Tetrahedron 64 (2008) 6909–6919

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Selective tandem enyne metathesis for the synthesis of functionalized cycloheptadienes☆

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ARTICLE INFO

Article history:
Received 30 January 2008
Received in revised form 5 March 2008
Accepted 7 March 2008
Available online 12 March 2008

Keywords:
Ring synthesis
Ring expansion
Enyne metathesis
Grubbs' catalyst
1,3-Cycloheptadiene
Regioselectivity
Site-selectivity

ABSTRACT

The regio- and site-selective ring expansion of dienes and the regioselective ring expansion of substituted cyclopentenes provide 1,3-cycloheptadienes by enyne metathesis under methylene-free conditions. Site-selectivity results from differential ring strain among two different cycloalkenes in diene reactants. The high regioselectivity found in the ring expansion of tetrahydroindene (THI) is explained on the basis of a selective ring opening by the second generation Grubbs' ruthenium carbene complex. The ring opening of substituted cyclopentenes and cyclopentene contained in a bicyclic ring system was also achieved. The ring expansion of bicyclic dienes provided seven-membered dienes contained in the bicyclo[5.2.0]nonane ring system. Details of the structural analysis are also discussed. A mechanistic analysis is provided to account for the data presented herein.

1. Introduction

Metathesis has become a powerful synthetic transformation in organic synthesis. In particular, the ring-closing metathesis has been well used in complex molecule synthesis. More recently, cross-metathesis methods have developed to conjoin two different alkenes in alkene metathesis or an alkene and an alkyne in enyne metathesis. Ring synthesis from two unsaturated reactants in an intermolecular reaction is less common. Ring synthesis between an alkene and an alkyne is actually an in situ sequence of cross-metathesis followed by ring-closing metathesis occurring in a cascade. As a result, the ring synthesis is both potentially complex and potentially very powerful. In this report, we extend the ring synthesis of 1,3-cycloheptadienes to furnish bicyclic ring systems (Scheme 1). In this process, cycloalkene reactivity determines site-selectivity and the factors controlling regioselectivity are addressed.

There are a number of concerns in achieving an effective cross-metathesis. In general, cross-metathesis methods suffer from poor control of alkene stereoselectivity. The selectivity often depends on the catalyst being used. Usually, the more reactive second generation Grubbs' ruthenium carbene **1** gives products predominantly with *E*-selectivity. This process occurs due to the greater alkene reactivity of the metal carbene, and it can equilibrate the products by a subsequent cross-metathesis reaction. For instance, in enyne metathesis, the equilibration of initially produced *Z*-diene products was found in mechanistic studies using the second generation Grubbs' carbene complex.[1] This study also showed that *Z*-dienes were kinetically produced along with the *E*-isomer and the former underwent subsequent equilibration to give predominantly the *E*-isomer. On the other hand, control of *Z*-selectivity is not presently controlled simply through selection of an appropriate metal carbene complex. This defines a major problem in olefin metathesis today. One of the major problems in the intermolecular ring synthesis is also one of stereoselection. To bring together the ends and achieve a ring-closing metathesis, the intermediate must have the *Z*-alkene double bond geometry. Scheme 2 illustrates the intermediate carbene that can experience ring closure. The *Z*-vinyl carbene holds the ruthenium carbene close to the pendant alkene so that an intramolecular ring-closing metathesis can occur to give diene **2** (Eq. 1). Since the ring closure is believed to be stereospecific with respect to alkene geometry, the *E*-isomer cannot close to give the cycloheptadiene product and instead proceeds to an intermolecular reaction manifold (Eq. 2).

In fact, the first example of ring synthesis by cross-enyne metathesis produced two products illustrating no control of stereoselectivity (Eq. 3). In this reaction, 1,5-hexadiene reacted with 1-alkynes to give two products in an approximately 1:1 ratio.[2] The

☆ The authors wish to congratulate Professor John Hartwig for recognition of his outstanding accomplishments in mechanistic organometallic chemistry and organic synthesis.

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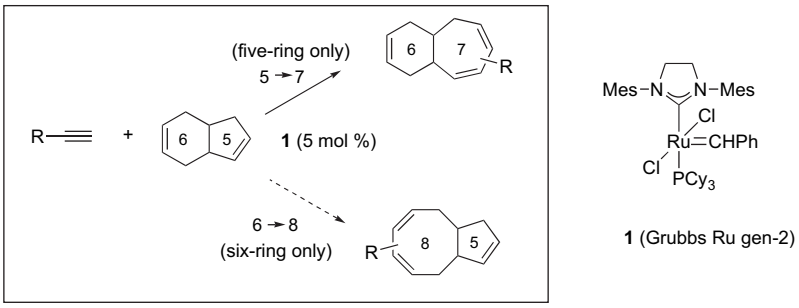
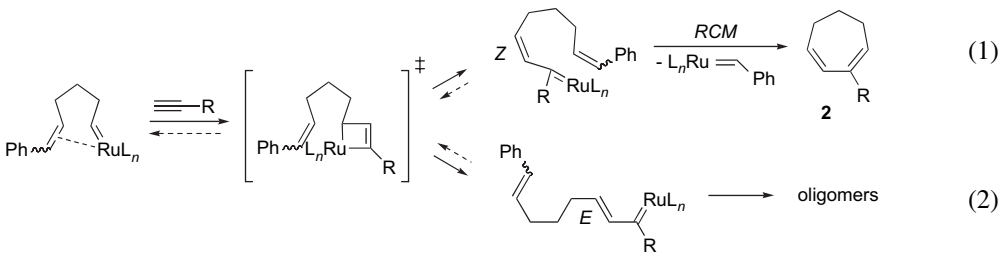
doi:10.1016/j.tet.2008.03.027



Scheme 1. Site-selective ring synthesis from bicyclic diene.

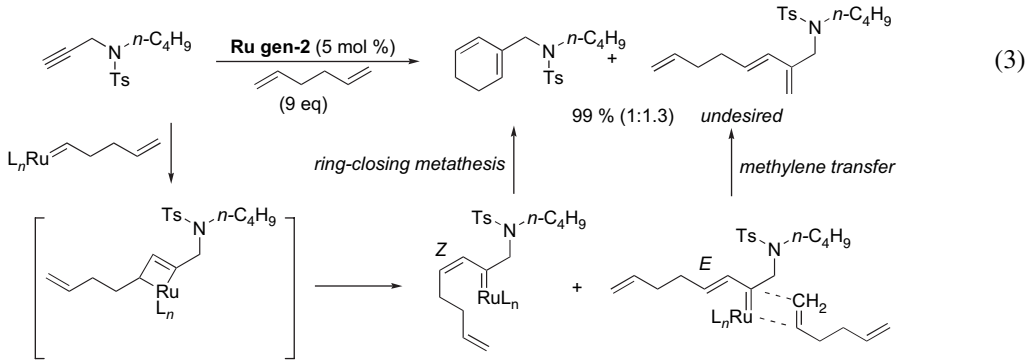


Scheme 2. Stereochemistry of intermediates leading to a successful ring synthesis.

desired 2-substituted-1,3-cyclohexadiene product arises from the appropriate intermediate vinyl carbene with the *Z*-stereochemistry, which has the right geometry for the ring-closing metathesis step. The *E*-isomer does not have the right geometry for ring closure and instead finds a CH_2 group with which to react, supplied by the large excess of 1,5-hexadiene reactant. Remarkably, this early example of a cyclohexadiene ring synthesis gave good yields of products, albeit in a 1:1 ratio. The 1:1 ratio shows that a nearly stereorandom process led to the formation of the intermediate vinyl carbenes. The rapid participation of the *Z*-diene in ring-closing metathesis presumably maintained the kinetic ratio of the intermediate vinyl carbenes. Ultimately, our attention focused on improving the yield of the desired 1,3-cyclohexadiene by removing the source of methylene.

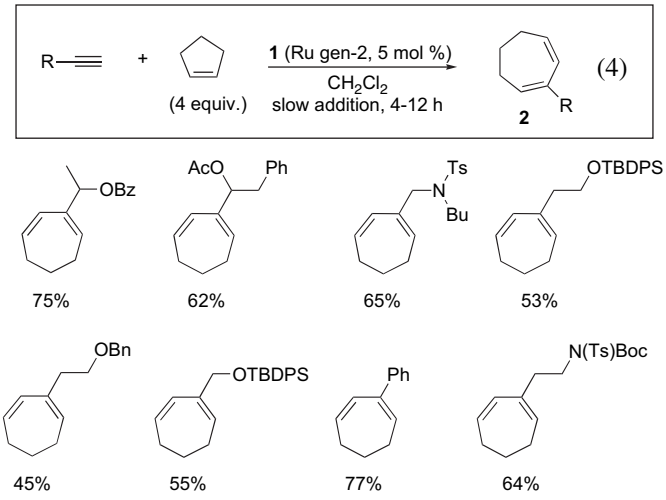
Our efforts toward the ring synthesis of both six- and seven-membered ring dienes focused on the scenario where no methylene (CH_2) sources were present. On the most simplistic mechanistic level, the *E*-intermediate in Scheme 3, which found a CH_2 group to give an unwanted byproduct, would not have this pathway available. Depriving the carbenes of CH_2 sources led us to characterize the reaction conditions as 'methylene-free'.[3] Early on, this drew an important contrast between typical cross-enyne metatheses,[4] which had exclusively used 1-alkenes in conjunction with either terminal or internal alkynes (by far terminal alkynes saw the most reaction development).[5] In the earlier examples, there was always a source of CH_2 because the 1-alkene was used and always used in molar excess. Our aim to eliminate the CH_2 source was also somewhat unconventional at the time since an $L_nRu{=}CH_2$ was considered to be the reactive carbene intermediate, which reacted with the alkyne (known as a 'methylidene-first' mechanism). We hypothesized that in the absence of a CH_2 source, the two vinyl carbenes might equilibrate. The development of the ring synthesis was largely based on our working model for the reaction mechanism, which eventually led to more detailed kinetic analysis.[6] The absence of methylene source led to the development of a ring synthesis to form six-membered rings.[3] For the synthesis of cycloheptadienes **2**, the reaction mechanism is believed to involve a ring opening of cyclopentene, alkyne insertion, equilibration of vinyl carbenes, and a ring-closing metathesis to furnish the products (Scheme 2, above). The six-membered ring synthesis has also been shown to be scalable, and when conducted on larger scale, the catalyst loading was decreased.[7]

The ring expansion by enyne metathesis provides an effective means for the synthesis of 2-substituted-1,3-cycloheptadienes.[8] The cycloheptadiene can be fashioned from the five carbons available from cyclopentene. This ring synthesis actually starts from



Scheme 3. Ring synthesis (with methylene sources) using 1,5-hexadiene.

an existent ring, so it is a special case of methylene-free enyne metathesis known as ring expansion. Some examples of 2-substituted 1,3-cycloheptadienes formed in this reaction are shown in Scheme 4. The ring expansion using a variety of 1-alkynes worked effectively giving yields that exceeded 50%. A variety of heteroatom functionality could be carried out on the alkyne reactant. In addition, substitution was tolerated at the propargylic center. We noted lower isolated yields using alkynes with potentially coordinating heteroatoms at the homopropargylic position, though these reactions were not further optimized from the standard conditions. Fifty percent yields would have been predicted on the basis of a completely stereorandom process, such as that depicted in Eq. 3. We supposed that either the *E*- and *Z*-vinyl carbenes could equilibrate or that additional back-biting could be occurring from an oligomeric structure (or some combination of the two). These possibilities are discussed in greater detail in the previous report. We did not previously examine substituted cyclopentenes though we did report one case of a silicon-containing ring that underwent expansion to give a silepin.[8]



Scheme 4. Ring expansion of five-membered rings by enyne metathesis (Ref. 8).

With the successful ring expansion to make seven-membered rings, we were interested in extending the reaction scope further. We had four questions that guided our efforts to improve the scope of ring expansion by enyne metathesis. First, do substituted cyclopentenes give the reaction? Second, in nonsymmetric cyclopentenes, what factors will influence the regioselectivity? For instance, in substituted cyclopentenes **A**, the carbene can approach in two different ways giving rise to regioisomeric alkylidenes **B** and **C**, which would produce a mixture of products (Scheme 5, panel a). Third, in dienes where there are two different potentially reactive cycloalkenes, can one be induced to react selectively over the other (site-selectivity; Scheme 5, panel b)? If so, what controls the differences in reactivity between cycloalkenes? Finally, can the hypothesized equilibration of carbene intermediates under methylene-free conditions provide good yields of ring-containing products in systems with additional complexity (rings or additional alkene functionality)? These questions guided us in our investigation and have led us to preliminary conclusions in each of these areas of inquiry.

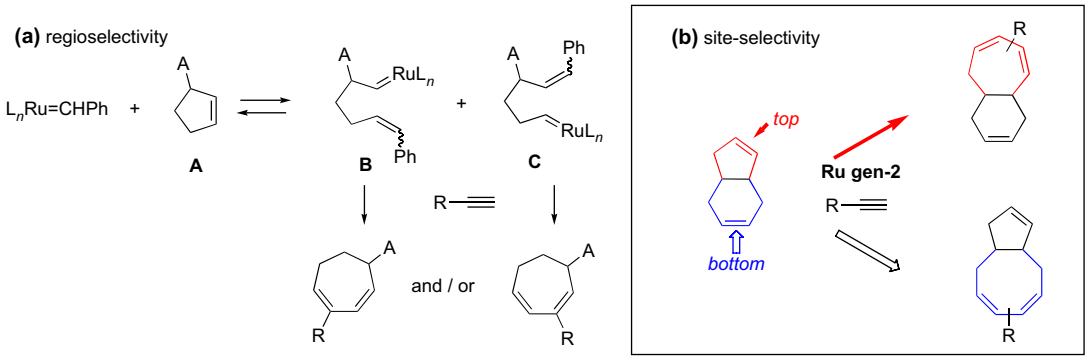
2. Results and discussion

Given the expectation that different ring sizes might confer differential reactivity in the ring expansion, we sought a diene that contained two isolated alkenes in different rings. Tetrahydroindene (THI) has a cyclopentene and a cyclohexene available for reaction and it is commercially-available. The two alkenes are distant enough from each other that little interaction was expected between the two. With a suitable test system in hand, we investigated the cycloheptadiene synthesis under standard conditions, which we had optimized previously, using 5 mol % Grubbs' catalyst **1** and fourfold excess of the cyclopentene.

Under the standard conditions, a variety of 1-alkynes underwent selective ring expansion. In these runs, we simply used 4 equiv of THI instead of cyclopentene. The results are summarized in Table 1.

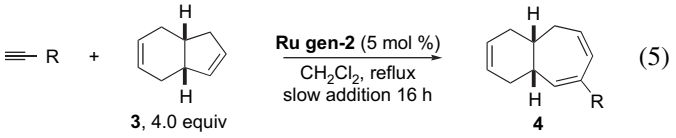
As it can be seen from Table 1, the reaction shows a wide substrate scope with terminal alkynes. Propargylic esters as well as silyl ethers are good substrates for this transformation (entries 1 and 2). In the next three entries, the presence of homopropargylic oxygen functionality was evaluated. In general, the ester functionality performed well, even at this homopropargylic position (entry 3). The more Lewis basic benzyl ether in entry 4 gave slightly lower isolated yields, possibly due to its ability to coordinate to the intermediate vinyl carbene. Interestingly, the tosyl group can be handled in the ring synthesis (entry 5) despite its tendency to undergo E2 elimination to produce a conjugated enyne. Nitrogen in the alkyne side chain is also tolerated whether it is spaced two or three carbons away (entries 6 and 7). A more remote naphthoate ester posed no difficulties, again despite the potential for chelation at this position (which would form a six-membered chelate with the proximal vinyl carbene). Finally, this procedure is well suited for the incorporation of hydrocarbon side chains on the bicyclic triene (entries 9 and 10) using the appropriate alkyne substrates. Due to the effectiveness of the reaction, we did not evaluate additional ruthenium carbenes for this transformation.

Additional observations not included in the table also shed light on the scope and effectiveness of the ring synthesis. In one case, an α-substituted propargylic ester gave good conversion using the conditions of Table 1. Unfortunately, the product proved to be an

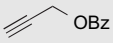
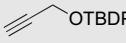
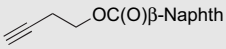
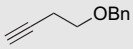
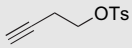
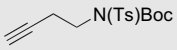
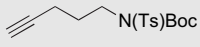
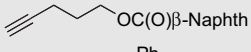
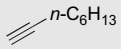


Scheme 5. Possibilities in more complex systems: regio- and site-selection.

Table 1
Site-selective ring expansion using the diene tetrahydroindene



(5)

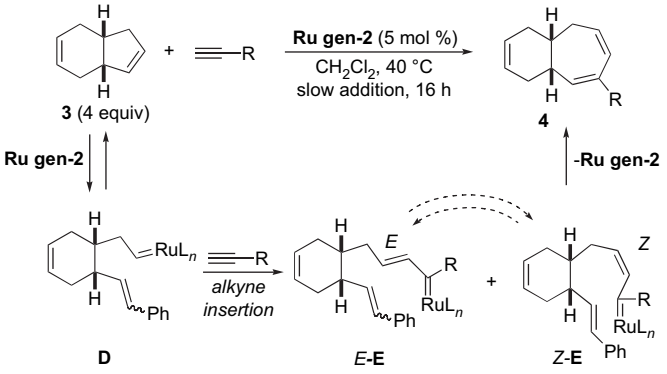
Entry	Alkyne	Bicyclic triene **4**	Yield (isolated, %)
1		**4A**, R=CH_2OBz	76
2		**4B**, R=$CH_2OTBDPS$	55
3		**4C**, R=$(CH_2)_2OC(O)\beta$-Naphth	58
4		**4D**, R=$(CH_2)_2OBn$	46
5		**4E**, R=$(CH_2)_2OTs$	45
6		**4F**, R=$(CH_2)_2N(Ts)Boc$	64
7		**4G**, R=$(CH_2)_3N(Ts)Boc$	62
8		**4H**, R=$(CH_2)_3OC(O)\beta$-Naphth	59
9		**4I**, R=Ph	77
10		**4J**, R=n-C_6H_{13}	45

inseparable mixture of diastereomers. Most of the transformations summarized in Table 1 (entries 2–10) were performed on a relatively small scale (0.2 mmol of the alkyne or lower). On such a scale, the isolation of the product by silica gel flash column chromatography resulted in partial decomposition of the triene products **4**. It was observed that the reaction affords higher yield when run on a larger scale (1 mmol of the alkyne). One such example is the use of propargyl benzoate as alkyne (entry 1). When the reaction was performed on a 0.2 mmol scale (alkyne), the product **4A** was obtained in 56% isolated yield; when the same transformation was carried out on a 1.0 mmol scale (alkyne), the isolated yield of the product **4A** was found to be 76%. The other entries of Table 1 were not duplicated on larger scale, but it is anticipated that material losses will be proportionally less significant as the reactions are conducted on larger reaction scale.

The syringe pump addition is a somewhat specialized procedure used to suppress alkyne polymerization. Alkyne oligomerization is believed to be particularly problematic with terminal alkynes and more reactive carbene initiators. Slow addition is used in the ring expansion to keep the alkyne concentration low to minimize alkyne oligomerization. Alkyne oligomerization can occur by multiple alkyne insertion into carbene intermediates. In fact, we had recently identified a process of alkyne oligomerization involving the ruthenium vinyl carbene intermediates in a phosphine-free system.[9] The slow addition is also meant to allow the *E*-vinyl carbene intermediate to undergo equilibration.

The regiochemistry of alkyne insertion follows the 'alkylidene-first' mechanism of enyne metathesis.[6,10–12] We assume that the cyclopentene reacts first with Grubbs' benzylidene. Once the ring opening has occurred, alkyne insertion takes place to give the isomeric vinyl carbenes *E*-**E** and *Z*-**E** (Scheme 6). We suggest that the ring closure arises from the *Z*-isomer and the *E*-isomer undergoes partial equilibration under the reaction conditions.[3,8] Based on the DFT calculations for enyne metathesis by Lippstreu and Straub, the alkyne insertion is believed to be irreversible.[13] Our own experiments to effect reversal and crossover in 2-substituted-1,3-cycloheptadienes failed, which indicated no net reversibility.[14]

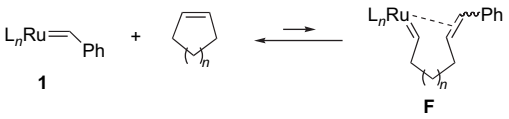
Based on this, we suggest that the alkyne insertion represents a 'high commitment' step for the catalyst and the resulting vinyl carbene intermediates do not revert to carbene **D** under the normal reaction conditions.



Scheme 6. Proposed mechanism of site- and regioselective ring synthesis.

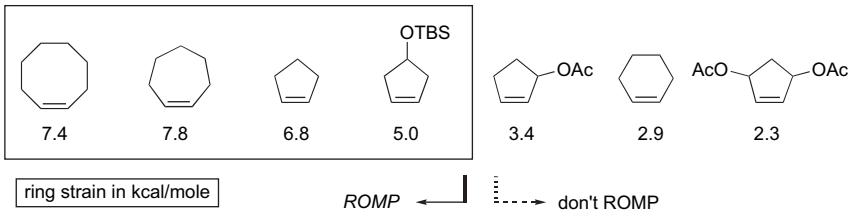
The synthesis of small and medium rings by the enyne metathesis-based ring synthesis depends on the strain in the cycloalkene reactant. On one hand, strain is required to open the cycloalkene in the first place. However, with too much strain, the cycloalkene will participate in a rapid self-metathesis and lead to ring-opening metathesis polymerization (ROMP).[15] If we were to use strained alkenes in the ring synthesis, ROMP will become a competing process consuming the alkene. To minimize this competing process, we have preferred not to use highly strained cycloalkenes. For the seven-membered ring synthesis, cyclopentene is used. Cyclopentene is considered to be a 'low-strain' cycloalkene (ca. 2–10 kcal/mol range).

Since different cycloalkenes have different ring strain, we expected that selectivity might be possible among diene reactants that possess two different cycloalkenes (as depicted in Scheme 1). Our analysis focused on strain as a determinant for reactivity in the ring-opening step. The ring opening is a reversible process that generates a reactive alkylidene species **F** (Eq. 6). The alkylidene is born with a coordinated alkene, which is poised to undergo the reverse reaction, ring-closing metathesis. If there are two different cycloalkenes competing for reaction with the ruthenium carbene catalyst, the one that is most kinetically accessible (steric approach) and most strained will result in the highest population of reactive alkylidene **F**. Greater cycloalkene ring strain will limit the back reaction, thereby permitting the alkylidene time to bind and react with the alkyne. Though the ring opening is not the sole determinant of an effective overall ring synthesis, it is the necessary first step. An inefficient reaction could be predicted in the case of a very stable, unreactive alkene or in the case where the back reaction is accelerated due to enforced proximity (e.g., Thorpe–Ingold effect). In either instance, any small amount of alkylidene produced in the reaction of Eq. 6 would quickly fall back to reactant.



(6)

Ring strain data is available from the ROMP literature. ROMP is similar to the ring synthesis in many ways. First, it involves a cycloalkene, which must be able to open by the metal carbene initiator. Second, once the cycloalkene has opened, it needs to participate in a cross-metathesis with additional cycloalkene rather

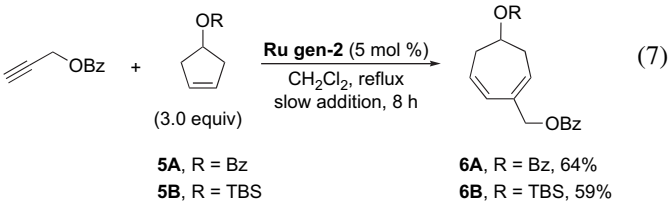


Scheme 7. Some 'low strain' cycloalkenes (Refs. 16 and 17).

than being engaged in the reverse reaction (ring-closing metathesis). When the ROMP reaction proceeds with another cycloalkene, the metal carbene telomerizes and the process can repeat, each time partitioning between forward reaction (ring opening) and back reaction (ring closing). The ring-opening steps should collectively release some degree of strain to keep ROMP productive. The stability of products from ROMP and the ring expansion may also dictate favorable reaction. ROMP produces a polymer, which can be destabilized by too many substituents in the backbone due to nonbonding interactions. As a result, monomers that are strained but highly substituted do not engage in ROMP, not because they do not open (kinetics), but because they do not form a thermodynamically stable product. ROMP works best for strained cycloalkenes such as norbornene. For comparison, the ring strain of norbornene is 27.2 kcal/mol.[16] Yet less strained cycloalkenes also participate in ROMP. What is the cutoff? Grubbs' group have studied low strain cycloalkenes and evaluated their ability to undergo ROMP. Grubbs et al. correlated ring strain with polymerization ability.[17] For example, all the neat cycloalkenes in the box of Scheme 7 undergo ROMP. The cutoff is in the vicinity of 4–5 kcal/mol of ring strain.

The data in Scheme 7 show that cyclopentene and cyclohexene are divided by their ability to undergo ROMP. Focusing on cyclopentene and cyclohexenes, there is ca. 4 kcal/mol difference in their ring strain (6.8 kcal/mol vs 2.9 kcal/mol). In metathesis, the ring opening of cyclohexene is difficult and rare.[18] The ring strain data above suggest that there should be a slight preference of the cyclopentene ring to undergo productive opening as compared to the cyclohexene ring, under nominal conditions of metathesis (CH_2Cl_2, reflux, 1–24 h).

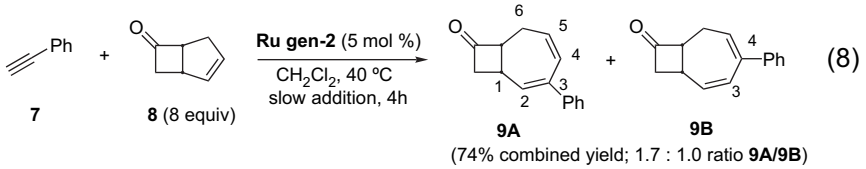
Given that 4-oxysubstituted cyclopentenes give ROMP, we examined their ability to participate in ring synthesis. Based on the data above, the 4-substituted cyclopentenes possess ca. 5 kcal/mol ring strain, which is similar to the amount of ring strain found in cyclopentene. The substrates **5A**[19] and **5B**[20] were prepared using known procedures. In the event, the substituted cyclopentenes **5A** and **5B** underwent an efficient ring expansion giving the corresponding 1,3-cycloheptadienes **6** in good yield. Presumably substituents located in the homoallylic position are too remote to affect the stability of intermediate carbenes or participate in chelation. The products of Eq. 7 are interesting for a number of reasons. First, the alkyne insertion process results in desymmetrization of a prostereogenic *meso*-substrate **5**. One can imagine that this process might be controlled through the use of chiral catalysis. Second, the resulting 1,3-cycloheptadienes can be readily functionalized, e.g., by Diels–Alder chemistry, and the rings feature substitution at the remote 6-position. As a result, the use of functionalized cyclopentene reactants permits access to more highly functionalized cycloheptadienes with remote substituents that would be difficult to introduce through conventional methods.



(7)

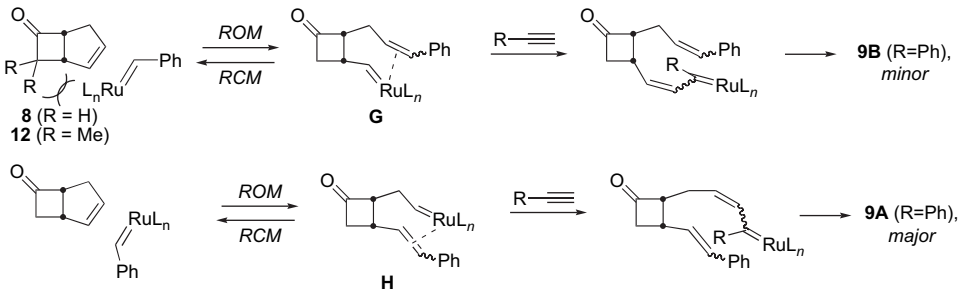
To further probe the effect of substitution on the cyclopentene, we next investigated a cyclopentene with a fused ring. In this instance, there is a single alkene reaction site, so there is no issue of site selection. However, we thought this system was interesting because of the potential to conduct further transformation on the diene products. Moreover, this bicyclic ring system presents a different framework that could influence regiochemistry. Because the regioselectivity had been high in the THI-alkyne ring expansion, we also expected high regioselectivity in the present case. Bicyclo[3.2.0]heptene **8** is commercially available. Applying the conditions in Table 1 to this ring expansion resulted in incomplete conversions, so the number of alkene equivalents was increased to eight. Under these conditions, complete consumption of phenylacetylene was found, but two products were formed (Scheme 8).

The cycloheptadiene mixture was obtained as a 1.7:1.0 mixture of **9A** and **9B**. Proton NMR spectroscopy was used to assign the constitution of the major and minor regioisomers that were formed. In Eq. 8, the major product bears phenyl substitution at the 3-position. The major isomer showed three vinyl protons: (1) a doublet at δ 6.48 (J=4.5 Hz) for the H2 proton coupled to the angular methine (H1), which appears as a broad multiplet at δ 3.94–3.87 ppm; (2) a doublet at δ 6.16 (J_{cis}=11.0 Hz, H4) coupled to, (3) a ddd appearing at δ 6.29 (J=11.0, 7.0, 7.0 Hz, H5), which shows an apparent triplet substructure due to ^3J coupling with the allylic methylene at C6. The minor isomer shows two distinct vinylic resonances at 6.39 (app t, J=7.0 Hz) and 6.37 (dd, J=12.0, 4.0 Hz) for H5 and H2, respectively. The combined yields proved comparable to those observed in the THI examples and in our previous work. Though the scope of the reaction looked promising with respect to yield, we wanted to understand the factors accounting for the reduced regioselectivity.



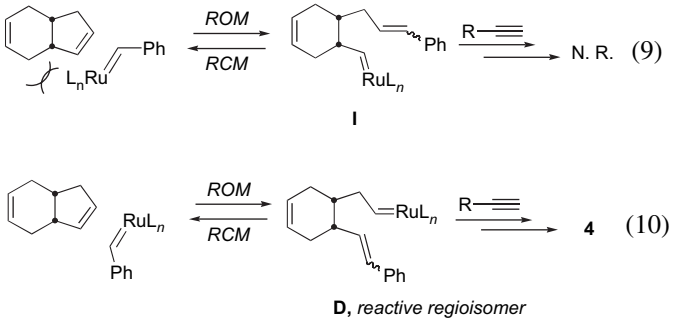
(8)

Scheme 8. Ring-opening of bicyclo[3.2.0]heptene.



Scheme 9. The reversible formation of carbene intermediates in preequilibrium.

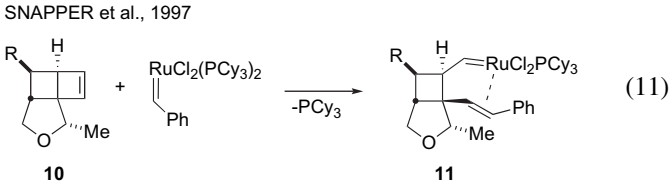
At this point, we considered possible reaction mechanisms to explain the difference in regioselectivity seen in the two bicyclic systems. There are two scenarios to explain the differences between the cyclopentene and THI above. First, it is conceivable that the carbenes **G** and **H** are formed by reversible ring opening and have different reactivity with alkynes in the next step (Scheme 9). Although the mechanism of enyne metathesis is not completely understood,[21] the reaction of 1-hexene and 1-alkynes shows a fast alkyne insertion and a slow turnover of the resultant *E*- and *Z*-vinyl carbenes.[6] Since the ring opening of the cyclopentene is believed to occur before the rate-determining step, it is possible that the ring opening is a preequilibrium that samples both carbene states **G** and **H**. Once carbenes **G** and **H** react with the alkyne, they are committed to enyne metathesis and are thus fated to form the regioisomeric products (e.g., **9B** and **9A**, above) in a regiospecific manner. In the preequilibrium state, where the energy barrier to RCM is lower than the alkyne insertion step, a Curtin–Hammett situation applies. In this case, the product ratio depends not on the relative ratio of the two carbenes, but rather depends on the barrier for each respective carbene to insert the alkyne. The results in Eq. 8 indicate that the carbene **H** reacts predominantly with alkyne to account for 63% of product **9A** and carbene **G** accounts for the remaining 37% of product **9B**. Though this analysis appears sound, it does not account for the marked difference in insertion barriers seen in the THI example above. That is to say, if we view the THI results above in terms of the Curtin–Hammett principle, then the corresponding carbenes **I** and **D** form under rapid preequilibrium conditions but only **D** reacts (Scheme 10). Why would carbene **D** (THI) behave so much differently than the corresponding carbene **H**?[22] The Curtin–Hammett analysis seems inconsistent because similarities of carbene substitution (e.g., **I** is like **G** and **D** is like **H**) predict similar reactivity, which is inconsistent with the different product ratios observed.



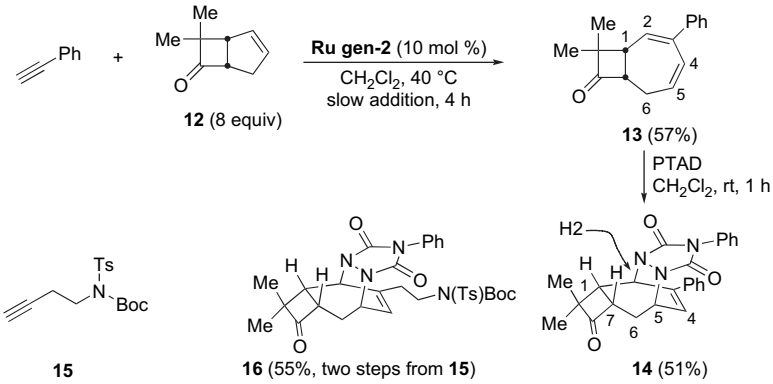
Scheme 10. Reversible formation of carbene intermediates with tetrahydroindene.

Another possible explanation is that of stereoselective ring opening by Grubbs' carbene complex. The cycloaddition of the metal carbene is sensitive to the steric environment of the alkene and will position the 'bulky' metal fragment away from the greatest steric bulk. In this picture, the different ratios of products are interpretable due to different steric factors of THI compared to the bicyclo[3.2.0]heptene. This analysis posits that the orientation depicted in Eq. 9 is unfavorable due to the steric bulk of the allylic substituent. As a result, the carbene adds predominantly with the orientation in Eq. 10 and carbene **D** forms exclusively. The most populous carbene then dominates the regiochemical path of reaction leading to product **4**. In the case of bicyclo[3.2.0]heptene shown in Scheme 9, the substituted allylic positions have less steric bulk. The endocyclic CH_2 group in the four-membered ring presents less bulk due to its angle constraint in the rigid four-membered ring. Loss of selectivity may be explained by nonselective opening of the cyclopentene giving carbenes **G** and **H**.

Steric bulk is known to account for selectivity in ring-opening metathesis. In pioneering work by Snapper et al.,[23] it was found that ring-opening cross-metathesis of strained cyclobutenes was possible (Eq. 11). In conjunction with the cross-metathesis, they discovered that the first generation Grubbs' carbene complex $(Cy_3P)_2Cl_2Ru{=}CHPh$ reacted with cyclobutene **10** to give a stable product **11** that contained a new carbene signal in the proton NMR. They isolated the new complex and determined its structure of a carbene 'caught in the act' of ring opening. Importantly, due to the unsymmetrical steric environment, Snapper observed a highly stereoselective reaction, consistent with a selective approach of the metal carbene. The observation of carbene **11** supports the notion that selectivity in ring opening of an unsymmetrical cycloalkene can be governed by the approach of Grubbs' complex. It is a noteworthy feature of this cyclobutenyl system that once ring opening occurs, there is no reverse reaction, so there are no concerns about a competing ring-closing metathesis obfuscating a kinetic result (the cyclobutene ring strain is 30.6 kcal/mol).[16] It should also be noted that Snapper's study was conducted with the first generation Grubbs' carbene, which has the bis(tricyclohexylphosphine) ligand environment.



To probe the theory that less bulk in the bicyclo[3.2.0]heptene accounts for the loss of regioselectivity, we tested the corollary hypothesis that greater steric bulk should 'restore' selectivity. The introduction of geminal methyl groups at the α-position increases the steric bulk of the small endocyclic CH_2 group. The larger group would impose steric strain between the L_nRu fragment and the allylic R groups (**8** vs **12**, Scheme 9, above). Steric bulk was introduced at the α-position and the analogous bicycloalkene **12** was used in the ring expansion. The synthesis of the required substrate



(12)

Scheme 11. Regiochemical outcome with α,α-disubstitution on bicyclo[3.2.0]heptene **12**.

followed a literature procedure[24] (2+2 cycloaddition of dimethylketene and cyclopentadiene). In the ring synthesis under the conditions above, a good yield of diene **13** was obtained. Significantly, the bicyclic product was obtained as a single regioisomer with none of the minor isomer detected in the crude ^{1}H NMR spectrum (Scheme 11).

Similar results were obtained using alkyne **15**, however, the obtained diene proved unstable to chromatography on silica gel and was trapped in situ with PTAD to afford the cycloadduct *endo*-**16** obtained in 55% yield over two steps. The adduct **16** was also obtained as a single regioisomer. Though a large excess of the bicycloalkene **12** was used, most could be recovered unchanged from the reaction (95% recovery of theoretical 7.0 equiv).

Spectroscopic analysis firmly established regiochemistry. The proton NMR of the bicyclodiene **13** showed the expected vinylic doublet at δ 6.39 (J=5.0 Hz), coupled to the angular methine proton at C1. Similarly, the vinylic proton H4 appears as a doublet at δ 6.13 (J=11.0 Hz) coupled to a doublet of triplets at δ 6.28 (dt, J=11.0, 6.5 Hz), which also shows ^3J allylic coupling to the methylene at C6. The crude ^{1}H NMR spectrum of the diene from **15** showed a single isomer with characteristic vinylic resonances at δ 6.07 (dt, J=13.0, 8.5 Hz), a broad singlet at δ 5.87, and a doublet at δ 5.86 (J=13 Hz). Similarly, the cycloadduct **14** showed the contiguous H4–H5–H6–H7–H1–H2 connectivity determined from ^{1}H–^{1}H COSY analysis. The structure of the adduct **14** corroborated the diene regiochemistry, which was assigned on the basis of coupling in the 1D ^{1}H NMR spectrum.

We verified the assignment of regiochemistry through single crystal X-ray structural analysis of the crystalline Diels–Alder cycloadduct **14**. Diene **13** was subjected to Diels–Alder cycloaddition with *N*-phenyl-1,3,5-triazolo-2,4-dione (1.1 equiv PTAD) to provide the cycloadduct **14**, mp 133–135 °C, in good yield (Scheme 11, above). X-ray quality crystals were grown from benzene by slow diffusion of pentanes. The ORTEP drawing of the resulting structure is depicted in Figure 1. Not surprisingly, the cycloadduct was formed exclusively by cycloaddition to the convex face of the bicyclic diene and was produced solely as the *endo*-diastereomer.

The mechanism to account for the high regioselectivity in these cases is consistent with a selective ring opening by Grubbs' carbene **1**. The ligand set on ruthenium is positioned away from the allylic substituent to avoid steric strain (see **18**, Eq. 13). The ring opening accesses one major carbene species, which inserts an alkyne to give

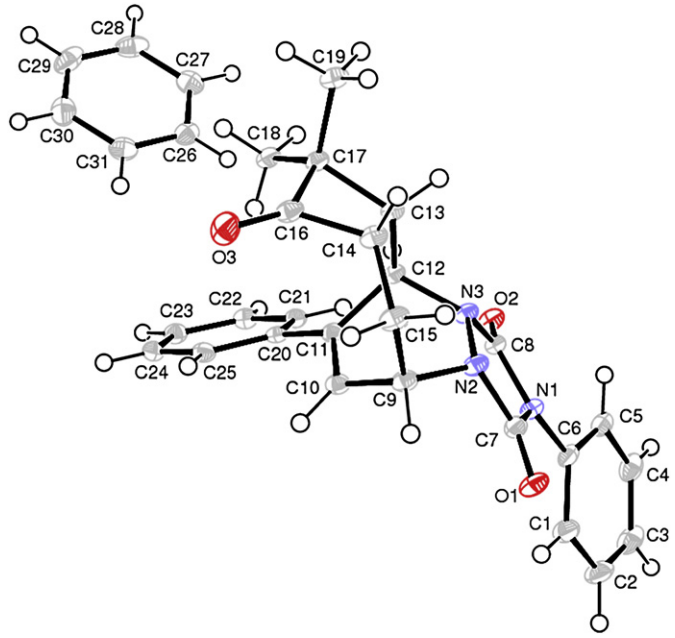
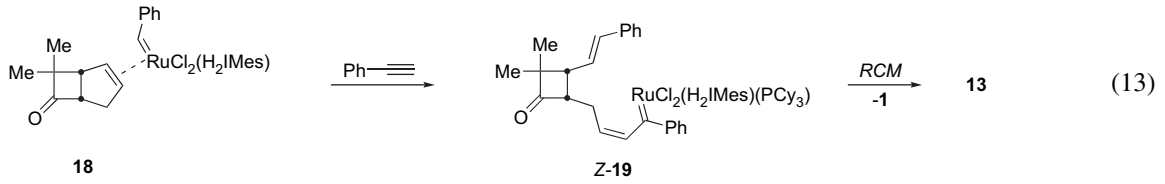


Figure 1. ORTEP drawing of *rac*-14. Thermal ellipsoids are drawn at 50% probability. One molecule of benzene was found in the unit cell. Note that the crystallographic numbering is not the same as that used in Scheme 11.

vinyl carbene intermediates, e.g., **19**. Progression through RCM would then give the ring expansion product **13**.

In conclusion, the regio- and site-selective ring synthesis of 1,3-cycloheptadienes has been achieved using differential ring strain as the basis for chemical reactivity in the ring expansion. The high regioselectivity found in the ring synthesis derived from the diene tetrahydroindene (THI) can be explained by a selective ring opening by Grubbs' ruthenium carbene complex. The ring opening of substituted cyclopentenes and cyclopentene contained in a bicyclic ring system was also achieved. In accordance with the regioselectivity model, bulkier substituents at the allylic position lead to high selectivity. Future studies are directed to extend the reaction to other bicycloalkenes, expanding the repertoire of cyclopentenes



(13)

and alkynes participating in the reaction and further mechanistic studies to better understand the role of ring strain in the overall ring synthesis.

3. Experimental

3.1. General information

Reactions were conducted under argon atmosphere unless otherwise noted. Solvents were dried and degassed under argon by a solvent purification system and drawn immediately prior to use. Dichloromethane, tetrahydrofuran, and ether were dried by passage through alumina, and benzene and toluene were dried and deoxygenated using columns of alumina and Q5. Ruthenium [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidine]dichloro(phenylmethylene)(tricyclohexylphosphine) (Grubbs' second generation catalyst) was obtained from Materia, Inc. (Pasadena, CA) or purchased from Aldrich Chemical Co. 1,5-Hexadiene was purified by distillation from sodium metal. All other chemicals were purchased from Aldrich Chemical Co. and used as-received. Column chromatography was carried out on Merck silica gel 60 (230–400 mesh). ^{1}H NMR spectra were recorded at 300, 400, or 500 MHz and ^{13}C NMR spectra at either 75 or 125 MHz in the indicated solvent. ^{1}H NMR spectra were referenced on the TMS signal. The ^{13}C NMR spectra were referenced at 77 ppm for $CDCl_3$. Enantiomeric excesses were determined by HPLC using a Chiralcel OD-H column (4.6 mm×250 mm, 5 μm particle size) using UV detection.

3.2. General procedure for the THI—alkyne tandem metathesis (Table 1)

An oven-dried 50 mL Schlenk tube equipped with a magnetic stir bar and a cold finger condenser was charged with 10 mL CH_2Cl_2 followed by Grubbs' second generation catalyst (10.5 mg, 5 mol %) and this solution was immersed into an oil bath maintained at 45 °C. Alkyne (0.25 mmol) and THI (120 mg, 1 mmol) were dissolved in 2.0 mL CH_2Cl_2. This solution was added to the solution of the catalyst in CH_2Cl_2, maintained at 45 °C over a period of 16 h by means of a gas-tight syringe (syringe pump). After the addition was complete, the reaction mixture was stirred at reflux for an additional 45 min. At this stage, the reaction mixture was concentrated to yield dark brown oil. The latter was purified by flash column chromatography using silica gel. Elution with the indicated eluent yielded the corresponding bicyclic trienes.

*3.2.1. {(5E,7Z)-4,4a,9,9a-Tetrahydro-1H-benzo[7]annulen-6-yl}methyl benzoate (**4A**)*

The experiment was performed as per the general experimental. The bicyclic triene **4A** was obtained as pale yellow oil (53 mg, 76% yield) after purification of the crude reaction mixture using silica gel flash column chromatography (elution with 2% ethyl acetate in hexanes). Analytical TLC: R_f 0.41 (10% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.06–8.04 (m, 2H), 7.55 (t, *J*=8.0 Hz, 1H), 7.43 (t, *J*=8.0 Hz, 2H), 5.88–5.83 (m, 1H), 5.82–5.80 (m, 2H), 5.66–5.62 (m, 1H), 5.57–5.54 (m, 1H), 4.74 (m, 2H), 2.76 (d, *J*=3.5 Hz, 1H), 2.47–2.40 (m, 1H), 2.37–2.23 (m, 3H), 2.15–2.09 (m, 1H), 2.04–2.00 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 166.5, 136.4, 133.4, 132.8, 131.0, 130.4, 129.6, 128.3, 126.5, 124.9, 124.0, 70.9, 38.3, 34.3, 33.7, 31.0, 30.8; FTIR (thin film, cm^{-1}) 2939, 1719, 1237, 1097. High-resolution MS (EI$^+$, *m*/*z*) molecular ion calcd for $C_{19}H_{20}O_2$: 280.1458, found: 280.1466.

*3.2.2. tert-Butyldiphenyl{[(5E,7Z)-4,4a,9,9a-tetrahydro-1H-benzo[7]annulen-6-yl]methoxy}silane (**4B**)*

The experiment was performed as per the general experimental. The bicyclic triene **4B** was obtained as colorless oil (57 mg, 55% yield) after purification of the crude reaction mixture using silica gel flash column chromatography (elution with 1% ethyl acetate in hexanes). Analytical TLC: R_f 0.44 (10% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.69–7.67 (m, 4H), 7.44–7.35 (m, 6H), 5.80–5.75 (m, 1H), 5.68–5.64 (m, 3H), 4.11 (s, 2H), 2.73–2.69 (m, 1H), 2.43–2.37 (m, 2H), 2.27–2.19 (m, 2H), 2.12–1.97 (m, 3H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 135.6, 134.3, 133.9, 132.1, 131.1, 129.5, 127.6, 126.6, 124.9, 124.3, 68.9, 38.0, 34.4, 33.9, 31.6, 30.8, 26.8, 19.3; FTIR (thin film, cm^{-1}) 2858, 1428, 1111, 824, 703, 613. High-resolution MS (EI$^+$, *m*/*z*) molecular ion calcd for $C_{28}H_{34}O_1Si_1$: 414.2373, found: 414.2364.

*3.2.3. 2{(5Z,7Z)-4,4a,9,9a-Tetrahydro-1H-benzo[7]annulen-6-yl}ethyl 2-napthoate (**4C**)*

The experiment was performed as per the general experimental. The bicyclic triene **4C** was obtained as pale yellow oil (50 mg, 58% yield) after purification of the crude reaction mixture using silica gel flash column chromatography (elution with 2% ethyl acetate in hexanes). Analytical TLC: R_f 0.40 (10% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.59 (s, 1H), 8.05 (d, *J*=8.0 Hz, 1H), 7.94 (d, *J*=8.0 Hz, 1H), 7.88–7.66 (m, 2H), 7.60–7.52 (m, 2H), 5.85–5.80 (m, 1H), 5.75 (d, *J*=12.5 Hz, 1H), 5.67–5.51 (m, 3H), 4.42 (m, 2H), 2.68 (s, 1H), 2.53 (m, 2H), 2.32 (m, 2H), 2.24–2.20 (m, 2H), 2.01–1.97 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 166.7, 135.5, 133.3, 132.9, 132.5, 131.9, 131.0, 129.3, 128.1, 128.0, 127.73, 127.68, 127.4, 126.7, 126.5, 125.3, 124.3, 64.6, 39.1, 38.0, 35.2, 34.6, 31.5, 30.6; FTIR (thin film, cm^{-1}) 2899, 1716, 1283, 1228, 1196, 1097. High-resolution MS (EI$^+$, *m*/*z*) molecular ion calcd for $C_{24}H_{24}O_2$: 344.1771, found: 344.1769.

*3.2.4. (4a,5Z,7Z,9a)-6-{2-(Benzyloxy)ethyl}-4,4a,9,91-tetrahydro-1H-benzo[7]annulene (**4D**)*

The experiment was performed as per the general experimental. The bicyclic triene **4D** was obtained as colorless oil (32 mg, 46% yield) after purification of the crude reaction mixture using silica gel flash column chromatography (elution with 1% ethyl acetate in hexanes). Analytical TLC: R_f 0.44 (10% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.35–7.31 (m, 4H), 7.28–7.55 (m, 1H), 5.77–5.73 (m, 1H), 5.66 (dd, *J*=12.0, 1.0 Hz, 1H), 5.62–5.60 (m, 1H), 5.47 (d, *J*=5.5 Hz, 1H), 4.51 (s, 2H), 3.53 (t, *J*=7.5 Hz, 2H), 2.67–2.63 (m, 1H), 2.36 (t, *J*=7.5 Hz, 2H), 2.30 (t, *J*=5.5 Hz, 2H), 2.24–2.19 (m, 2H), 2.09–2.04 (m, 1H), 2.00–1.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 138.6, 133.4, 132.6, 132.3, 128.3, 127.8, 127.6, 127.4, 126.6, 124.3, 72.8, 70.4, 40.1, 38.0, 35.0, 34.4, 31.3, 30.8; FTIR (thin film, cm^{-1}) 3021, 2898, 1451, 1361, 1101, 736. High-resolution MS (ESI$^+$, *m*/*z*) molecular ion calcd for $C_{20}H_{24}O_1Na_1$: 303.1719, found: 303.1724 $(M+Na)^+$.

*3.2.5. 2-{(4a,5Z,7Z,9a)-4,4a,9,9a-Tetrahydro-1H-benzo[7]annulen-6-yl}ethyl-4-methylbenzenesulfonate (**4E**)*

The experiment was performed as per the general experimental. The bicyclic triene **4E** was obtained as pale yellow oil (39 mg, 45% yield) after purification of the crude reaction mixture using silica gel flash column chromatography (elution with 10% ethyl acetate in hexanes). Analytical TLC: R_f 0.37 (30% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.78 (d, *J*=8.0 Hz, 2H), 7.33 (d, *J*=8.0 Hz, 2H), 5.75–5.71 (m, 1H), 5.62–5.58 (m, 1H), 5.55–5.49 (m, 2H), 5.40 (d, *J*=5.5 Hz, 1H), 4.05 (t, *J*=7.0 Hz, 2H), 2.62–2.58 (m, 1H), 2.45 (s, 3H), 2.35 (t, *J*=7.0 Hz, 2H), 2.27 (t, *J*=5.5 Hz, 2H), 2.21–2.14 (m, 2H), 2.07–2.02 (m, 1H), 1.96–1.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 144.6, 134.9, 133.3, 133.2, 130.3, 129.8, 127.9, 126.8, 126.5, 124.6, 70.0, 39.0, 38.0, 34.8, 34.3, 31.1, 30.7, 21.6; FTIR (thin film, cm^{-1}) 2900, 1599, 1361, 1178, 1098, 963, 817, 773. High-resolution MS (ESI$^+$, *m*/*z*) molecular ion calcd for $C_{20}H_{24}O_3S_1Na_1$: 367.1338, found: 367.1339 $(M+Na)^+$.

*3.2.6. tert-Butyl 2-{(4a,5Z,7Z,9a)-4,4a,9,9a-tetrahydro-1H-benzo[7]annulen-6-yl}ethyl(tosyl)carbamate (**4F**)*

The experiment was performed as per the general experimental. The bicyclic triene **4F** was obtained as pale yellow oil (70 mg, 64% yield) after purification of the crude reaction mixture using silica gel flash column chromatography (gradient elution with 5% ethyl acetate in hexanes, followed by 10% ethyl acetate in hexanes). Analytical TLC: R_f 0.34 (30% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.79 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.0 Hz, 2H), 5.82–5.74 (m, 2H), 5.63–5.60 (m, 1H), 5.56–5.52 (m, 2H), 3.87–3.83 (m, 2H), 2.69–2.65 (m, 1H), 2.47–2.45 (m, 2H), 2.43 (s, 3H), 2.34–2.30 (m, 2H), 2.27–2.19 (m, 2H), 2.11–2.06 (m, 1H), 2.01–1.94 (m, 2H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 150.8, 144.0, 137.5, 134.1, 132.7, 132.2, 129.1, 127.8, 127.4, 126.4, 124.2, 84.0, 47.3, 40.5, 38.1, 34.5, 34.3, 31.1, 30.9, 27.8, 21.5; FTIR (thin film, cm^{-1}) 2901, 1727, 1357, 1289, 1158, 673. High-resolution MS (ESI^+, m/z) molecular ion calcd for $C_{25}H_{33}O_4N_1S_1Na_1$: 466.2023, found: 466.2017 $(M+Na)^+$.

*3.2.7. tert-Butyl 3-{(4a,5Z,7Z,9a)-4,4a,9,9a-tetrahydro-1H-benzo[7]annulen-6-yl}propyl(tosyl)carbamate (**4G**)*

The experiment was performed as per the general experimental. The bicyclic triene **4G** was obtained as pale yellow oil (86 mg, 62% yield) after purification of the crude reaction mixture using silica gel flash column chromatography (gradient elution with 5% ethyl acetate in hexanes followed by 10% ethyl acetate in hexanes). Analytical TLC: R_f 0.34 (30% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.77 (d, J=8.0 Hz, 2H), 7.29 (d, J=8.0 Hz, 2H), 5.80–5.76 (m, 1H), 5.67–5.62 (m, 2H), 5.58–5.55 (m, 1H), 5.43 (d, J=5.0 Hz, 1H), 3.81–3.77 (m, 2H), 2.67–2.63 (m, 1H), 2.44 (s, 3H), 2.32 (t, J=5.0 Hz, 2H), 2.26–2.20 (m, 2H), 2.11–2.05 (m, 2H), 2.03–1.96 (m, 3H), 1.89–1.83 (m, 2H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 150.9, 143.9, 137.5, 134.7, 132.4, 132.0, 129.2, 127.8, 127.7, 126.7, 124.4, 83.9, 46.9, 37.9, 37.1, 35.0, 34.4, 31.4, 30.8, 29.8, 27.9, 21.6; FTIR (thin film, cm^{-1}) 2904, 1727, 1358, 1287, 1158, 1090, 674. High-resolution MS (ESI^+, m/z) molecular ion calcd for $C_{26}H_{35}O_4N_1S_1$: 480.2172, found: 480.2175 $(M+Na)^+$.

*3.2.8. 3-{(5Z,7Z)-4,4a,9,9a-Tetrahydro-1H-benzo[7]annulen-6-yl}propyl 2-napthoate (**4H**)*

The experiment was performed as per the general experimental. The bicyclic triene **4H** was obtained as pale yellow oil (53 mg, 59% yield) after purification of the crude reaction mixture using silica gel flash column chromatography (elution with 2% ethyl acetate in hexanes). Analytical TLC: R_f 0.40 (10% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.61 (s, 1H), 8.07 (dd, J=8.0, 1.5 Hz, 1H), 7.96 (d, J=8.0 Hz, 1H), 7.88 (d, J=8.0 Hz, 2H), 7.61–7.53 (m, 2H)5.82–5.78 (m, 1H), 5.69 (dd, J=12.0, 1.5 Hz, 1H), 5.64–5.61 (m, 1H), 5.56–5.52 (m, 1H), 5.47 (d, J=5.0 Hz, 1H), 4.39–4.34 (m, 2H), 2.67–2.63 (m, 1H), 2.33–2.31 (m, 2H), 2.25–2.19 (m, 3H), 2.11–1.89 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 166.8, 135.5, 134.6, 132.6, 132.5, 132.4, 130.9, 129.3, 128.1, 120.1, 127.74, 127.72, 127.6, 126.58, 126.56, 125.3, 124.4, 64.5, 38.0, 36.2, 35.0, 34.5, 31.4, 30.9, 28.4; FTIR (thin film, cm^{-1}) 2899, 1717, 1283, 1228, 1196, 1098, 779. High-resolution MS (EI^+, m/z) molecular ion calcd for $C_{25}H_{26}O_2$: 358.1927, found: 358.1927.

*3.2.9. (5E,7Z)-6-Phenyl-4,4a,9,9a-tetrahydro-1H-benzo[7]-annulene (**4I**)*

The experiment was performed as per the general experimental. The bicyclic triene **4I** was obtained as pale yellow oil (43 mg, 77% yield) after purification of the crude reaction mixture using silica gel flash column chromatography (elution with 1% ethyl acetate in hexanes). Analytical TLC: R_f 0.48 (5% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.35–7.28 (m, 4H), 7.23–7.21 (m, 1H), 6.05 (d, J=9.0 Hz, 1H), 6.05–6.00 (m, 1H), 5.94 (d, J=5.5 Hz, 1H), 5.69–5.66 (m, 1H) 5.62–5.60 (m, 1H), 2.81–2.78 (m, 1H), 2.43–2.29 (m, 3H), 2.25–2.19 (m, 1H), 2.14–2.03 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 143.8, 137.9, 134.9, 133.7, 128.1, 128.06, 127.0, 126.6, 125.5, 124.6, 38.5, 37.9, 34.7, 31.2, 30.8; FTIR (thin film, cm^{-1}) 3021, 2898, 1600, 1493, 1443, 937. High-resolution MS (EI^+, m/z) molecular ion calcd for $C_{17}H_{18}$: 222.1403, found: 222.1406.

*3.2.10. (4a,5Z,7Z,9a)-6-Hexyl-4,4a,9,9a-tetrahydro-1H-benzo[7]annulene (**4J**)*

The experiment was performed as per the general experimental. The bicyclic triene **4J** was obtained as pale yellow oil (26 mg, 45% yield) after purification of the crude reaction mixture using silica gel flash column chromatography (elution with 1% ethyl acetate in hexanes). Analytical TLC: R_f 0.52 (5% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 5.78–5.72 (m, 1H), 5.65–6.61 (m, 2H), 5.57–5.54 (m, 1H), 5.37 (d, J=5.5 Hz, 1H), 2.66–2.62 (m, 1H), 2.30 (t, J=5.5 Hz, 2H), 2.24–2.18 (m, 2H), 2.05–1.95 (m, 5H), 1.38–1.26 (m, 8H), 0.88 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 136.2, 131.8, 131.4, 128.2, 126.6, 124.5, 39.9, 37.9, 35.2, 34.5, 31.8, 31.6, 30.8, 29.5, 28.8, 22.7, 14.1; FTIR (thin film, cm^{-1}) 3020, 2956, 2855, 1652, 1440, 653. High-resolution MS (EI^+, m/z) molecular ion calcd for $C_{17}H_{26}$: 230.2029, found: 230.2030.

3.3. General procedure for the cycloheptadiene synthesis using 4-substituted cyclopentene derivatives

Cyclopentenes **5A**[19] and **5B**[20] were synthesized as reported in the literature.

Into an oven-dried 50 mL Schlenk tube equipped with magnetic stir bar and a cold finger condenser was added dichloromethane (5 mL) followed by Grubbs' second generation catalyst (4.5 mg, 5 mol %) and the solution was heated to reflux. Propargyl benzoate (16 mg, 0.1 mmol, 1.0 equiv) and the requisite cycloalkene (0.3 mmol, 3.0 equiv) were dissolved in 2.0 mL of CH_2Cl_2 and this solution was then added to the catalyst solution in CH_2Cl_2 at 45 °C over a period of 8 h by means of a gas-tight syringe (syringe pump). After the addition was complete, the reaction mixture was stirred in the oil bath for additional 45 min. The solvent was removed in vacuo. The crude oil thus obtained was further purified by flash chromatography using silica gel (using the indicated eluent) to provide the corresponding dienes as colorless oils.

*3.3.1. Cycloheptadiene-bis-benzoate (**6A**)*

The experiment was performed as per the general experimental. The cycloheptadiene derivative **6A** was obtained as colorless oil (23 mg, 66% yield) after purification of the reaction mixture through silica gel column chromatography (elution with 5% ethyl acetate in hexanes). Analytical TLC: R_f 0.27 (25% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.07–8.02 (m, 4H), 7.58–7.53 (m, 2H), 7.46–7.40 (m, 4H), 6.04–5.99 (m, 2H), 5.96–5.92 (m, 1H), 5.43 (septet, J=4.0 Hz, 1H), 4.82 (s, 2H), 2.76–2.59 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 166.4, 165.7, 134.3, 133.0, 132.9, 130.5, 130.2, 129.7, 129.6, 129.5, 128.4, 12.3, 127.4, 127.1, 74.7, 69.2, 35.9, 34.6; FTIR (thin film, cm^{-1}) 2953, 1715, 1450, 1273, 1111, 709. High-resolution MS (EI^+, m/z) molecular ion calcd for $C_{22}H_{20}O_4Na_1$: 371.1257, found: 371.1263 $(M+Na)^+$.

*3.3.2. Cycloheptadiene TBS-OBz (**6B**)*

The experiment was performed as per the general experimental. The cycloheptadiene derivative **6B** was obtained as colorless oil (23 mg, 66% yield) after purification of the reaction mixture through silica gel column chromatography (elution with 5% ethyl acetate in hexanes). Analytical TLC: R_f 0.27 (15% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.05 (d, J=7.5 Hz, 2H), 7.56 (t, J=7.5 Hz, 1H), 7.44 (t, J=7.5 Hz, 2H), 5.92–5.89 (m, 2H), 5.86–5.82 (m, 1H), 4.76 (s, 2H), 4.11 (septet, J=4.0 Hz, 1H), 2.52–2.36

(m, 4H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 166.4, 133.4, 132.9, 130.3, 130.2, 129.6, 128.3, 127.9, 126.6, 72.7, 69.5, 40.5, 39.3, 25.8, 18.2, −4.8; FTIR (thin film, cm^{-1}) 2954, 1222, 1462, 1272, 1069, 836. High-resolution MS (EI^+, m/z) molecular ion calcd for $C_{21}H_{30}O_3Si_1Na_1$: 381.1858, found: 381.1864 $(M+Na)^+$.

3.4. Synthesis of bicyclic diene 9

*3.4.1. (2E,4Z)-3-Phenylbicyclo[5.2.0]nona-2,4-dien-8-one (**9A**) and (2Z,4E)-4-phenylbicyclo[5.2.0]nona-2,4-dien-8-one (**9B**)*

To a 50 mL Schlenk tube fitted with a cold-finger condenser and magnetic stirrer under argon gas were added 16 mg **1** (Grubbs' Ru gen-2, 0.02 mmol, 10 mol %), bicycle **8** (1.6 mmol, 8 equiv), and benzene (2.5 mL). The reaction mixture was warmed to 60 °C in a pre-heated oil bath. Phenylacetylene (0.2 mmol) was dissolved in benzene (2 mL) and the solution was loaded into a 5 mL gas tight syringe. The alkyne solution was added via syringe pump over a 4 h period to the Schlenk tube above. After complete addition, the reaction mixture was allowed to stir at 60 °C for 1 h before being quenched with 1 mL of a methanolic solution of KO_2CCH_2NC[25] (0.1 mmol, 5 equiv based on Grubbs' catalyst). The resulting yellow solution was filtered through a plug of silica gel, concentrated in vacuo (rotatory evaporator), and purified by silica gel column chromatography (1″×7″) using a gradient elution (100 mL each petroleum ether, 2%, 8% ethyl acetate/petroleum ether), which provided 31 mg of **9** (75%) as a clear liquid, obtained as an inseparable 1.7:1 mixture of regioisomers. Analytical TLC (20% ethyl acetate/petroleum ether) R_f 0.45. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.25 (m, 6.76H), 6.47 (d, J=4.5 Hz, 1.42H), 6.37 (ddt, J=12, 7, 4.5 Hz, 1H), 6.29 (ddt, J=10.5, 7, 3 Hz, 1.54H), 6.16 (d, J=10.5 Hz, 1.61H), 3.94–3.87 (m, 1.61H), 3.38–3.29 (m, 1.87H), 3.24–3.18 (m, 1.69H), 3.13–3.05 (m, 1.98H), 2.51–2.34 (m, 3.37H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.9, 141.7, 138.5, 136.8, 133.2, 132.4, 130.8, 128.8, 128.5, 128.3, 128.2, 127.4, 126.4, 126.1, 73.5, 73.0, 54.3, 54.2, 28.0, 27.9, 26.1, 26.3; FTIR (thin film, cm^{-1}) 1786. High resolution ESI molecular ion calcd for $C_{15}H_{14}O$: 210.1045, found: 210.1050 ($C_{15}H_{14}O$).

3.5. Regioselective ring expansions

*3.5.1. (2E,4Z)-9,9-Dimethyl-3-phenylbicyclo[5.2.0]nona-2,4-dien-8-one (**13**)*

To a 50 mL Schlenk tube fitted with a cold-finger condenser and magnetic stirrer under argon gas were added 16 mg **1** (Grubbs' Ru gen-2, 0.02 mmol, 10 mol %) and benzene (2 mL). The reaction mixture was warmed to 60 °C in a pre-heated oil bath. Phenylacetylene (0.2 mmol) and bicycle **12** (1.6 mmol, 8 equiv) were dissolved in benzene (2 mL) and loaded into a 5 mL gas tight syringe. This solution was added via syringe pump over a 4 h period to the Schlenk tube above. After complete addition, the reaction mixture was allowed to stir at 60 °C for further 30 min before being quenched with 1 mL of a methanolic solution of KO_2CCH_2NC (0.1 mmol, 5 equiv based on Grubbs' catalyst). The resulting yellow solution was filtered through a plug of silica gel, concentrated in vacuo (rotatory evaporator), and purified by chromatography on silica gel (1″×7″) using gradient elution (100 mL each 2%, 4%, 10% ethyl acetate/petroleum ether), which gave 27 mg of **13** (57%) as a clear liquid. Analytical TLC (20% ethyl acetate/petroleum ether) R_f 0.60. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.31 (m, 5H), 6.39 (d, J=5 Hz, 1H), 6.28 (dt, J=11, 6.5 Hz 1H), 6.13 (d, J=11 Hz, 1H), 4.03 (dt, J=11, 5 Hz 1H), 3.03 (dd, J=11, 3.5 Hz, 1H), 2.44–2.37 (m, 2H), 1.21 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.8, 142.5, 138.9, 132.8, 130.7, 129.7, 128.3, 127.3, 126.5, 126.1, 68.4, 68.9, 41.5, 26.5, 24.8, 18.4; FTIR (thin film, cm^{-1}) 1775. High resolution ESI molecular ion calcd for $C_{17}H_{18}O$: 238.1352, found: 238.1357 ($C_{17}H_{18}O$).

*3.5.2. PTAD cycloadduct **14***

To a 25 mL round bottom flask under argon gas were added diene **13** (0.16 mmol) and dichloromethane (10 mL). PTAD (0.17 mmol) was added portionwise over a 15 min period. When a red color persisted, the reaction mixture was concentrated in vacuo (rotatory evaporator) and the crude residue loaded directly onto a silica gel column (1″×6″) purified by elution with 50% ethyl acetate/petroleum ether to give 34 mg **14** (51%) as a white solid, mp 133–135 °C. The cycloadduct was dissolved in a small portion of benzene (0.25 mL) and crystallized in an atmosphere saturated with pentane vapor at room temperature to afford crystals suitable for X-ray structural analysis. Analytical TLC (50% ethyl acetate/petroleum ether) R_f 0.25. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.32 (m, 5H), 7.25–7.19 (m, 5H), 6.26 (d, J=7 Hz, 1H), 5,54 (br s, 1H), 5.02 (dt, J=7.5, 7 Hz, 1H), 3.78 (t, J=10 Hz, 1H), 2.78 (dd, J=10.5, 3 Hz, 1H), 2.49 (dd, J=15, 3 Hz, 1H), 2.19–2.13 (m, 1H), 1.27 (s, 3H), 0.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 152.7, 151.4, 140.5, 137.7, 131.5, 129.2 (CH), 129.1 (CH), 128.6 (CH), 128.1 (CH), 127.8 (CH), 125.4 (CH), 125.1 (CH), 59.3, 54.6 (CH), 52.2 (CH), 51.2 (CH), 44.3 (CH), 29.1 (CH_3), 27.7 (CH_2), 17.2 (CH_3); FTIR (KBr, cm^{-1}) 2927, 1775, 1709, 1512, 1420. High resolution ESI molecular ion calcd for $C_{25}H_{23}O_3N_3$: 413.1734, found: 413.1740 ($C_{25}H_{23}O_3N_3$).

*3.5.3. PTAD cycloadduct **16***

To a 50 mL Schlenk tube fitted with a cold-finger condenser and magnetic stirrer under argon gas were added 16 mg **1** (Grubbs' Ru

Table 2
Crystal data and data collection information for **14**

Crystal data	
Identification code	PTAD cycloadduct **14**
Moiety formula	$C_{25}H_{23}N_3O_3$, C_6H_6
Sum formula	$C_{31}H_{29}N_3O_3$
Formula weight	491.57
Crystal system, space group	Monoclinic, *C*2/*C*
Unit cell dimensions	a=17.5848(9) [Å]
	b=8.7847(5) [Å]
	c=31.6268(14) [Å]
	α=90 [°]
	β=94.154(2) [°]
	γ=90[°]
Volume	4872.8(4) [$Å^{-3}$]
Z, calculated density	8, 1.340 [Mg/m^3]
Radiation	Mo Kα
Wavelength	λ=0.71073 [Å]
θ Range for data collection	1.29–27.12 [°]
sin θ/λ_{max}	0.64 [$Å^{-1}$]
Absorption coefficient	μ=0.087 [mm^{-1}]
Temperature	90(1) [K]
F(000)	2080
Crystal size	0.20×0.15×0.10 [mm]
Crystal shape	Prism
Crystal color	Colorless
Data Collection	
Diffractometer	APEXII CCD area detector diffractometer
Measurement method	ϖ-Scan
Absorption correction	Multi-scan (SADABS 2004/1; Sheldrick, 2004)
Max and min transmissions	T_{max}=0.9913, T_{min}=0.9828
Reflections collected/unique/R_{int}	34,770/5403/0.0261
Completeness to θ=25.68°	100.0 [%]
Limiting indices	h=−22→22
	k=−11→11
	l=−40→40
Refinement	
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	5403/0/336
R [$I>2\sigma(I)$]	$R1$=0.0346/$wR2$=0.0822
R (all data)	$R1$=0.0416/$wR2$=0.0868
Goodness-of-fit on F^2=S	1.025
$\Delta\rho_{max}$	0.337 [e $Å^{-3}$]
$\Delta\rho_{min}$	−0.177 [e $Å^{-3}$]

gen-2, 0.02 mmol, 10 mol %) and benzene (2 mL). The reaction mixture was warmed to 60 °C in a pre-heated oil bath. Alkyne (0.2 mmol) and bicycle **12** (1.6 mmol, 8 equiv) were dissolved in benzene (2 mL) and loaded into a 5 mL gas tight syringe. This solution was added via syringe pump over a 4 h period to the above Schlenk tube. After complete addition, the reaction mixture was allowed to stir at 60 °C for 1 h before being quenched with 1 mL of an ethanolic solution of isocyanide KO_2CCH_2NC (0.1 mmol, 5 equiv based on Grubbs' catalyst). The resulting yellow solution was filtered through a plug of silica gel and concentrated in vacuo (rotatory evaporator). The crude product was dissolved in dichloromethane (10 mL) and PTAD (0.2 mmol) was added portionwise over a 15 min period at room temperature until a red color persisted. The reaction mixture was subsequently concentrated in vacuo (rotatory evaporator), and loaded directly onto a silica gel column (1″×6″) and purified by elution with 50% ethyl acetate/petroleum ether to give 70 mg **16** (55% over two steps). Analytical TLC (50% ethyl acetate/petroleum ether) R_f 0.26. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J=8.5 Hz, 2H), 7.49 (d, J=8.5 Hz, 2H), 7.39 (t, J=7.5 Hz, 2H), 7.31 (t, J=7 Hz, 1H), 7.25 (d, J=7 Hz, 2H), 6.20 (d, 7.5 Hz, 1H), 5.08 (br s, 1H), 4.97–4.95 (m, 1H), 3.87–3.82 (m, 2H), 3.67 (dt, J=14.5, 15 Hz, 1H), 2.48 (dd, J=10.5, 3 Hz, 1H), 2.74–2.68 (m, 1H), 2.64–2.59 (m, 1H), 2.47 (dd, J=15, 3 Hz, 1H), 2.40 (s, 3H), 2.18–2.12 (m, 1H), 1.44 (s, 3H), 1.27 (s, 9H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.3, 151.2, 150.7, 150.0, 144.2, 137.0, 131.8, 129.2, 129.1, 128.9, 127.9, 127.7, 125.6, 84.6, 58.9, 54.4, 51.4, 51.1, 46.0, 44.7, 36.0, 28.8, 27.8, 27.1, 21.5, 18.2; FTIR (thin film, cm^{-1}) 2976, 2939, 1778, 1716, 1422, 1360, 1160. High resolution ESI molecular ion calcd for $C_{33}H_{38}O_7N_4SNa$: 657.2353, found: 657.2372.

3.6. Crystal structural analysis

X-ray diffraction data on **14** were collected at 90(1) K using a Bruker SMART APEX2 CCD diffractometer installed at a rotating anode source (Mo Kα radiation, λ=0.71073 Å), and equipped with an Oxford Cryosystems nitrogen gas-flow apparatus. The data were collected by the rotation method with 0.3° frame-width (ω scan) and 20 s exposure time per frame. Four sets of data (600 frames in each set) were collected, nominally covering complete reciprocal space. The data were integrated, scaled, sorted, and averaged using the APEXII software package.[26] The structure was solved by direct method using SHELXS.[2] The structure was refined by full-matrix least squares against F^2 using SHELXL.[27] All non-hydrogen atoms were refined anisotropically. X–H distances were set to idealized values and not refined. Hydrogen atoms were refined with the 'riding' model with U_{iso}=1.5U_{eq} for CH_3 and U_{iso}=1.2U_{eq} for the remaining hydrogens. One benzene solvent molecule was found in the crystal structure.

Crystal data and data collection information are summarized in Table 2. Atomic coordinates, anisotropic displacement parameters, bond lengths, angles, and torsion angles are given in Tables S1–S4 (Supplementary data).

The data have been submitted to the CCDC.

Acknowledgements

This work was supported by the Petroleum Research Fund (PRF AC-44202) and the NSF (CHE-601206). D.A.C. acknowledges Wyeth-Ayerst for a graduate stipend during the summer of 2006. We thank Dr. Mateusz Pitak for determining the X-ray crystal structure of **14**, Materia for their generous catalyst support, and Dr. Andrew Bell (Promerus, Cleveland, OH) for a gift of tetrahydroindene (THI).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.03.027.

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