Organic LETTERS

Letter

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Gold-Catalyzed *Anti*-Markovnikov Selective Hydrothiolation of Unactivated Alkenes

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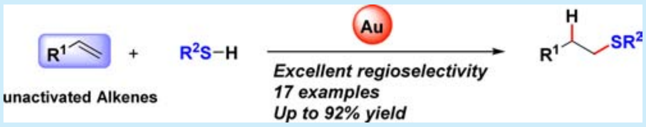
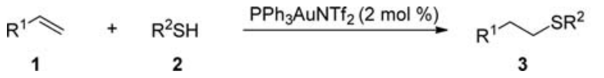
Supporting Information

ABSTRACT: Despite the widespread use of transition-metal catalysts in organic synthesis, transition-metal-catalyzed reactions of organosulfur compounds, which are known as catalyst poisons, have been difficult. In particular, the transition-metal-catalyzed addition of organosulfur compounds to unactivated alkenes remains a challenge. A novel gold-catalyzed hydrothiolation of unactivated alkenes is presented, which proceeds effectively to give the *anti*-Markovnikov-selective adducts in good yields and in a regioselective manner.



Transition-metal-catalyzed addition of heteroatom compounds is a very attractive strategy for the selective synthesis of heteroatom-functionalized molecules.[1] Organosulfur compounds, for example, have widespread utility as synthetic intermediates, bioactive compounds, and functional materials.[2] Although organosulfur compounds are known to poison transition-metal catalysts,[3] several examples of transition-metal-catalyzed additions of organosulfur compounds to alkynes and allenes have been reported in the last two decades.[4,5] However, there are very limited examples of the transition-metal-catalyzed addition of organosulfur compounds to alkenes,[6] as the poor coordination ability of alkenes renders this reaction difficult. We recently reported the Pd-catalyzed hydrothiolation of alkenes bonded directly to heteroatoms, such as vinyl ethers and vinyl lactams;[7] however, the transition-metal-catalyzed hydrothiolation of unactivated alkenes remains an unresolved challenge.[8,9]

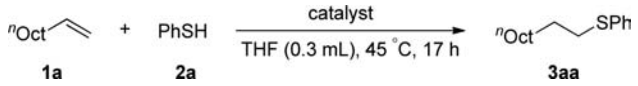
Recently, gold catalysts have gained importance because of their unique affinity toward unsaturated compounds, including unactivated alkenes.[10,11] Hence, we focused on the use of gold catalysts to overcome the limitations of the hydrothiolation of alkenes. Herein, we report a novel gold-catalyzed addition of thiols **2** to unactivated alkenes **1**, which proceeds with excellent regioselectivity to afford the corresponding *anti*-Markovnikov adducts **3** in good yields (eq 1).



(1)

We first attempted to search for a catalyst that would aid the selective hydrothiolation of unactivated alkenes (Table 1). The reaction of 1-decene **1a** and benzenethiol **2a** in the presence of 2 mol % of PPh_3AuNTf_2, a highly reactive gold catalyst,[12] at 45 °C for 17 h led to the formation of the *anti*-Markovnikov-type adduct **3aa** in 65% yield; no Markovnikov-type adduct was observed (entry 1). With a slight reduction in the amount of PPh_3AuNTf_2 to 1 mol %, the *anti*-Markovnikov hydrothiolation proceeded efficiently (entry 2). However, the reaction was ineffective when the catalyst amount was increased to 5 mol %, giving **3aa** in only 23% yield; on the other hand, in the absence of the catalyst, only a trace amount of the desired product was formed (entries 3 and 4).

Table 1. Screening of Catalysts for Hydrothiolation of 1-Decene[a]



entry	catalyst	yield[b] (%)
1	PPh_3AuNTf_2 (2 mol %)	65
2	PPh_3AuNTf_2 (1 mol %)	73
3	PPh_3AuNTf_2 (5 mol %)	23
4	none	trace
5	$(Me_2S)AuCl$ (1 mol %)	66
6	PPh_3AuCl (1 mol %)	trace
7	$AuCl_3$ (1 mol %)	16
8	PPh_3AuNTf_2 (2 mol %) + $CuCl_2$ (2 mol %)	ND

[a] Reaction conditions: 1-decene (**1a**, 0.5 mmol), benzenethiol (**2a**, 0.5 mmol), THF (0.3 mL). [b] Determined by ^{1}H NMR analysis.

$(Me_2S)AuCl$ as the gold catalyst also promoted the desired hydrothiolation and afforded the product in good yield (entry 5). PPh_3AuCl and $AuCl_3$ were ineffective for the reaction, and the product yield was unsatisfactory (entries 6 and 7). Furthermore, when Pd, Ru catalysts and Lewis acid were used, the hydrothiolation did not proceed at all (see the Supporting Information). Moreover, when 2 mol % of $CuCl_2$ was used as an oxidant with PPh_3AuNTf_2 (to clarify whether higher valent Au species exhibits catalytic activity toward the hydrothiolation of alkene), the hydrothiolation product was not obtained (entry 8).

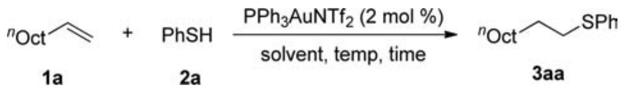
Next, we optimized the reaction conditions for the gold-catalyzed hydrothiolation using PPh_3AuNTf_2 as the catalyst

Received: March 15, 2016
Published: April 8, 2016

DOI: 10.1021/acs.orglett.6b00746

(Table 2). First, we focused on the solvents and reaction temperatures for the hydrothiolation. The use of toluene and CH_3CN as solvents for the hydrothiolation led to a substantial decrease in the yields of the desired adducts (entries 4 and 6). In comparison, the reaction yields were reasonable when using tetrahydrofuran (THF). Further, high temperatures were unsuitable for the gold-catalyzed hydrothiolation (entries 3 and 5), probably because of the decomposition of PPh_3AuNTf_2.

Table 2. Optimization of Reaction Conditions for Hydrothiolation of 1-Decene[a]



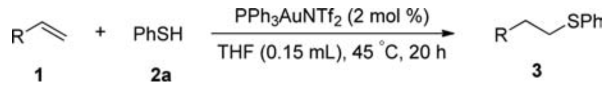
entry	solvent	temp (°C)	time (h)	yield[b] (%)
1	THF (0.3 mL)	45	17	65
2[c]	THF (0.3 mL)	45	17	73
3	THF (0.3 mL)	70	17	11
4	toluene (0.3 mL)	45	17	3
5	toluene (0.3 mL)	90	17	10
6	CH_3CN (0.3 mL)	45	17	2
7[c]	THF (0.15 mL)	45	17	13
8	THF (0.15 mL)	45	17	80
9	THF (0.15 mL)	45	20	87
10[d]	THF (0.15 mL)	45	20	99

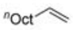
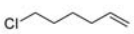
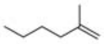
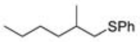
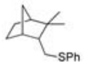
[a] Reaction conditions: 1-decene (**1a**, 0.5 mmol), benzenethiol (**2a**, 0.5 mmol), PPh_3AuNTf_2 (2 mol %). [b] Determined by ^1H NMR analysis. [c] PPh_3AuNTf_2 (1 mol %) was used. [d] Excess amounts of benzenethiol (**2a**, 0.33 mmol) were added after 4 h.

Next, we examined the amounts of THF for the gold-catalyzed hydrothiolation (see the Supporting Information) and found that a combination of 2 mol % of PPh_3AuNTf_2 and 0.15 mL of THF gave **3aa** in good yield, 80% (entry 8). In addition, the yield of the hydrothiolation product was improved by prolonging the reaction to 20 h (entry 9). Furthermore, when excess PhSH was added to the reaction mixture additionally after 4 h, the desired product **3aa** was obtained in almost quantitative yield (entry 10).

We next examined the scope and limitations of the gold-catalyzed hydrothiolation of unactivated alkenes; the results are summarized in Table 3. The reaction of allylbenzene **1b** and 4-phenyl-1-butene **1c** afforded the corresponding *anti*-Markovnikov hydrothiolation products in excellent yields (entries 2 and 3). The reaction of phenyl allyl ether gave the desired hydrothiolation product in moderate yield (entry 4). Alkenes bearing a variety of functional groups such as nitrile, hydroxyl, and chloro were tolerated in the gold-catalyzed hydrothiolation, and the corresponding adducts **3ea**, **3fa**, and **3ga** were obtained in moderate yields, respectively (entries 5−7). In the case of 1,6-heptadiene **1h**, the bishydrothiolation product **3ha** was obtained in 47% yield, along with 20% of the monohydrothiolation product **3ha′** (entry 8). The reaction of a 1,1-disubstituted alkene, 2-methyl-1-hexene **1i**, proceeded efficiently to afford the hydrothiolation product **3ia** in 50% yield (entry 9). In the cases of norbornene **1j** and 2,2-dimethyl-3-methylene-bicyclo[2.2.1]-heptane **1k**, the hydrothiolation products were obtained in moderate yield; *exo*- and *endo*-isomers, respectively, were obtained stereoselectively (entries 10 and 11). Furthermore, when the sterically demanding alkenes, such as 3,3-disubstituted alkene and tri- and tetrasubstituted alkenes, were used for the gold-catalyzed hydrothiolation, the desired reaction did not proceed at all.[13]

Table 3. Gold-Catalyzed Hydrothiolation of Several Unactivated Alkenes[a]



entry	substrate	product	3	yield, %
1			**3aa**	92
2			**3ba**	88
3			**3ca**	85
4			**3da**	55
5			**3ea**	45
6			**3fa**	51
7			**3ga**	53
8			**3ha**	47
9			**3ia**	50
10			**3ja**	69
11			**3ka**	66

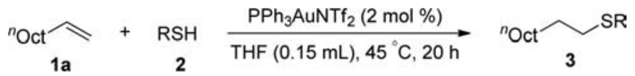
[a] Reaction conditions: alkene (**1**, 0.5 mmol), benzenethiol (**2a**, 0.83 mmol), PPh_3AuNTf_2 (2 mol %), THF (0.15 mL), 45 °C, 20 h. *Anti*-Markovnikov adducts were obtained regioselectively without formation of Markovnikov adduct in all entries.

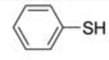
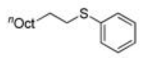
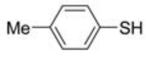
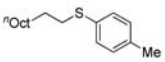
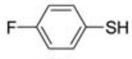
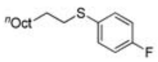
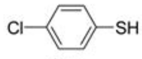
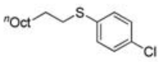
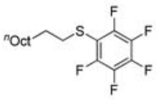
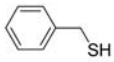
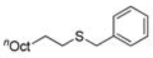
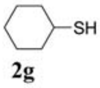
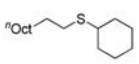
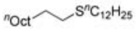
Subsequently, the gold-catalyzed hydrothiolation of unactive alkene **1a** was extended to several thiols; the results are summarized in Table 4. Benzenethiols bearing an electron-donating or electron-withdrawing group such as methyl, fluoro, or chloro were suitable for this catalytic hydrothiolation, and the *anti*-Markovnikov adducts were obtained in high yields (entries 2−4). The use of pentafluorobenzenethiol resulted in a moderate yield of the *anti*-Markovnikov adduct (entry 5). Aliphatic thiols such as phenylmethanethiol **2f**, cyclohexanethiol **2g**, and dodecanethiol **2h** afforded the desired *anti*-Markovnikov-type hydrothiolation products in a regioselective fashion (entries 6−8).

To clarify whether the present gold-catalyzed hydrothiolation reaction involves a radical pathway, we examined the hydrothiolation of a vinylcyclopropane derivative (Scheme 1). The rate constant for the ring opening of the cyclopropylcarbinyl radical is very large ($k = 1.3 \times 10^8$ s^{-1}).[14] Therefore, if the gold-catalyzed hydrothiolation proceeds via a radical pathway, ring opening of cyclopropane may be observed. The hydrothiolation of 1-cyclopropyl-1-phenylethene **1l** afforded *anti*-Markovnikov adduct **3la** without cyclopropyl ring opening. This result indicated that the present gold-catalyzed hydrothiolation did not proceed via a radical reaction (also see the Supporting Information).

To obtain insights into the reaction mechanism, the catalytic hydrothiolation of 1-decene **1a** with benzenethiol **2a** was monitored by ^{31}P NMR analysis. The ^{31}P NMR spectrum during the hydrothiolation immediately showed peaks at 35.3 ppm,

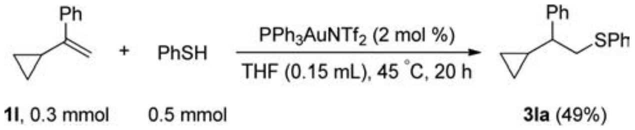
Table 4. Gold-Catalyzed Hydrothiolation Using Several Thiols[a]



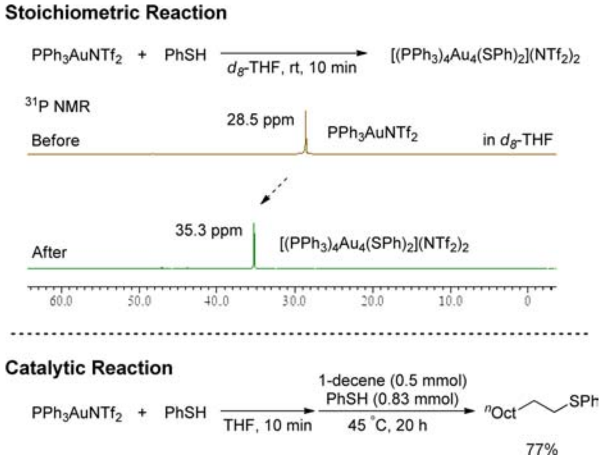
entry	RSH, 2	product	3	yield, %
1	 **2a**		**3aa**	92
2	 **2b**		**3ab**	76
3	 **2c**		**3ac**	78
4	 **2d**		**3ad**	87
5	C_6F_5SH **2e**		**3ae**	32
6	 **2f**		**3af**	31
7	 **2g**		**3ag**	68
8	$^nC_{12}H_{25}SH$ **2h**		**3ah**	80

[a]Reaction conditions: 1-decene (**1a**, 0.5 mmol), thiol (**2**, 0.5 mmol), PPh$_3$AuNTf$_2$ (2 mol %), THF (0.15 mL), 45 °C, 20 h. *Anti*-Markovnikov adducts were obtained regioselectively without formation of Markovnikov adduct in all entries.

Scheme 1. Examination of Radical Pathway of Gold-Catalyzed Hydrothiolation



Scheme 2. Effects of Gold Catalyst on Hydrothiolation



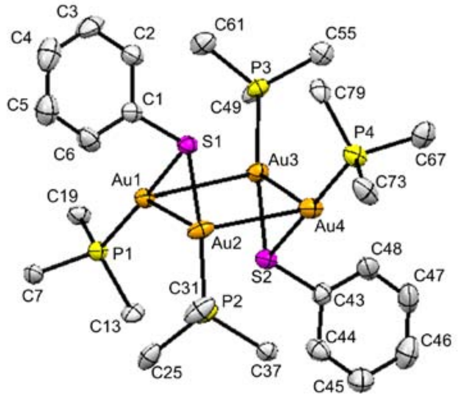
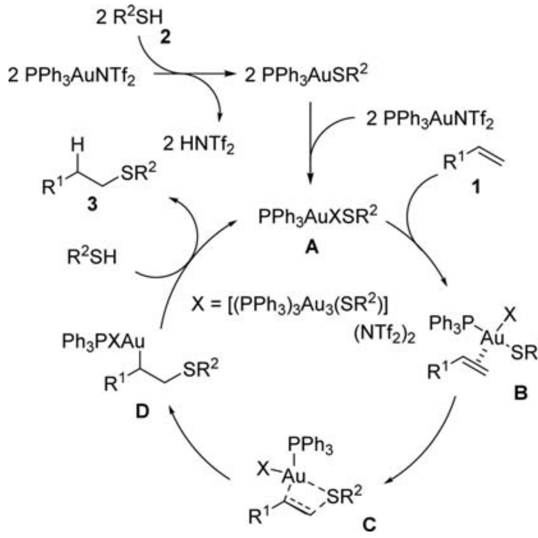


Figure 1. ORTEP drawing of gold−sulfide complex A (50% thermal ellipsoids). For clarity, all hydrogen atoms and counteranion have been omitted, and only the ipso-carbons of the phenyl ring of triphenylphosphine are shown.

Scheme 3. Plausible Reaction Pathway for Gold-Catalyzed Hydrothiolation of Unactivated Alkenes



attributed to the formation of gold−thiolate complex **A**. To determine the structure of **A**, a stoichiometric reaction of PPh$_3$AuNTf$_2$ with PhSH was performed (Scheme 2). After the reaction, the ^{31}P NMR spectrum showed a signal at 35.3 ppm. Complex **A** was recrystallized, and X-ray analysis unambiguously established that it was a tetranuclear gold complex, [(PPh$_3$)$_4$Au$_4$(SPh)$_2$](NTf$_2$)$_2$ (Figure 1). The NMR data of [(PPh$_3$)$_4$Au$_4$(SPh)$_2$](NTf$_2$)$_2$ were identical to those for a very similar tetranuclear gold complex reported in the literature.[15] Next, we conducted the hydrothiolation using the synthesized [(PPh$_3$)$_4$Au$_4$(SPh)$_2$](NTf$_2$)$_2$. Interestingly, the desired hydrothiolation proceeded efficiently, indicating that tetranuclear gold complex **A** is a key intermediate in the hydrothiolation of unactivated alkenes (or one of the resting state of catalyst).

Based on these mechanistic studies and previous studies,[11,16] we propose a plausible reaction pathway for the hydrothiolation of unactivated alkene **1** with thiol **2** (Scheme 3). The PPh$_3$AuNTf$_2$ catalyst reacts with the thiol to form PPh$_3$AuSR^2, which in turn reacts with PPh$_3$AuNTf$_2$ to form tetranuclear gold complex **A**. Then, **1** is activated by the coordination of complex **A**. Subsequent addition of the Au−S species into the double bond of the unactivated alkene affords gold−alkene complex **D** through a transition structure **C**. Finally, protonation of intermediate **D** by the thiol provides the *anti*-Markovnikov hydrothiolation product selectively, with the regeneration of **A**.

In summary, we have developed a novel gold-catalyzed *anti*-Markovnikov-selective hydrothiolation of unactivated alkenes. Conventional transition-metal-catalyzed reactions of organosulfur compounds to unactivated alkenes are difficult. However, our results reveal that the highly cationic gold catalyst enables selective hydrothiolation of unactivated alkenes to afford the desired *anti*-Markovnikov adducts. We believe that this gold-catalyzed hydrothiolation will open up the possibility of synthesizing diverse functionalized alkenes with potential applications in chemistry.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00746.

X-ray data for complex **A** (CIF)

Detailed experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research for JSPS Fellows (1381002900). T.T. thanks the Japan Society for the Promotion of Science for the Research Fellowship for Young Scientists. We also thank the Nara Institute of Science and Technology (NAIST) for assistance with the X-ray crystal structural analysis.

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