Published in final edited form as:

Tetrahedron Lett. 2017 January 4; 58(1): 106–108. doi:10.1016/j.tetlet.2016.11.121.

Allenyl esters as quenching agents for ruthenium olefin metathesis catalysts

Animesh Roy, Maximilian A. Silvestri, Robert A. Hall, and Salvatore D. Lepore*

^aDepartment of Chemistry and Biochemistry, Florida Atlantic University, Boca Raton, FL 33431

Abstract

In the attempt to synthesize substituted allenyl esters through a metathesis coupling of unsubstituted allenyl esters and alkenes using a variety of ruthenium catalysts, it was discovered that allenyl esters themselves cleanly arrested the activity of the catalysts. Further studies suggests possible utility of allene esters as general quenching agents for metathesis reactions. To explore this idea, several representative olefin metathesis reactions, including ring closing, were successfully terminated by the addition of simple allenyl esters for more convenient purification.

Graphical abstract

Keywords

Metathesis quenching; Metathesis poison; Allenyl esters

Our recent work in the area of allenyl carbonyl chemistry has focused on the development of synthetic methods for their construction¹ and utilization in the synthesis of densely functionalized bridged bicycles.² Recently, we investigated the reactivity of simple allenyl esters in cross metathesis reactions with alkenes to form more substituted allenyl esters using catalysts **1** – **4** developed by Grubbs and Hoveyda (Figure 1). Although the use of ruthenium catalysts for olefin metathesis, ring-closing metathesis, and enyne metathesis are well documented in the literature, their use with carbonyl-conjugated allenes is unknown.³ In the present work, we describe our attempts to form γ -substituted allenyl esters using a metathesis approach. As will be discussed, ruthenium based catalysts failed to afford the

*Corresponding author. Tel: (561) 297-0330. Fax: (561) 297-2759, slepore@fau.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Supplementary data

Supplementary data (general experimental details, characterization data of all products, ¹H and ¹³C NMR spectra of representative products) associated with this article can be found, in the online version, at...

desired cross-coupling (or even homo-coupling) products. Instead, we found that allenyl esters acted as effective catalyst quenching agents.

We began our studies with commercially available allenyl ester ethyl 2,3-butadienoate (**5**). Attempts to react allene **5** with 4-pentenyl acetate (**6**) utilizing olefin metathesis catalysts **1** – **4** in refluxing CDCl₃ failed to yield the desired cross metathesis product **7** (Scheme 1).

When catalysts **1** and **3** were used, unreacted starting materials were primarily recovered from the reaction. Additional attempts to promote the cross metathesis reaction with **1** or **3** under varying reaction conditions (solvent, temperature, and concentration) primarily resulted in allene decomposition. However, with catalysts **2** and **4**, which contain heterocyclic carbene units, we observed that allenyl ester **5** was converted to an oligomeric material containing a 2-butenate repeating unit (such as structure **8**) although we have not been able to determine the exact structure.⁴

Others have reported oligomerization products with aliphatic allenes.^{3a} These oligomerization reactions may proceed by a carbene catalyzed process.⁵ Interestingly, homo-metathesized allene and alkene products were also not detected in these metathesis reactions. Attempts to cross-metathesize allenyl ester **5** and alkyl allenyl **9** (Figure 2) using catalyst **4** led only to oligomeric material derived from allenyl ester **5**. We found this somewhat surprising since others have shown that hydrocarbon allenes readily undergo homo-metathesis.^{3a} Under both high-dilution and standard conditions, ring-closing metatheses (RCM) of **10** and **11** also failed (Figure 2). Based on these studies, we surmised that allenyl esters react irreversibly with the catalysts in our study to form a catalytically inactive ruthenium species.

To test this hypothesis, we reacted catalyst **4** with allene **14** using one-to-one stoichiometry; with this allene, no oligomeric product is observed (Scheme 2). In monitoring this reaction by NMR, we noted that the characteristic Ru=C(H) carbene shifts of catalyst **4** and the allenic (sp and sp²) shifts of **14** disappeared in the ¹³C NMR. Isopropoxy styrene **15** peaks were also observed. These data suggest that allenyl ester **14** underwent a single metathesis cycle with the ruthenium catalyst possibly to give a vinylidene complex⁶ but ultimately leading to an unknown ruthenium species (see Supplementary data for NMR spectra of **16**)⁷ that was no longer active in olefin metathesis. In another experiment (not shown), catalyst **3** was first reacted with allene **5** (3 eq) followed by the addition of alkene **6**. No homo-metathesis product of **6** was observed further confirming the loss of catalytic activity upon addition of an allenyl ester.

To explore the use of allenyl esters as catalyst quenching agents we sought to inhibit the ring closing metathesis of diethyl diallyl malonate (**17**). This substrate was chosen as a challenging case for metathesis inhibition due to the rapidity of this intramolecular reaction to give cyclopentene **18** (< 2 h). Indeed, ring closing metathesis of **17** is completely arrested when 10 equivalents (relative to catalyst **4**) of allenyl ester (**5**, **12** – **14**) is added at the start of the reaction. Allenyl ester **14** was particularly effective in this regard (Table 1) since no oligomer byproducts were formed during catalyst arrest. Importantly, excess quenching agents are easily removed in vacuo due to their low boiling points.

Typically, metathesis reactions generate colored ruthenium byproducts, which can be difficult to remove and often require multiple chromatographic purifications. Incomplete removal of the ruthenium byproducts may lead to double bond isomerization during distillation or a decomposition of reaction products.⁸ Due to this persistent problem, a variety of approaches have been employed to remove these colored impurities. The majority of these strategies involve the use of oxidizers or chelating agents that deactivate the metal and facilitate its removal often by aqueous extraction.⁹ More recently, a variety of alternative approaches have also been reported such as the use of a redoxdriven processes to control the activity of Ru catalysts and facilitate their removal from reactions mixtures.¹⁰ Others have developed metathesis catalysts with an affinity for commercially available silica gel.¹¹ A complementary technique has also been reported involving unmodified catalysts that are sequestered by resins modified to contain an isocyanide ligand.¹²

To examine the potential utility of allene **14** as a non-oxidizing quenching agent¹⁴ in the context of typical metathesis reactions, we examined several inter- and intramolecular coupling reactions (Scheme 3). We observed that the addition of allene **14** after the completion of metathesis reactions facilitated the removal of colored metathesis impurities in a single chromatographic separation. The cross-metathesis of olefin **6** with methyl acrylate using catalyst **4** led to a 61% isolated yield of **19** (after a second purification over alumina), which is a known compound.⁵ After the addition of **14** upon reaction completion, we realized an improved isolated yield of 91%. Similarly, the isolated yield of RCM reactions of **22** improved with the addition of allene **14** as a quenching agent upon reaction completion.

The amount of Ru impurity left after quenching with allene ester was found to be significantly lower compared to metathesis product without treating with allene ester. This is verified by measuring strong absorbance of Ru carbene complexes (at 376 nm due to MLCT to π^* of Ru=CHR) using UV-VIS spectroscopy.¹³ For example, after the metathesis reaction of compound **20** was complete, a portion of product **21**, was purified over standard flash silica gel (40–63 μm , 60Å). A UV/Vis analysis of this product revealed a strong absorption at 376 nm, which indicated that the colored byproducts were likely derived from the Ru catalyst (Scheme 4).¹³

A second portion of product **21** was treated with allene **14** after the metathesis reaction was complete and stirred at room temperature for an hour before purifying using the same flash chromatography conditions.¹⁵ A UV/Vis analysis suggests that quenching with allene ester removed the majority of Ruthenium impurities (Scheme 4, Ru absorbance at 376 nm was not observed).

In summary, our studies suggest that allenyl esters do not undergo olefin metathesis with traditional ruthenium catalysts. Instead, these allenyl esters completely inhibit metathesis activity. The organometallic complex that forms between ruthenium catalyst and allenyl esters is conveniently removed using standard silica chromatography. This use of simple allenyl esters offers a useful alternative to traditional quenching agents for the removal of Ru impurities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by a grant from the National Institutes of Health (GM110651). We thank Prof. Deguo Du and Haiyang (Ocean) Liu for their help in acquiring UV/Vis spectra.

References and notes

1. (a) Roy A, Bhat BA, Lepore SD. *Org. Lett.* 2016; 18:1230. [PubMed: 26925611] (b) Roy A, Bhat BA, Lepore SD. *Org. Lett.* 2015; 17:900. [PubMed: 25662282]
2. (a) Maity P, Lepore SD. *J. Am. Chem. Soc.* 2009; 131:4196. [PubMed: 19271702] (b) Silvestri MA, Bromfield DC, Lepore SD. *J. Org. Chem.* 2005; 70:8239. [PubMed: 16277359]
3. However, two reports indicate that aliphatic allenes undergo homometathesis in the presence of ruthenium catalysts: Ahmed M, Arnauld T, Barrett AGM, Braddock CD, Flack K, Procopiou PA. *Org. Lett.* 2000; 2:551. [PubMed: 10814374] Janben CE, Krause N. *Eur. J. Org. Chem.* 2005:2322.
4. The chromatography profile and spectroscopic characterization of this waxy solid using ^1H , ^{13}C NMR, and MS (MALDI TOF) argue for an oligomeric compound: ^1H NMR (400 MHz, CDCl_3) δ 5.82 (s, 1H), 4.07 (q, 2H, $J = 7.2$ Hz), 3.51 (s, 2H), 1.22 (t, 3H, 7.2 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 165.7, 154.2, 119.6, 59.7, 39.9, 14.1; MS (MALDI TOF) 393.4613 (base), 407.4503, 519.5390, 631.6328, 742.7199. These last few peaks are 112 m/z units apart which is the mass of allene **5**.
5. Lipshutz BH, Aguinaldo GT, Ghorai S, Voigtritter K. *Org. Lett.* 2008; 10:1325. [PubMed: 18335947]
6. For vinylidene complexes please see Bruce MI. *Chem. Rev.* 1991; 91:197. Bruneau C, Dixneuf PH. *Acc. Chem. Res.* 1999; 32:311. Schwab P, Grubbs RH, Ziller JW. *J. Am. Chem. Soc.* 1996; 118:100. Lynam JM. *Chem. Eur. J.* 2010; 16:8238. [PubMed: 20607768] For allenylidene complex: Castarlenas R, Fischmeister C, Bruneau C, Dixneuf PH. *J. Mol. Catal. A: Chem.* 2004; 213:31.
7. We noticed that one equivalent of allene ester leads to the dissociation of styrene isopropoxy ligand from ruthenium catalyst **4** suggesting the initial formation of a Ru vinylidene species. However, we did not observe characteristic peaks for $\text{Ru}=\text{C}(\text{H})$, $\text{Ru}=\text{C}$, or $\text{Ru}=\text{C}=\text{C}$ (see Supplementary data): Ríos Isaac, De Los, Bustelo, E., Puerta, MC., Valerga, P. *Organometallics*. 2010; 29:1740.
8. Maynard HD, Grubbs RH. *Tetrahedron Lett.* 1999; 40:4137.
9. *For a review see:* Clavier H, Grela K, Kirschning AM, Nolan SP. *Angew. Chem. Int. Ed.* 2007; 46:6786. *For more recent strategies see:* Hobbs C, Yang Y, Ling J, Nicola S, Su H, Bazzi HS, Bergbreiter DE. *Org. Lett.* 2011; 13:3904. [PubMed: 21707117] Allen DP, Van Wingerden MM, Grubbs RH. *Org. Lett.* 2009; 11:1261. [PubMed: 19239246]
10. Rosen EL, Varnado CD, Arumugam K, Bielawski CW. *J. Organomet. Chem.* 2013; 201:745.
11. Schachner JA, Cabrera J, Padilla R, Fischer C, Van der Schaaf PA, Pretot R, Rominger F, Limbach M. *ACS Catal.* 2011; 1:872.(b) Cabrera J, Padilla R, Dehn R, Deuerlein S, Gułajski Ł, Chomiszczak E, Teles JH, Limbach M, Grela K. *Adv. Synth. Catal.* 2012; 354:1043.
12. French JM, Caras CA, Diver ST. *Org. Lett.* 2013; 15:5416. [PubMed: 24128003]
13. Others have reported a strong Ru absorbance ($\epsilon = 7000\text{--}20,000 \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$) at 376 nm, which are likely due to metal-to-ligand charge transfer (MLCT) into the π^* orbital of the $\text{Ru}=\text{CHR}$, Please see Table 2 and S32 (supporting information) of Thiel V, Hendann M, Wannowius K, Plenio H. *J. Am. Chem. Soc.* 2012; 134:1104. [PubMed: 22188483]
14. Ethyl vinyl ether (EVE) is known to arrest metathesis activity after a single cycle and used to quench ruthenium carbene catalysts. Excess EVE (~100 equiv. relative to catalyst) was added to quench any metathesis active species. It forms stable complex with Ru carbene: Nagarkar AA, Kilbinger AFM. *Nature Chem.* 2015; 7:718. [PubMed: 26291943] Wu Z, Nguyen ST, Grubbs RH, Ziller JW. *J. Am. Chem. Soc.* 1995; 117:5503.

15. *Representative procedure - metathesis of 20 followed by allene quenching:* (Please see Supplementary Data for additional detail) After the metathesis reaction was complete, the heating bath was removed and the reaction mixture was allowed to cool for 5 min. Allene ester **14** (~100 equiv. relative to catalyst) was added as a DCM solution to arrest any metathesis active species. This was stirred at room temperature for one hour. The solvent was then removed by evaporation and the resulting crude product was directly transferred to a silica column for purification.

Highlights

- Allenyl esters cleanly arrested the activity of the ruthenium metathesis catalysts.
- These allenes are effective as mild catalyst quenching agents.
- The allenes also facilitated catalyst removal during purification.

Figure 1.
Catalysts used in this study (Grubbs and Grubbs – Hoveyda).

Figure 2.
Substrates for various metathesis studies.

Scheme 1.
Metathesis reactions with allenyl ester **5** and primary alkene **6**.

Scheme 2.
Proposed catalyst poisoning reaction.

Comparison of metathesis reactions with and without **14** added at the end of the reaction as a quenching agent.

Scheme 4.

(a) Various purification schemes for product **21**; (b) Comparison of Ru content by UV/Vis spectra (in toluene); (I) Catalyst **4**, (II) product **21** after simple silica gel flash chromatography and (III) **21** was treated with allene **14** followed by flash chromatography.

Table 1

Inhibition of ring closing olefin metathesis with **14** added in varying amounts at the beginning of the reaction.

Reaction scheme: **17** $\xrightarrow[\text{allene } \mathbf{14}]{\mathbf{4}, \text{CHCl}_3, \text{rt}}$ **18**

Entry	Equiv 14 ^a	% yield 18 ^b
1	0	89 (86 ^c)
2	2.0	61
3	4.0	36
4	6.0	3
5	8.0	<1
6	10	0
7 ^d	10	0

^aEquivalents based on limiting substrate **17**. Quenching agent **14** was added at the beginning of the reaction.

^bYield determined by GC with the balance being unreacted **17**.

^cIsolated yield.

^dReaction was refluxed in benzene for 12 h.