# Metathesis in the Synthesis of Aromatic Compounds†

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## 1. Introduction

The importance of aromatic structures in organic chemistry can never be underestimated. Nature uses compounds containing aromatic or heteroaromatic nuclei extensively as the skeletal core for compounds involved in many important biological processes. In addition, modern medicinal and pharmaceutical chemists have found that aromatic cores are indeed "privileged structures" for the discovery of molecules with novel medicinal characteristics.[2]

Ring-closing metathesis (RCM) also needs little introduction; the explosion of applications of this useful methodology ultimately culminated in the award of the 2005 Nobel Prize in Chemistry to its discoverers and primary developers. One just has to look at the numbers of recent reviews highlighting this area of chemistry to realize the impact of ene−ene and ene−yne metathesis on modern synthetic chemistry, as well

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† This review is dedicated to Prof. Dr. H.-G. (Hagga) Schmalz, Institute of Organic Chemistry, University of Cologne, Cologne, Germany—a scientist, mentor, and friend who wrote one of the first reviews on the emerging field of metathesis in synthesis in 1995.[1]

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Willem van Otterlo was born in Amsterdam, The Netherlands. In 1999 he graduated with a Ph.D. under the mentorship of Professors C. B. de Koning and J. P. Michael (School of Chemistry, University of the Witwatersrand, Johannesburg, South Africa). He then spent two years in the research group of Professor S. Hanessian (University of Montreal, Quebec, Canada) as a postdoctoral research fellow in projects involving peptide-based building blocks. In 2001 he returned to the University of the Witwatersrand to take up a lecturing position and initiated a research program involving the application of organometallic reagents to the synthesis of small benzo-fused molecules; currently he holds the position of Associate Professor. In July 2008 he joined Professor H. Waldmann's Chemical Biology group at the Max Planck Institute, Dortmund, as a von Humboldt Georg-Forster Research Fellow, for a sabbatical year to learn more about the interaction between chemistry and biology. Currently his research interests are focused on the synthesis of small molecules with potential bioactivity, particularly molecules based on natural templates, for example pancratistatin and podophyllotoxin.

Charles de Koning completed his Ph.D. at the University of Cape Town in 1988 under the supervision of Professor R. G. F. Giles. He then spent a year with Professor G. H. Büchi at the Massachusetts Institute of Technology, Boston, MA, followed by two years of postdoctoral study at the University of Hawaii with Professor R. E. Moore. At the end of 1991, he took up a lectureship position at the University of Witwatersrand in Johannesburg, South Africa. Since 2005 he has held the position of Personal Professor of Organic Chemistry at the University of the Witwatersrand. He has spent sabbaticals at the CSIR in South Africa and with Professor Dr. H.-G. Schmalz when he was at the Technical University of Berlin, Germany. His interests embrace the synthesis of aromatic and heteroaromatic compounds, particularly those that are active against cancer cell lines and malaria. In 2007, he was the recipient of the South African midcareer creative mentoring award in science from the journal *Nature*.

as the development and application of new catalyst systems.[1,3−36] The mention of RCM normally brings to mind the metathetic interaction of two alkenes, two alkynes, or an alkene with an alkyne to furnish carbo- or heterocycles with one internal unsaturated bond. In this review, we will strive to demonstrate the impact that RCM strategies have had on the de novo assembly of *aromatic* and *heteroaromatic* ring systems.

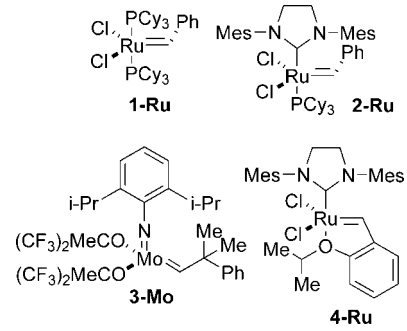



**Figure 1.** Structure of some of the most commonly applied metathesis catalysts.

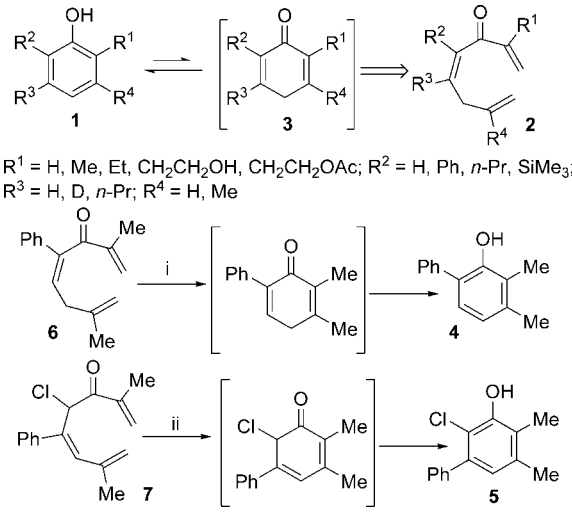
During evaluation of the examples relevant to this review, it quickly becomes evident that a small group of catalysts have been the reagents of choice. These catalysts are shown in Figure 1 and include the Grubbs first- and second-generation catalysts **1-Ru** and **2-Ru**,[37] respectively, the Schrock catalyst **3-Mo**,[38] and the second-generation Hoveyda−Grubbs catalyst **4-Ru**.[39] Other catalysts utilized for the synthesis of aromatic substrates will be highlighted in the appropriate schemes where the work is described.

As first glance, RCM and aromatic compounds seem to have little in common; however, the use of the metathesis approach to generate aromatic or heteroaromatic compounds, directly or after a few additional steps, has recently seen significant application. This review, containing literature up until the beginning of 2009, will aim to demonstrate how powerful the metathesis approach is for the synthesis of aromatic compounds. Other authors have commented on the application of metathesis for the synthesis of aromatic molecules, be it in review "Highlights",[41] "Concepts",[42] or as part of chapters or reviews commenting on interesting aspects of metathesis.[43,44] However, to the best of our knowledge, this work is the first description that attempts to comprehensively review the relationship between metathesis and aromatic compounds. In the first part of this review, the synthesis of aromatic carbocycles by ene−ene and ene−yne metathesis will be summarized as well as the contributions due to metathetic cyclotrimerization reactions (section 2). This is followed by the application of RCM (ene−ene and ene−yne) to the synthesis of carbocycles fused to heterocyclic rings (section 3) and finally a description of ene−ene, ene−yne, and yne−yne metathetic approaches to obtain heteroaromatic compounds (section 4).

## 2. Synthesis of Aromatic Carbocycles by RCM−Aromatization

Substituted benzenes and related systems are extremely important as structural units in natural products and synthetic compounds. In this section, approaches to the synthesis of aromatic and benzo-fused compounds using RCM as a key, if not the only, step will be reviewed. This section will also review the synthesis of polyaromatic compounds by this approach including, for example, naphthalenes[45] and phenanthrenes.[46]

**Scheme 1**[a]




[a] Reagents and conditions: (i) **2-Ru** (7.5 mol %), $CH_2Cl_2$, 40 °C, 2 h (92%); (ii) **2-Ru** (7.5 mol %), toluene, 80 °C, 12 h (84%).

## 2.1. Ene−Ene RCM−Aromatization Strategies for the Synthesis of Aromatic Carbocycles

The application of RCM−aromatization to the synthesis of aromatic carbocycles has begun to represent valuable synthetic methodology for obtaining a wide variety of polysubstituted aromatic structures. The use of this strategy will be described in the next section.

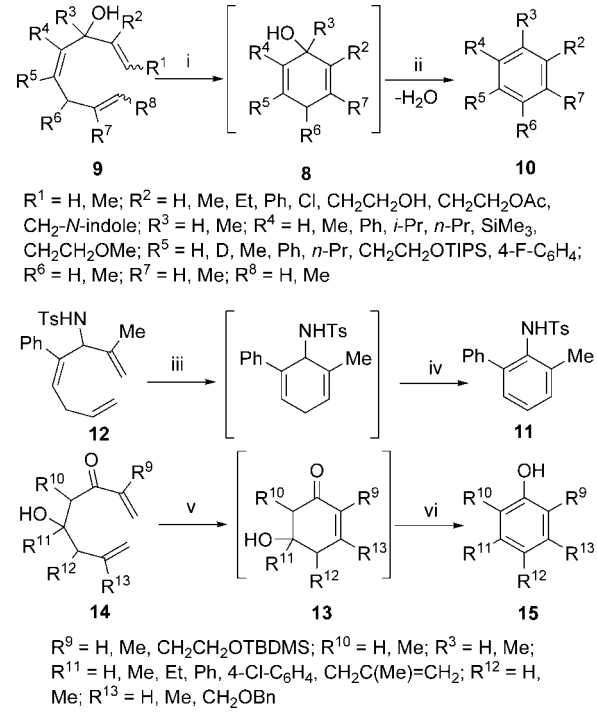
### *2.1.1. Synthesis of Benzenes*

Over the past few years, Yoshida and Imamoto have elegantly demonstrated the power of utilizing RCM−aromatization strategies for the synthesis of substituted benzene systems. These researchers have described systems where aromatization is facilitated with a leaving group (i.e., by elimination) or by the tautomerization of the RCM product to provide the aromatic system. These complementary approaches will be described in the following section.

The first work to be described, utilizing a RCM−tautomerization strategy, involved the synthesis of substituted phenols **1**. Yoshida and Imamoto's strategy for the synthesis of phenols started from acyclic 1,4,7-triene-3-ones **2** and formed the desired aromatic products by way of intermediates of type **3** (as shown in the disconnection in Scheme 1).[47] Two examples of the phenols synthesized are compounds **4** and **5**, prepared from precursors **6** and **7**, respectively. This methodology demonstrated the tolerance of extensive substitution of the precursors. One of the advantages of this approach is that it gives rise to aromatic compounds with multiple substituents, which may be difficult to synthesize by classical approaches. Another advantage is the relative ease with which the 1,4,7-triene-3-ones **2** were constructed by the treatment of appropriately substituted vinyl bromides with *t*-butyl lithium and reaction with acrolein, followed by an oxidation of the resultant alcohol to the ketone (not shown).

The same group also modified their methodology to afford substituted benzenes by invoking a dehydration to facilitate aromatization after metathesis (Scheme 2). In this general approach, the dehydration of the intermediates **8**, formed from triene **9** by reaction with catalysts **1-Ru** or **2-Ru**, was accomplished by the addition of *p*-TsOH or $SiO_2$ to give

**Scheme 2**[a]



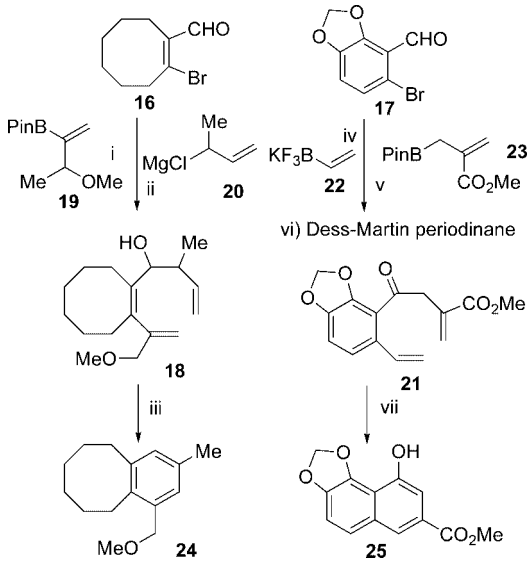

[a] Reagents and conditions: (i) **1-Ru** or **2-Ru** (7.5 mol %), $CH_2Cl_2$, rt−40 °C, 2 h; (ii) *p*-TsOH (10 mol %) or $SiO_2$ (excess), rt, 1 h (87−99% over 2 steps); (iii) **2-Ru** (7.5 mol %), $CH_2Cl_2$, rt−40 °C, 2 h (99%); (iv) $MnO_2$ (excess), rt (77%); (v) **2-Ru** (7.5 mol %), $CH_2Cl_2$, rt−40 °C, 2 h (81−99%); (vi) *p*-TsOH (10 mol %), $C_6H_6$, 70 °C, overnight (85−99%) or *t*-BuOK (4.4 mol equiv), MsCl (3.2 mol equiv), $CH_2Cl_2$, rt, 2.5 h (88−99%).

the functionalized aromatics **10**.[48,49] It was even possible to synthesize an aniline derivative **11** from triene **12** using this approach.[49] The group also developed a method that involved dehydration, oxidation, and tautomerization of the metathesis product **13** (from **14**), which afforded a number of substituted benzenes **15** in excellent yields (Scheme 2).[50] A related process utilizing 4-cyclohexene-1,3-diols as intermediates was also reported by this group.[51]

These workers were also successful in extending their methodology to include the synthesis of styrenes, albeit using a ene−yne approach that will be described in section 2.2.1.[52]

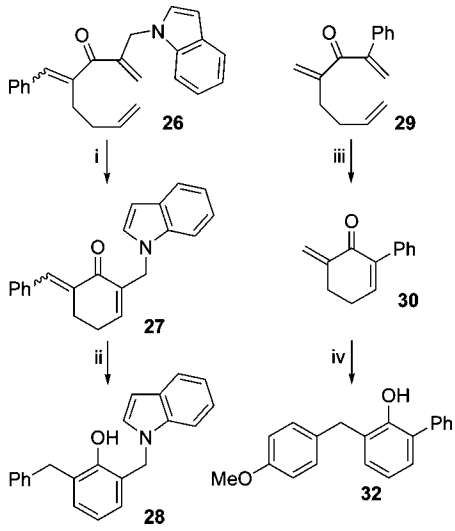
Another contribution by Yoshida and Imamoto, described in this review, concerns a versatile approach to fused-ring aromatic systems based on their previously published approaches.[53] The major difference was that the precursors for their RCM/dehydration or RCM/tautomerization approach were synthesized from $\beta$-halo-$\alpha,\beta$-unsaturated aldehydes such as **16** or **17**. RCM substrate **18** was thus constructed by the coupling of vinylborane **19** to aldehyde **16**, followed by the addition of the allyl Grignard reagent **20** to the resultant product (Scheme 3). In a similar fashion, diene **21** was constructed from the sequential addition of vinyl and allyl boranes **22** and **23** to bromobenzaldehyde **17**, followed by an oxidation to give the desired ketone **21**. RCM of diene **18** readily afforded the bicyclic product **24** after the elimination of water. Second, a RCM−tautomerism sequence afforded naphthalene **25** from **21**. Yoshida and Imamoto also utilized $\beta$-halo-$\alpha,\beta$-unsaturated esters for the synthesis of additional RCM substrates, although this necessitated an additional DIBAL-H reduction, followed by an oxidation to afford the aldehydes required for the metal-mediated allylations (not shown). All in all, this impressive publication

**Scheme 3**[a]




[a] Reagents and conditions: (i) **19**, $Pd(OAc)_2$ (5 mol %), $PPh_3$ (10 mol %), $Cs_2CO_3$ (3 mol equiv), $THF/H_2O$ (5:1), 50 °C, 2 h (compound used directly in next reaction); (ii) **20** (2 mol equiv), THF, 0 °C−rt, 30 min, (83% over 2 steps); (iii) (a) **2-Ru** (7.5 mol %), toluene, 80 °C, 2 h, (b) *p*-TsOH·$H_2O$, rt, 1 h (98% over 2 steps); (iv) **22**, $Pd(OAc)_2$ (5 mol %), $PPh_3$ (10 mol %), $Cs_2CO_3$ (3 mol equiv), $THF/H_2O$ (5:1), 50 °C, 3 h (96%); (v) **23**, (1.2 mol equiv), $CH_2Cl_2$, rt, 48 h (88%); (vi) Dess−Martin periodinane, pyridine, $CH_2Cl_2$, 0 °C, 30 min. (79%); (vii) **4-Ru** (7.5 mol %), toluene, 80 °C, 12 h (81%).

**Scheme 4**[a]

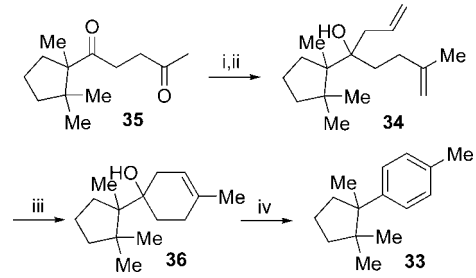



[a] Reagents and conditions: (i) **2-Ru** (1.5 mol %), toluene, 40 °C, 2 h (81%); (ii) $[RhCl(cod)]_2$ (1 mol %), $Cs_2CO_3$ (1 equiv), dioxane−$H_2O$, 60 °C, 5 h (69%); (iii) **2-Ru** (1.5 mol %), toluene, 40 °C, 2 h (92%); (iv) *p*-$MeOC_6H_4N_2BF_4$ **31**, $Pd(OAc)_2$ (5 mol %), MeCN−$H_2O$ (1:1), 60 °C, 12 h (60%).

describes the synthesis of more than 30 substituted aromatic compounds by using either the RCM−aromatization or RCM−tautomerizations strategy, clearly demonstrating the power of this synthetic approach.

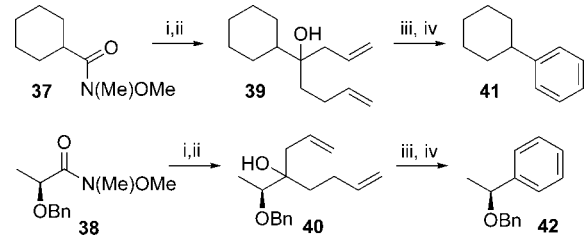
Yoshida, Narui, and Imamoto also utilized an "RCM−aromatization" approach for the synthesis of substituted phenolic compounds.[54] An example of this work is depicted in Scheme 4 in which the diene **26** was readily metathesized into the substituted 6-methylene-2-cyclohexenone **27** using the catalyst **2-Ru**. The researchers investigated a number of procedures for the aromatization of **27** and found that the use of the rhodium catalyst $[RhCl(cod)]_2$ gave the best results, in this particular example affording the substituted phenol **28** in a yield of 69%. The researchers also demonstrated how a Mizoroki−Heck reaction of compound **30** (obtained from precursor **29**) with *p*-methoxybenzenediazonium tetrafluoroborate **31** successfully afforded the phenol **32** in which substitution of the benzylic position and aromatization had occurred.

**Scheme 5**[a]




[a] Reagents and conditions: (i) $Ph_3P{=}CH_2$, $C_6H_6$, 0 °C, 30 min (90%); (ii) allyl bromide, Li, THF, 15−20 °C, 1 h, sonochemical irradiation (92%); (iii) **2-Ru** (3 mol %), $C_6H_6$, reflux, 30 min (quantitative); (iv) *p*-TSA, $C_6H_6$, reflux, 4 h (77%).

**Scheme 6**[a]

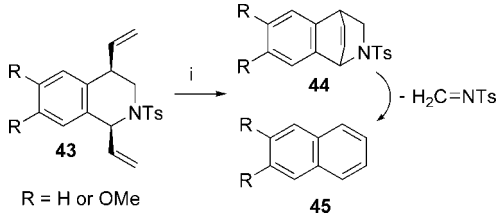



[a] Reagents and conditions: (i) butenylMgBr, THF, 80% from **37** and 75% from **38**; (ii) allylMgBr, THF, 81% for **39** and 71% for **40**; (iii) **1-Ru**, $CH_2Cl_2$, 88% from **39** and 78% from **40**; (iv) (a) $SOCl_2$, pyridine, (b) DDQ, reflux, 78% for **41** and 66% for **42**.

The benzene portion of the natural product (±)-cuparene **33** was also synthesized by a RCM−aromatization strategy, demonstrating the usefulness of this approach in total synthesis. Srikrishna and co-workers synthesized the diene **34** by a selective Wittig olefination of **35**, followed by the addition of an allyl group under modified Barbier conditions (Scheme 5).[55] RCM with **2-Ru** then gave the substituted cyclohexene **36** in quantitative yield. This compound was then aromatized under acidic conditions to afford (±)-cuparene **33** without any major problems, yielding the natural product as a racemate in very few steps.

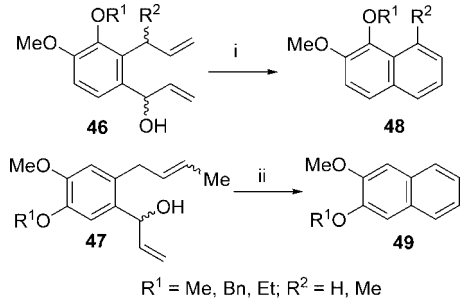
The idea of synthesizing benzene rings from Weinreb amides, where the amide carbonyl carbon forms part of the benzene ring, was developed by Clive and co-workers.[56] In the 12 examples shown in this paper, Weinreb amides such as **37** and **38** were converted into the dienes **39** and **40**, respectively, as shown in Scheme 6. These compounds were then treated with either **1-Ru** or **2-Ru** (the two examples shown here were metathesized with **1-Ru**) to afford the intermediate cyclohexenes (not shown). These products were then exposed to thionyl chloride and pyridine, followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), to provide the desired benzene-containing compounds **41** and **42**.

**Scheme 7**[a]




[a] Reagents and conditions: (i) **1-Ru** (10 mol %), $CH_2Cl_2$, 40 °C, 14 h (for R = H, 44:25:31 of **43**:**44**:**45**, no yield given; for R = OMe, only **45**, no yield given).

**Scheme 8**[a]




[a] Reagents and conditions: (i) **1-Ru** (5 mol %), $CH_2Cl_2$, rt, 2 h, then silica gel, 18 h (80−89%); (ii) **1-Ru** (5 mol %), $CH_2Cl_2$, rt, 2 h, then silica gel, 18 h (82−89%).

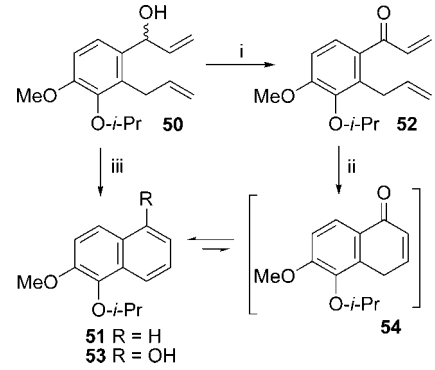
### 2.1.2. Synthesis of Naphthalenes

An interesting, if somewhat serendipitous, synthesis of a naphthalene skeleton by RCM was reported by Grigg and co-workers, and to the best of our knowledge this work constitutes the first example describing the use of RCM to afford naphthalenes.[57] RCM of the *N*-tosyl protected tetrahydroisoquinolines (THIQs) **43** containing two alkenes (Scheme 7), followed by subsequent expulsion of the tosylimine fragment from intermediate **44**, gave the naphthalenes **45** in unspecified yields, among other products. The authors of this work attributed the unsatisfactory yields of the naphthalenes to the poisoning of the metathesis catalyst by the *N*-tosyl imine byproduct.

To the best of our knowledge, the first purposeful application of RCM to the synthesis of a naphthalene core was reported by Huang and Wang.[58] These researchers synthesized substrates **46** and **47**, using Claisen or Claisen/Cope rearrangements and vinylmagnesium bromide additions to substituted benzaldehydes, as key reactions. Treatment of compounds **46** and **47** with Grubbs first-generation catalyst **1-Ru** then afforded the substituted naphthalenes **48** and **49**, respectively, in good yields, after a silica gel-mediated dehydration step (Scheme 8). Wang and co-workers have subsequently published a full report on this work, describing the synthesis of naphthalenes and naphthols using the approach described above.[59]

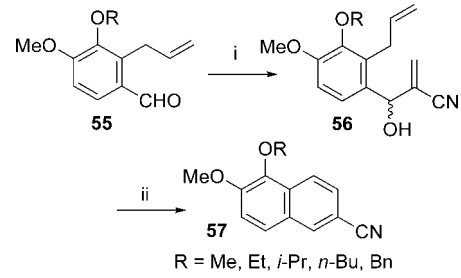
van Otterlo used a very similar approach when investigating the application of RCM to a variety of benzo-fused compounds, i.e., the conversion of **50** into **51**, except that they also oxidized the alcohol **50** with $MnO_2$ to give ketone **52** (Scheme 9). RCM of compound **52** with **2-Ru** then afforded naphthol **53**, presumably by way of intermediate **54**.[60] This work therefore constitutes another example of where tautomerism to the more stable naphthol has been beneficial for the synthesis of aromatic systems by the RCM−aromatization approach.

**Scheme 9**[a]



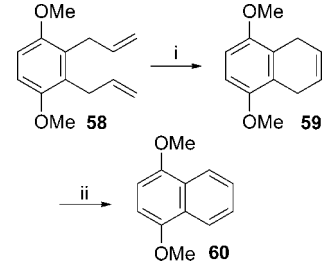

[a] Reagents and conditions: (i) $MnO_2$, $C_6H_6$ (54%); (ii) **2-Ru** (5 mol %), $CH_2Cl_2$, reflux, (69%); (iii) **2-Ru** (5 mol %), $CH_2Cl_2$, reflux (98%).

**Scheme 10**[a]




[a] Reagents and conditions: (i) acrylonitrile, DABCO, $H_2O$, rt, 3−5 d, (48−67%); (ii) **2-Ru** (5 mol %), $CH_2Cl_2$, rt, 5−8 h (81−90%).

**Scheme 11**[a]



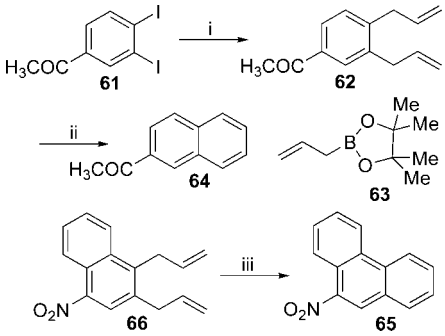

[a] Reagents and conditions: (i) **1-Ru** (6 mol %), $CH_2Cl_2$, rt, 20 h (76%); (ii) DDQ, xylene, reflux, 12 h (72%).

Wang and co-workers also synthesized a number of substituted cyanonaphthalenes, first using the Claisen rearrangement to afford the aryl−allyl compounds **55** (Scheme 10). The next synthetic step involved the Baylis−Hillman reaction in which the aldehydes **55** were reacted with acrylonitrile and DABCO to afford the adducts **56**. Subsequent RCM with Grubbs catalyst **2-Ru**, followed by the elimination of water, then afforded the substituted cyanonaphthalenes **57** in good yields of 81−90%.[61]

Other researchers who have used RCM to synthesize a naphthalene core have been Chattopadhyay and co-workers.[62] This group treated compound **58**, formed from the Claisen rearrangement of hydroquinone diallyl ether and subsequent methylation, with catalyst **1-Ru** to afford the dihydronaphthalene **59** (Scheme 11). This compound was then converted into the naphthalene **60** in good yield, using DDQ as an oxidant.

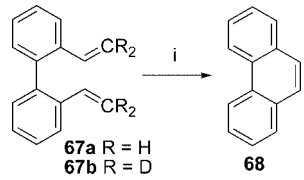
Finally in this section, Kotha and co-workers made use of a Suzuki−Miyaura cross-coupling reaction[63] to synthesize 3,4-diallyl derivatives from the respective diiodo compounds

**Scheme 12**[a]



[a] Reagents and conditions: (i) **63**, CsF, $Pd(PPh_3)_4$, THF, reflux (89%); (ii) **1-Ru** (3 mol %), $CH_2Cl_2$, rt, 20 min, then DDQ, $C_6H_6$, reflux (82% over 2 steps); (iii) **1-Ru** (3 mol %), $CH_2Cl_2$, rt, 20 min, then DDQ, $C_6H_6$, reflux (82% over 2 steps).

**Scheme 13**[a]



[a] Reagents and conditions: (i) $Mo(NO)_2Cl_2[P(octyl)_3]_2$ or $W(NO)_2Cl_2[P(octyl)_3]_2$, hexane, $N_2$, $[(Me)_3Al_2Cl_3]$, rt, 30 s, then EtOH, (yields 1−2%).

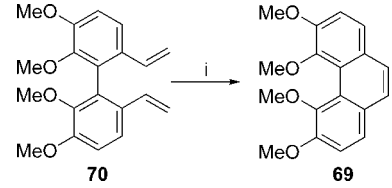
(see, for example, the conversion of the diiodo compound **61** into **62** with allylboronic acid pinacol ester **63**, Scheme 12). Compound **62** was then converted into the substituted naphthalene **64** by RCM, followed by an oxidation with DDQ.[64] In this paper, four other examples of this methodology were reported, including the formation of phenanthrene **65** from substrate **66** (for more on this class of compounds, see the next section of this review).

### 2.1.3. Synthesis of Phenanthrenes

Among some of the earliest investigations into the mechanism of olefin metathesis is a paper by Katz and Rothchild.[65] This work describes probably the first application of an ene−ene metathesis reaction, promoted by a Fischer carbene complex, which resulted in the formation of an aromatic structure. The paper outlines the conversion of a mixture of 2,2′-divinylbiphenyl **67a** and the deuterated derivative **67b** to afford phenanthrene **68** (Scheme 13). The design of the experiment required the addition of molybdenum or tungsten catalysts to a mixture of **67a** and **67b** for a short period of time, followed by the analysis of the reaction contents by mass spectrometry. Although the conversion of the dienes into phenanthrene **68** was only about 1−2%, due to the short reaction times involved (30 s), this experiment demonstrated the possibility of using RCM to synthesize aromatic compounds.

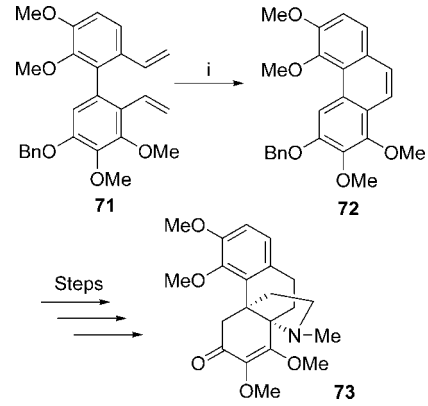
Recently, this specific idea has been expanded to a synthetically useful level by the group of Iuliano,[66] who applied RCM to the synthesis of substituted phenanthrenes (Scheme 14). The biaryl bonds of the precursors were formed by using Ullman or Suzuki−Miyaura couplings, and the vinyl groups were installed using Wittig alkenylation of the aromatic aldehydes. RCM of these precursors using Grubbs first- or second-generation catalysts, **1-Ru** or **2-Ru**, then afforded the substituted phenanthrenes in excellent yields,

**Scheme 14**[a]



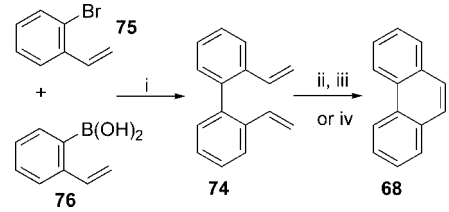
[a] Reagents and conditions: (i) **2-Ru** (5 mol %), $CH_2Cl_2$, 40 °C, $N_2$ (quantitative).

**Scheme 15**[a]



[a] Reagents and conditions: (i) **2-Ru** (5 mol %), $CH_2Cl_2$, 40 °C (99%).

**Scheme 16**[a]



[a] Reagents and conditions: (i) $Pd_2(dba)_3$, *t*-$Bu_3Ph\cdot BF_4$, KF, THF, 20 °C, 18 h (40%);[68] (ii) **2-Ru** (10 mol %), $CH_2Cl_2$, 20 °C, 24 h (50%);[68] (iii) **2-Ru** (10 mol %), $CD_2Cl_2$, 25 °C, 8 h, (87% by NMR);[69] (iv) **3-Mo** (10 mol %), $CS_2$, rt, 1 h, then silica gel (71%).[69]

with catalyst **2-Ru** proving to be superior. Even highly substituted phenanthrenes such as **69** were readily obtained from precursor **70**, highlighting the utility of this approach.

Castle and co-workers have used a similar idea to that published by Iuliano, in a total synthesis project. In this work, the diene **71** was converted into the substituted phenanthrene **72** in excellent yield, by using the catalyst **2-Ru** (Scheme 15).[67] This compound was then elaborated into the natural product (±)-hasubanonine **73**.

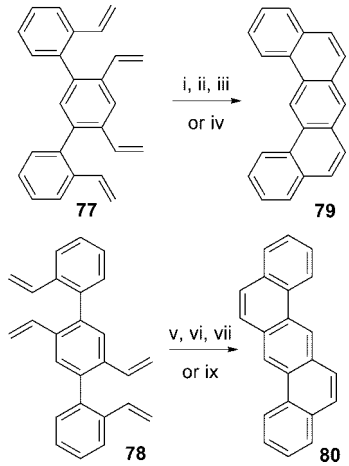
Barrett and co-workers have reported an approach to the synthesis of phenanthrene **68** using a Suzuki−Miyaura coupling followed by RCM with catalyst **2-Ru** as the key steps.[68]

King and co-workers have also published their efforts toward the synthesis of phenanthrene **68** from **74** using catalyst **2-Ru** (50%) and catalyst **3-Mo** (71%). The biphenyl compound **74** was synthesized from the substituted styrenes **75** and **76** using a Suzuki−Miyaura coupling strategy as shown in Scheme 16.[69]

### 2.1.4. Synthesis of Polyaromatic Hydrocarbons

In the same King paper (from the previous section), application of the RCM of vinyl aromatic compounds to

**Scheme 17**[a]

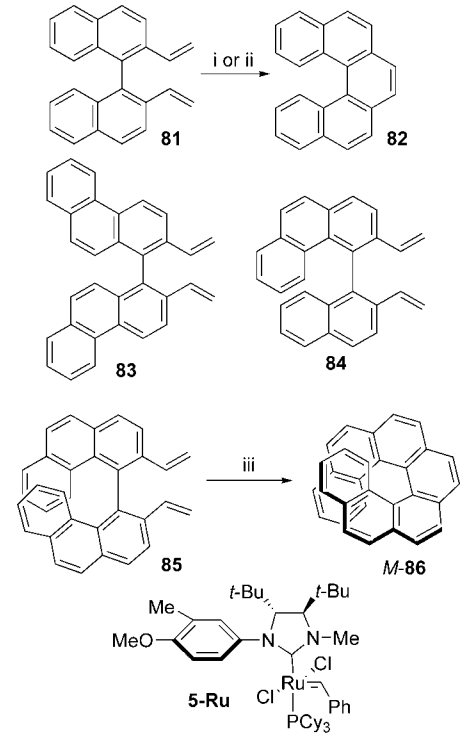



[a] Reagents and conditions: (i) **1-Ru** (5 mol %), $CD_2Cl_2$, 25 °C, 8.5 h (88% by NMR); (ii) **2-Ru** (5 mol %), $CD_2Cl_2$, 25 °C, 2.5 h (92% by NMR); (iii) **3-Mo** (5 mol %), $C_6D_6$, 25 °C, 2.5 h (87% by NMR); (iv) **3-Mo** (10 mol %), $CS_2$, 25 °C, 1 h (68%); (v) **1-Ru** (5 mol %), $CD_2Cl_2$, 25 °C, 18.5 h (88% by NMR); (vi) **2-Ru** (5 mol %), $CD_2Cl_2$, 25 °C, 3.5 h (92% by NMR); (vii) **3-Mo** (5 mol %), $C_6D_6$, 25 °C, 1.5 h (95% by NMR); (viii) **3-Mo** (20 mol %), $CS_2$, 25 °C, 1 h (79%).

afford polycyclic aromatic hydrocarbons (PAHs) has been elegantly described.[69] The tetravinyl terphenyls **77** and **78** were efficiently synthesized by Suzuki−Miyaura reactions, and metathesis of the substrates gave excellent yields of the isomeric dibenzanthracenes **79** and **80**, respectively. Scheme 17 also describes the results of the RCM reactions using the catalysts **1-Ru**, **2-Ru**, and **3-Mo** in $CD_2Cl_2$ or $CS_2$ as solvent. The reason that $CS_2$ was deemed to be important is that this would allow for the synthesis of larger PAH systems because the precursors to these compounds would be insoluble in solvents traditionally utilized in metathesis reactions. Of interest was that, under these conditions, the catalyst **3-Mo** proved to be the most efficacious catalyst.

The synthesis of polycyclic aromatic hydrocarbons (PAHs) described above was complimented by the demonstration that a number of helicenes could also be synthesized by olefin metathesis. Collins and co-workers proved that the treatment of substrates such as **81** with catalyst **2-Ru** (microwave conditions, 100 °C) or catalyst **4-Ru** (sealed tube, 40 °C) resulted in the [5]helicene **82** in excellent yields approaching 80−90% (Scheme 18).[70] The group also successfully implemented their methodology on a number of substrates, including compounds **83**−**85**, and obtained [6]- and [7]-membered helicenes, in mostly excellent yields. In addition, Grandbois and Collins extended their methodology to the asymmetric synthesis of [7]helicene *M*-**86**, obtained in a maximum of 80% enantiomeric excess (38% conversion), using the ruthenium catalyst **5-Ru** shown in Scheme 18 with a $C_1$-symmetric *N*-heterocyclic carbene ligand. The use of simple olefin additives and hexafluorobenzene as solvent also proved critical in the synthesis of *M*-[7]helicene **86**.[71] The authors of this work speculate that the olefin additives could play two roles. The first is that the olefin additive allows for the *reversible* binding of the helicene precursor **85** to the catalyst, which could aid in the enantioselection of the catalyst. The second possible role of the olefin additive could be that it changes the propagating carbene species of the catalytic cycle, making it more stable, hence resulting in more conversions; in addition to that, it also could have an influence on the enantiomeric excess (ee) of the process. The

**Scheme 18**[a]




[a] Reagents and conditions: (i) **2-Ru** (10 mol %), $CH_2Cl_2$, microwave, 100 °C, 25 min (90%);[70] (ii) **4-Ru** (10 mol %), $C_6H_6$, sealed tube, 40 °C, 24 h (78−93%);[70] (iii) **5-Ru** (5 mol %), $C_6F_6$, vinylcyclohexane (10 mol equiv), rt, 2 h, (38% conversion, 80% ee).[71]

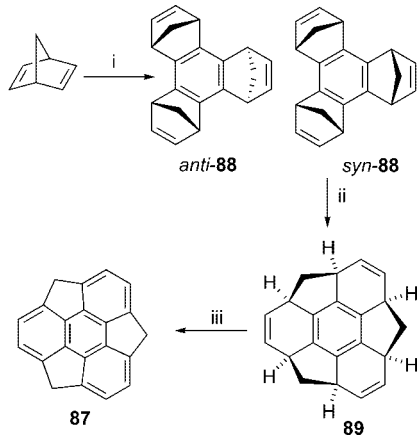
fact that hexafluorobenzene as solvent gave the highest ee was surprising to the authors because **85** was only sparingly soluble in this solvent.

The use of the metathesis reaction for the synthesis of more complex aromatic molecular-bowl hydrocarbons, and related compounds,[72,73] has seen some recent interest. In particular, the impressive asymmetric synthesis of trimethylsumanene,[74] as well as the synthesis of sumanene **87**, has been accomplished. This is an example of a metathesis reaction forming an aromatic compound, which is the basis of a patent.[75] The synthesis of sumanene **87** is described in Scheme 19.[76] Trimerization of norbornadiene using the conditions described in the paper resulted in the formation of both *syn*- and *anti*-**88** in low yield (a two-step procedure involving a tin-norbornadiene intermediate improved the yield of this transformation to 47% over the two steps). Exposure of only the *syn*-isomer of **88** to **1-Ru**, under an ethylene atmosphere, resulted in the production of **89** in a 30% yield by way of a ring-opening metathesis−ring-closing metathesis (ROM−RCM) reaction. The product **89** was then oxidized with DDQ to give sumanene **87**, which is a bowl-shaped symmetric subunit of fullerene ($C_{60}$). Higashibayashi and Sukurai also used this ROM−RCM−aromatization approach to perform an asymmetric synthesis of trimethylsumanene (not shown),[74] resulting in the synthesis of a chiral "buckybowl".

### *2.1.5. Synthesis of Naphthoquinones and Related Compounds*

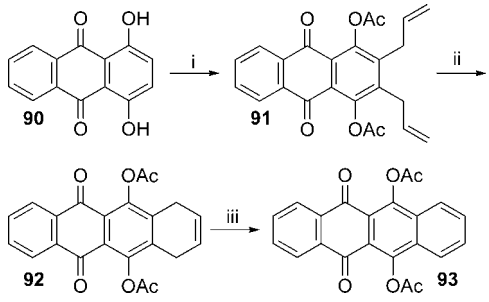
The metathesis reactions described, for example, in Schemes 16, 17, and 18 constitute formal benzannulation reactions in that they form an aromatic ring in one step. However, the use of RCM to extend the skeleton of a

**Scheme 19**[a]




[a] Reagents and conditions: (i) BuLi, *t*-BuOK, $BrCH_2CH_2Br$, THF, −78 °C−rt, then CuI, rt (7%, *syn*/*anti* = 1:3); (ii) **1-Ru** (10 mol %), ethylene, toluene, −78 °C−rt, 24 h (30%); (iii) DDQ, toluene, 110 °C, 3 h, (70%).

**Scheme 20**[a]




[a] Reagents and conditions: (i) (a) allyl bromide, $K_2CO_3$, acetone, reflux (81%); (b) $Na_2S_2O_4$, DMF−$H_2O$ (1:1), 130 °C (71%); (c) $Ac_2O$, pyridine (95%); (ii) **2-Ru** (5 mol %), $CH_2Cl_2$, rt, 24 h; (iii) DDQ, $C_6H_6$, reflux (51% over 2 steps).

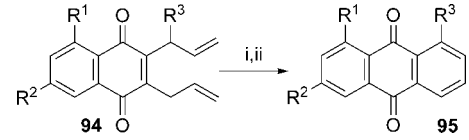
substance with an additional ring, which is then sometimes aromatized (as in Scheme 19), has seen a reasonable amount of interest. Kotha and Mandal[77] have used a double Claisen rearrangement,[64] followed by a RCM and subsequent oxidation reactions, to achieve the benzannulations of naphthoquinones (Scheme 20). Starting from, for instance, naphthoquinone **90**, bis-*O*-allylation, followed by a double Claisen rearrangement and further phenolic protection (which was necessary as the free phenols inhibited any metathesis), furbished bisacetate **91**. This compound was then subjected to the metathesis reaction with catalyst **2-Ru**, to afford tetracycle **92**, which was subsequently oxidized with DDQ to afford product **93** in a good yield of 51%, over two steps in one pot.

A similar approach to that described above was used by De Kimpe and co-workers for the synthesis of functionalized anthraquinones.[78] Once again, the diene precursors **94** were subjected to RCM using catalyst **1-Ru**. The corresponding anthraquinones **95** were then obtained after aromatization by palladium on carbon (Scheme 21).

### *2.1.6. Synthesis of Indenes and Related Compounds*

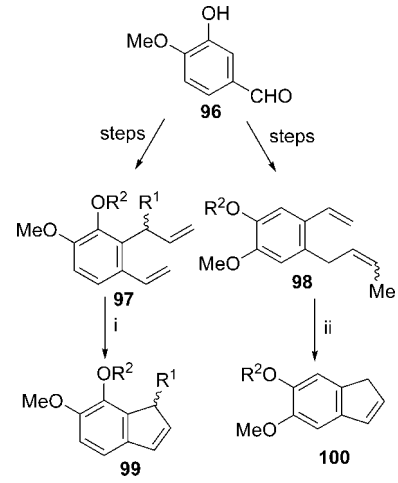
Although by definition the five-membered ring of the indene skeleton in itself is not aromatic, applications of the indenyl ligand, particularly as ligands for homogeneous catalysts where the five-membered ring of the indene has been made aromatic,[79−81] has prompted us to include this class of compounds in the review.

**Scheme 21**[a]



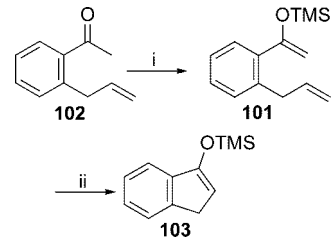

[a] Reagents and conditions: (i) **1-Ru** (7 mol %), toluene, rt, 12 h; (ii) Pd/C, toluene, heat, yields over 2 steps: $R^1 = R^2 = OMe$, $R^3 = H$ (83%); $R^1 = OH$, $R^2 = R^3 = H$ (89%); $R^1 = OMe$, $R^2 = R^3 = H$ (86%); $R^1 = R^2 = R^3 = H$ (83%); $R^1 = R^2 = H$, $R^3 = Me$ (78%).

**Scheme 22**[a]




[a] Reagents and conditions: (i) **1-Ru** (5 mol %), $CH_2Cl_2$, rt, 2 h, yields: $R^1 = H$, $R^2 = Me$ (94%); $R^1 = H$, $R^2 = Et$ (92%); $R^1 = H$, $R^2 = Bn$ (93%); $R^1 = R^2 = Me$ (92%); $R^1 = Me$, $R^2 = Et$ (93%); $R^1 = Me$, $R^2 = Bn$ (96%); (ii) **1-Ru** (5 mol %), $CH_2Cl_2$, rt, 2 h, yields: $R^2 = Me$ (90%); $R^2 = Et$ (90%); $R^2 = Bn$ (93%).

**Scheme 23**[a]



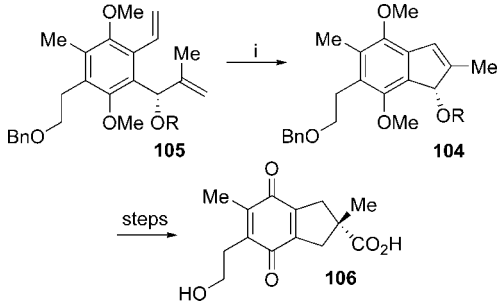

[a] Reagents and conditions: (i) LDA, TMSCl, THF, −78 °C; (ii) **2-Ru** (7 mol %), $C_6H_6$ (0.005 M), 65 °C, 1 h (90% over 2 steps).

Huang and Wang published a paper in 2004 that described the synthesis of substituted indenes using isovanillin **96** as starting material.[82] As before, the methodology of this research group made use of the Claisen rearrangement followed by Wittig alkenylation reactions to afford dienes **97** and **98**, which were converted into the desired indenes **99** and **100** respectively, by RCM with the catalyst **1-Ru** (Scheme 22).

As part of a study investigating the metathesis of enol silyl ethers, Shibasaki and co-workers demonstrated that the RCM of the silyl enol ether **101**, readily obtained from the ketone **102**, could afford the indene **103** in excellent yield (Scheme 23).[83]

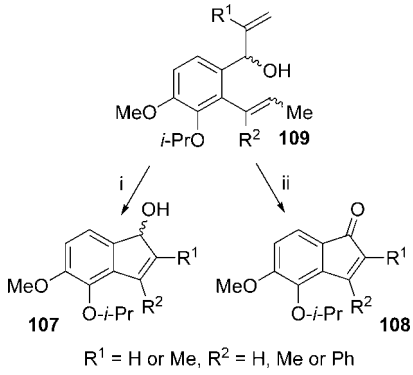
Clive and co-workers reported the synthesis of a polysubstituted indenol **104** (R = H), starting from diene precursor **105** (R = H) (Scheme 24).[84,85] Of interest was that, if the

**Scheme 24**[a]



[a] Reagents and conditions: (i) for R = H, **2-Ru** (10 mol %), $CH_2Cl_2$, reflux, 20 h (88%).

**Scheme 25**[a]



[a] Reagents and conditions: (i) **2-Ru** (5−12 mol %), $CH_2Cl_2$ or toluene, rt−80 °C, 1−24 h (16−87%); (ii) **2-Ru** (5−15 mol %), toluene or xylene, 60−110 °C, 2−48 h (45−89%).

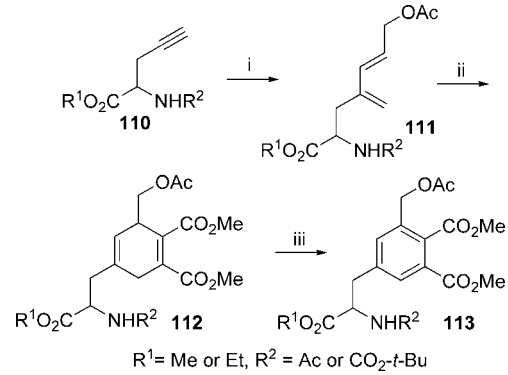
secondary alcohol was protected with a *tert*-butyldimethylsilyl (TBDMS) group, the cyclization of **105** (R = TBDMS) was unsuccessful; even the application of the more reactive Schrock's catalyst **3-Mo** resulted in no formation of **104** (R = TBDMS), demonstrating the sensitivity of the reaction to steric hindrance. Compound **104** (R = H) was then transformed into the optically pure (+)-puraquinonic acid **106** in a number of synthetic steps.

Finally in this section describing the synthesis of indenes, van Otterlo and co-workers recently published work describing the synthesis of a small set of indenols and indenones (Scheme 25).[60,86,87] A strength of their synthetic methodology was that, by adapting the reaction conditions, either the substituted indenols **107** (at lower reaction temperatures) or the indenones **108** (at higher reaction temperatures) could be obtained from substituted dienes **109**, mostly in acceptable yields. For the formation of the indenones, a novel tandem catalytic process, namely, a ring-closing metathesis followed by a dehydrogenative oxidation process without an additional hydrogen transfer agent, was postulated.

## 2.2. Ene−Yne RCM−Aromatization Strategies for the Synthesis of Aromatic Carbocycles

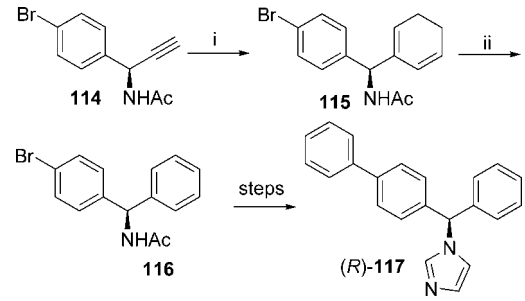
The use of ene−yne metathesis, followed by a Diels-Alder reaction, has seen a considerable amount of attention.[88−101] It should, therefore, not be surprising that another popular approach to the synthesis of aromatic rings involves an ene−yne metathesis−Diels-Alder strategy, followed by an aromatization.

**Scheme 26**[a]



[a] Reagents and conditions: (i) **1-Ru** (10−12 mol %), allylacetate, $C_6H_6$, reflux, 40−50 h (37−56%, *E*/*Z* 1:1); (ii) DMAD, toluene, reflux; (iii) DDQ, $C_6H_6$, reflux (32−56% over 2 steps).

**Scheme 27**[a]



[a] Reagents and conditions: (i) **2-Ru** (10 mol %), toluene, cyclooctadiene, microwave, 20 min (60%); (ii) DDQ, toluene, reflux (48%).

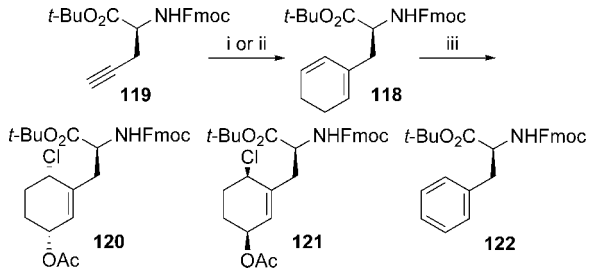
### 2.2.1. Synthesis of Benzenes

One of the major contributers in this area, Kotha and his research group, have applied an ene−yne metathesis−aromatization strategy for the synthesis of constrained amino acid analogues; in this particular work, they synthesized a set of highly functionalized phenylalanine derivatives.[102,103] Scheme 26 describes the synthesis of these amino acids and highlights the cross-ene−yne metathesis between racemic acetylenes **110** and the olefin allylacetate, to generate the dienes **111** in moderate yields. Subsequent reaction of these compounds with dimethyl acetylenedicarboxylate (DMAD) afforded the substituted cyclohexenes **112**, and aromatization with DDQ then afforded phenylalanine derivatives **113** in acceptable yields (77−90%).

Botta and co-workers have made use of an innovative RCM reaction, followed by an aromatization, to synthesize substituted aromatic rings, in particular, both enantiomers of the antifungal agent bifonazole.[104] The first example described here involved the metathesis reaction of enantiomerically pure alkyne **114** with cyclooctadiene, mediated by Grubbs second-generation catalyst **2-Ru**, to afford the cyclohexadiene **115** (Scheme 27).[105] This compound was then aromatized to afford **116** in moderate yield, using DDQ as oxidant. Compound **116** was then readily converted into (*R*)-bifonazole **117** in a number of steps.

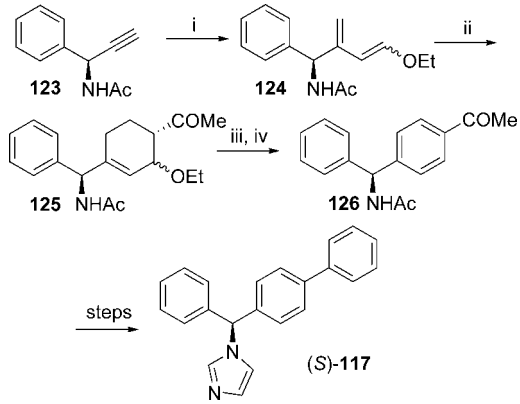
Of interest is that Diver and co-workers have recently extended this strategy used for the synthesis of cyclohexadienes, i.e., the methodology for the assembly of compound **115**, to make a range of cyclohexadienes. Their approach utilizes ene−yne metathesis reactions involving alkynes and tethered alkenes including 1,5-hexadiene, 1,5-cyclooctadiene (1,5-COD), and even polybutadiene.[106−108]

**Scheme 28**[a]




[a] Reagents and conditions: (i) **2-Ru** (10 + 4 mol %), $CH_2Cl_2$, 1,5-cyclooctadiene (4 mol equiv, high dilution), syringe pump, reflux, 4 + 2 h (68%); (ii) **2-Ru** (7.5 mol %), $CH_2Cl_2$, 1,5-cyclooctadiene (9 mol equiv, high dilution), syringe pump, reflux (80%); (iii) $Pd(OAc)_2$ (5 mol %), AcOH, LiCl, LiOAc, benzoquinone, acetone, **120** (24%), **121** (24%), **122** (17%).

**Scheme 29**[a]




[a] Reagents and conditions: (i) **2-Ru** (10 mol %), toluene, microwave, 80 °C (88%, ratio *E*/*Z* 2:1); (ii) $CH_2$=CHCOMe, $BF_3$·$OEt_2$, $CH_2Cl_2$, −78 °C (96%); (iii) $H_2SO_4$ (20%), THF, rt, 24 h (80%); (iv) DDQ, toluene, reflux, 3 h (48%).

Diver and co-workers even reported the isolation of aromatic compounds following the application of an ene−yne metathesis strategy with 1,5-COD.[109] The 1,3-cyclobutadiene **118** was readily generated from alkyne **119** in reasonable yield, with higher concentrations of 1,5-COD allowing for lower catalyst loadings. Further manipulation of this structure using a palladium catalyst then gave a mixture of diastereoisomers **120** and **121**, as well as the phenylalanine derivative **122** (17%), presumably formed by way of an oxidation process during the reaction. Even though this product **122** was not desired, it demonstrates the possibility of utilizing this approach to synthesize interesting aromatic structures by the ene−yne RCM−aromatization approach (Scheme 28).

In synthesizing the enantiomeric (*S*)-bifonazole **117**, Botta and co-workers made use of an alternative strategy (Scheme 29).[104] Alkyne (*R*)-**123** was initially reacted with ethyl vinyl ether, in the presence of catalyst **2-Ru**, to afford the diene **124** in a good yield of 88%. This compound was then successfully reacted in a Diels−Alder fashion with methyl vinyl ketone to give compound **125**. Compound **125** was readily converted into the aromatic product **126** over two steps. Further manipulation of the acetyl functional group and elaboration of the acetamide then afforded (*S*)-bifonazole **117**. This particular paper thus succinctly demonstrated how two different metathesis−aromatization strategies (Scheme 27 and Scheme 29) could give rise to the desired substituted aromatic compounds.

Pandey and co-workers successfully constructed a carbohydrate functionalized carbocycle appended to a chlorin scaffold using ene−yne metathesis.[110] The reason for this strategy was that the group wanted to investigate the use of chlorin−carbohydrate conjugates as gal-1 photosensitizers for photodynamic therapy. To this end, chlorin analogue **127** was converted into the diene **128** by way of an ene−yne cross-metathesis reaction with substituted carbohydrate **129**. Subsequent reaction of compound **128** with DMAD afforded the Diels−Alder cycloadduct, 1,4-cyclohexadiene **130**, in a low yield of 33% (Scheme 30). Removal of the *O*-acetyl substituents on the carbohydrate then afforded compound **131** as the major component, as well as a reasonable amount of the aromatized ring system **132**, which had lost the carbohydrate appendage.

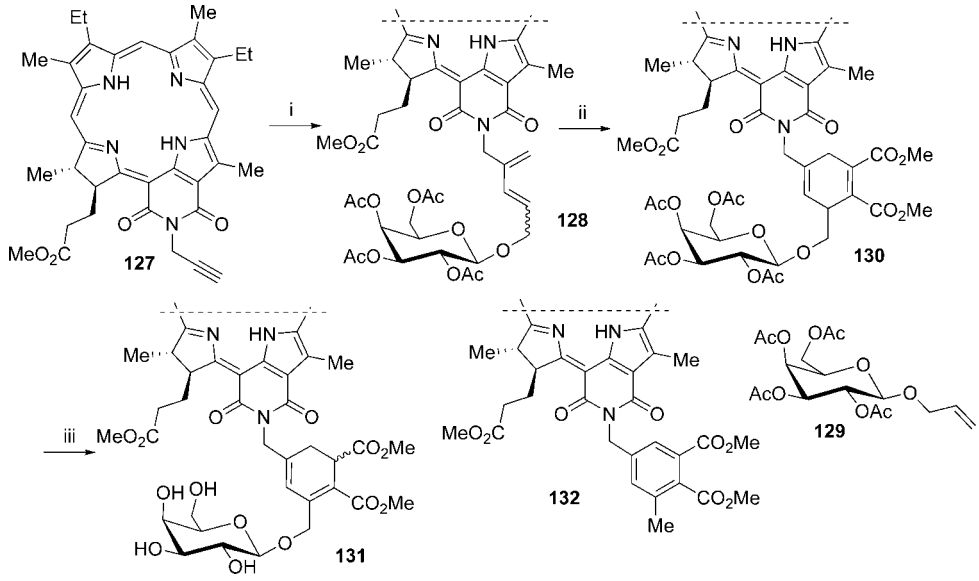
Kaliappan and Grée have communicated the outcomes of their research efforts into the synthesis of benzylic fluorides using an ene−yne metathesis−aromatization strategy.[111] This work utilized the propargylic fluorides[112] **133** and **134** to readily afford the dienes **135** and **136**, respectively (Scheme 31). Subsequent reaction of these substrates with diethyl acetylenedicarboxylate in a Diels−Alder reaction then afforded the corresponding 1,4-cyclohexadienes, which were readily oxidized to the respective benzylic fluorides **137** and **138**. Of interest was that the diol obtained from the lithium aluminum hydride reduction of diester **137** was found to have an enantiomeric excess of 84%, meaning that very little loss of enantiomeric integrity had occurred during the RCM−Diels-Alder−aromatization process (the ee of the propargylic alcohol from which propargylic fluoride **133** was synthesized was 88%).

Finally in this section, the work of Yoshida, Imamoto, and co-workers is described.[52] These workers very successfully used ene−ene metathesis−aromatization strategies to synthesize substituted benzenes (see section 2.2.1). In a recent contribution from this research group, an ene−yne metathesis approach was also utilized for this task, namely, the synthesis of substituted styrenes.[52] The generalized Scheme 32 describes the simple, yet versatile approach utilized by these authors. The trienes **139** were readily constructed from ene−yne substrates **140**, and upon metathesis and aromatization afforded the styrenes **141** in low-to-excellent yields (34−99%). Highly substituted styrenes, including the representative examples **142**, **143**, and **144**, were readily synthesized despite the fact that they would be considerably more difficult to synthesize using other approaches. In addition, even a disubstituted styrene **145** was accessible in good yield from substrate **146**, in which the alkene and alkyne had been "swopped".

### 2.2.2. Synthesis of Naphthalenes

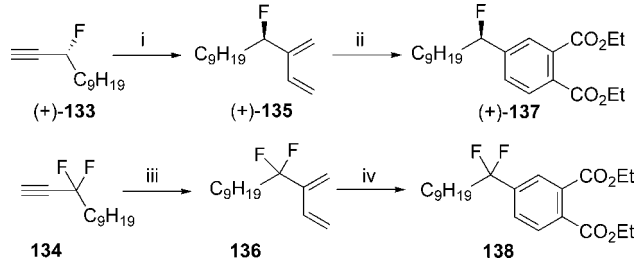
In a paper describing the application of nonclassical metathesis, Yamamoto and co-workers found that the treatment of 1,7-ene−ynes containing an aromatic ring, as shown by the generic substrate **147**, with $PtBr_2$ afforded a range of substituted naphthalenes **148** (Scheme 33).[113] A number of organometallic complexes (Pd, Pt, Rh, and Ni) were screened for the ability to catalyze a model ene−yne system, and it was found that $PtBr_2$ in 1,4-dioxane at 120 °C was the best combination. An advantage of this methodology was that substrates **147** were readily synthesized from substituted 2-bromobenzaldehydes using Sonogashira cross-coupling, followed by an allylation with allyltrimethylsilane in the presence of scandium triflate. The authors of this work were able to support their claim that the formation of the naphthalenes **148** was by an ene−yne metathetic pathway

**Scheme 30**[a]



[a] Reagents and conditions: (i) **129** (4 equiv), **1-Ru** (2 × 13 mol %), $CH_2Cl_2$, rt, Ar, 2 × 24 h (30%); (ii) DMAD, toluene, reflux, Ar, 3 h (33%); (iii) NaOMe, $CH_2Cl_2$, Ar, 1 h, **131** (44%), **132** (25%).

**Scheme 31**[a]



[a] Reagents and conditions: (i) **2-Ru** (10 mol %), ethylene, $CH_2Cl_2$, reflux, 15 h (63%); (ii) (a) $EtO_2CC{\equiv}CCO_2Et$, 60 °C, 3 h (71%), (b) $MnO_2$, $CH_2Cl_2$, reflux, 48 h (81%); (iii) **2-Ru** (5 mol %), ethylene, $CH_2Cl_2$, reflux, 15 h (80%); (iv) (a) $EtO_2CC{\equiv}CCO_2Et$, 60 °C, 4 h (75%), (b) $MnO_2$, $CH_2Cl_2$, reflux, 36 h (89%).

by the isolation of the proposed reaction intermediates, cyclobutene **149** and dihydronaphthalene **150**, using careful sequential reaction steps.

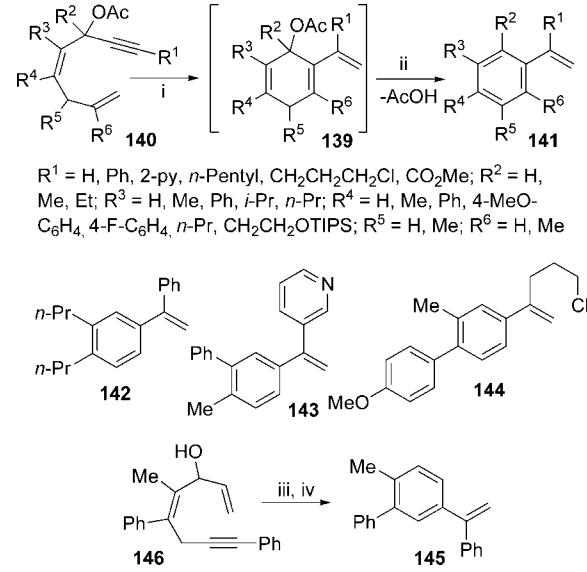
### 2.2.3. Synthesis of Phenanthrenes

To the best of our knowledge, the first example of a catalytic ene−yne metathesis approach to the synthesis of aromatic molecules was described by Sivavec and Katz.[114] In this work, these researchers demonstrated that 9-vinylphenanthrenes, such as compound **151**, could be generated metathetically by the addition of a tungsten carbene catalyst **6-W** to the ene−yne **152**, albeit in modest yields (only one of six examples reported in the paper is shown in Scheme 34).[114] Later Katz extended this approach to other substituted phenanthrene systems, with the limitation being that these transformations required stoichiometric amounts of tungsten and chromium carbenes.[115]

### 2.2.4. Synthesis of Naphthoquinones

Kaliappan and Ravikumar applied an ene−yne RCM−aromatization approach to the synthesis of a number of naturally occurring angucyclinones.[116,117] For example, the synthesis of (+)-ochromycinone **153** was initiated by the ene−yne metathesis reaction between compound **154** and

**Scheme 32**[a]

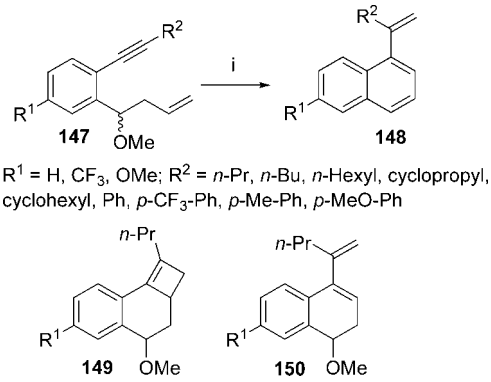


[a] Reagents and conditions: (i) **2-Ru** (2.5−10 mol %), toluene, 80 °C, 2 h; (ii) *p*-TsOH (15 mol %), rt, 1 h [34−99% over 2 steps, examples shown: **142** (99%), **143** (81%), **144** (86%)]; (iii) **2-Ru** (7.5 mol %), toluene, 80 °C, 2 h; (iv) *p*-TsOH (15 mol %), rt, 1 h (74% over 2 steps).

ethylene gas to give compound **155**, followed by a reduction with lithium aluminum hydride to afford diene **156** in excellent yield (Scheme 35). A [4 + 2]-cycloaddition with 6-bromo-5,8-dioxo-5,8-dihydronaphthalen-1-yl acetate, followed by deprotection of the acetyl group, then gave compound **157** in an acceptable yield of 45% over the last three synthetic steps. A photooxygenation then afforded (+)-ochromycinone **153** in good yield. Kaliappan and Ravikumar also adapted this approach to readily afford YM-181741 **158** and (−)-tetrangomycin **159**, from ene−ynes **160** and **161**, respectively, as well as the angucyclinones (+)-rubiginone $B_2$ and MM-47755 (not shown).

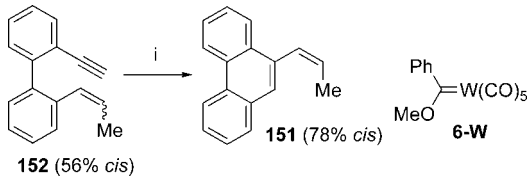
Kotha and co-workers also prepared dienes from alkynes to synthesize a number of "quinone−amino acid hybrids".[118] The masked amino acid diene compounds **162** and **163** were

**Scheme 33**[a]



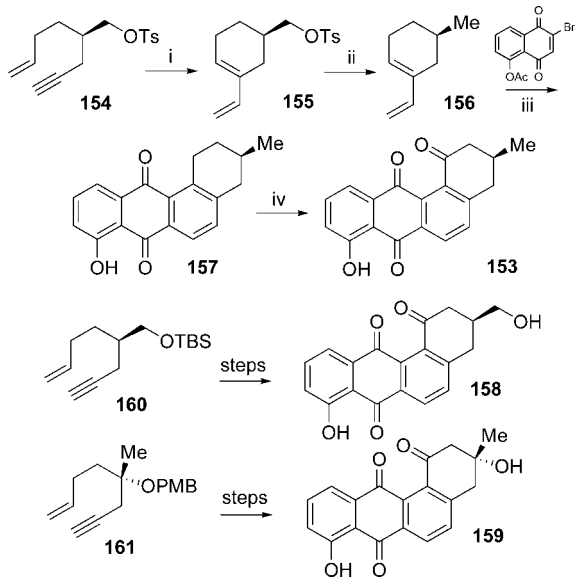

[a] Reagents and conditions: (i) $PtBr_2$ (2 mol %), 1,4-dioxane, 120 °C, Ar, 18 h (35−76%).

**Scheme 34**[a]




[a] Reagents and conditions: (i) **6-W** (10 mol %), toluene, sealed tube, 75 °C, 18 h (26%).

**Scheme 35**[a]

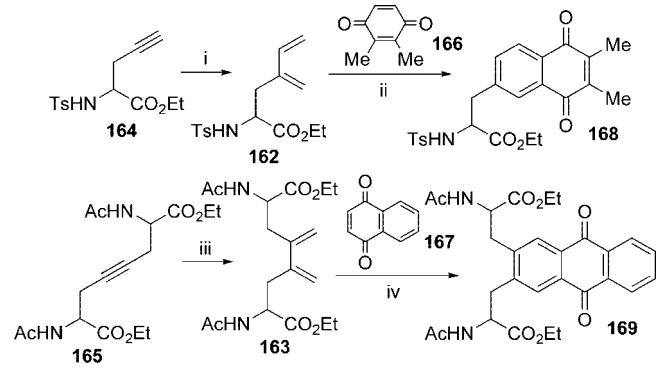



[a] Reagents and conditions: (i) $CH_2$═$CH_2$, **1-Ru** (10 mol %), $CH_2Cl_2$, reflux 12 h (quantitative); (ii) $LiAlH_4$, THF, 0 °C−rt, 12 h; (iii) (a) toluene, 80 °C, 16 h, (b) $K_2CO_3$, MeOH (45% over 3 steps); (iv) h$\upsilon$, $O_2$, $C_6H_6$, 20 h (82%).

readily synthesized from compounds **164** and **165** by ene−yne metathesis and were then reacted with quinone dienophiles to afford aromatized systems in good yields. Scheme 36 contains two examples where Diels−Alder reactions between **162** and **166**, and between **163** and **167**, gave substituted racemic amino acids **168** and **169**, respectively.

Finally in this section, the use of an ene−yne RCM−aromatization sequence, resulting in the formation of C-aryl glycosides, will be described.[119] Kaliappan and Subrahmanyam converted a number of *C*-alkynyl glycosides to their corresponding dienes; see, for example, the conversion of

**Scheme 36**[a]




[a] Reagents and conditions: (i) $CH_2$═$CH_2$ (1 atm), **1-Ru** (6 mol %), $CH_2Cl_2$, rt, 24 h (68%); (ii) (a) **166**, toluene, 90 °C, 24 h, (b) $MnO_2$, dioxane, reflux, 30 h (81% over two steps); (iii) $CH_2$═$CH_2$ (sealed tube), **4-Ru** (7 mol %), $C_6H_6$, 80 °C, 24 h (96%); (iv) (a) **167**, toluene, 110 °C, 72 h, (b) $MnO_2$, dioxane, rt, 12 h (86% over 2 steps).

**170** to **171**, by the use of **2-Ru** under an ethylene atmosphere (remarkably 5 mol % of **2-Ru** gave excellent yields, while the authors mention that the use of only 3% catalyst resulted in "disappointingly low yields of diene"). The authors of this work also synthesized dienes **172**−**175** in this manner (Scheme 37). These dienes were then reacted with a number of different dienophiles, and the unpurified products were treated with triethylamine and silica gel to promote oxidative aromatization. In this way, quinones **176**−**179** were obtained in acceptable yields from diene **171**, as well as for the other dienes **172**−**175** (not shown).

### 2.2.5. Synthesis of Indenes[120]

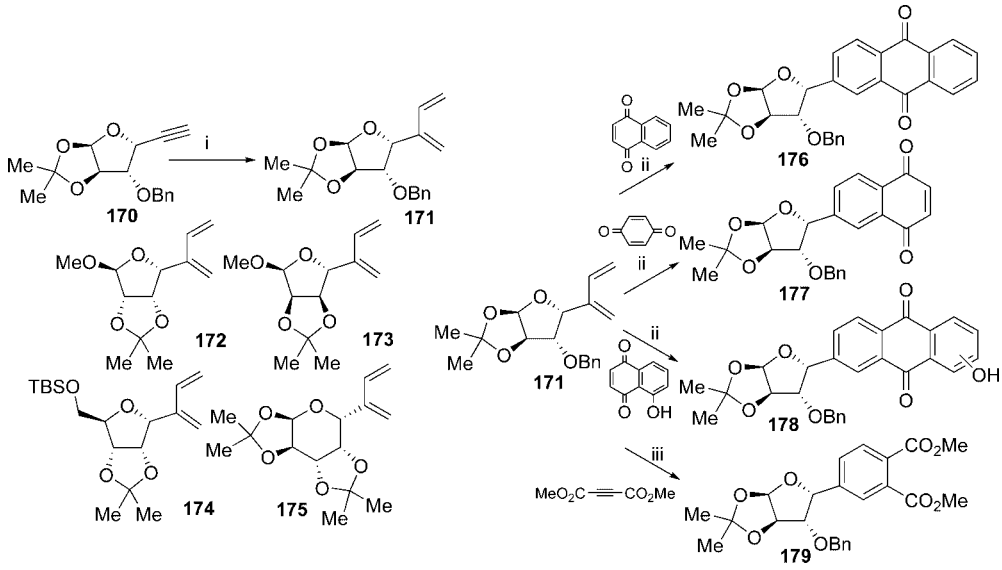
An ene−yne RCM reaction described by Kozmin and co-workers resulted in a direct route to enones from siloxy-alkyne−alkene precursors.[121] In particular, the reaction of substrate **180** with the catalyst **1-Ru** resulted in the formation of substituted indene **181** in excellent yield over the two synthetic steps, via intermediate **182** (Scheme 38).

### 2.2.6. Synthesis of Benzene Rings Fused to Nonaromatic Carbocycles

One of the first examples of the versatile ene−yne RCM−Diels-Alder−aromatization strategy published in the literature was performed by Kotha and co-workers to obtain constrained indane-based α-amino acid derivatives.[122,123] For example, the ene−yne compound **183** was subjected to metathesis conditions with catalyst **1-Ru**, to afford diene **184** (Scheme 39). Treatment of this compound with DMAD then gave the cycloadduct **185**, which was aromatized with DDQ to afford the benzannulated amino acid derivative **186**. Two examples of the interesting skeletons **187** and **188**, which were generated when diene **184** was reacted with the dienophiles benzoquinone and naphthoquinone, respectively, are included in Scheme 39.

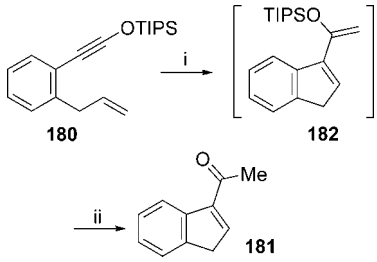
Undheim and co-workers also investigated the use of an ene−yne metathesis/aromatization strategy to synthesize rigid bis(α-amino acid) derivatives.[124] To this end, yne−dienes **189a** and **189b** were converted into the conjugated dienes **190a** and **190b** in excellent yields of 92% and 96%, respectively, making use of the Grubbs catalysts **2-Ru** and **1-Ru**, respectively (Scheme 40). These researchers were also able to show that the use of microwaves improved the yield of compounds **190** from precursors **189**.[125] Unfortunately

**Scheme 37**[a]



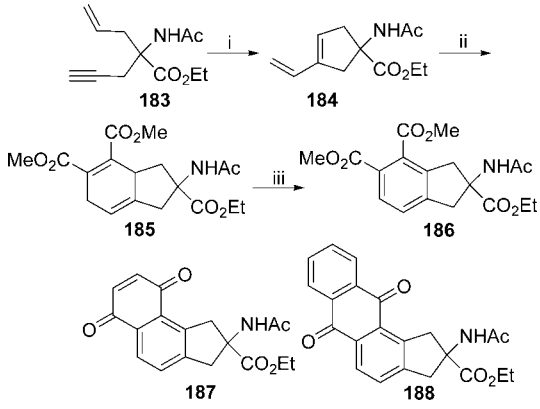
[a] Reagents and conditions: (i) **2-Ru** (10 mol %), $CH_2{=}CH_2$, toluene, 80 °C, 12 h, then DMSO, rt, 12 h (89%); (ii) toluene, reflux, then $NEt_3$, $CHCl_3$, silica gel, rt, **176** (60%), **177** (59%) and **178** (56%, mixture of regioisomers); (iii) DMAD (1.2 mol equiv), toluene, reflux, then $MnO_2$, $CH_2Cl_2$, reflux, 12 h, **179** (82%).

**Scheme 38**[a]



[a] Reagents and conditions: (i) **2-Ru** (3−10 mol %), $C_6H_6$ (0.1 M), 50−60 °C, 15−60 min; then (ii) HF (1.5−2 mol equiv), MeCN, 30 min (88% over 2 steps).

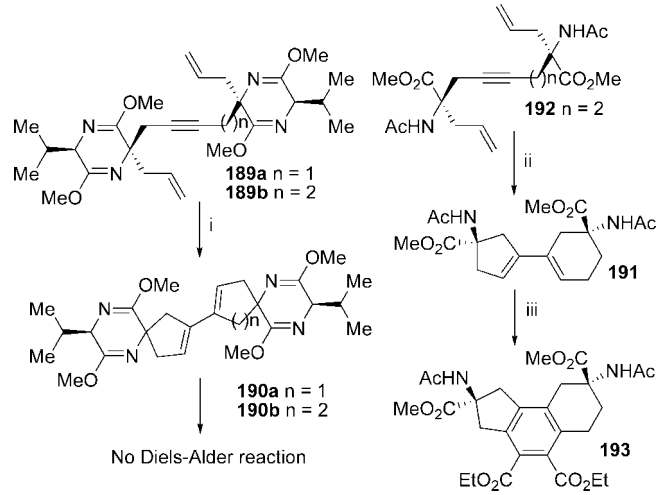
**Scheme 39**[a]



[a] Reagents and conditions: (i) **1-Ru** (10 mol %), $CH_2Cl_2$, rt, 24 h (75%); (ii) DMAD, hydroquinone (1 mol %), $C_6H_6$ or toluene, reflux, 3 d; (iii) DDQ, $C_6H_6$ or toluene, reflux (88% over 2 steps).

compounds **190a** and **190b** would not undergo Diels−Alder reactions with diethyl acetylene dicarboxylate, probably due to the substantial steric crowding not allowing them to adopt a cisoid arrangement. Of interest was that substrate **191**, readily synthesized from ene−yne **192** as shown in Scheme 40, underwent the Diels−Alder and subsequent aromatization

**Scheme 40**[a]



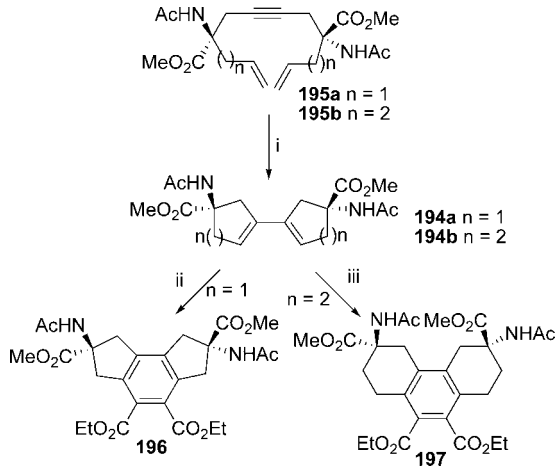
[a] Reagents and conditions: (i) for $n = 1$: **2-Ru** (3 × 10 mol %), toluene, 85 °C, 3 × 3 h (92%), for $n = 2$: **1-Ru** (2 × 5 mol %), toluene, 85 °C, 2 × 5 h (96%); (ii) **1-Ru** (2 × 8 mol %), toluene, 90 °C, 2 × 5 h (97%); (iii) (a) $EtO_2CC{\equiv}CCO_2Et$, anisole, 145 °C, 14 h, (b) $MnO_2$ or DDQ, dioxane, 100 °C, 5 h (62−65% over 2 steps).

reactions to afford substituted benzene **193**, thus providing a rigid bis(α-amino acid) derivative.

In addition, in another approach by Undheim and co-workers, the symmetrical dienes **194a** and **194b** were synthesized in good yields from **195a** and **195b**, respectively (Scheme 41).[126] These substrates were then efficiently converted into their rigid bis(α-amino acid) derivatives **196** and **197**, respectively, by a thermal Diels−Alder reaction with diethyl acetylene dicarboxylate, followed by an aromatization step using $MnO_2$ or DDQ as oxidant.[124] In this way the tricyclic amino acids were obtained in good yields of 57% for **196** and 60% for **197**, over the two steps involved.

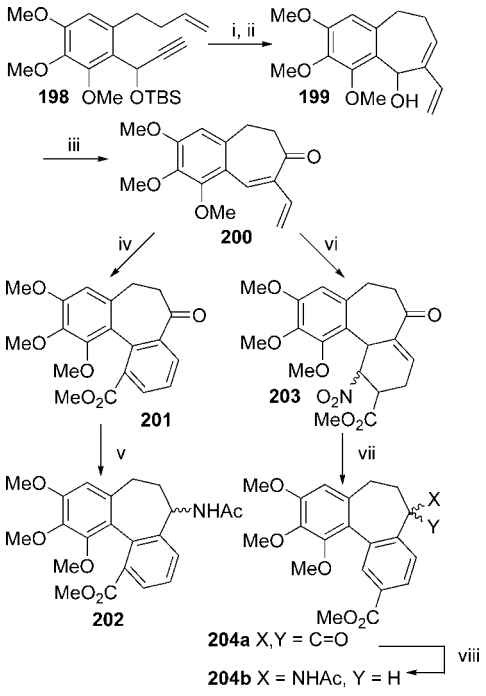
Finally in this section is the description of an elegant application of ring-closing ene−yne metathesis, followed by a Diels−Alder reaction and an aromatization to form a series of novel allocolchicines.[127,128] In this work by Boyer and

**Scheme 41**[a]




[a] Reagents and conditions: (i) **1-Ru** (2 × 5 mol %), toluene, 85 °C, 2 × 5 h, for $n = 1$ (86%), for $n = 2$: (85%); (ii) (a) $EtO_2CC{\equiv}CCO_2Et$, anisole, 145 °C, 14 h, (b) $MnO_2$, dioxane, rt, 14 h (57% over 2 steps); (iii) (a) $EtO_2CC{\equiv}CCO_2Et$, anisole, 145 °C, 14 h, (b) $MnO_2$, dioxane, rt, 14 h (60% over 2 steps).

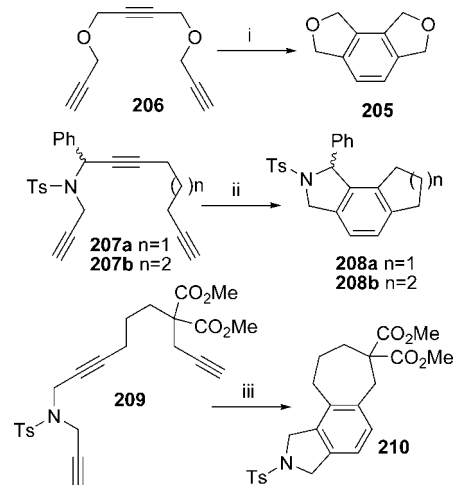
**Scheme 42**[a]




[a] Reagents and conditions: (i) **2-Ru** (5 mol %), $CH_2Cl_2$, reflux, 4 h (92%); (ii) TBAF, THF, rt, 48 h (95%); (iii) PCC, $CH_2Cl_2$, rt (55%); (iv) (a) $HC{\equiv}CCO_2Me$, toluene, 115 °C, (b) DDQ, $CH_2Cl_2$, rt (85% over 2 steps); (v) (a) $NH_4OAc$, $NaBH_3CN$, MeOH, 60 °C, (b) $Ac_2O$, pyridine (69% over 2 steps); (vi) $MeO_2CCH{=}CHNO_2$, $CH_2Cl_2$, rt (97%); (vii) (a) DBU, THF, rt, (b) DDQ, $CH_2Cl_2$, rt (50% over 2 steps); (viii) (a) $NH_4OAc$, $NaBH_3CN$, MeOH, 60 °C, (b) $Ac_2O$, pyridine (57% over 2 steps).

Hanna, compound **198** was ring-closed with the second-generation catalyst **2-Ru** and subsequently desilylated with TBAF to afford bicyclic compound **199** in excellent yield of 87% over the two steps (Scheme 42). An innovative rearrangement of the allyl alcohol then afforded the conjugated diene **200** required for the extension of the aromatic portion, with the ketone functionality in the correct position for further manipulation. The construction of the aromatic portion occurred readily (see paper for details of another longer route) by the thermal cycloaddition of methyl propiolate to afford only regioisomer **201**, after aromatization with DDQ as oxidant. Reductive amination of the ketone functionality, followed by an acetylation then readily afforded the allocolchicine **202**. An allocolchicine substituted in the 10-position was also accessed by treatment of **200** with methyl $\beta$-nitroacrylate, remarkably reacting at room temperature, giving only the desired regioisomer **203**. Nitrous acid was then eliminated under basic conditions, and subsequent aromatization with DDQ then afforded compound **204a**, which was readily converted into the regioisomer of **201**, compound **204a**. A reductive amination of the ketone **204a** also allowed for the synthesis of allocolchicine **204b**. Finally, the authors also reported the synthesis of allocolchicinoids containing an 8-membered B-ring[128] utilizing a similar strategy to that described for compound **202**, as well as a diene−yne tandem RCM approach to the tricyclic core of colchicine.[129]

**Scheme 43**[a]



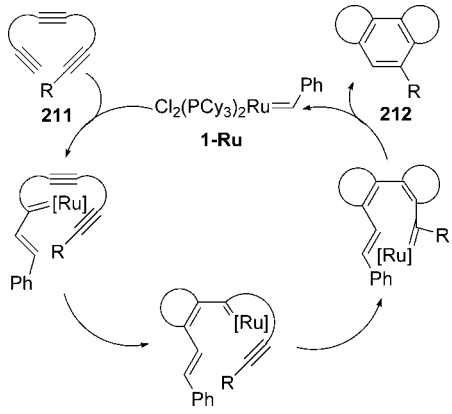

[a] Reagents and conditions: (i) **1-Ru** (0.5 mol %), $CH_2Cl_2$ (1 M), rt, 2 h (88%); (ii) for $n = 1$, **1-Ru** (5 mol %), $CH_2Cl_2$ (1 M), rt, 12 h (74%), for $n = 2$, **1-Ru** (5 mol %), $CH_2Cl_2$ (1 M), rt, 48 h (35%); (iii) **1-Ru** (5 mol %), $CH_2Cl_2$ (1 M), rt, 48 h (15%).

## 2.3. Metathetic Cyclotrimerization Strategies for the Synthesis of Aromatic Carbocycles

Transition metal-catalyzed cyclotrimerizations[130−132] are a very important method for the synthesis of polysubstituted aromatic systems.[133]

In 1997, Peters and Blechert published an interesting application of a metathesis cascade to afford substituted benzenes from triyne compounds.[134] For example, tricyclic compound **205** was readily synthesized from the triyne precursor **206** upon the application of catalyst **1-Ru** (Scheme 43). Only 0.5 mol % of catalyst was required for this transformation, which is indeed remarkable when one views the proposed mechanistic cascade to this product in Scheme 44. Other benzo-fused compounds were also synthesized by this strategy, and a number of these are shown in Scheme 43, i.e., **207a**,**b** → **208a**,**b** and **209** → **210** (with yields of the aromatization step shown in the legend in parentheses). It is interesting to note that yields diminished sharply with an increase in the size of the fused rings, and that these particular reactions necessitated larger amounts of catalyst and longer reaction times. The authors postulated that the lower yields were due to competing polymerization reactions.

**Scheme 44**[a]




[a] Proposed mechanism for the "metathesis cascade" leading to substituted benzenes.

Peters and Blechert proposed a mechanism, a "metathesis cascade", for the transformations described in the Scheme 43. This mechanism, as shown for the conversion of triyne **211** into the substituted aromatic system **212**, has been cited by other researchers (see other examples in this section) and is depicted in brief in Scheme 44. For a further discussion of this cascade of metathesis reactions and other proposed mechanisms for [2 + 2 + 2]-alkyne cyclotrimerizations, see ref 135.

In another one of their approaches to the synthesis of conformationally constrained and rigid bis(α-amino acid) derivatives (see also section 2.2.6),[136] Undheim and co-workers elegantly utilized the metathetic trimerization reaction. Triyne **213** was treated with two aliquots of the **1-Ru** catalyst, necessary due to decomposition of the ruthenium catalyst, which gave, after chromatography, the bis-spiro pentacyclic product **214** in an excellent yield of 90% (Scheme 45).[137] Compound **214** was then readily converted into the bis-amino acid **215a** by hydrolytic cleavage. The acetyl-protected version **215b** was also synthesized by way of a ruthenium-mediated cascade from triyne **216** in a moderate yield of 58%.

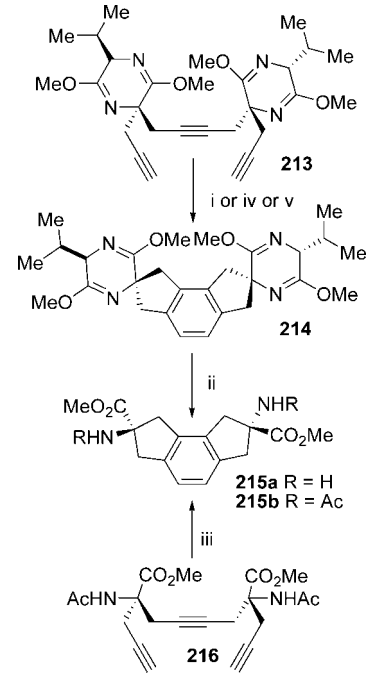
In a subsequent paper, by the same group, the effect of microwave irradiation was evaluated on the conversion of triyne **213** into **214** (Scheme 45).[125] Remarkably, on this occasion only 20 min and one 5% loading of catalyst **1-Ru** was required to achieve 100% conversion for this microwave-mediated transformation. Of note was that, when the second-generation catalyst **2-Ru** was utilized under the microwave conditions,[138−140] only a low yield of 36% was obtained for the desired bis-spiro compound **214**.

The ruthenium-mediated trimerization cascade was also utilized by Roglans and co-workers to synthesize a number of interestingly substituted aromatic systems. These workers found that the treatment of macrocycles such as **217** with Grubbs catalyst **1-Ru** afforded the corresponding triazatriindane **218** in moderate yields (Scheme 46).[141] Even increasing the catalyst loading to 20 mol % did not improve the yields obtained. The use of the ruthenium catalytic system proved to give similar results compared to when a cobalt system, [$CpCo(CO)_2$], was utilized. However, $RhCl(CO)(PPh_3)_2$ turned out to be the catalyst of choice, resulting in the desired triazatriindanes in >80% yield with low (1%) catalyst loadings.

In 1999, Das and Roy demonstrated that this trimerization approach was also applicable for the intermolecular trimerization of alkynes.[142] They demonstrated that the treatment of the peracylated 2-propynyl α-D-mannopyranoside **219** with Grubbs first-generation **1-Ru** afforded a mixture of the regioisomers **220** (major) and **221** (minor), as shown in Scheme 47. Other alkynol substrates, substituted with different sugars and protecting groups, were also successfully trimerized. In all cases, the regioselectivity of the reaction was better than 3:1 in favor of the 1,2,4-trisubstituted aromatic core. Of interest was that the co-workers were able to demonstrate that, after the completion of a trimerization reaction, the catalyst was still active, giving support to the mechanism proposed by Peters and Blechert.[134] Gan and Roy also published a subsequent paper in which the propargylated sialoside **222** was successfully cyclotrimerized with the first-generation catalyst **1-Ru**.[143]

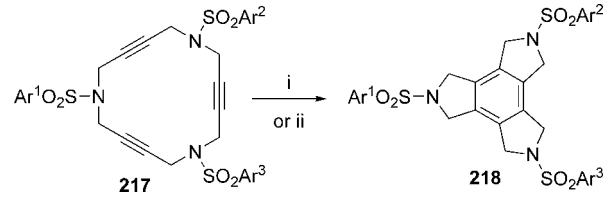
Witulski and co-workers also applied a Grubbs catalyst-mediated intermolecular cyclotrimerization to 1,6-diynes with terminal alkynes.[144] The 1,6-diynes **223** and **224**, depicted in Scheme 48, were reacted with a representative number of terminal alkynes, e.g., **225**, to afford the corresponding isoindolines **226** or **227** and indolines **228** or **229** in acceptable yields, respectively (Scheme 48). Of particular

**Scheme 45**[a]



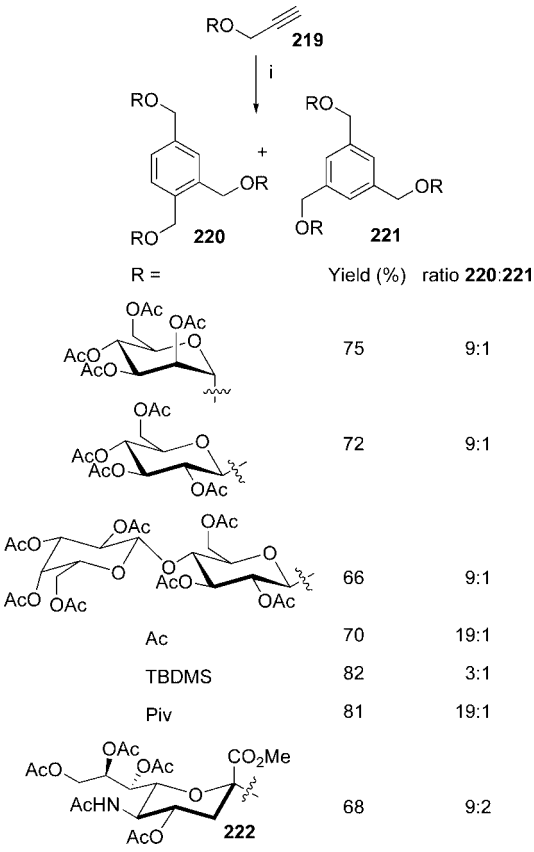

[a] Reagents and conditions: (i) **1-Ru** (2 × 5 mol %), toluene, 85 °C, 14 h (90%); (ii) TFA (0.1 M), $MeCN/H_2O$ (1:1), rt, 4 d (35% of **215a**); (iii) **1-Ru** (2 × 5 mol %), toluene, 85 °C, 14 h (58% of **215b**); (iv) **1-Ru** (∼10 mol %), toluene, 160 °C, microwave, 20 min (100% conversion); (v) **2-Ru** (∼5 mol %), toluene, 160 °C, microwave, 10 min (36%).

**Scheme 46**[a]



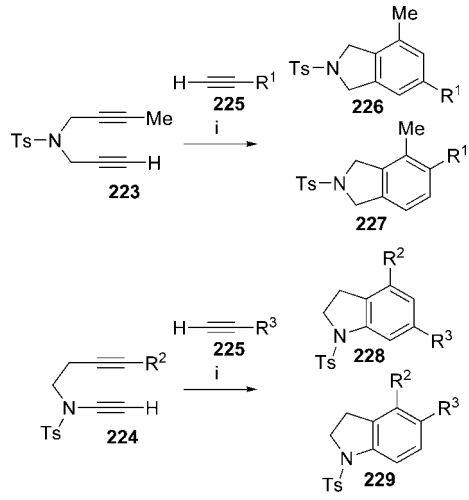

[a] Reagents and conditions: (i) **1-Ru** (7 mol %), toluene, reflux, 22 h, for $Ar^1 = Ar^2 = 4\text{-Me-}C_6H_4$-, $Ar^3$ = ferrocenyl- (42%), for $Ar^1 = Ar^2 = Ar^3 = 2,4,6\text{-}i\text{-}PrC_6H_2$- (36%, same result with 20% **1-Ru**); (ii) $RhCl(CO)(PPh_3)_2$ (1−5 mol %), toluene, 65 °C (>80%).

**Scheme 47**[a]




[a] Reagents and conditions: (i) **1-Ru** (1.5 mol %), $CH_2Cl_2$ (1 M), 12 h, rt; for yields, see table in scheme; for substrate **222** in Table: **1-Ru** (5 mol %), $ClCH_2CH_2Cl$, 24 h, reflux.

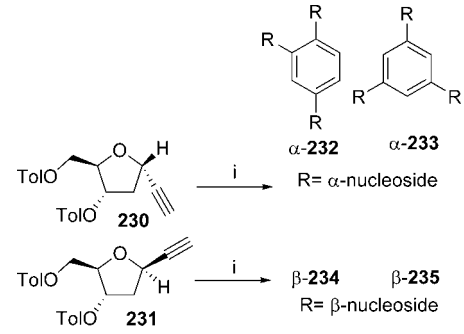
**Scheme 48**[a]




[a] Reagents and conditions: (i) **1-Ru** (5−10 mol %), $CH_2Cl_2$, alkyne **225** (5 mol equiv), 40 °C, sealed tube, 10−20 h; for substrate **223** (ratio **226**:**227**): $R^1$ = Ph (82%, 5:1), $R^1$ = *n*-Pr (92%, 6:1), $R^1 = CH_2OH$ (81%, 6:1), $R^1 = CH_2CH_2OH$ (89%, 6:1); for substrate **224** (ratio **228**:**229**): $R^2$ = Me, $R^3 = CH_2OH$ (70%, 9:1), $R^2$ = Me, $R^3 = CH_2CH_2OH$ (51%, 9:1), $R^2$ = Me, $R^3 = CH_2CH_2CH_2OH$ (57%, 9:1), $R^2$ = Ph, $R^3 = CH_2OH$ (60%, 9.5:1).

interest is that, while the ruthenium catalysis gave mainly the *meta*-substituted benzenes **226** and **228**, the application of Wilkinson's catalyst [$RhCl(PPh_3)_3$] gave a reversed selectivity, i.e., for the *para*-regiosiomers, in several of the examples. The selectivity for the *meta*-substituted compounds

**Scheme 49**[a]




[a] Reagents and conditions: (i) **1-Ru** (15 mol %), $CH_2Cl_2$, 20 °C, 48 h, for **230** (45%), α-**232**/α-**233** (5:6), for **231** (30%), *β*-**234**/*β*-**235** (1:1).

was postulated to be due to the preferred addition of the carbene reagent to the less-substituted alkyne and subsequent intramolecular coordination to the other triple bond. The even higher *meta*/*para* ratio observed for substrate **224** was explained by the increased ability of the alkylated alkyne to coordinate to the ruthenium catalyst.

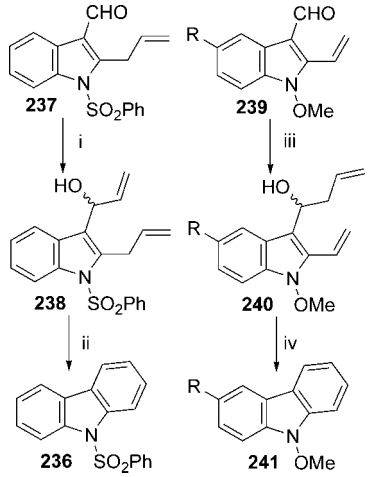
Hocek, Kotora, and co-workers also utilized an intermolecular cyclotrimerization reaction to make interesting C-trisaccharide derivatives.[145] In an attempt to minimize the formation of side-products, the researchers applied **1-Ru** to the cyclotrimerization of the modified nucleosides **230** and **231** (Scheme 49). The reaction of the α-**230** gave a mixture of the 1,2,4-**232** and 1,3,5-trisubstituted **233** benzenes in a 5:6 ratio, respectively, and in a combined yield of 45%. On the other hand, use of the *β*-isomer **231** gave a 30% yield return with an equimolar ratio for compounds **234** and **235**. Of interest is that the catalyst **1-Ru** gave better results for the reaction with substrate **230** than when Cp*Ru(cod)Cl was utilized for this transformation (13%); however, for substrate **231**, the Cp*Ru(cod)Cl catalyst proved superior (40%).

A point to note is that a number of researchers have attempted the use of the Grubbs catalysts for cyclotrimerization reactions, but this application proved to be unsuccessful. These examples were both for intra-[146] and intermolecular reactions,[147,148] and in one case it was mentioned that the catalyst appeared unable to cyclotrimerize electron-deficient alkenes.[148] Another paper of interest, describing decomposition pathways in ene−yne metatheses, mentions as a footnote that in "some cases, trisubstituted benzenes were also observed in the crude $^1$H NMR spectra" due to competing trimerization processes.[149]

## 3. Synthesis of Aromatic Carbocycles Fused to Heterocycles by RCM−Aromatization

Compounds containing a heterocyclic ring fused to an aromatic ring are also ubiquitous in nature. It is, therefore, very important to develop synthetic techniques capable of the "benzannulation" of heterocycles. It should therefore not be surprising that the construction of an aromatic ring fused to another ring structure has been an important theme in organic synthesis; for a recent review on this topic, see ref 150. In this section of the present review, work involving the use of ene−ene metathesis for the construction of aromatic systems fused to a ring containing one or more heteroatoms will be described.

**Scheme 50**[a]




[a] Reagents and conditions: (i) $BrMgCH{=}CH_2$, THF, −78 to 0 °C, 3 h (75%); (ii) **1-Ru** (5 mol %), rt, $CH_2Cl_2$ (62%); (iii) allyltributyltin, *n*-BuLi, −78 °C (R = H 74%, R = Me 83%); (iv) **1-Ru** (5 mol %), $CH_2Cl_2$, rt to reflux (R = H 66%, R = Me 72%).

## 3.1. Ene−Ene RCM−Aromatization Strategies for the Synthesis of Aromatic Carbocycles Fused to Heterocycles

The use of ene−ene RCM followed by aromatization, to create an aromatic carbocyclic ring fused to a heterocycle, has solicited considerable interest from the organic synthetic community and will be reviewed in the next section of this paper.

### *3.1.1. Synthesis of Carbazoles*

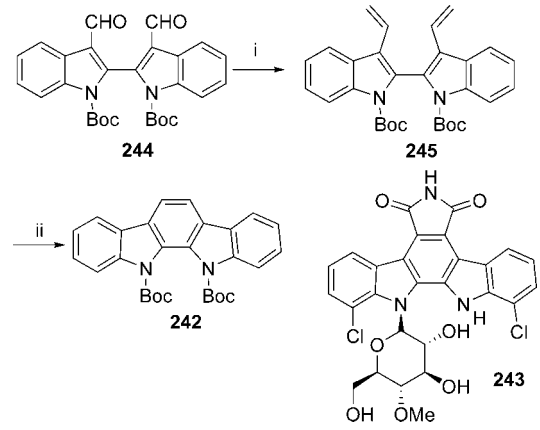
Bennasar and co-workers utilized a similar approach to that described by Huang and Wang[82] and van Otterlo[60] (sections 2.1.2 and 2.1.6, respectively) to synthesize the carbazole **236**.[151] The aldehyde **237** was treated with vinylmagnesium bromide to afford compound **238** in good yield (Scheme 50). A RCM reaction mediated by catalyst **1-Ru**, followed by an in situ dehydration, then afforded the carbazole **236** in 62% yield (Knochel and co-workers performed the same type of RCM strategy to afford a dihydrocarbazole but did not dehydrogenate this compound).[152]

Selvakumar and co-workers, on the other hand, used a slightly different approach to achieve the same type of carbazole framework.[153] These researchers initially synthesized the 3-formyl substituted indole **239**, which was subsequently allylated with allyltributyltin to afford **240**. This compound, when treated with Grubbs catalyst **1-Ru**, readily afforded the corresponding carbazole **241** after spontaneous dehydration under the reaction conditions utilized.

de Koning and co-workers have used a RCM approach to synthesize the indolo[2,3-*a*]carbazole core **242** of the anticancer agent rebeccamycin **243** (Scheme 51).[154] A Wittig alkenylation of the bisaldehyde **244** afforded substrate **245**. This compound was then immediately treated with catalyst **2-Ru** to give in hand the indolo[2,3-*a*]carbazole core **242** in a reasonable yield of 64% over the two steps from **244**.

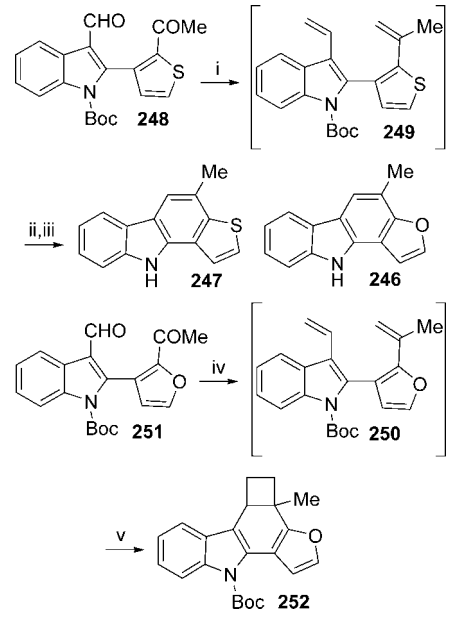
de Koning and co-workers then attempted to use this general strategy to synthesize furostifoline **246** and its thioanalogue **247**.[154] To this end, dicarbonyl **248** was prepared and converted to the unstable diene **249** (Scheme 52).

**Scheme 51**[a]




[a] Reagents and conditions: (i) $MePPh_2Br$, *n*-BuLi, $Et_2O$, 0 °C; (ii) **2-Ru** (8 + 4 mol %), toluene, 80 °C, 20 + 4 h (64% over 2 steps).

**Scheme 52**[a]



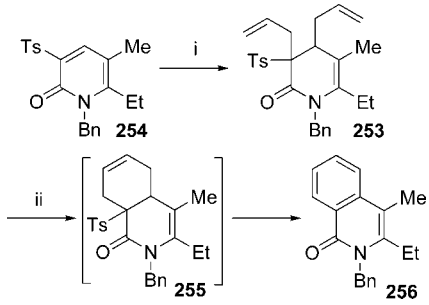

[a] Reagents and conditions: (i) $MePPh_2Br$, *n*-BuLi, $Et_2O$, 0 °C; (ii) **2-Ru** (11 mol %), toluene, 25 °C (40% over 2 steps); (iii) TFA, $CH_2Cl_2$, reflux (72%); (iv) $MePPh_2Br$, *n*-BuLi, $Et_2O$, 0 °C; (v) **2-Ru** (11 mol %), toluene, rt (28% over 2 steps).

Subsequent metathesis of this compound, followed by removal of the Boc group, led to the sulfur analogue of furostifoline **247**. However, when this strategy was used in an attempt to obtain the naturally occurring compound **246**, it met with unexpected failure. The diene **250**, prepared as before from compound **251**, rapidly converted to the fused cyclobutane **252**, most probably by a spontaneous $\pi_8$ electrocyclization reaction followed by a $\pi_6$ electocyclization process.

### *3.1.2. Synthesis of Benzo-Fused Pyridones and Pyridines*

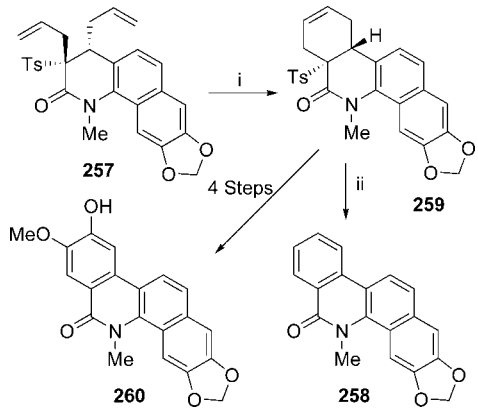
Chang and co-workers have used a RCM−aromatization protocol to afford a number of polysubstituted 2-pyridones.[155] The benzannulation procedure was initiated by way of sequential allylation process to afford bisallyl **253** starting from **254** (Scheme 53). A RCM reaction with **1-Ru** then afforded compound **255**, which was not isolated, as a

**Scheme 53**[a]




[a] Reagents and conditions: (i) (a) allylmagnesium bromide, THF, rt, (b) allyl bromide, NaH, THF, rt (67% over 2 steps); (ii) (a) **1-Ru** (10 mol %), $CH_2Cl_2$, rt, 12 h, (b) *t*-BuOK, *t*-BuOH, reflux, 24 h (81% over 2 steps).

**Scheme 54**[a]




[a] Reagents and conditions: (i) **1-Ru** (10 mol %), $CH_2Cl_2$, rt, 7.5 h (96%); (ii) (a) DBU, THF, 60 °C, 20 h (93%), (b) DDQ, THF, reflux, 2 h (99%).

dehydrosulfonation of the tosyl group then gave the isoquinolinone **256** after spontaneous aromatization.

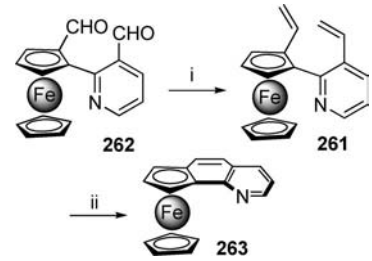
Another aromatization−RCM approach by the Chang group was also reported in the same paper,[155] using substrate **257** as precursor (Scheme 54). This compound readily afforded the benzannulated pyridone **258** in good yield after RCM to cyclohexene **259** and base-induced aromatization. Compound **259** was also readily converted into the more substituted analogue **260** after a number of synthetic steps.

An interesting application of RCM to afford aromatic structures has been described by Mamane and Fort in their bid to develop routes to novel chiral ligands.[156] In this study, which involved the synthesis of chiral ferroceno-(iso)quinolines, the researchers constructed the bisvinyl compound **261** by the Wittig olefination of bisaldehyde **262**. Subsequent RCM, using **2-Ru** as catalyst, then afforded the aromatic ferroceno[*h*]quinoline **263** in acceptable yield (Scheme 55).

### *3.1.3. Synthesis of Benzo-Fused Imidazoles and Related Compounds*

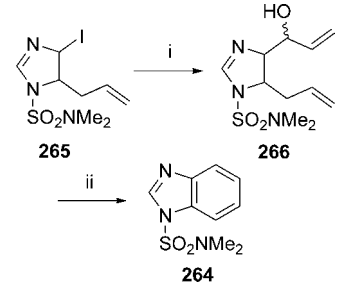
The benzannulation of imidazoles with RCM has also been achieved with mixed success, as discussed in a recent review.[157] Lovely and co-workers were able to synthesize a benzo-fused imidazole **264** starting from the precursor **265** (Scheme 56).[158,159] Metalation of precursor **265**, followed by a reaction with acrolein afforded bisallyl compound **266**. This compound was then converted to the respective imidazolium salt, a modification required for the metathesis to work, and catalytic amounts of **2-Ru** then afforded benzimidazole **264**

**Scheme 55**[a]



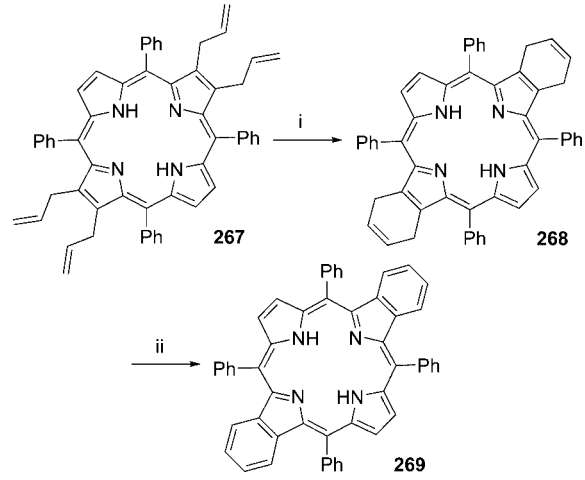

[a] Reagents and conditions: (i) $Ph_3P{=}CH_2$, (3 mol equiv), THF, −40 °C−rt (69%); (ii) **2-Ru** (20 mol %), toluene, reflux, 30 min (66%).

**Scheme 56**[a]




[a] Reagents and conditions: (i) EtMgBr, $CH_2Cl_2$, rt, then $CH_2{=}CHCHO$ (49%); (ii) *p*-TsOH (1.1 equiv), $CH_2Cl_2$ (0.1 M), reflux, 30 min, then **2-Ru** (5 mol %), reflux, 20 min, then rt, 1.5 h, (45%).

**Scheme 57**[a]

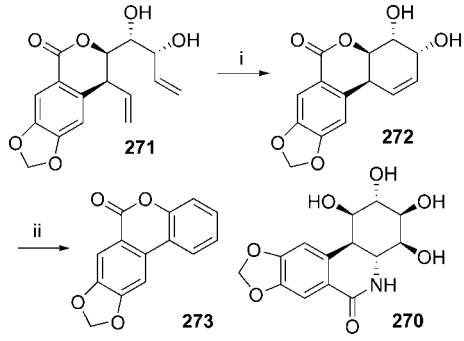



[a] Reagents and conditions: (i) **2-Ru** (10 mol %), $CH_2Cl_2$, 0.001 M, Ar, reflux, overnight (82−91%); (ii) DDQ, toluene, no further details ("almost quantitative").

as the initial RCM product spontaneously underwent elimination of water.

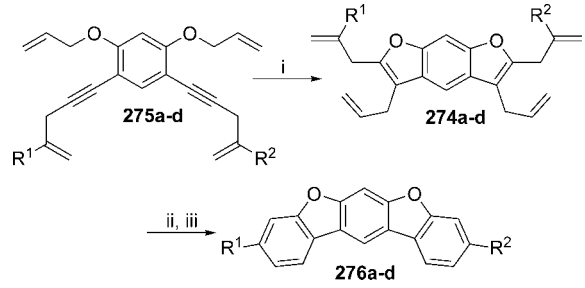
Smith and co-workers demonstrated an elegant application of an RCM−aromatization process to assemble benzo-fused porphyrins.[160] In a representative example from this work, compound **267**, obtained by the Suzuki−Miyaura coupling of the tetrabromo porphyrin precursor with allylboronic acid pinacol ester, was reacted with the catalyst **2-Ru** to afford **268** (Scheme 57). Aromatization of compound **268** was subsequently achieved by the use of DDQ, yielding the bisbenzannulated porphyrin **269** in good yield. The same research group also synthesized a number of other mono-, di-, and tribenzoporphyrins using this innovative approach.

**Scheme 58**[a]




[a] Reagents and conditions: (i) **4-Ru** (5 mol %), $CH_2Cl_2$, reflux, 5 h (75%); (ii) $(imidazole)_2CO$, toluene, 50 °C, then phthalimide, $Pd(PPh_3)_4$, THF, 65 °C (yield unspecified).

**Scheme 59**[a]




[a] Reagents and conditions: (i) $Pd_2(dba)_3 \cdot CHCl_3$ or $Pd(PPh_3)_4$ (5 mol %), $PPh_3$, DMF, 60 °C, Ar, 9 h: **274a** $R^1 = R^2 = H$ (88%), **274b** $R^1 = R^2 =$ Me (88%), **274c** $R^1 = R^2 =$ Bu (66%), **274d** $R^1 =$ H, $R^2 =$ Bu (51%); (ii) **2-Ru** (5 mol %), $CH_2Cl_2$, reflux, Ar, 11 h, then solvent removed by evaporation; (iii) DDQ (3 mol equiv), toluene, 80 °C, 4 h (yields over 2 steps); **276a** $R^1 = R^2 = H$ (59%), **276b** $R^1 = R^2 =$ Me (70%), **276c** $R^1 = R^2 =$ Bu (53%), **276d** $R^1 =$ H, $R^2 =$ Bu (55%).

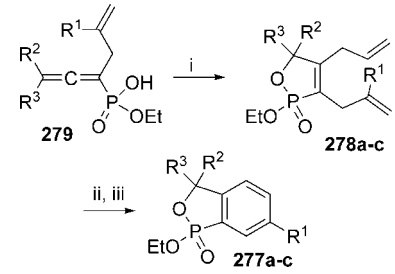
### 3.1.4. Synthesis of a Benzo-Fused Lactone

Sometimes the formation of an aromatic ring is not the desired result! One of the synthetic pathways to 7-deoxypancratistatin **270**, a potent, naturally occurring anticancer agent isolated from the *Amaryllidaceae* family,[161] investigated by Madsen and co-workers involved the synthesis of diene **271**.[162] The RCM reaction of **271** with catalyst **4-Ru**—the Grubbs first- and second-generation catalysts were much slower—then readily afforded the diol **272** (Scheme 58). However, attempted conversion of **272** into the cyclic carbonate and treatment with a palladium(0) catalyst and phthalimide to invoke an allylic substitution only afforded the aromatized product **273** in unspecified yield, resulting in this promising synthetic approach to 7-deoxypancratistatin being abandoned.

### 3.1.5. Synthesis of Benzodifurans

Ma and co-workers utilized an interesting strategy, involving palladium-catalyzed double cyclizations with concomitant allyl group migration, to synthesize the benzodifurans **274a**−**d** from substrates **275a**−**d** (Scheme 59).[163] Subsequent treatment of the tetraenes **274a**−**d** with **2-Ru**, followed by an oxidative aromatization with DDQ, then gave four novel, fused pentacyclic compounds **276a**−**d** in acceptable yields of 53−70% over the last two steps.

**Scheme 60**[a]




[a] Reagents and conditions: (i) allyl bromide, $PdCl_2(PhCN)_2$ (5 mol %), DMF, 80 °C, $N_2$, **278a** $R^1 = R^2 = R^3 = H$ (72%), **278b** $R^1 =$ H, $R^2 = R^3 =$ Me (47%), **278c** $R^1 = R^2 = R^3 =$ Me (56%); (ii) **2-Ru** (5 mol %), $CH_2Cl_2$, reflux, 1 h, then evaporation; (iii) DDQ (1.5 equiv), toluene, 80 °C, overnight, **277a** $R^1 = R^2 = R^3 = H$ (68%), **277b** $R^1 =$ H, $R^2 = R^3 =$ Me (83%), **277c** $R^1 = R^2 = R^3 =$ Me (58%).

### 3.1.6. Synthesis of Benzoxaphosphole 1-Oxides

Three substituted 1,3-dihydro[2,1]benzoxaphosphole 1-oxides **277a**−**c** were synthesized by Ma and co-workers utilizing the RCM−oxidation strategy reviewed in this paper (Scheme 60).[164] Substrates **278a**−**c** were readily synthesized from the reaction of the suitably substituted 1,2-allenyl phosphonic acid monoesters **279** with allyl bromide, under palladium-mediated catalysis. A subsequent RCM reaction with the catalyst **2-Ru**, followed by removal of the solvent and oxidation of the resultant intermediates by DDQ, then afforded the desired benzo-fused phosphorus-containing compounds **277a**−**c** in reasonable yields.

## 3.2. Ene−Yne Metathesis−Aromatization Strategies for the Synthesis of Aromatic Carbocycles Fused to Heterocycles

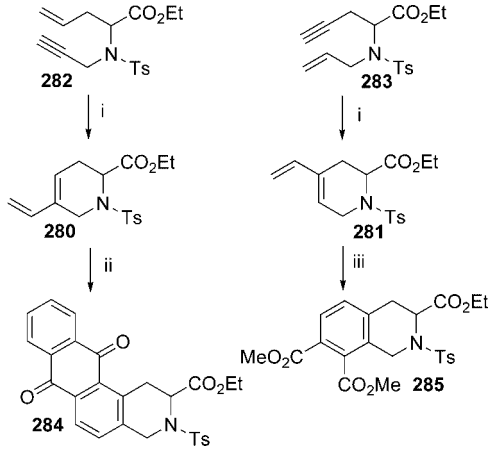
The ene−yne metathesis strategy for the synthesis of aromatic carbocyclic rings that are fused to heterocycles has seen sporadic use over the past few years. Of particular interest is that a Diels−Alder reaction is often utilized after the ene−yne metathesis step to afford an unsaturated carbocycle,[88] which is subsequently aromatized. This strategy, as well as other related ones, will be discussed in the next section of the review.

### 3.2.1. Synthesis of Dihydroisoquinolinones and Tetrahydroisoquinolines

Kotha and Sreenivasachay used an innovative ene−yne RCM−Diels-Alder approach to synthesize a number of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids.[165,166] The "inner−outer" ring dienes **280** and **281** were readily synthesized by an ene−yne metathesis strategy from **282** and **283**, respectively (Scheme 61). Treatment of compounds **280** and **281** with a variety of dienophiles and subsequent oxidation with DDQ afforded a small library of THIQ derivatives. Two examples of the THIQs synthesized, from the five described in the paper, are shown in Scheme 61, namely, compounds **284** and **285**. Kotha and Khedkar also modified this strategy to synthesize similar compounds with a 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine skeleton, i.e., with an additional methylene in the heterocyclic ring when compared to compound **285**.[167]

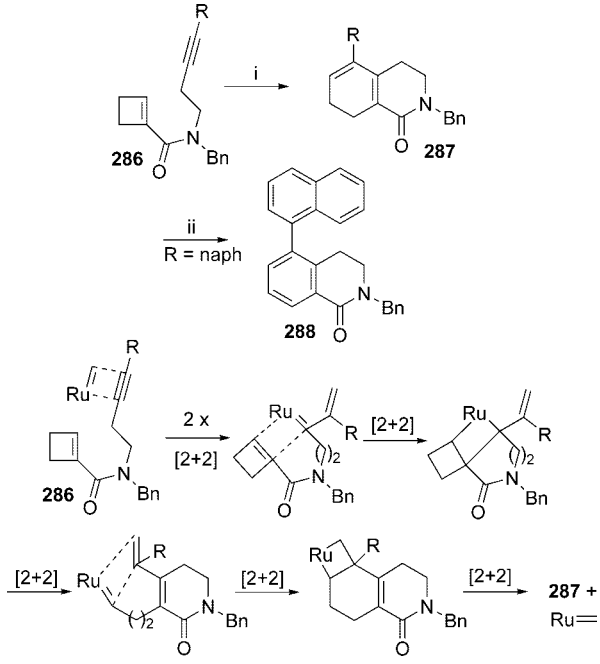
Interesting methodology, resulting in the synthesis of substituted THIQs, was also developed by Mori and co-workers.[168] Their strategy involved the ring-opening

**Scheme 61**[a]



[a] Reagents and conditions: (i) **1-Ru** (mol % not given in paper), toluene, reflux, 36 h, **280** (65%), **281** (70%); (ii) 1,4-naphthoquinone, then DDQ (52% over 2 steps); (iii) DMAD, then DDQ (85% over 2 steps).

**Scheme 62**[a]



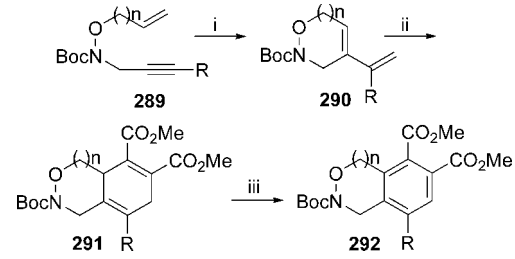
[a] Reagents and conditions: (i) **2-Ru** (10 mol %), toluene, 80 °C, 0.5 h, yields: R = H (61%), R = Me (56%), R = Ph (82%), R = *p*-$CO_2$Et-Ar (83%), R = naph (71%); (ii) DDQ, toluene, 3 h, 80 °C (76%).

metathesis−ring-closing metathesis (ROM−RCM) of, for example, cycloalkene−ynes such as **286**, which afforded compound **287** (Scheme 62). Mori's approach resulted in a number of dihydro-THIQ derivatives that could all be readily converted into their aromatic counterparts. For example, upon aromatization of compound **287** with DDQ, the biaryl THIQ **288** was obtained in a good yield of 76%. The authors proposed a mechanism for the formation of **288** as shown in Scheme 62, which includes a number of skeletal rearrangements, all by putative [2 + 2]-cycloadditions and -cycloreversions.

### *3.2.2. Synthesis of Annulated 1,2-Oxaza- and 1,2-Bisazacycles and Related Compounds*

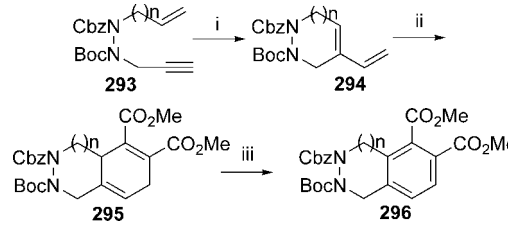
Tae and co-workers have also utilized an ene−yne metathesis−Diels-Alder−aromatization approach to synthe-

**Scheme 63**[a]



[a] Reagents and conditions: (i) **1-Ru** (10 mol %), $CH_2Cl_2$ (0.007−0.02 M), 45 °C, 4−34 h, yields: R = H, *n* = 1 (92%), R = Me, *n* = 1 (94%), R = H, *n* = 2 (87%), R = Me, *n* = 2 (90%), R = H, *n* = 3 (76%); (ii) DMAD, toluene, reflux, 6−9 h, yields: R = H, *n* = 1 (94%), R = Me, *n* = 1 (96%), R = H, *n* = 2 (90%), R = Me, *n* = 2 (89%), R = H, *n* = 3 (75%, product obtained aromatized under reaction conditions); (iii) DDQ (1 mol equiv), $C_6H_6$, reflux, yields: R = H, *n* = 1 (88%), R = Me, *n* = 1 (94%), R = H, *n* = 2 (86%).

**Scheme 64**[a]



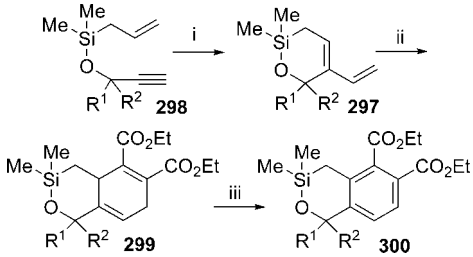
[a] Reagents and conditions: (i) **1-Ru** (10 mol %), $CH_2Cl_2$ (0.02 M), reflux, 4−10 h, yields: *n* = 1 (99%), *n* = 2 (70%), *n* = 3 (70%); (ii) DMAD (1.2 mol equiv), toluene, reflux, 6 h, yields: *n* = 1 (88%), *n* = 2 (97%), *n* = 3 (92%); (iii) DDQ (2 mol equiv), toluene, reflux, yields: *n* = 1 (82%), *n* = 2 (87%), *n* = 3 (92%).

size a range of 1,2-oxaza[169] (Scheme 63) and 1,2-bisaza[170] (Scheme 64) polycycles in the past few years. In their first paper concerning this subject, the ene−yne substrates **289** were subjected to catalyst **1-Ru** to afford conjugated dienes **290** in excellent yields. These compounds were subsequently subjected to Diels-Alder reactions with DMAD to afford bicyclics **291** in good-to-excellent yields (Scheme 63). Oxidative aromatization was then performed with DDQ to give the annulated heterocycles of general structure **292**.

Tae and Hanh applied a similar strategy to synthesize cyclic-protected hydrazines.[170] To this end, substrates **293** were converted into their corresponding dienes **294**, which reacted facilely with DMAD to give the cycloadducts **295** in good yields (Scheme 64). These compounds were then oxidatively dehydrogenated using DDQ, to give the benzannulated cyclic hydrazines **296**, also in good yields. The researchers also found that the Boc-protecting group could be readily removed from **296** by using trifluoroacetic acid (yields: 50−75%).

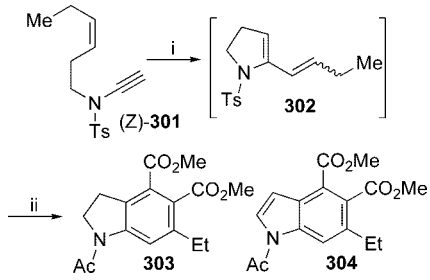
Benzannulated cyclic siloxanes have also been prepared by the application of an RCM−Diels-Alder−DDQ sequence by Dixneuf and co-workers.[171,172] These researchers synthesized dienes **297** from ene−ynes **298**, utilizing a catalytic system generated, in situ, from $[RuCl_2(p\text{-cymene})]_2$, 1,3-bis(mesityl)imidazolin-2-ylidene chloride ($MesH_2ImCl$), and $Cs_2CO_3$.[173,174] The resultant dienes **297** were then treated with the dienophile diethyl acetylene dicarboxylate to afford cyclohexadienes **299**, in mostly reasonable yields. Subsequent oxidation of compounds **299**, with DDQ in toluene at reflux, then afforded the benzo-fused siloxanes **300** (Scheme 65), which can presumably modified by chemical means to afford alternatively substituted aromatic compounds.

**Scheme 65**[a]



[a] Reagents and conditions: (i) $[RuCl_2(p\text{-cymene})]_2$, $MesH_2ImCl$ and $Cs_2CO_3$ (molar ratio 1:2:4) (2.5 mol %), toluene, 80 °C, 15−16 h, yields: $R^1$ = Me, $R^2$ = Ph (81%), $R^1$, $R^2$ = $-(CH_2)_5-$ (87%), $R^1$ = Me, $R^2$ = $CH_2CHMe_2$ (34%), $R^1 = R^2$ = Ph (70%); (ii) $EtO_2CC{\equiv}CCO_2Et$ (2 mol equiv), reflux, 5 h, yields: $R^1$ = Me, $R^2$ = Ph (79%, over 2 steps), $R^1$, $R^2$ = $-(CH_2)_5-$ (41%), $R^1$ = Me, $R^2$ = $CH_2CHMe_2$ (70% over 2 steps), $R^1 = R^2$ = Ph (61%); (iii) DDQ (3 mol equiv), toluene, reflux, 15 h, yields: $R^1$ = Me, $R^2$ = Ph (86%), $R^1$,$R^2$ = $-(CH_2)_5-$ (90%), $R^1$=Me, $R^2$ = $CH_2CHMe_2$ (80%), $R^1 = R^2$ = Ph (85%).

**Scheme 66**[a]



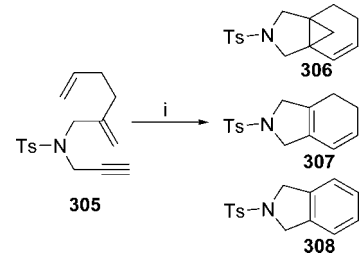
[a] Reagents and conditions: for example, (i) **2-Ru** (10 mol %), toluene, 80 °C, 15 min; (ii) (a) DMAD, toluene, 100 °C, 3 h, (b) DDQ, toluene, 80 °C, 20 h, **303** (20%), **304** (12%), over 3 steps.

### 3.2.3. Synthesis of Indoles and Isoindolines

Mori, Sato, and co-workers also briefly investigated the synthesis of indoles in a study dedicated to the synthesis of cyclic dienamides.[175] In this work, (*Z*)-**301** was synthesized in multiple steps and exposed to catalyst **2-Ru** for 15 min, presumably forming intermediate **302** by way of ene−yne metathesis (Scheme 66). This presumably was followed by an intramolecular cross-metathesis to effectively shift the ethyl group. DMAD was then added to the reaction mixture, and the reaction was heated to 100 °C for a further 3 h. DDQ was subsequently added and the reaction was stirred, while heating, for a further 20 h. Chromatography then resulted in the isolation of two compounds: the indoline **303** in 20% yield and the substituted indole **304** in a yield of only 12%. Unfortunately the authors of this work did not optimize this particular reaction or investigate the applicability of the ene−yne metathesis−Diels-Alder−aromatization sequence to other indole systems; however, they did provide tantalizing evidence that this methodology could be valuable for the synthesis of polysubstituted indoles.

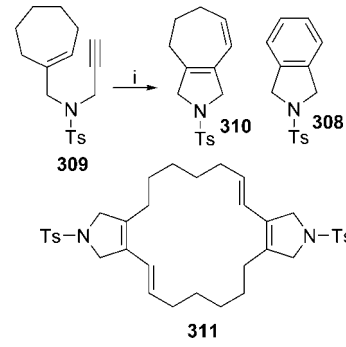
A catalytic tandem cyclopropenation−RCM process discovered by Peppers and Diver could also have potential for the synthesis of substituted aromatic rings.[176] When these researchers reacted diene−yne **305** with **2-Ru** or **4-Ru** in dichloromethane or benzene at reflux, they were able to isolate cyclopropyl **306**, diene **307**, and other minor byproducts which included "1 to 2% aromatization of **307**", i.e., presumably compound **308** (Scheme 67). This reaction could thus be an indication of an interesting possible route to isoindolines.

**Scheme 67**[a]



[a] Reagents and conditions: (i) **2-Ru** or **4-Ru** (5 mol %), $CH_2Cl_2$ or toluene, reflux or rt, 0.8−2.5 h, **306** (7−21%), **307** (74−76%), **308** ("1 to 2%").

**Scheme 68**[a]



[a] Reagents and conditions: (i) **2-Ru** (10 mol %), toluene, 80 °C, 21 h, **310** (36%), **311** (8%), **308** (6%).

Another ROM−RCM process investigated by Mori and co-workers also resulted in the isoindoline **308**, again in only low yield.[177] When cycloalkene−yne **309** was subjected to Grubbs second-generation catalyst **2-Ru**, the unsaturated 5,7-fused ring compound **310**, a dimeric compound **311**, and the isoindoline **308** were isolated in yields of 36%, 8%, and 6%, respectively (Scheme 68). Again, although compound **308** is only a side-product of this reaction, its presence could hint to interesting methodology for synthesizing isoindolines.

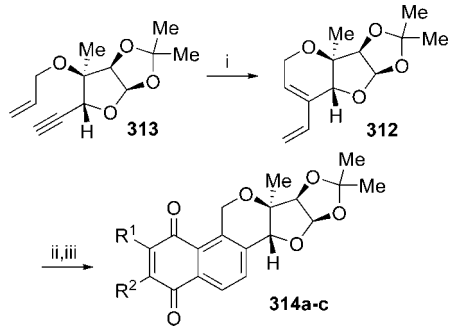
### 3.2.4. Synthesis of Substituted Naphthoquinones and Related Compounds

The ene−yne RCM−Diels-Alder approach has also been utilized to construct quinone-containing aromatic systems. Kaliappan and Ravikumar have used this approach to synthesize novel sugar−oxasteroid−quinone hybrids with the quinone portion being introduced by the strategy under discussion.[178] In the first step, the diene **312** was obtained from precursor **313** in good yield (Scheme 69). Three different 1,4-quinones were then added by way of a Diels−Alder reaction, to afford compounds **314a**−**c** in good yield after aromatization with triethylamine and silica gel (49−75% over two steps). In this manner, compounds **314a**, **314b**, and **314c** were synthesized by the reaction of diene **312** with 1,4-benzoquinone, 1,4-naphthoquinone, and 1,4-anthraquinone, respectively.

### 3.2.5. Synthesis of β-Lactams

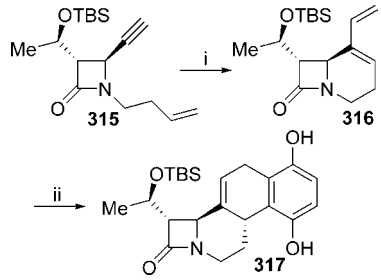
Another application of an ene−yne metathesis/Diels−Alder strategy was used by Genêt and co-workers to produce a small library of polycyclic β-lactams.[179] Starting from the ene−yne **315**, metathesis with **2-Ru** afforded the diene **316** in a good yield of 87% (Scheme 70). Subsequent cycload-

**Scheme 69**[a]



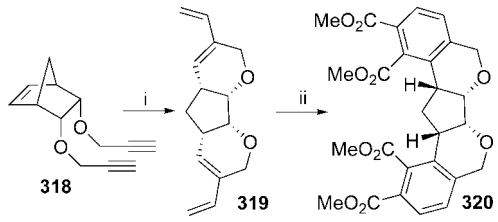

[a] Reagents and conditions: (i) **1-Ru** (12 mol %), $CH_2Cl_2$, reflux, 11 h (74%); (ii) 1,4-benzoquinone, 1,4-naphthoquinone or 1,4-anthraquinone, toluene, reflux, 12 h; (iii) $NEt_3$, silica gel, $CHCl_3$, rt, 1 h, yields over 2 steps, **314a** $R^1 = R^2 = H$ (49%), **314b** $R^1 = R^2 =$ fused benzene (75%), **314c** $R^1 = R^2 =$ fused naphthalene (65%).

**Scheme 70**[a]




[a] Reagents and conditions: (i) **1-Ru** (5 mol %), $CH_2Cl_2$, 50 °C, 22 h (87%); (ii) 1,4-benzoquinone (4 mol equiv), $CH_2Cl_2$, 80 °C, sealed tube, 20 h (90%).

**Scheme 71**[a]




[a] Reagents and conditions: (i) **1-Ru** (5 mol %), $CH_2Cl_2$, $CH_2{=}CH_2$, rt, 2−6 h (53%); (ii) DMAD; (iii) DDQ (56% over 2 steps).

dition of this compound with benzoquinone at 80 °C then afforded the desired cycloadduct **317**, once again in a good yield. According to the authors, this compound, along with other $\beta$-lactam cycloadducts, would be tested as potential antibiotics.

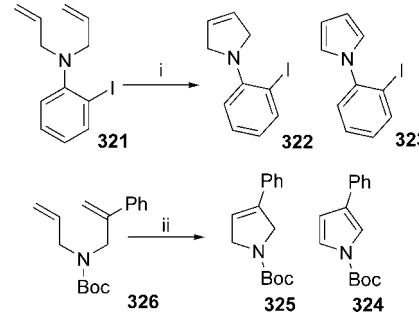
### 3.2.6. Synthesis of a Substituted Isochroman

A recent example by Banti and North describes a formal tandem ene ring-opening-ene−yne RCM strategy, starting from the substituted norbornene scaffold **318** to give the tetraene **319** in moderate yield (Scheme 71).[180] Treatment of this compound with DMAD, followed by DDQ oxidation, then gave the pentacycle **320** in hand, once again in acceptable yield for the formation of such a complex structure.

## 4. Synthesis of Aromatic Heterocycles by Metathesis−Aromatization

In this portion of the review, work involving the use of metathesis to form the heterocyclic ring of the aromatic compounds will be reviewed. It will be demonstrated that a range of heteroatom-containing aromatic compounds (including the heteroatoms N, O, and B−O or B−N) have been synthesized using the ene−ene and ene−yne metathesis strategies.

**Scheme 72**[a]




[a] Reagents and conditions: (i) **1-Ru** (2 mol %), THF, 65 °C, 12 h, **322** (93%), **323** ("some pyrrole formation is observed"); (ii) **1-Ru** (3 mol %), $CH_2Cl_2$, reflux, 24 h, **325** (25%), **324** ("major product", no yield given).

### 4.1. Ene−Ene RCM−Aromatization Strategies for the Synthesis of Aromatic Heterocycles

In this section, we will highlight how the synthesis of pyrroles, quinolines, indoles, and benzofurans, among other aromatic heterocycles, have been synthesized using RCM reactions.

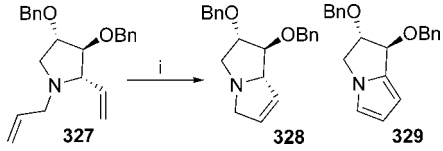
#### 4.1.1. Synthesis of Pyrroles

Reports of the unwanted formation of pyrroles as side-products during RCM reactions represent some of the first examples of heteroaromatic compounds being formed by RCM.[181,182] In 1999, Grigg and co-workers commented that, when compound **321** was treated with **1-Ru** at higher temperatures (65 °C), the desired 3-pyrroline **322**[183] was contaminated with the corresponding dehydrogenated pyrrole **323** (Scheme 72).[184] Shortly after this report, Gouverneur, Mioskowski, and co-workers described how they isolated pyrrole **324** as the major product when attempting to obtain the 3-pyrroline **325** from precursor **326** (Scheme 72).[185] It appears from the paper that the aromatization process occurred during chromatographic purification of **325**.

After these initial reports, a number of groups reported the inadvertent synthesis of pyrroles by a RCM−aromatization process. Examples include those described by Díaz-de-Villegas and Gálvez (RCM/catalytic dihydroxylation),[186] Rutjes (RCM/aromatization during purification),[187] and Liotta (see below).[188] Sletten and Liotta recently described how they had to alter their strategy in a synthesis of polyhydroxylated pyrrolizidines after the RCM of **327** failed to afford any **328** and only a small amount of pyrrole **329** was isolated (Scheme 73).[188]

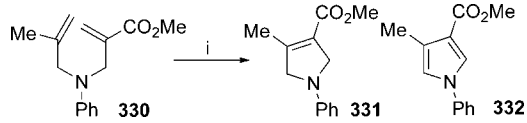
Among the first groups that purposely set out to make pyrroles from alkene precursors are those of Wilson,[189] Stevens,[190,191] Donohoe,[192] and Lamaty.[193] Wilson and co-workers claim to be the first group to use RCM to make pyrroles (although others had already noted the formation of pyrroles as undesired products). Wilson's group exposed substrates such as **330** to the Grubbs second-generation catalyst **2-Ru**, in the presence of microwaves, and found that not only **331** was formed but also a significant proportion of the pyrrole **332** was produced (Scheme 74).[189] In some

**Scheme 73**[a]



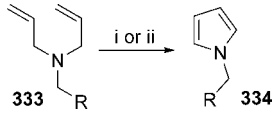

[a] Reagents and conditions: (i) **2-Ru** (5−10 mol %), toluene, 75 °C, 12 h, **328** (0%), **329** (40%); or (i) **2-Ru** (2 × 10 mol %), toluene, reflux, 2 h, **328** (0%), **329** (13%).

**Scheme 74**[a]




[a] Reagents and conditions: (i) **2-Ru** (12 mol %), $ClCH_2CH_2Cl$, 150 °C, pressure tube, microwave, 60−80 W, 60 psi, 5 min, **331** (16%), **332** (48%).

**Scheme 75**[a]




[a] Reagents and conditions: (i) **2-Ru** (2 × 5 mol %), $RuCl_3 \times H_2O$ (2 × 1 mol %), $ClCH_2CH_2Cl$ (0.05 M), 60 °C, 2 h + 10 h, ultrasonic bath, (conversion by $^1H$ NMR spectroscopy, yield after chromatography): R = Ph (74%, 55%), R = $CO_2Me$ (91%, 63%), R = $CH_2CN$ (44%, 30%), R = $P(O)(OEt)_2$ (71%, 60%); (ii) **2-Ru** (2 × 5 mol %), chloranil (2 × 0.75 mol equiv), $ClCH_2CH_2Cl$ (0.05 M), 70−75 °C, 1 h + 1 h, (only conversion by $^1H$ NMR spectroscopy listed, yields ∼20% lower after chromatography): R = Ph (quantitative), R = $CO_2Me$ (96%), R = $P(O)(OEt)_2$ (95%).

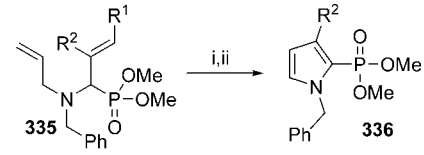
cases, the pyrrole was the only product isolated after chromatography.

Stevens and co-workers used a modified Grubbs catalyst, described as a Grubbs carbene−$RuCl_3$ catalytic system, for the synthesis of pyrroles.[190] It was shown, for example, that diene **333** could be converted into pyrrole **334** using this catalytic system (eight other successful examples are described in the paper). In addition, this pyrrole formation was greatly favored in the presence of 2% $RuCl_3 \times H_2O$, although reaction times were rather long and the yields were moderate (Scheme 75). An additional disadvantage was that that the methodology did not generally allow for the use of substituted alkenes. The researchers also noted that diallylamines with strong electron-withdrawing groups (EWGs) on the nitrogen atom (e.g., Ts, Boc, and Ac) did not aromatize under their conditions, presumably because the lone pair on the nitrogen is instrumental in initiating the aromatization by expelling the hydride from the dihydropyrrole.

Subsequent research by this group showed that the combination of **2-Ru** and chloranil as oxidant appeared to be the better method for the conversion of substituted diallylamines to pyrroles (addition of $RuCl_3 \times H_2O$ was not required), resulting in the formation of the desired compounds in much higher conversions.[191] In addition, the reaction now tolerated the use of substituted alkenes to give 3-alkyl-substituted pyrroles, although chloro-substituted alkenes were still not useful as substrates.

A further contribution to this area by the Stevens' group demonstrated the efficient synthesis of 2-phosphonopyrroles by way of a one-pot RCM−oxidation sequence.[194] The precursors **335** were first subjected to Grubbs second-generation catalyst **2-Ru**, followed by the addition of the

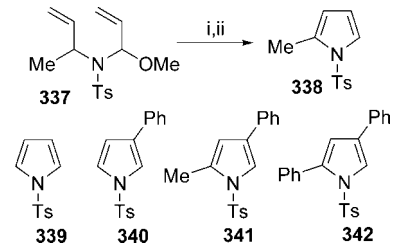
**Scheme 76**[a]




$R^1$=Me or Ph; $R^2$=H, Me, Bn, *i*-amyl, Ph or $CH_2CH_2Ph$

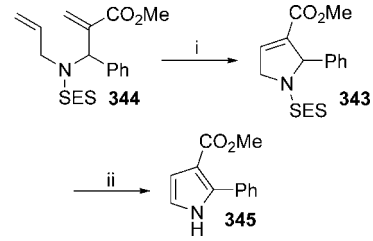
[a] Reagents and conditions: (i) **2-Ru** (5 mol %), chloranil (1 mol equiv), $CH_2Cl_2$, rt, 5−7 h (70−84%).

**Scheme 77**[a]




[a] Reagents and conditions: (i) **2-Ru** (10 mol %), $CH_2Cl_2$, reflux, then (ii) TFA (0.6 mol equiv) $CH_2Cl_2$, rt (**338** 61%, **339** 78%, **340** 74%, **341** 54%, **342** not formed, all yields over 2 steps).

**Scheme 78**[a]



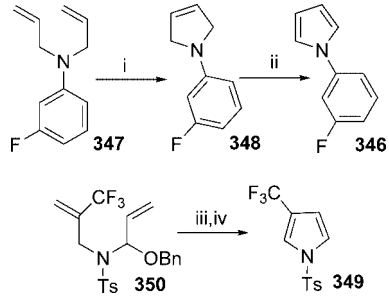

[a] Reagents and conditions: (i) **2-Ru** (5 mol %), $CH_2Cl_2$, rt, (98%); (ii) *t*-BuOK, DMF, rt, 2 h (80−83%).

oxidant chloranil in stoichiometric quantities, to afford a small set of 2-phosphonopyrroles **336** in good yields, over the two-step process (Scheme 76).

The Donohoe group took a different approach and prepared precursors such as **337** which contained methanol as a "built-in" leaving group. Treatment of these substrates with Grubbs second-generation catalyst **2-Ru**, followed by TFA, afforded pyrroles such as **338** in acceptable yields (Scheme 77). Both 2- and 3-substituted pyrroles could be prepared using this methodology, which included compounds **339**, **340**, and **341**.[192,195] The advantage of using methanol as a leaving group (instead of a hydride) becomes obvious as this methodology allows for the use of EWGs such as tosyl for the protection of the amine functionality. However, there were limitations of this methodology in that the sterically more encumbered pyrrole **342** was not formed by the Donohoe RCM−aromatization approach.[195]

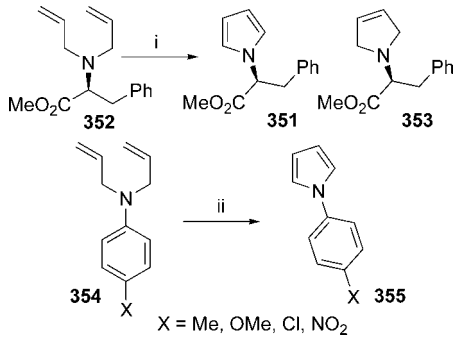
Researchers in the group of Lamaty chose to use the 2-trimethylsilylethylsulfonyl (SES) group[196] as the protecting group for nitrogen. An example of this work is depicted in Scheme 78 in which the initially formed pyrroline product **343** was synthesized from the precursor **344**. This compound was then treated with potassium *t*-butoxide to readily afford the substituted pyrrole **345** with the concomitant release of the SES protecting group.[193,197] The researchers were satisfyingly able to synthesize a number of other substituted pyrroles in this manner, all with differently substituted phenyl groups.

**Scheme 79**[a]




[a] Reagents and conditions: (i) **1-Ru** (5 mol %), $C_6H_6$ or toluene, 60 °C (74−79%); (ii) Pd/C, decalin (89%); (iii) **2-Ru** (7 mol %), toluene, 100 °C, 1.5 h; then (iv) TFA, rt, 30 min (80% over 2 steps).

**Scheme 80**[a]




[a] Reagents and conditions: (i) **2-Ru** (5 mol %), $CH_2Cl_2$ (0.1 M), 150 °C, microwave, 10 min (**351** 57% and **352** 40%); (ii) **1-Ru** (2−5 mol %), $CH_2Cl_2$ (0.1 M), 100 °C, microwave, 10 min (89−98%).

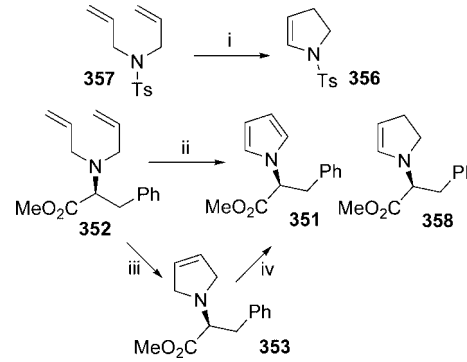
Sánchez and Pujol used a different aromatization methodology to afford (3-fluorophenyl)pyrrole **346**.[198] The tertiary amine **347** readily cyclized to afford the 3-pyrroline **348**, which was facilely dehydrogenated to pyrrole **346** with palladium on carbon as the reagent of choice (Scheme 79).

Rutjes and co-workers were also able to synthesize a trifluoromethyl-substituted pyrrole **349** in good yield by the treatment of bisalkene **350** with the second-generation Grubbs catalyst **2-Ru** (Scheme 79),[199] followed by aromatization with TFA in a similar fashion to that reported by Donohoe.[192,195]

Xiao and co-workers have published an approach to the synthesis of *N*-substituted pyrroles such as **351** by the microwave-assisted RCM of diallylamines exemplified by compound **352**.[200] The chiral substrates like **352** were generated from L-amino acids, and the metathesis reactions with **2-Ru** generally resulted in a mixture of pyrrole and 3-pyrroline, **351** and **353**, respectively (Scheme 80). When the RCM reactions were performed on a group of phenyl-substituted diallylamines **354**, in which the nitrogen is less basic, the corresponding pyrroles **355** were isolated as the sole product in excellent yields, even when using the less active catalyst **1-Ru**.

Xiao and Yu also reported a single example where ring-closing metathesis was performed on the HCl salt of compound **352**, resulting exclusively in the isolation of the corresponding pyrrole **351** (73% over two steps) after neutralization of the salt with NaOH.[201] In this same paper, they also disclosed how treatment of the diallylamine precursors with the metathesis catalyst in the presence of a catalytic quantity of Lewis acid (normally titanium isopropoxide) resulted in exclusive formation of the pyrrolines. This example again highlights the importance of a basic nitrogen atom in the formation of the pyrroles, rather than the pyrrolines.

**Scheme 81**[a]



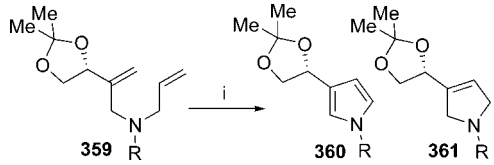

[a] Reagents and conditions: (i) **2-Ru** (5 or 10 mol %), $CH_2Cl_2$ (0.02 M), reflux, 5−6 h (65%, 73% in Supplementary Information); (ii) **2-Ru** (10 mol %), Ti(O-*i*-Pr)$_4$, toluene (0.02 M), reflux, 3 h, **351** (56%), **358** (0%); (iii) see ref 201; (iv) **2-Ru** (10 mol %), Ti(O-*i*-Pr)$_4$, toluene (0.02 M), reflux, 3 h, (only **351** formed, no yield given).

Fustero and co-workers also confirmed the importance of the nature of the protecting group on nitrogen by their investigation of a tandem RCM−olefin isomerization strategy that included the synthesis of 2-pyrrolines such as **356**, from diallyl compound **357** with an electron-withdrawing tosyl group on the nitrogen (Scheme 81).[202] However, their methodology failed to afford any of the 2-pyrroline **358** when using **352** as the substrate; instead, only the aromatic pyrrole **351** was obtained. Of note was that these researchers used titanium isopropoxide to minimize complexation between the amine and the catalyst during the RCM reaction in order to try to access **358**. Compound **353** was subsequently also synthesized using the Xiao approach;[201] however, treatment of this compound with the same conditions [**2-Ru**, Ti(O-*i*-Pr)$_4$] did not afford the desired isomerized enamine **358**, as only the pyrrole **351** was isolated in an unspecified yield. The researchers postulated that the protecting groups were playing an important role in the formation of the different products, with electron-withdrawing groups preventing the dehydrogenation step from taking place to afford the aromatic pyrrole from precursor **357** while the activated amine in **352** (Scheme 81) and **354** (Scheme 80) resulted in facile aromatization.

Another example that elegantly demonstrates the importance of the *N*-protecting group in the product distribution between pyrroles and 3-pyrrolines was published by Thomas and co-workers.[203] When these workers subjected the benzyl-protected diallyl precursor **359** to catalytic amounts of **2-Ru**, only the aromatized pyrrole **360** was ever isolated, even when the reaction conditions were moderated. However, when a similar precursor was used, this time with a Boc-protecting group, the results were reversed and 3-pyrroline **361** was obtained in quantitative yield (Scheme 82). This would again seem to indicate that electron-withdrawing groups on the amine hinder the alkene isomerization and dehydrogenation processes, which would result in the formation of the aromatic pyrroles. However, it should be noted that an example describing the formation of a mixture of *N*-Boc-protected pyrrole and 3-pyrroline has been reported.[185]

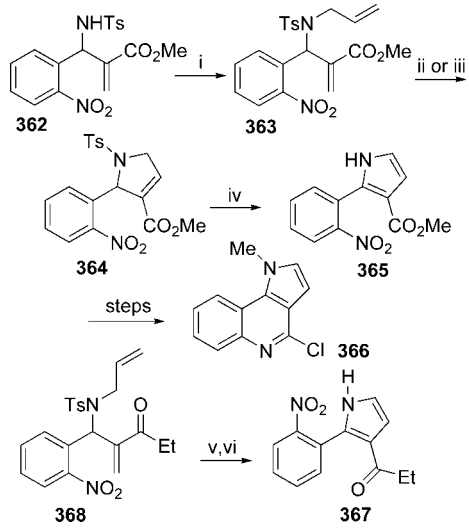
Lamaty and co-workers utilized a microwave-promoted metathesis reaction, followed by an aromatization step to synthesize an important intermediate in their synthesis of a

**Scheme 82**[a]



[a] Reagents and conditions: (i) for R = Bn, **2-Ru** (1 mol %), toluene or $CH_2Cl_2$, **360** (quantitative), **361** (0%); for R = Boc, **2-Ru** (1 mol %), $CH_2Cl_2$, 36 h, **360** (0%), **361** (quantitative) or **2-Ru** (1 mol %), $CH_2Cl_2$, microwave, 20 min, 100 °C, **360** (0%), **361** (quantitative).

**Scheme 83**[a]

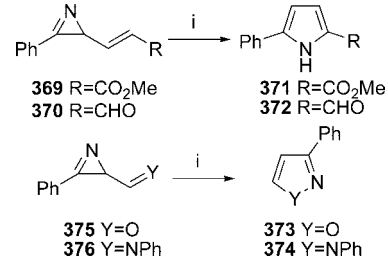


[a] Reagents and conditions: (i) allyl bromide, $K_2CO_3$, DMF (98%); (ii) **2-Ru** (14 mol %), $CH_2Cl_2$, rt, overnight, then DMSO, rt, overnight (87%); (iii) **2-Ru** (4 mol %), $CH_2Cl_2$, microwave, 150 °C, 2 h, then DMSO, rt, 24 h (82%); (iv) *t*-BuOK, DMF, rt, 2 h (89%); (v) **2-Ru** (5 mol %), $CH_2Cl_2$, rt, 12 h (86%); (vi) *t*-BuOK, DMF, 0 °C, 2.5 h (47%).

number of novel pyrrolo-[3,2-*c*]quinolines.[204] Scheme 83 shows how nitro compound **362**, itself generated by a 3-component aza-Baylis−Hillman reaction, was alkylated with allyl bromide to afford the diene **363**. This compound readily underwent a RCM reaction with 4% of catalyst **2-Ru**, under microwave radiation, to afford pyrroline **364** in good yield (82%). A point of interest was that the nitro group seemed to have a deleterious effect on the rate of the metathesis reaction, possibly by coordinating with the ruthenium catalyst. An elimination−aromatization event, mediated by the base *t*-BuOK, then afforded the substituted pyrrole **365**, in which the tosyl group had been removed. Further synthetic manipulation of this compound then afforded the desired pyrrolo-[3,2-*c*]quinoline **366**. Lamaty also utilized similar methodology to synthesize ketopyrrole **367** from the diene **368**.[205]

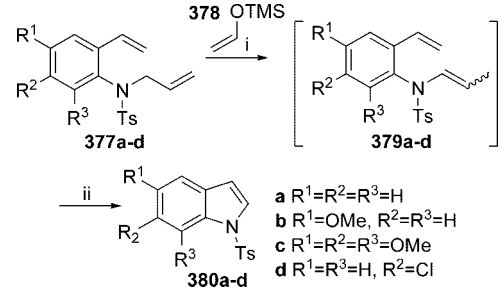
Finally, for completeness, Padwa and Strengel published details of a novel pyrrole synthesis using Grubbs catalyst **1-Ru**, albeit not by a metathetic pathway (Scheme 84).[206] In this work, 2-phenyl-3-vinyl substituted 2*H*-azirines, such as examples **369** and **370**, were treated with catalyst **1-Ru**, resulting in the formation of the substituted pyrroles **371** and **372**, respectively, both in good yield. In addition, the same strategy afforded the 3-phenylisoxazole **373** and the 1,3-diphenylpyrazole **374** from 2*H*-azirines **375** and **376**, respectively.

**Scheme 84**[a]



[a] Reagents and conditions: (i) **1-Ru** (5 mol %), $CH_2Cl_2$, 25 °C, 2−3 h (**371** quantitative, **372** 90%, **373** 90%, **374** 89%).

**Scheme 85**[a]



[a] Reagents and conditions: (i) **378** (10 mol equiv), **2-Ru** (5 mol %), $CH_2Cl_2$, 50 °C, 1.5 h; (ii) for **380a**, **2-Ru** (5 mol %), $C_6H_6$, 80 °C, 1 h (94%), for **380b**, **2-Ru** (5 mol %), $C_6H_6$, 80 °C, 3 h (quantitative), for **380c**, **2-Ru** (5 mol %), toluene, 110 °C, 17 h (83%), for **380d**, **2-Ru** (5 mol %), toluene, 110 °C, 13 h (79%), all yields over 2 steps.

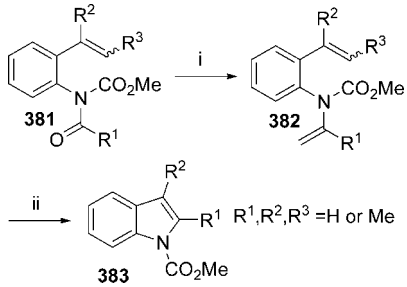
### 4.1.2. Synthesis of Indoles

The synthesis of the indole nucleus has also been innovatively achieved using RCM by Nishida and co-workers.[207] Over two steps, four potential indole precursors **377a−d** (out of 12 examples described in the paper) were treated with Grubbs second-generation catalyst **2-Ru**, together with silyl enol ether **378** (Scheme 85).[208,209] The addition of **378** generated, in situ, a catalyst that promoted the isomerization of allylamines **377a−d** to enamines **379a−d**, faster than the competing RCM reaction.[15,210−224] These compounds were then reacted under standard RCM conditions, using Grubbs catalyst **2-Ru** at 80 °C in benzene, to give the expected indoles **380a−d** in good yields over the two steps. The researchers also demonstrated that substituents *ortho* to the vinyl group led to reduced yields. In addition, they were also able to show that a number of other protecting groups on the nitrogen atom were conducive to the metathetic cyclization procedure (viz. Ac, Bzm, Boc, Cbz, and Ms). This group has also published related papers concerning the synthesis of indolines and a 3-hydroxyindole example by way of a **2-Ru**-mediated cycloisomerization.[208,209,225]

Bennasar and co-workers also applied a metathesis−RCM strategy for the formation of indoles.[226] Their novel approach involved a Tebbe olefination[227] of the amide-protected compounds **381** to afford the dienes **382** (Scheme 86). Application of the catalyst **2-Ru** then afforded the indoles **383** in moderate-to-excellent yields.

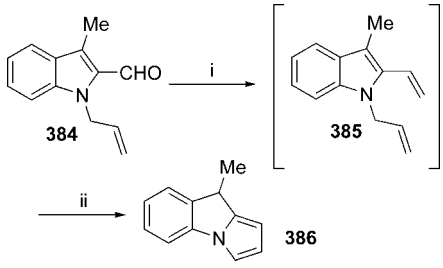
Preformed indoles have also been used as substrates to make systems with additional rings by the Pérez-Castells group.[228] In this particular work, indole aldehyde **384** was converted in situ into an allylvinylindole **385**, and subjecting this compound to the Grubbs first-generation catalyst **1-Ru** then gave the corresponding 9*H*-pyrrolo[1,2-*a*]indole **386** in an acceptable yield, as shown in Scheme 87.

**Scheme 86**[a]



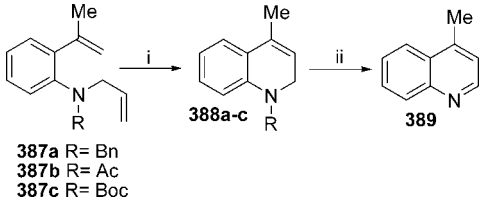

[a] Reagents and conditions: (i) $Cp_2TiMe$ (1.5 mol equiv), toluene−pyridine (100:1), reflux, 4 h (25−61%); (ii) **2-Ru** (6 mol %), toluene, 80 °C or reflux, 4 h (40−90%, some over 2 steps).

**Scheme 87**[a]




[a] Reagents and conditions: (i) $MePPh_3Br$, KHMDS, Ar, rt, 30 min; (ii) **1-Ru** (5 mol %), $CH_2Cl_2$, rt, overnight (65% over 2 steps).

**Scheme 88**[a]



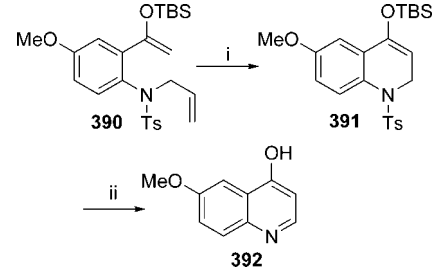

[a] Reagents and conditions: (i) for **387a** (a) **1-Ru** (5 mol %), $CH_2Cl_2$, reflux, 1 h (99%), for **387b 1-Ru** (5 mol %), $CH_2Cl_2$, reflux, 1 h (0%), or **2-Ru** (5 mol %), $CH_2Cl_2$, reflux, 1 h (98%), for **387c 1-Ru** (5 mol %), $CH_2Cl_2$, reflux, 1 h (63%), or **2-Ru** (5 mol %), $CH_2Cl_2$, reflux, 1 h (97%); (ii) $SiO_2$, air (quantitative).

### 4.1.3. Synthesis of Quinolines

The ideas outlined by Nishida and Nakagawa for the synthesis of indoles have been extended to include the synthesis of quinolines.[229−231] In this particular body of work, a large number of quinolines were synthesized of which only a few representative examples are shown in Scheme 88. Substrates **387a−c** were treated with the ruthenium-based metathesis catalysts to afford the protected dihydoquinolines **388a−c** in good yield. In general it was found that the Grubbs first-generation catalyst **1-Ru** was not as versatile or high yielding as the second-generation catalyst **2-Ru**. Once the dihydroqinolines **388a−c** had formed, all three protecting groups were removed during silica gel chromatography and spontaneous oxidization to give the desired quinoline **389** in quantitative yield. Nishida and Nakagawa extended this approach to also synthesize the substituted quinoline portions of quinine and chloroquine, among others.[230]

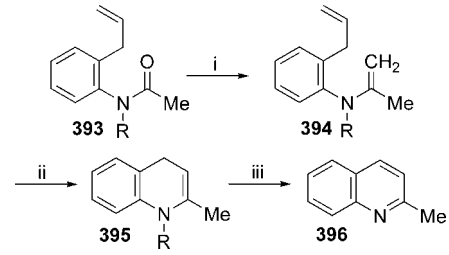
Sánchez and Pujol synthesized quinoline in a very similar manner, with the difference being that the aromatization to the quinoline was facilitated by palladium on carbon at 220 °C (in decalin).[198] This, and the previous example, thus demonstrate that the synthesis of substituted quinolines is thus feasible using a RCM−aromatization strategy.

**Scheme 89**[a]




[a] Reagents and conditions: (i) **2-Ru** (5 mol %), $CH_2Cl_2$, reflux, 1 h (98%); (ii) NaOH, MeOH, reflux, 18 h (98%).

**Scheme 90**[a]




[a] Reagents and conditions: (i) $Cp_2TiMe_2$ (1.5 mol equiv), toluene−pyridine (100:1), reflux, 4 h, R = Boc (55%), R = $CO_2Me$ (51%); (ii) **2-Ru** (6 mol %), toluene (0.1 M), 80 °C, 4 h, R = Boc (75%), R = $CO_2Me$ (75%); (iii) Pd/C (5 mol %), $O_2$, THF, reflux, 6 h (80%).

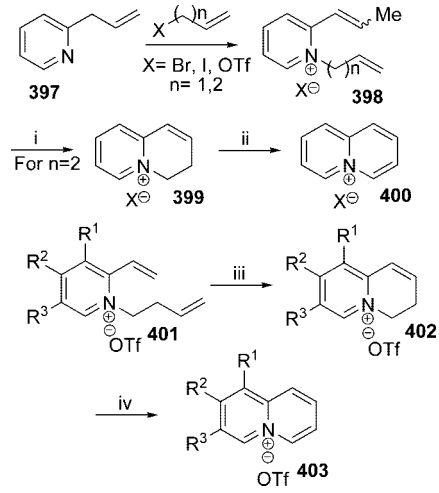
Arisawa et al. have also demonstrated that ene−enol metathesis reactions could be performed on compounds such as **390**, as exposure of bisalkene **390** to Grubbs second-generation catalyst **2-Ru** gave an excellent yield of **391**. This compound was subsequently treated with NaOH in methanol to furnish the substituted quinolin-4-ol **392** (Scheme 89) in a yield of 98%.[229,231]

Bennasar and co-workers also generated a small set of quinolines by using RCM as the key step.[232] Initial Petasis olefination of the amides **393** to afford compounds **394**, followed by RCM reaction, generated the 1,4-dihydroisoquinolines **395** in acceptable yields (Scheme 90). These compounds were then facilely oxidized to the corresponding quinoline **396** using palladium on carbon, under an oxygen atmosphere. This research group also successfully synthesized quinoline by using the formanilide instead of the acetanilide **393**. It was also noted that the application of excess dimethyltitanocene in the olefination step did not result in a metathetic ring-closure as described by others;[227] unfortunately only complex reaction mixtures were obtained.

### 4.1.4. Synthesis of Quinolizinium Cations and Related Compounds

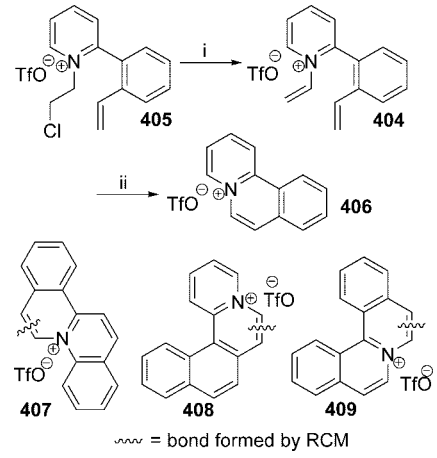
A novel approach to the synthesis of quinolizinium cations, which involved a RCM reaction on a cationic substrate, was developed by Cuadro, Vaquero, and co-workers.[233] In their initial approach, when 2-allylpyridine **397** was propenylated with allyl iodide or bromide, they were surprised to obtain the vinyl isomer **398**, due to double-bond migration under the reaction conditions (Scheme 91). This isomerization also occurred when the reaction was performed with allyl- and homoallyltriflates. Fortunately, compound **398** ($n = 2$) readily underwent RCM with 10% **1-Ru** to afford the dihydroquino-

**Scheme 91**[a]




[a] Reagents and conditions: (i) **1-Ru** (10 mol %), $CH_2Cl_2$, rt, 23 h (55%); (ii) Pd/C, $MeCO_2H$ (80−90%, individual yields not stated in paper); (iii) **2-Ru** (5 mol %) or **1-Ru** (2 mol %), $CH_2Cl_2$, rt, (a) $R^1 = R^2 = R^3 = H$ (83%), (b) $R^1 = R^2 = H$, $R^3 = Br$ (80%), (c) $R^1 = Br$, $R^2 = R^3 = H$ (80%), (d) $R^1 = R^2 = H$, $R^3 = Me$ (82%), (e) $R^1 = -N(CH_2CH_2)_2O$, $R^2 = R^3 = H$ (85%), (f) $R^1$=H, $R^2$,$R^3$ = fused benzene ring (75%); (iv) Pd/C, $MeCO_2H$ (80−90%).

**Scheme 92**[a]

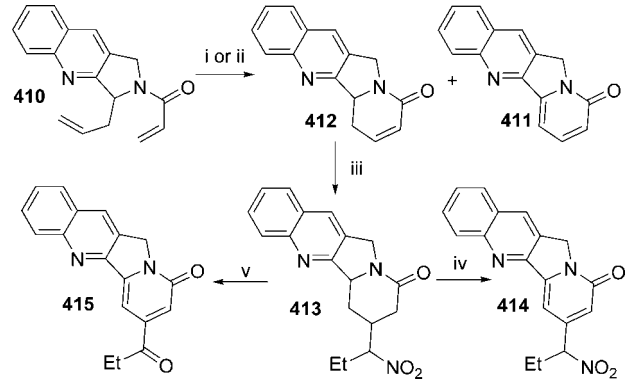



[a] Reagents and conditions: (i) NaOH (10 N), EtOH/MeOH, −10 °C (92%); (ii) **4-Ru** (5 mol %), $ClCH_2CH_2Cl$, 83 °C, 2.5 h (83%).

lizium product **399**, which was readily converted into the corresponding quinolizinium salt **400**. The researchers then modified their original approach to utilize the reaction of substituted 2-vinylpyridines with 3-butenyltriflate to afford the pyridinium intermediates **401**, among other substrates. These compounds then readily underwent RCM with **2-Ru** to afford products **402**, respectively; these compounds were then treated with palladium on carbon to afford the corresponding aromatic quinolizium salts **403** in high yield (80−90%).

This research group also extended their work to the utilization of *N*-vinylpyridinium salts and related compounds for the formation of aromatic heterocycles.[234] An example is shown in Scheme 92, in which the bisalkene **404** was generated by a base-induced elimination from the triflate salt **405**. The RCM reaction on compound **404** efficiently afforded the benzo[*a*]quinolizinium triflate **406** in a good yield of 83%. A number of other compounds were synthesized by this methodology, including **407**−**409**, with the bond

**Scheme 93**[a]




[a] Reagents and conditions: (i) **1-Ru** (10 mol %), $C_6H_6$, reflux, 26 h, **412** (∼50%), **411** (∼30%); (ii) **1-Ru** (10 mol %), Ti(O*i*-Pr)$_4$, $CH_2Cl_2$, reflux, 16−20 h, **412** (89%), **411** (0%); (iii) nitropropane, DBU, rt, 16 h (86%); (iv) DDQ, dioxane, reflux, 5 h (25%); (v) NaOH, MeOH, rt, 3 h, then HCl (conc), 0 °C, 1 h and rt, 12 h (23%).

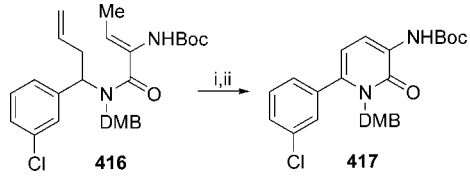
of disconnection shown in Scheme 92. Of interest is that the Hoveyda−Grubbs catalyst **4-Ru** was used in preference to **1-Ru** and **2-Ru** because it gave significantly higher yields under a higher temperature regime (83% yield as compared to 25−58% under various reaction temperatures). It is also worthwhile to note that there was another synthetic approach to this class of compounds attempted by these authors that utilized ene−yne metathesis.[235] This work resulted in the versatile syntheses of 1- and 2-vinyl substituted 3,4-dihydroquinolizinium salts but ultimately did not result in any additional heteroaromatic cations related to compounds **400**, **403** (Scheme 91), or **406**−**409** (Scheme 92).

### *4.1.5. Synthesis of Pyridones and Pyridines*

The addition of aromatic rings, in particular pyridone rings, to the quinoline-based nucleus of **410** using RCM has also been achieved by Chavan and co-workers, although this was an undesired outcome resulting in product **411** (∼30% by NMR).[236] The major product required by these researchers was the dihydropyridone **412**, which was obtained in ∼50% yield (Scheme 93). When the researchers added titanium isopropoxide during the RCM reaction, only the desired dihydropyridone **412** was isolated in an excellent yield of 89%. A conjugated addition of nitropropane, mediated by DBU, then afforded compound **413**, which readily underwent aromatization to afford pyridone **414** in poor yield. An unoptimized Nef reaction also afforded pyridone **415** in low yield, in which the conversion to the carbonyl group and aromatization had occurred simultaneously. The ketone functionality in **415** was then reduced to the corresponding alcohol (not shown), which completed a formal synthesis of the well-known anticancer agent camptothecin.

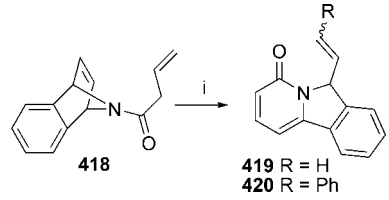
Nan and co-workers[237] have used a RCM−oxidative aromatization approach to assemble a library of 3-amino-2-pyridones. One example (**416** → **417**) is shown in Scheme 94. Their methodology involved a one-pot, two-step procedure in which the RCM reaction of **416** with **2-Ru** was followed by the addition of DDQ to afford the pyridone **417**. The yields for this approach, on a number of substrates, varied between 51−84% over the two steps. During the course of this work, it was found that the 2,4-dimethoxybenzyl (DMB)-protecting group was necessary to obtain the best results; the RCM reaction on the free acrylic amide proved fruitless under a number of different metathetic

**Scheme 94**[a]



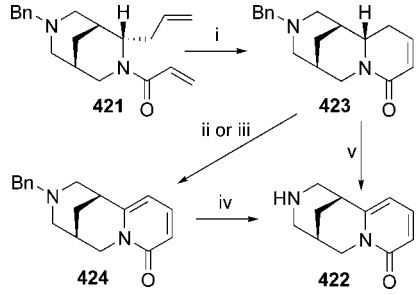

[a] Reagents and conditions: (i) **2-Ru** (10 mol %), $CH_2Cl_2$, rt, 12−36 h; (ii) DDQ, $CH_2Cl_2$, rt (52% over 2 steps).

**Scheme 95**[a]




[a] Reagents and conditions: (i) **2-Ru** (10 mol %), $CH_2Cl_2$, $CH_2{=}CH_2$, rt, 12 h, **419** (25%), (*E*/*Z*)-**420** (10%).

**Scheme 96**[a]



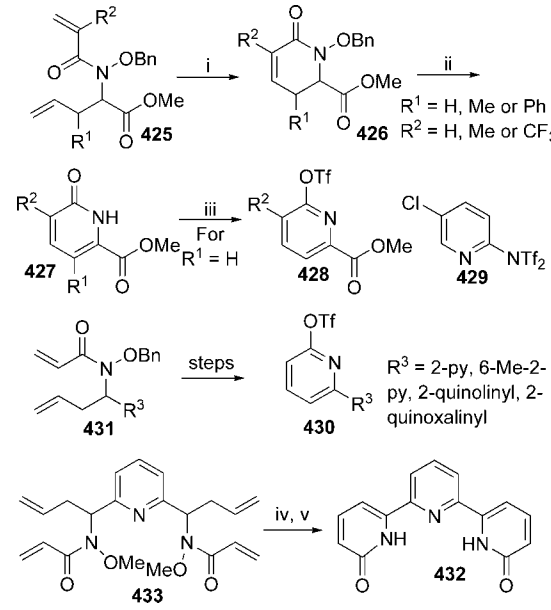

[a] Reagents and conditions: (i) **1-Ru** (10 mol %), toluene, reflux, 15 min (89%); (ii) $MnO_2$ (2 mol equiv), $C_6H_6$, reflux, 3 h (6%); (iii) Pd/C (10 mol %), 1,4-dioxane−cyclohexene (3:1), 100 °C, 8 h (41%); (iv) Pd/C;[241] (v) Pd/C (10 mol %), toluene−cyclohexene (2:1), 100 °C, 12 h (76%).

reaction conditions. The reaction did tolerate substitution α to the *N*-DMB group, including aromatic, aliphatic, and styrene groups, and yields for the pyridones obtained were generally good over the RCM and oxidation steps (51−84%).

Maison and co-workers have encountered the synthesis of a substituted pyridone in an interesting ROM−RCM sequence involving the desymmetrization of 7-azabicycloalkene **418**. When this compound was subjected to the catalyst **2-Ru** under ethylene gas, the pyridones **419** and **420** were unexpectedly obtained in low yield (Scheme 95).[238,239] The formation of compound **420** was presumably due to a subsequent cross-metathesis of **419** with the styrene liberated by the original catalyst.

Diene **421** was utilized by O'Brien and co-workers as a key intermediate in the synthesis of the naturally occurring lupin alkaloid (±)-cytisine **422**.[240] The diene **421** was treated with the Grubbs first-generation catalyst **1-Ru** to afford the desired dihydropyridone **423** in a yield of 89% after just 15 min (Scheme 96). This compound was then converted into the natural product **422** by two routes. The first approach utilized a two-step process involving an oxidative aromatization, followed by a debenzylation via **424**. Unfortunately, the aromatization step proved to be challenging with standard procedures; oxidation with DDQ proved untenable, and the use of $MnO_2$ or Pd/C in a 1,4-dioxane−cyclohexene solution suffered from very low yields (6% and 41% for each oxidant, respectively). However, modification of the second method

**Scheme 97**[a]



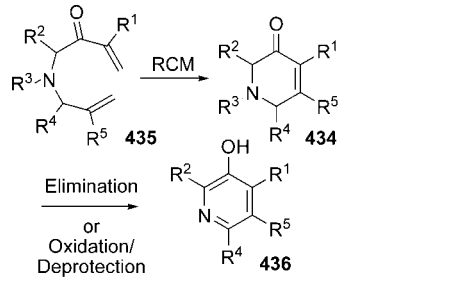

[a] Reagents and conditions: (i) **4-Ru** (5−10 mol %), $CH_2Cl_2$, reflux, or toluene, 95°C (59−97%); (ii) DBU, THF, 50 °C, (65−94%); (iii) **429**, KHMDS, THF, −78 °C (67−94%); (iv) **4-Ru** (10 mol %), $CH_2Cl_2$, reflux (quantitative); (v) DBU, THF, 50 °C (56%).

with Pd/C to utilize a toluene−cyclohexene solvent system gave the aromatized pyridine **422**, with concomitant debenzylation in an excellent yield of 76% over both steps. The authors note in their paper that it seems likely that in this process the cyclohexene acts first as a hydrogen donor and then as a hydrogen acceptor.

The efficient synthesis of 2-pyridones and related pyridines has recently been described by Donohoe and co-workers.[242,243] These researchers found that the use of the Hoveyda−Grubbs catalyst **4-Ru** gave optimal results when converting dienes **425** into dihydropyridones **426** (Scheme 97). DBU was then found to be the base of choice for aromatization of these substrates into their corresponding 2-pyridones **427** in good yields (>50%). The pyridones were also readily transformed into the substituted pyridines **428** by utilizing the reagent **429**. The advantage of having the *O*-triflate group is obvious, seeing that a number of cross-coupling techniques have been developed that can utilize this coupling partner. A series of substituted pyridines **430** were also readily accessed using the RCM−aromatization−triflation methodology from precursor **431**. Of interest was that, when $R^3$ was a phenyl group, this approach did not work. Finally, to demonstrate the scope of this approach, dipyridone **432** was synthesized from precursor **433** using a double RCM, followed by a base-induced aromatization strategy, to afford 6,6′-(pyridine-2,6-diyl)dipyridin-2(1*H*)-one **432** in a reasonable yield.

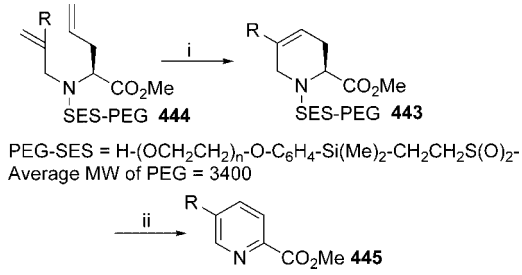
Yoshida et al. applied a strategy previously used for the synthesis of substituted phenols (see section 2.2.1) to afford 3-hydroxypyridines.[244] In this work, 1,6-dihydro-2*H*-pyridin-3-ones **434** were synthesized from the corresponding dienes **435** using the Grubbs second-generation catalyst **2-Ru**. Compounds **434** were then converted to the desired substituted pyridines **436** by the application of two different strategies, which depended on the protecting group used on the nitrogen atom: an elimination process (for example, **437** → **438** → **439**), or an oxidation process followed by a *N*-deprotection (for example, **440** → **441** → **442**). Two examples of this methodology are shown in Scheme 98

**Scheme 98**[a]




[a] Reagents and conditions: (i) **2-Ru** (7.5 mol %), toluene, 60 °C, 20 min (89%); (ii) DBU (2 mol equiv), DMF, rt, 1 h (74%); (iii) **2-Ru** (7.5 mol %), toluene, 60 °C, 20 min (83%); (iv) (a) DDQ (1.2 mol equiv), dioxane, (b) Pd/C, $H_2$, MeOH, rt, 4 h (81% over 2 steps).

**Scheme 99**[a]

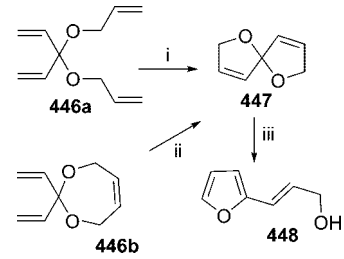



[a] Reagents and conditions: (i) **1-Ru** (10 mol %), $CH_2Cl_2$, rt, 16 h, R = H (86%) or R = $CO_2Me$ (93%), R = Me (94%); (ii) CsF, DMF, 110 °C, overnight R = H (57%) or R = $CO_2Me$ (76%).

giving the desired substituted pyridines in good overall yields. The researchers were also able to synthesize a 3-aminopyridone (not shown) by converting the ketone functionality in **434** into an oxime prior to the oxidation−deprotection step.

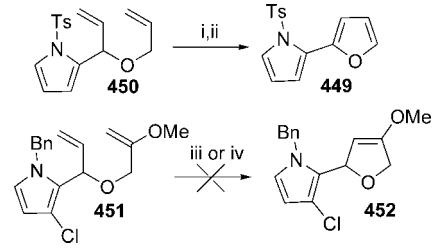
Finally, substituted pyridines were also readily synthesized from acyclic dienes by Lamaty and co-workers, although admittedly this was not the initial goal of their research.[245] These researchers utilized a poly(ethylene glycol) (PEG)-supported tether, linked to a modified 2-(trimethylsilyl)ethylsulfonyl (SES) group, in their synthesis of cyclic α-amino acids. For example, didehydropipecolic esters **443** were readily afforded by the application of catalyst **1-Ru** on diene substrates **444** (Scheme 99). However, most conventional fluoride anion-based deprotection strategies resulted in the formation of substituted pyridines, i.e., the formation of pyridines **445** readily occurred because the fluoride source was basic enough to abstract the acidic proton of the amino ester, thereby promoting the aromatization process. Fortunately, the authors found that acidic cleavage (6 N HCl) of the SES−PEG group was successful in affording the desired didehydropipecolic esters.

**Scheme 100**[a]




[a] Reagents and conditions: (i) **1-Ru** (5 mol %), $CH_2Cl_2$ (0.1 M), 25 °C, 6 h (90%); (ii) **1-Ru** (15 mol %), $CH_2Cl_2$ (0.1 M), 40 °C, 36 h (50%); (iii) TsOH (cat.), rt, 1 h (no yield given in paper).

**Scheme 101**[a]




[a] Reagents and conditions: (i) **1-Ru** (3 mol %), $C_6H_6$, rt, 4 h (88%); (ii) $NiO_2$ (40 equiv), cyclohexane, reflux, 5 d, 8%; (iii) **1-Ru** (20 mol %), $CH_2Cl_2$, only starting material; (iv) 3-Mo (20−100 mol %), hexane, decomposition.

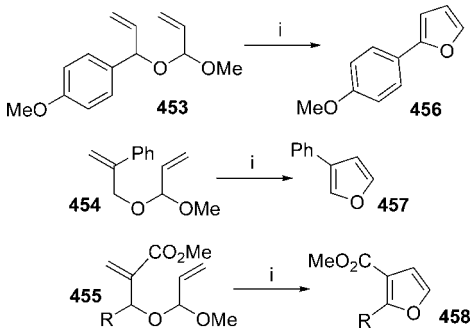
### 4.1.6. Synthesis of Furans

Furans are heteroaromatic skeletons often encountered in natural products and have been routinely utilized in organic synthesis.[246,247] It should therefore come as no surprise that these structures have also been synthesized using a metathesis−aromatization strategy. To the best of our knowledge, the first reported synthesis of a furan using a RCM−aromatization approach was by Harrity and co-workers.[248] These researchers reported that the treatment of tetraene **446a** or triene **446b** with Grubbs first-generation catalyst **1-Ru** afforded the spirocyclic acetal **447** in excellent and moderate yields, respectively (Scheme 100). Subsequent treatment of the [4,4]-spirocycle **447** with a catalytic amount of TsOH then gave 2-substituted furan **448**, although no details concerning the yield of the reaction are provided in the communication.

Another early contribution describing the application of RCM−aromatization to the synthesis of furans was by Robertson et al. in their pursuit of the pyrrolofuran portion of roseophilin.[249] These researchers described the synthesis of the model furan **449** from diene **450**, by the use of catalyst **1-Ru**, followed by oxidation with excess nickel(II) oxide (Scheme 101). It was mentioned that the RCM occurred in good yield (88%), but that recovery of the product after oxidation was difficult due to the excess of oxidant used (40 equiv). However, when the same approach was attempted on the fully substituted system **451**, required for the roseophilin synthesis, the first-generation **1-Ru** was unable to induce metathesis to yield **452**. In addition, application of the Schrock catalyst **3-Mo** only resulted in decomposition of the starting material. Of interest would have been to use the Grubbs second-generation catalyst (**2-Ru**) for this substrate, but this was not attempted in the study.

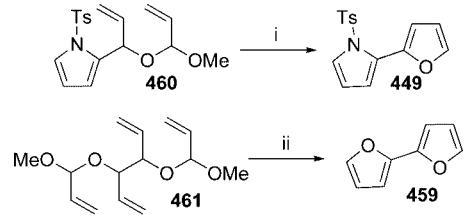
Another report describing the synthesis of substituted furans was published by Donohoe and co-workers, in which

**Scheme 102**[a]




[a] Reagents and conditions: (i) **1-Ru** (10 mol %), $CH_2Cl_2$, reflux, then TFA, **456** (79%), **457** (70%), **458** R = Me (79%), R = *m*-$MeC_6H_4$ (70%), R = *m*-$CF_3C_6H_4$ (59%), R = *p*-$NO_2C_6H_4$ (81%).

**Scheme 103**[a]




[a] Reagents and conditions: (i) **1-Ru** (10 mol %), $CH_2Cl_2$, reflux, then TFA, **449** (62%), **459** (54%).

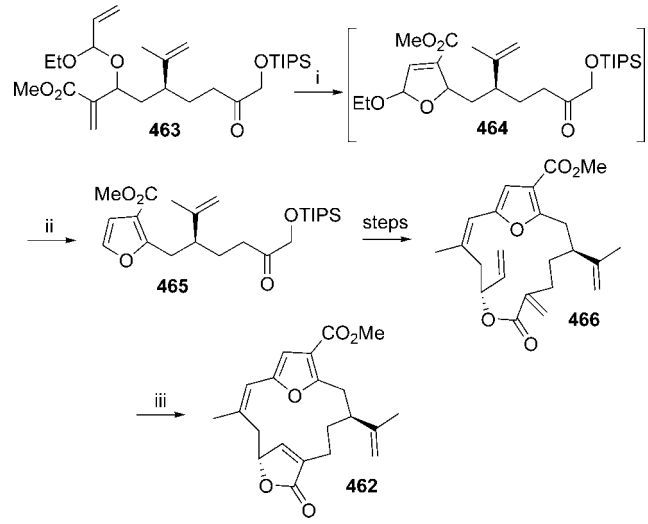
a number of unsymmetrical mixed acetals, for example, compounds **453**, **454**, and **455**, were treated with **2-Ru** to afford the corresponding substituted furans **456**, **457**, and **458**, in good yields (Scheme 102).[192] In this transformation, the elimination of methanol was key to the aromatization process, i.e., the OMe group in the 2-position acts as a leaving group.

The same group also applied their method of RCM, followed by aromatization, to the synthesis of two biheteroaromatic compounds.[192] In this manner, compounds **449** and **459** were synthesized from **460** and **461**, respectively (Scheme 103).

Donohoe and co-workers elegantly used an approach from previous work published by their group in the synthesis of a natural product, (−)-(*Z*)-deoxypukalide **462**.[250] The disubstituted furan portion of this 14-membered macrocycle was constructed in a two-step−one-pot procedure. First, the application of catalyst **2-Ru** to substrate **463** gave compound **464**, which was readily aromatized to the furan **465** in good yield, using the acid pyridinium *p*-toluenesulfonate. With this key step complete, the rest of (−)-(*Z*)-deoxypukalide **462** was constructed using a number of steps, which included another RCM reaction to form the butenolide portion of the natural product as shown in the transformation of **466** → **462** (Scheme 104).

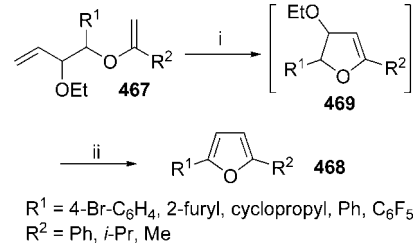
Another approach to substituted furans described in this review, published by the Donohoe group, involved the application of an enol ether−olefin RCM reaction. This strategy involved the synthesis of a range of enol ether substrates **467**, which were then treated with the Grubbs second-generation catalyst **2-Ru** to afford the substituted furans **468**, after acid-induced aromatization of the intermediates **469** (Scheme 105).[195,251] Of interest is that, in this methodology, the leaving group that facilitates that aromatization process, OEt, is in the 3-position of the intermediates

**Scheme 104**[a]




[a] Reagents and conditions: (i) **2-Ru** (7.5 mol %), $CH_2Cl_2$, reflux, 16 h; (ii) then PPTS, reflux, 2 h (85% over 2 steps); (iii) **2-Ru** (15 mol %), toluene, reflux, (72%).

**Scheme 105**[a]




[a] Reagents and conditions: (i) **2-Ru** (10 mol %), toluene, 60 °C; (ii) TFA (cat.) (50−64%, over 2 steps).

produced. In addition, a *t*-butyl or a trifluoromethyl group was not tolerated in the $R^2$ position.

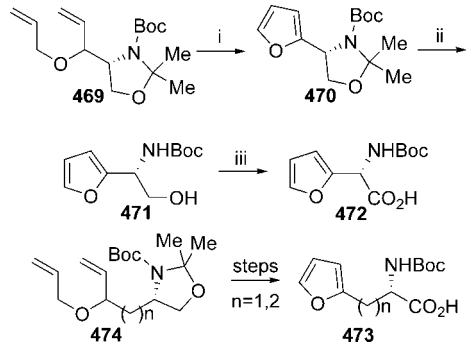
Novel approaches toward the synthesis of nonproteinogenic α-amino acids have seen much research activity in recent years.[252] One example by Chattopadhyay and coworkers utilized a RCM reaction on compound **469**, followed by an aromatization of the resulting dihydrofuran with DDQ, to afford the furan **470**.[253] Further deprotection of the oxazolidine group then gave **471**. Oxidation of compound **471** to the carboxylic acid then afforded the desired furanylglycine α-amino acid derivative **472** (Scheme 106). In addition, the furanylalanine and homofuranylalanine derivatives **473** were synthesized in a similar manner from dienes **474** in reasonable yields.

### *4.1.7. Synthesis of Benzofurans*

The synthesis of benzofurans by using RCM as a key step was first reported by Grubbs in 1994.[254] In this particular paper, three examples were described using the Schrock catalyst **3-Mo** to achieve the desired metathetic transformation. It is important to note that all the examples involved the use of olefinic enol ethers, synthesized by using titanium-based reagents on the corresponding ester,[227] in the metathetic transformation; for example, the dienes **475** and **476** were converted into 2-substituted benzofurans **477** and **478**, respectively, in good yields (Scheme 107).

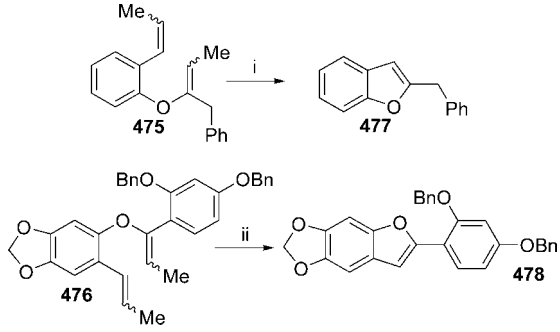
To the best of our knowledge, it was not until 2003 that the next example of the synthesis of benzofurans by RCM

**Scheme 106**[a]



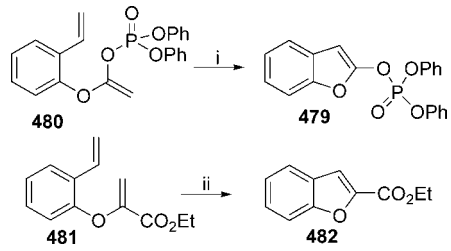
[a] Reagents and conditions: (i) (a) **1-Ru** (5 mol %), $CH_2Cl_2$, rt, 4 h, then (b) DDQ, $C_6H_6$, reflux, 16 h (56% over 2 steps); (ii) MeOH−HCl (5%), 0 °C, 30 min (82%); (iii) $H_2CrO_4$, $Et_2O-H_2O$, rt, 2 h (49%).

**Scheme 107**[a]



[a] Reagents and conditions: (i) **3-Mo** (12−13 mol %), *n*-hexane, 60 °C, 7 h (87%); (ii) **3-Mo** (12 mol %), $C_6H_6$, 60 °C, 2 h (85%).

**Scheme 108**[a]

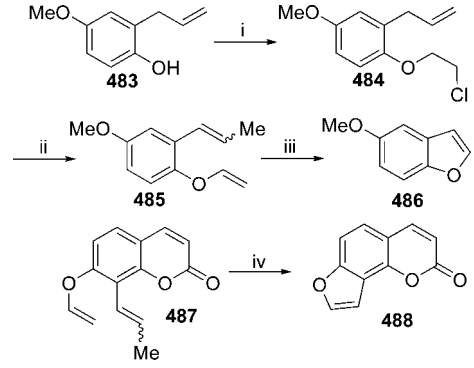


[a] Reagents and conditions: (i) **2-Ru** (5 mol %), $CH_2Cl_2$, 40 °C (99%); (ii) **2-Ru**, (5 mol %), toluene, 70 °C, 30 min (89%).

was reported. Hanson described in the literature the synthesis of benzofuran-2-yl enol phosphates such as **479** from diene **480**, in an excellent yield of 99%.[255] This was followed by work from Rutjes and co-workers, who reported the RCM reaction of an alkoxyacrylate **481** to afford the 2-ester substituted benzofuran **482**, also in a good yield (Scheme 108).[256]

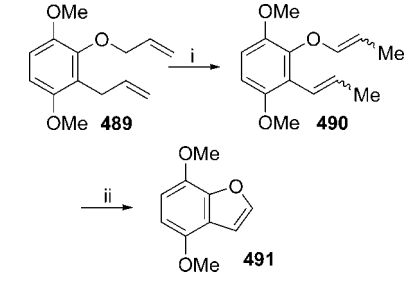
In recent years, only a few isolated examples describing the syntheses of benzofurans have been reported. Wang and co-workers have been quite active in this area and have published a number of examples of vinyl enol ethers undergoing metathesis reactions to give the desired benzofuran products. For example, phenol **483** has been converted into compound **484**, and then further transformed into the vinyloxy ether **485**. When substrate **485** was subjected to Grubbs catalyst **2-Ru**, the product obtained was benzofuran **486** (Scheme 109).[257−259] Other related examples, such as the conversion of compound

**Scheme 109**[a]



[a] Reagents and conditions: (i) $BrCH_2CH_2Cl$, NaOH, $H_2O$, TBAB (82%); (ii) *t*-BuOK, THF, reflux (89%); (iii) **2-Ru** (5 mol %), $CH_2Cl_2$ (75%); (iv) **1-Ru** (1 mol %), $CH_2Cl_2$ (90%).

**Scheme 110**[a]



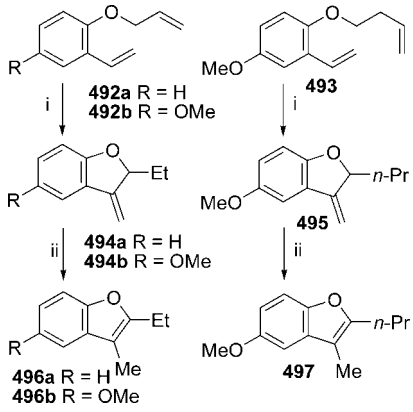
[a] Reagents and conditions: (i) 5% $[RuHCl(CO)(PPh_3)_3]$, toluene, 65 °C, 14 h (99%); (ii) **2-Ru** (5 mol %), toluene, 90 °C, 3 h (75%).

**487** to the substituted benzofuran **488**, have also been reported by this group.[260]

One of the challenges with the above approach is that the vinyl ethers have to be synthesized using basic conditions. This has generally been done by initially making the 2-chloroethoxybenzenes; for example, compound **484** was synthesized from phenol **483** using sodium hydroxide, dichloroethane, and a phase-transfer catalyst as reagents. The products were then subjected to potassium *t*-butoxide to afford the desired RCM precursors such as vinyloxy-containing **485** (Scheme 109). van Otterlo and co-workers have used a complementary approach by making the *O*-allyl substrates (see, for example, compound **489**) rather than *o*-vinyl substrates.[261−263] These *O*-allyl substrates were readily synthesized by treatment of the appropriate phenols with allyl bromide. The intermediates were then subjected to an isomerization−RCM sequence, i.e., compound **489** was reacted with $[RuHCl(CO)(PPh_3)_3]$[264] to provide the isomerized product **490**, a vinyl enol ether. This compound was then treated with the Grubbs second-generation catalyst **2-Ru** to afford the desired benzofuran **491** in reasonable yield (Scheme 110). The benzofuran **491** is one of 12 examples reported in this particular research initiative, with Br, $NO_2$, CHO, *t*-Bu, and Ph all being tolerated, with varying success, as substituents on the aromatic ring.[261−263]

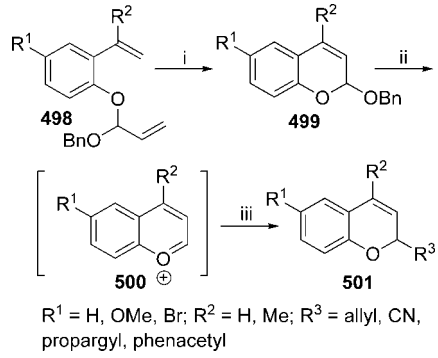
Arisawa and Nishida have been responsible for the synthesis of three substituted benzofurans, albeit by a cycloisomerization reaction promoted by **2-Ru**.[265] The treatment of diene substrates **492a−b** and **493** with catalytic **2-Ru** and a molar equivalent of trimethylsilyl vinyl ether afforded the cycloisomerized compounds **494a−b** and **495**, respectively, all in good yields (Scheme 111). According to the researchers, these compounds were readily isomerized to the

**Scheme 111**[a]




[a] Reagents and conditions: (i) **2-Ru** (5 mol %), trimethylsilyl vinyl ether, toluene, reflux, **494a** (78%), **494b** (76%), **495** (73%); (ii) HCl (1 M) or $CF_3CO_2H$ (yields not given).

**Scheme 112**[a]




[a] Reagents and conditions: (i) **1-Ru** (8−15 mol %), $CH_2Cl_2$, rt, Ar, 4−15 h (60−87%), or **2-Ru** (3−10 mol %), toluene, 80 °C, Ar, 1−4 h (60−87%); (ii) $BF_3 \cdot OEt_2$, $CH_2Cl_2$, 0 °C; (iii) $allylSiMe_3$, $Me_3SiCN$, $allenylSnBu_3$ or $PhC(=CH_2)OSiMe_3$ (2 mol equiv) (42−88% over 2 steps).

corresponding 3-methylbenzofurans **496a**−**b** and **497** under acidic conditions (HCl (1 M) or trifluoroacetic acid).

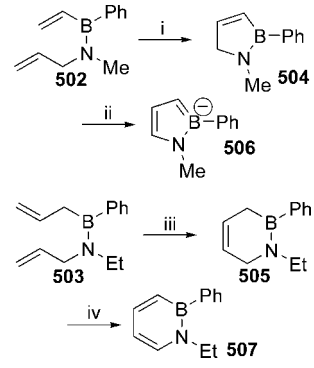
### 4.1.8. Synthesis of 1-Benzopyrylium Cations

An example of an ene−ene RCM reaction affording chromenes, which were converted into stable 1-benzopyrylium cations as useful synthetic intermediates, was disclosed by Doodeman, Rutjes, and Hiemstra (Scheme 112).[266] These workers described how the treatment of allylic acetals **498** with the Grubbs first- or second-generation catalysts **1-Ru** or **2-Ru** afforded the corresponding chromenes **499** in good yields. These compounds were then treated with the Lewis acid boron trifluoride etherate complex to generate in situ the stable 1-benzopyrylium cations **500**. The cations were then successfully quenched with a variety of nucleophiles (allyltrimethylsilane, trimethylsilyl cyanide, allenyl tributyl tin, and the silyl enol ether derived from acetophenone) to give rise to chromenes **501**, with the nucleophiles selectively incorporated in the electrophilic 2-position.

### 4.1.9. Synthesis of B−N-, B−O-, and B−S-Containing Aromatic Heterocycles

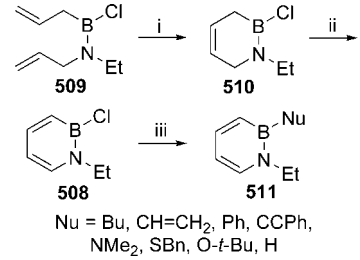
A number of interesting aromatic boron-containing ring systems[267] have also been made by using the metathesis−aromatization sequence. One of the main drivers of this research has been the quest for boron-containing cycles that possess aromatic character,[268] particularly to investigate their use as ligands in organometallic catalytic processes and to determine their value in medicinal chemistry applications.

**Scheme 113**[a]




[a] Reagents and conditions: (i) **1-Ru** (5 mol %), $CH_2Cl_2$, rt, 10 h (82%); (ii) LDA, $Et_2O$ (81%); (iii) **1-Ru** (5 mol %), $CH_2Cl_2$, rt, 10 h (86%); (iv) DDQ, pentane, 35 °C, 24 h (58%).

**Scheme 114**[a]

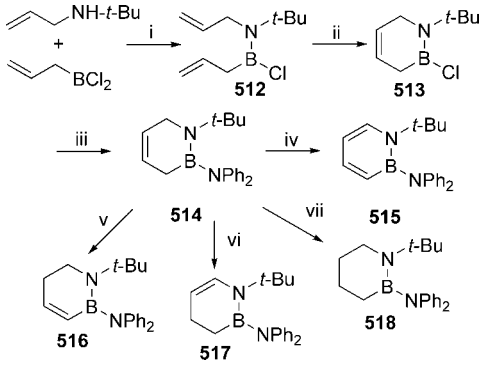



[a] Reagents and conditions: (i) **1-Ru** (2 mol %), $CH_2Cl_2$, rt, 1 h (66%); (ii) Pd black (20 mol %), cyclohexene, 80 °C, 16 h (57%); (iii) $Nu^-$ (50−92%).

To the best of our knowledge, the first example of this approach resulting in the formation of both five- and six-membered B−N heterocycles using RCM−aromatization has been described by Ashe and co-workers.[269] In this work, exposure of dienes **502** and **503** to the Grubbs catalyst **1-Ru** gave cyclized compounds **504** and **505**, respectively (Scheme 113). Compound **504** was then treated with lithium diisopropyl amide (LDA) to afford azaborolide **506**, a boron-containing analogue of pyrrole. In addition, compound **505** was oxidized with DDQ to yield the benzene analogue **507**, which had spectroscopic characteristics supporting a "weakly" aromatic nature. In related work, Ashe was also able to demonstrate that 1,2-dihydro-1,2-azaborines similar to **507** underwent classical electrophilic substitution reactions.[270]

This work on boron-containing isosteres of benzene was extended by Liu and co-workers in that they were able to synthesize the heterocyclic compound **508**, from precursor **509**, by way of a RCM reaction to initially afford heterocycle **510**, which was followed by aromatization with palladium black and a hydrogen acceptor (Scheme 114).[271] 1,2-Dihydro-1,2-azaborine **508**, which contains a labile B−Cl bond, was subsequently converted into a range of B-substituted products **511** by the nucleophilic displacement of the chloride atom. In particular, when Superhydride was utilized in this step, the 1,2-azaborine compound with a B−H functionality was produced (**511**, Nu = H), one step removed from the synthesis of the desired unsubstituted benzene isostere. The researchers were also able to synthesize a BN-isostere of a compound that has demonstrated potent hypolipidemic activity, namely, **511** with Nu = $OCH_2CO_2Me$, demonstrat-

**Scheme 115**[a]



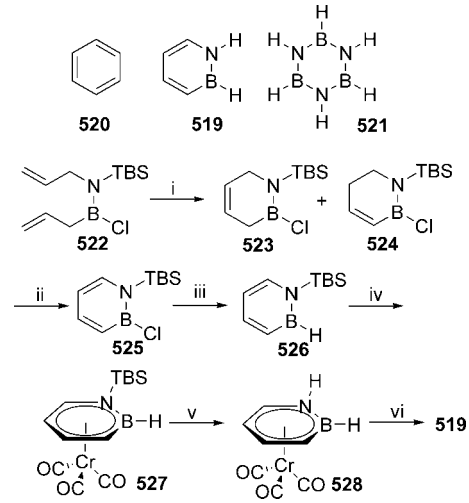

[a] Reagents and conditions: (i) $NEt_3$, −78 °C, 18 h (71%); (ii) **1-Ru** (1 mol %), $CH_2Cl_2$, rt, 45 min (84%); (iii) $KNPh_2$, THF, −20 °C to rt, 16 h (49%); (iv) Pd black (20 mol %), cyclohexene, 80 °C, 20 h (17%); (v) $[Ru(Cl)_2(PPh_3)_3]$ (4 mol %), $C_6H_6$, 60 °C, 22 h, then 70 °C, 24 h (71%, also performed on a NMR spectroscopy scale in $C_6D_6$, 93% yield by NMR); (vi) $[RuHCl(CO)(PPh_3)_3]$ (10 mol %), $C_6H_6$, 80 °C, 16 h (15%, also performed on a NMR spectroscopy scale in $C_6D_6$, 95% yield by NMR); (vii) Pd black (10 mol %), $H_2$ (1 atm), $C_6H_6$, 65 °C, 15 h (58%).

ing the utility of this methodology in synthesizing interesting B,N-containing compounds for potential application in medicinal chemistry.

Another chapter in this interesting series of investigations was published by Zaharov and Liu, who provided interesting crystallographic evidence for the aromatic character of the 1,2-dihydro-1,2-azaborines synthesized.[272] The diene **512**, synthesized by the straightforward condensation of *t*-butylallylamine with allylboron chloride, readily underwent metathesis with the Grubbs first-generation catalyst **1-Ru** to afford the desired product **513** (Scheme 115). As described in their previous work (see previous example in this review), nucleophilic attack by the anion of diphenylamide gave compound **514** in moderate yield. The "fully aromatic" heterocycle **515** was then generated by treatment with palladium black in cyclohexene, unfortunately only in a poor yield of 17%. However, this compound afforded crystals that allowed for X-ray crystallography to confirm the aromatic nature of **515**. In addition, crystalline compounds **516** and **517**, the two regioisomeric boron-containing "dienes", were elegantly synthesized by regioselective isomerizations utilizing ruthenium complexes. Together with compound **518**, in which only C−C single bonds occur, the researchers were able to compare the delocalized bonds of substituted 1,2-azaborine **515** with the formal double and single bonds of the nonaromatic systems **516**, **517**, and **518**, by way of a crystallographic analysis.

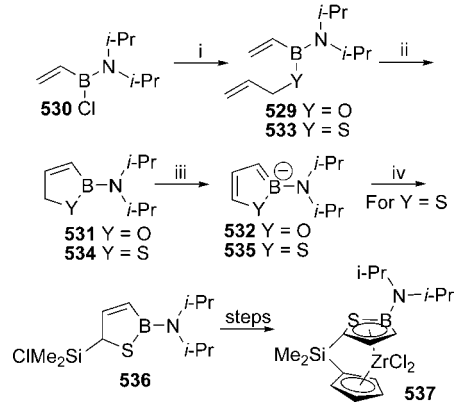
Dixon, Liu, and co-workers recently contributed to the field of B−N heteroaromatic compounds by synthesizing a "hybrid organic/inorganic benzene".[273] These researchers were able to synthesize 1,2-dihydro-1,2-azaborine **519**, the elusive hybrid organometalloidal compound of the organic benzene **520** and the inorganic borazine **521** (Scheme 116). The synthesis of **519** started with the RCM reaction of diene **522** to afford a mixture of the compounds **523** and **524** in good yield. These isomers were then dehydrogenated with palladium on carbon to afford **525**, which was dehalogenated with $LiBHEt_3$ to give **526** in near quantitative yield. Direct deprotection of the silyl group proved unsatisfactory so an innovative strategy was devised to afford **519**. The chromium tricarbonyl piano-stool complex **527** was then synthesized from **526** and the nitrogen was desilylated with HF·pyridine complex to afford **528**. Final decomplexation of the chromium with triphenylphosphine then gave the desired hybrid compound **519** as a stable, but volatile liquid. Dixon and Liu utilized spectroscopic and computational techniques, as well as reactivity studies, to demonstrate that compound **519** had distinct features, consistent with significant aromaticity, which were different from the related compounds **520** and **521**. The authors also concluded that "given the importance and ubiquity of benzene derivatives in scientific research, the development of benzene mimics such as 1,2-azaborines will undoubtedly lead to new discoveries".

**Scheme 116**[a]




[a] Reagents and conditions: (i) **1-Ru** (2 mol %), $CH_2Cl_2$, rt, 30 min (74%, 60:40); (ii) Pd/C (15 mol %), cyclohexene, 100 °C, 16 h, then PhC≡CMgBr (1 M, THF) (35%); (iii) $LiBHEt_3$ (1 M, THF), $Et_2O$, −78 °C−rt, 6 h (99%); (iv) $(MeCN)_3Cr(CO)_3$, THF, 60 °C, 16 h (71%); (v) HF·pyridine, THF, −20 °C, 3 h, then rt, 1 h (76%); (vi) $PPh_3$, isopentane, rt, 3 h (84% by NMR, 10% yield).

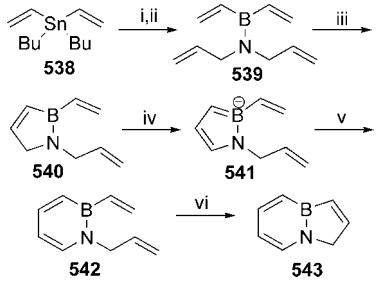
**Scheme 117**[a]




[a] Reagents and conditions: (i) for Y = O, $LiOCH_2CHCH_2$ (1 equiv), THF, −78 °C, 2 h, then rt, 3 h (87%), for Y = S, $HSCH_2CH{=}CH_2$, $NEt_3$, −78 °C, then rt, 10 h (74%); (ii) for Y = O, **1-Ru** (2 mol %), $CH_2Cl_2$, rt, 10 h (92%), for Y = S, **1-Ru** (1 mol %), $CH_2Cl_2$, rt, 10 h (95%); (iii) for Y = O, *t*-BuLi, $C_5H_{12}$, −78 °C, 1 h, then rt, 15 min (53%), for Y = S, LDA, $Et_2O$, −78 °C, 2 h, then rt, 3 h (82%); (iv) $Me_2SiCl_2$, THF, −78 °C to rt, 5 h (93%).

Ashe and co-workers also extended the RCM−aromatization methodology to include the synthesis of a boron analogue of furan. Allyloxyvinylborane **529** was initially prepared by the treatment of vinyl borane **530** with lithium alloxide in a good yield of 87% (Scheme 117).[274] Cyclization was then readily promoted by the catalyst **1-Ru** to give **531** in an excellent yield of 92%; this compound was then deprotonated

**Scheme 118**[a]




[a] Reagents and conditions: (i) $BCl_3$, pentane, −78 °C to rt, then (ii) $HN(allyl)_2$, $NEt_3$, −78 °C to rt, 10 h (79% over 2 steps); (iii) **1-Ru** (5 mol %), $CH_2Cl_2$, −78 °C to rt, 10 h (62%); (iv) LDA, $Et_2O$, −78 °C to rt, 12 h (67%); (v) $CH_2Cl_2$, LDA, −78 °C to rt, 12 h (30%); (vi) **1-Ru** (5 mol %), $CH_2Cl_2$, rt, 10 h (30%).

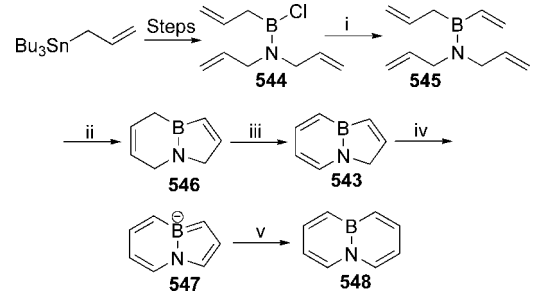
with *t*-butyl lithium to afford the anionic, aromatic 2-substituted 1,2-oxaborolide **532**. The capability of this compound to act as a Cp surrogate in transition metal chemistry was then investigated by these researchers.

A heteroaromatic ligand containing both boron and sulfur, 1,2-thiaborolide **535**, was also synthesized by way of this approach.[275] The treatment of compound **530** with allyl mercaptan afforded **533**, which was readily ring-closed with **1-Ru** to give product **534** in excellent yield. Deprotonation with LDA then gave thiaborolide **535** in good yield. This compound proved to readily form transition metal complexes, and the ability of these complexes to be polymerization catalysts was also tested. To this end, thiaborolide **535** was silylated to afford compound **536**, and this compound was then readily converted into the zirconium bis-Cp analogue **537** over a number of synthetic steps. This compound, among other 1,2-azaborolyl zirconium complexes,[276] has been patented as being a good catalyst for the polymerization of olefins.[277,278]

Ashe and co-workers were also successful in extending their RCM methodology to the synthesis of aromatic ring-fused boron-containing compounds.[279] Dibutyldivinylstannane **538** was converted into the tetraene **539** by treatment with $BCl_3$, followed by the reaction of the resultant boron halide with diallylamine (Scheme 118). However, on cyclization with Grubbs catalyst **1-Ru**, only the monocyclized compound **540** was obtained in 62% yield; forcing conditions involving higher temperatures and more catalyst failed to give the bicyclic desired compound. According to the authors of this work, this result was not unexpected as other [5,5]-fused ring systems have previously also not been formed in the RCM reaction of 1-allyl-2-vinyl-substituted heterocycles.[280] The azaborolide **541**, formed by the treatment of compound **540** with LDA, then underwent a LDA/$CH_2Cl_2$ carbenoid ring-expansion to afford compound **542** in a yield of only 20% for the combined synthetic steps. Subsequent treatment of this compound with the catalyst **1-Ru** then afforded the desired 3a,7a-azaborindene **543**, which is isoelectronic with indene.

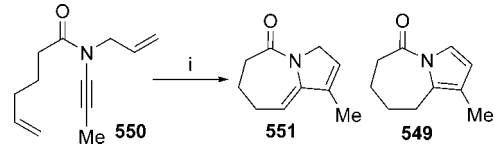
Given that the end-game for the synthesis of **543** was relatively disappointing, Ashe and co-workers also developed a second-generation synthesis toward this compound.[279] In this reported work, compound **544** was initially synthesized from allyltributylstannane in high yield over three steps. Subsequent treatment of compound **544** with vinylmagnesium bromide then afforded the aminoborane **545**, which readily gave the bis-cyclized compound **546** when treated with the catalyst **1-Ru** in 59% yield. Subsequent further

**Scheme 119**[a]




[a] Reagents and conditions: (i) $CH_2$=CHMgBr (84%); (ii) **1-Ru** (5 mol %), $CH_2Cl_2$ (59%); (iii) DDQ, 30%; (iv) $KN(SiMe_3)_2$, toluene, −78 °C−rt, 6 h (85%); (v) $CH_2Cl_2$, *n*-BuLi, −78 °C−rt, 4 + 2 h (43%).

**Scheme 120**[a]




[a] Reagents and conditions: (i) **2-Ru** (5−10 mol %), toluene, 75 °C, 12 h, **551** (0%), **549** (40%).

oxidation with DDQ then gave the desired product **543** in a yield of 30% (Scheme 119). This process represented a much more efficient synthesis of this compound (14% vs 3% as shown in the previous scheme). Finally, compound **543** was readily deprotonated with potassium bis(trimethylsilyl)amide to give the azaborindenyl compound **547**. This compound is isoelectronic with indenyl and, according to the researchers, had a "strong indene-like odor".[281] Subsequent reaction of **547** with a mixture of $CH_2Cl_2$ and *n*-BuLi afforded 4a,8a-azabornaphthalene **548**, which interestingly also had a characteristic "naphthalene-like odor." The structure of compound **548**, which is isoelectronic and isostructural to naphthalene, was subsequently confirmed by an X-ray diffraction study.

## 4.2. Ene−Yne RCM−Aromatization Strategies for the Synthesis of Aromatic Heterocycles

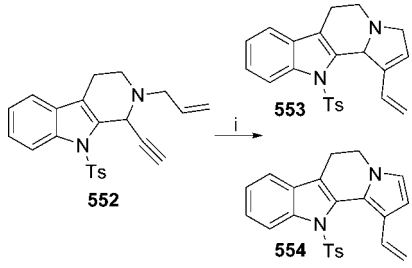
The application of ene−yne metathesis to the synthesis of aromatic heterocycles has been investigated to a much lesser degree than the corresponding examples utilizing the ene−ene metathesis approach. In this section, the synthesis of substituted pyrroles, indoles, and furans, among others, will be discussed.

### *4.2.1. Synthesis of Pyrroles*

Hsung and co-workers reported the interesting formation of the substituted pyrrole **549** after a tandem RCM reaction of the diene−ynamide **550** (Scheme 120).[282] In this particular example, it was proposed that the migration of the double bond in the expected product **551** had occurred to afford pyrrole **549** because of the additional aromatic stabilization.

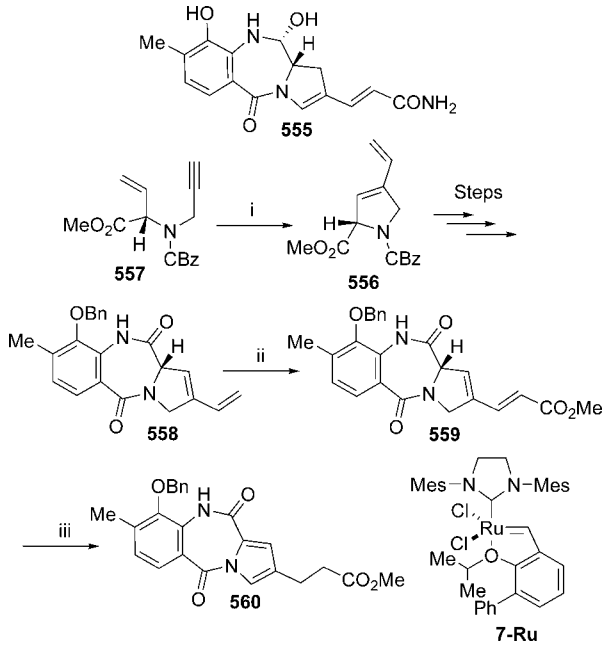
Castells and co-workers synthesized a relatively complex pyrrole using an ene−yne RCM reaction, albeit as a side-product.[283] In this work, treatment of the ene−yne **552** with the second-generation Grubbs catalyst afforded diene **553** in a reasonable yield along with the oxidized pyrrole **554** in only 9% yield (Scheme 121).

**Scheme 121**[a]




[a] Reagents and conditions: (i) **2-Ru** (10 mol %), conditions not specified, **553** (62%), **554** (9%).

**Scheme 122**[a]

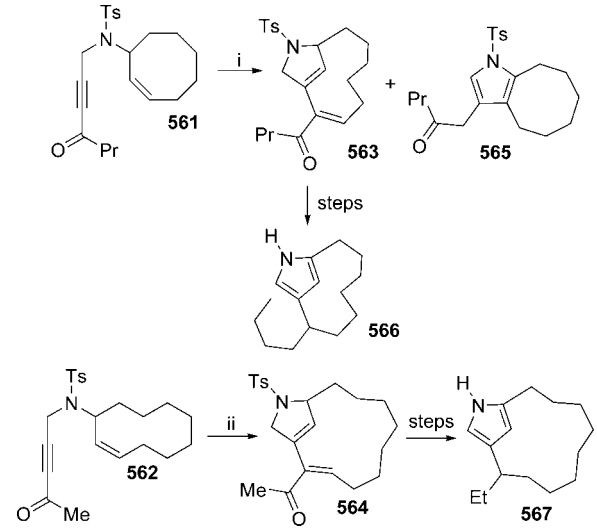



[a] Reagents and conditions: (i) **1-Ru** (5 mol %), $CH_2Cl_2$, $CH_2{=}CH_2$, rt, 24 h (76%); (ii) **7-Ru** (10 mol %), $CH_2{=}CHCO_2Me$, $CH_2Cl_2$, rt, 17 h (63%); (iii) $[RuHCl(CO)(PPh_3)_3]$, toluene, reflux, 8 h (66%).

Another example in this section describing a pyrrole synthesis, albeit by a multistep approach utilizing a metathesis reaction as the key step, was published by Mori and co-workers (Scheme 122).[284] In their investigations toward the synthesis of (+)-anthramycin **555**, the pyrroline core **556** found in the natural product was constructed by a ring-closing ene−yne metathesis procedure, starting from precursor **557**. Quite a few steps later in the synthesis, compound **559** was assembled from **558** by a cross-metathesis reaction with methyl acrylate using the Blechert catalyst **7-Ru**. In an attempt to isomerize the double bond in **559** to the orientation found in the natural product, a well-known isomerization catalyst, $[RuHCl(CO)(PPh_3)_3]$, was used.[264] This, however, only resulted in the isolation of the pyrrole-containing compound **560**. Ultimately the isomerization was successfully performed by utilizing a rhodium catalyst, leading to the synthesis of a number of anthramycin analogues.

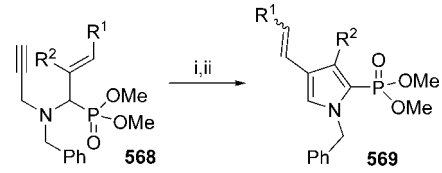
An innovative application, involving a nonclassical application of metathesis, was reported by Fürstner and co-workers in their work on the synthesis of analogues of the antibiotics metacycloprodigiosin and streptorubin B (Scheme 123).[285] These researchers applied a platinum-catalyzed rearrangement of the ene−yne substrates **561** and **562** to

**Scheme 123**[a]




[a] Reagents and conditions: (i) $PtCl_2$ (5 mol %), toluene, 50 °C, 66 h, **563** (79%), **565** (5%); (ii) $PtCl_2$ (5 mol %), toluene, 100 °C, 21 h (42%), or $BF_3{\cdot}OEt_2$, toluene, rt, 22 + 17 h (54%).

**Scheme 124**[a]




$R^1$=Me, 2-furyl, Ph or propyl; $R^2$=H or Me

[a] Reagents and conditions: (i) **2-Ru** (5 mol %), chloranil (1 mol equiv), $C_6H_6$, reflux, $N_2$, 16 h (48−85%).

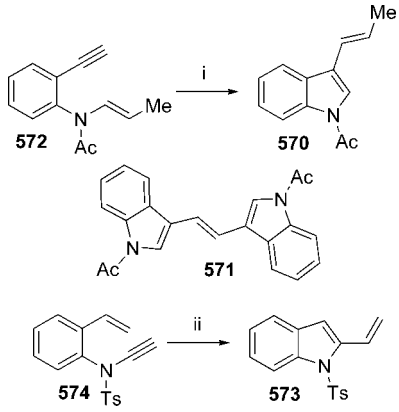
afford the bicyclic compounds **563** and **564** in good (79%) to moderate (42%) yields, respectively. Of particular interest was that one of the minor byproducts isolated along with compound **563** was pyrrole **565**, supporting the postulate that the reaction occurs by way of "nonclassical" cation-type intermediates. Both compounds **563** and **564** were converted into their respective bicyclic pyrroles **566** and **567** over a number of steps. Compound **566** constitutes the core structure of streptorubin B, while the synthesis of pyrrole **567** represents a formal approach to the natural product metacycloprodigiosin.

Stevens and co-workers developed an efficient ene−yne metathesis strategy toward the synthesis of 2-phosphono pyrroles related to their previous synthetic routes (see section 4.1.1).[286] Reaction of a family of ene−yne substrates **568** with 5% of the second-generation catalyst **2-Ru** in the presence of chloranil afforded the substituted 2-phosphono pyrroles **569** (mainly *E*-isomer). The group was also able to determine that the reactions proceeded by way of the "yne-then-ene" pathway (Scheme 124).

### *4.2.2. Synthesis of Indoles*

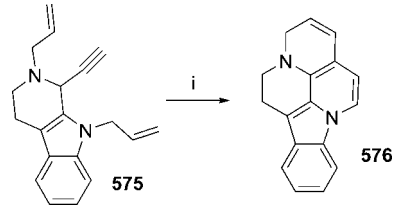
Ene−yne metathesis has also been successfully used to make varying proportions of indoles **570** and **571** from ene−yne **572** (Scheme 125), with the best results being obtained under dilute reaction conditions.[287] Presumably compound **571** is formed by the cross-metathesis reaction of indole **570** when utilizing the Grubbs second-generation catalyst **2-Ru**. This compound could be obtained in a yield

**Scheme 125**[a]




[a] Reagents and conditions: (i) **2-Ru** (5 mol %), toluene, 80 °C, 2 h, **570** (60%), **571** (25%); (ii) **2-Ru** (5 mol %), toluene, 80 °C, **573** detected in crude but decomposed on purification.

**Scheme 126**[a]




[a] Reagents and conditions: (i) **4-Ru** (6 mol %), toluene, 80 °C, 3 d (67%) or **2-Ru** (6 mol %), toluene, 80 °C, 3 d (45%).

of 70% with the use of catalyst **4-Ru** and the application of longer reaction times (18 h). Pérez-Castells and co-workers also managed to detect the presence of *N*-tosyl-2-vinylindole **573** when utilizing the catalyst **2-Ru** on ene−yne substrate **574**. However, these workers were unable to isolate the pure compound **573**, possibly due to its instability in the presence of ruthenium contaminants.

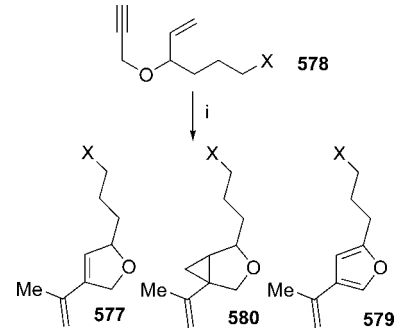
### 4.2.3. Synthesis of a β-Carboline

Another interesting application, described by Pérez-Castells, resulting in a fused β-carboline skeleton is shown in Scheme 126.[283] With the Hoveyda−Grubbs catalyst system **4-Ru**, compound **575** was converted into the pentacyclic product **576**, via a metathesis and oxidation process. The Grubbs second-generation catalyst system **2-Ru** also gave the same product but in lower yields.

### 4.2.4. Synthesis of Furans

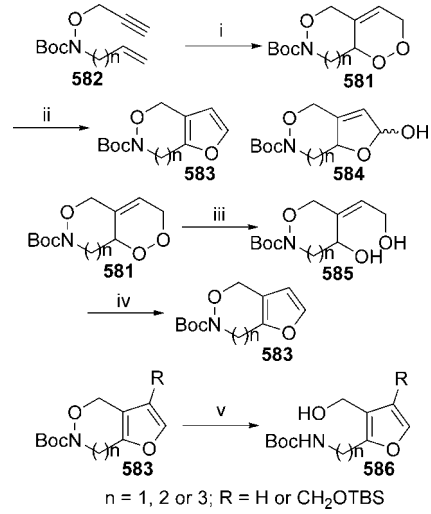
It was during the synthesis of 3-isopropenyldihydrofurans **577** from precursors **578** that Nay and co-workers isolated appreciable amounts of the corresponding isopropenylfurans **579** (Scheme 127).[288] In fact, treatment of **578** (X = OTBS) with the catalyst **1-Ru**, followed by removal of the TBS group by TBAF (not shown), resulted in up to 34% of the substituted furan **579** (X = OH), together with **580** (X = OH). The formation of furan was attributed to the contamination of the compounds by ruthenium catalyst; of interest was that freshly added **2-Ru**, under an atmosphere of ethylene, was unable to dehydrogenate **577** (X = OTBS), indicating that the transformation was probably catalyzed by a ruthenium byproduct being formed during the ene−yne metathesis process.

**Scheme 127**[a]




[a] Reagents and conditions: (i) **1-Ru** (10 mol %), $CH_2{=}CH_2$, $CH_2Cl_2$, reflux, 16 h, for X = OTBS **577** (54%), **580** (6%), **579** (3%), for X = Br **577** (52%), **580** (9%), **579** (17%).

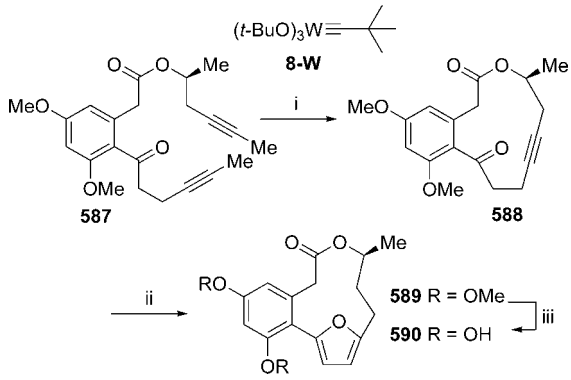
**Scheme 128**[a]




[a] Reagents and conditions: (i) (a) **1-Ru** (10 mol %), $CH_2Cl_2$, 45 °C, 4−34 h, $n$ = 1 (97%), $n$ = 2 (90%), $n$ = 3 (93%),[169] (b) $O_2$, rose bengal (cat.), 400 W tungsten lamp, MeCN, $n$ = 1 (82%), $n$ = 2 (75%), $n$ = 3 (80%); (ii) $FeSO_4 \cdot 7H_2O$, THF−$H_2O$ (1:1), rt, $n$ = 1 (**583** 0%, **584** 70%), $n$ = 2 (**583** 98%, **584** 0%), $n$ = 3 (**583** 88%, **584** 0%); (iii) Zn, AcOH, $CH_2Cl_2$ rt, $n$ = 1 (84%), $n$ = 2 (78%), $n$ = 3 (79%); (iv) pyridine/$SO_3$, DMSO, $NEt_3$, $CH_2Cl_2$ rt, $n$ = 1 (64%), $n$ = 2 (77%), $n$ = 3 (87%); (v) $Mo(CO)_6$ (0.2 mol equiv), $NaBH_4$ (1.2 mol equiv), MeCN−$H_2O$ (4:1), 85 °C, for R = H, $n$ = 1 (98%), $n$ = 2 (87%), $n$ = 3 (67%), for R = $CH_2OTBS$, $n$ = 1 (98%), $n$ = 2 (65%).

An application of an ene−yne−RCM/Diels-Alder strategy,[169] resulting in the formation of 2,3-di- and 2,3,4-trisubstituted furans by way of intermediate 1,2-dioxines **581**, was recently described by Tae and co-workers.[289] The general strategy described in this work is shown in Scheme 128. Ene−ynes **582** were ring-closed by the application of catalyst **1-Ru**, followed by a Diels−Alder reaction with singlet oxygen, to afford 1,2-dioxines **581** in good yield.[290] Treatment of these compounds **581** with iron(II) sulfate then afforded the respective bicyclic furans **583**, although in the case where $n$ = 1, lactol **584** was obtained instead. An alternative two-step sequence, involving reductive cleavage of the O−O bond of **581** in the presence of zinc, afforded **585**. This was followed by oxidative dehydration to afford the desired di- or trisubstituted furans **583**. Finally, cleavage of the N−O bond of **583** was also achieved with $Mo(CO)_6$ and $NaBH_4$, to afford the ring-opened 2,3-di- and 2,3,4-trisubstituted furans **586** in good yield.

**Scheme 129**[a]




[a] Reagents and conditions: (i) **8-W** (10 mol %), toluene, 85 °C, 1 h (78−81%); (ii) *p*-TsOH, toluene, 85 °C, 5.5 h (85%); (iii) 9-iodo-9-BBN, $CH_2Cl_2$, −10 °C, 4 h (60% crude, 27% by HPLC).

### 4.3. Yne−yne Metathesis−Aromatization Strategies for the Synthesis of Aromatic Heterocycles

Ring-closing alkyne metathesis (RCAM) has not been significantly used for the synthesis of aromatic molecules, as these strategies usually involve RCAM followed by Lindlar- or Birch-type reductions to afford the cyclic alkenes.[8,17]

However, it should be realized that the alkyne can potentially "encode" for a variety of functional groups, and a fascinating paper by Fürstner and co-workers demonstrates this point.[291] In this work, the RCAM of the diyne structure **587**, with Schrock's well-defined alkylidyne catalyst **8-W**, readily afforded the cyclic alkyne **588** in reproducible yields of ∼80% (Scheme 129). The functional value of the alkyne was then employed as treatment of **588** with *p*-toluenesulfonic acid readily afforded the substituted furan **589** in good yield (85%). A problematic deprotection then afforded the natural product (*S*)-(+)-citreofuran **590**. It is of interest to note that the authors of this work appreciated that their approach of utilizing RCAM in this way "may prove relevant for heterocycle synthesis as well".

## 5. Conclusions

The purpose of this review has been to highlight the importance of RCM in the synthesis of aromatic compounds. As can be seen from the examples cited in this work, RCM has been applied to many aromatic and heteroaromatic substrates, often providing unique access to substrates otherwise synthetically challenging to assemble by classical synthetic approaches. It is hoped that this review will stimulate researchers to reevaluate the structures of aromatic compounds classes not traditionally considered amenable to synthesis by a RCM approach. This will potentially have an impact on the use of this versatile synthetic approach for the generation of novel aromatic compounds and their applications in medicinal and materials chemistry.

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## 7. Note Added in Proof

During the review of this manuscript a number of papers related to the topic of this review were published. For completeness, they are listed as follows: (a) The synthesis of substituted styrenes by ring-closing ene−yne metathesis followed by dehydration or tautomerization, by Yoshida, Yanagisawa, and co-workers;[292] (b) the synthesis of 2,5-dihydrofuran-fused quinones using an ene−ene RCM−DDQ oxidation strategy, by Yamamoto and co-workers;[293] (c) the synthesis of quinolizinium cations using ene−ene RCM followed by oxidation, by Cuadro, Vaquero and co-workers;[294] (d) the synthesis of $\beta$-carbolines (and a pyrrole variant) by ene−yne metathesis, by Pérez-Castells and co-workers;[295] (e) the synthesis of substituted pyridines and pyridazines utilizing ene−ene metathesis followed by elimination, by Donohoe and co-workers.[296] Finally, a paper by Dixneuf, Osipov and co-workers, describing an ene−yne RCM−Diels-Alder−DDQ aromatization sequence to afford a substituted isoindoline, also came to our attention.[297]

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