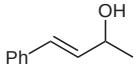
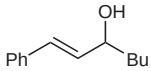
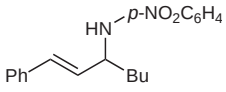
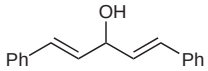
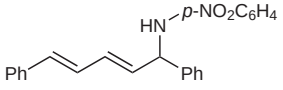
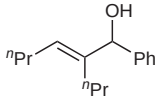
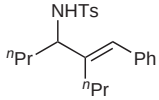
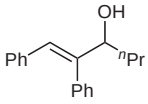
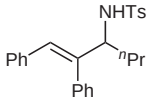
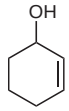
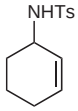
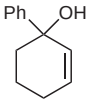
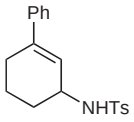
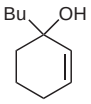
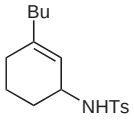
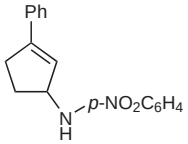
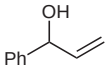
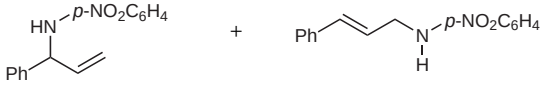
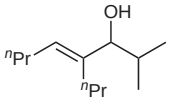
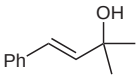
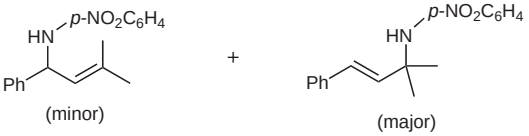
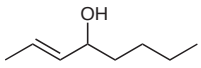
Entry	Allylic alcohol	RNH_2	Time (h)	Product	Yield (%)[a]
1	 **1b**	$TsNH_2$	1	 **2g**	90
2	 **1c**	$TsNH_2$	1	**2g**	82
3	 **1d**	*p*-$NO_2C_6H_4NH_2$	1	 **2h**	85
4	 **1e**	*p*-$NO_2C_6H_4NH_2$	0.25	 **2i**	96
5	 **1f**	$TsNH_2$	0.25	 **2j**	66[b,c]

Table 2 $AuCl_3$-Catalyzed Direct Amination of Allylic Alcohol **1b–o** (continued)

Entry	Allylic alcohol	RNH_2	Time (h)	Product	Yield (%)[a]
6	 **1g**	$TsNH_2$	2	 **2k**	80[b,c]
7	 **1h**	$TsNH_2$	1	 **2l**	84[d]
8	 **1i**	$TsNH_2$	1	 **2m**	89
9	 **1j**	$TsNH_2$	1	 **2n**	75
10	 **1k**	p-$NO_2C_6H_4NH_2$	1	 **2o**	86
11	 **1l**	p-$NO_2C_6H_4NH_2$	24	 **2p**, 1:1	72[d,e]
12	 **1m**	$TsNH_2$	2	 (minor) + (major) **2q**, 1:9	76[b,e,f]
13	 **1n**	p-$NO_2C_6H_4NH_2$	1.5	 (minor) + (major) **2r**, 1:1.2	58[e]
14	 **1o**	$TsNH_2$	1	 (major) + (minor) **2s**, 1.9:1	64[d,e,g]

[a] Isolated yield. Unless noted, all the reactions were carried out at r.t. using 2 equiv of nucleophile and 2 mol% of $AuCl_3$.
[b] 4 Equiv of $TsNH_2$ were used.
[c] The *E*-configuration of C=C bond in the product was determined by NOESY spectroscopy.
[d] The reaction was carried out at 50 °C.
[e] Combined yield.
[f] The *E*-configuration of C=C bond in the major isomer was determined by NOESY spectroscopy. Only one alkene isomer of minor isomer was obtained, the geometry of C=C bond in minor isomer was not defined.
[g] Two regioisomers were obtained; however, the geometry of C=C bond in these isomers could not be defined due to the overlapping of the signals of vinylic protons in ^1H NMR.

In summary, we have developed a gold-catalyzed direct substitution of allylic alcohols with sulfonamide or aryl amines under mild reaction conditions, which provided an efficient route to substituted allylic sulfonamides or amines. Further studies to elucidate the mechanism of this reaction and to extend the scope of synthetic utility are in progress in our laboratory.

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(26) **Typical Procedure for $AuCl_3$-Catalyzed Direct Amination of Allylic Alcohols**

A solution of $AuCl_3$ in MeCN (0.05 M) was prepared. Under N_2 atmosphere, 1,3-diphenylprop-2-en-1-ol (**1a**, 0.11 g, 0.5 mmol) and *p*-$ClC_6H_4NH_2$ (0.13 g, 1 mmol) were added to a 25 mL round-bottomed flask containing a stirring bar, and then 5 mL MeCN was added. To the mixture, 0.2 mL $AuCl_3$ (0.01 mmol) was added. The resulting solution was stirred at 50 °C until the reaction was completed as monitored by thin-layer chromatography (3 h). The solvent was removed in vacuo and the residue was purified by flash chromatography on silica gel (PE–EtOAc = 30:1) afforded product **2c** in 92% isolated yield.

N-(*E*)-(4-Chlorophenyl)-(1,3-diphenylallyl)amine (**2c**): ^{1}H NMR ($CDCl_3$, TMS): δ = 4.12 (br s, 1 H), 5.02 (d, *J* = 5.7 Hz, 1 H), 6.35 (dd, *J* = 6.0, 15.9 Hz, 1 H), 6.50–6.61 (m, 3 H), 7.04–7.09 (m, 2 H), 7.19–7.41 (m, 10 H). ^{13}C NMR ($CDCl_3$, TMS): δ = 60.65, 114.64, 122.23, 126.48, 127.13, 127.67, 127.77, 128.56, 128.87, 128.93, 130.12, 131.25, 136.40, 141.53, 145.66. HRMS (EI): *m/z* calcd for $C_{21}H_{18}ClN$: 319.1128; found: 319.1121.