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Synthesis of heterocyclic compounds using ring-closing enyne metathesis reaction

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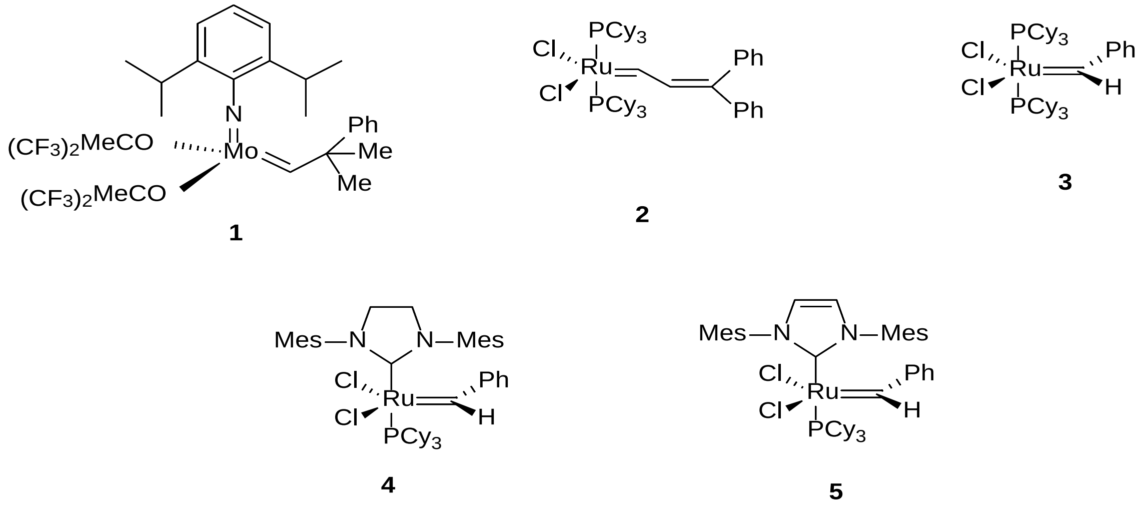
Abstract

Ring-closing enyne metathesis reaction has emerged as an elegant tool in organic synthesis for the creation of molecular complexity and used to prepare diverse heterocycles. In this mini review, I discuss that various linearly and angularly architecture heterocyclic compounds may be prepared using RCEM as key steps.

Keywords: Enyne metathesis, Diels Alder reaction, aromatisation.

Introduction

Enyne metathesis may be defined as the reorganization of covalent bonds between an alkene and alkyne to develop a 1, 3-diene unit. This reaction is catalysed by Schrock's molybdenum catalyst **1** (Fig. 1) and Grubbs' first- and second-generation catalysts **2-5**.



Cy = cyclohexyl; Mes = mesityl

Fig. 1. Schrock's molybdenum catalyst 1 and Grubbs' first- and second-generation catalysts 2-5.

Three possible pathways for ring-closing enyne metathesis (RCEYM) with ruthenium carbene catalysts are illustrated in Figure 2 (Barrett et al., 2000; Chattopadhyay et al., 2007; Hoye et al., 1999; Mori et al., 2000; Poulsen and Madsen, 2003; Diver and Giessert, 2004; Mori, 1998; Kotha et al., 2019). In pathway **A**, ruthenium carbene has been shown to react initially with the alkene part of the enyne, then a sequential intramolecular [2+2] cycloaddition and retrocycloaddition have been proposed to lead to the 1,3-diene unit. Whereas, in pathway **B**$_1$, **B**$_2$ and **C** ruthenium carbene is supposed to react with alkyne moiety in two possible mode to generate ruthenacyclobutene regioisomers **8** and **9** which have been converted into two different 1,3-dienes following similar type retro-cycloaddition and cycloaddition reaction sequence.

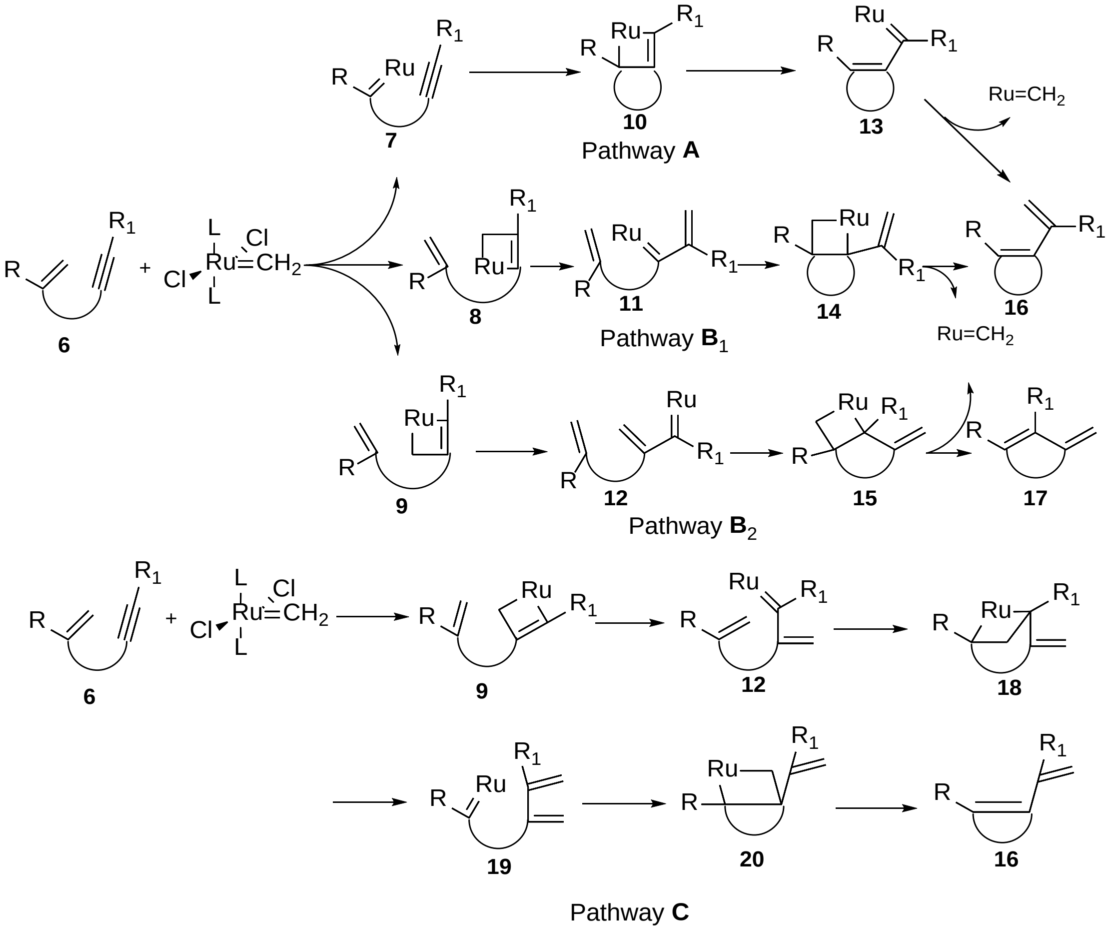
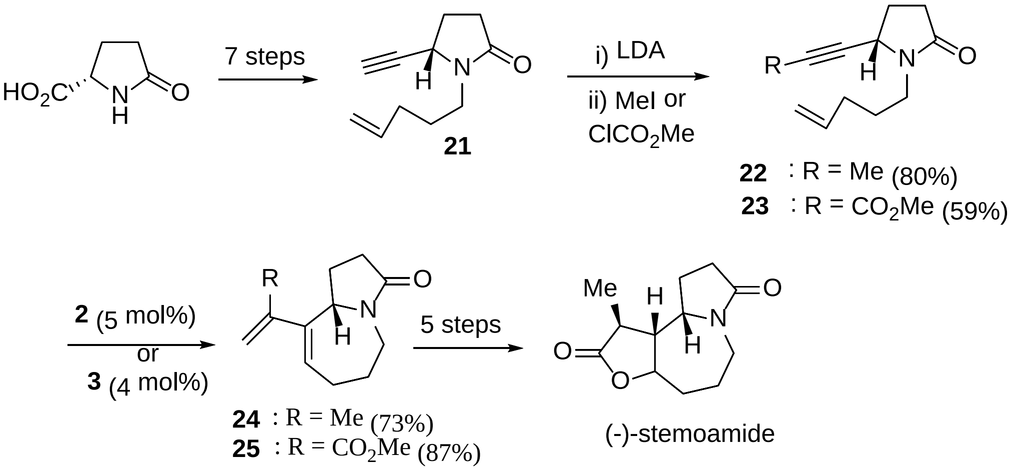


Fig. 2. Possible pathways for ring-closing enyne metathesis (RCEYM).

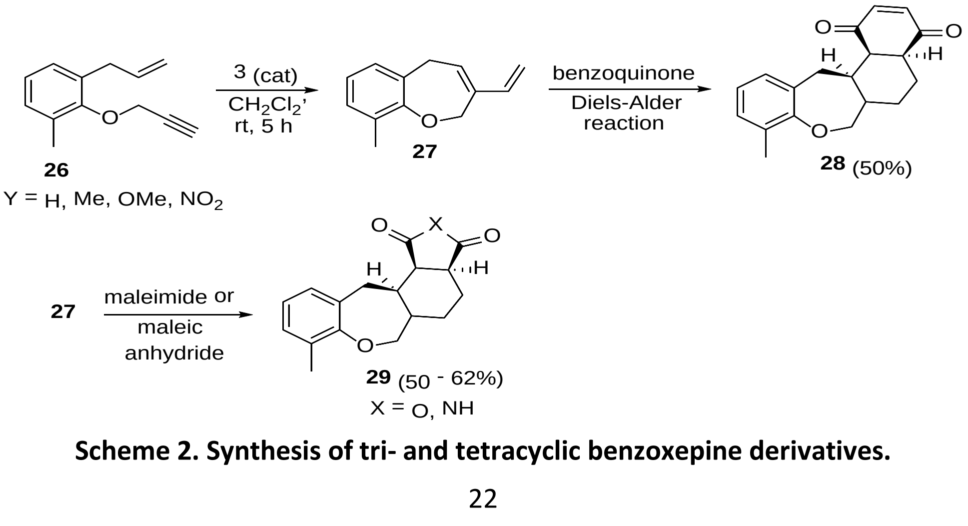
Intramolecular diene metathesis is an entropically favorable reaction, as cycloalkene and ethylene are generated from starting diene on RCM. Whereas, no such inherent driving force is present during the intramolecular ring-closing enyne metathesis reaction. Thus, medium-ring formation is very difficult via enyne metathesis. In most of the cases, it requires prolonged reaction time and high catalyst loading. It was reported that construction of seven-membered rings needed longer reaction times and products were formed in varying yields (Schramm et al., 2001; Fürstner et al., 2001; Mori et al., 1998; Clark et al., 2002; Mori et al., 2001) . The formation of eight- and nine-membered rings are very difficult, as, in these cases, the dimerization product is found to be a competitor of the cyclized product (Renaud et al., 2000). However, moderate yields of the eight- and nine-membered products were reported (Renaud et al., 2000) when two heteroatoms or quaternary centres were present as enyne tether.

Using RCEYM as the key step, Kinoshita and Mori were the first to demonstrate (Kinoshita and Mori, 1996; Kinoshita and Mori, 1997) the total synthesis of the natural product, (-)-stemoamide (an insecticide alkaloid). Thus, treatment of enyne **22** (Scheme **1**) with catalyst **2** (5 mol%) afforded the diene **24** (73%). Whereas, ester substituted enyne **23** on RCEYM with catalyst **3** (4 mol %) produced **25** in 87% yield. Interestingly, in both cases the two newly generated double bonds were not in conjugation due to steric effects, as reported by NMR chemical shifts. The diene **25** was then elaborated into stemoamide in 5 steps (Kinoshita and Mori, 1996).



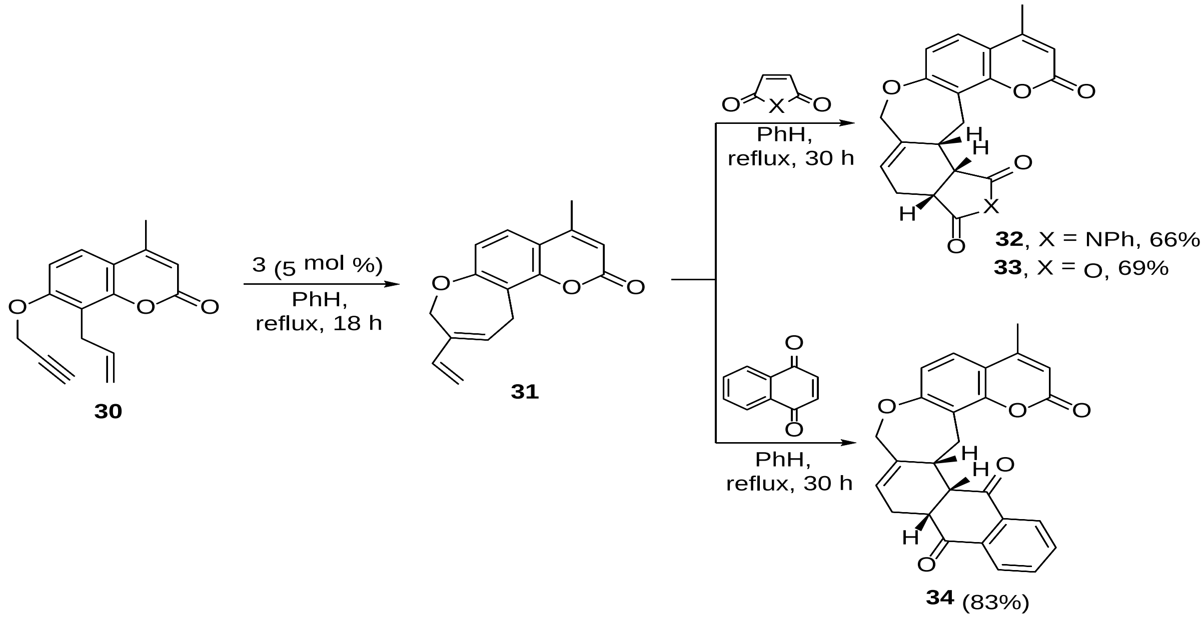
Scheme 1. Total synthesis of the natural product, (-)-stemoamide.

Moreno-Manas et al., (2001) reported the synthesis of tri- and tetracyclic benzoxepine derivatives (**28** and **29**) (Scheme2) by a one-pot enyne metathesis/ Diels–Alder reaction starting from differently substituted 2-allyl-1-propargyloxybenzenes **26**. Enyne metathesis on **26** with Grubbs' catalyst **3** in dichloromethane at room temperature for 5h afforded the corresponding vinyl oxepines **27**. The resulting dienes underwent Diels–Alder reactions with a range of dienophiles to afford the corresponding **28** and **29**. The stereochemistry of these products was unambiguously determined from extensive NMR experiments.



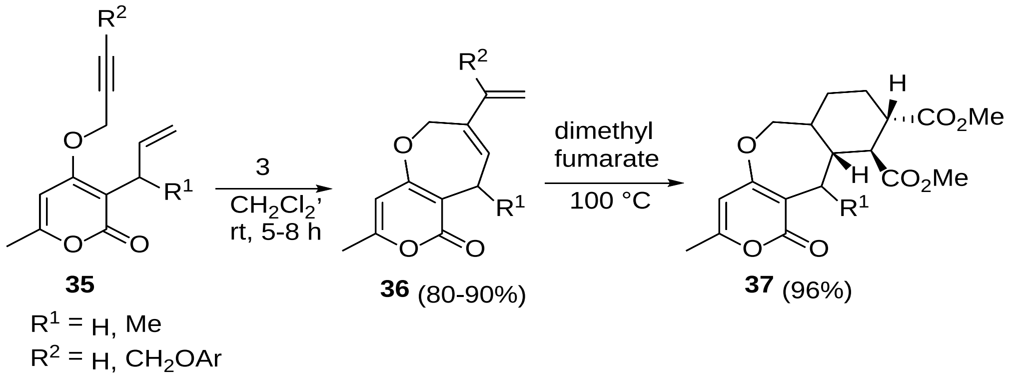
Scheme 2. Synthesis of tri- and tetracyclic benzoxepine derivatives.

Various coumarin derivatives are known (Murakami et al., 2000; Wu et al., 2001) to display important photophysical and biological activities. Chattopadhyay et al., (2006) described the synthesis of several 6, 6, 7, 6, 5- and 6, 6, 7, 6, 6, 6-ring fused, hitherto unknown, coumarin derivatives utilizing tandem applications of three atom-economic processes, viz. Claisen rearrangement, RCEYM and Diels–Alder reaction. Thus, RCEYM of enyne **30** (Scheme 3), derived from an appropriate coumarin derivative employing Claisen rearrangement as the key step, with Grubbs' catalyst **3** afforded the 6, 6, 7-fused diene **31**. The latter was then subjected to a Diels–Alder reaction separately with N-phenylmaleimide and maleic anhydride in refluxing benzene to provide 6,6,7,6,5-ring fused coumarin derivatives **32** and **33**, respectively. Similarly, the 6, 6, 7, 6, 6, 6 ring fused coumarin derivative **34** was obtained when naphthaquinone was used as the dienophile. Similar types of other linearly and angularly architecture polycyclic coumarin derivatives have also been synthesized.



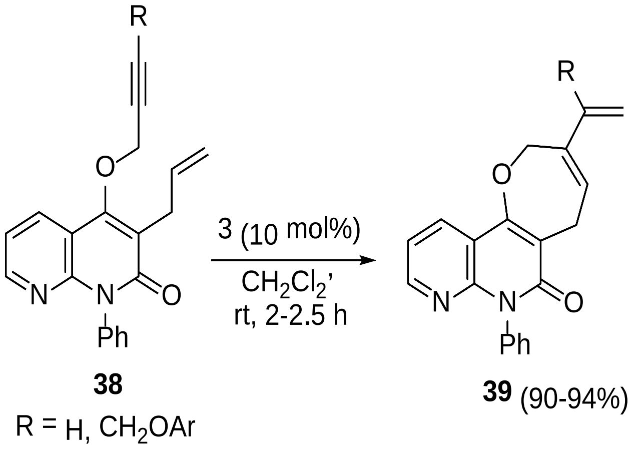
Scheme 3. Synthesis of polycyclic coumarin derivatives.

Majumdar et al., (2006) synthesized tricyclic oxepine-annulated pyrone derivatives by the tandem Claisen rearrangement and RCEYM protocol. When a dichloromethane solution of the enyne **35** (Scheme 4) and catalyst **3** were stirred at room temperature for 5–8 h, the corresponding oxepine derivative **36** was obtained in 80–90% yield. The Diels–Alder reaction of these cyclized products with dimethyl fumarate proceeded smoothly to afford the tricyclic compounds **37** in excellent yield.



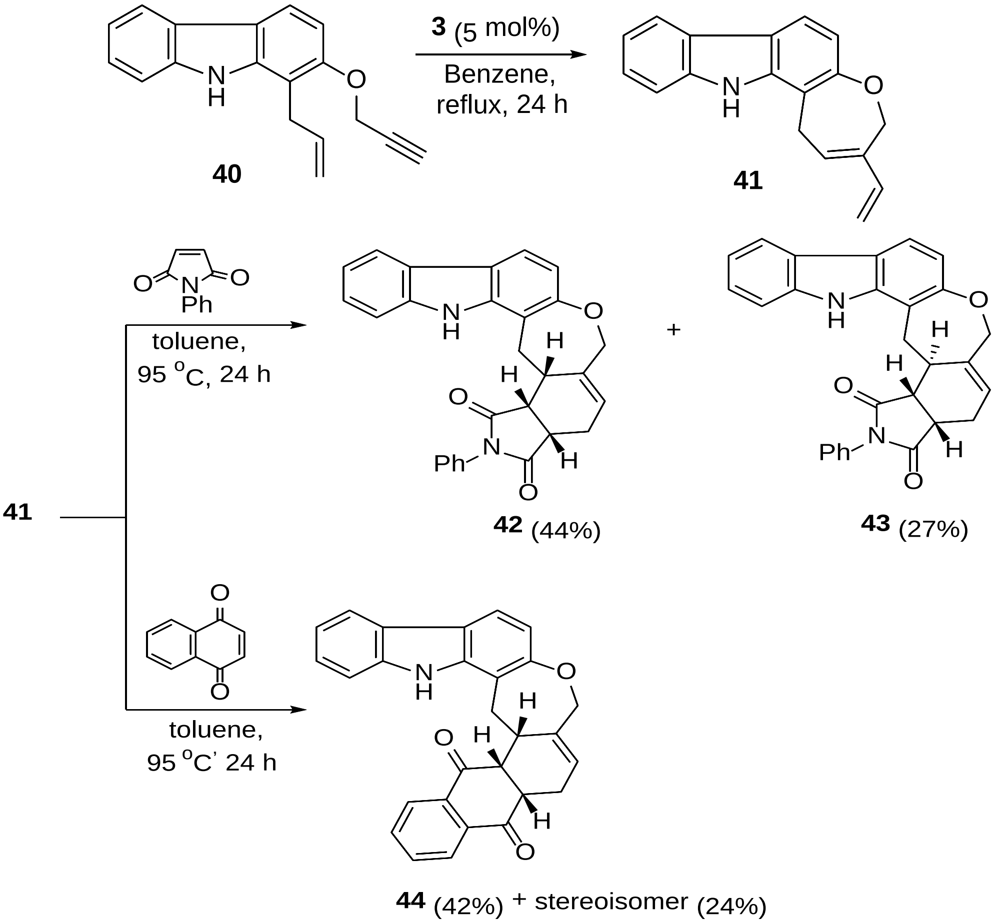
Scheme 4. Synthesis of tricyclic oxepine- annulated pyrone derivatives.

The importance of naphthyridine derivatives is due to their exceptionally broad spectrum of biological activities. Substituted 1, 8-naphthyridine derivatives are used for the diagnostic therapy of human diseases including AIDS and for combating exo- and endo-parasites in agriculture (Litvinov et al., 2000). Majumdar et al., (2006) reported the utility of the tandem Claisen rearrangement and ring-closing enyne metathesis methodology for the synthesis of oxepine annulated naphthyridine derivatives. When a dichloromethane solution of the enyne **38** (Scheme 5) and the catalyst 3 was stirred at room temperature for 2–2.5 h, the ring-closed product **39** was obtained in almost quantitative yield.



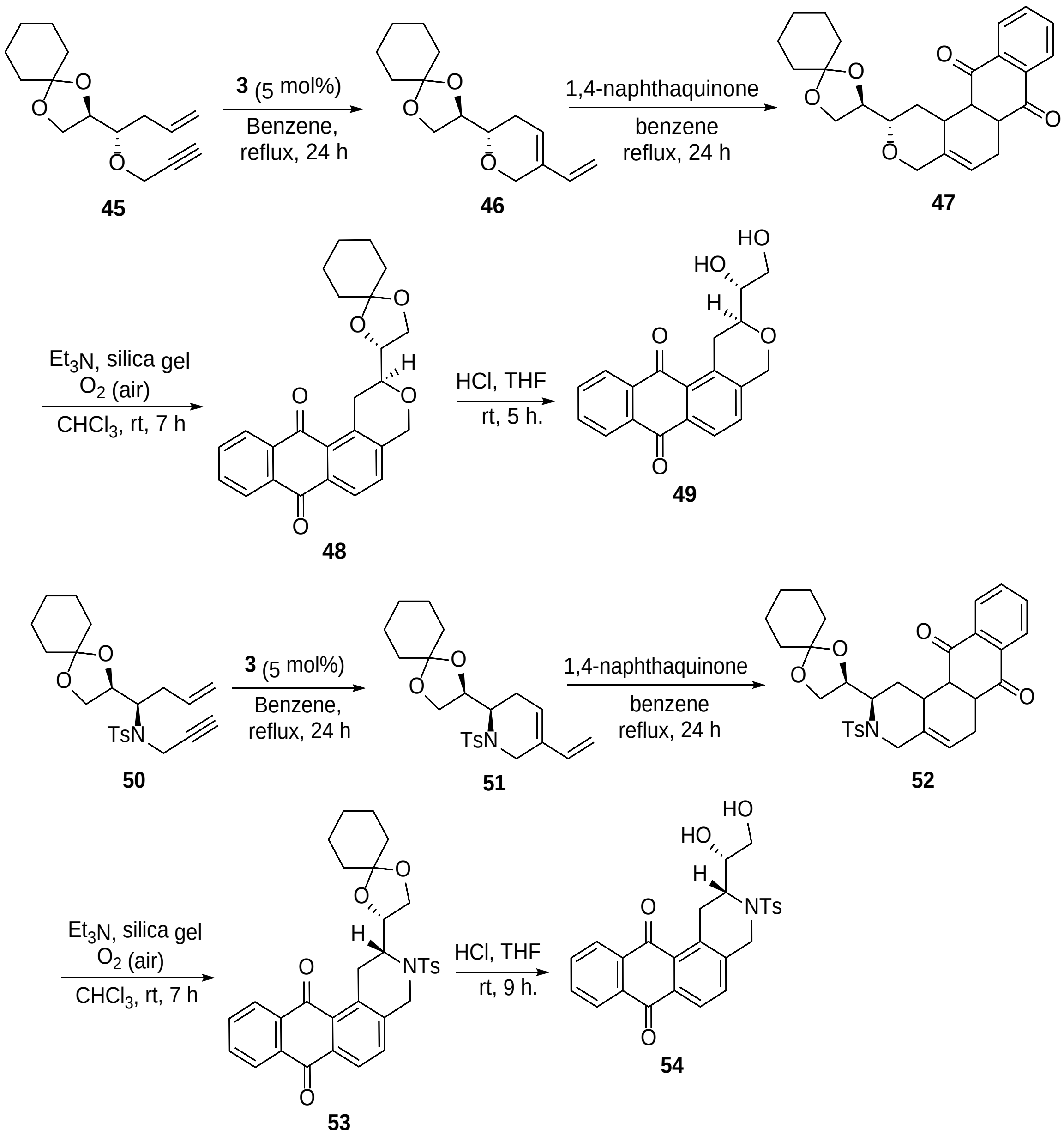
Scheme 5. Synthesis of oxepine annulated naphthyridine derivatives.

Chattopadhyay et al., (2006) prepared various oxepine- annulated polycyclic carbazole frameworks by successive applications of three atom economic processes, viz., Claisen rearrangement, ring-closing enyne metathesis and Diels–Alder reactions. Thus, RCEYM of enyne **40** (Scheme 6), derived from an appropriate carbazole derivative employing Claisen rearrangement as the key step, with Grubbs' catalyst **3** provided the diene **41** in good yield. When diene **41** was refluxed with N-phenylmaleimide two products **42** and **43** were formed in a ratio ~3:2. The major product **42** the endo stereochemistry, while the other product **43** appeared to be the exo stereochemistry. Similarly, cycloaddition of the same diene **41** with 1, 4 naphthoquinone afforded a separable mixture of the major endo product **44** and its exo isomer.



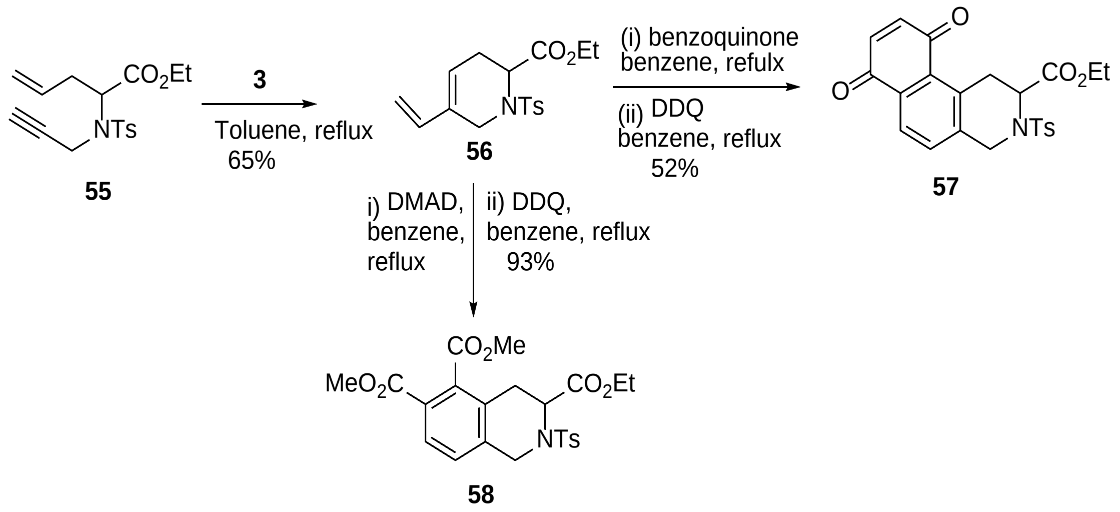
Scheme 6. Synthesis ofoxepine- annulated polycyclic carbazole derivatives.

Chattopadhyay et al., (2006) developed a convenient protocol for the synthesis of chiral pyran and piperidine ring-fused anthraquinone derivatives using sequential applications of enyne metathesis, Diels–Alder reaction and aromatization as key steps (Scheme 7). Thus, RCEYM of the enyne **45** with Grubb's catalyst **3** afforded the diene **46** in good yield. Diels–Alder reaction of the diene **46** with 1,4-naphthaquinone provided the product **47** which on aromatisation and then deprotection of cyclohexylidene group afforded the anthrapyran derivative **49**. Similarly, the aza-analogue of compound **49** was derived from the enyne **50**. Ring closing enyne metathesis of **50** with Grubb's catalyst **3** in refluxing benzene provided the diene **51** in good yield. Diels–Alder reaction of the diene **51** with 1, 4-naphthaquinone provided the product **52.** Aromatisation of **52** and then deprotection afforded the piperidine ring-fused anthraquinone derivative **54.**



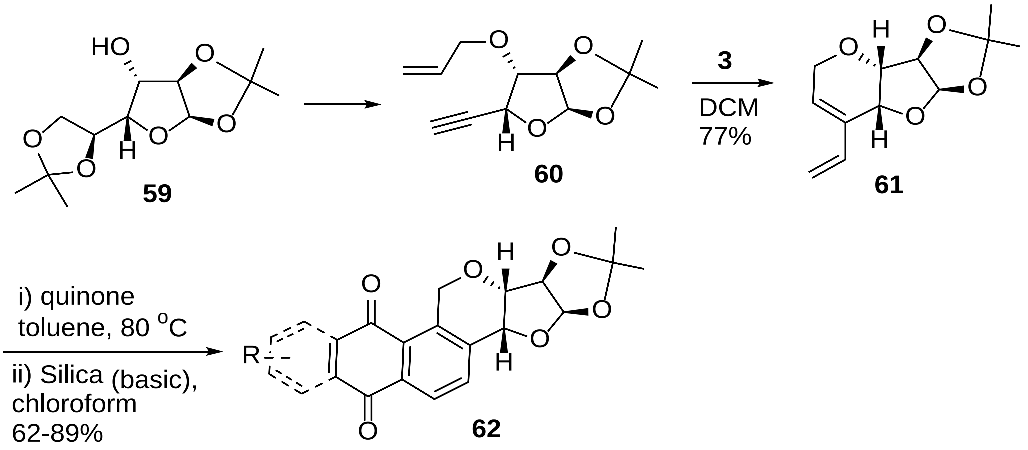
Scheme 7. Synthesis of chiral pyran and piperidine ring-fused anthraquinone derivatives.

Kotha and Sreenivasachary applied the strategy involving enyne metathesis-Diels-Alder reactions for the synthesis of topographically constrained Tic derivatives **57**-**58** [Tic, a constrained analogue of Phenylalanine (Phe), Scheme 8] (Kotha et al., 2000). The enyne building block **55** was prepared from Schiff base ester via C-allylation and hydrolysis reaction followed by the N-tosylation and N-propargylation. Enyne metathesis of building block **55** using the Grubb's catalyst **3** gave the diene **56** (65%). Finally, the Diels-Alder reactions of the diene **56** with dimethyl aceylenedicarbixylate (DMAD) and quinone, followed by subsequent oxidation of the Diels-Alder adducts, generated the Tic derivatives **57** (52%) and **58** (93%) respectively.



Scheme 8. Synthesis of topographically constrained Tic derivatives.

Kaliappan and Sayyad reported (Sayyad et al., 2017) sequential enyne metathesis-Diels Alder strategy to synthesize a novel class of sugar-oxasteroid-quinone hybrid molecules (Scheme 9). They synthesized varieties of sugar derived enynes from common starting precursors 1, 2, 5, 6-diisopropylidine-D-glucose. Then they prepared a library of sugar-oxasteroid-quinone hybrids by treating of those various enyne-containing sugar molecules with various quinone dienophiles in Diels-Alder reaction conditions.



Scheme 9. Synthesis of a novel class of sugar-oxasteroid-quinone hybrid molecules.

Conclusions

In conclusion, the examples mentioned above illustrate the broad applicability of the ring closing enyne metathesis reactions for the synthesis of various heterocycles of importances. It is clear that these reactions have already found a unique position in organic chemistry in view of their ability to form heterocyclic rings of almost any size. For various heterocyclic rings, it is beneficial to use conformational constraints such as cyclic tethers, bulky substituents or stereoelectronic effects. Tandem reactions involving RCEM are becoming more popular, as such processes enable the rapid construction of complex skeletal architectures. Improved catalysts for specific applications, including enantioselective synthesis, continue to be discovered. Future applications are expected to emerge along these general directions.

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