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Preparation of cyclic molecules bearing "strained" olefins using olefin metathesis

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Abstract

Recent advancements in metathesis catalyst design have allowed chemists to re-examine olefin metathesis as a route to systems bearing strained olefins embedded in their skeletons. Such ring systems include various azabicyclo [3.3.1] and [4.2.1] rings systems, the unique tricyclic ring system of the natural product ingenol, and strained macrocyclic systems exhibiting atropisomerism. Several examples of forming strained aromatic systems is also presented. The variety of different catalysts that have been developed allows for the possibility to select a catalyst having the necessary level of reactivity to access a strained system but also to avoid catalysts which may be so reactive as to favour ring-opening of the desired ring system.

1. Introduction

There is little doubt that the discovery of well-defined catalysts designed for olefin metathesis has greatly influenced the manner in which organic chemists approach synthesis [1]. Ring closing metathesis (RCM) in particular is now a standard method for the preparation of both carbocyclic and heterocyclic ring systems in sizes ranging from five- and six-membered cycles to macrocyclic compounds. Despite its popularity, the preparation of certain molecules via olefin metathesis remains a challenge. In particular, strained ring systems are problematic. In some cases, the ring opening process can be far more thermodynamically favourable than ring closing while in other cases, the system may be too strained to permit cyclization. Herein, we describe several instances where novel conformational restraints and catalyst improvements have allowed chemists to tackle the challenge associated with constructing strained ring systems using olefin metathesis.

2. Bicyclic ring systems

Small bicyclic ring systems that contain olefins are typically excellent substrates for ring opening reactions [2]. These processes are often conducted with bicyclic compounds where a cascade of ring openings is planned to result in polymerization [3]. As such, synthetic chemists have traditionally shied away from attempting to use olefin metathesis to construct bicyclic compounds. In recent years however, several research groups have revisited this synthetic challenge, inspired by the unique cyclic structures of biologically active natural products. Several types of bicyclic compounds have now been prepared, although [2.2.2] and [2.2.1] bicycles are likely still not possible. Martin and co-workers have investigated the preparation of azabicyclo [*n*.3.1] type ring systems (Scheme 1) [4].

This work is inspired by the fact that this skeleton is found in many natural products which exhibit potent biological activity. Inspired by the azabicyclo skeleton of the tropane alkaloids, Martin and co-workers investigated cyclizations of precursors such as **1**. The formation of the azabicyclo frameworks is made possible by the conformation directing effects of the *N*-acyl group. The *cis*-2,6-disubstituted piperidine **1** prefers to exist in chair conformation

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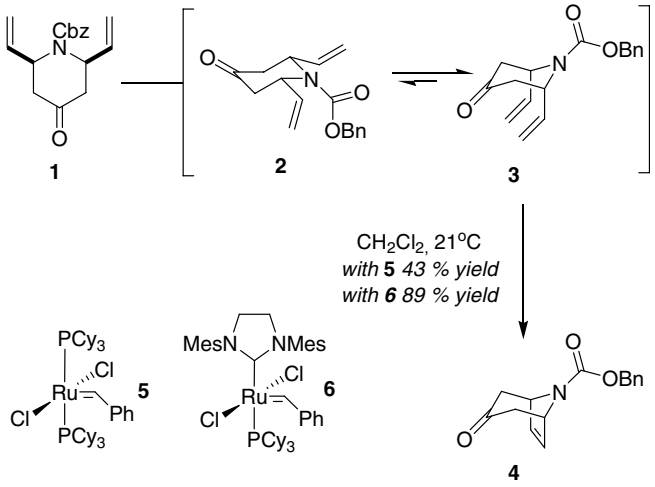
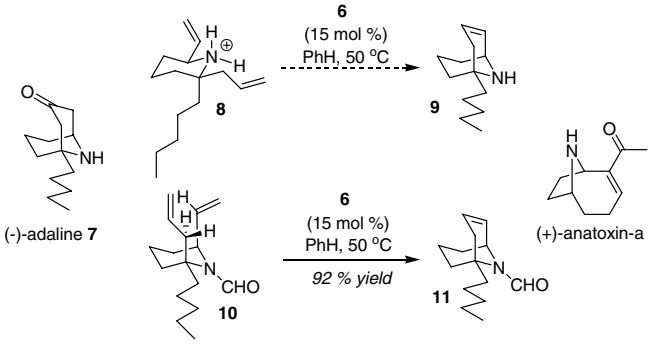


Scheme 1.



Scheme 2.

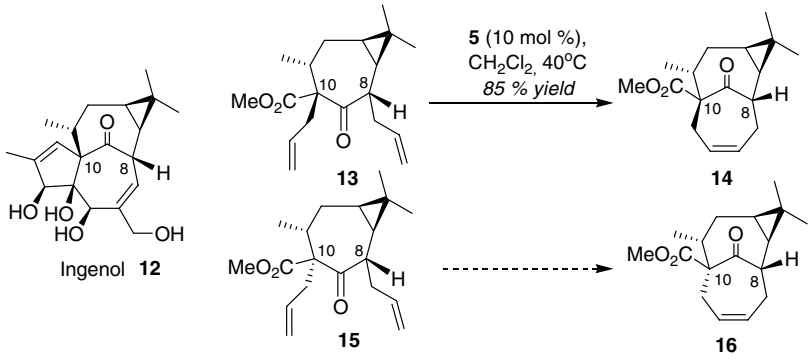
3, as the axial orientation of the vinyl substituents avoid any potential $A^{1,3}$ strain with the *N*-acyl group [5]. The cyclization to afford **4** was found to be much more efficient using Grubbs' 2nd generation catalyst **6**.

The *N*-acyl group is vital to the success of these olefin metathesis reactions. Kibayashi and co-workers have recently described an asymmetric synthesis of (−)-adaline **7** in which RCM was used to afford a [3.3.1] azabicyclic ring system (Scheme 2) [6]. It was found that the hydrochloride salt **8** was unable to induce the same conformational control as a *N*-acyl group. When the formamide **10** was subjected to catalyst **6** in benzene at 50 °C, the desired ring system was formed in 92% yield. Again, this is believed to be due to the *N*-acyl group enforcing a conformation in which the alkenyl chains are axial. This strategy has now also been applied to ring closing enyne metathesis, as Martin and co-workers have prepared (−)-anatoxin-a using a *N*-acyl group to produce a successful metathesis reaction to afford an azabicyclo[4.2.1]nonane framework [7].

The Wood group has demonstrated the utility of RCM as a method to construct the strained carbon skeleton of the natural product ingenol **12** (Scheme 3) [8]. Although it possesses potent biological activity, the synthetic challenge associated with preparing the tricyclic skeleton, bearing the correct *in–out* stereochemistry, has no doubt contributed to the plethora of synthetic routes that have been under development [9]. The strain in the parent ring system has been evaluated through molecular modelling, and it is estimated that isoingenol, which is epimeric at the C-8 center and thus possesses the *out–out* stereochemistry, is 5.9 kcal/mol more stable than ingenol itself [8]. The Wood group found that conformational control of the metathesis precursors was essential in preparing the desired ring systems. Wood and co-workers reported that **13** cyclized efficiently to **14** (possessing the wrong stereochemistry at C–10), however, all attempts to cyclize **15** failed [10]. Through molecular modelling calculations, it was determined that the olefins in **18** were considerably closer in space than the olefins in **15** (Scheme 4). The change in conformation is due to the twisting of the seven-membered ring upon installation of the five-membered ring in **18**. When **18** was treated with Grubbs–Hoveyda 2nd generation catalyst **17** [11], the ingenol skeleton was formed having the correct *in–out* strained bicyclic system, **19**, in 76% yield. The successful formation of the ingenol ring system would not have been possible without the advances in catalyst design that afforded catalyst **17**. Indeed, it is important to note that conformational restraints and improved catalyst reactivity were required to overcome the synthetic challenge.

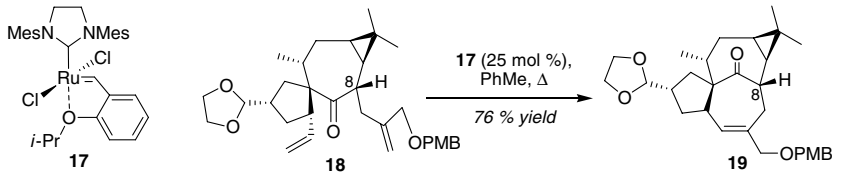
3. Macrocyclic ring systems exhibiting atropisomerism

Ring closing olefin metathesis has become one of the most efficient methods for macrocyclization [12]. How-

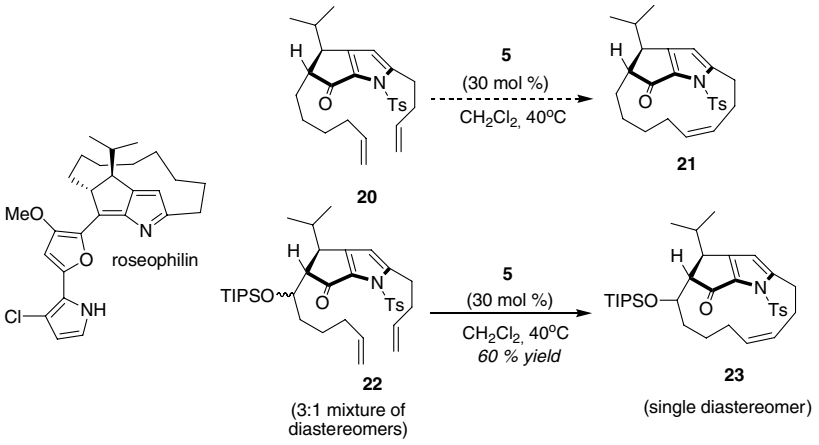


Scheme 3.

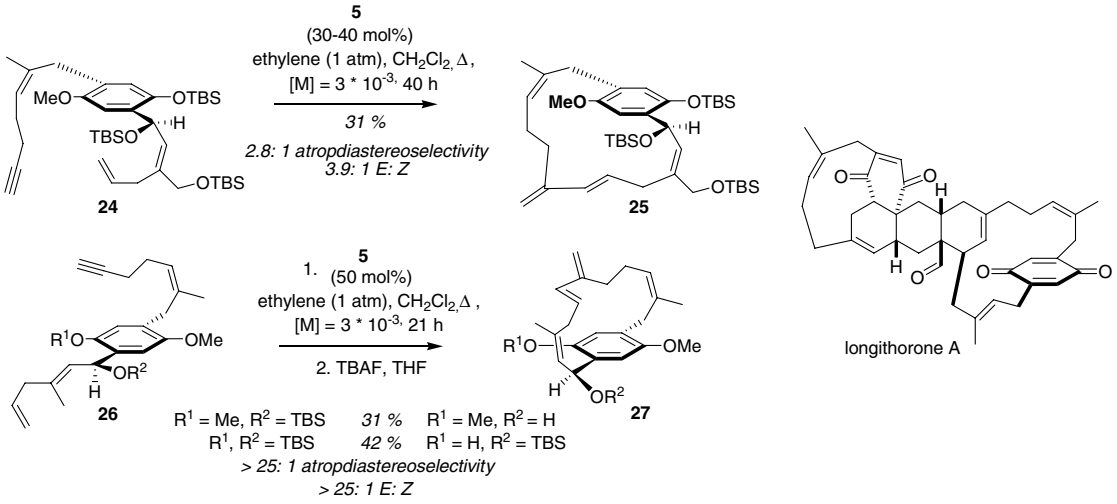
ever, certain natural products contain macrocyclic ring systems which are strained or extremely rigidified. This often occurs when the macrocycle is tied across an aromatic or heteroaromatic ring system, where the hindered rotation of the macrocycle usually results in atropisomerism. Although dilution, templates and slow-addition techniques can improve some macrocyclizations [13], typically chemists resort to the installation of conformational control elements to favour cyclization. Most often, this takes the form of a large substituent on the methylene group adjacent to the aromatic moiety. This strategy has been exploited by several research groups during the synthesis of natural products [14]. Fuchs and co-workers utilized this strategy during studies directed towards the preparation of roseophilin (Scheme 5) [15,16]. When the azafulvene precursor **20** was treated with **5** in dilute CH_2Cl_2 solution, only a macrocyclic dimer or recovered starting material was isolated. Consequently **22** was prepared as a mixture of diastereomers where the pendant OTIPS group is believed to help orient the reactive alkene partners closer together in space. When **22** was subjected to identical reaction conditions, the azafulvenophane **23** was obtained in 60% yield as a single diastereomer. This suggests that an enantioenriched starting material may act to control the atroposelectivity of the cyclization.



Scheme 4.



Scheme 5.



Scheme 6.

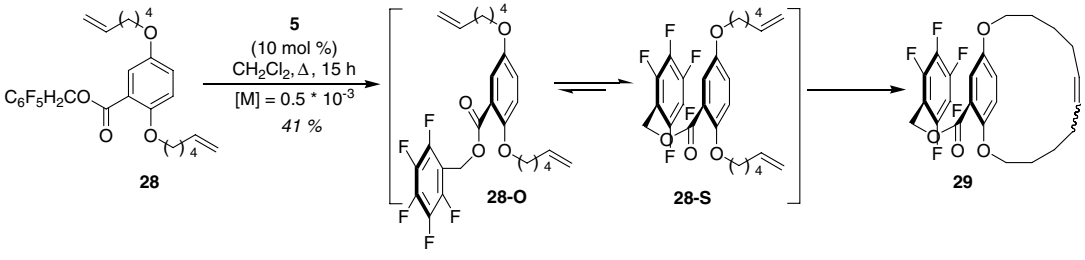
The application of enantiomerically pure substituted methylene group as an atropselective control element was demonstrated by the Shair research group in 2002 (Scheme 6) [17]. During the preparation of the natural product longithorone A, it was necessary to prepare enantioenriched [12] paracyclophanes possessing 1,3-diene functionality embedded in the *ansa*-bridge. Consequently, Shair and co-workers envisioned using a macrocyclic enyne metathesis [18] reaction to install the necessary diene functionality. A *t*-butyldimethylsilyloxy (OTBS) group was strategically placed adjacent to the aromatic ring as a conformational control element. Minimization of $A^{1,3}$ strain was believed to be responsible for the gearing of the alkenyl and alkynyl sidechains. Nonetheless, these macrocyclization reactions proved to be exceedingly difficult and no cyclization was observed without the pendant OTBS group. Large amounts of catalyst were necessary as well as extended reaction times, high dilution and the presence of an ethylene atmosphere [19]. Despite optimizing the conditions, **24** cyclized to afford macrocycle **25** in 31% yield. Furthermore the *E*:*Z* ratio was 3.9:1 and the atropdiastereoselectivity was modest at 2.8:1. It is important to note that the nature of the substrate controls the resulting *E*:*Z* ratios and atropdiastereoselectivity. For example, when **26** was subjected to nearly identical reaction conditions, the yield of the macrocyclic product **27** was identical to that obtained in the formation of **25**. However, both the *E*:*Z* ratio and atropdiastereoselectivity had increased to greater than 25:1 in the formation of **27**. These results demonstrate the ability of substituted methylene groups to act as conformation controlling groups, and to control the transfer of their chirality to atropisomeric centers. Although the Shair group successfully applied this methodology towards the asymmetric total synthesis of longithorone A, it is clear that there is a need for new and more efficient gearing elements for macrocyclization.

The Collins group has developed a novel gearing element to access strained macrocyclic systems that exploits perfluorophenyl–phenyl interactions in the solution state [20]. Collins and co-workers reported model studies directed towards the total synthesis of the 12-membered macrocyclic paracyclophane longithorone C (Scheme 7) [21]. They reported that numerous attempts at cyclizing various substituted [12]paracyclophanes using **5** were unsuccessful, despite varying the concentration and mode of addition. Consequently, a strategy employing perfluorophenyl–phenyl interactions as a novel gearing element to favour the desired intramolecular macrocyclization was envisioned (Scheme 7).

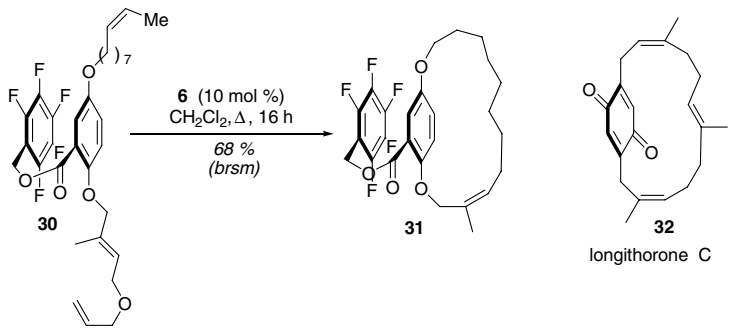
These non-bonding interactions are the result of the orthogonal electron densities of aromatics and perfluoroaromatics [22,23]. These interactions have attracted considerable interest due to the predictable preference for face-to-face stacking with other aromatics in the solid state [24–26], however, little use had been demonstrated in catalysis [27]. The pentafluorobenzyl ester **28** was demonstrated through molecular modelling to prefer the solution state conformation **28–S** to a much greater degree than **28–O**. In fact Moller–Plesset (MP2) [28] perturbation theory with a 6-31G* basis set predicted that conformer **28–S** was estimated to be more stable than **28–O** by approximately −24.0 kcal/mol [29]. When **28** was treated with **5** the cyclized cyclophane product **29** was isolated in 41% and no dimeric product had formed. It should be noted that catalyst **6** was shown to ring-open these strained macrocycles. In addition, the quadrupolar interaction gearing element was effective in a variety of solvents, although the rate of metathesis was reduced in several instances. The Collins group subsequently prepared even more strained macrocycles incorporating stereodefined trisubstituted olefins similar to those present in longithorone C (Scheme 8). Exploiting a relay ring closing metathesis protocol [30] in tandem with the gearing effect of the pentafluorophenyl–phenyl interaction, the cyclophane **31** was isolated in 68% after **30** was treated with **6** in refluxing CH_2Cl_2. Cyclophane **31** is isolated as a single isomer with the tertiary olefin in the *Z* configuration. These studies suggest that pentafluorophenyl–phenyl interactions represent a novel π-shielding element with possible application in other face selective transformations, and the potential to be modified to act as chiral auxiliaries.

4. Sterically demanding aromatic ring systems

In Katz's seminal paper on the mechanism of olefin metathesis [31], 2,2′-divinylbiphenyl was converted to phenanthrene. This experiment was run as a mechanistic probe and only allowed to proceed to ∼1% conversion. It's quite surprising that despite the power of ring closing olefin metathesis to prepare a variety of cyclic structures, so few examples have been documented for formation of benzenes, undoubtably one of the most important cycles



Scheme 7.

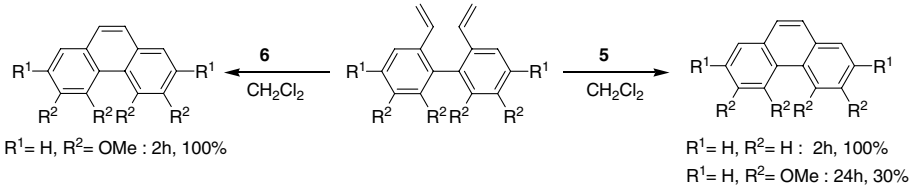


Scheme 8.

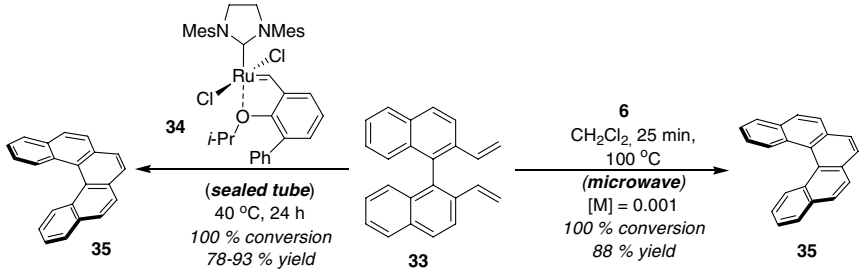
in all of organic chemistry. Since the work by Katz, few examples have been reported, all in the last three years [32–34]. In 2004, Iuliano and co-workers reported the use of catalysts **5** and **6** in the preparation of phenanthrene from 2,2′-divinylbiphenyl precursors (Scheme 9).

Using catalyst **5**, unsubstituted phenanthrene can be prepared in quantitative yield in 2 h at room temperature. However, methylether substitution at the 5,5′,6,6′-position inhibits RCM at room temperature using the same catalyst. The ring strain caused by the substituent at the 6,6′-position might prevent the coplanar disposition of the two phenyl rings and hence cyclization. However, quantitative conversion can be achieved in 2 h using the more active catalyst **6** at 40 °C. This work clearly demonstrates that unstrained benzene rings can be constructed from divinyl precursors using **6** as catalyst. Collins and co-workers subsequently examined whether olefin metathesis could be feasible as a route to the strained benzenes found embedded in the [5] helicene structure [35]. Although strained, the normally competing reverse ring-opening reaction would not be possible. Olefin metathesis represents a novel and mild method to access these carbon skeletons (Scheme 10) [36]. Two optimal protocols for the formation of [5] helicene from the divinyl precursor **33** were developed that can form the benzene ring despite the strain in the final structure. The first utilizes **6** in combination with microwave heating (100 °C) to afford excellent conversions in relatively short periods of time (25 min) with reproducible isolated yields of approximately 88% for [5] helicene **35**. Although this protocol is extremely rapid, a second procedure was developed employing lower reaction temperatures. Using the modified Grubbs–Hoveyda catalyst **34** [37], similar isolated yields of 78–93% for [5] helicene **35** could be obtained at only 40 °C in a sealed tube vessel.

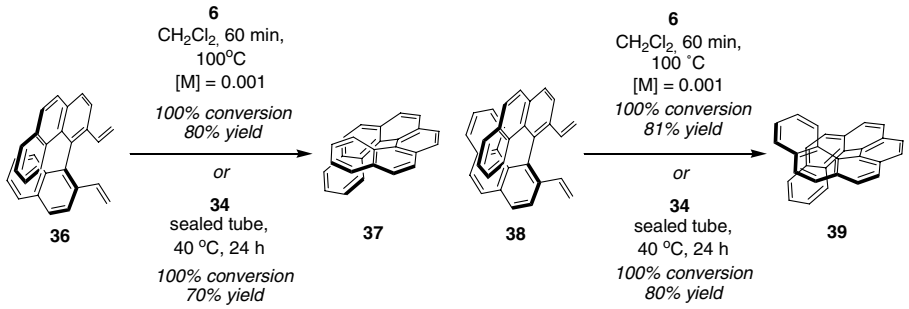
Consequently, higher helicenes having extended π-systems were targeted. These systems possess added aryl groups fused to the interior of helical structure. Both protocols were found to be quite efficient for the formation of [6,7] helicene (Scheme 11). Precursor **36** underwent smooth conversion (100%) to the [6] helicene **37** after 60 minutes under microwave irradiation and was isolated in 80% yield. Similar yields were obtained using catalyst **34** at 40 °C in a sealed tube (70%). Substrate **38** also



Scheme 9.



Scheme 10.



Scheme 11.

required 60 min of microwave irradiation with **6** to undergo complete conversion to [7] helicene (81% isolated yield). Milder conditions with catalyst **34** also produced a 80% isolated yield of [7] helicene. The two reaction systems developed reinforce that recent advances in olefin metathesis catalyst development have afforded catalysts that can be remarkably effective in generating strained molecular architectures. Furthermore, they emphasize that RCM can be a powerful route to prepare aromatics, despite the substitution patterns.

5. Conclusions

The above case studies demonstrate that olefin metathesis is a viable strategy towards strained ring systems. In many cases, the use of auxiliaries that act as conformational restraints greatly influences the outcome of the metathesis reaction. To date, these ''gearing elements'' render certain conformations more favourable through purely steric interactions such as the minimization of $A^{1,3}$ strain, or a combination of steric and electronic factors, such as through π-stacking interactions. In addition, the variety of different catalysts that have been developed allows for the possibility to select a catalyst having the necessary level of reactivity to access a strained system but also to avoid catalysts which may be so reactive as to favour ring-opening of the desired ring system. It is evident that more diverse gearing elements are necessary so that greater variety of ring systems could be formed via olefin metathesis. In addition, it is conceivable that as further advancements in catalyst design are made, different and more varied ring systems will become accessible via a RCM.

Acknowledgements

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