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Ruthenium-Catalyzed Propargylic Substitution Reaction of Propargylic Alcohols with Thiols: A General Synthetic Route to Propargylic Sulfides

Youichi Inada,† Yoshiaki Nishibayashi,† Masanobu Hidai,*,‡ and Sakae Uemura*,†

Department of Energy and Hydrocarbon Chemistry, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan, and Department of Materials Science and Technology, Science University of Tokyo, Noda, Chiba 278-8510, Japan

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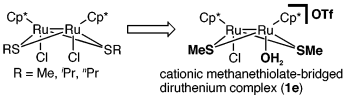
We recently disclosed the ruthenium-catalyzed efficient propargylic substitution reactions of propargylic alcohols with various heteroatom- and carbon-centered nucleophiles to afford the corresponding propargylic products in high yields.[1] The reactions are catalyzed only by thiolate-bridged diruthenium complexes[2] such as [Cp*RuCl(μ_2-SR)$_2$RuCp*Cl] (Cp* = η^5-C$_5$Me$_5$; R = Me (**1a**), ^{i}Pr (**1b**), ^{n}Pr (**1c**)) and [Cp*RuCl(μ_2-S^{i}Pr)$_2$RuCp*(OH$_2$)]OTf (OTf = OSO$_2$CF$_3$; **1d**). The reactions proceeded more smoothly in the presence of a catalytic amount of NH_4BF_4. In these catalytic substitution reactions, available substrates were unfortunately strictly limited to the propargylic alcohols *bearing terminal alkyne group* because the reactions proceeded via allenylidene intermediates, which can be produced only from this type of propargylic alcohols. On the other hand, some other groups have already found transition metal-catalyzed propargylic substitution reactions of propargylic phosphates and acetates with nitrogen (Cu and Ti),[3a,b] oxygen (Ti),[3c] and carbon-centered (Ir)[3d] nucleophiles, but a catalytic reaction with a sulfur-centered nucleophile to afford the corresponding propargylic sulfides has not yet been reported, probably due to the long known fact that sulfur-containing compounds act as catalyst poisons because of their strong coordinating properties.[4] During our ongoing study on the catalytic propargylic substitution reactions, we recently found a general synthetic method for propargylic sulfides. Namely, a novel cationic *methanethiolate-bridged* diruthenium complex [Cp*RuCl(μ_2-SMe)$_2$RuCp*(OH$_2$)]OTf (**1e**) (Chart 1) has been

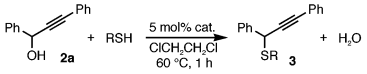
Chart 1



disclosed to promote the catalytic propargylic substitution reaction of propargylic alcohols bearing not only *terminal* alkyne group but also *internal* alkyne group with thiols. Preliminary results on this catalytic reaction are described here.

First, we investigated the substitution reaction of propargylic alcohols bearing an *internal* alkyne group such as 1,3-diphenyl-2-propyn-1-ol (**2a**). Treatment of **2a** with 1-butanethiol in 1,2-dichloroethane in the presence of **1e** (5 mol %) at 60 °C for 1 h afforded 1-butyl 1,3-diphenyl-2-propynyl sulfide (**3aa**) in 92% isolated yield (Table 1, run 1).[5] No other products or regioisomers of **3aa** were detected by GLC and ^{1}H NMR. The reaction proceeded even at room temperature, but a slightly prolonged reaction time (3 h) was required (Table 1, run 2). The complex with the sterically demanding S^{i}Pr group exhibited almost the same catalytic activity in this reaction (Table 1, run 3). It is noteworthy that neutral thiolate-bridged diruthenium complexes (**1a**−**1c**), which were known to promote the propargylic substitution reactions of propargylic alcohols *bearing terminal alkyne group* with various heteroatom- and carbon-centered nucleophiles,[1] did not work at all, even in the presence of NH_4BF_4 (Table 1, runs 4 and 5). When other simple alkanethiols such as cyclohexanethiol and 3-methyl-1-butanethiol were used in place of 1-butanethiol, the corresponding propargylic sulfides (**3ab** and **3ac**) were obtained in 93 and 76% yields, respectively (Table 1, runs 6 and 7). The most characteristic feature of this reaction is the direct use of propargylic alcohols as effective propargylating reagents where the reaction occurs in an environmentally friendly manner, with the only stoichiometric byproduct being water (H_2O).

Table 1. Reaction of Propargylic Alcohol (**2a**) with Thiols[a]



run	thiol	catalyst	yield of **3**, %[b]
1	^{n}BuSH	[Cp*RuCl(μ-SMe)$_2$Cp*Ru(OH$_2$)]OTf (**1e**)	**3aa**, 92
2	^{n}BuSH	[Cp*RuCl(μ-SMe)$_2$Cp*Ru(OH$_2$)]OTf (**1e**)	**3aa**, 79[c]
3	^{n}BuSH	[Cp*RuCl(μ-S^{i}Pr)$_2$Cp*Ru(OH$_2$)]OTf (**1d**)	**3aa**, 92
4	^{n}BuSH	[Cp*RuCl(μ-SMe)$_2$Cp*RuCl] (**1a**)[d]	**3aa**, trace
5	^{n}BuSH	[Cp*RuCl(μ-S^{i}Pr)$_2$Cp*RuCl] (**1b**)[d]	**3aa**, trace
6	^{c}C$_6$H$_{11}$SH	[Cp*RuCl(μ-SMe)$_2$Cp*Ru(OH$_2$)]OTf (**1e**)	**3ab**, 93
7	Me$_2$CHCH$_2$CH$_2$SH	[Cp*Ru(Cl(μ-SMe)$_2$Cp*Ru(OH$_2$)]OTf (**1e**)	**3ac**, 76

[a] All the reactions of **2a** (0.30 mmol) with thiol (1.50 mmol) were carried out in the presence of catalyst (0.015 mmol) in ClCH$_2$CH$_2$Cl (8 mL) at 60 °C for 1 h. [b] Isolated yield. [c] At room temperature for 3 h. [d] No reaction proceeded even in the presence of NH_4BF_4.

Reactions of **2a** with thiols containing functional groups have been carried out in the presence of **1e** (5 mol %) at 60 °C for 1 h.[6] Typical results are shown in Table 2. In all cases, **2a** was completely consumed, and the corresponding propargylic sulfides (**3ad**−**3ag**) were obtained in good to excellent yields. Functional groups, such as phenyl (Table 2, run 1), methoxycarbonyl (Table 2, run 2), chloro (Table 2, run 3), and hydroxyl (Table 2, run 4), in thiols did not affect this catalytic reaction. The reaction of 1-alkenyl-substituted propargylic alcohol **2b** with 1-butanethiol gave the allylpropargylic sulfide **3ba** in 96% isolated yield (Table 2, run 5). Unfortunately, a similar reaction of dialkynyl-substituted alcohol **2c** did not proceed (Table 2, run 6). Other various alkyl- and aryl-substituted propargylic alcohols (**2d**−**2h**) reacted with thiols to afford the corresponding propargylic sulfides (**3da**−**3ha**) in excellent yields with complete regioselectivity (Table 2, runs 7−14).[7]

Next, we examined the substitution reaction of propargylic alcohols bearing *terminal* alkyne group such as 1-phenyl-2-propyn-1-ol (**4a**) with thiols in the presence of **1e** (5 mol %) at 60 °C for 1 h.[8] Thus, a variety of thiols such as 1-butanethiol, 1-octanethiol, 3-methyl-1-butanethiol, cyclohexanethiol, phenylmethanethiol, and 3-chloropropanethiol could be employed to give the corresponding

* Corresponding author. E-mail: uemura@scl.kyoto-u.ac.jp.
† Kyoto University.
‡ Science University of Tokyo.

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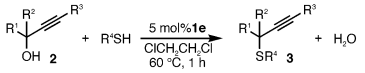
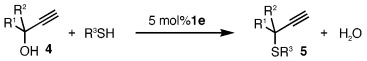
Table 2. Reaction of Propargylic Alcohols (**2**) with Thiols in the Presence of **1e**[a]



run	propargylic alcohol	thiol	yield of **3**, %[b]
1	**2a**, R^1 = Ph, R^2 = H, R^3 = Ph	R^4 = Ph	**3ad**, 70
2	**2a**, R^1 = Ph, R^2 = H, R^3 = Ph	R^4 = $CH_2CH_2CO_2Me$	**3ae**, 92
3	**2a**, R^1 = Ph, R^2 = H, R^3 = Ph	R^4 = $CH_2CH_2CH_2Cl$	**3af**, 90
4[c]	**2a**, R^1 = Ph, R^2 = H, R^3 = Ph	R^4 = CH_2CH_2OH	**3ag**, 52
5	**2b**, R^1 = Ph_2C=CH, R^2 = H, R^3 = Ph	R^4 = ^{n}Bu	**3ba**, 96
6	**2c**, R^1 = PhC≡C, R^2 = H, R^3 = Ph	R^4 = ^{n}Bu	**3ca**, trace
7	**2d**, R^1 = Ph, R^2 = H, R^3 = ^{n}Bu	R^4 = ^{n}Bu	**3da**, 87
8	**2d**, R^1 = Ph, R^2 = H, R^3 = ^{n}Bu	R^4 = $CH_2CH_2CHMe_2$	**3db**, 90
9	**2e**, R^1 = Ph, R^2 = H, R^3 = ^{n}hexyl	R^4 = ^{n}Bu	**3ea**, 83
10	**2f**, R1 = Ph, R^2 = H, R^3 = ^{t}Bu	R^4 = ^{n}Bu	**3fa**, 86
11	**2f**, R^1 = Ph, R^2 = H, R^3 = ^{t}Bu	R^4 = $CH_2CH_2CHMe_2$	**3fb**, 87
12	**2g**, R^1 = *p*-MeC_6H_4, R^2 = H, R^3 = Ph	R^4 = ^{n}Bu	**3ga**, 90
13	**2g**, R^1 = *p*-MeC_6H_4, R^2 = H, R^3 = Ph	R^4 = $CH_2CH_2CHMe_2$	**3gb**, 92
14	**2h**, R^1 = Ph, R^2 = Me, R^3 = Ph	R^4 = ^{n}Bu	**3ha**, 84

[a] All the reactions of **2** (0.30 mmol) with thiol (1.50 mmol) were carried out in the presence of **1e** (0.015 mmol) in $ClCH_2CH_2Cl$ (8 mL) at 60 °C for 1 h. [b] Isolated yield. [c] 10 mol % of **1e** was used.

Table 3. Reaction of Propargylic Alcohols Bearing Terminal Alkyne Group with Thiols[a]

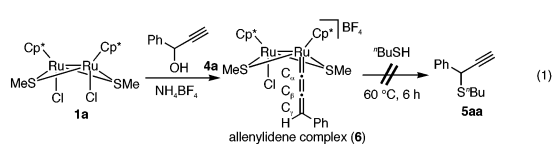


run	propargylic alcohol	thiol	yield of **5**, %[b]
1	**4a**, R^1 = Ph, R^2 = H	R^3 = ^{n}Bu	**5aa**, 86
2	**4a**, R^1 = Ph, R^2 = H	R^3 = ^{n}octyl	**5ab**, 87
3	**4a**, R^1 = Ph, R^2 = H	R^3 = $CH_2CH_2CHMe_2$	**5ac**, 88
4	**4a**, R^1 = Ph, R^2 = H	R^3 = $^cC_6H_{11}$	**5ad**, 82
5	**4a**, R^1 = Ph, R^2 = H	R^3 = $PhCH_2$	**5ae**, 79
6	**4a**, R^1 = Ph, R^2 = H	R^3 = $CH_2CH_2CH_2Cl$	**5af**, 79
7	**4a**, R^1 = Ph, R^2 = H	R^3 = Ph	**5ag**, 24
8	**4b**, R^1 = *p*-MeC_6H_4, R^2 = H	R^3 = ^{n}Bu	**5ba**, 83
9	**4c**, R^1 = *p*-FC_6H_4, R^2 = H	R^3 = ^{n}Bu	**5ca**, 84
10	**4d**, R^1 = 2-naphthyl, R^2 = H	R^3 = ^{n}Bu	**5da**, 94
11	**4e**, R^1 = $^cC_6H_{11}$, R^2 = H	R^3 = ^{n}Bu	**5ea**, 62
12[c]	**4f**, R^1 = Ph_2C=CH, R^2 = H	R^3 = ^{n}Bu	**5fa**, 47
13[d]	**4g**, R^1 = Ph, R^2 = Ph	R^3 = ^{n}Bu	**5ga**, 60

[a] All the reactions of **4** (0.60 mmol) with thiol (3.00 mmol) were carried out in the presence of **1e** (0.03 mmol) in $ClCH_2CH_2Cl$ (15 mL) at 60 °C for 1 h. [b] Isolated yield. [c] For 6 h. [d] For 24 h.

alkyl 1-phenyl-2-propynyl sulfide (**5aa**−**5af**) in good yields with complete regioselectivity. Typical results are shown in Table 3. Other isomers and products were not observed in the reaction mixture. The use of benzenethiol led to the formation of phenyl 1-phenyl-2-propynyl sulfide (**5ag**) in a lower yield (Table 3, run 7). Various propargylic alcohols reacted smoothly to give the corresponding sulfides in good to excellent yields as shown in runs 8−13 of Table 3, although in the cases of 1-alkenyl-substituted alcohol **4f** and 1,1-diaryl-substituted alcohol **4g** the reaction became slower.[9]

A stoichiometric reaction of the allenylidene complex **6** with 1-butanethiol did not afford the corresponding propargylic sulfide **5aa** (eq 1). This is in sharp contrast to our previous finding that



(1)

the nucleophilic attack of alcohols and carbon-centered nucleophiles on the electrophilic C_γ atom in allenylidene intermediates such as **6** gave the corresponding propargylic products.[1] The results indicate that the reaction of propargylic alcohols bearing a terminal alkyne group **4** with thiols may proceed via other reactive intermediates. On the other hand, a stoichiometric reaction of the cationic complex **1e** with a propargylic alcohol bearing an internal alkyne group (**2a**) at room temperature was investigated by ^{1}H NMR in CD_2Cl_2, but no intermediates were observed. Addition of an excess amount of 1-butanethiol to this reaction mixture led to the formation of the sulfide **3aa** together with **1e**. These results indicate that the intermediates of this catalytic reaction are too labile to be identified. Although direct evidence of the reactive intermediates has not yet been obtained, we suppose that the present catalytic reactions between propargylic alcohols and thiols may proceed via (η-propargyl)ruthenium species[10] at the diruthenium site. Nucleophilic attack of a thiol to this species affords the corresponding propargylic sulfides. Further investigation to elucidate the detailed reaction mechanism is currently in progress.

In summary, we have found a highly selective and efficient propargylic substitution reaction of propargylic alcohols with thiols catalyzed by the cationic diruthenium complex **1e**.[11] The Nicholas reaction has been found to be the most reliable tool for selective propargylation of nucleophiles by using a *stoichiometric* amount of cationic propargyl complexes $[(propargyl)Co_2(CO)_6]^+$.[12] However, only a few studies on the propargylation of thiols by the Nicholas reaction have been reported,[13] and the preparative methods for propargylic sulfides by other methods are quite limited so far.[14]

Supporting Information Available: Experimental procedures and spectral data for all of the new compounds and crystallographic data for **1e** (cif). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Other di- and monoruthenium complexes such as $[CpRuCl(PPh_3)_2]$ (Cp = η^5-C_5H_5), $[RuCl_2(PPh_3)_3]$, $[RuCl_2(p\text{-cymene})]_2$, $[(indenyl)RuCl(PPh_3)_2]$, and $[Cp^*RuCl(\mu_2\text{-}Cl)_2RuCp^*Cl]$ were ineffective for the propargylic substitution reaction.

(6) Unfortunately, no propargylic substitution reactions of **2a** with alcohols, amines, acetone, and silyl enol ethers in the presence of **1e** occurred under similar reaction conditions.

(7) In contrast to the reaction of 2,4-diphenyl-3-butyn-2-ol (**2h**) (Table 2, run 14), the reaction of 1,1,3-triphenyl-2-propyn-1-ol with ^{n}BuSH at 60 °C for 16 h afforded not the corresponding propargylic product but 1,3,3-triphenyl-2-propen-1-one in 80% yield as a sole product.

(8) Previously, the reaction of **4a** with *p*-toluenethiol in the presence of **1a** (5 mol %) and NH_4BF_4 (10 mol %) was carried out at 60 °C for 4 h, but the corresponding propargylic sulfide was obtained in only 53% yield.[12]

(9) When (*R*)-**4a** was treated with ^{n}BuSH at room temperature, racemic **5aa** was formed.

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(11) Independently, Mitsudo and co-workers reported the propargylic substitution reaction with propargylic carbonates with thiols catalyzed by monoruthenium complexes such as $CpRuCl(PPh_3)_2$ and CpRuCl(cod) at 100 °C, but available substrates were strictly limited to the propargylic carbonates *bearing an internal alkyne group*: Kondo, T.; Kanda, Y.; Baba, A.; Fukuda, K.; Nakamura, A.; Wada, K.; Morisaki, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **2002**, *124*, 12960.

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