ENYNE METATHESIS REACTIONS IN THE SYNTHESIS OF SMALL RING HETEROCYCLES

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Daniele Castagnolo

Institute of Pharmaceutical Science, King's College London,
Franklin-Wilkins Building, 150 Stamford Street, SE1 9NH London, United Kingdom
(e-mail: daniele.castagnolo@kcl.ac.uk)

Abstract. *The reaction between an alkene and an alkyne catalysed by ruthenium catalysts, such as the Grubbs' catalyst, is known as enyne metathesis reaction and represents one of the most useful methods for the synthesis of conjugated 1,3-diene systems. Enyne metathesis has been widely used both in its intramolecular (ring–closing enyne metathesis RCEYM) and intermolecular (enyne cross–metathesis EYCM) variants for the synthesis of a range of substrates, including small ring heterocycles. Nitrogen and oxygen heterocycles, such as pyrrolines, tetrahydropyridines or pyrans, can be easily synthesised in high yields from appropriate amines or ethers via RCEYM. Moreover, the combination of EYCM and cycloaddition reactions as well as the combination of enyne and classical olefin metathesis reactions allow the synthesis of small heterocyclic systems from a variety of readily available alkyne substrates.*

Contents

1. Introduction

Olefin metathesis is an organic reaction that entails the redistribution of fragments of two alkenes (olefins) by the scission and regeneration of carbon-carbon double bonds. Olefin metathesis, and the catalysts that allow the reaction to take place in an efficient manner under mild conditions, have been mainly developed by Robert H. Grubbs, Richard R. Schrock and Yves Chauvin who were awarded with the Nobel Prize in Chemistry in 2005 for "*making metathesis into one of organic chemistry's most important reactions*". It is undeniable that olefin metathesis has revolutionised the approach toward the synthesis of

many organic molecules, with implications also in the synthesis of many natural products. Nowadays olefin metathesis is a popular organic reaction, also due to the progresses made in the development of new and more efficient catalysts. The reaction can be catalysed by molybdenum-carbene (Schrock catalyst) or ruthenium-carbene (Grubbs' type catalysts) complexes. In particular, the Ru-carbenes (Grubbs' 1st, 2nd and 3rd generation **Ru1**-**3**, Hoveyda **Ru4** and Blechert **Ru5** catalysts, Figure 1) found broad application in organic synthesis due to their greater stability toward moisture and air.

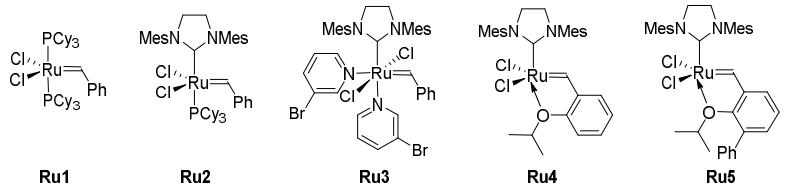
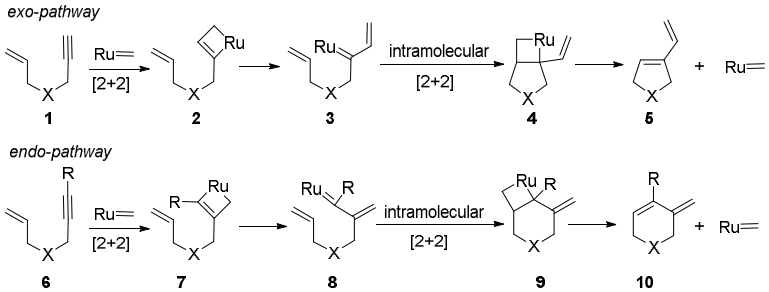


Figure 1. Ruthenium catalysts for olefin metathesis reactions.

However, olefin metathesis is not only limited by the reaction of two alkenes. In fact, depending on the type of unsaturated bond involved in the process, olefin metathesis can be distinguished in diene (between two alkenes), enyne (between an alkene and an alkyne) and diyne (between two alkynes) metathesis. Moreover, the structural change occurring during the chemical process can lead to ring closing (RCM), ring opening (ROM), and cross (CM) metathesis reactions.

The enyne metathesis variant is the metathesis reaction occurring between an alkene and an alkyne. This transformation has been reported by Katz[1] for the first time and by Mori later[2] who found that Grubbs' catalysts **Ru1** and **Ru2** were effective in catalysing the metathesis between a double and a triple bond leading to a 1,3-diene product. Despite uncertainty regarding the exact mechanism, it is generally accepted that the reaction proceeds as reported in Scheme 1.[3]



Scheme 1. Mechanism of enyne metathesis reaction. *exo*- and *endo*-pathways.

Two possible pathways (*endo*- and *exo*-) are possible. In the *exo*-pathway, the ruthenium carbene attacks the triple bond leading to the Ru-cyclobutene **2** intermediate through a [2+2] cycloaddition. Ring opening leads to Ru-carbene **3** which upon further [2+2] cycloaddition with the other alkene leads to the bicyclic intermediate **4**. Finally, the ring opening allows the regeneration of the Ru-catalyst and the formation of the final diene product **5**. In general, the *exo*-pathway is preferred, but in some cases the *endo*-

pathway may occur, especially in enyne systems having a di-substituted alkene or a non-terminal alkyne.[4] The reasons for this are still not clear but may be due to the steric effect of substituents on the multiple bond that affects the ring size of the product. The driving force for the reaction relies on the enthalpic stability of the conjugated 1,3-diene product. Despite enyne metathesis having been less studied than alkene metathesis, in the last decade several examples of both intramolecular (ring closing enyne RCEYM) and intermolecular (cross enyne EYCM) reactions have been reported and used in the synthesis of a variety of compounds. In fact, with the enyne bond reorganization being an atom economical process, the reaction is also appealing in term of green chemistry. Moreover, the diene product formed in enyne metathesis may be in turn used as a substrate for Diels-Alder reactions leading, through multicomponent or domino cascades, to a multiplicity of chemical structures.

This chapter review describes the use of enyne metathesis as a valid and versatile reaction for the synthesis of small ring (5-, 6-membered rings) heterocyclic compounds. In particular, the synthesis of nitrogen and oxygen heterocycles (pyrrolines and pyrroles, tetrahydropyridines, dihydrofurans, hydropyrans) via multicomponent or domino processes will be emphasised.

2. Synthesis of nitrogen heterocycles

Enyne metathesis has been widely used for the synthesis of nitrogen heterocycles both in its inter- or intramolecular version. Nitrogen heterocycles represent the core of many natural compounds as well biologically active drugs, and thus new methods, including metathesis approaches, for the synthesis of these molecules are continuously investigated. The intramolecular RCEYM reaction of enyne systems to access nitrogen heterocycles has been widely investigated, more than the intermolecular counterpart EYCM. However, examples of EYCM combined with cycloaddition reactions may often represent a good alternative to standard intramolecular approaches to access small ring heterocycles.

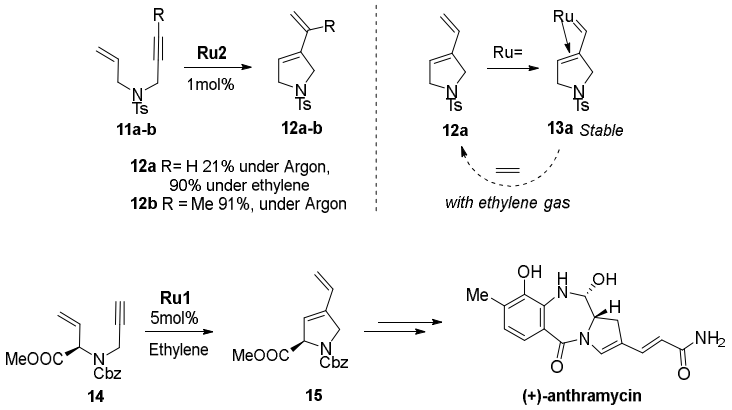
2.1. Synthesis of pyrrolines

2.1.1. Ring-closing enyne metathesis (RCEYM)

The first example of enyne metathesis applied to the synthesis of nitrogen heterocycles was reported by Mori et al. who described the synthesis of a series of 3-pyrrolines **12** from enyne substrates **11** using 1mol% **Ru2** catalyst[5] (Scheme 2). Interestingly, terminal alkyne **11a** led to **12a** in poor yield whilst higher conversion was observed for enyne **11b** bearing an internal triple bond. Mori hypothesised that the terminal alkene of **12a** could further react with the Ru-catalyst leading to the intermediate **13a** where the Ru is stabilised by the pyrroline double bond. This decreases the catalytic activity and accounts for the low yields observed with **11a**. On the other hand, the presence of a methyl substituent on the double bond of the diene system makes **12b** less reactive toward additional side metathesis reactions, mainly due to steric factors, thus allowing the formation of **12b** in 91% yield.

To overcome this issue, the same reaction was carried out under ethylene gas leading to a dramatic increase of the yield of **12a** to 90%. In fact, ethylene gas reacts continuously with the Ru-intermediate **13a** allowing, via alkene cross metathesis, the regeneration of the substrate **12a**. In the presence of ethylene, the catalyst loading can be also reduced to 1mol% and the reaction is completed in few hours. The ethylene approach developed by Mori represents the turning point in the exploitation of RCEYM for the synthesis of

a variety of heterocyclic compounds. As an example, this approach has been used for the synthesis of (+)-anthramycin. (Scheme 2). In fact, the pyrroline ring **15** has been obtained from the enyne **14** via RCEYM under ethylene atmosphere using **Ru1** as catalyst.[6]



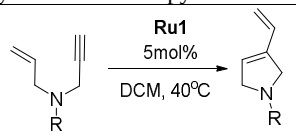
Scheme 2. Mori's synthesis of 3-pyrrolines via RCEYM

As an evolution of Mori's pioneering work, Lloyd-Jones and co-workers recently described a practical alternative to the "Mori's conditions" where the ethylene was replaced by the easier to handle allylbromide.[7] However, the presence of ethylene does not appear fundamental for some RCEYM reactions and its use is strictly dependant on the nature of the enyne substrate. In fact, Yiang et al. described the synthesis of a series of chiral pyrrolines **17** via RCEYM by using 5mol% of **Ru1**.[8] The compounds were synthesised smoothly from appropriate amino acids in high yields in the absence of ethylene gas as shown in Table 1. However, since secondary and tertiary amines may prevent the metathesis reaction by binding to the ruthenium, in the case of substrate **16h**, the Lewis acid $Ti(_iPrO)_4$ was added to the reaction mixtures. In fact, in the presence of 40mol% $Ti(_iPrO)_4$ the diallylamine **16h** containing a basic and nucleophilic N atom can successfully undergo olefin metathesis reactions leading to **17h** in 68% yield.[9] No reaction occurred when the same reaction was carried out in absence of $Ti(_iPrO)_4$. Nevertheless, it is noteworthy that most of the substrates **16** were successfully obtained without $Ti(_iPrO)_4$ in high yields. This may be due to the steric hindrance of **16** that may prevent the poisoning of the Ru catalyst by the nitrogen. Also the *N*-phenyl-diallylamine **16i** was converted into the pyrroline **17i** without the addition of any additive to the reaction mixture. The aniline nitrogen of **16i** is less nucleophilic than an aliphatic amine and thus it is not poisoned by the Ru-catalyst.

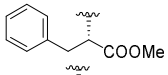
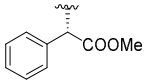
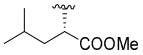
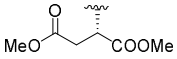
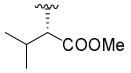
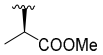
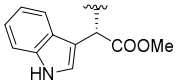
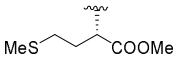
In addition to standard Grubbs' catalysts, some authors developed new and more efficient Ru-precatalysts. Nolan and co-workers reported the use of a series of phosphabicyclononane (Phoban)-containing ruthenium-based pre-catalysts **18-20** (Scheme 3) for the synthesis in high yield of a variety of nitrogen heterocycles, including 3-pyrrolines.[10]

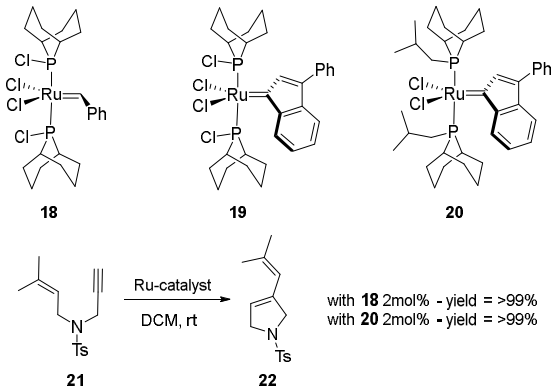
The catalysts **18-20** were first synthesised in 2004 by Forman and co-workers[11] who showed their efficacy in a series of self-metathesis reactions. Phoban catalysts proved to be efficient as they fulfil the requirements of steric bulk and basicity essential for metathesis reactions and phoban ligand represents an adequate compromise in terms of lability and stabilization in binding Ru.

Table 1. Synthesis of chiral pyrrolines via RCEYM.



16 17

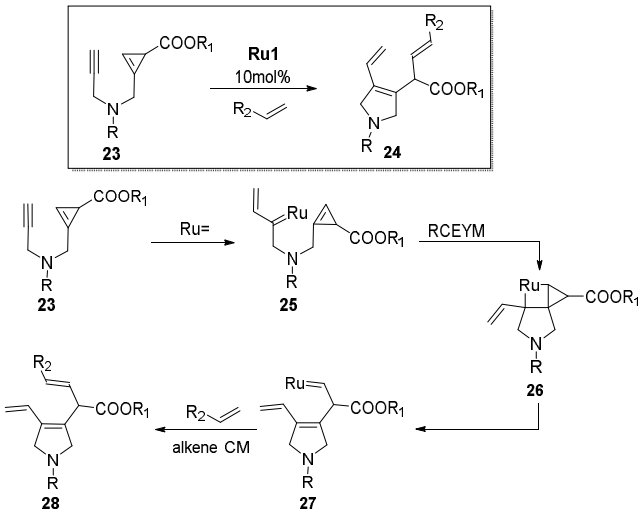
Entry	R	Pyrroline	Yield (%)	Note
1		**17a**	84	-
2		**17b**	81	-
3		**17c**	86	-
4		**17d**	89	-
5		**17e**	81	-
6		**17f**	78	-
7		**17g**	76	-
8		**17h**	68	40 mol % of $Ti(OiPr)_4$ was added. Without $Ti(OiPr)_4$, no reaction occurred.
9		**17i**	80	-



Scheme 3. Structures of Phoban-containing pre-catalysts **18-20** and RCEYM

Nolan carried out a comparative study of complexes **18-20** and Grubbs' catalysts in a number of RCM reactions, including the RCEYM of substrate **21**. Compound **22** was obtained in 6-8 h in excellent yields in the presence of both phoban-catalysts **18** and **20**.

Cascade and tandem reactions exploiting enyne metathesis have been reported for the synthesis of nitrogen heterocycles. An elegant cascade reaction has been recently described by Zhu and Shi to access polysubstituted 3-pyrroline substrates **28**.[12] The reaction exploits a series of sequential metathesis reactions as shown in Scheme 4. The 1,6-cyclopropene-yne **23** reacts with **Ru1** catalysts leading through a RCEYM to the intermediate **27**. The latter, a Ru-carbene intermediate, reacts with an external alkene in a CM reaction leading to the final pyrroline **28**. Several compounds have been synthesised at r.t. and obtained in variable yields (35%-78%).



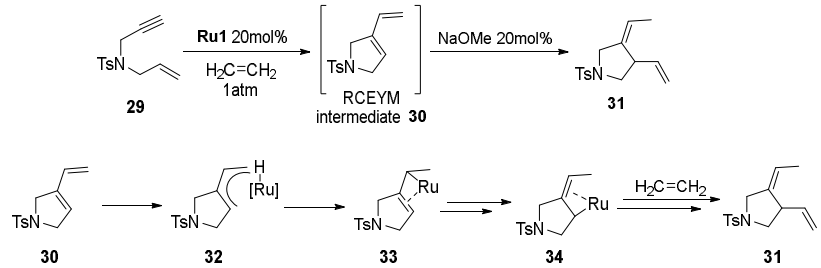
Scheme 4. Synthesis of chiral pyrrolines via RCEYM.

Snapper and co-workers reported a series of tandem enyne metathesis/hydrovinylation reactions on a variety of enyne substrates, leading to pyrroline **31**.[13] The reaction is catalysed by **Ru1** catalyst which leads to intermediate **30** via RCEYM under ethylene atmosphere. In the presence of ethylene, **Ru1** and NaOMe promote the 1,4-hydrovinylation reaction in MeOH/toluene at 75 ^{o}C, leading to the selective formation of **31** as *E* isomer in 64% yield. The proposed mechanism for the selective 1,4-hydrovivnilation is described in Scheme 5.

2.1.2. Enyne cross-metathesis (EYCM)

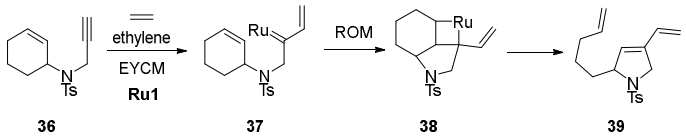
EYCM has been comparatively less employed for the synthesis of nitrogen heterocycles and only few examples are reported in the literature. EYCM is an intermolecular reaction leading to the formation of 1,3-diene products.

The latter are reactive species that can undergo a number of reactions (i.e. cycloaddition, further metathesis reactions) leading to cyclic nitrogen compounds.



Scheme 5. Snapper's tandem RCEYM-hydrovinylation approach.

Mori and co-workers described an elegant approach to synthesise the 3-pyrroline **39** through a metathesis cascade from the enyne **36**.[14] Compound **36** undergoes EYCM with ethylene leading to the Ru-carbene intermediate **37**. This further reacts with the double bond of the cyclohexene moiety leading through ROM to the final pyrroline **39** (Scheme 6).



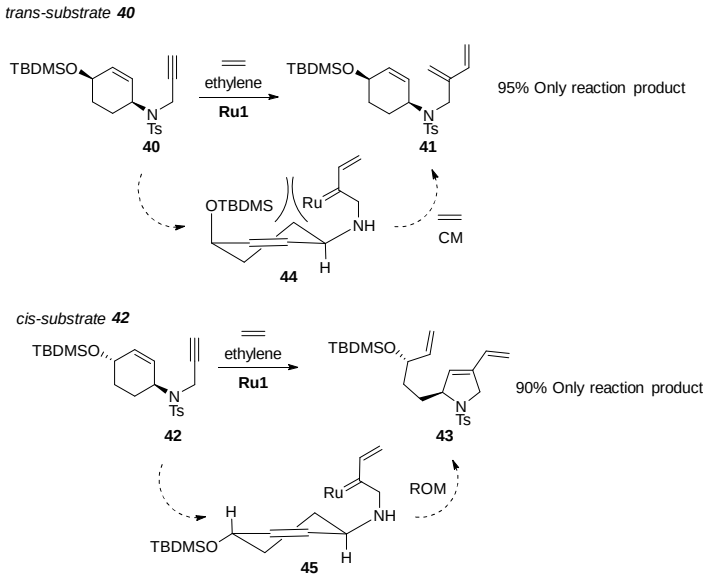
Scheme 6. Synthesis of pyrrolines **39** via EYCM-ROM cascade.

Interestingly, the presence of a chiral substituent on the cyclohexene ring in **40** and **42** influences the outcome of the reaction (Scheme 7). The *trans*-enyne **42** is fully converted into pyrroline **43** whilst the *cis*-substrate **40** is converted into the EYCM product **41** under the same reaction conditions. It has been suggested that the steric hindrance between the Ru-carbene and the TBDMS-group in intermediate **44** prevents the ROM reaction. The Ru-carbene then reacts with ethylene leading to the EYCM product **41**. On the other hand, there is no steric hindrance in the intermediate **45** arising from the *trans*-substrate **42**, which can then be successfully converted into pyrroline **43** in high yields.

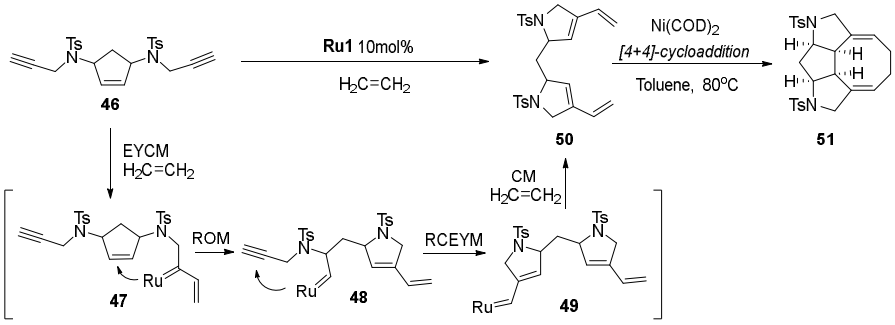
An elegant approach for the synthesis of pyrroline **50** through an EYCM-ROM-RCEYM cascade was reported by Blechert et al. (Scheme 8).[15] The reaction of the easy accessible **46** with ethylene leads in the first instance to the formation of the Ru-carbene intermediate **47**. The latter undergoes ROM on the cyclohexene ring allowing the formation of the first pyrroline nucleus. The formed carbene **48** then reacts with the terminal alkyne affording, through RCEYM, the intermediate **49**. This latter finally reacts with ethylene leading to the final product **50** which was in turn converted into the tetracyclic derivative **51** via [4+4]-cycloaddition catalysed by $Ni(COD)_2$.

2.2. Synthesis of indolines and pyrroles

An interesting approach to indolines **55** was described by Mori et al. (Scheme 9).[4b] The authors reported the synthesis of 2-pyrroline compounds via enyne metathesis starting from ynamide substrates **52**. Ynamides are interesting compounds where the nitrogen is directly conjugated with an alkyne.



Scheme 7. The influence of TBDMSO substituent on the EYCM-ROM outcome.



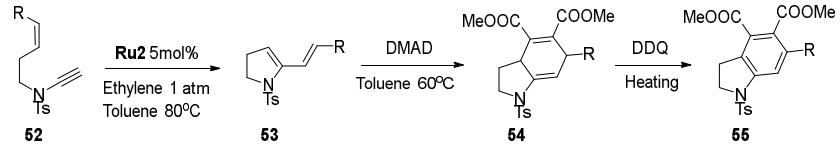
Scheme 8. Blechert's approach to pyrrolines **50** via a EYCM-ROM-CM cascade.

Several ynamides have been synthesised and reacted in the presence of **Ru1** and under ethylene atmosphere. When the reaction of **52** was carried out at room temperature the RCEYM product **53** was formed in only 10% yield. Increasing the temperature did not lead to any improvement in the yield, whilst the use of **Ru2** (5mol%) led to **53** in 66% yield. Finally, the optimal reaction conditions were set up in toluene at 80 °C and in the presence of **Ru2** leading to **53** in 83% yield and in few minutes (Table 2).

Table 2. RCEYM of **52**.

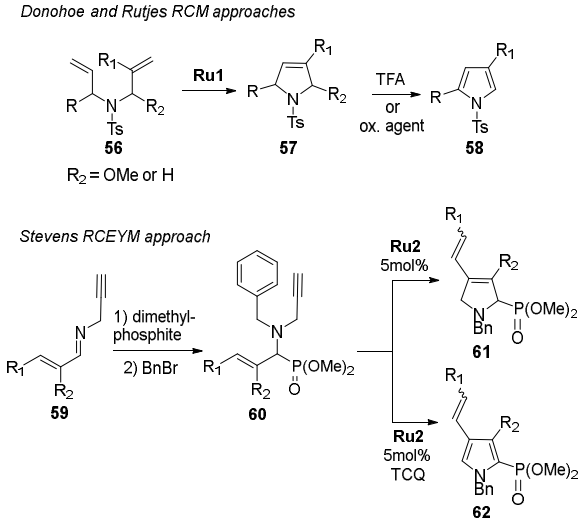
Catalyst	Solvent	Temperature	Atmosphere	Yield (%)
Ru1	CH_2Cl_2	r.t.	Ethylene	10
Ru1	CH_2Cl_2	reflux	Ethylene	7
Ru2	CH_2Cl_2	reflux	Ethylene	66
Ru2	Toluene	80 °C	Ethylene	83
Ru2	Toluene	80 °C	Argon	76

It is noteworthy that the reaction proceeds well when carried out in the presence of ethylene which allows the regeneration of **Ru2** catalyst, whilst in the presence of argon the yield of **53** dropped down to 76%. The 1,3-diene product **53** was then used as substrate for the synthesis of indole derivatives **55** through Diels-Alder (DA) cycloaddition using dimethyl acetylenedicarboxylate (DMAD) as dienophile, followed by oxidation with DDQ (Scheme 9).[4b]



Scheme 9. Synthesis of indolines **55** via RCEYM-DA.

Metathesis reactions can be exploited in the synthesis of pyrrole substrates. In general, pyrroles can be synthesised via olefin alkene metathesis as reported in Donohoe[16] and Rutjes[17] pioneering works. Both authors described the synthesis of pyrroles from diallyl amides via alkene RCM (Scheme 10). The alkene RCM of **56** led to 3-pyrrolines **57** which were in turn converted into pyrroles **58** via an acid catalysed elimination-aromatization step. Later, other approaches have been developed to convert the pyrroline **57** into pyrrole **58** such as through the use of peroxides, $RuCl_3$ and $FeCl_3$ employed as oxidizing agents.[18]

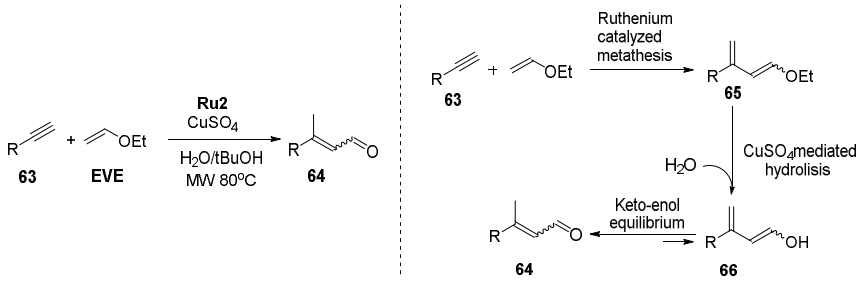


Scheme 10. Alkene RCM and RCEYM approaches to pyrroles.

However, to date, only a few synthetic approaches to pyrroles via enyne metathesis reactions have been described in the literature. Stevens and co-workers described the synthesis of pyrroles **62** via a RCEYM-aromatization approach.[19] The authors reported the synthesis of a series of phosphono-3-pyrroles **62** from enynes **60**. The RCEYM of **60** led to the 3-pyrrolines derivatives **61** which were in turn oxidised *in*

situ to pyrrole **62** via a one-step protocol with the addition of tetrachloroquinone (TCQ). Interestingly, when DDQ was used as oxidizing agent in place of TCQ, decomposition of the Grubbs' catalyst was observed.

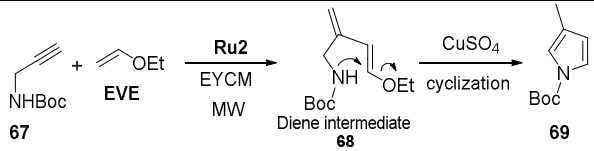
An EYCM approach to substituted pyrroles has been recently developed by Castagnolo and co-workers.[20] The authors synthesised a series of pyrrole derivatives in a single step from propargylamines which were reacted in the presence of Grubbs' catalyst **Ru2** with ethylvinyl ether (EVE). The idea of exploiting EYCM for the synthesis of pyrroles originates from a previous work by Castagnolo et al. where EYCM reactions were used for the one-pot conversion of terminal alkynes into crotonaldehydes.[21] (Scheme 11). In this paper the authors showed that reacting a terminal alkyne **63** with EVE under microwave irradiation led to crotonaldehyde **64** when the reaction was carried out on aqueous medium. It has been hypothesised that the EYCM led to the formation of ethoxydiene **65** which upon copper-mediated hydrolysis was converted into the enol derivative **66** and subsequently into the crotonaldehyde by tautomerization.



Scheme 11. EYCM approach to crotonaldehydes from terminal alkynes.

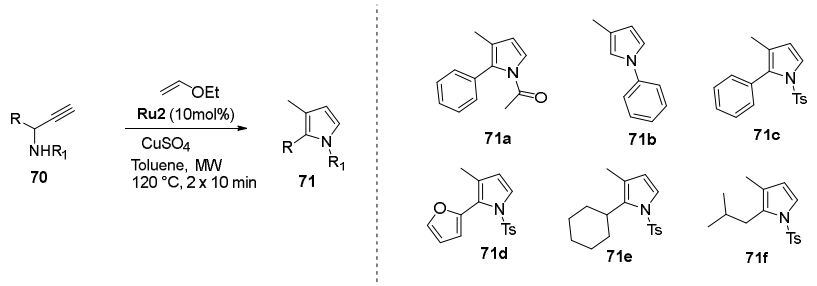
Starting from this work, it was reasoned that, if the same EYCM reaction was carried out on a propargylamine substrate such **67**, the nitrogen could collapse on the electrophilic enol/aldehyde intermediate **68** leading in a single step to the corresponding pyrrole product **69**. Table 3. Interestingly, the authors observed that the Boc-propargylamine **67** was poorly converted into the pyrrole **69** when the reaction was carried out in aqueous medium, whilst higher conversions were obtained in dry toluene and under higher temperature.

Table 3. EYCM-cyclization approach to pyrroles.



Solvent	Ru2 (mol%)	$CuSO_4$	T °C / Time	Yield (%)
$H_2O/^tBuOH$	10	2 eq.	80 °C/20min	25%
Toluene	5	2 eq.	80 °C/30min	36%
Toluene	5	2 eq.	120 °C/30min	56%
Toluene	5	-	120 °C/30min	0%
Toluene	5	1 eq.	120 °C/30min	18%
Toluene	10	2 eq.	120 °C/30min	55%

Moreover, the reaction takes place only when $CuSO_4$ is added to the reaction medium. It is plausible that the nitrogen of the intermediate **68** can collapse on the diene because of the coordination of Cu^{2+} to the ethoxy group. Reducing the amount of $CuSO_4$ the pyrrole **69** was obtained in lower yields, whilst comparable yields were obtained when $Cu(OTf)_2$ was used as copper source. A series of pyrroles was then synthesised using this methodology in good yield and in a few minutes (Scheme 12). The method proved to be versatile leading to a variety of pyrroles **71** substituted on C2 with both aromatic and aliphatic groups as well as bearing a variety of aromatic and EWG-substituents on the nitrogen.

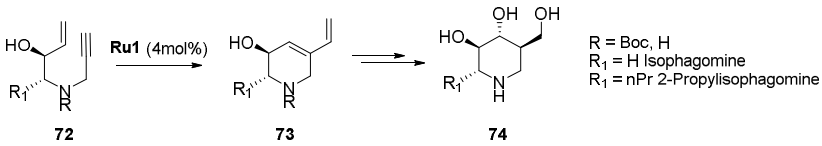


Scheme 12. Synthesis of pyrroles **71** from propargylamines via EYCM.

2.3. Synthesis tetrahydropyridines and tetraisoquinolines

In parallel to the synthesis of 5-membered heterocycles, enyne metathesis has been also used, especially in its intramolecular variant, for the synthesis of tetrahydropyridines (THPs). These latter have in turn been used as substrates to access natural products or pyridine derivatives.

A practical use of enyne metathesis was described by Takahata[22] and Imahori[23] who reported the asymmetric synthesis of 2-propylisofagomine and isophagomine via a RCEYM cyclization reaction. (Scheme 13). The authors treated enyne **72** with **Ru1** (4mol%) leading to the formation of tetrahydropyridine (THP) **73** which was in turn converted into desired product **74**.

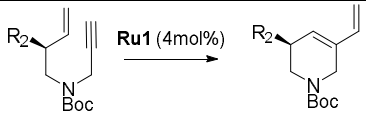


Scheme 13. RCEYM approach to isophagomine.

The presence of the free hydroxyl group proved to be fundamental to accelerate and improve the yield of the metathesis reaction. In fact, when the reaction was carried out on substrate **75a** bearing no substituents, THP **76a** was recovered only in 32% yield. Table 4. Interestingly, under ethylene atmosphere the yield of **76a** rose to 96%. In the presence of an OH substituent, the RCEYM went to completion within few hours. Lower yield was obtained when the bulkier substrates **75c** and **75d** were used. It has been hypothesised that the allylic hydroxyl group accelerate the re-entry of the propagating Ru-alkylidene species into the next catalytic cycle. A similar acceleration effect of an allylic hydroxyl group has also been observed in olefin metathesis in the presence of the first-generation Grubbs' catalyst.[24] Kinetic studies have been

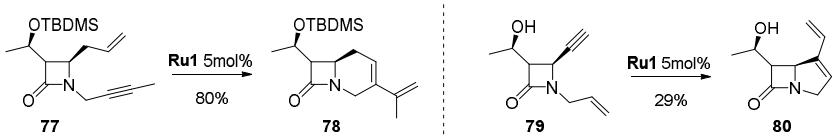
carried out by the authors showing that the hydroxyl group is responsible for a rate-determining step of ring-closing enyne metathesis.

Table 4. Influence of the substituent on the RCEYM.



Substrate	R_2	Time (h)	Atmosphere	Product	THP (yield %)
75a	H	41	Argon	**76a**	32
75a	H	1.5	Ethylene	**76a**	96
75b	OH	1.5	Argon	**76b**	>99
75c	OBn	41	Argon	**76c**	44
75d	OTBDPS	41	Argon	**76d**	7

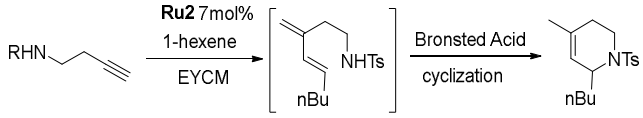
Barret and coworkers reported the synthesis of a fused system of carbacephem via olefin metathesis and RCEYM.[25] A set of dienes and enynes **77** was synthesised and converted in high yield into the cyclic products **78** after treatment with **Ru1** catalyst. It is noteworthy that the yield of the analogue 4,5-derivative **80** obtained from **79**, is lower than **78**. This is supposed to be due mainly to the fused and highly strained 4,5-membered ring system which prevents the reaction from taking place efficiently. Also, the presence of an internal alkyne in **77** favours the endo-cyclization leading to a 6-membered ring (Scheme 14).



Scheme 14. RCEYM approach to carbacephem systems

As previously reported, EYCM has been less used in the synthesis of heterocyclic rings. Diver and coworkers reported an elegant approach for the synthesis of tetrahydropyridine systems via EYCM followed by Brønsted acid heterocyclization.[26] The homopropargyl amines **81** were first reacted with different alkenes in the presence of **Ru2** or **Ru3** 7mol% and an appropriate acid catalyst leading in one step to substituted tetrahydropyridines **83**. Excellent yields were obtained when TfOH or $MeSO_3H$ were used as catalysts, or if TFA was used in excess, whilst poor conversion was observed with HCl or CSA. The reaction proceeds as reported in Table 5. The alkyne **81** and the alkene react in an EYCM leading to the metathesis product **82**, which is in turn converted into the final tetrahydropyridine **83** via a hydroamination cyclization catalysed by a Brønsted acid. The reaction conditions with TfOH were finally adopted by the authors who reported the synthesis of a variety of tetrahydropyridine derivatives under these conditions. The compounds **83a-f** were obtained in high yields and the methodology proved to be tolerant to a variety of substituents on the homopropargylamine and the alkene substrates. Examples are shown in Table 6. Interestingly, when chiral amine **84** was used as substrate, the reaction proceeded stereoselectively leading to the formation of *cis*-isomer **88** as the only reaction product.

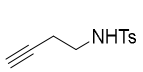
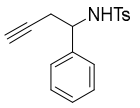
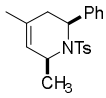
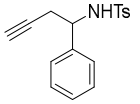
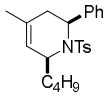
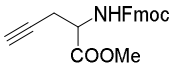
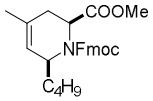
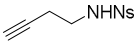
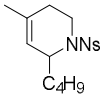
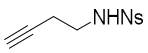
Table 5. EYCM-Brønsted acid heterocyclization.



81 **82** **83**

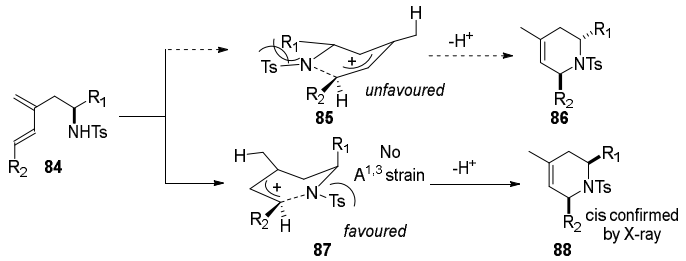
Acid	Equiv.	Conv. (%)	Yield (%)
TFA	9.0	100	81
HCl	0.4	59	ND
CSA	0.4	78	ND
$MeSO_3H$	0.4	100	67
TfOH	0.4	100	83

Table 6. Examples of tetrahydropyridines **83** synthesised via EYCM.

Alkyne	Alkene	Product		Yield (%)
	1-hexene		**83a**	83
	propene		**83b**	65
	1-hexene		**83c**	76
	1-hexene		**83d**	73
	1-hexene		**83e**	67
	ethylene		**83f**	66

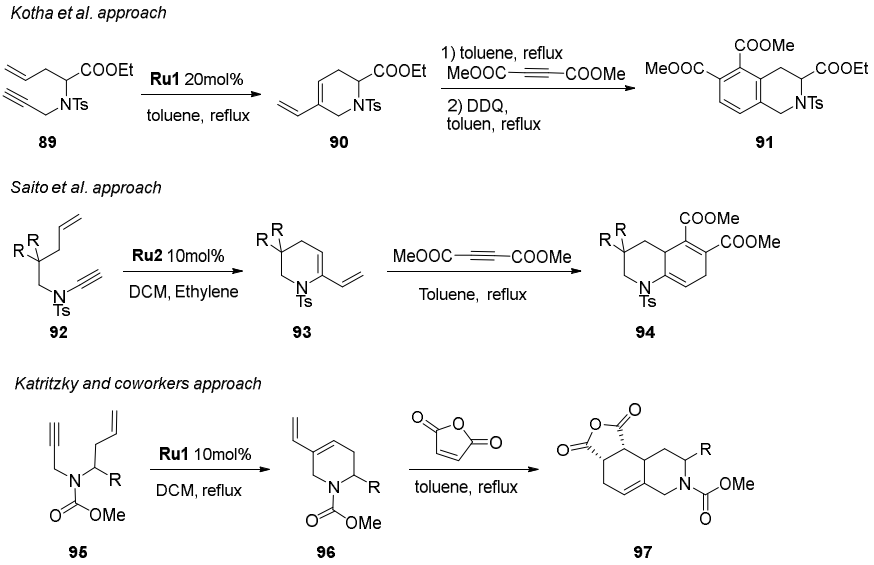
The rationale for the selectivity of the reaction is shown in Scheme 15 and the configuration of **88** was assigned by X-ray crystallography. The protonation of **84** led to the formation of two possible carbocation intermediates **85** and **87**. In intermediate **85** the R_1 substituent produces strains with the tosyl group, whilst this is alleviated in **87**. Thus, this second conformation is favoured leading to the selective formation of *cis*-**88**.

Kotha et al. applied RCEYM to the synthesis of tetraisoquinoline-3-carboxylic acids (Tic) **91** through the combination of enyne metathesis with Diels-Alder reaction[27] (Scheme 16).



Scheme 15. Stereoselective formation of *cis*-tetrahydropyridine **88**.

The propargylamine **89** was treated with **Ru1** catalyst leading to the vinyl-tetrahydroquinoline **90**. Treatment of the latter compound with DMAD in refluxing toluene, followed by aromatization with DDQ led to the Tic derivative **91**. A similar approach has been reported by Mori and coworkers[28] who described the RCEYM of the ene-ynamide **92** followed by Diels-Alder reaction for the synthesis of the cyclic dienamide **94** (Scheme 16).

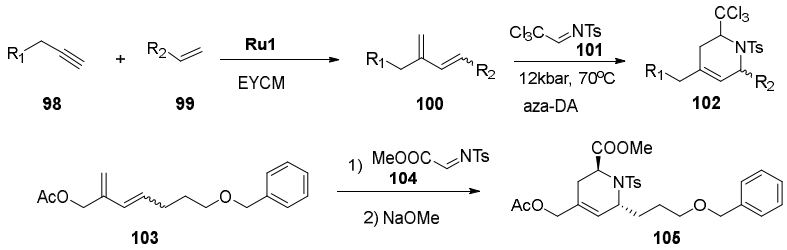


Scheme 16. RCEYM - Diels-Alder cascades for the synthesis of cyclic amines.

The enyne metathesis of the substrate **92** proceeds under ethylene atomosphere and with **Ru2** catalyst leading to the formation of the 1,4,5,6-tetrahydropyridine **93**. The latter was in turn reacted with DMAD to afford desired cyclic derivative **94**. Similarly, Katritzky and co-workers[29] synthesised the vinyl tetrahydropyridine **96** via RCEYM by treatment of **95** with **Ru1**. Diels-Alder reaction of the latter with maleic anhydride led to polycyclic derivative **97** (Scheme 16).

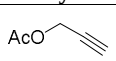
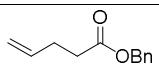
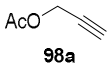
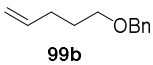
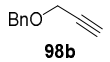
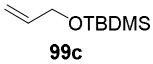
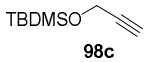
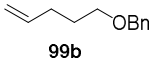
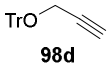
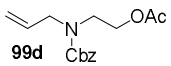
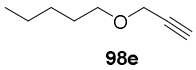
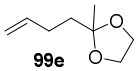
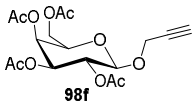
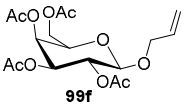
Blechert and co-workers reported an interesting approach to yield THPs via a tandem EYCM-aza-Diels-Alder reaction.[30] Different alkynes **98** and alkenes **99** were reacted together in the presence of **Ru1** leading to a number of dienes **100** (Scheme 17, Table 7). In general, the metathesis products were obtained

in good-excellent yields with the exception of dienes **100d-e**, where the reaction seems affected by the steric demand of the alkyne reagent.



Scheme 17. EYCM - aza-Diels-Alder approach to tetrahydropyridines **102**.

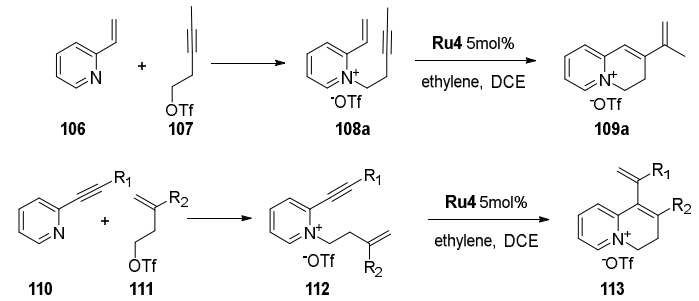
Table 7. EYCM of alkynes **98** and alkens **99**.

Alkyne	Alkene	Diene	Yield (%)
 **98a**	 **99a**	**100a**	87
 **98a**	 **99b**	**100b**	80
 **98b**	 **99c**	**100c**	70
 **98c**	 **99b**	**100d**	47
 **98d**	 **99d**	**100e**	51
 **98e**	 **99e**	**100f**	74
 **98f**	 **99f**	**100g**	58

All the dienes were then treated with the electron-deficient *N*-trichloro-ethylidene-*p*-toluenesulfonamide dienophile **101**, leading to the formation of tetrahydropyridines **102** in high yields (60-91%). Interestingly, the metathesis reaction of the sugar derivatives **98f** and **99f** led to the diene **100g**, which was converted into the corresponding pseudo-oligosaccharide after aza-DA reaction. Finally, the procedure was successfully used for the synthesis of pipecolinic acid derivatives such **104**. Interestingly, only the *trans*-isomer of the compound **104** was obtained from the aza-DA reaction.

2.4. Synthesis of other nitrogen heterocycles

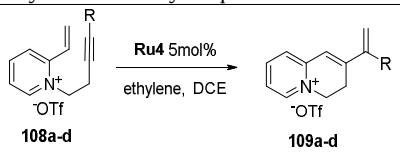
RCEYM has been recently employed for the synthesis of a variety of nitrogen containing heterocycles. Alkenyl-substituted 3,4-dihydroquinolizinium triflates **109** and **113** were synthesised via RCEYM in ethylene atmosphere using **Ru4** catalysts[31] (Scheme 18).



Scheme 18. Synthesis of 3,4-dihydroquinolizinium triflates via RCEYM.

The authors reported that the polymerization of the substrate **108a** was observed during the RCEYM when the reaction was carried out without an ethylene atmosphere. On the other hand, the compound **109a** was obtained in 83% yield when the ring closure was performed under ethylene in refluxing DCE. Interestingly, when **Ru2** was used as the catalyst the product **109a** was recovered in only 66% yield.

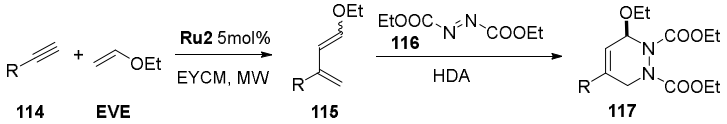
Table 8. Synthesis of dihydroquinolizinium triflates **109**.



Substrate	R	Product	Yield (%)
108a	Me	**109a**	83
108b	Ph	**109b**	81
108c	H	**109c**	38
108d		**109d**	ND

Different triflates **108a-d** were treated with **Ru4** as reported in Table 8. The presence of different substituents on the alkyne moiety affects the outcome of the cyclization. Good yields were obtained with the terminal alkynes **108a-b**, whilst the terminal alkyne **108c** led to **109c** in poor yield. The thiophene derivative **108d** was not converted into the cyclic product **109d** probably due to the low stability of the salt under the reaction conditions. The compounds **109** and **113** were then used as precursors in the synthesis of benzoquinolizinium systems.

Castagnolo et al. investigated the EYCM reaction of different alkynes with ethyl vinyl ether (EVE) under microwave irradiation to obtain ethoxy-dienes **115** (Scheme 19).

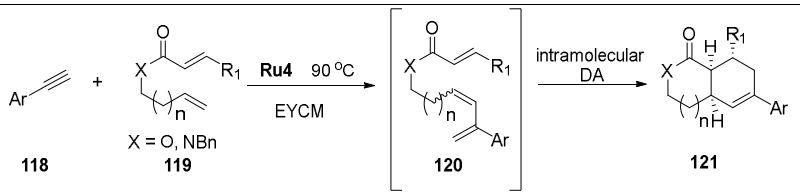


Scheme 19. Synthesis of diazine derivatives via EYCM - hetero Diels-Alder reaction.

These latter were then coupled with different dienophiles, including the diethyl azodicarboxylate **116**, leading through hetero Diels-Alder to the diazine derivative **117**.[32]

An interesting tandem cross enyne metathesis (EYCM) – intramolecular Diels–Alder reaction to access linear bicyclic scaffolds has been developed more recently by Miro' et al.[33] (Table 9).

Table 9. Tandem EYCM – intramolecular Diels-Alder.



Alkyne	Ar	X	R_1	n	Product	Isomer endo/exo	Yield (%)
118a	Ph	O	H	1	**121a**	100:0	57
118b	Ph	NBn	H	1	**121b**	100:0	62
118c	4-F-Ph	NBn	H	1	**121c**	100:0	45
118d	4-MeO-Ph	NBn	H	1	**121d**	100:0	35
118e	Ph	NBn	H	0	**121e**	100:0	50
118f	Ph	NBn	H	2	**121f**	100:0	44
118g	Ph	NBn	Ph	1	**121g**	53:47	78
118h	Ph	NBn	Napht	1	**121h**	66:34	47

The authors reacted the aryl-acetylenes **118** with oxygen/nitrogen-dienes **119** in the presence of **Ru4** (5 mol%) affording the intermediates **120** through EYCM reaction. Compounds **120** contain a diene moiety as well as a dienophilic alkene, thus leading under the reaction conditions to the bicyclic derivatives **121** via intramolecular Diels-Alder. All the bicyclic products **118a-f** with R_1 = H were obtained as *endo*-isomer. On the other hand, when R_1 was a phenyl or naphthyl substituent, the products **121g-h** were obtained as a mixture of *endo/exo* isomers.

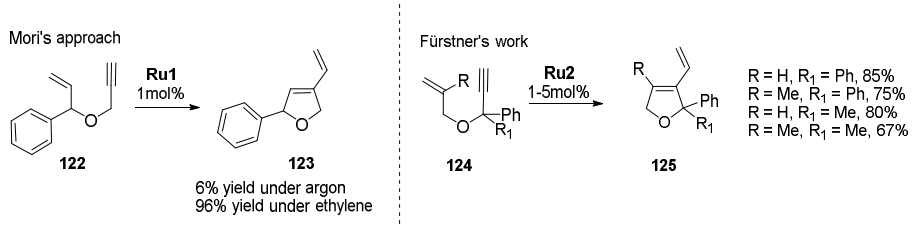
3. Synthesis of oxygen-heterocycles

Enyne metathesis has been widely used for the synthesis of oxygen heterocycles both in its inter- or intramolecular versions. Most of the procedures described before for the synthesis of 3-pyrrolines or tetrahydropyridines have been also used for the synthesis of the corresponding oxygen-heterocycles. The RCEYM reaction has been exploited to covert an enyne system containing an oxygen atom into a dihydrofuran, a tetrahydro-pyran or 5- and 6-membered lactones. The intermolecular EYCM reaction between an alkene and an alkyne leads to a 1,3-diene system that can be used as substrate in hetero Diels-Alder reactions to obtain tetrahydropyran scaffolds.

3.1. RCEYM approaches to oxygen-heterocycles

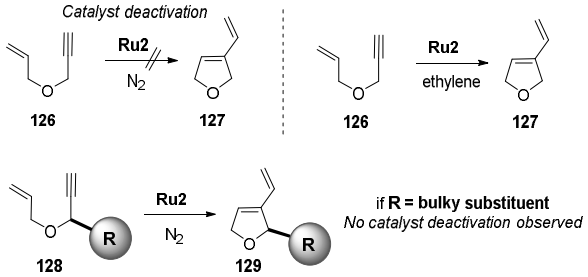
The use of RCEYM for the synthesis of dihydrofurans has been first described by Mori et al. who investigated the role of the ethylene atmosphere in promoting the enyne metathesis cyclization.[34] As observed for RCEYM on nitrogen containing substrates, the synthesis of diene **123** was favoured when the

reaction was carried out under ethylene atmosphere and in the presence of **Ru1** catalyst leading to the desired product in 96% yield (Scheme 20). In contrast, under an inert argon atmosphere, compound **123** was isolated in only a 6% yield. Fürstner et al. investigated the efficacy of different Ru-catalysts in RCEYM for a series of enyne ethers **124** and concluded that **Ru2** are generally the best in promoting the synthesis of heterocycles **125** (Scheme 20).[35]



Scheme 20. RCEYM approaches for the synthesis of dihydrofurans.

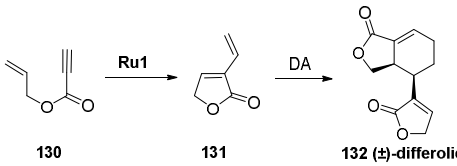
Geminal substitution slowed the reaction rate substantially, but all of the substrates were obtained generally in high yields. Interestingly, the reactions also proceeded efficiently under argon atmosphere and without the presence of ethylene. Recently Fogg and co-workers investigated the ethylene-promoted versus ethylene-free RCEYM reactions using both **Ru1** and **Ru2** catalysts.[36] As a general rule, under nitrogen/inert atmosphere Ru-catalysts are deactivated and poor conversion is observed for substrates with minimal propargylic bulk such as **126**. For these substrates, ethylene is necessary to suppress the catalyst deactivation and to allow the reaction to reach completion. However, in substrates with bulky propargylic substituents such **128**, catalysts deactivation was not observed and the RCEYM also proceeded under nitrogen atmosphere. (Scheme 21).



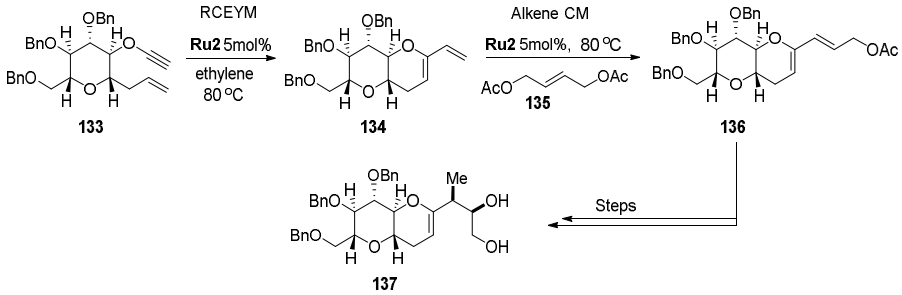
Scheme 21. Fogg's studies on the ethylene-promoted/ethylene-free RCEYM.

RCEYM has been used for the synthesis of natural products, such as the (±)-differolide **132** obtained from the lactone precursor **131** through a self-Diels Alder reaction. The enyne **130** was converted by treatment with **Ru1** into **131** which acting both as diene and dienophile in a self-cycloaddition led to **132** (Scheme 22).[37]

Clark and co-workers successfully employed RCEYM for the synthesis of polyether systems such as those found in the marine natural products gambierol or hemibrevetoxin B (Scheme 23).[38]



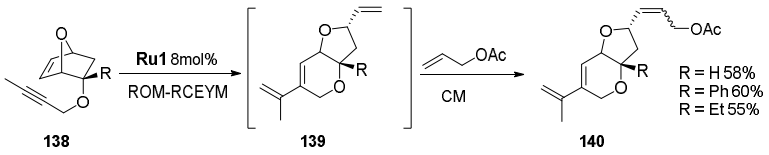
Scheme 22. RCEYM-self-DA approach to (±)-differolide **132**.



Scheme 23. Clark's RCEYM approach to polyether systems.

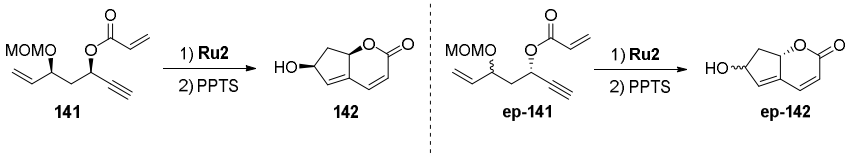
The polycyclic system **137** was constructed through sequential RCEYM and alkene CM reactions from alkynyl ether **133**. This latter was treated with **Ru2** catalyst under ethylene atmosphere leading to the ring-closing metathesis product **134**. Diene **134** was then treated with the (*E*)-2-butene-1,4-diol diacetate **135** in the presence of **Ru2** leading to the substrates **136** via alkene CM reaction. Finally, **136** was converted into the synthon **137** via Sharpless asymmetric epoxidation followed by epoxide ring opening. It is noteworthy that the alkene CM led to **136** in higher yields when the diacetate **135** was used in place of allylacetate.

Another approach to the polyether system **140** has been reported by Plumet et al. via a tandem ROM-RCEYM reaction followed by olefin CM.[39] The norbornenyl substrate **138** was treated with **Ru1** leading via enyne ROM to the formation of the bicyclic system **139**. The reaction was carried out in the presence of vinyl acetate which in turn reacted with **139** to afford the desired product **140** via CM reaction (Scheme 24).



Scheme 24. Synthesis of polyether **140** via ROM-RCEYM.

Krishna reported a synthetic study to elucidate the structure of ilexlactone **142**, which was obtained from the precursor **141** through an elegant domino RCEYM – RCM approach.[40] All the diastereoisomers **142/ep-142** were synthesised, leading to the discovery that the structure previously reported and proposed for the ilexlactone was incorrect (Scheme 25).

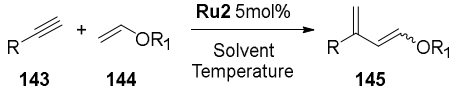


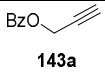
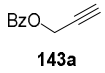
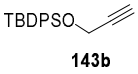
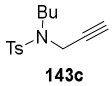
Scheme 25. Krishna's approach to ilexlactone

3.2. EYCM approaches to oxygen-heterocycles

The enyne CM reaction has been widely investigated by Diver and co-workers who described an interesting approach to 6-membered oxygen heterocycles.[41] The authors described the EYCM reaction of a variety of terminal alkynes **143** with enol ethers **144**, such as ethyl vinyl ether, butyl vinyl ether and vinylacetate. Alkynes reacted promptly with vinyl ethers in the presence of **Ru2** affording the dienes **145** as shown in Table 10.

Table 10. EYCM for the synthesis of alkoxy-dienes **145**.

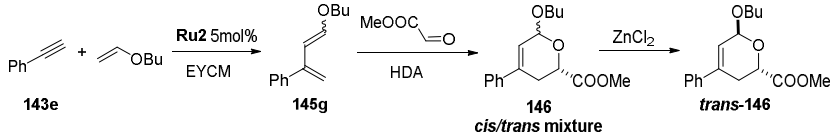


Alkyne	Alkene	Product	Yield (%)
 **143a**		**145a**	98
 **143a**		**145b**	98
 **143b**		**145c**	97
 **143c**		**145d**	92
 **143d**		**145e**	86
 **143d**		**145f**	70

The resulting dienes **145** were generally obtained as E/Z isomers in a 2:1 ratio and high yields. The resulting 1,3-diene **145** products of EYCM reactions can be used as substrates both in Diels-Alder as well as hetero-Diels Alder reactions, leading in the second case to tetrahydropyrans. The diene **145g** was treated with methyl glyoxalate leading to the tetrahydropyran **146** as a mixture of *cis-trans* diastereoisomers in a 2:1 ratio. Finally, treatment of the mixture with $ZnCl_2$ allowed the full conversion of the isomer ***cis*-146** into the isomer ***trans*-146** (Scheme 26).

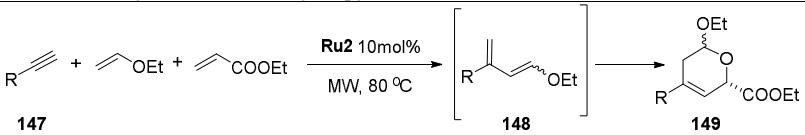
A similar approach has been reported by Castagnolo et al. for the synthesis of the pyran ring of fused furanose-pyranose 1,3-C-C-linked-disaccharides.[42] A series of 2,3-dihydropyrans **149** was synthesised from

different terminal alkynes **147** through a one-pot microwave assisted multicomponent enyne cross-metathesis/hetero-Diels-Alder reaction (Table 11).



Scheme 26. Diver's approach to tetrahydropyran **146**.

Table 11. Synthesis of tetrahydropyrans **149** via EYCM-hetero Diels Alder reaction.

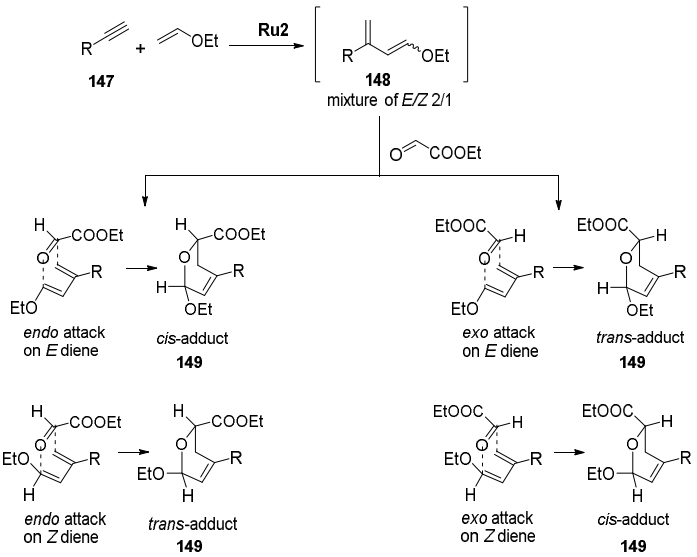


Alkyne	R	Product	*trans/cis*	Yield (%)
147a	TMS	**149a**	2:1	71
147b	$PBMOCH_2$	**149b**	2:1	51
147c	$TMSOCH_2$	**149c**	2:1	54
147d	Ph	**149d**	2:1	75
147e	$BocNHCH_2$	**149e**	2:1	62
147f	$(EtO)_2CH$	**149f**	2:1	69

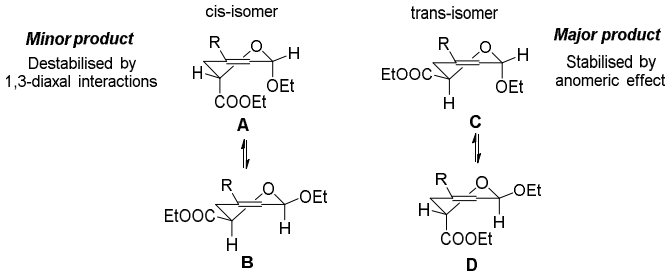
All the compounds **149** were obtained in good yields and in a few minutes. Interestingly, the stereoselectivity of the reaction was in contrast with the data reported previously by Diver and co-workers. In fact, compounds **149** were obtained as a *cis/trans* isomer mixture in 1:2 ratios, opposite to that observed by Diver on the similar substrate **146**. The hetero Diels Alder reactions generally proceed respecting the Alder rule and affording the *cis* isomer (namely the *endo* product) as the major compound. However, in this case, the *trans* isomer was obtained as the major product and its formation can be explained only if an *exo* attack is supposed.

The first step of the reaction, the cross metathesis of alkyne **147** with ethyl vinyl ether, led to a mixture of *E/Z*-diene **148** in a 2:1 ratio. Thus, if an *endo* attack happened on both *E/Z*-dienes XX, a 2:1 *cis/trans* mixture of products **149** should have been expected. On the contrary only an *exo* attack can explain the observed 2:1 *trans/cis* regioselectivity as illustrated in Scheme 27. In order to explain the unexpected preference for the formation of trans isomer Castagnolo et al. reasoned that two factors, namely the anomeric effect and the 1,3-diaxial interactions, need to be taken in consideration.

It is known that dihydropyrans exist in rapidly inverting half-chair forms as shown in Scheme 28. The anomeric effect favours the forms A and C over respectively B and D for both isomers. However, form A is destabilized also by the additional 1,3-diaxal interactions between –OEt and –COOEt moieties which should lead the *cis*-isomer to prefer a B form counterbalancing the anomeric effect. On the other hand, the *trans*-isomer form C is the most stable since it is favoured by both factors, the anomeric effect and the pseudo-equatorial position of the ethylcarboxylate moiety which does not suffer from the 1,3-diaxal interactions.



Scheme 27. Stereoselectivity in the hetero Diels-Alder reaction of **148** with ethyl glyoxalate.

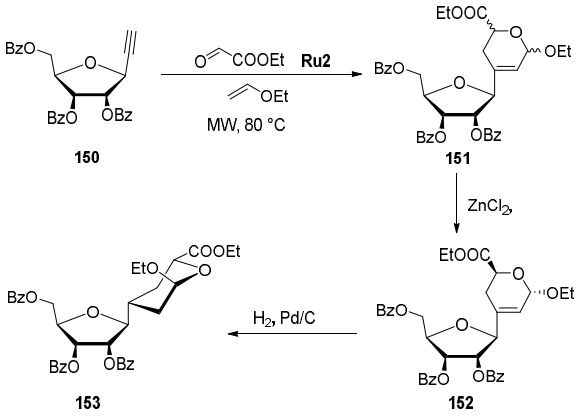


Scheme 28. Anomeric effect and 1,3-diaxal interactions in pyrans **149**

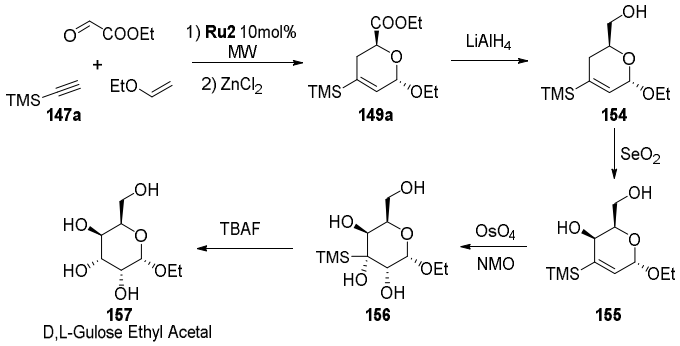
Hence, these two factors can explain the stereoselectivity data observed for **149**. It is known that the magnitude of the anomeric effect is also related to the nature of the alkoxy group bound close to the pyran oxygen. Thus, in the case of Diver's substrate **146** the use of the butylvinyl ether as dienophile might have also contributed to the formation of the *endo* adduct as the major product in the HDA reaction. Finally, the multicomponent approach has been used for the synthesis of 1,3-C-C-linked furanose-pyranose disaccharides from alkyne **150** as shown in Scheme 29. The alkyne **150** was reacted with EVE and ethylglyoxalate in the presence of **Ru2** under microwave irradiation affording the desired C-linked furanose-dihydropyrane **151** as a mixture of four diastereoisomers. Equilibration of **151** in the presence of $ZnCl_2$ led to the *trans* diasteroisomers **152**, that were converted by hydrogenation into the desired 1,3-C-C-linked furanose-pyranose disaccharide **153**.

The multicomponent EYCM-HDA approach developed by Castagnolo et al. was also used for the stereoselective protecting group free synthesis of D,L-gulose.[43] The TMS-acetylene **147a** was reacted with ethyl vinylether and ethylglyoxalate under microwave irradiation leading to **149a** as a mixture of

diastereoisomers. These latter were converted into the *trans*-isomer by equilibration with $ZnCl_2$. The isomer **149a** was then diastereoselectively functionalised leading in a few steps to D,L-gulose ethyl acetal **157** (Scheme 30).



Scheme 29. Synthesis of C-linked pseudo-disaccharide **153** via tandem EYCM-HAD reaction.



Scheme 30. A EYCM-HAD approach to D,L-gulose

4. Conclusions

Nowadays, metathesis reactions constitute a powerful and unique method for the synthesis of a wide variety of chemicals, including heterocycles. Despite the fact that alkene-alkene still represent the most largely used type of metathesis reactions, the interest toward the enyne variant is constantly increasing due to enormous potentialities offered by this transformation. The intramolecular enyne metathesis offers an easy approach to heterocycles like pyrrolines, dihydrofurans or tetrahydropyridines via the cyclization of ether or amine enyne systems. These products are obtained as cyclic diene systems and thus can be exploited for further chemical transformations, such as cycloaddition or tandem metathesis reactions.

Similarly, the intermolecular version leads to 1,3-dienes that can be used as substrates in cycloaddition and hetero-Diels-Alder reactions affording small ring heterocycles through tandem or domino processes. Finally, the continuous development of novel, more efficient and selective catalysts makes the enyne

metathesis an established, efficient and reliable method for the manufacturing of heterocyclic chemicals not only at academic level but also in industry.

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