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Ruthenium-Catalyzed *S*-Propargylation of Thiols Enables the Rapid Synthesis of Propargylic Sulfides

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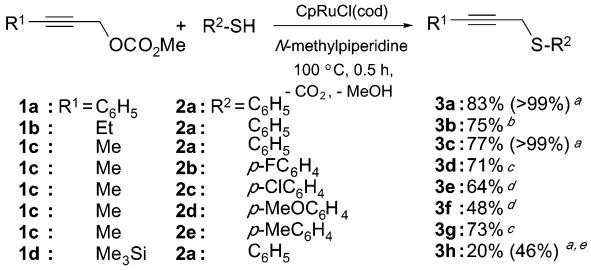
Propargylic sulfides and their derivatives are biologically active compounds,[1] as well as attractive building blocks in the synthesis of sulfur-containing functional monomers.[2] The most promising and straightforward method for preparing propargylic sulfides is the transition-metal complex-catalyzed substitution reaction of propargylic alcohol derivatives with sulfur nucleophiles such as thiols. However, this type of reaction has not yet been reported, while a detailed study was performed on propargylic substitution of carbonucleophiles.[3] The widespread belief that organosulfur compounds are catalyst poisons may have precluded intensive research in this area.[4] Recent progress in the catalytic synthesis of propargylic sulfides without poisoning of the catalyst has included (1) Ce-exchanged Zeolite-catalyzed reactions of cyclohexanethiol and benzenethiol with propargyl bromide[5] and (2) the thiolate-bridged diruthenium complex-catalyzed reaction of 4-methylbenzenethiol with 1-phenylprop-2-yn-1-ol.[6] However, these two reactions have serious drawbacks. In the former, the substrates bearing functional groups sensitive to acidic conditions cannot be used.[5] In the latter, the ruthenium catalyst used is very specific, and it is easy to speculate that no reaction occurs with internal propargylic alcohols via a reaction mechanism involving an (allenylidene)ruthenium intermediate.[6]

On the basis of our study of π-allylruthenium chemistry[7] combined with ruthenium-catalyzed sulfur chemistry,[8] we recently succeeded in developing the first ruthenium-catalyzed allylic substitution of thiols,[9] which has prompted us to examine ruthenium catalysts for use in the propargylic substitution of thiols. After many trials, we finally found a novel ruthenium-catalyzed *S*-propargylation of both aromatic and aliphatic thiols with internal propargylic carbonates under neutral conditions. We report here the development of this new ruthenium-catalyzed reaction which enables a rapid synthesis of propargylic sulfides.

Treatment of benzenethiol (**2a**) with methyl 3-phenylprop-2-ynyl carbonate (**1a**) in the presence of 10 mol % CpRuCl(cod) [Cp = cyclopentadienyl, cod = 1,5-cyclooctadiene] in *N*-methylpiperidine at 100 °C for 0.5 h under an argon atmosphere gave the corresponding aryl propargylic sulfides, phenyl 3-phenylprop-2-ynyl sulfide (**3a**), in quantitative yield. In contrast to the earlier work on the ruthenium-catalyzed *S*-allylation of thiols,[9] the present reaction required elevated temperatures over 80 °C and an appropriate solvent, that is, *N*-methylpiperidine[7c,d,10] (vide infra), since propargylic carbonates are less reactive than allylic carbonates.[3b]

First, the effect of the catalyst was examined in the synthesis of **3a** from **1a** and **2a**. Among the catalysts examined, only CpRuCl(cod) (**3a**, >99%) and CpRuCl(PPh_3)$_2$ (**3a**, 66%) showed high catalytic activity. Other di- and zerovalent ruthenium complexes, such as Cp*RuCl(cod) [Cp* = pentamethylcyclopentadienyl], CpRuCl(CO)$_2$, RuCl$_2$(PPh_3)$_3$, RuH$_2$(PPh_3)$_4$, [RuCl$_2$(CO)$_3$]$_2$, Ru$_3$(CO)$_{12}$, and Ru(η^6-cot)(dmfm)$_2$ [cot = 1,3,5-cyclooctatriene, dmfm = dimethyl fumarate] were almost ineffective. Cp*RuCl(cod) showed no catalytic activity. This means that tuning of both the steric and electronic conditions of the active ruthenium center is highly important for the success of the present reaction.[11] No reaction occurred with Pd(PPh_3)$_4$, which is a highly active catalyst for the stereoselective addition of organic disulfides to alkynes,[12] or RhCl(PPh_3)$_3$, which is also an active catalyst for the highly regio- and stereoselective hydrothiolation of alkynes with thiols.[13] Thus, the present reaction is characteristic of ruthenium catalysts.

Scheme 1[a]



[a] Figures in the parentheses are GLC yield. [b]For 1 h. [c]For 3 h. [d]For 8 h. [e]For 2 days.

The use of an appropriate solvent is also critically important. No reaction occurred in toluene, 1,4-dioxane, DMF, or propionitrile as a solvent. Only tertiary amines such as *N*-methylpiperidine (**3a**, >99%), and triethylamine (**3a**, 92%) were suitable as solvents for the present reaction. These results strongly suggest that amines such as *N*-methylpiperidine act as both a suitable ligand for an active ruthenium intermediate and a solvent to prevent catalyst poisoning by thiols.[10]

The *S*-propargylation of several aromatic thiols (**2**) with propargylic carbonates (**1**) proceeded smoothly with a CpRuCl(cod) catalyst in *N*-methylpiperidine, and the results are summarized in Scheme 1.

In all cases, propargylic carbonates (**1**) were completely consumed to give the corresponding aryl propargylic sulfides (**3a**−**g**) in good to high isolated yields. Allenylic sulfides, which sometimes became a main product in the reactions of propargylic compounds with sulfur compounds,[14] and *vicinal*-dithioethers, which may be derived from the double thiolation of a (σ-allenyl)ruthenium intermediate, were not obtained at all (vide infra). The substituents at the terminal acetylenic carbon in **1** and the electron-donating and -withdrawing substituents on the aromatic ring in **2** did not affect the reaction. Note that the trimethylsilyl-substituted propargylic carbonate, **1d**, gave the corresponding propargylic sulfide in

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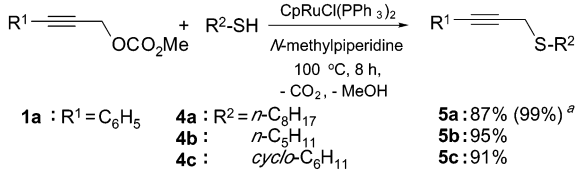
Scheme 2[a]



[a] Figure in the parentheses is GLC yield.

only 46% yield because of the desilylation of the starting **1d** and the product **3h**. As can be readily seen from Scheme 1, general internal propargylic carbonates are suitable substrates for the present reaction. Functional groups such as OCH_3 and Cl on the phenyl substituent in **1a** were also tolerated. Unsubstituted terminal propargylic carbonates are poor substrates for the present reaction.[15]

Surprisingly, CpRuCl(cod) was totally inefficient for the *S*-propargylation of aliphatic thiols such as octanethiol (**4a**) with **1a**. It has been pointed out that ruthenium-catalyzed reactions require highly careful tuning of the reaction conditions with substrates to obtain products in high yields and selectivities.[11] By screening the catalysts again, we finally found that $CpRuCl(PPh_3)_2$ is specifically effective for the *S*-propargylation of aliphatic thiols (**4**) (Scheme 2). Since the coordination ability of aliphatic thiols (**4**) is higher than that of aromatic thiols (**2**), a more basic ligand such as PPh_3 is needed to prevent catalyst poisoning by thiols.

While the reaction mechanism is not yet clear, we now believe that the (σ-propargyl)ruthenium complex[16] is a key intermediate in the present reaction. *N*-Methylpiperidine and PPh_3 may contribute to the formation of this (σ-propargyl)ruthenium intermediate. It has been found that propargylic compounds add oxidatively to transition metals to give either (σ-allenyl)metal complexes or (σ-propargyl)-metal complexes.[17] Generally, (σ-allenyl)metal complexes were generated from *terminal* propargylic compounds.[18] *Internal* propargylic compounds gave (σ-propargyl)metal complexes because of the bulkiness of the terminal substituent on the alkyne moiety.[18b] If the present reaction proceeds via a (σ-allenyl)ruthenium intermediate, *vicinal*-dithioethers by double nucleophilic thiolation of a (σ-allenyl)ruthenium intermediate as well as allenylic sulfides should be obtained as in the palladium-catalyzed reaction of propargylic compounds with nucleophiles.[3a,c] However, the present reaction exclusively gave the corresponding propargylic sulfides without the formation of allenylic sulfides or *vicinal*-dithioethers (vide supra), which suggests that the present reaction proceeds via the (σ-propargyl)ruthenium intermediate.

In conclusion, simple and readily available ruthenium complexes of the type $CpRuClL_2$ were found to act as efficient catalysts for the synthesis of propargylic sulfides via *S*-propargylation of aromatic or aliphatic thiols under neutral conditions. This reaction may complement the previously reported thiolato-bridged diruthenium complex-catalyzed *S*-propargylation of thiols with *terminal* propargylic alcohols.[6] This reaction should also open up new opportunities in transition-metal complex-catalyzed sulfur chemistry.

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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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(15) Further, the reaction of **2a** with a secondary propargylic carbonate, methyl 1,3-diphenylprop-2-ynyl carbonate (**1e**), is quite complicated. The yield of the normal *S*-propargylic substitution product, phenyl 1,3-diphenylprop-2-ynyl sulfide, was low (>10%), while the addition of diphenyl disulfide generated from **2a** to the triple bond in **1e** as well as reduction of a OCO_2-Me group occurred to give unexpected (*Z*)-1,2-bis(phenylthio)-1,3-diphenylprop-1-ene (**6a**) in an isolated yield of 38%. Further studies are apparently required for these reactions using secondary and *tertiary* propargylic carbonates.

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