First Ruthenium-Catalyzed Allylation of Thiols Enables the General Synthesis of Allylic Sulfides

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The transition-metal complex-catalyzed substitution reaction of allylic alcohol derivatives with nucleophilic reagents is now a well-established methodology in organic synthesis and is widely used to construct complex organic molecules.[1,2] However, even though a wide range of nucleophiles, such as carbon, nitrogen, and oxygen nucleophiles, and transition-metal catalysts, especially those involving palladium,[2] have been studied,[3] a general method for synthesizing allylic sulfides by the transition-metal complex-catalyzed allylation of sulfur nucleophiles has not yet been reported, since, in catalytic reactions, sulfur-containing compounds have long been known to act as catalyst poisons because of their strong coordinating properties.[4] Recent progress in the transition-metal complex-catalyzed synthesis of allylic sulfides without poisoning of the catalyst has included (1) rearrangement of *O*-allylphosphoro- or phosphonothionates,[5] (2) conversion of *O*-allyl or *S*-allyl dithiocarbonates with liberation of carbon oxide sulfide (COS),[6] and (3) allylic substitution by silylated thiols,[7] heterocyclic sulfur nucleophiles,[8] sodium thiophenoxides,[9,10c] and aromatic thiols.[10] However, some of these reactions have a serious drawback with regard to substrate preparation. In addition, the catalyst systems reported so far are strictly limited to palladium catalysts,[5−10] and in the simple allylic substitution with thiols, only aromatic and heteroaromatic thiols can be used.[10]

On the other hand, we recently reported that ruthenium complexes, such as Ru(cod)(η^6-C$_8$H$_{10}$)[11a] (cod = 1,5-cyclooctadiene, η^6-C$_8$H$_{10}$ = 1,3,5-cyclooctatriene) and Cp*RuCl(cod)[11b] (Cp* = pentamethylcyclopentadienyl), facilitate the highly selective catalytic allylation of both carbon and nitrogen nucleophiles at the more-substituted allylic termini. In our further investigation of the reactivity of several ruthenium complexes toward sulfur-containing compounds,[12] we found the first example of the transition-metal complex-catalyzed addition of organic disulfides to alkenes.[13] Therefore, the ruthenium complex seems to be one of the most promising catalysts for the transformation of sulfur-containing compounds. After many trials, we finally found the first ruthenium-catalyzed allylation of both aliphatic and aromatic thiols with various allylic reagents, including allylic alcohols, under extremely mild reaction conditions. We report here the development of this new ruthenium-catalyzed reaction which enables a simple and general synthesis of allylic sulfides.

Treatment of aliphatic and aromatic thiols, represented by pentanethiol (**2a**) and benzenethiol (**2b**), with allyl methyl carbonate (**1a**) in the presence of 5 mol % Cp*RuCl(cod) in CH$_3$-CN at room temperature for 1 h under an argon atmosphere gave the corresponding allylic sulfides, allyl pentyl sulfide (**3a**) and allyl phenyl sulfide (**3b**), in high yields, respectively (eq 1).

First, the catalytic activity of several ruthenium complexes was examined in the reaction of **1a** with **2a**. The results are summarized in Table 1. Among the catalysts examined, Cp*RuCl-(cod) and CpRuCl(cod) showed high catalytic activity. Other di- and zerovalent ruthenium complexes, such as CpRuCl(PPh$_3$)$_2$, (*p*-cymene)RuCl$_2$(PPh$_3$), RuCl$_2$(PPh$_3$)$_3$, Ru(cod)(η^6-C$_8$H$_{10}$), and Ru$_3$-(CO)$_{12}$, were totally ineffective. Almost no reaction occurred with Pd(PPh$_3$)$_4$, RhCl(PPh$_3$)$_3$, or IrCl(CO)(PPh$_3$)$_2$ catalysts, and the present reaction is characteristic of ruthenium catalysts. The use of an appropriate solvent is also critically important for a successful reaction. Among the solvents examined, CH$_3$CN gave the best result, which strongly suggests that CH$_3$CN acts as a suitable ligand to an active ruthenium intermediate as well as a solvent to prevent catalyst poisoning by thiols.

Various allylic compounds, such as allyl ethyl carbonate (**1b**), allyl trifluoroacetate (**1c**), and allyl acetate (**1d**), can be used in the present allylation reaction of pentanethiol (**2a**) to give allyl pentyl sulfide (**3a**) in high yield (eq 2). On the other hand, the yield of **3a** decreased to 38% with allyl phenyl ether (**1e**). Furthermore, under the present reaction conditions, it is difficult to cleave the allylic carbon−sulfur bond with the ruthenium catalyst,[14] as shown in the reaction of allyl phenyl sulfide (**3b**) with **2a**. Note that allyl alcohol *itself* (**1f**), which is considered to be a poor substrate for the formation of π-allyl transition-metal complexes, gave **3a** in high yield (88%). The direct use of allyl alcohols as an effective allylating reagent is an important theme in transition-metal complex-catalyzed allylation reactions and is highly economical in terms of atoms used.[15]

The allylation of several aliphatic and heteroaromatic thiols (**2c−j**) with allyl methyl carbonate (**1a**) also proceeded smoothly

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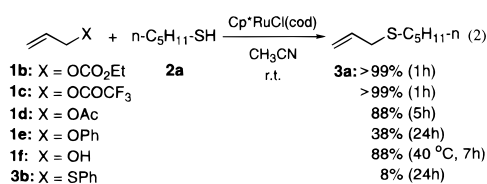
Communications to the Editor

Table 1. Catalytic Activity of Several Ruthenium Complexes on the Synthesis of **3a** by Allylation of **2a** with **1a**[a]

catalyst	convrsn of **1a** (%)[b]	yield of **3a** (%)[c]
Cp*RuCl(cod)	100	96 (84)
CpRuCl(cod)	87	86
CpRuCl(PPh$_3$)$_2$	5	2
(*p*-cymene)RuCl$_2$(PPh$_3$)	5	trace
RuCl$_2$(PPh$_3$)$_3$	34	trace
Ru(cod)(η^6-C$_8$H$_{10}$)	9	4
Ru$_3$(CO)$_{12}$[d]	0	0
RuCl$_3$·3H$_2$O	0	0

[a] **1a** (1.0 mmol), **2a** (1.2 mmol), catalyst (0.050 mmol), and CH$_3$CN (2.0 mL) at room temperature for 1 h under an argon atmosphere. [b] Determined by GLC. [c] Determined by GLC on the basis of the amount of **1a** charged. Figure in the parentheses is an isolated yield. [d] Ru$_3$(CO)$_{12}$ (0.017 mmol) was used.

1b: X = OCO$_2$Et
1c: X = OCOCF$_3$
1d: X = OAc
1e: X = OPh
1f: X = OH
3b: X = SPh

3a: >99% (1h)
>99% (1h)
88% (5h)
38% (24h)
88% (40 °C, 7h)
8% (24h)

Table 2. Cp*RuCl(cod)-Catalyzed Allylation of Thiols with Allyl Methyl Carbonate (**1a**)[a]

Run	Thiol	Product	Isolated Yield (%)[b]
1	n-C$_4$H$_9$-SH **2c**	⌇S-C$_4$H$_9$-n **3c**	(97)[c]
2	n-C$_8$H$_{17}$-SH **2d**	⌇S-C$_8$H$_{17}$-n **3d**	93
3	**2e**	**3e**	72
4	**2f**	**3f**	77
5	**2g**	**3g**	97
6	HS⌇OH **2h**	⌇S⌇OH **3h**	90
7	HS⌇CO$_2$Me **2i**	⌇S⌇CO$_2$Me **3i**	87
8[d]	**2j**	**3j**	70

[a] **1a** (1.0 mmol), **2** (1.2 mmol), Cp*RuCl(cod) (0.050 mmol), and CH$_3$CN (2.0 mL) at room temperature for 1 h under an argon atmosphere. [b] Based on the amount of **1a** charged. [c] GLC yield. [d] For 10 h.

with a Cp*RuCl(cod) catalyst, and the results are listed in Table 2.[16] In all cases, **1a** was completely consumed, and the corresponding allylic sulfides were obtained in high isolated yields. No byproducts could be detected by GLC. Some functional groups, such as hydroxyl (**2h**) and methoxycarbonyl groups (**2i**), did not affect the reaction.

Allylic rearrangements consistent with the formation of a π-allylruthenium intermediate were observed. The two regioisomeric allylic carbonates, (*E*)-crotyl methyl carbonate (**1g**) and 3-buten-2-yl methyl carbonate (**1h**), reacted with **2a** to give identical mixtures of regioisomeric sulfides ((*E*)-**3k** + **3k′**) (eq 3). Interestingly, the regioselectivity is totally different from those observed in the ruthenium-catalyzed allylation of carbon[11a] and nitrogen nucleophiles.[11b] In the present reaction, the attack of sulfur nucleophiles predominantly occurred at the less-substituted allylic termini of a π-allylruthenium intermediate.
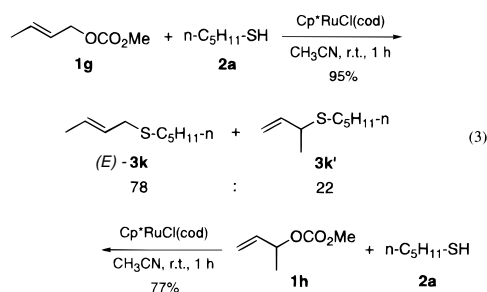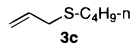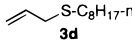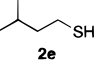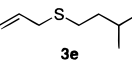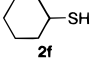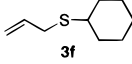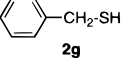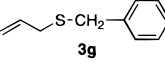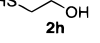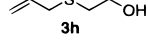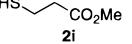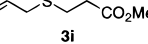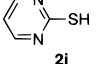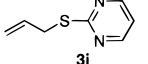
To further clarify the intermediacy of a π-allylruthenium complex, the stoichiometric reaction of Cp*RuCl$_2$(η^3-C$_3$H$_5$) (**4**) with **2a** was examined, and the corresponding allyl pentyl sulfide (**3a**) was obtained in an isolated yield of 66% (eq 4).
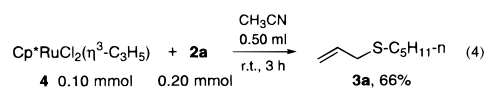
The stereochemical course of the reaction was also investigated (eq 5). Since the reactivity of cyclic allylic carbonate, *trans*-5-(methoxycarbonyl)-2-cyclohexen-1-yl methyl carbonate (**1i**), was lower than those of acyclic allylic carbonates, relatively severe reaction conditions (i.e., reflux (97 °C) in CH$_3$CH$_2$CN for 10 h)

were required for completion of the reaction, in which the product (**3l**), with a net retention of configuration, was obtained exclusively in an isolated yield of 70% by the reaction of **1i** with **2a**. This result suggests that the reaction proceeds with a double-inversion mechanism,[17] considering that nucleophilic attack of soft nucleophiles to π-allylruthenium complexes proceeded via an inversion of configuration.[18]
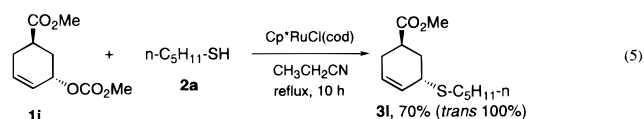
In conclusion, a ruthenium complex was found to be a new and highly efficient catalyst for the allylation of both aliphatic and aromatic thiols under extremely mild reaction conditions, which enables the general and practical synthesis of allylic sulfides. This reaction should open up new opportunities in transition-metal complex-catalyzed sulfur chemistry, since organosulfur compounds are quite useful intermediates in organic synthesis.[19] The development of a catalyst system which gives the opposite regioselectivity, leading to the enantioselective version of this reaction, is currently under investigation.

Supporting Information Available: Complete experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Treatment of **1a** with **2a** by the catalyst system of Pd$_2$(dba)$_3$ and dppb reported by Sinou and co-workers (refs 10a,b) in THF at 60 °C for 12 h gave allyl pentyl sulfide (**3a**) in only 35% yield.

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