



## Di(ethylene glycol) vinyl ether: a highly efficient deactivating reagent for olefin metathesis catalysts

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### ABSTRACT

A highly efficient method for deactivating commonly used olefin metathesis catalysts is described. Inexpensive and commercially available di(ethylene glycol) vinyl ether is found to quench both first- and second-generation Grubbs' carbenes in less than 10 min at room temperature. The resulting ruthenium byproducts are readily removed by silica gel purification.

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Olefin metathesis has increasingly found applications in both academia and industry in the past decade.<sup>1</sup> The utility of this powerful synthetic method has recently been demonstrated in Boehringer Ingelheim's large-scale production of 400 kg of a 15-membered macrocyclic intermediate for the complex HCV/NS3 inhibitor BILN 2061.<sup>2</sup> However, challenges such as high dilution, selectivity, isomerization, and high catalyst loading need to be overcome to execute metathesis reactions on a large scale.<sup>3</sup> A few novel metathesis catalysts have recently been developed with enhanced stability and activity.<sup>4</sup> Catalyst loadings are significantly lower with these catalysts, but their enhanced stability can result in undesired side reactions during reaction workup due to the reversible nature of the metathesis reaction. In small scale metathesis reactions, the reaction mixture can typically be concentrated uneventfully or distilled to a small volume for convenient workup and purification. For large scale industrial reactions, however, the evaporation of solvent can result in serious side reactions such as ring-opening, cross-metathesis, or isomerization due to the presence of the active catalytic species over longer operation times.<sup>3,5</sup> Efficient and convenient removal of toxic ruthenium byproducts is also required for metathesis reactions to be viable in making pharmaceutical products on large scale.<sup>3,6</sup> Recently, a more efficient synthesis of BILN 2061 has been disclosed where significant research was dedicated to optimizing the diene substrate with re-

gard to concentration and catalyst loading.<sup>7</sup> This impressive optimization was necessary to overcome the issues mentioned previously, and develop a commercial process. Unfortunately, early phase kilogram deliveries utilizing metathesis reactions will continue to suffer from the aforementioned problems. In these cases, and cases where substrate optimization is not possible, a reagent that could rapidly deactivate the catalyst and assist the removal of the ruthenium byproducts would be very useful to the industrial community.

Various methods for deactivating the active catalytic species in the workup of metathesis reactions, such as  $\text{Pb}(\text{OAc})_4$ ,<sup>8a</sup> DMSO,<sup>8b</sup>  $\text{Ph}_3\text{P}=\text{O}$ ,<sup>8b</sup> tris(hydroxymethyl) phosphine (THMP),<sup>6</sup> activated carbon,<sup>8c</sup> mesoporous silicates,<sup>8d</sup> and 2-mercaptopyridine,<sup>3</sup> have been reported. Effective cleanup procedures provided by these methods are often associated with high loading of ruthenium scavengers and long processing times. Diver and co-workers<sup>9</sup> have recently demonstrated a novel method for quenching Grubbs' carbene complexes via ligand insertion with a polar isocyanide ( $\text{NCCH}_2\text{CO}_2\text{Et}$ ). Although this new isocyanide provides a faster and more effective method for deactivating many commonly used metathesis catalysts, it also has limitations, such as limited tolerance towards functional groups, toxicity, and the lack of commercial availability, which may hinder its wide application. A new reagent that is devoid of the above issues and performs as well as or better than this isocyanide is desired.

Ethyl vinyl ether is known to react with ruthenium carbene to form a stable Fischer carbene complex.<sup>10</sup> It has been adopted as a quenching reagent in ring-opening polymerization (ROMP) to

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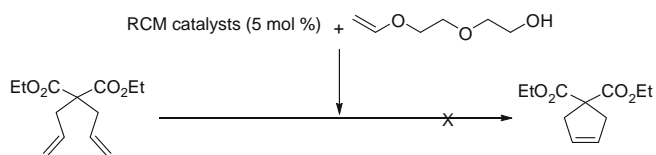
stop the reaction propagation and produce an olefin-capped polymer chain.<sup>11</sup> The Grubbs group reported<sup>12</sup> that the formation of a Fischer carbene by reaction of a large excess of ethyl vinyl ether with both 1st and 2nd generation Grubbs' catalysts is quantitative and irreversible by <sup>1</sup>H NMR spectroscopy. Ethyl vinyl ether shows the ability to deactivate the ruthenium carbene, but it is not suitable for use as a scavenger for the metathesis catalysts due to its high volatility and the low polarity of the formed Fischer carbene. We envisioned that a vinyl ether with low volatility containing polar functional groups might deactivate metathesis catalysts efficiently and allow for the removal of the ruthenium byproducts by silica gel purification. We herein report an efficient and convenient procedure to deactivate metathesis catalysts and remove the ruthenium byproducts by utilizing the inexpensive and commercially available di(ethylene glycol) vinyl ether (Scheme 1).

The effectiveness of di(ethylene glycol) vinyl ether as a new quenching reagent for metathesis reactions was determined in a typical ring-closing metathesis reaction (RCM), in which diethyl diallylmalonate cyclizes to give diethyl cyclopent-3-ene-1,1-dicarboxylate. Under standard reaction conditions, the Zhan-1 catalyst promoted the RCM reaction of diethyl diallylmalonate to comple-

tion (>95% conversion) in 60 min. A typical experiment designed to evaluate the quenching ability of di(ethylene glycol) vinyl ether is conducted in the following manner: A mixture of metathesis catalyst (5 mol %) and di(ethylene glycol) vinyl ether (20 mol %) in dichloromethane (0.01 M) was stirred at room temperature (10–60 min). To the reaction was added diethyl diallylmalonate, and the resulting mixture was stirred at room temperature for 15 h. A HPLC method was developed to monitor the formation of any cyclized product. The results are listed in Table 1.

Four equivalents of di(ethylene glycol) vinyl ether efficiently deactivated the Zhan-1 catalyst in just 10 min of stirring with no trace of the cyclized product in the reaction mixture after 15 h (entry 3). Even 2 equiv of di(ethylene glycol) vinyl ether was enough to inhibit >95% of RCM progression with only 4.8% (HPLC area%) of cyclized product present in the reaction after 15 h (entry 2). The efficiency of di(ethylene glycol) vinyl ether as a quenching reagent for metathesis catalysts was next examined for a few other commonly used catalysts (Fig. 1). As depicted in Table 1, this process was effective for all metathesis catalysts listed including Grubbs' gen-1 and gen-2 (entries 9 and 10), Hoveyda gen-1 (entry 11), Grela gen-2 (entry 7), Zhan-1 (entries 3 and 4), and Degussa catalysts (entry 8). This protocol also worked effectively in toluene, another commonly used solvent for metathesis reactions, even though a slightly longer quenching time was required to achieve the complete deactivation of the catalyst (entry 6).

The kinetic effectiveness of the vinyl ether quench was also tested. Zhan-1 catalyst (5.0 mol %) and diene (0.2 g) were mixed and stirred in DCM for 2 h at room temperature. HPLC and TLC showed that the RCM reaction was complete (>99% conversion). Di(ethylene glycol) vinyl ether (20 mol %) was added to the reaction and the reaction mixture was stirred for 30 min. The second



Scheme 1. Deactivating the RCM catalysts.

Table 1  
Deactivating RCM catalysts with di(ethylene glycol) vinyl ether

Entry	Catalyst	Di(ethylene glycol) vinyl ether	Solvent	Time (min)	RCM product
1	Zhan-1	2.0 equiv	DCM	10	5.0%
2	Zhan-1	2.0 equiv	DCM	30	4.8%
3	Zhan-1	4.0 equiv	DCM	10	N/D
4	Zhan-1	4.0 equiv	DCM	30	N/D
5	Zhan-1	4.0 equiv	Toluene	30	4.3%
6	Zhan-1	4.0 equiv	Toluene	60	N/D
7	Grela gen-2	4.0 equiv	DCM	30	N/D
8	Degussa	4.0 equiv	DCM	30	N/D
9	Grubbs gen-1	4.0 equiv	DCM	30	N/D
10	Grubbs gen-2	4.0 equiv	DCM	30	N/D
11	Hoveyda gen-1	4.0 equiv	DCM	30	N/D

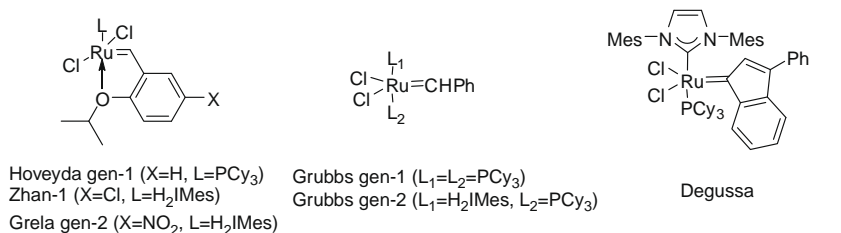


Figure 1. Representative RCM catalysts.

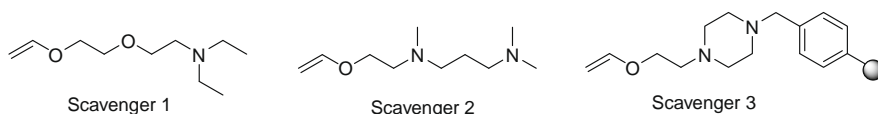


Figure 2. Amine or resin-based scavengers.

portion of diene (0.2 g) was added and the reaction mixture was stirred overnight. HPLC analyses of the aliquots sampled at 1 h, 2 h, and 15 h showed no change for the yield of RCM product in the reaction mixture, indicating that the catalyst was effectively deactivated.

It was envisioned previously that this polar Fisher carbene complex formed by the reaction of di(ethylene glycol) vinyl ether with metathesis catalyst would be readily removed by silica gel purification. The purification procedure was conducted using the following standard protocol. A mixture of diethyl diallylmalonate and Zhan-1 catalyst (5 mol %) in dichloromethane (0.01 M) was stirred at room temperature. After the starting material was consumed completely, di(ethylene glycol) vinyl ether (20 mol %) was added to the reaction and the mixture was stirred for an additional 30 min. The reaction mixture was concentrated under vacuum and purified by chromatography on silica gel to provide the diethyl cyclopent-3-ene-1,1-dicarboxylate, which was analyzed by ICP-MS for ruthenium levels. The residual ruthenium level in the product using the vinyl ether cleanup procedure was only 2 ppm, far superior to those reported previously that normally decrease the ruthenium level to a few hundred parts per million. When 40 mol % of di(ethylene glycol) vinyl ether was used, the ruthenium level was decreased to less than 1 ppm. The results showed that it was not necessary to use extra vinyl ether beyond 4 equiv in the purification of RCM reactions.

The positive results using di(ethylene glycol) vinyl ether as a deactivating reagent for the RCM catalysts prompted us to pursue other scavengers such as amine or resin-based vinyl ether derivatives (Fig. 2), which may obviate the need for purification by silica gel chromatography. Scavenger **1** was first synthesized and tested in the scavenging experiments with Zhan-1 as the RCM catalyst based on the assumption that the formed amine-based Fisher carbene might be washed away from the product with aqueous acids. The catalyst was effectively deactivated by heating the catalyst (2 mol %) and scavenger **1** (8 mol %) in toluene at 50 °C for 2 h.

In a typical RCM experiment, washing the organic mixture of the RCM reaction (scavenged with **1**) with 2 N aqueous HCl failed to remove the ruthenium from the product; however, a simple silica gel plug effectively reduced the ruthenium level to <43 ppm. Scavenger **2** was prepared to improve the hydrophilic properties of the Fisher carbene and was effective in deactivating the Zhan-1 catalyst. In a typical RCM reaction catalyzed by the Zhan-1 catalyst, the catalyst was scavenged with 4 equiv of **2** in toluene at 50 °C and the resulting mixture was washed with 2 N aqueous HCl three times. The ruthenium level in the concentrated crude product was reduced to <15 ppm. A resin-based scavenger **3** was also synthesized but was found not to be effective in deactivating the Zhan-1 catalyst.

In summary, commercially available di(ethylene glycol) vinyl ether was demonstrated to be a superior deactivating reagent for metathesis catalysts. As low as 4 equiv of vinyl ether (based on cat-

alyst loading) is enough to deactivate most commonly used metathesis catalysts in just 10–60 min. The resulting Fisher carbene complex was readily removed by silica gel purification and the ruthenium levels in the product were reduced to single-digit ppm. Amine-based vinyl ether analogues **1** and **2** were synthesized and also shown to be effective in deactivating the RCM catalyst. These scavengers have the potential to remove the ruthenium without the tedious chromatographic purification. The limited reactivity of vinyl ether should allow tolerance of a wide range of functional groups in metathesis reactions. Further studies on the application of the amine-based scavengers to large-scale RCM reactions are under active investigation.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2009.08.055](https://doi.org/10.1016/j.tetlet.2009.08.055).

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