Ruthenium-catalyzed rearrangement of propargyl sulfoxides: Formation of α,β -unsaturated thioesters

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ABSTRACT

Our previously developed strategy of generating ketene intermediates via Ru-catalyzed intramolecular oxidation of terminal alkynes is applied to propargyl sulfoxides. The reaction undergoes interesting further rearrangement upon the ketene generation to afford α,β -unsaturated thioesters in good to excellent yields in the reported cases.

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Introduction

Ruthenium vinylidenes^[1] are versatile intermediates in organic synthesis and can be readily generated from terminal alkynes. They have served as key and versatile intermediates in a diverse range of efficient transformations.^[2]

Recently, we^[3] reported that in situ-generated Ru vinylidenes can be oxidized^{[4],[5]} by appropriately tethered sulfoxides to afford ketenes.^[6] These synthetically versatile intermediates can be trapped by tethered olefins or separate imines to afford cyclobutanones and β -lactams, respectively (Scheme 1).

Scheme 1 The oxidation of in-situ generated Ru vinylidenes into ketenes by using tethered sulfoxides and examples of their trapping.

During that study, we examined an aryl propargyl sulfoxide (i.e., **1a**) and discovered that besides the expected β -lactam

product **2a** the thioacrylate **3a** was formed as a byproduct in 5% yield (Scheme 2). In the absence of the imine reaction partner, the yield of **3a** was improved to an unoptimized 31%. A mechanism is proposed to rationalize its formation and entails initial oxidative generation of the sulfide ketene **A**, then cyclization of the sulfide moiety of **A** to its ketene part to form the zwitterionic dihydrothietium species **B**, and finally electrocyclic ring opening of **B**. Since this side reaction offers a unique access to synthetically useful α,β -unsaturated thioesters, we set out to optimize the reaction conditions and examine its scope. Herein we report our findings.

Scheme 2 Ru-catalyzed reactions of aryl propargyl sulfoxides and a proposed mechanism for the formation of **3a**.

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Results and discussion

On the outset, we chose the aryl sulfoxide **1b** as the substrate for condition optimization. At first, we employed the conditions used in Scheme 2 with the exception of the loading of the ligand and the Ru catalyst. As shown in Table 1, entry 1, 2 mol% of $\text{CpRu}(\text{PPh}_3)_2\text{Cl}$ and 4 mol% of **L2** led to a highly efficient catalysis, and the expected α,β -unsaturated thioester product **3b** was formed in an excellent 91% yield and with excellent *E*-selectivity (>20:1). The structures of **L2** and its less accessible homolog **L1** are shown in Table 1 equation. Notably, both ligands are members of AZARPHOS having their pyridine nitrogen sterically shielded from coordinating to Ru^[7] and known to facilitate Ru-catalyzed anti-Markovnikov hydration of terminal

alkyne^[8] via accelerating the isomerization of terminal alkynes into Ru vinylidenes.^[9] In the absence of **L2** or by replacing it with PPh_3 (entry 2) little reaction occurred. With **L1** as ligand, the reaction yield was a lower 82% yield (entry 3). Lowering the reaction temperature (entry 4), changing the chloride scavenger from $\text{NaBAR}^{\text{F}}_4$ to NaPF_6 (entry 5) or AgNTf_2 (entry 6), and skipping 4 Å MS (entry 7) all led to lower yields. DCE turned out to be the optimal solvent as toluene (entry 8) and PhF (entry 9) were much inferior and PhCF_3 (entry 10) was also less effective. While increasing the reaction concentration by 10 times slightly impacted the reaction efficiency (entry 11), lowering the catalyst loading to 0.5 mol% had a much worse impact on the yield (entry 12).

Table 1. Initial condition optimization.^a

Entry	Catalyst	Ligand	Conditions	Yield (%) ^b
1	$\text{CpRu}(\text{PPh}_3)_2\text{Cl}$, $\text{NaBAR}^{\text{F}}_4$ (4%)	L2 (4%)	DCE, 60 °C, 3h	91(91) ^c
2	$\text{CpRu}(\text{PPh}_3)_2\text{Cl}$, $\text{NaBAR}^{\text{F}}_4$ (4%)	PPh_3 (4%)	DCE, 60 °C, 6 h	<5
3	$\text{CpRu}(\text{PPh}_3)_2\text{Cl}$, $\text{NaBAR}^{\text{F}}_4$ (4%)	L1 (4%)	DCE, 60 °C, 3h	82
4	$\text{CpRu}(\text{PPh}_3)_2\text{Cl}$, $\text{NaBAR}^{\text{F}}_4$ (4%)	L2 (4%)	DCE, 40 °C, 12h	73
5	$\text{CpRu}(\text{PPh}_3)_2\text{Cl}$, NaPF_6 (4%)	L2 (4%)	DCE, 60 °C, 3h	76
6	$\text{CpRu}(\text{PPh}_3)_2\text{Cl}$, AgNTf_2 (4%)	L2 (4%)	DCE, 60 °C, 3h	84
7 ^d	$\text{CpRu}(\text{PPh}_3)_2\text{Cl}$, $\text{NaBAR}^{\text{F}}_4$ (4%)	L2 (4%)	DCE, 60 °C, 3h	65
8	$\text{CpRu}(\text{PPh}_3)_2\text{Cl}$, $\text{NaBAR}^{\text{F}}_4$ (4%)	L2 (4%)	Toluene, 60 °C, 3h	31
9	$\text{CpRu}(\text{PPh}_3)_2\text{Cl}$, $\text{NaBAR}^{\text{F}}_4$ (4%)	L2 (4%)	PhF, 60 °C, 3h	44
10	$\text{CpRu}(\text{PPh}_3)_2\text{Cl}$, $\text{NaBAR}^{\text{F}}_4$ (4%)	L2 (4%)	PhCF_3 , 60 °C, 3h	80
11 ^e	$\text{CpRu}(\text{PPh}_3)_2\text{Cl}$, $\text{NaBAR}^{\text{F}}_4$ (4%)	L2 (4%)	DCE, 60 °C, 3h	85
12	$\text{CpRu}(\text{PPh}_3)_2\text{Cl}$ (0.5%), $\text{NaBAR}^{\text{F}}_4$ (1%)	L2 (4%)	DCE, 60 °C, 3h	61

^a Initial [**1b**] = 0.05 M.

^b Estimated by ¹H NMR using diethyl phthalate as the internal reference.

^c Isolated yield.

^d 4 Å MS not used.

^e Initial [**1b**] = 0.5 M.

With the optimal conditions as shown in Table 1, entry 1 in hand, the scope of this reaction was investigated, and the results are summarized in Table 2. With the phenethyl group of **1b** replaced by an *n*-pentyl group, the reaction proceeded smoothly to afford the desired thioester **3c** in 89% (entry 1). Similarly, the methyl derivative reacted without incident, albeit with a lower yield (entry 2). The bulky 2,6-dimethylphenyl group approved to be optimal but not uniquely effective as a 2,6-dichlorophenyl (entry 3) and even the parent phenyl group (entry 4) were suitable groups on sulfur, leading to good yields of the corresponding products. Interestingly, even *n*-butyl (entry 5) was an effective substituent on the sulfoxide, and the α,β -unsaturated thioester **3g** was formed in 83% yield. When the optimized conditions were applied to the substrate **1a** used in Scheme 2, to our surprise, the yield was much higher (entry 6) than the originally observed 31%. The difference is the loadings of the Ru catalyst and the ligand as higher 5% and 10% were employed in the original study, respectively. Propargyl butyl sulfoxide, i.e., **1h**, was also a suitable substrate, and the desired thioacrylate **3h** was isolated in 82% yield (entry 7).

Table 2. Formation of α,β -unsaturated thioesters.

Entry	Substrate	Product	Yield %
1			89
2			79
3			84
4			71
5			83

6	1a	3a	81
7	1h	3h	82

Conclusions

In summary, we have developed an efficient ruthenium-catalyzed transformation of propargyl sulfoxides into synthetically useful α,β -unsaturated thioesters. In this reaction, a ruthenium vinylidene intermediate generated from terminal alkyne is oxidized by the tethered sulfoxide to generate a synthetically versatile ketene species, which in this particular reaction is trapped by the nascent sulfide to eventually afford the product upon rearrangement.

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