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

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ABSTRACT

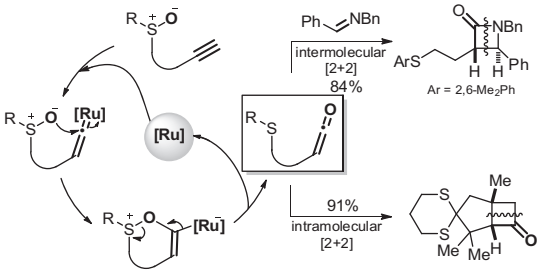
Our previously developed strategy of generating ketene intermediates via Ru-catalyzed intramolecular oxidation of terminal alkynes is applied to propargyl sulfoxides. The reaction undergoes interesting further rearrangement upon the ketene generation to afford α,β-unsaturated thioesters in good to excellent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

Introduction

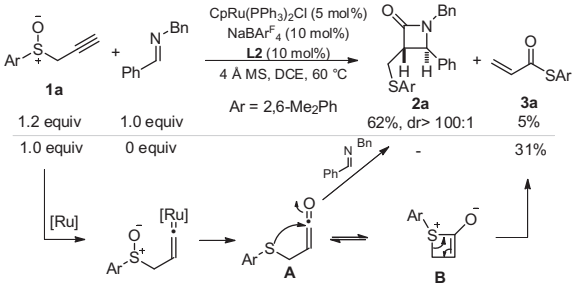
Ruthenium vinylidenes[1] are versatile intermediates in organic synthesis and can be readily generated from terminal alkynes. They have served as key and versatile intermediates in a diverse range of efficient transformations.[2]

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).

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



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

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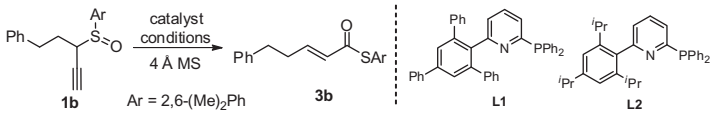
0040-4039/

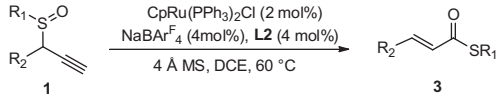
Table 1
Initial condition optimization[a]

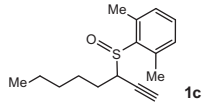
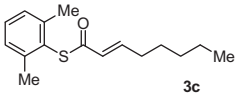
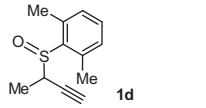
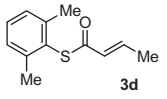
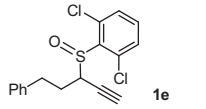
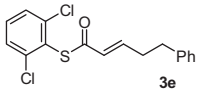
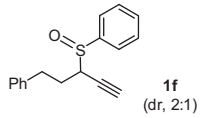
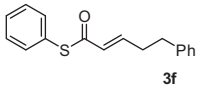
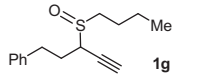
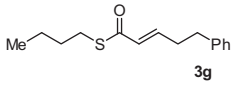
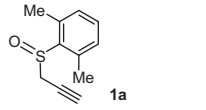
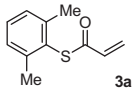
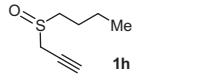
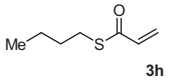


Entry	Catalyst	Ligand	Conditions	Yield[b] (%)
1	**CpRu(PPh$_3$)$_2$Cl (2%), NaBAr$^F_4$ (4%)**	**L2 (4%)**	**DCE, 60 °C, 3 h**	**91 (91)[c]**
2	CpRu(PPh$_3$)$_2$Cl (2%), NaBAr$^F_4$ (4%)	PPh$_3$ (4%)	DCE, 60 °C, 6 h	<5
3	CpRu(PPh$_3$)$_2$Cl (2%), NaBAr$^F_4$ (4%)	**L1** (4%)	DCE, 60 °C, 3 h	82
4	CpRu(PPh$_3$)$_2$Cl (2%), NaBAr$^F_4$ (4%)	**L2** (4%)	DCE, 40 °C, 12 h	73
5	CpRu(PPh$_3$)$_2$Cl (2%), NaPF$_6$ (4%)	**L2** (4%)	DCE, 60 °C, 3 h	76
6	CpRu(PPh$_3$)$_2$Cl (2%), AgNTf$_2$ (4%)	**L2** (4%)	DCE, 60 °C, 3 h	84
7[d]	CpRu(PPh$_3$)$_2$Cl (2%), NaBAr$^F_4$ (4%)	**L2** (4%)	DCE, 60 °C, 3 h	65
8	CpRu(PPh$_3$)$_2$Cl (2%), NaBAr$^F_4$ (4%)	**L2** (4%)	Toluene, 60 °C, 3 h	31
9	CpRu(PPh$_3$)$_2$Cl (2%), NaBAr$^F_4$ (4%)	**L2** (4%)	PhF, 60 °C, 3 h	44
10	CpRu(PPh$_3$)$_2$Cl (2%), NaBAr$^F_4$ (4%)	**L2** (4%)	PhCF$_3$, 60 °C, 3 h	80
11[e]	CpRu(PPh$_3$)$_2$Cl (2%), NaBAr$^F_4$ (4%)	**L2** (4%)	DCE, 60 °C, 3 h	85
12	CpRu(PPh$_3$)$_2$Cl (0.5%), NaBAr$^F_4$ (1%)	**L2** (4%)	DCE, 60 °C, 3 h	61

[a] Initial [**1b**] = 0.05 M.
[b] Estimated by ^{1}H NMR using diethyl phthalate as the internal reference.
[c] Isolated yield.
[d] 4 Å MS not used.
[e] Initial [**1b**] = 0.5 M.

Table 2
Formation of α,β-unsaturated thioesters



Entry	Substrate	Product	Yield (%)
1	 **1c**	 **3c**	89
2	 **1d**	 **3d**	79
3	 **1e**	 **3e**	84
4	 **1f** (dr, 2:1)	 **3f**	71
5	 **1g**	 **3g**	83
6	 **1a**	 **3a**	81
7	 **1h**	 **3h**	82

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 CpRu(PPh$_3$)$_2$Cl, 4 mol% of NaBAr$^F_4$, 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 an 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 Ph$_3$P (entry 2) little reaction occurred. With **L1** as ligand, the reaction yield was a lower 82% (entry 3). Lowering the reaction temperature (entry 4), changing the chloride scavenger from NaBAr$^F_4$ 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).

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 groups (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 loadings of the Ru catalyst and the ligand as higher 5% and 10% were employed in the original study, respectively. Propargyl butyl sulfoxide, that is, **1h**, was also a suitable substrate, and the desired thioacrylate **3h** was isolated in 82% yield (entry 7).

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.

Acknowledgments

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Supplementary data

Supplementary data (copies of ^{1}H NMR and ^{13}C NMR spectra of substrates and products. Experimental procedures and data for substrates and products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.138. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Murahashi, S. *Ruthenium in Organic Synthesis*; Wiley-VCH: Weinheim, 2004.
2. (a) Trost, B. M.; McClory, A. *Chem. Asian J.* **2008**, *3*, 164–194; (b) Bruneau, C.; Dixneuf, P. H. *Metal Vinylidenes and Allenylidenes in Catalysis: From Reactivity to Applications in Synthesis*; Wiley-VCH: Weinheim, 2008; (c) Bruneau, C.; Dixneuf, P. H. *Acc. Chem. Res.* **1999**, *32*, 311–323; (d) Varela, J. A.; Gonzalez-Rodriguez, C.; Rubin, S. G.; Castedo, L.; Saa, C. *Pure Appl. Chem.* **2008**, *80*, 1167–1177.
3. Wang, Y.; Zheng, Z.; Zhang, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 9572–9576.
4. (a) Madhushaw, R. J.; Lin, M.-Y.; Sohel, S. M. A.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, *126*, 6895–6899; (b) Lin, M.-Y.; Madhushaw, R. J.; Liu, R.-S. *J. Org. Chem.* **2004**, *69*, 7700–7704; (c) Lin, M.-Y.; Maddirala, S. J.; Liu, R.-S. *Org. Lett.* **2005**, *7*, 1745–1748; (d) Pati, K.; Liu, R.-S. *Chem. Commun.* **2009**, 5233–5235.
5. For recent studies using Rh catalysts, see: (a) Kim, I.; Lee, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 10023–10026; (b) Kim, I.; Roh, S. W.; Lee, D. G.; Lee, C. *Org. Lett.* **2014**, *16*, 2482–2485.
6. For a review on ketenes, see: Tidwell, T. T. *Eur. J. Org. Chem.* **2006**, *2006*, 563–576.
7. Hintermann, L.; Dang, T. T.; Labonne, A.; Kribber, T.; Xiao, L.; Naumov, P. *Chem.-Eur. J.* **2009**, *15*, 7167–7179.
8. Labonne, A.; Kribber, T.; Hintermann, L. *Org. Lett.* **2006**, *8*, 5853–5856.
9. Grotjahn, D. B.; Miranda-Soto, V.; Kragulj, E. J.; Lev, D. A.; Erdogan, G.; Zeng, X.; Cooksy, A. L. *J. Am. Chem. Soc.* **2007**, *130*, 20–21.