Preprint Title	Polycyclic High Density Cage Compounds via Cross Metathesis
Authors	Sambasivarao Kotha and Usha N. Chaurasia
Publication Date	07 Okt. 2022
Article Type	Full Research Paper
Supporting Information File 1	Supporting Information Document.pdf; 2.0 MB
ORCID® iDs	Sambasivarao Kotha - https://orcid.org/0000-0002-7173-0233; Usha N. Chaurasia - https://orcid.org/0000-0002-5766-6431

Polycyclic High Density Cage Compounds via Cross Metathesis

Sambasivarao Kotha* Usha Nandan Chaurasia

Prof. Dr. S. Kotha, U.N. Chaurasia
Department of Chemistry,
Indian Institute of Technology-Bombay, Powai, Mumbai,
Maharashtra, India-400076
Prof. Sambasivarao Kotha***** - email-srk@chem.iitb.ac.in

Abstract

Synthesis of various highly functionalized caged systems suitable for high energy density materials was accomplished by utilization olefin cross metathesis strategy. Here we observed 100% E selectivity during cross-metathesis by using Grubbs II and N-tolyl Grubbs catalyst. The stereochemistry of olefin formed by cross-metathesis has been determined unambiguously by single-crystal X-ray diffraction study.

Keywords

Cookson’s dione, Grignard addition, Cross-metathesis and Cycloaddition.

Introduction

Cross metathesis (CM) is a useful tool to construct carbon-carbon double bonds [1]. CM provide access to functionalized olefins such as unsaturated silanes, boronates, phosphonates starting with terminal olefins. Traditional methods available to generate such compounds is not an easy task. Cyclic or acyclic alkenes can be obtained in a regio and stereoselective manner by the use of transition metal catalysts involving cross-coupling reactions. Due to wide functional group tolerance, mild reaction conditions employed, olefin metathesis has gained a widespread application in synthetic chemistry. CM proved to be a useful method to assemble functionalized olefins in organic synthesis including heterocycles, carbocycles and provide access to modified compounds suitable for further synthetic manipulation. Two olefinic moieties with similar reactivities can yield an equilibrium distribution of several metathesis products (Figure 1). Also, using olefins of different steric environment, one can get good yields of newly functionalized olefins. Moreover, CM has the ability to provide highly functionalized reagents suitable for further synthetic manipulation.

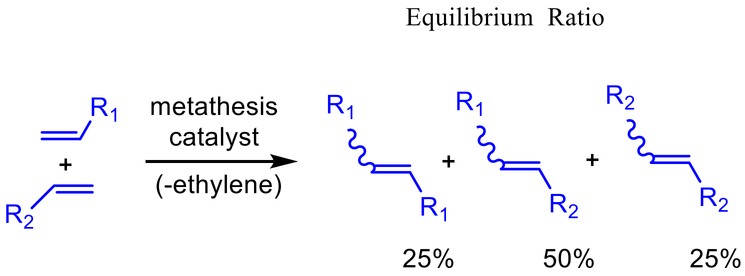


Figure 1. General representation of Cross-metathesis

Several theoretically interesting cage molecules such as cubane **1** [2], trinorbornane **2** [3], trishomocubane **3** [4] and oxa-cage compounds **4** [5], **5** [6] and **6** [7] are being synthesized and these molecules are interesting substrate for further exploration.

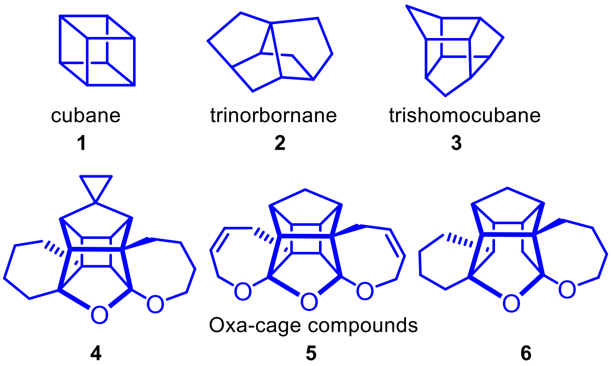
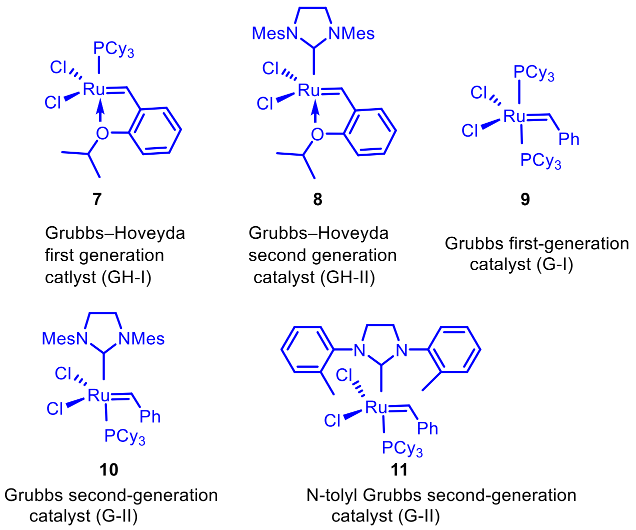


Figure 2. Theoretically interesting molecules

This work involves expanding the library of cage polycycles by synthesizing highly functionalized derivatives which are useful candidates for further synthetic manupilation. Cage compounds are known to be useful as high energy density materials [8], pharmaceutical products [9], supramolecular chemistry [10], thermostable oils [11], polymers and ligands for asymmetric synthesis [12] and precursors to intricate naturals as well as non-natural products [13].

In CM, selectivity depends on the steric and electronic factors of the olefins involved in the metathesis strategy. When sterically bulky olefins and commercially available non-bulky olefins are coupled by CM, interesting products are produced that are inaccessible by traditional methods. High energy density materials are useful as fuels. Therefore, we are interested in designing new cage systems by CM sequence and understand their density behavior. Here, Cookson's dione was utilized as a starting material for designing highly functionalized high-density materials by exploring CM sequence with different olefinic partners such as Type I (fast homodimerization, dimers are consumed) olefins like allyltrimethylsilane, allyltriisopropylsilane, cis-1,4-diacetoxy-2-butene which are electron rich species and Type II (slow homodimerization, dimers are sparingly consumed) olefins such as methyl vinyl ketone which is electron deficient [14]. Various metal catalysts such as Grubbs-Hoveyda first generation catalyst **7**, Grubbs-Hoveyda second generation catalyst **8**, Grubbs first generation catalyst **9**, Grubbs second generation catalyst **10** and *N*-tolyl Grubbs catalyst **11** have been screened. But Grubbs second generation **10** and *N*-Tolyl Grubbs catalyst **11** proved to be suitable for cross metathesis sequence.



7
Grubbs–Hoveyda first generation catlyst (GH-I)

8
Grubbs–Hoveyda second generation catalyst (GH-II)

9
Grubbs first-generation catalyst (G-I)

10
Grubbs second-generation catalyst (G-II)

11
N-tolyl Grubbs second-generation catalyst (G-II)

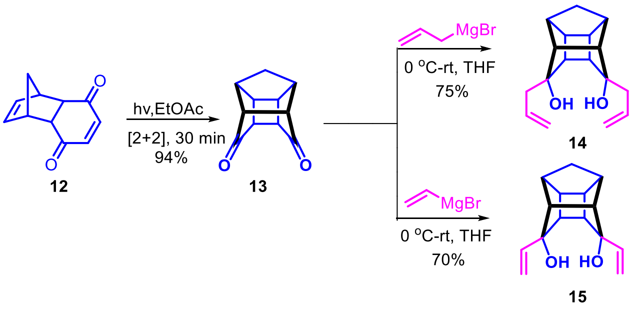
Figure 3. Commonly used transition metal-based catalysts for metathesis

N-Tolyl Grubbs catalyst show better efficiency in CM towards sterically congested olefins. With the availability of advances in catalyst development, the range of substrates suitable for CM are expanded gradually with time.

We plan to assemble various functionalized cage compounds using Diels–Alder (DA) reaction, [2+2] cycloaddition, Grignard addition and cross metathesis as key steps. The two allyl and vinyl moieties present in the cage systems serve as a useful handle to incorporate new functional groups in these molecular frameworks.

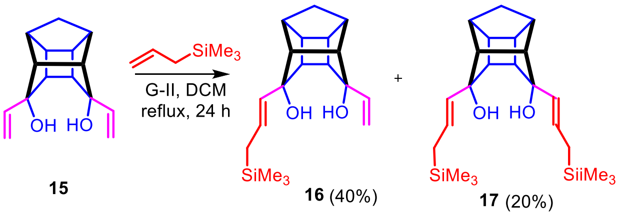
Results and Discussion

We started our journey with the preparation of Diels-Alder adduct **12** by using p-hydroquinone as a starting material for this purpose, *p*-hydroquinone was subjected to oxidation using $KBrO_3$ to produce 1,4-benzoquinone, which was then treated with a freshly cracked cyclopentadiene to generate the DA adduct **12**, which was subjected to [2+2] photocycloaddition under UV irradiation to afford the Cookson's dione **13** [15]. Treatment of the dione **13** with allyl Grignard reagent and vinyl Grignard reagent generated the unsaturated starting materials **14** and **15** in 75% and 70% yields respectively [16]. These diols were identified as suitable substrates for CM sequence. Due to their bulky nature, these two diols **14** and **15** may not undergo self-metathesis (*i.e*. homodimerization). For CM purpose, we selected type I olefins and type II olefins which can participate readily in CM sequence with hindered olefins. Since the olefinic moieties are exo face of the cage system, we expect them to participate in CM sequence.



Scheme 1. Synthesis of diols **14** and **15**

In view of these speculations, the unsaturated compounds **14** and **15** were subjected to CM sequence with different olefinic partners such as allyltrimethylsilane, allyltriisopropylsilane, cis-1,4-diacetoxy-2-butene and methyl vinyl ketone in the presence of metathesis catalysts like Grubbs second generation catalyst **10** and *N*-tolyl Grubbs catalyst **11** using DCM or toluene as a solvent under reflux conditions. Some of these catalysts are known to be useful in CM sequence. For example *N*-tolyl catalyst is useful in Z selective olefin formation with sterically hindered substrates.

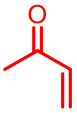
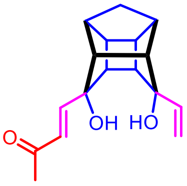
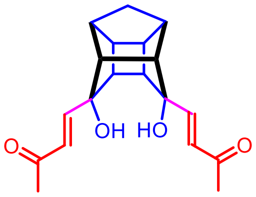
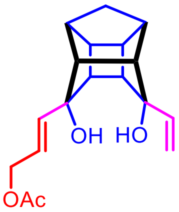
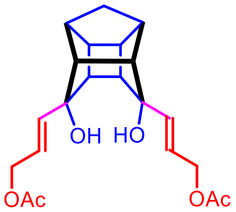
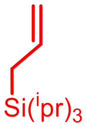
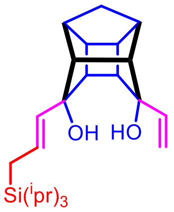


Scheme 2. Synthesis of cross products **16** and **17**.

We successfully obtained mono CM product **16** as well as di CM product **17** with allyltrimethylsilane in presence of a G-II catalyst in good yield.

Table 1. List of Cross metathesis compounds prepared from diol **15**

$$\mathbf{15} \xrightarrow[\text{catalyst}]{\text{Olefinic partner II}} \text{mono cross product} + \text{di cross product}$$

S.No	Olefinic Partner II	Cross monoproduct	Cross diproduct
1.		 **18** (45%)	 **19** (30%)
2.		 **20** (45%)	 **21** (25%)
3.		 **22** (40%)	

The CM products **(18, 19** and **22)** obtained using G-II catalyst (10 mol%) and products (**20** and **21**) obtained using *N*-tolyl Grubbs catalyst (10 mol%) under DCM and toluene reflux conditions respectively.

So, we attempted to prepare other CM products with alternate olefinic partners. To study the stereochemistry of new double bond formed we had crystallized allyltrimethylsilane CM product **16**. Here also we obtained mono as well as bicapped CM products with olefinic partners such as methyl vinyl ketone and cis-1,4-diacetoxy-2-butene. The bicapped CM product was not obtained with allyltriisopropylsilane because of the steric nature of isopropyl groups attached to silicon. List of cross metathesis products prepared from the diol **15** are shown in Table 1.

Later, single-crystal X-ray diffraction studies confirmed the stereochemistry of the double bond present in the compound **16** and established as E selectivity of double bond. X-Ray crystal structure of the compound **16** is shown in Figure 4.

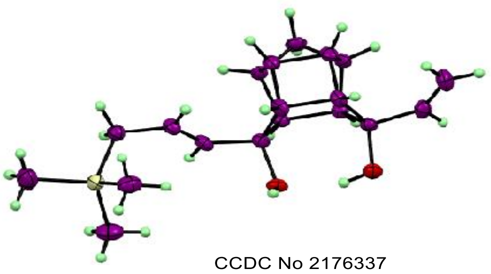


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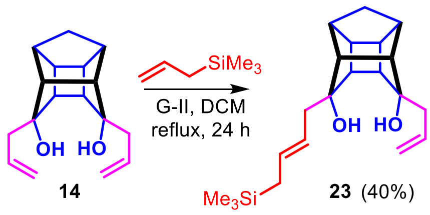
Figure 4. Single crystal X-ray diffraction of Compound **16**

Along similar lines, we had prepared CM products with dihydroxy allyl Grignard product **14** derived from the Cookson’s dione **13**. Later, the diallyl diol **14** was subjected to CM with allyltrimethylsilane to obtain CM product **23** as a solid.

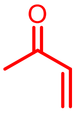
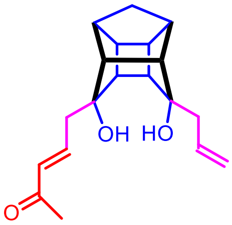
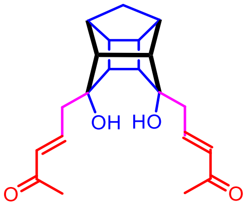
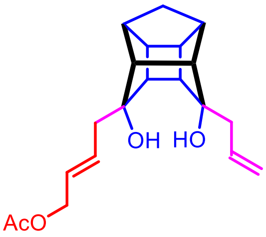
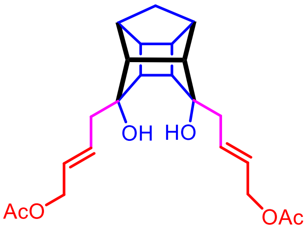


Scheme 3. Synthesis of cross products **23**.

Then, the compound **14** was also treated with other olefinic partners to produce diverse CM products. In this regard methyl vinyl ketone and cis-1,4-diacetoxy-2-butene were used as a CM partners. The catalysts used here are G-II and *N*-tolyl Grubbs catalysts and they are employed under high dilution conditions to minimize the polymerization of the starting olefins. The list of compounds prepared by CM sequence in this context are included in Table 2.

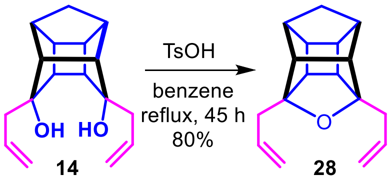
Table 2. List of Cross metathesis compounds prepared from diol **14**

$$\mathbf{28} \xrightarrow[\text{catalyst}]{\text{Olefinic partner II}} \text{mono cross product} + \text{di cross product}$$

S.No	Olefinic Partner II	Cross monoproduct	Cross diproduct
1.		 **24** (45%)	 **25** (30%)
2.		 **26** (45%)	 **27** (25%)

The cross- metathesis products (**24** and **25**) obtained using G-II catalyst (10 mol%) and products (**26** and **27**) obtained using *N*-tolyl Grubbs catalyst (10 mol%) under DCM and toulene reflux conditions respectively.

Next, to expand the library of CM products it was decided to synthesize cyclic ethers **28** and **33** [17] and study their CM behaviour. To this end, we treated the diols **14** and **15** with *p*-toluenesulphonic acid to generate cyclic ethers **28** and **33** (Scheme **4**). Subsequently, they were subjected to CM sequence with Type I and Type II olefins using different catalysts under diverse conditions.

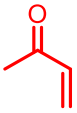
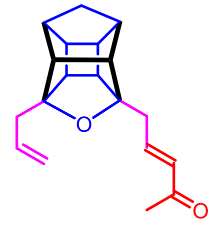
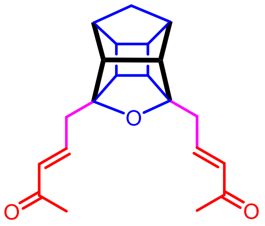
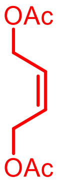
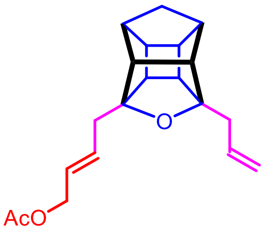
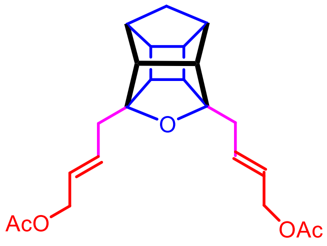


Scheme 4. Synthesis of allyl ether compound **28**.

Table **3** include list of the cross products formed with compound **28**.

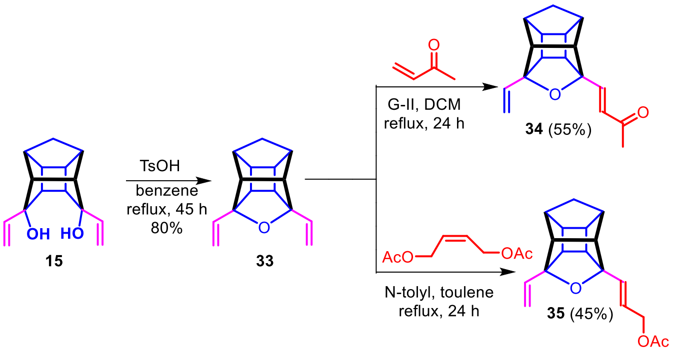
Table 3. List of Cross metathesis compounds prepared from cyclic ether **28**

$$\mathbf{28} \xrightarrow[\text{catalyst}]{\text{Olefinic partner II}} \text{mono cross product} + \text{di cross product}$$

S.No	Olefinic Partner II	Cross monoproduct	Cross diproduct
1.		 **29**(30%)	 **30** (30%)
2.		 **31**(25%)	 **32** (30%)

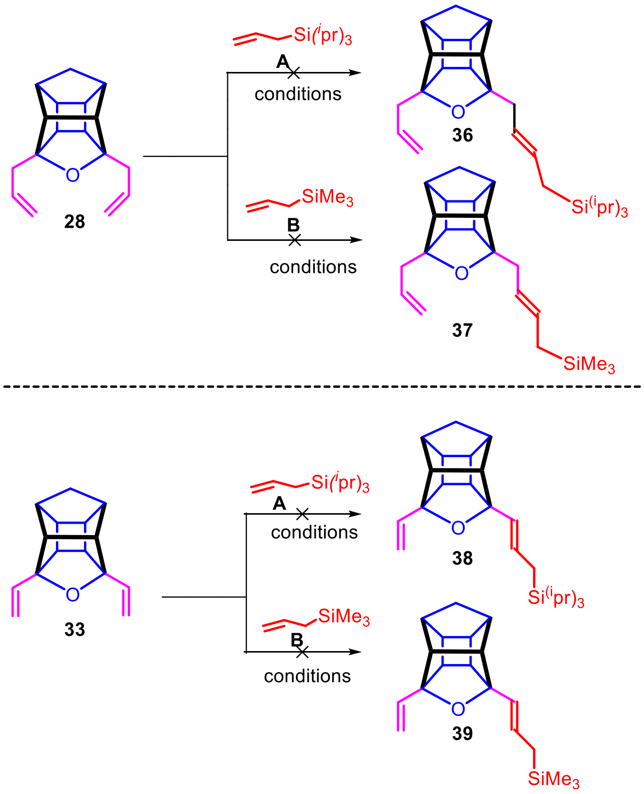
The cross- metathesis products (**29** and **30**) obtained using G-II catalyst (10 mol%) and products (**31** and **32**) obtained using N-tolyl Grubbs catalyst (10 mol%) under DCM and toulene reflux conditions respectively.

Also, to expand metathesis [18-19] strategy in general and CM specifically the diol **15** was treated with *p*-toluene sulphonic acid to produce vinyl ether **33**. It was further subjected to CM sequence with different olefinic partners such as methyl vinyl ketone and cis-1,4-diacetoxy-2-butene. The successful results are shown in Scheme **5**.



Scheme 5. Synthesis of cross products **34** and **35**.

Allyl and vinyl ethers **28** and **33** were subjected to CM with allyltrimethyl silane and allyltriisopropyl silane to produce the CM products under different reaction conditions (Scheme **6**). Unfortunately, we failed to get the cross products with these two substrates and the starting materials were recovered. It may be due to large size of the substituents present in silane group and also steric hindrance associated with the cage olefinic partners such as **28** and **33**.



Scheme 6. Synthesis of cross products **36, 37, 38** and **39**.

Table 4. Attempted conditions for CM of compound **28** and **33** with cross coupling partners A and B.

Entry	Catalyst (10 mol%)	Solvent	Temp (^{o}C), Time
1.	G-II	DCM	rt, 24 h
2.	G-II	Toluene	reflux, 48 h
3.	N-tolyl Grubbs	Toluene	reflux, 48 h

4.	G-I	Toulene	reflux, 48 h

Conclusion

We have developed a simple synthetic strategy to highly functionalized polycyclic cage compounds by CM sequence using G-II and *N*-tolyl Grubbs catalysts. Various products obtained here are characterized by spectroscopic data. In one case, we have established the stereochemistry of the double bond present in product as E by single crystal X-ray diffraction data. When the diols (**14** and **15**) were converted to ether, the CM with allyltrimethylsilane and allyltriisopropylsilane as olefinic partners did not occur. This is due to the steric crowding created during the ether formation and also the Type I olefin used here contain bulky substituents. Moreover, olefinic bonds in ether are less accessible as compared to olefinic bonds present in diol derivatives. For the first time, we have demonstrated that cage diols containing olefins are useful substrates for CM sequence and they did not undergo homodimerization (*i.e*. self-metathesis). In essence, we have used CM to increase the diversity and chemical space of cage compounds. This is an excellent method for chain elongation with readily available type I and II alkenes by late-stage CM process. The convergent nature of CM and mild reaction conditions makes it as a useful synthetic tool in cage systems. The density of the CM product **16** as determined from X-ray data is 1.202 g/cm^3.

Supporting Information

File 1:

General information, characterization data, copies of NMR spectra, X-ray data and refinement parameters.

File 2: CIF Files (Compound **16**)

Acknowledgements

We thank University Grants Commission (UGC), New Delhi, India for the financial assistance. We thank Dr Satyanarayana Chava, Laurus Labs for financial support.

Funding

Defense Research and Development Organization (DRDO, NO. ARDB/01/1041849/M/1), New Delhi-India.

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