Hydroamination

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Efficient Gold-Catalyzed Hydroamination of 1,3-Dienes**

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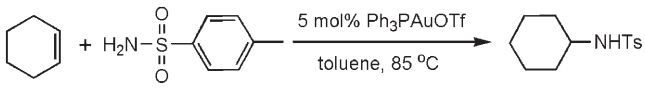
Homogenous gold catalysis has proven to be a powerful tool in organic synthesis in recent years.[1,2] Gold(I) and gold(III) are soft and hence carbophilic Lewis acids, which can activate unsaturated C–C bonds toward nucleophilic attack. Despite much success in alkyne activation, the activation of olefins by gold ions has remained relatively unexplored. Our group recently showed that phenols and carboxylic acids can undergo intermolecular addition to inert olefins in the presence of $Ph_3PAuOTf$ (Tf = trifluoromethanesulfonyl).[3] This represents a rare example of carbon–heteroatom bond formation by the gold-catalyzed activation of inert olefins. This method can be extended to the hydroamination of simple alkenes (Scheme 1).[4] These types of transformations have



Scheme 1. Hydroamination of inert olefins with $TsNH_2$. Ts = *p*-toluenesulfonyl.

also been carried out with palladium,[5] platinum,[6] ruthenium,[7] and Brønsted acids.[8,9] However, they are limited in scope, and in the case of palladium, β-hydride elimination occurs to afford unsaturated products. Owing to the ability of gold(I) to activate inert alkenes,[3,4] we envisioned that this method could potentially be used in the addition of nucleophiles to 1,3-dienes as well. 1,3-Dienes are more active than simple alkenes owing to conjugation, thus the addition reaction could be more facile and occur at moderate temperatures.

Reported herein is a gold-catalyzed hydroamination of 1,3-dienes. The resulting allylic amine[10] products are important precursors in organic synthesis and are encountered in many natural products. Transition-metal-catalyzed hydroamination of conjugated dienes is not new: a nickel-catalyzed process was reported as early as 1971.[11] Since then, there have been a few examples in which Pd^0, Rh^I, Rh^{III}, or Co^{II} is

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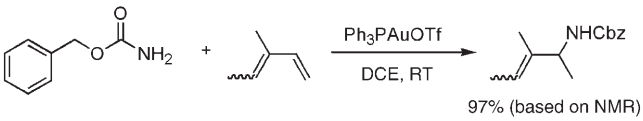
used.[12] Telomerization often occurs in the palladium- and nickel-catalyzed reactions.[13] Regioselectivity is also difficult to control, and mixtures of 1,2- and 1,4-addition products are often formed. In fact, mild and selective 1,2-hydroamination of dienes is rather rare, in particular, with a 1:1 ratio of nucleophile and diene employed to afford products in high yields. Often excess amounts of dienes must be employed to allow good conversions.

In a series of preliminary screening of nucleophiles, it was found that benzyl carbamate, $CbzNH_2$ (Cbz = benzyloxycarbonyl), was an excellent candidate for hydroamination of 1,3-dienes. The hydroamination of 3-methyl-1,3-pentadiene can be catalyzed by $Ph_3PAuOTf$ at room temperature ($CbzNH_2$/diene 1:1.2) to give the product in almost quantitative yield (by NMR spectroscopy; Scheme 2). As the Cbz group can be



Scheme 2. Hydroamination of 3-methyl-1,3-pentadiene.

readily removed from the product, this reaction offers an efficient method to prepare various allylic amines. Notably, the reaction works almost exclusively for carbamates and sulfonamides; attempts with alkyl and aromatic amines, acetamides, phthalimides, and phosphinamides gave no or only nominal conversions. On the basis of the above-mentioned hydroamination as our model reaction, a series of solvents was screened. We found that coordinating solvents such as 1,4-dioxane and nitromethane tend to shut down the reacting system, whereas noncoordinating solvents such as 1,2-dichloroethane (DCE) and chloroform seem to be ideal.

Using DCE as the solvent, we next set out to find an ideal catalyst system (Table 1). Neither Ph_3PAuCl, nor AgOTf by themselves effect the reaction (Table 1, entries 2 and 3). Other counteranions such as OTs^-, NO_3^-, and CF_3COO^- do not support the hydroamination activity, perhaps due to their binding to the gold(I) ion (Table 1). Noncoordinating anions are required, and OTf^- and ClO_4^- are the best counteranions for the reaction. Gold(III) works (Table 1, entries 14 and 15), but seems to be too active and requires a higher ($\approx$4 equiv) diene loading, perhaps due to oligomerization of the diene. Other metals tested (Table 1, entries 16–18) showed no catalytic activity at all. It is evident that gold(I) is an appropriate catalyst for the hydroamination of conjugated dienes.

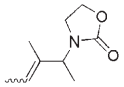
Table 2 illustrates the scope of the hydroamination. Benzyl carbamate **1b** readily adds to diene **1a** to give the product in a very good yield. Other carbamates underwent the transformation; however, the yields varied, depending on the nucleophile employed (Table 2, entries 2–5). Cyclic carbamate **3b** added less readily, and higher temperature was required. The use of 1,3-cyclohexadiene (**7a**) as the substrate also required a higher reaction temperature (Table 2, entry 7). The N-alkylation for these reactions was firmly established by comparison of the product **7c** to the known compound.

Table 1: Catalyst screening for hydroamination of 3-methyl-1,3-pentadiene.[a]

Entry	Metal salt	Silver salt	Conversion [%][b]
1	Ph_3PAuCl	AgOTf	97
2	Ph_3PAuCl		0
3		AgOTf	0
4	Ph_3PAuCl	AgOTs	0
5	Ph_3PAuCl	$AgNO_3$	0
6	Ph_3PAuCl	$AgOOCCF_3$	0
7	Ph_3PAuCl	$AgSbF_6$	60
8	Ph_3PAuCl	$AgNTf_2$	77
9	Ph_3PAuCl	$AgPF_6$	89
10	Ph_3PAuCl	$AgBF_4$	92
11	Ph_3PAuCl	$AgClO_4$	99
12	AuCl		0
13	AuCl	AgOTf	90
14	$AuCl_3$		29[c]
15	$AuCl_3$	AgOTf	89[c]
16	$Cu(OTf)_2$		0
17	$Sc(OTf)_3$		0
18	$Zn(OTf)_2$		0

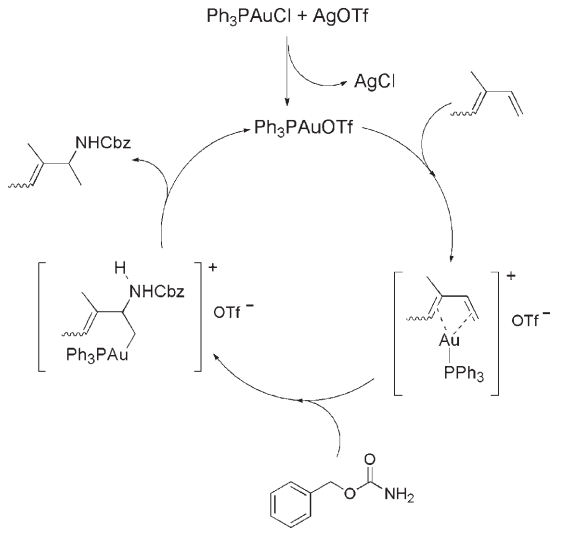
[a] Conditions: 25 °C, overnight, metal salt (5%), silver salt (5%), dichloroethane (2.0 mL), carbamate (1.0 equiv), diene (1.2 equiv). [b] Conversion determined by ^1H NMR with dibromomethane as internal standard. [c] Diene: 4.0 equiv.

Table 2: Hydroamination of dienes: reaction scope.[a]

Entry	Olefin		Nucleophile		Product		Yield [%][b]
1		**1a**	$CbzNH_2$	**1b**		**1c**	86
2		**1a**	$FmocNH_2$	**2b**		**2c**	33
3		**1a**		**3b**		**3c**	63[c]
4		**1a**	$MocNH_2$	**4b**		**4c**	77
5		**1a**	$TsNH_2$	**5b**		**5c**	81
6		**6a**		**1b**		**6c**	86
7		**7a**		**1b**		**7c**	87[c]

[a] Reactions were carried out at room temperature, under N_2, in the absence of light, overnight. Typically: diene (1.2 mmol per 1.0 mmol of substrate), $Ph_3PAuOTf$ (0.05 mmol), DCE (2 mL). [b] Yields of isolated products. [c] 50 °C. Fmoc = 9-fluorenylmethoxycarbonyl; Moc = methoxycarbonyl.

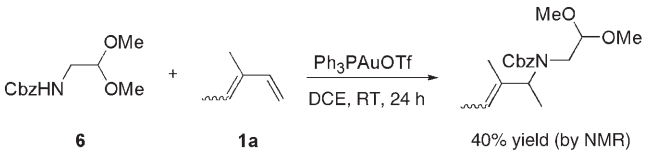
Our proposed reaction mechanism is shown in Scheme 3. $Ph_3PAuOTf$, generated by the reaction of Ph_3PAuCl with AgOTf binds to the diene, as supported by ^{31}P NMR spectroscopic studies in which the gold(I) catalyst was



Scheme 3. Proposed reaction mechanism.

monitored. Mixing $CbzNH_2$ with $Ph_3PAuOTf$ did not lead to an observable shift of the original ^{31}P NMR signal, suggesting no or a weak interaction between the nucleophile and the gold(I) catalyst. Upon addition of the diene substrate, a shift of the ^{31}P signal was observed which indicates the formation of a gold(I)–diene complex (Supporting Information). An independent ^{13}C NMR spectroscopic study also suggests the coordination of gold(I) ion to the diene, in particular, to the double bond that results in the most stable resonance form (Supporting Information).[14] After the formation of this complex, the nucleophile attacks *anti* to the gold center, as suggested by recent studies.[2,4] The resulting Au^I–C bond is then protonated to give the desired product and to regenerate the active catalyst.

This reaction also tolerates certain functional groups. For example, (2,2-dimethoxyethyl)carbamic acid benzyl ester (**6**)[15] retains its dimethyl acetal in the reaction with diene **1a**. (Scheme 4). Gold(I) catalyzes the addition, not only of



Scheme 4. Tolerance to dimethyl acetal.

carbamates and of sulfonamides, but also of alcohols to 1,3-dienes, albeit with lower efficiency (≈30–40% conversion) based on preliminary studies.

To summarize, we report a novel method for the hydroamination of 1,3-dienes in the presence of $Ph_3PAuOTf$ catalyst under mild conditions. A variety of carbamates and sulfonamides add to conjugated dienes to afford protected allylic amines in good to high yields. The use of excess diene is not necessary in this gold-mediated process. We are currently exploring the enantioselective version of the reaction, which will be reported in due time.[16]

Experimental Section

Typical procedure: Ph_3PAuCl (25 mg, 0.050 mmol) and AgOTf (13 mg, 0.050 mmol) were allowed to react in a minivial loaded with benzyl carbamate (0.15 g, 1.0 mmol) in anhydrous 1,2-dichloroethane (2.0 mL) for 5 min. 3-Methyl-1,3-pentadiene (0.14 mL, 1.2 mmol) was then added, and the reaction mixture was stirred overnight under nitrogen at room temperature in the dark. The solvent was evaporated in vacuo, and the residue was purified by flash-column chromatography on silica gel (hexanes/EtOAc 1:0→9:1, $R_f = 0.13$). Product **1c** was isolated in 86% yield (0.20 g, 0.86 mmol) after removal of solvent.

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