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Allyl sulphides in olefin metathesis: catalyst considerations and traceless promotion of ring-closing metathesis†

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Allyl sulphides are reactive substrates in ruthenium-catalysed olefin metathesis reactions, provided each substrate is matched with a suitable catalyst. A profile of catalyst activity is described, along with the first demonstration of allyl sulphides as traceless promoters in relayed ring-closing metathesis reactions.

Ruthenium catalysed olefin metathesis continues to inspire ambitious applications in organic synthesis,[1] materials science,[2] and chemical biology.[3] The development of high-performance, commercially available catalysts has contributed in large part to these efforts. At the same time, the discovery of reactive substrates also enables challenging olefin metathesis reactions. In particular, allyl sulphides[4] and other allyl chalcogenides[5] have proven extraordinarily reactive with the Grubbs–Hoveyda Second Generation Catalyst (**1**).[6] The reactivity of allyl sulphides is attributed to favourable coordination of the substrate to ruthenium through the sulphur atom—a binding event that guides the alkene to the alkylidene and provokes metathesis.[4a,5] Importantly, the alkene in allyl sulphides is a distance from sulphur such that catalyst sequestration through the formation of stable chelates is not observed.[4a,7] In these reactions, the sulphur of the allyl sulphide is not merely tolerated by **1**; the rate of olefin metathesis of allyl sulphides is greater than that of unfunctionalised alkenes.[4a] As such, allyl sulphides have since been incorporated explicitly into substrates in order to render them reactive in olefin metathesis. This strategy has enabled olefin cross-metathesis on enzymes,[4,5] histones[8] and other proteins;[8] the synthesis of stable analogues of peptidic hormones[9] and other covalent modifications of peptides;[10] the preparation of functional compound libraries;[11] and the synthesis of chiral building blocks[12] (Fig. 1).

Our continued interest in allyl sulphide promoted metathesis was motivated by two goals. First, we sought to clarify which ruthenium catalysts are reactive in the olefin metathesis of allyl sulphides. While high reactivity is typically observed with Grubbs–Hoveyda Second Generation Catalyst (**1**) (all reactions in Fig. 1 were catalysed by **1**), variable reactivity of allyl sulphides has been observed with other metathesis catalysts.[13] Given the increased commercial availability of catalysts with diverse structure and reactivity, we considered it worthwhile to examine their reactivity with allyl sulphides. With this information in hand, our second goal was to demonstrate that allyl sulphides can be integrated into relay metathesis strategies[14] in such a way that their superior reactivity can be harnessed, yet the allyl sulphide itself need not be contained in the product. Such a demonstration is complementary to the efforts in Fig. 1 in which all targets contain an allyl sulphide.

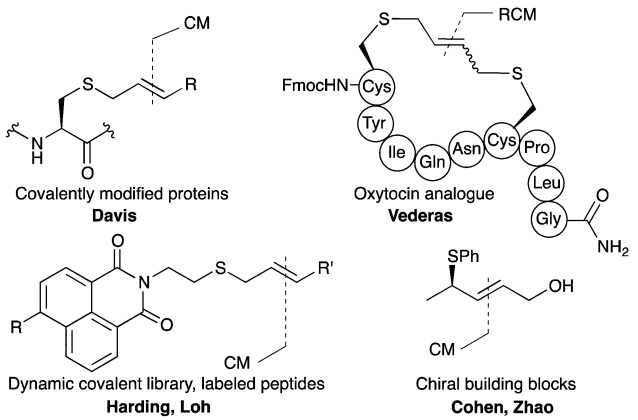

Fig. 1 Allyl sulphide promoted olefin cross-metathesis (CM) and ring-closing metathesis (RCM) catalysed by Grubb–Hoveyda Second Generation Catalyst (**1**).[4,5,9–12]

As a starting point, we examined the ring-closing metathesis (RCM) of diallyl sulphide (**2**) using a variety of ruthenium catalysts (Table 1). Because product **3** is volatile, the reactions were run in CD_2Cl_2 and reaction conversions were analysed directly by ^1H NMR spectroscopy and reflect the ratio of **3** to **2**. (ESI†) Consistent with previous reports of allyl sulphides in olefin metathesis,[4,5] the conversion of **2** to **3** was remarkably

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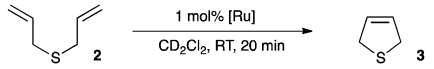
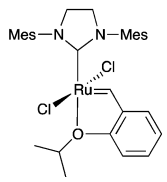
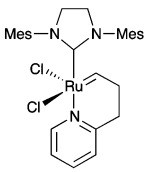
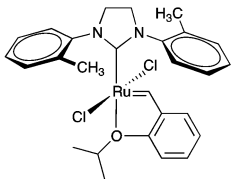
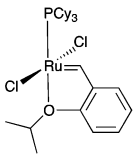
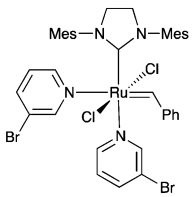
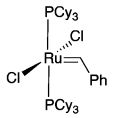
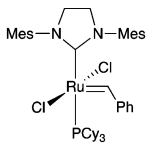
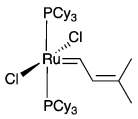
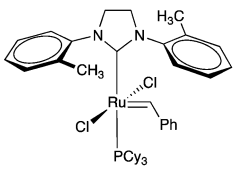
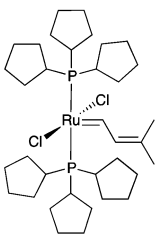
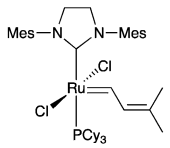
Table 1 Ring-closing metathesis of diallyl sulphide with various ruthenium catalysts.[15] Reactions were analysed directly by ^{1}H NMR and conversions correspond to the ratio of **3** to **2**



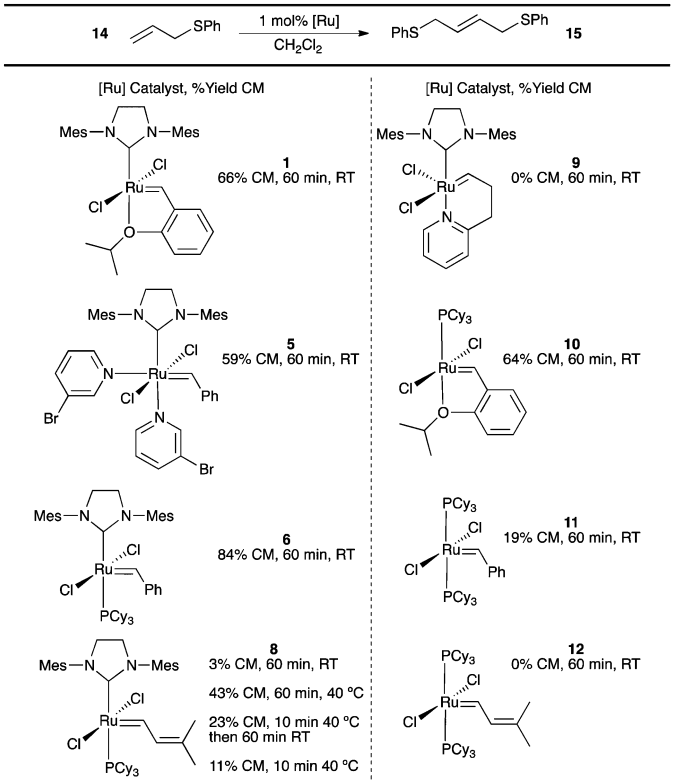
[Ru] Catalyst, %Conversion RCM		[Ru] Catalyst, %Conversion RCM	
	**1** 100% RCM		**9** 0% RCM
	**4** 88% RCM		**10** 4% RCM
	**5** 53% RCM		**11** 6% RCM
	**6** 11% RCM		**12** 6% RCM
	**7** 6% RCM		**13** 0% RCM
	**8** 3% RCM		

efficient when using the Grubbs–Hoveyda Second Generation Catalyst (**1**).[6] In fact, full conversion to the ring-closed product was observed within 20 minutes at room temperature when using 1 mol% loading of catalyst **1**. Structurally related catalyst **4**[16] also provided high conversions under the same conditions. In contrast, catalysts **6–13** resulted in low conversions.[15] This result revealed that the allyl sulphide alone is not sufficient to result in high olefin-metathesis reactivity. Rather, it appears that the allyl sulphide's reactivity in ring-closing olefin metathesis is most pronounced when such substrates are paired with the Grubbs–Hoveyda Second Generation Catalyst (**1**) or structurally related catalysts. For ring-closing metathesis of allyl sulphide **2**, catalysts that contain both an N-heterocyclic carbene ligand and another weakly coordinating ligand appear most suitable. These ligands—such as the styrenyl ether in **1** and **4** or the 3-bromopyridyl ligand in **5**[17]—do not interfere with sulphur coordination to ruthenium.[18] In contrast, catalysts **6–8** and **10–13** contain a phosphine ligand that may preclude or compete with the allyl sulphide in its binding to the ruthenium centre. In the case of allyl sulphides, it is thought that their rapid reaction with catalyst **1** is due, in part, to sulphur's ability to bind to ruthenium and bring the allyl group into close proximity to the alkylidene—provoking the initial metathesis event.[4a] This sulphur-assisted delivery of the alkene to the catalyst would be discouraged should a phosphine ligand compete for the coordination site. For the short reaction times examined, it is also expected that rapidly initiating catalysts would be well-suited for allyl sulphide promoted metathesis. Catalyst **5**,[17] for instance, is a rapidly initiating olefin metathesis catalyst and transformed **2** into **3** in moderate conversions within 20 minutes. Slow-initiating catalysts such as **9**[19] did not provide the cyclized product in the same timeframe.

In Table 1, it is noteworthy that the ring-closed product **3** did not appear to inhibit catalysts **1**, **4**, or **5**—an important consideration for our subsequent efforts in relay metathesis (*vide infra*). We also considered the possibility that **3**, or a related cyclic sulphide, could *activate* catalysts for RCM. To explore this possibility more directly, we premixed catalysts **1**, **6**, and **8–12** (1 mol%) with tetrahydrothiophene (10 mol%) for 10 minutes and then examined the RCM conversion of **2** to **3** (Table S3, ESI†). There was no significant difference in RCM conversions in comparison to Table 1, suggesting catalyst activation by the RCM product is not critical in these systems.

Interestingly, a different reactivity profile was observed in the cross-metathesis (CM) of allyl phenyl sulphide (**14**) (Table 2). Good to excellent isolated yields of the cross-metathesis product **15** were obtained using catalysts **1**, **5**, **6**, and **10** after an hour of reaction time at room temperature. Low yields were obtained when using catalysts **8**, **9**, **11**, and **12**. It appears that the presence of two phosphine ligands on the catalyst (*e.g.* **11** and **12**) are detrimental to the cross-metathesis. In contrast to the ring-closing metathesis in Table 1, the single phosphine in catalysts **6** and **10** was tolerated in cross-metathesis. To understand this difference in reactivity, catalysts **6** and **10** were re-evaluated in RCM with diallyl sulphide and run for 60 minutes to provide a direct comparison to CM activity (Table S2, ESI†). Catalyst **6** provided 43% RCM conversion to product **3** after 1 hour of reaction time, revealing this catalyst is indeed active in RCM, but proceeds more slowly than the CM of **14**. Catalyst **10**, however, rapidly darkens in solution and results in only 6% RCM product **3** after 60 minutes of reaction time (Table S2, ESI†). This results suggests **2** or **3** may deactivate **10** in a way that is not observed in the CM of **14**. The difference in CM reactivity between **6** and **8** is also noteworthy. As both are expected to feature the same propagating Ru species, the stark difference in CM yield should reflect a difference in rates of initiation. Indeed, running the CM of **14** with catalyst **8** at 40 °C for 1 hour resulted in a marked increase in yield of **15** (53%). Furthermore, the reaction can be initiated by heating for 10 minutes at 40 °C; continuing the reaction at room temperature for an additional hour resulted in 23% yield of **15**. A yield of 11% was obtained with only 10 minutes

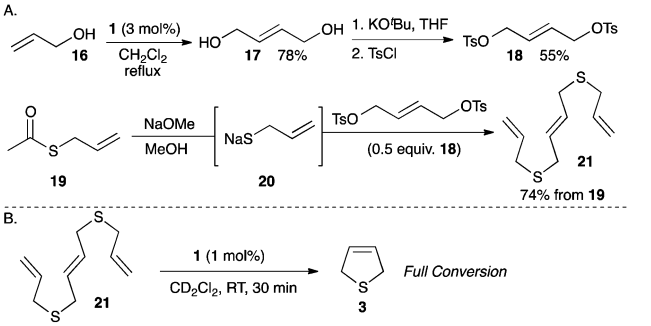
Table 2 Olefin cross-metathesis of allyl phenyl sulphide using various ruthenium catalysts.[15] Isolated yields of **15** are reported for all reactions



of total reaction time at 40 °C, indicating that propagation can occur at room temperature and catalyst initiation is the limiting factor when using catalyst **8** in the CM of **14** (Table 2 and Table S19, ESI†).

The results in Tables 1 and 2 reveal subtle differences in ruthenium-based olefin metathesis catalysts and their ability to react with allyl sulphides. Furthermore, while allyl sulphides have rightfully been characterized as "privileged substrates" in olefin metathesis,[4a] the results in Tables 1 and 2 suggest this high reactivity holds true only for certain catalysts. Identifying suitable catalysts is therefore important in allyl sulphide promoted metathesis and Tables 1 and 2 provide some revealing information in this regard.

In the targets shown in Fig. 1, allyl sulphides were explicitly incorporated into their precursors to promote rapid olefin metathesis with catalyst **1**. Such strategies, however, necessitate an allyl sulphide in both the starting material and product. For some of these targets, the allyl sulphide was present naturally in the target molecule.[12] In other cases, the allyl sulphide was tolerated in the product because the metathesis was most efficient when the allyl sulphide promoter was used.[4,5,9–11] For example, allyl sulphides as olefin metathesis substrates have enabled rapid modification of peptides and proteins in aqueous media where other alkenes proved far less reactive or completely unreactive.[4,5,9,10] It is our contention, however, that the reactivity of allyl sulphides in olefin metathesis can be leveraged in contexts where rapid metathesis is desirable, yet the product does not necessarily need to contain sulphur. Specifically, it was

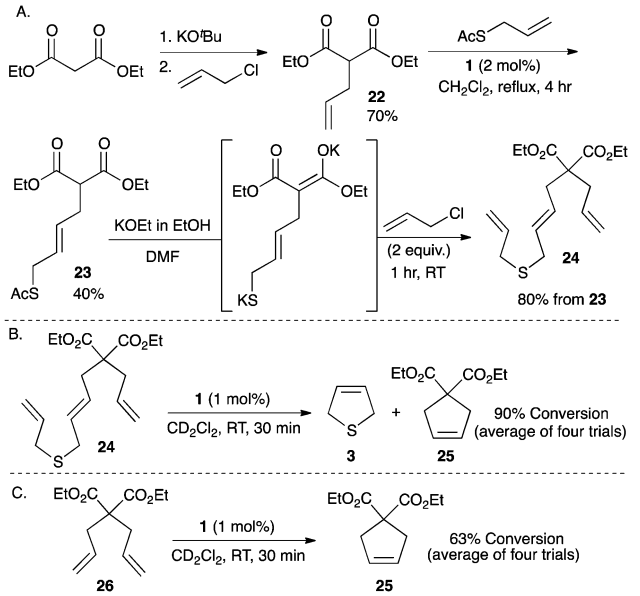


Scheme 1 Allyl sulphide promoted relay ring-closing metathesis. Isolated yields are reported in (A). In (B), the reaction conversion was determined directly by ^{1}H NMR.

our hypothesis that by incorporating an allyl sulphide into a substrate for relay metathesis, it could promote the desired reaction as a sacrificial initiator. We were further motivated to pursue this hypothesis given the results in Table 1 which demonstrate that not only is diallyl sulphide (**2**) reactive in ring-closing metathesis when paired with catalyst **1**, but also that the ring-closed product **3** did not inhibit this catalyst. Therefore, we next set out to demonstrate that allyl sulphides are compatible with relay olefin metathesis.

As a starting point we targeted triene **21** to determine if relay olefin metathesis is indeed compatible with allyl sulphides (Scheme 1). Notably, this substrate was also constructed using olefin cross-metathesis—further highlighting the strategic reach of this venerable reaction.[1,20] First, cross-metathesis of allyl alcohol (**16**) provided diol **17**, which was subsequently tosylated to give **18**. Next, allyl thioacetate (**19**) was deacetylated to generate allyl thiolate **20**, which was subsequently reacted with di-tosylate **18** in a one-pot procedure that provided the key triene **21**. With this substrate in hand, relay metathesis was investigated next. Guided by the results in Table 1, catalyst **1** was used at 1 mol% loading and the reaction was monitored directly by ^{1}H NMR spectroscopy. Gratifyingly, full conversion of triene **21** to **3** was observed after only 30 minutes of reaction time (ESI†). This result demonstrated that allyl sulphides are not merely compatible with relay metathesis, but that they are remarkably reactive in this reaction manifold.

The results in Scheme 1 clearly show that allyl sulphides are promoters in the relay metathesis strategy. However, it was also our goal to demonstrate that the allyl sulphide does not need to be present in the final target. Therefore, we synthesized triene **24** as a substrate that could provide a product of ring-closing metathesis (**25**) that does not contain sulphur. Starting from diethyl malonate, allylation and olefin-cross metathesis supplied thioester **23** as a key intermediate (Scheme 2). Next, **23** was treated with potassium ethoxide to both deacetylate the thioester and generate an enolate. Treatment with 2 equivalents of allyl chloride provided the key triene **24** in an excellent 80% yield from **23**. The stage was then set for the key relay metathesis. Triene **24** was treated with 1 mol% catalyst **1** and monitored by ^{1}H NMR spectroscopy. Gratifyingly, an average of 90% conversion to ring-closed products **3** and **25** was observed over four trials



Scheme 2 An allyl sulphide as a traceless promoter in ring-closing metathesis. Isolated yields are reported in (A). In (B) and (C), reaction conversions were determined directly by ^{1}H NMR.

with a mere 30 minutes of reaction time. In comparison, when diene **26** was subjected to the same reaction conditions, an average of 63% conversion was observed over four trials. These experiments demonstrate that not only are allyl sulphides compatible with relay olefin metathesis, but that the allyl sulphide promotes a rapid reaction to a ring-closed product that does not necessarily contain sulphur. In this way, the allyl sulphide is a traceless promoter of ring-closing olefin metathesis.

We are currently taking advantage of this strategy to enable challenging olefin metathesis reactions on biomolecules such as peptides and proteins that often employ or require aqueous media. In such cases, rapid olefin metathesis is necessary to outcompete catalyst decomposition.[4,5,8] In these efforts, we aim to enable carbon–carbon formation on biomedically relevant molecules without requiring sulphur in the final product—a distinction from the previously published efforts in olefin metathesis on peptides and proteins highlighted in Fig. 1.[4,5,8–10] Such a strategy would expand the bioconjugate targets accessible by olefin metathesis. More generally, we encourage consideration of allyl sulphides as traceless promoters for olefin metathesis in synthetic sequences where challenging or sluggish metathesis reactions are encountered. The ease of assembly of the allyl sulphide promoters (Schemes 1A and 2A) and the favourable rates compared to non-relayed metathesis (**24** *vs.* **26**) bode well for productive use of this strategy in chemical synthesis.

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