The Synthesis of Novel Cyclohexyne Precursors for an Intramolecular Pauson-Khand Type Reaction

Honors Thesis by Samuel Isaac Etkind

In partial fulfillment of the requirements for graduation with the
Dean's Scholars Honors Degree in Chemistry

_____ _____

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Supervising Professor

Date

Table of Contents

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Abstract

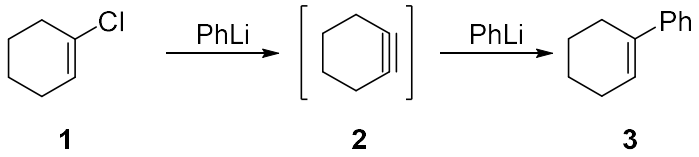
Strained cycloalkynes, particularly cyclohexyne and cyclopentyne, are interesting synthetic intermediates that have largely been overlooked in organic synthesis. In addition, the Pauson-Khand reaction is a formal [2+2+1] cycloaddition that utilizes an alkene, an alkyne, and carbon monoxide. The use of strained cycloalkynes in the Pauson-Khand reaction has been surveyed, but it has not been performed successfully for cyclohexyne and cyclopentyne containing substrates. Design and optimization of such a reaction could lead to the swift synthesis of a polycyclic scaffold that is found in many natural products, many of which have not been synthesized.

This thesis presents several approaches to a new class of vinyl triflates that could serve as cyclohexyne precursors for the Pauson-Khand reaction. While only a few cyclohexyne precursors were successfully synthesized, a synthetic route is presented that can access this class of molecules in moderate yield over three steps. In addition, use of these cyclohexyne precursors in the Pauson-Khand reaction led to the formation of the desired polycyclic product.

1. Introduction

1.1 The Synthesis and Application of Strained Cycloalkynes

Strained cycloalkynes are highly reactive synthetic intermediates, the use of which has been demonstrated through a variety of reactions, including Diels-Alder reactions, nucleophilic additions, and a number of other cycloadditions.[1] While rings with eight atoms or more contain alkyne bonds that can be stabilized via the use of a transition metal, the isolation of smaller cycloalkynes is impractical due to their instability, making their *in situ* production more practical in synthetic applications.[2] The presence of cyclohexyne was first theorized by Roberts in 1957 as the intermediate in the coupling of phenyllithium and chlorocyclohexene (**1**) (Scheme 1).[3] Elimination of chloride produces cyclohexyne (**2**), which can then undergo carbolithiation to form cyclohexene **3**.



Scheme 1 Generation of cyclohexyne from chlrocyclohexene.

Similarly, cyclopentyne (**4**) was first theorized as an intermediate by Wittig in 1960 as an intermediate in the reaction of dibromide **5** with magnesium and dihydrazone **6** with HgO (Figure 1).[4] This reactive intermediate could then undergo a Diels-Alder reaction with furan **7** to yield molecule **8** in low yield, providing evidence for the presence of cyclopentyne (**4**). It has also been demonstrated that cyclopentyne can be produced from a rearrangement of cyclobutanone.[5]

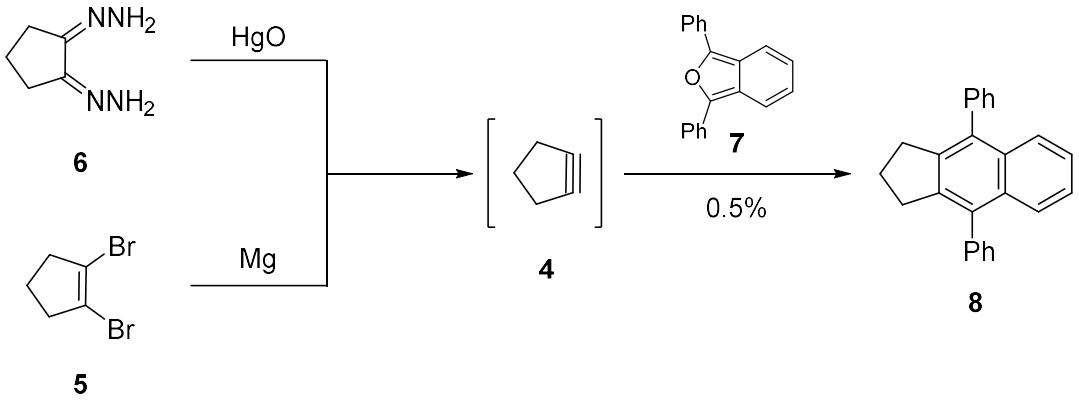
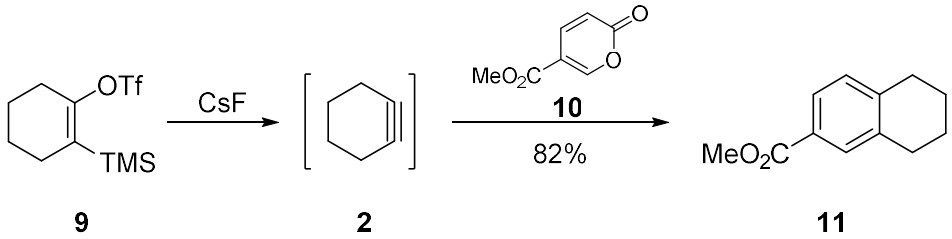


Figure 1 Generation of a cyclopentyne intermediate.

The reactivity of these small cycloalkynes can be attributed to their significant angle strain.[1] While a typical alkyne has a bond angle of 180°, unsubstituted cyclohexyne (**2**) and cyclopentyne (**4**) have bond angles of 132° and 116° respectively, according to computational studies. Substitution adjacent to the alkyne can further distort the ring structure.[1]

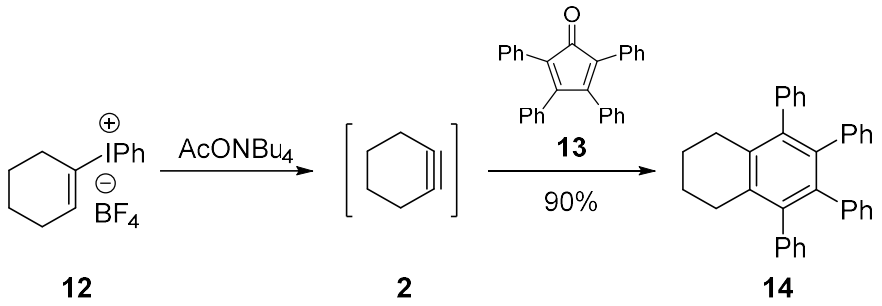
Since the initial discoveries regarding cyclohexyne and cyclopentyne, there have been efforts to produce small cycloalkynes using milder conditions. Guitián has demonstrated that vinyl triflate **9**, when combined with an excess of cesium fluoride, can be used to produce cyclohexyne (**2**) *in situ* (Scheme 2).[6] The nucleophilic attack of the TMS group followed by the elimination of triflate ion yields the desired intermediate. Cyclohexyne (**2**) can then be trapped with pyranone **10** in a Diels-Alder-decarboxylation cascade that yields tetraline **11** in good yield.



Scheme 2 Generation of cyclohexyne form vinyl triflate **9**.

Using a similar elimination mechanism, Fujita has developed vinyl hydroiodonium salt **12**, which can produce cyclohexyne (**2**) in the presence of base (Scheme 3).[7] Again, cyclohexyne (**2**)

can then be used for a variety of cycloaddition reactions, in this case a Diels-Alder reaction with cyclopentadienone **13** followed by decarbonylation to yield tetralin **14**.



Scheme 3 Hyperiodonium salts as cyclohexyne precursors.

Using Guitián's cyclohexyne precursor, the vinyl triflate **9**, Garg has demonstrated that cyclohexyne (**2**) can undergo a number of cycloadditions (Figure 2).[1] Generally, each reaction proceeded with moderate to excellent yield, producing **15-19**. This methodology demonstrates the use of cyclohexyne in swiftly producing unique molecular architectures with various cycloaddition partners. The analogous five-membered ring precursors have been demonstrated to produce cyclopentyne, which was used for similar cycloadditions; however, the substrate scope was more limited and yields were lower, owing possibly to the reduced stability of cyclopentyne versus cyclohexyne.[1]

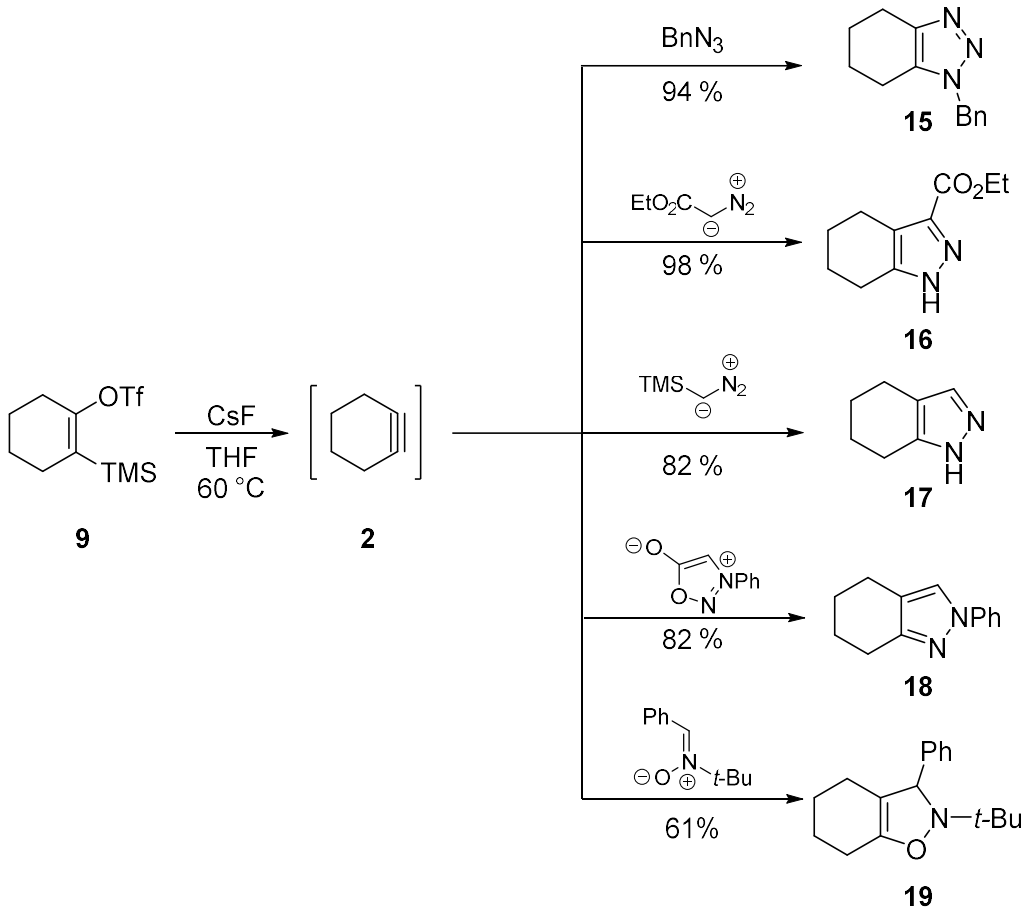
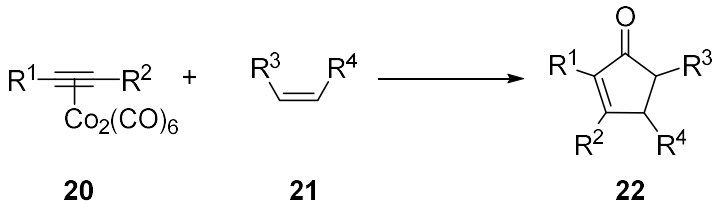


Figure 2 Cycloadditions of cyclohexyne with a variety of compounds.

Indeed, the chemistry of small cycloalkynes has proven to be a diverse but largely overlooked topic in organic synthesis.[1] In addition, except for work regarding the cyclotrimerization of cyclohexyne and cyclopentyne, little has been done in regards to utilizing these unstable intermediates in transition metal catalyzed cycloadditions.[8]

1.2 The Pauson-Khand Reaction

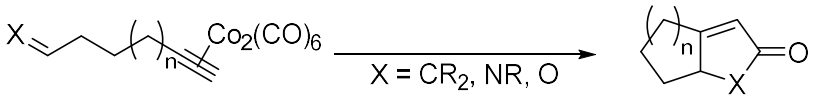
The Pauson-Khand reaction (PKR) was first reported in 1973.[9] It in involves the reaction of alkyne **20** coordinated to a. dicobalt complex, alkene **21**, and carbon monoxide, forming cyclopentenone **22** in a single step (Scheme 4).[9]



20 **21** **22**

Scheme 4 General form of the Pauson-Khand reaction.

While the intermolecular version of the reaction was the first to be reported and explored, it was found that the intramolecular form, in which the alkene and alkyne are linked, proceeds in better yield with fewer issues in regards to regiochemistry.[10] In addition, the intramolecular reaction can be used to swiftly form bicycles from linear molecules (Scheme 5). Finally, replacement of the alkene with either an imine or an aldehyde, such as in alkyne **23**, can form the corresponding lactams and lactones **24**, greatly expanding the substrate scope of the reaction.[10]



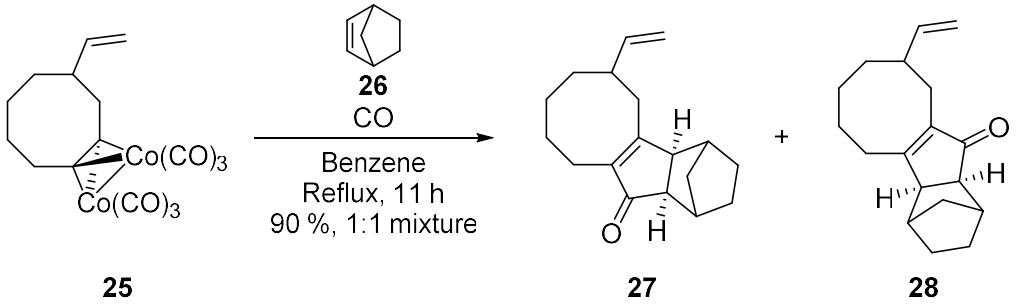
23 **24**

Scheme 6 Synthesis of cyclopentenones, lactams and lactones via the PKR.

Although the original procedure for the reaction required a stoichiometric amount of the dicobalt complex, more recent advances have allowed this cycloaddition to proceed with a catalytic amount of transition metal and a carbon monoxide source.[11] Likewise, enantioselective varieties of the PKR have been developed using phosphine ligands in various systems.[10]

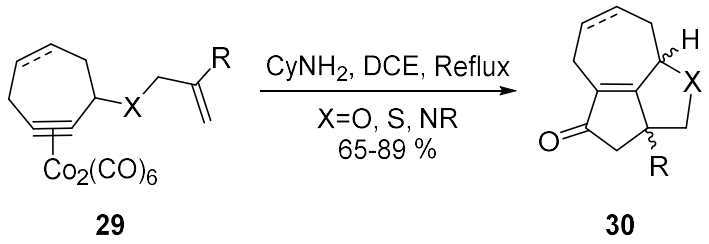
The PKR has also been used on cyclic alkynes, primarily cycloheptyne and cyclooctyne, in order to swiftly form polycyclic structures. Schreiber first reported the use of the cyclooctyne containing substrates **25** with norbornene (**26**), producing cyclopentenones **27** and **28** in high yield, although no selectivity was observed for the orientation of the cyclopentenone (Scheme 7).[12] It

was found, however, that the intramolecular reaction proceeded with an excellent regiochemical outcome and with good yield.



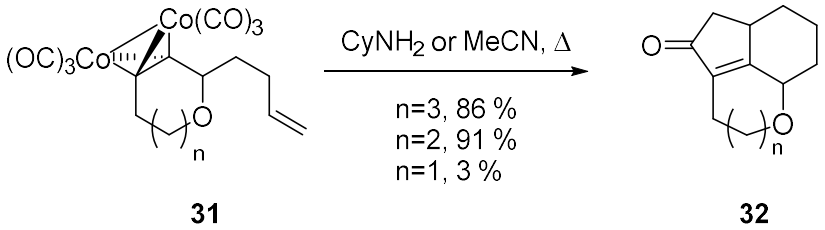
Scheme 7 First example of a strained cycloalkyne in the PKR.

Masuda and coworkers developed a similar methodology using cycloheptyne **29** to form polycycle **30** (Scheme 8).[13] In addition to quickly accessing these complex substrates, heteroatoms were incorporated into the carbon chain linking the alkyne and alkene, demonstrating some amount of functional group tolerance in this reaction.



Scheme 8 Use of cycloheptyne in the PKR.

A very similar approach was taken by Shea and coworkers, who utilized cyclooctyne, cycloheptyne, and cyclohexyne containing substrates **31** in the intramolecular PKR to form polycycles **32** (Scheme 9).[14] Again, this demonstrates the tolerance of heteroatoms in the reaction, but it also demonstrates the first attempt at using cyclohexyne as a substrate in the PKR. It is important to note, however, that the reaction proceeded with only 3 % yield, which the authors attribute to the instability of the carbocation intermediate in the preceding Nicholas reaction.

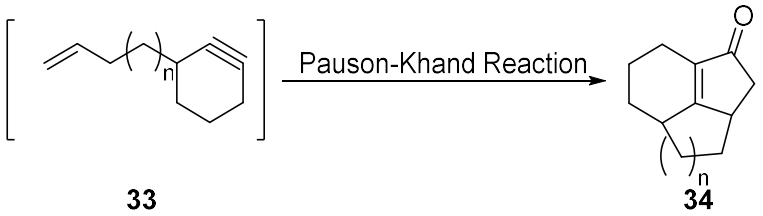


31 **32**

Scheme 9 Use of various sized alkyne rings in the PKR.

1.3 Potential Utility of Cyclohexyne in a Pauson-Khand Reaction

The use of cyclohexyne **33** in the PKR would result in the construction of polycycle **34**, which contains a synthetically challenging tetrasubstituted alkene (Scheme 10).



33 **34**

Scheme 10 Use of cyclohexyne in the PKR.

This proposed approach differs from Schreiber's, Shea's, and Masuda's use of cycloalkynes in the PKR.[12–14] Instead of two step sequence that complexes the alkyne to a transition metal followed by the PKR, a cycloalkyne precursor would be used that can produce the cycloalkyne *in situ* followed by the PKR in a single pot. This approach could allow the utilization of more strained alkynes, preventing the low yielding cyclohexyne PKR that Shea and coworkers observed, and could potentially allow the use of cyclopentyne as well.[14]

There are several natural products with interesting biological activity that contain the structural motif that such a PKR would produce (Figure 3). Natural products isolated from the *Pseudopterogorgie elisabethae*, such as amphilectolide (**35**) and sandresolide A (**36**), have been shown to have a variety of biological activity against inflammation, tuberculosis, cancer, and antiplasmodial activity.[15] The biological activity of many Daphniphyllum alkaloids, such as

daphnipaxianine A and B (**37**), has not been assessed, but other compounds in the family exhibit activity against cancer cell lines.[16] Finally, guanacastapene A has demonstrated antiobiotic activity, but other members of the family, such as guanacastapene N (**38**) and M (**39**) have yet to be assessed.[17] By developing a method by which this important motif can be swiftly synthesized, it might be possible to provide concise routes to molecules that display interesting biological activity.

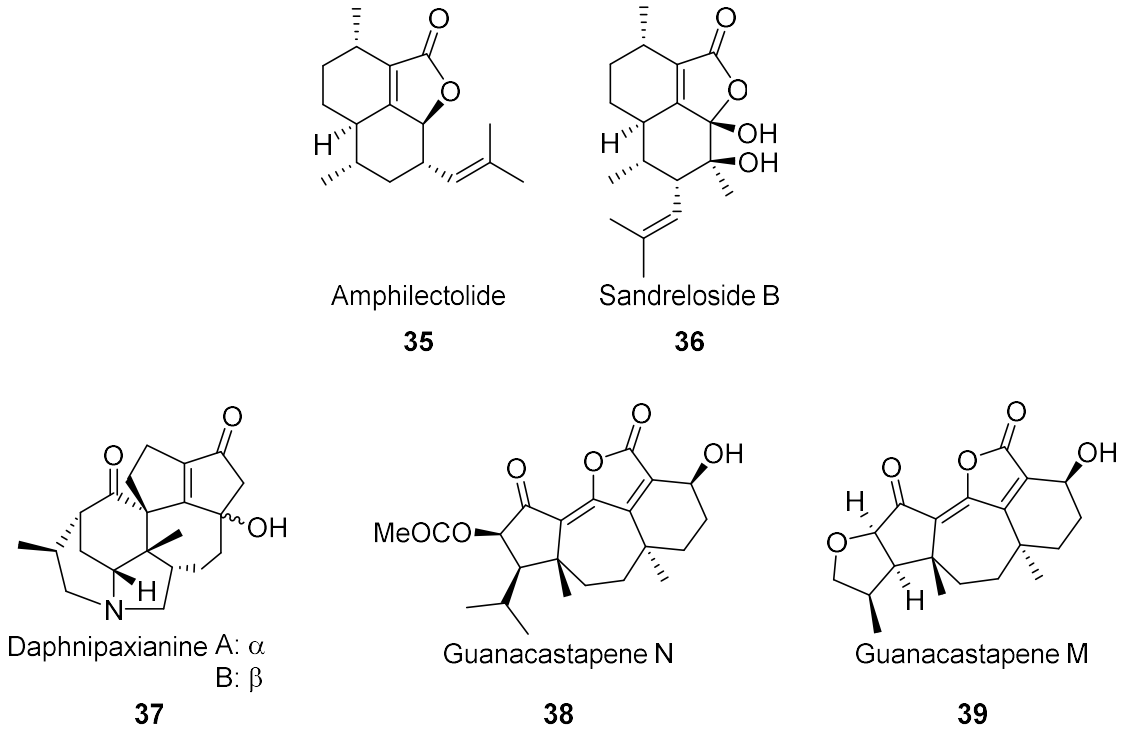


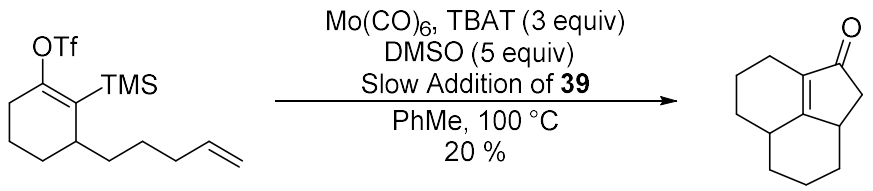
Figure 3 Natural products with relevant polycyclic moiety.

Other researchers have attempted to synthesize the polycyclic, tetra-substituted olefein as part of total syntheses, but this usually required two synthetic steps that were typically low yielding.[18–20] A recent paper by Trauner in the synthesis of the caribenol alkaloids presents a higher yielding synthesis of this motif; however, this methodology still requires two steps.[21] The development and optimization of such a Pauson-Khand reaction could overcome these shortfalls

and allow for a more concise synthesis of molecules with this polycyclic moiety. In addition, this methodology could demonstrate an additional synthetic utility for cyclohexyne.

1.4 Previous Work Towards This Goal

Before my opportunity to work on this project, several advances had been made by the Martin lab towards this goal. The original strategy utilized the vinyl triflate precursors developed by Guitián and coworkers.[6] Although this method was heavily pursued, under optimized conditions with vinyl triflate **40**, polycycle **41** could only be obtained in 20% yield (Scheme 11). A significant amount of starting material was recovered after the reaction, suggesting that the fluoride anion was not removing the TMS group via nucleophilic attack. It was theorized that the fluoride, instead, reacted with the molybdenum complex, thereby stopping the reaction. While the reaction was not high yielding, it did present thus far the highest yielding PKR that utilized cyclohexyne. In addition, it validated our synthetic approach towards cyclohexyne production and use.

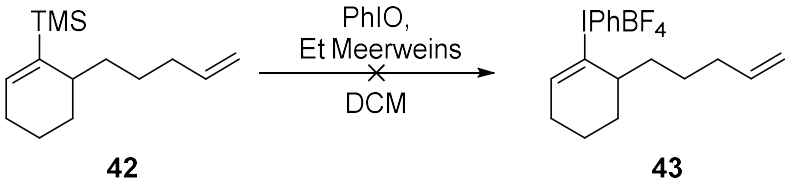


40 **41**

Scheme 11 Optimized PKR conditions using vinyl triflate **40**.

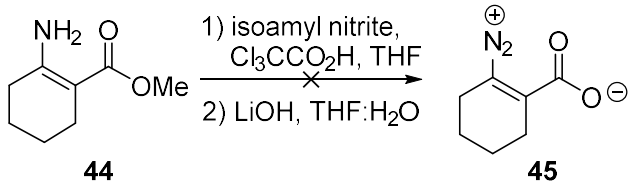
After the initial results, alternative cyclohexyne precursors were targeted, specifically ones that did not require fluoride as an activating agent. A synthesis of hyperiodonium salt **43**, which was based on Fujita's cyclohexyne precursors, from vinyl TMS **42** was attempted, but the product was found to be remarkably unstable and, therefore, unsuitable for reaction screening (Scheme

12).[7] Indeed, Fujita reports that substitution in positions adjacent to the alkene results in reduced stability for the iodonium species.[7]



Scheme 12 Attempted synthesis of a hyperiodonium cyclohexyne precursor.

In addition, an attempt was made to synthesize diazocarboxylate **45** from enamine **44**, which has been shown to produce benzyne with analogous aromatic precursors (Scheme 13).[22] The use of this cyclohexyne precursor seemed advantageous because it could be thermally activated. Unfortunately, it was found that this substrate was unable to be prepared.



Scheme 13 Attempted synthesis of a diazocarboxylate cyclohexyne precursor.

In order to move the project forward, alternate, novel cyclohexyne precursors were surveyed. It was theorized that vinyl-triflates could produce cyclohexynes via a decarboxylation followed by elimination of triflate. To this end, the three potential cyclohexyne precursors, **48**-**50**, were synthesized form *tert*-butyl ester **46** and allyl ester **47** (Figure 4). It was theorized that the *tert*-butyl ester and free acid could be thermally activated, while the allyl ester could be activated catalytically via transition metal deallylation.

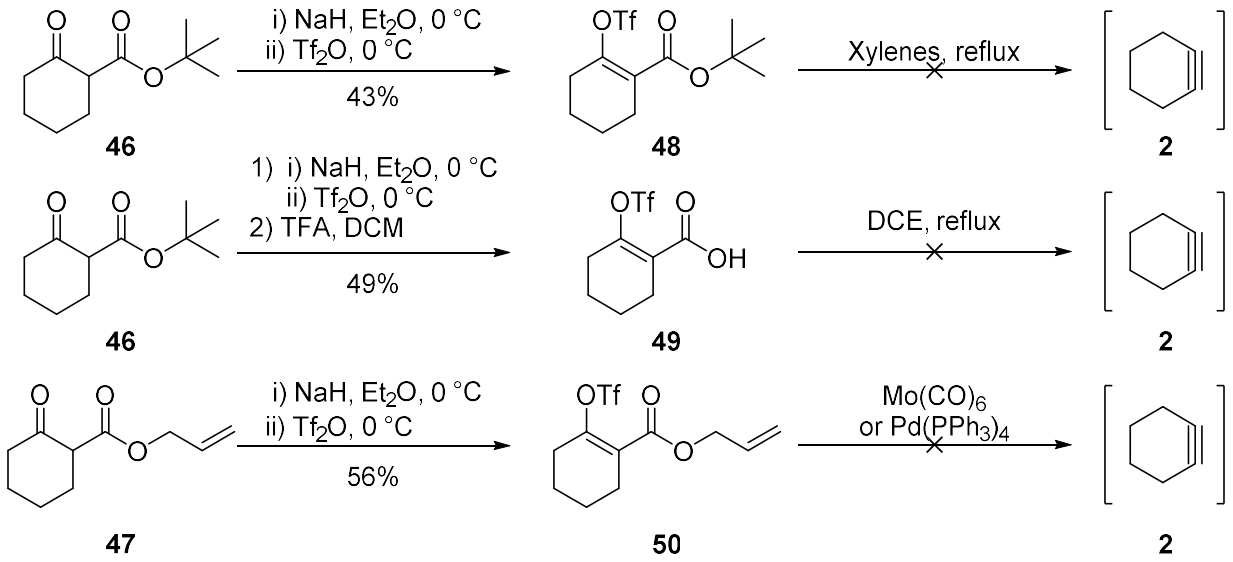
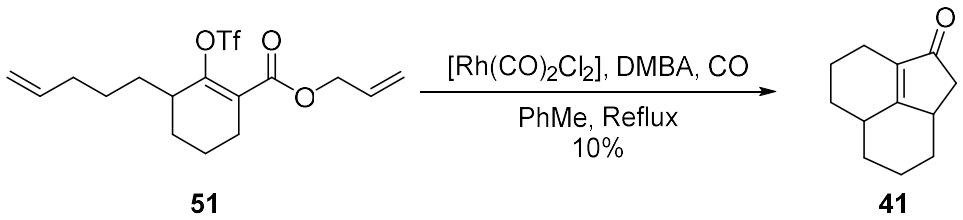


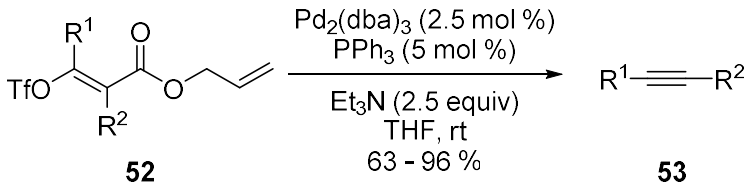
Figure 4 Approaches toward novel cyclohexyne precursors.

Unfortunately, none of these initial conditions led to cyclohexyne formation; however, it was reported in the Martin group that $[Rh(CO)_2Cl]_2$ could be used in an allylation-PKR cascade.[23] Gratifyingly, it was found that when this catalyst was combined vinyl triflate **51**, production of polycycle **41** was observed (Scheme 14).



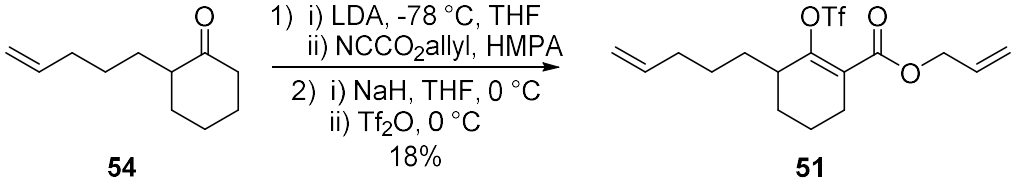
Scheme 14 Synthesis of polycyclic tetra-substituted olefin using a rhodium complex.

During the course of this project a similar methodology was published that used vinyl triflate **52** to produce linear alkyne **53** (Scheme 15).[24] While this methodology could not be used to produce cyclic alkynes, it provides some evidence that our reaction involves a cyclohexyne intermediate.



Scheme 15 Vinyl triflates as precursors for linear alkynes.

The synthesis of vinyl triflate **51** from cyclohexanone **54**, however, was fairly low yeilding (Scheme 16). With 18% yield over two steps, producing enough starting material was neither plausible nor economical. In order to properly screen conditions for the PKR, it was first necessary to develop a scalable method for the production of starting material.

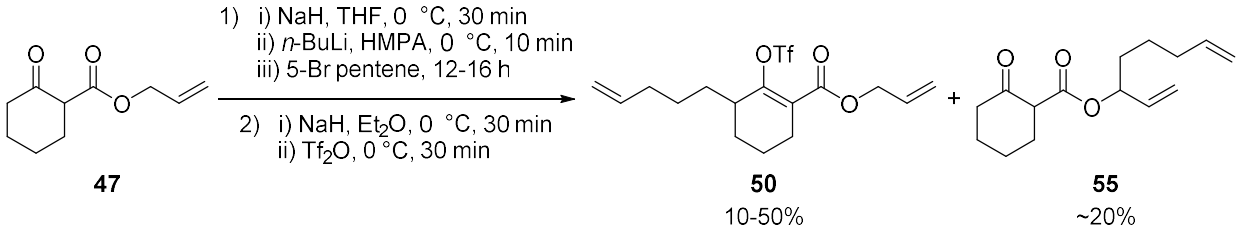


Scheme 16 Initial conditions for substrate synthesis.

2. Results

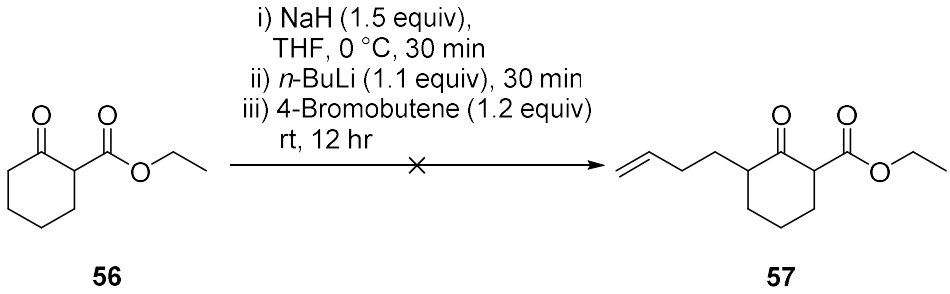
2.1 Second Generation Approach to Cyclohexyne Precursors

Due to the poor yield obtained in Scheme 16, we envisioned that an alternate approach would allow us to access these precursors in a significantly higher yield. The dianion chemistry developed by Weiler seemed to provide a concise route to the desired triflates.[25] To this end, allyl ester **47** was deprotonated twice, first with NaH and then with *n*-BuLi, creating the dianion, which should undergo alkylation to the keto-group (Scheme 17). It was found, however, that the allylic position was somewhat acidic, leading to competitive alkylation, producing both allyl ester **50**, the target compound, and allyl ester **55**, an unwanted byproduct.



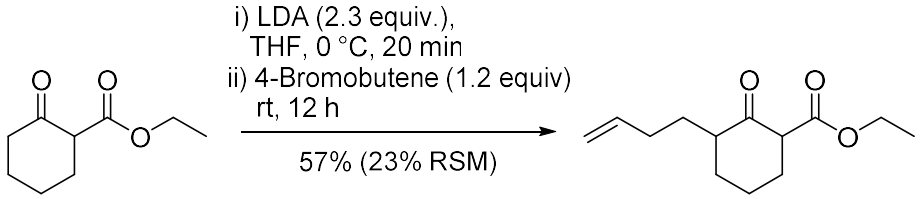
Scheme 17 Alkylation of allyl ester **54**, leading to a mixture of products.

In order to prevent this problem, ethyl ester **56** was employed, with the assumption that a simple trans-esterification reaction following the alkylation should result in a higher yielding pathway to the substrates of interest. It was found, however, that ethyl ester **57** was not formed after alkylation with 4-bromobutene (Scheme 18).



Scheme 18 Unsuccessful alkylation of ethyl ester **56**.

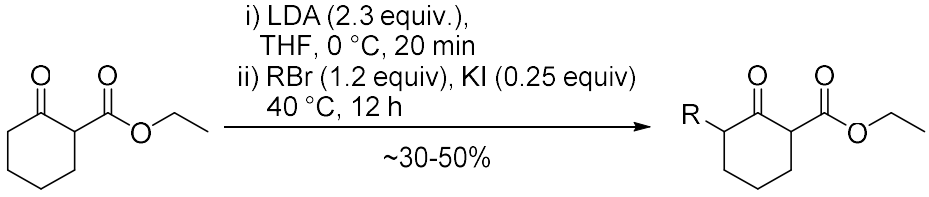
Two equivalents of LDA were employed instead of the stepwise deprotonation with NaH and *n*-BuLi, which is cited as an alternate method to produce the dianion.[25] To our delight, ethyl ester **57** was obtained in moderate yield.



56 **57**

Scheme 19 Successful alkylation of ethyl ester **56**.

For longer chain alkenes, such as 5-bromopentene and 6-bromohexene, the obtained yield of ethyl ester **58** was significantly reduced to around 10%. It was rationalized that this may be due to the reduced electrophilicity of the longer chain alkyl bromides. We decided, instead, to attempt an *in situ* Finkelstein reaction with potassium iodide in order to catalytically produce the corresponding iodides, which should serve as better electrophiles (Scheme 20). While yields of the desired product were generally higher using this method, yields were inconsistent, and heating would occasionally produce a viscous fluid that would complicate aqueous work-up.

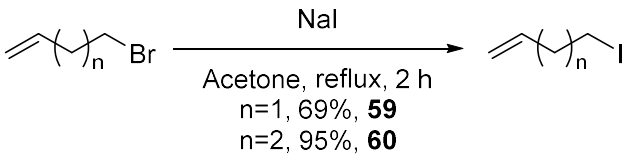


56 **58**

Scheme 20 Alkylation of ethyl ester **56** using an *in situ* Finkelstein reaction.

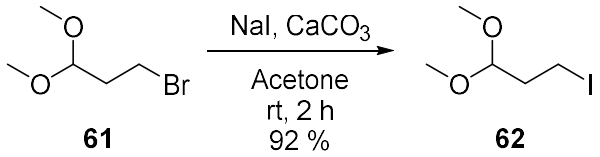
After the promising results from the *in situ* Finkelstein reaction, it was hypothesized that the direct use alkyl iodides might result in better yields. The iodides could be produced from the analogous bromides using a simple Finkelstein reaction in acetone (Scheme 21). While 5-

iodopentene (**60)** was obtained in good yield and could be used without issue, it was found that 4-iodobutene (**59**) was light sensitive. Since the alkylation proceeded in moderate yield with 4-bromobutene, the use of 4-iodobutene was abandoned.



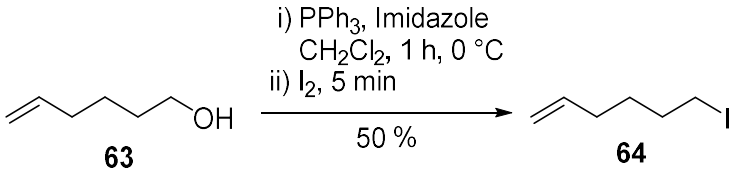
Scheme 21 Production of alkyl iodides using the Finkelstein reaction.

Similarly, we imagined that dimethyl acetal **61** would serve as a viable precursor for an aldehyde, which could be a substrate for the hetero PKR. A slight modification of the Finkelstein reaction using $CaCO_3$ at room temperature could convert bromide **61** to iodide **62** (Scheme 22).[26] Under standard conditions, it was found that a portion dimethyl acetal **61** was converted to the aldehyde.



Scheme 22 Conversion of dimethyl acetal **61** to its corresponding iodide.

Finally, 6-hexenol (**63**) could be converted to 6-iodohexene (**64**) via an Appel reaction with triphenyl phosphine, iodine, and imidazole in moderate yield (Scheme 23).[27]



Scheme 23 Appel reaction of 6-hexenol.

With these electrophiles in hand, we attempted to alkylate ethyl ester **56** again. In general, the yields were greatly improved using the iodide electrophiles for molecules **65**-**67** (Figure 5). Indeed, the 89% yield of ethyl ester **65** represented a significant improvement.

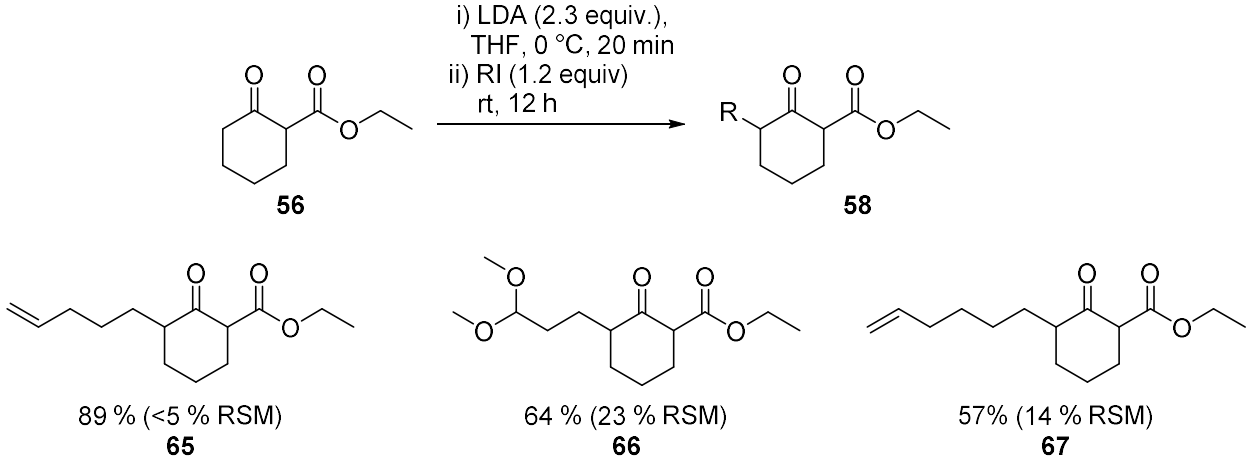
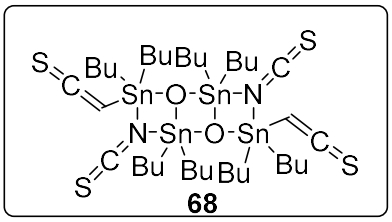


Figure 5 Alkylation of ethyl ester **56** using iodide electrophiles.

After initial optimizations of the alkylation, we started exploring methods to introduce the allyl ester moiety. Initial attempts at trans-esterification using traditional acidic and basic conditions gave at most 50% yield and required reaction times on the order of days. Certain Lewis acids were also screened, but results were still unsatisfactory. Finally, we used conditions developed in the Martin lab using Otera's catalyst (**68**) under microwave conditions for trans-esterification.[28] Unfortunately, initial attempts at trans-esterification gave only ketone **69** instead of allyl ester **70**, indicating decarboxylation of the β-keto ester (Figure 6).



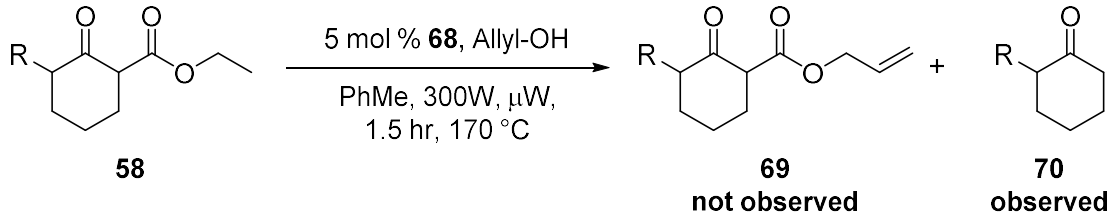
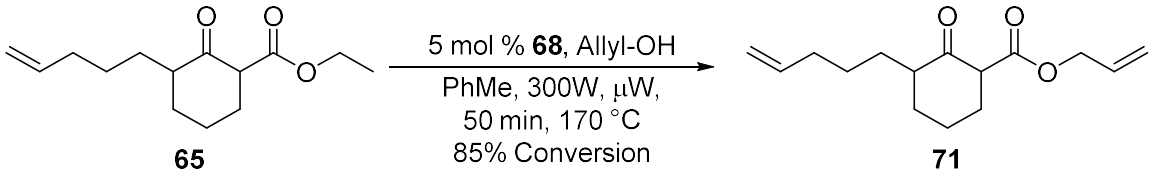


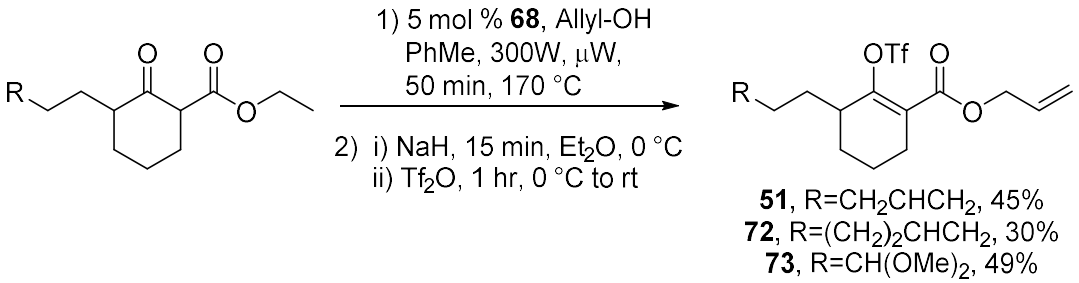
Figure 6. Initial attempts at trans-esterification using Otera's catalyst.

However, after close monitoring of the reaction by ^{1}H-NMR, it was found that the reaction proceeds with a high level on conversion after 50 minutes, yielding the allyl-ester **71** (Scheme 24). It should be noted that this reaction was highly time sensitive, and that reaction times of 1 hour could result in cleavage of the ester and a considerable amount of ketone being formed.



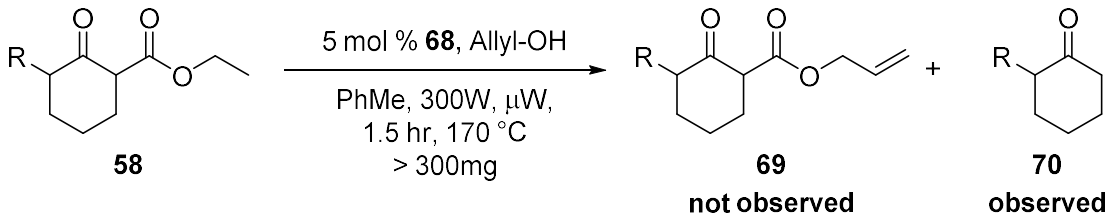
Scheme 24 Optimization of trans-esterification catalyzed by Otera's catalyst.

Trans-esterification followed by triflation gave the desired triflates in poor to moderate yields over three steps, starting from ethyl-ester **56** to form triflates **51**, **72**, and **73** (Scheme 25). While these yields were not ideal, they provided a higher yielding procedure to produce the desired substrates than what was previously attempted.



Scheme 25 Successful synthesis of PKR substrates.

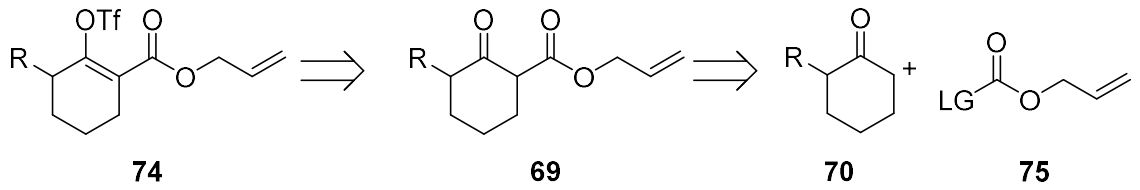
Issues arose, however, when these reactions were run on a larger scale. As more ethyl ester **58** was introduced to the trans-esterification reaction, less allyl-ester **69** was observed, and the cleaved ketone **70** was instead recovered (Scheme 26). Due to this issue, this synthetic route was abandoned.



Scheme 26 Decarboxylation during the trans-esterification on larger scales.

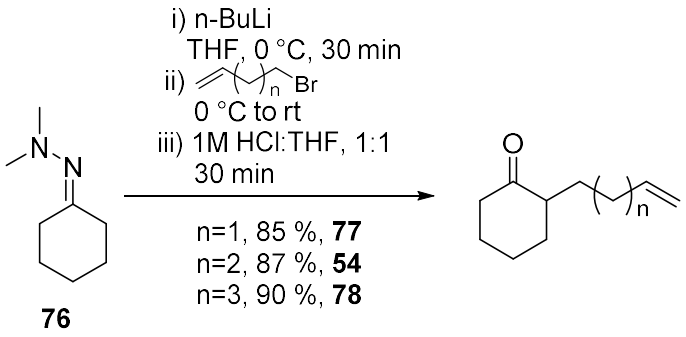
2.2 Third Generation Approach to Cyclohexyne Precursors

In order to produce the triflates of interest, we developed a different strategy that could access allyl ester **69** via the acylation of **70** with acylating agent **75**, which can then be used to access vinyl triflate **74** (Scheme 27). This method avoids the tricky trans-esterification and may provide a more scalable route to the desired cyclohexyne precursors. In addition, this method is more similar to the initial approach presented in Scheme 16.



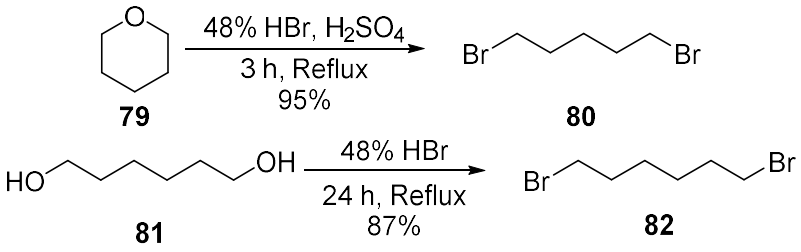
Scheme 27 Retrosynthetic approach to cyclohexyne precursors.

Ketones **77**, **54**, and **78** were produced via the alkylation of cyclohexanone dimethylhydrazone (**76**) followed by hydrolysis to yield the ketone (Scheme 28).[29] Use of the dimethylhydrazone **76** prevents polyalkylation, an issue frequently observed with the alkylation of cyclohexanone.[29] The process is high yielding and requires only an aqueous work up to yield sufficiently pure product, allowing the substrates to be quickly produced.



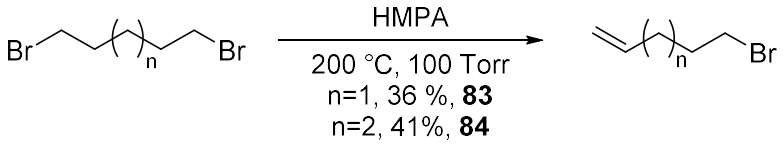
Scheme 28 Alkylation of cyclohexanone dimethylhydrazone.

In addition, a method was determined for the production of the alkylating agents, particularly 6-bromohexene and 5-bromopentene. This started with the production of the dibromides **80** and **82** from tetrahydropyrone (**79**) and 1,6-hexanediol (**82**), which could be done in excellent yield using HBr as a bromide source (Scheme 29).[30,31]



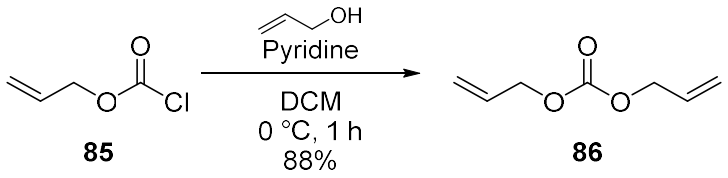
Scheme 29 Synthesis of dibromide compounds from economic starting materials.

The terminal alkene was then be produced using a simple HMPA promoted elimination, producing 5-bromopentene (**83**) and 6-bromohexene (**84**) (Scheme 30).[32] The reaction is done at a temperature significantly higher than the boiling point of the desired alkene, so a short path distillation apparatus is attached in order to collect the product. Similarly, the reaction is performed at reduced pressure in order to prevent over elimination of the product. Despite the relatively low yields of this reaction, the starting materials are cheap and easily accessible, and the reaction is scalable, allowing gram amounts to be made in a single reaction.



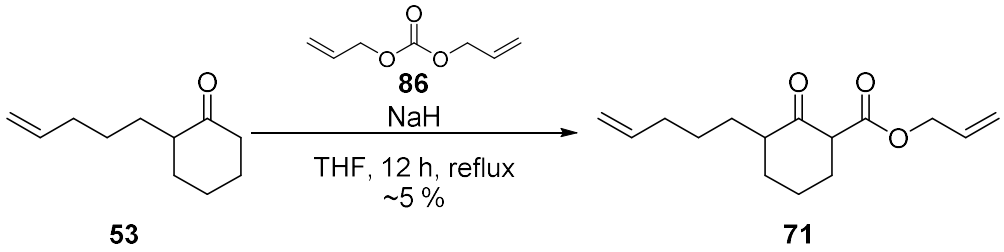
Scheme 30 HMPA-promoted elimination of dibromide compounds to form a terminal alkene.

Following the production of the ketones, we surveyed methods to introduce the allyl ester moiety. Our first attempt involved the use of diallyl carbonate (**86**), which has been shown to be able to introduce allyl esters to wide range of compounds, producing β-keto esters.[33] In addition, diallyl carbonate (**86**) could be produced in high yield through the reaction of allylchloroformate (**85**), allyl alcohol and pyridine (Scheme 31).



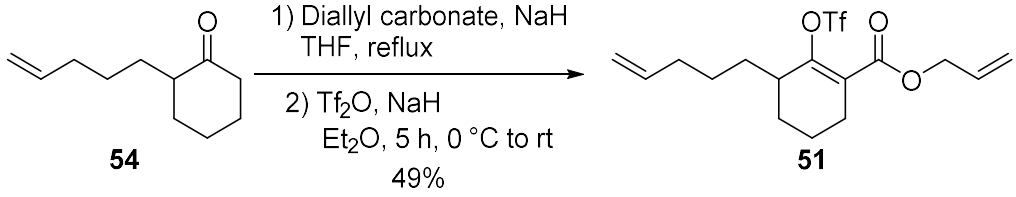
Scheme 31 Synthesis of diallyl carbonate.

Using conditions from the literature, initial attempts showed high conversion of starting material, but only trace amounts of allyl ester **71** after 12 hours (Scheme 32).[33]



Scheme 32 Unsuccessful acylation of ketone **53**.

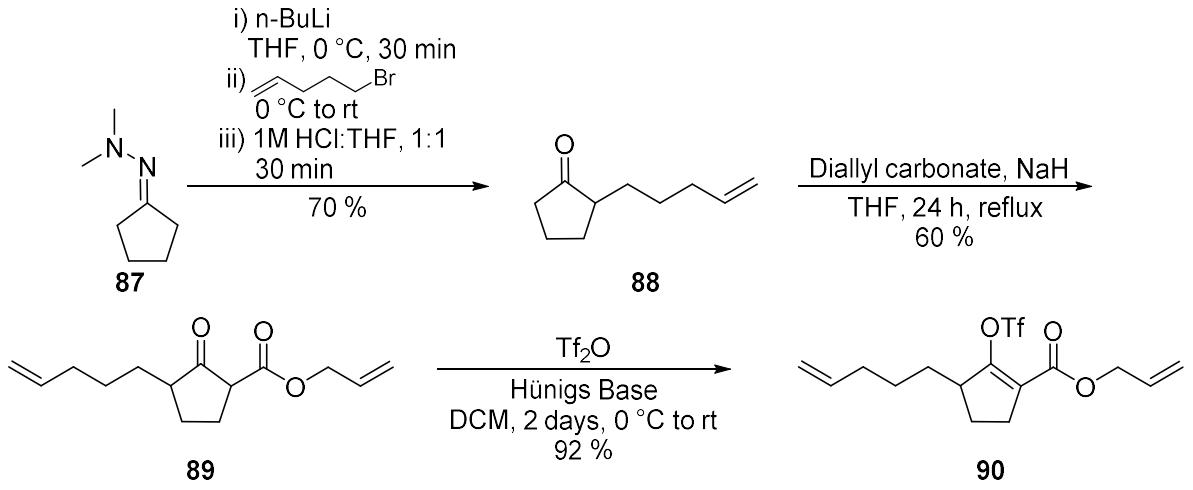
Reaction monitoring with ^{1}H NMR, however, revealed a 90% conversion after only 3 hours, with approximately 70% of the product being the desired β-keto ester **71** (Scheme 33). Triflation of the crude product gave a 49% yield of **51**, a process comparable to our work with Otera's catalyst (Scheme 25).



Scheme 33 Synthesis and triflation of a β-keto ester.

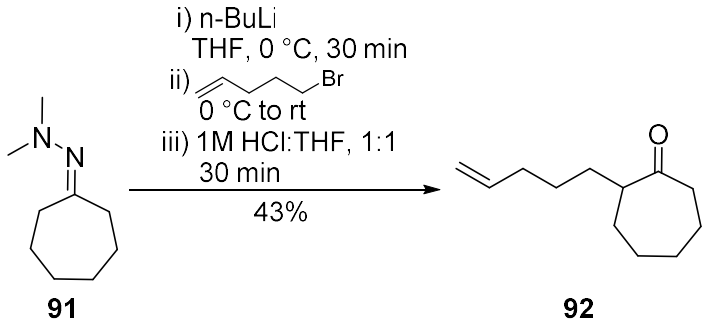
It was also possible to apply this three step process to hydrazone **87**, which could serve as a cyclopentyne precursor. Hydrazone **87** was alkylated, producing ketone **88**, which was then acylated to form allyl ester **89** (Scheme 34). Allyl ester **89** was then converted to vinyl triflate **90** in excellent yield using Hünig's base and triflic anhydride. In general, this method seemed to

provide satisfactory yield and could be used to produce material on the scale of several hundred milligrams, an amount much more convenient for reaction screening.



Scheme 34 Synthesis of cyclopentyne precursor via a three-step process.

In addition, ketone **92** was produced from hydrazone **91**, in the interest of producing the analogous cycloheptyne precursors (Scheme 35). Currently, yields for this transformation are low, and studies are ongoing to optimize this reaction.

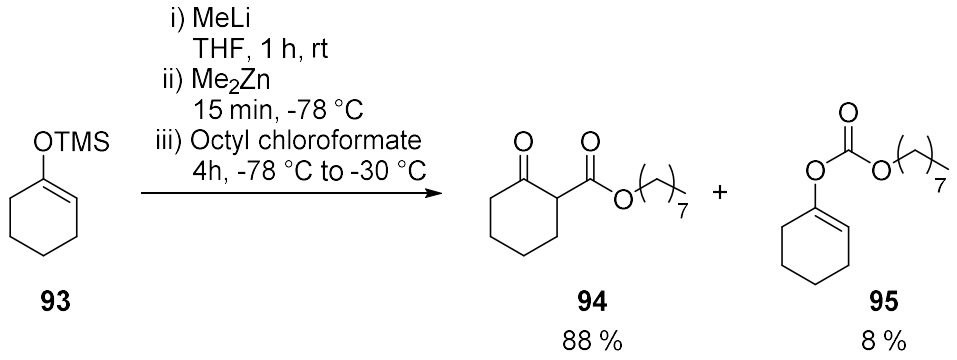


Scheme 35 Progress towards a cycloheptyne precursor.

Unfortunately, it was found that this acylation process is not amenable to small scale processes, especially on the scale of 50-100 mg. At these smaller scales, starting material was converted at a high rate, but only an unidentified byproduct was produced. Due to the significant keto-enol tautomerization of allyl ester **71**, it was also impractical to attempt to purify any product

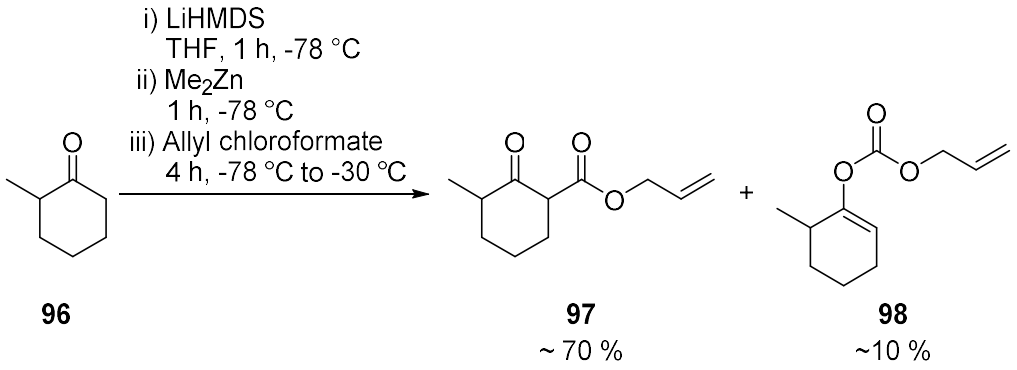
that did form via flash chromatography due to the broad range of R_f values that the compound displayed. It is not clear why the nature of the reaction changes so drastically as scale is reduced. Nonetheless, different methods for acylation were surveyed.

Our first attempt to synthesize the β-keto ester utilized chemistry developed by Noyori, which could produce β-keto esters from a TMS-protected ketone **93**, using MeLi to produce the Li-anion followed by the addition of dimethylzinc in order to form mixed Zn-Li aggregates, giving octyl ester **94** and carbonate **95** (Scheme 36).[34] This method seemed advantageous because it used the commercially available chloroformate as an acylating agent.



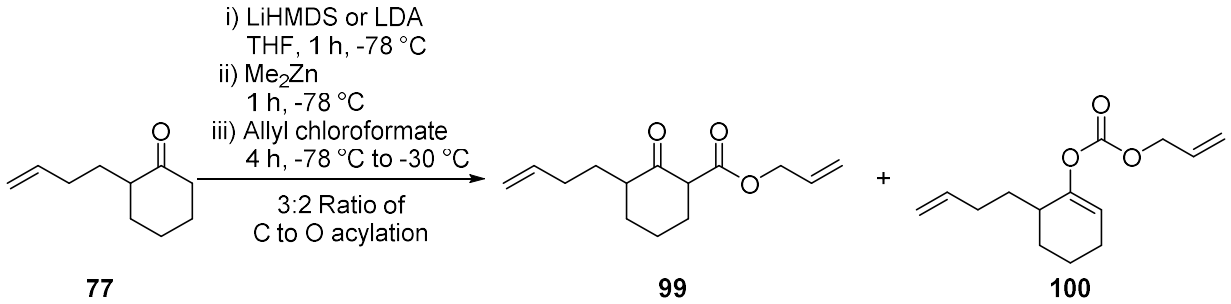
Scheme 36 Synthesis of β-keto esters using mixed Li-Zn aggregates.

Before applying this methodology to our system, we wanted to determine if the lithium anion could be produced by a sterically hindered lithium base, such as LDA or LiHMDS, if the technique tolerated substitution alpha to the ketone, and if allyl chloroformate could be used as an acylating agent. As a model substrate, we used 2-methylcyclohexanone (**96**) and LiHMDS as a base (Scheme 37). To our delight, C-acylated product **97** dominated over O-acylated product **98**.



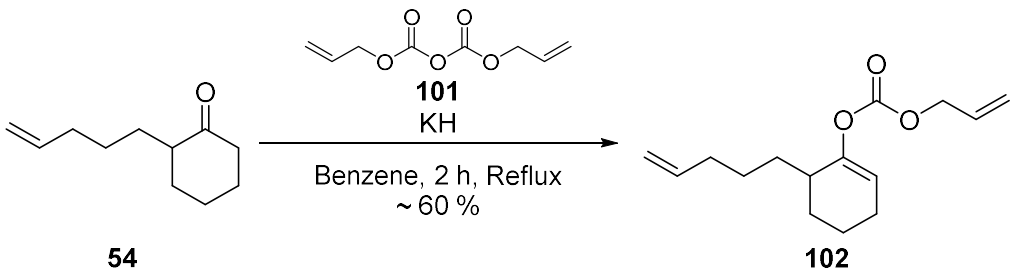
Scheme 37 Synthesis of a β-keto ester. Yields are estimated by ^{1}H NMR.

When applying this to our system, however, we found that the extended substitution at the 2-position encouraged higher rates of O-acylation (Scheme 37). To our knowledge, no research had been done in the application of this methodology to more complex systems. We therefore abandoned this method and looked for an alternative route to convert the ketones to the β-keto ester.



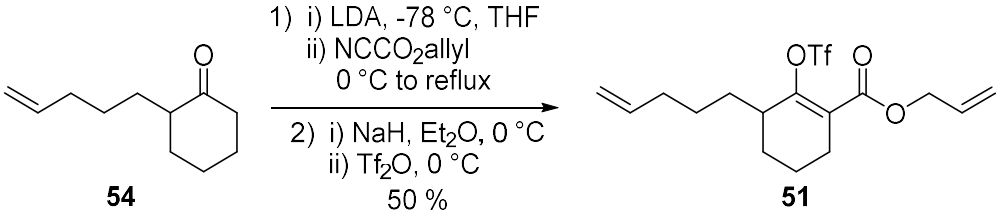
Scheme 37 Application of Noyori's production of β-keto esters. Ratio of C to O acylation was estimated by ^{1}H NMR.

In addition, we also attempted the acylation using diallyl dicarbonate (**101**) with potassium hydride in benzene (Scheme 38).[35,36] With unsubstituted cyclohexanones, it was demonstrated that C-acylation was preferred, but the O-acylated product **102** dominated when using ketone **54**.



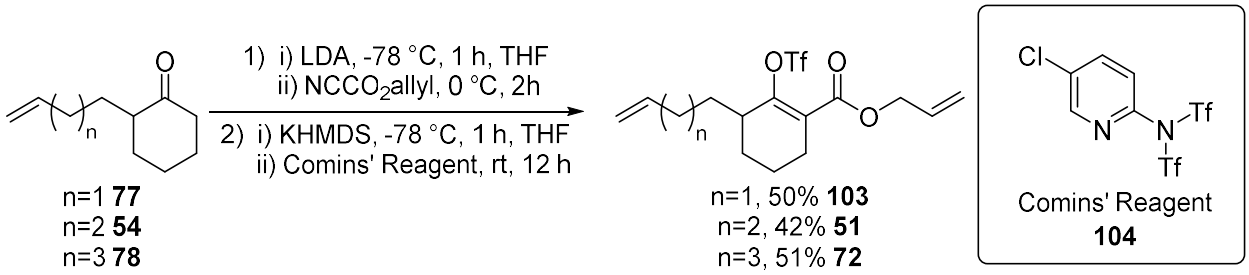
Scheme 38 Acylation of ketone **53** with diallyl dicarbonate.

Finally, acylation of ketone **54** with allyl cyanoformate was attempted again (Scheme 39). By heating the reaction under reflux, it was found that a larger amount of C-acylated product was formed. With subsequent triflation, a moderate yield of 50% of vinyl triflate **51** was obtained over two steps.



Scheme 39 Production of triflate with allyl cyanoformate followed by triflation.

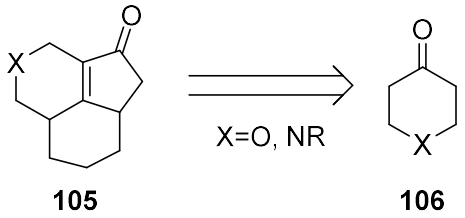
This prompted us to revisit the idea of using allyl cyanoformate as an acylating reagent. While initial results gave poor yield, we found that the reaction is time dependent, and that the product may not be indefinitely stable under the reaction conditions. After monitoring the reaction by ^{1}H NMR, it was determined that the C-acylation reaches a maximum after 2 hours at 0 °C. Using these new conditions, along with the use of Comins' reagent (**104**), a milder triflate source than triflic anhydride, it was possible to synthesize **51**, **72**, and **103** (Scheme 40).[37] While **51**, **72**, and **103** were synthesized in yields roughly equal to our previous syntheses, this process appears to be more reproducible. As it stands these are the optimized conditions for the production of the desired triflates.



Scheme 40 Synthesis of triflates using improved conditions.

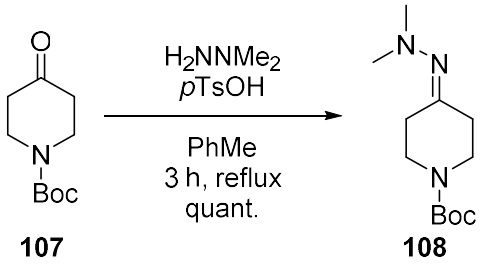
2.3 Synthesis of Heteroatom Containing Substrates

While synthesizing the all-carbon substrates, we wanted to start work towards the synthesis of heteroatom containing substrates, specifically N and O containing heterocycles **106** to form polycycles **105** (Scheme 41). This would allow us to both test the functional group tolerance of both the cyclohexyne production and the subsequent PKR.



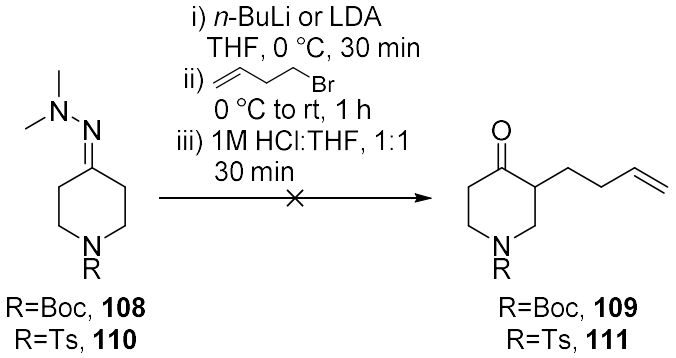
Scheme 41 Retrosynthetic analysis for the synthesis of N and O containing heterocycles.

We first started our work with a nitrogen containing substrate, N-Boc piperidone (**107**). Using a catalytic amount *p*-toluenesulfonic acid in toluene with a Dean-Starke trap, it was possible to obtain the hydrazone **108** in quantitative yield (Scheme 42).[38]



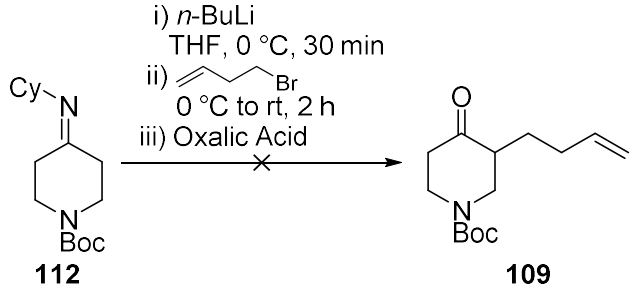
Scheme 42 Synthesis of N-containing dimethyl hydrazine.

Next, alkylation of hydrazone **108** was attempted. Despite literature precedent for alkylation of hydrazone **108**, only decomposition of starting material was observed instead of production of piperidone **109** (Scheme 43). Indeed, a D_2O quench following deprotonation also revealed decomposition of the starting material. It seems, however, that difficulty in alkylating dimethylhydrazone **108** is a known problem.[39] A similar procedure was attempted with the tosyl protected piperidone **110** to yield piperidone **111**, but this substrate gave similar results.



Scheme 43 Attempted alkylation of protected N-containing hydrazones.

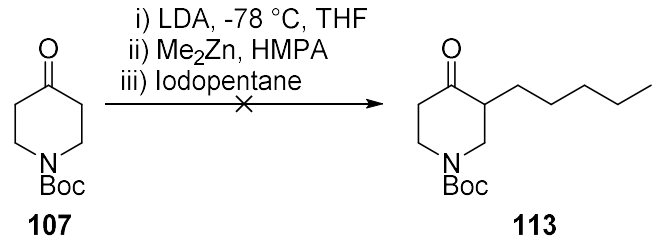
Similarly alkylation using enamine **112** was attempted (Scheme 44).[40] Unfortunately, piperidone **109** was not formed.



Scheme 44. Attempted alkylation of enamine **112**.

While the initial attempts at alkylation N-Boc piperidone (**107**) were unsuccessful, the Boc protecting group seemed advantageous because it could easily be exchanged for another protecting group. Conditions developed by Noyori using dimethylzinc as an additive were employed in order to alkylate this substrate (Scheme 45).[34] Since this method requires the use of an alkyl iodide as

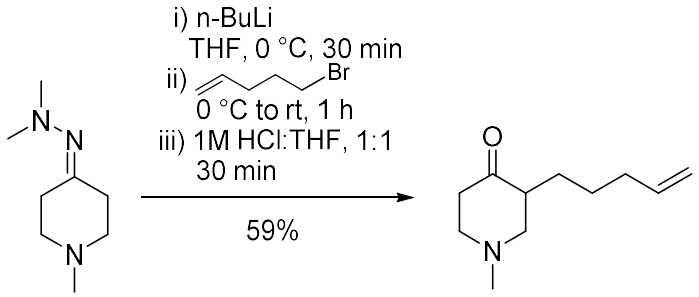
an electrophile, iodopentane was employed for reaction screening since it is more readily available than 5-iodopentene. Unfortunately, these conditions did not give piperidone **113**.



107 **113**

Scheme 45 Attempted alkylation of N-Boc piperidone.

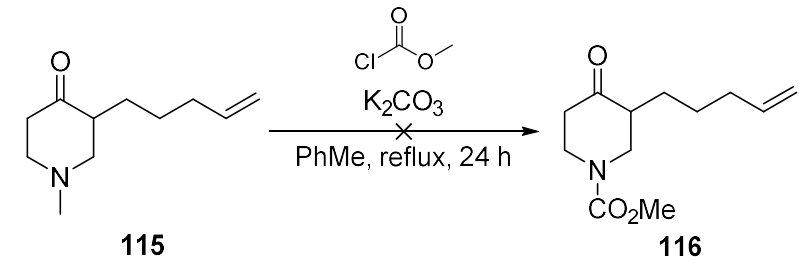
Finally, the alkylation of the dimethylhydrazone **114** was attempted. Gratifyingly this reaction proceeded with moderate yield to give piperidone **115** (Scheme 46).



114 **115**

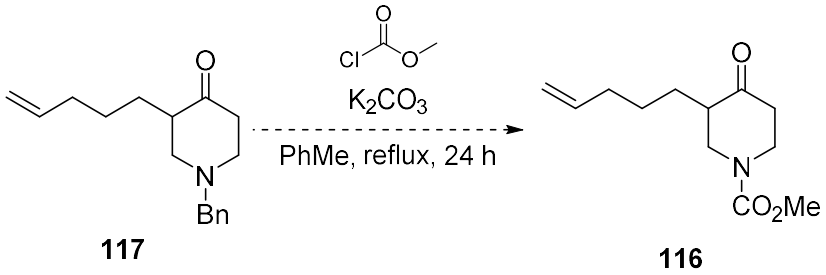
Scheme 46 Alkylation of dimethylhydrazone **114**.

It was hypothesized, however, that the free amine could bind to the metal catalyst in the PKR, poisoning the catalyst and halting the reaction. We, therefore, attempted to introduce a methylcarbamate moiety using methylchloroformate to produce carbamate **116** from piperidone **115** (Scheme 47). Under these conditions, no product was formed.[41] It was hypothesized that this may be due to the insolubility of the intermediate quaternary amine, preventing the reaction from preceding.



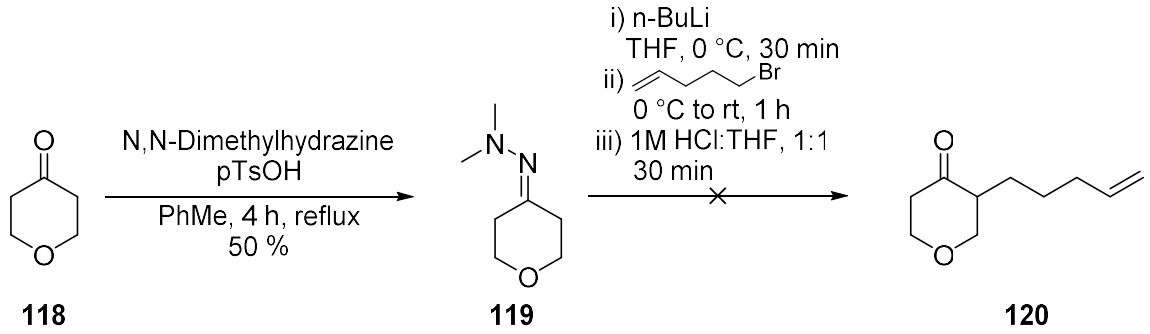
Scheme 47 Attempted introduction of methyl carbamate protecting group.

The scope of reactions to deprotect methyl amines is limited. It is, therefore, proposed that the corresponding benzylamine **117** might be a better candidate to produce carbamate **116** due to the increased electrophilicity of the benzyl position (Scheme 48). Experiments are ongoing to check the validity of this hypothesis.



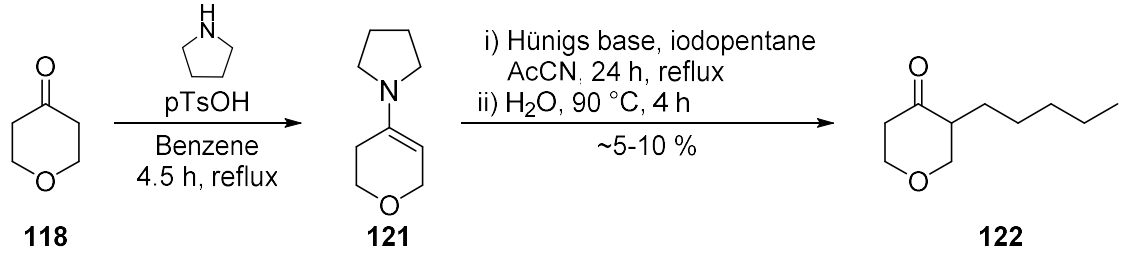
Scheme 48 Proposed substrate for introduction of methyl carbamate moiety.

Considerable work was also done in attempting to synthesize an O-containing heterocycle with a similar structure. Starting with pyranone **118**, dimethylhydrazone **119** was synthesized in moderate yield (Scheme 49). Alkylation of the substrate to produce pyranone **120**, however, did not proceed under standard conditions. ^{1}H NMR analysis of the crude product indicated decomposition of starting material under the reaction conditions.



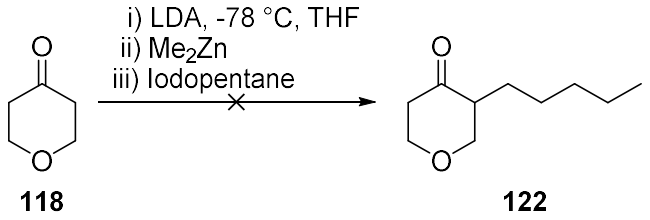
Scheme 49 Attempted alkylation of tetrahydropyanone **118**.

Next, alkylation of enamine **121**, which can be produced from pyranone **118**, was attempted (Scheme 50). While this reaction has been demonstrated to work on the same substrate using allyl bromide as an electrophile, it had not been demonstrated using longer alkyl chains.[42] While it was possible to detect product via GC-MS, this reaction did not produce a significant amount of alkylated pyranone **122**. In addition, enamine **121** was found to be unstable, making it inconvenient to use.



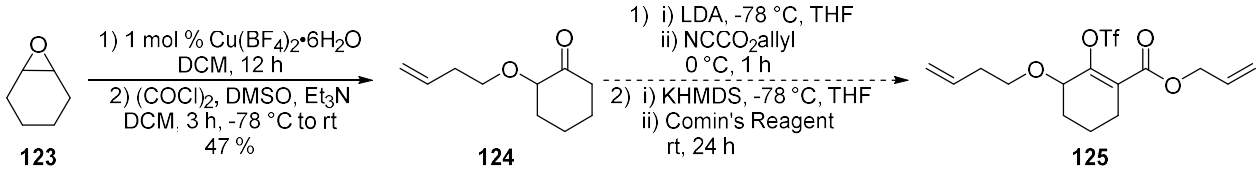
Scheme 50. Alkylation of pyranone **118** using an enamine intermediate.

Similar to trials with the N-Boc piperidone, alkylation of pyranone **118** was also attempted using the dimethyl zinc promoted alkylation conditions developed by Noyori; however, this also resulted in degradation of the starting material, producing none of the desired pyranone **122** (Scheme 51).[34]



Scheme 51 Attempted alkylation of pyranone **118** using dimethylzinc as an additive.

Finally, we decided to change our strategy and target a different O-containing substrate. The epoxide opening of cyclohexene oxide (**123**) followed by oxidation seemed to be a well precedented route which should reliably produce the desired motif. Indeed, using a $Cu(BF_4)_2$ catalyzed epoxide opening followed by a Swern oxidation, cyclohexanone **124** could be obtained in satisfactory yield over two steps (Scheme 52).[43] Subsequent acylation with allyl cyanoformate followed by triflation should deliver the desired vinyl triflate **125**.



Scheme 52 Synthesis of an O-containing substrate.

3. Future Work

While this work does provide the synthesis of a few cyclohexyne precursors, there are still more that are to be synthesized (Figure 7). In addition, the use of allyl cyanoformate as an acylating agent to produce the allyl esters of interest is promising, but further work must be done in ensuring consistency of yield across different trials.

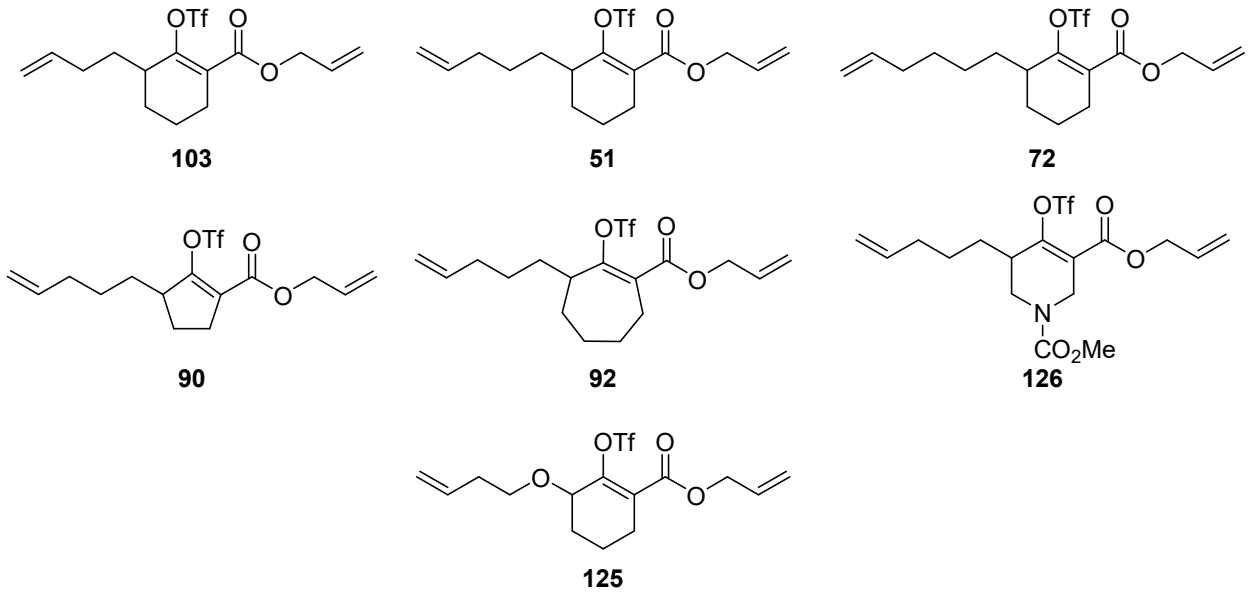
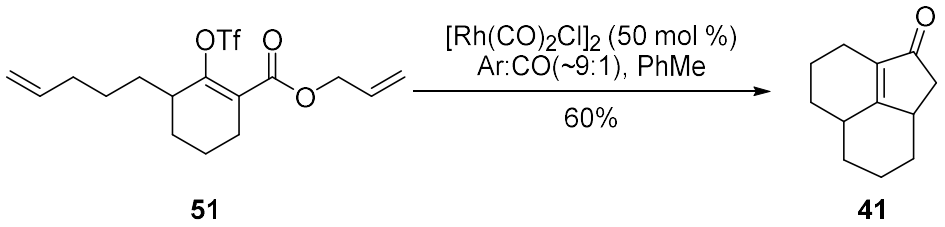


Figure 7. Triflates to by synthesized and screened for the PKR.

This work provides a series of methods that have been screened in order to produce cyclohexyne precursors; however, it is imperative that the conditions for the cyclohexyne production and the subsequent Pauson-Khand reaction are optimized. As it currently stands, the cascade requires a stoichiometric of Rh catalyst and proceeds in moderate yield (Scheme 53).



Scheme 53 Current conditions for the PKR.

While this represents a great improvement upon the original conditions, the requirement of stoichiometric rhodium makes this reaction impractical for the production of more than a few milligrams of material. This work does, however, display the synthetic utility of cyclohexyne. Although the use of stoichiometric amounts of rhodium is not ideal, it does provide proof of concept and may pave the way for other researchers to further develop this method.

4. Conclusion

Strained cycloalkynes, such as cyclohexyne and cyclopentyne, are substrates with significant potential utility that have largely been underused in organic synthesis. As a result, there are relatively few methods to produce cyclohexyne using conditions that are amendable to the use of a transition metal catalysts. This work provides both the mechanistic rationale and approaches to the synthesis of a novel cyclohexyne precursor. While the final conditions did not deliver the desired substrates in considerably higher yield, it does pave the way for further optimization of this method. In addition, this work does demonstrate the validity of our initial strategy. Using a novel cyclohexyne precursor, it was possible to perform the PKR using an *in situ* produced cyclohexyne.

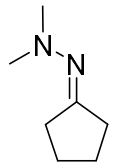
Supplementary Information

Experimental

General methods for chemistry: Tetrahydrofuran, toluene, and diethyl ether were dried by filtration through columns of activated, neutral alumina according to procedure described by Grubbs.[44] Allyl alcohol, diisoproylamine, pyridine, 4-bromobutene, 5-bromopentene, and 6-bromohexne were distilled from CaH_2 directly before use. Tf_2O was distilled from P_2O_5 directly before use. Allyl chloroformate was distilled from $CaCl_2$ directly before used. All other reagents were reagent grade and used without further purification unless otherwise noted. All solvents were determined to have less than 50 ppm H_2O by Karl Fischer coulometric moisture analysis. All reactions involving air or moisture sensitive reagents or intermediates were performed under and inert atmosphere of nitrogen or argon in glassware that was flame dried. Reaction temperatures refer to the temperature of the heating/cooling bath. Volatile solvents were removed under reduced pressure using a Büchi rotary evaporator at 35-40 ºC unless otherwise noted. Thin layer chromatography (TLC) was run on pre-coated plates of silica gel (0.25 mm thick with 60 F_{254} indicator) was visualized using one or more of the following methods: UV light (254 nm), and/or staining with $KMnO_4$ stain or cerium ammonium molybdate (CAM) stain. Chromatography was performed using forced flow (flash chromatography) and the indicated solvent system on SiliaFlash® F60 silica gel (Silicycle, 40-63 μm, 60 Å) according to the method of Still, unless otherwise noted.[45]

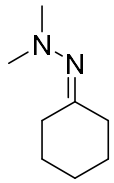
Infrared (IR) spectra were obtained either neat on sodium chloride or as solutions in the solvent indicated and reported as wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained at the indicated field as solution in $CDCl_3$ unless otherwise indicated. Chemical shifts are referenced to the

deuterated solvent are reported in parts per million (ppm, δ) downfield from tetramethylsilane (TMS, δ = 0.00 ppm). Coupling constants (*J*) are reported in Hz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet;, m, multiplet; comp, overlapping multiplets of magnetically nonequivalent protons; br, broad; app, apparent.



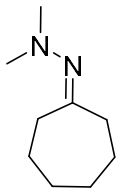
87

2-Cyclopentylidene-1,1-dimethylhydrazine (87). Prepared according to literature procedure by Mino, et al. with cyclopentanone (5.0 mL, 56 mmol), dimethylhydrazine (5.2 mL, 68 mmol) and trifluoracetic acid (0.25 mL), giving 4.1 g (58%) of a yellow oil after distillation.[46] ^{1}H NMR spectra were consistent with those reported in the literature.[46]



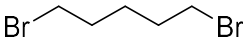
76

2-Cyclohexylidene-1,1-dimethylhydrazine (76). Prepared according to literature procedure by Mino, et al. with cyclohexanone (10 mL, 96 mmol), dimethylhydrazone (8.8 mL, 115 mmol) and trifluoroacetic acid (0.5 mL), giving 7.7 g (57%) of a clear oil after distillation.[46] ^{1}H NMR spectra were consistent with those reported in the literature.[46]



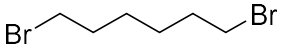
91

2-Cycloheptylidene-1,1-dimethylhydrazine (91). Prepared according to literature procedure by Mino, et al. with cycloheptanone (3.0 mL, 25 mmol), dimethylhydrazine (2.3 mL, 31 mmol) and trifluoroacetic acid (0.25 mL), giving 2.25 g (57%) of a pale yellow oil after distillation.[46] ^{1}H NMR spectra were consistent with those reported in the literature.[46]



80

1,5-Dibromopentane (80). Prepared according to literature procedure by Odinokov, et al. with tetrahydropyranone (9.8 mL, 100 mmol), 48% HBr (68 mL) and sulfuric acid (16 mL), giving 21.1 g (95%) as an orange oil.[30] ^{1}H NMR spectra were consistent with those reported in the literature.[30]

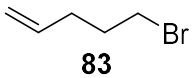


82

1,6-Dibromohexane (82). Prepared according to literature procedure by Coleman et al. with 1,6-hexanediol (10 g, 90 mmol) and 48% HBr (45 mL), giving 19.1 g (87%) as a yellow oil.[31] ^{1}H NMR spectra were consistent with those reported in the literature.[31]

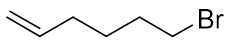
General procedure for HMPA induced elimination. This procedure was adapted from the procedure developed by Hoye.[32] A dibromide (93.4 mmol) was heated to 200 °C at 100 Torr with a short path distillation apparatus attached. HMPA (21.1 mL, 121 mmol) was added dropwise over 5 minutes, and the reaction was stirred for 1 hour. The solution in the receiving flask was then

dissolved in Et_2O (50 mL), washed with water (2 × 50 mL) and brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was distilled, giving the desired product.



83

5-Bromopentene (83). 5-Bromopentene (**83**) was prepared according to the general protocol using 1,5-dibromopentane (21.5 g, 93.4 mmol) and HMPA (21.1 mL, 121 mmol), giving 5.01 g (37 %) of a clear oil after distillation. ^{1}H NMR spectra were consistent with those reported in the literature.[47]

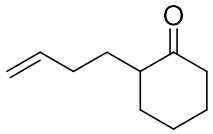


84

6-Bromohexene (84). 6-Bromohexene (**84**) was prepared according to the general protocol using 1,6-dibromohexane (19.1 g, 78.2 mmol) and HMPA (17.7 mL, 102 mmol), giving 5.30 g (41%) of a clear oil after distillation. ^{1}H NMR spectra were consistent with those reported in the literature.[48]

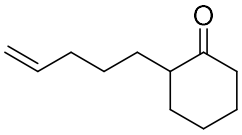
General protocol for the alkylations of dimethylhydrazones. A dimethyl hydrazone (3.57 mmol) was dissolved in THF (3.5 mL). The solution was brought to 0 °C, and *n*-BuLi (1.71 mL, 2.5 M in hexanes) was added in one portion. The solution was stirred for 30 minutes, after which a salt precipitated. An alkyl bromide (4.28 mmol) was then added, and the reaction was stirred for 1 h at room temperature. Hydrochloric acid (1 M, 3.5 mL) was added, and the reaction was stirred for 30 min. The mixture was then diluted with H_2O (15 mL) and was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with 1 M HCl

(60 mL) and brine (60 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure giving the desired compound.



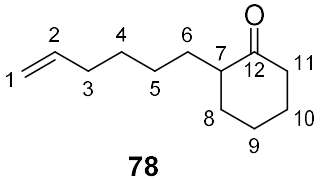
77

2-(But-3-en-1-yl)cyclohexan-1-one (77). Cyclohexanone **77** was prepared according to the general protocol using dimethylhydrazone **76** (500 mg, 3.57 mmol) and 4-bromobutene (0.43 mL, 4.28 mmol) giving 462 mg (85%) of a yellow oil. ^{1}H NMR spectra were consistent with those reported in the literature.[49]



54

2-(Pent-4-en-1-yl)cyclohexan-1-one (54). Cyclohexanone **54** was prepared according to the general protocol using dimethylhydrazone **76** (500 mg, 3.57 mmol) and 5-bromopentene (0.51 mL, 4.28 mmol), giving 516 mg (87%) of a yellow oil. ^{1}H NMR spectra were consistent with those reported in the literature.[50]

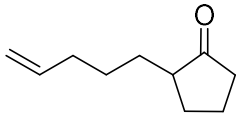


78

2-(Hex-5-en-1-yl)cyclohexan-1-one (78). Cyclohexanone **78** was prepared according to the general protocol using dimethyl hydrazone **76** (500 mg, 3.57 mmol) and 6-bromohexene (0.57 mL, 4.28 mmol), giving 577 mg (90%) of a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (ddtd, J = 16.9, 10.2, 6.7, 1.0 Hz, 1 H), 4.98 – 4.90 (m, 1 H), 4.88 (ddt, J = 10.2,

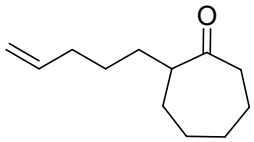
2.3, 1.1 Hz, 1 H), 2.34 (m, 1 H), 2.29 – 2.15 (m, 2 H), 2.12 – 1.91 (m, 4 H), 1.87 – 1.55 (m, 4 H), 1.42 – 1.08 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5, 139.0, 114.3, 50.8, 42.0, 33.9, 33.7, 29.30, 29.1, 28.1, 26.7, 24.9; IR (neat) 3077, 2929, 2859, 1713, 1641, 1462, 1449, 1312, 1127, 993, 910 cm^{-1}; HRMS (CI) *m/z* 180.1508 ($C_{12}H_{20}O$ requires 180.1514).

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (ddtd, *J* = 16.9, 10.2, 6.7, 1.0 Hz, 1 H, C2-H), 4.98 – 4.90 (m, 1 H, C1-H), 4.88 (ddt, *J* = 10.2, 2.3, 1.1 Hz, 1 H, C1-H), 2.34 (m, 1 H, C11-H), 2.29 – 2.15 (m, 2 H, C11-H, C3-H), 2.12 – 1.91 (m, 4 H, C7-H, C3-H, C6-H), 1.87 – 1.55 (m, 4 H, C8-H, C9-H, C5-H), 1.42 – 1.08 (m, 6 H, C8-H, C9-H. C10-H, C11-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5 (C12), 139.0 (C2), 114.3 (C1), 50.8 (C7), 42.0 (C11), 33.9 (C3), 33.7 (C8), 29.30 (C6), 29.1 (C4), 28.1 (C5), 26.7 (C9), 24.9 (C10).



88

2-(Pent-4-en-1-yl)cyclopentan-1-one (87). Cyclohexanone **88** was prepared according to the general protocol using dimethylhydrazone **87** (500 mg, 3.96 mmol) and 5-bromopentene (0.68 mL, 4.75 mmol), giving 426 mg (71%) of a yellow oil. ^{1}H NMR spectra were consistent with those reported in the literature.[51]

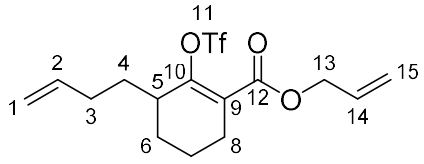


92

2-(Pent-4-en-1-yl)cycloheptan-1-one (92). Cyclohexanone **92** was prepared according to the general protocol using dimethylhydrazone **91** (300 mg, 1.94 mmol) and 5-bromopentene (0.28

mL, 2.33 mmol), giving 150 mg (43%) of a yellow oil. ^{1}H NMR spectra were consistent with those reported in the literature.[52]

General protocol for the synthesis of vinyl triflates. A ketone (0.33 mmol) was added to lithium diisoproplyamine (0.49 mL, 1.0 M in THF) at -78 °C in THF (1.0 mL). After 45 min, allyl cyanoformate (50 mg, 0.49 mmol) was added, and the reaction was warmed to 0 °C. After 3 h, the reaction was quenched with water (10 mL) and extracted with EtOAc (3 × 15 mL). The organic extracts were combined and washed with 1 M HCl (45 mL) and brine (45 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated under reduced pressure giving a yellow oil. A portion (0.28 mmol) of the crude product was dissolved in THF (1.5 mL) and KHMDS (0.39 mL, 0.84 M in PhMe) was added at - 78 °C. After 1 h, Comins' reagent (130 mg, 0.33 mmol) was added in THF (1 mL), and the reaction was warmed to room temperature and was stirred overnight. The reaction was then quenched with sat. NH_4Cl (10 ml) and extracted with EtOAc (3 × 10 mL). The organic extracts were combined and were washed with brine (30 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure.

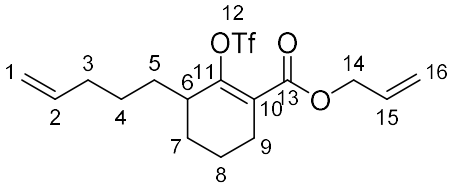


103

Allyl 3-(but-3-en-1-yl)-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate (103). Vinyl triflate **103** was prepared according to the general protocol using ketone **77** (50 mg, 0.33 mmol), and the resulting reside was purified by flash chromatography eluting with Et_2O/hexanes (1:20) to give 55 mg (50%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (ddt, J = 17.2, 10.4, 6.0 Hz, 1 H), 5.76 (dddd, J = 17.3, 10.2, 7.2, 6.1 Hz, 1 H), 5.35 (dq, J = 17.2, 1.5 Hz, 1 H), 5.27 (dt, J = 10.4, 1.3 Hz, 1 H), 5.11 – 4.86 (m, 2 H), 4.69 (qdt, J = 13.1, 5.9, 1.3 Hz, 2

H), 2.65 – 2.30 (m, 3 H), 2.25 – 2.13 (m, 1 H), 2.09 – 1.96 (m, 1 H), 1.94 – 1.80 (m, 2 H), 1.77 – 1.39 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 154.3, 137.2, 131.6, 123.7, 119.9, 119.0, 116.7, 115.6, 66.2, 37.6, 30.6, 30.6, 29.7, 27.1, 26.7, 18.6; IR (neat) 2944, 1730, 1425, 1277, 1249, 1210, 1142, 1039, 914, 821, 763, 603, 409 cm^{-1}; HRMS (ESI) *m/z* 391.0792 ($C_{15}H_{19}F_3O_5SNa$ requires 391.0803).

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (ddt, J = 17.2, 10.4, 6.0 Hz, 1 H, C14-H), 5.76 (dddd, J = 17.3, 10.2, 7.2, 6.1 Hz, 1 H, C2-H), 5.35 (dq, J = 17.2, 1.5 Hz, 1 H C15-H), 5.27 (dt, J = 10.4, 1.3 Hz, 1 H, C15-H), 5.11 – 4.86 (m, 2 H, C1-H), 4.69 (qdt, J = 13.1, 5.9, 1.3 Hz, 2 H, C13-H), 2.65 – 2.30 (m, 3 H, C5-H, C8-H), 2.25 – 2.13 (m, 1 H, C3-H), 2.09 – 1.96 (m, 1 H, C3-H), 1.94 – 1.80 (m, 2 H, C4-H, C6-H), 1.77 – 1.39 (m, 5 H, C4-H, C6-H, C7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5 (C10 or C12), 154.3 (C10 or C12), 137.2 (C2), 131.6 (C14), 123.7 (C9), 119.9 (C11), 119.0 (C15), 116.7 (C11), 115.6 (C1), 66.2 (C13), 37.6 (C5), 30.6 (C3 or C4), 30.6 (C3 or C4), 27.1 (C6), 26.7 (C7), 18.6 (C8).

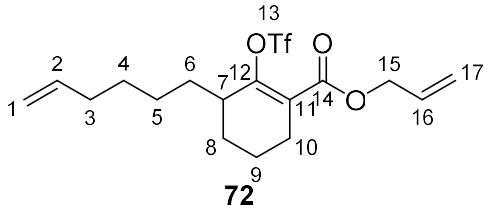


51

Allyl 3-(pent-4-en-1-yl)-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate (51). Vinyl triflate **51** was prepared according to the general protocol using ketone **53** (50 mg, 0.30 mmol), and the resulting reside was purified by flash chromatography eluting with Et_2O/hexanes (1:20) to give 46 mg (42%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (ddt, J = 17.6, 10.4, 5.9 Hz, 1 H), 5.76 (ddt, J = 17.0, 10.2, 6.7 Hz, 1 H), 5.33 (dq, J = 17.2, 1.5 Hz, 1 H), 5.25 (dq, J = 10.4, 1.3 Hz, 1 H), 5.07 – 4.86 (m, 2 H), 4.74 – 4.55 (m, 2 H), 2.66 – 2.35 (m, 2 H), 2.17 – 1.97 (m, 2 H), 1.93 – 1.83 (m, 1 H), 1.82 – 1.18 (m, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 164.5, 154.4, 138.0, 131.6, 123.6, 123.1, 119.9, 119.0, 116.7, 115.0, 66.1, 38.2, 33.5, 30.9, 27.4, 26.7, 25.8, 25.8, 18.7; IR (neat) 2945, 1730, 1425, 1248, 1211, 1142, 1038, 902, 816, 604, 442 cm^{-1}; HRMS (ESI) *m/z* 405.0954 ($C_{16}H_{21}F_3O_5SNa$ requires 405.0959).

NMR Assignments: ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (ddt, J = 17.6, 10.4, 5.9 Hz, 1 H, C15-H), 5.76 (ddt, J = 17.0, 10.2, 6.7 Hz, 1 H, C2-H), 5.33 (dq, J = 17.2, 1.5 Hz, 1 H, C16-H), 5.25 (dq, J = 10.4, 1.3 Hz, 1 H, C16-H), 5.07 – 4.86 (m, 2 H, C1-H), 4.74 – 4.55 (m, 2 H, C14-H), 2.66 – 2.35 (m, 2 H, C9-H), 2.17 – 1.97 (m, 2 H, C3-H), 1.93 – 1.83 (m, 1 H, C6-H), 1.82 – 1.18 (m, 8 H, C4-H, C5-H, C7-H, C8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5 (C11 or C13), 154.4 (C11 or C13), 138.0 (C2), 131.6 (C15), 123.6 (C16), 123.1 (C12), 119.9 (C12), 119.0 (C1), 116.7 (C12), 115.0 (C10), 66.1 (C14), 38.2 (C6), 33.5 (C3), 30.9 (C5), 27.4 (C4), 26.7 (C7), 25.8 (C8), 18.7 (C9).

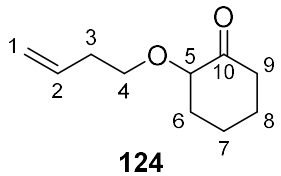


72

Allyl 3-(hex-5-en-1-yl)-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-1-ene-1-carboxylate (72).). Vinyl triflate **72** was prepared according to the general protocol using ketone **78** (50 mg, 0.28 mmol), and the resulting reside was purified by flash chromatography eluting with Et_2O/hexanes (1:20) to give 56 mg (51%) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.96 (ddt, J = 17.3, 10.4, 5.9 Hz, 1 H), 5.78 (ddt, J = 16.9, 10.1, 6.7 Hz, 1 H), 5.34 (dq, J = 17.2, 1.5 Hz, 1 H), 5.26 (dq, J = 10.4, 1.2 Hz, 1 H), 5.04 – 4.89 (m, 2 H), 4.69 (qdt, J = 13.1, 5.9, 1.4 Hz, 2 H), 2.64 – 2.31 (m, 3 H), 2.12 – 1.95 (m, 2 H), 1.92 – 1.81 (m, 1 H), 1.78 – 1.52 (m, 4 H), 1.48 – 1.16 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 154.4, 138.3, 131.4, 123.3, 122.9, 119.7, 118.8, 116.5, 114.4, 66.0, 38.1, 33.3, 31.1, 28.5, 27.2, 26.5, 25.8, 18.5; IR (neat) 2933, 1730, 1424, 1210,

1143, 1038, 912, 821, 604, 399 cm^{-1}; HRMS (ESI) *m/z* 419.1119 ($C_{17}H_{23}F_3O_5SNa$ requires 419.1116).

NMR Assignments: ^1H NMR (400 MHz, $CDCl_3$) δ 5.96 (ddt, J = 17.3, 10.4, 5.9 Hz, 1 H, C16-H), 5.78 (ddt, J = 16.9, 10.1, 6.7 Hz, 1 H, C2-H), 5.34 (dq, J = 17.2, 1.5 Hz, 1 H, C17-H), 5.26 (dq, J = 10.4, 1.2 Hz, 1 H, C17-H), 5.04 – 4.89 (m, 2 H, C1-H), 4.69 (qdt, J = 13.1, 5.9, 1.4 Hz, 2 H, C15-H), 2.64 – 2.31 (m, 3 H, C10-H, C3-H), 2.12 – 1.95 (m, 2 H (C10-H, C6-H), 1.92 – 1.81 (m, 1 H, C7-H), 1.78 – 1.52 (m, 4 H, C6-H, C8-H, C9-H), 1.48 – 1.16 (m, 5 H, C4-H, C5-H, C8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (C12 or C14), 154.4 (C12 or C14), 138.3 (C2), 131.4 (C16), 123.3 (C17), 122.9 (C13), 119.7 (C13), 118.8 (C1), 116.5 (C13), 114.4 (C9), 113.4 (C13), 66.0 (C15), 38.1 (C7), 33.3 (C3), 31.1 (C6), 28.5 (C4), 27.2 (C8), 26.5 (C5), 25.8 (C9), 18.5 (C10).

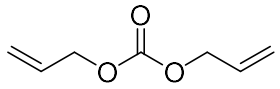


124

2-(But-3-en-1-yloxy)cyclohexan-1-one (124). Cyclohexene oxide (200 mg, 2.04 mmol) and 4-butenol (0.70 mL, 8.2 mmol) were added to a suspension of $Cu(BF_4)\cdot 6H_2O$ (7.0 mg, 0.02 mmol) in CH_2Cl_2 (2.0 mL). After 24 h, the reaction was quenched with H_2O (10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined and washed with water (30 mL) and brine (30 mL), dried with $MgSO_4$, filtered and concentrated to yield 279 mg of a pale-yellow oil. In a separate flask, oxalyl chloride (0.21 mL, 2.36 mmol) was dissolved in CH_2Cl_2 (12 mL), and DMSO (0.36 mL, 5.09 mmol) was added dropwise at -78 °C in CH_2Cl_2 (1 mL). After 20 min, a 271 mg portion of the crude reaction product was added dropwise to the mixture in CH_2Cl_2 (2 mL). After 30 min, Et_3N (1.43 mL, 10.3 mmol) was added dropwise, and after 10 minutes the reaction was warmed to room temperature. The reaction was stirred for 4 h

and was quenched with H_2O (30 mL). The layers were separated, and the organic layer was washed with 1 M HCl (30 mL), H_2O (30 mL), and sat. $NaHCO_3$ (30 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography with EtOAc/hexanes (1:20) to give 158 mg (47%) as a pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, J = 17.1, 10.3, 6.8 Hz, 1 H), 5.09 – 5.01 (m, 1 H), 4.98 (ddt, J = 10.3, 2.2, 1.2 Hz, 1 H), 3.75 (ddd, J = 9.9, 5.3, 1.3 Hz, 1 H), 3.63 (dt, J = 9.1, 6.8 Hz, 1 H), 3.37 (dt, J = 9.1, 6.9 Hz, 1 H), 2.52 – 2.42 (m, 1 H), 2.37 – 2.28 (m, 2 H), 2.28 – 2.18 (m, 1 H), 2.17 – 2.05 (m, 1 H), 1.93 – 1.82 (m, 2 H), 1.78 – 1.53 (m, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.3, 135.0, 116.5, 83.0, 69.5, 40.5, 34.5, 34.3, 27.7, 23.0; IR (neat) 2941, 2865, 1724, 1450, 1431, 1142, 1115, 1073, 1040, 996, 915 cm^{-1}; HMRS (ESI) *m/z* 191.1045 ($C_{10}H_{16}O_2Na$ requires 191.1043).

NMR Assignments: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, J = 17.1, 10.3, 6.8 Hz, 1 H, C2-H), 5.09 – 5.01 (m, 1 H, C1-H), 4.98 (ddt, J = 10.3, 2.2, 1.2 Hz, 1 H, C1-H), 3.75 (ddd, J = 9.9, 5.3, 1.3 Hz, 1 H, C5-H), 3.63 (dt, J = 9.1, 6.8 Hz, 1 H, C4-H), 3.37 (dt, J = 9.1, 6.9 Hz, 1 H, C4-H), 2.52 – 2.42 (m, 1 H, C3-H), 2.37 – 2.28 (m, 2 H, C9-H), 2.28 – 2.18 (m, 1 H, C3-H), 2.17 – 2.05 (m, 1 H, C6-H), 1.93 – 1.82 (m, 2 H, C6-H, C8-H), 1.78 – 1.53 (m, 3 H, C8-H, C7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3 (C10), 135.0 (C2), 116.5 (C1), 83.0 (C5), 69.5 (C4), 40.5 (C9), 34.5 (C3), 34.3 (C7), 27.7 (C8), 23.0 (C6).



86

Diallyl Carbonate (86). Allyl alcohol (3.14 mL, 46.2 mmol) and pyridine (3.72 mL, 46.2 mmol) were dissolved in DCM (10 mL) at 0 °C. Allyl chloroformate (4.46 mL, 42.0 mmol) was then added dropwise. After 30 min, the reaction was quenched with water (50 mL) and Et_2O (40 mL) was added. The layers were separated and the organic layer was washed with brine (50 mL),

dried with $MgSO_4$, filtered, and concentrated under reduced pressure, giving 5.26 g (82%) as a pale yellow oil. ^1H NMR spectra were consistent with those reported in the literature.[53]

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