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Communication

A Macrocyclic Ruthenium Carbene for Size-Selective Alkene Metathesis

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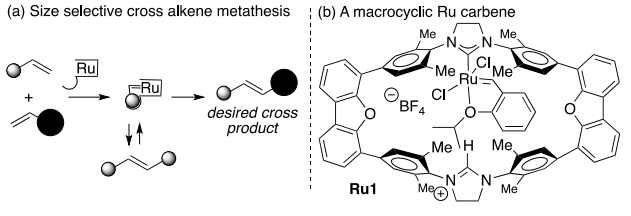
ABSTRACT: The synthesis of a macrocyclic Ru carbene catalyst for selective cross alkene metathesis is reported. The new catalyst showed different reactivity for various type 1 alkenes in homodimerization which correlated with the aggregate size of the allylic substituent. The altered reactivity profile allowed for selective product formation in competition cross alkene metathesis between two different type 1 alkenes and *tert*-butyl acrylate. Selectivity in these reactions is attributed to the ability of the macrocyclic catalyst to differentiate alkenes based on their size. Two preparative examples of cross metathesis with the macrocyclic catalyst are also provided.

Cross alkene metathesis is a powerful method for the synthesis of complex molecules.[1] Grubbs and co-workers formulated a useful predictive model for cross metathesis where alkenes are classified into groups based on their reactivity.[2] Type 1 alkenes are the most reactive and can be coupled with electron-deficient type 2 or type 3 alkenes. Because type 1 alkenes constitute a broad class of substrates, it would be desirable to promote cross metathesis between two different type 1 alkenes. This would be particularly useful in total synthesis for advanced alkene intermediates that need to be selectively coupled and/or where the use of one alkene in excess is impractical. Because joining type 1 alkenes selectively is not possible with current catalysts, we decided to approach this problem using a new class of Ru carbene catalyst featuring a macrocyclic N-heterocyclic carbene (NHC) ligand (Scheme 1). Use of an alkene metathesis catalyst that can envelop

Scheme 1. Simple Model for Size-Selective Cross Alkene Metathesis and Macrocyclic Ru Carbene



substrates and differentiate reactivity based on size of the alkene is a new paradigm for controlling selectivity in cross alkene metathesis. In this paper, we describe the synthesis and reactivity of a new macrocyclic Grubbs catalyst, report homodimerization rates, and examine size selectivity in a competition cross alkene metathesis with *tert*-butyl acrylate.

Selectivity among the same functional group is a current problem in catalysis. Site selectivity, the ability of a catalyst to differentiate between two of the same functional group in different parts of a molecule, is considered a key problem in modern catalysis.[3] For alkene substrates that differ in their aggregate size, a size-selective catalyst may differentiate them (Scheme 1). A new Ru carbene catalyst that can address this would be a valuable addition to the toolbox of task-specific Grubbs catalysts. The interior of the macrocycle is spatially restrictive. If the macrocyclic Ru carbene catalyst can accommodate only one alkene, such as the smaller alkene, a selective metathesis reaction is possible. Once formed, the resulting alkylidene may react externally with the larger alkene, giving the cross product (Scheme 1, panel a). The small alkene can reversibly dimerize. Reversibility is a key point of the Grubbs selectivity model for alkene cross metathesis. Type 1 homodimers are still reactive and continue to produce active metal carbenes that lead to a cross metathesis product.

There are several potential advantages of macrocyclic ligand design. For instance, in Grubbs' catalysts, the L-type ligand (H_2IMes) is situated trans to the alkene binding site so that it is difficult to sterically influence remote alkene binding. In the macrocyclic ligand, the bridging azolium ring in **Ru1**, can influence the outer sphere reactivity of the metal without inner sphere coordination, which would alter electronic and steric properties at the metal.[4] Second, the bridging element might be used to restrict substrate access, as a molecular recognition domain or to help stabilize the catalyst. However, macrocycles may adopt multiple conformations and can be difficult to synthesize. Since there are few examples of NHCs in macrocyclic rings,[5] it is difficult to find guidance for their design and synthesis. A recent report from our lab[6] described a macrocyclic NHC and Ru carbene, synthesized by a ring-closing metathesis (RCM), but these did not show size-selective reactions. In the present work, a concise synthesis of a macrocycle is reported and the reactivity of the Ru carbene is

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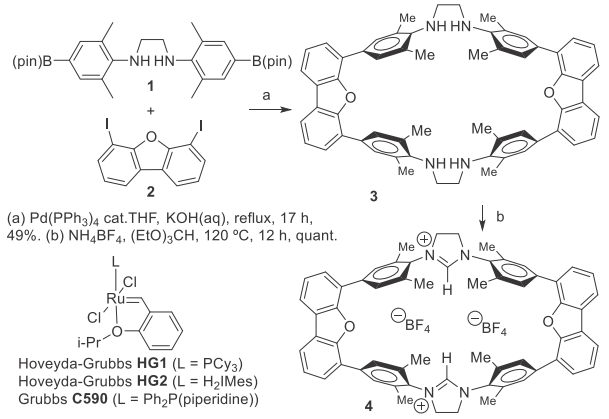
compared with that of a commercial catalyst, the Hoveyda–Grubbs catalyst (**HG2**).

The synthesis of the macrocyclic Ru carbene is shown in Scheme 2. The structure of **3** is a symmetrical, rectangular box

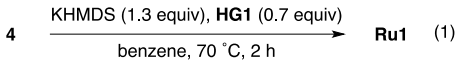
Scheme 2. Synthesis of Macrocyclic NHC Scaffold



shape with identical top and bottom and identical sides. A simple and efficient synthesis would form the macrocycle at once, in a single step between bifunctional building blocks. Using a Suzuki coupling, diamine **1** and dibenzofuran **2** were joined to form macrocycle **3** in 49% isolated yield. Efforts to improve the yield were unrewarded. Cyclization of tetraamine **3** with $(EtO)_3CH$ gave the bis(dihydroimidazolium) salt **4** with two tetrafluoroborate counterions.

Conversion to the Ru carbene complex required optimization. Salt **4** is not soluble in most organic solvents which complicated deprotonation. Following literature conditions to install a bulky NHC ligand, **4** was deprotonated and reacted with **HG1** (benzene, 1.3 equiv of KHMDS, 70 °C, 2 h), to provide a 20% isolated yield of **Ru1** (Table 1, entry 1). An

Table 1. Optimization of NHC Transfer to Synthesize Macrocyclic Ruthenium Carbene Ru1



entry	change from above conditions	isolated yield
1	none	20%
2	2.5 equiv of KHMDS, CuCl, 1 h	51%
3	2.5 equiv of KHMDS, CuCl, **C590** instead of **HG1**, 1 h	68%

aliquot at the end of the reaction showed unreacted salt **4**, unreacted **HG1**, and an intermediate. Use of more KHMDS resulted in a color change from light yellow to orange. If this color change was not observed, **Ru1** was not obtained. Longer reaction times decreased yield and mass recovery; control studies revealed that the parent Hoveyda–Grubbs carbene **HG1** decomposed in the presence of KHMDS at 70 °C over a 2 h period. Based on these observations, higher equivalents of KHMDS were used, along with shorter reaction times. ^{1}H NMR analysis of aliquots showed complete conversion of starting **HG1** with an intermediate still present after 1 h. It was found that CuCl helped convert the intermediate to **Ru1**, which improved the yield to an acceptable 51% (entry 2). Use of a superior phosphine leaving group Ph_2P(piperidine) further improved yield, with added CuCl (entry 3, 68%). The resulting carbene complex has a characteristic green color with a carbene signal at δ 16.3 ppm ($CDCl_3$). ^{19}F NMR confirmed the presence of the BF_4 counterion, which appears at δ −152.6 ppm ($CDCl_3$) for **Ru1**.

A single crystal X-ray structure verified the structure and revealed the conformation of macrocyclic **Ru1** (Figure 1). **Ru1**

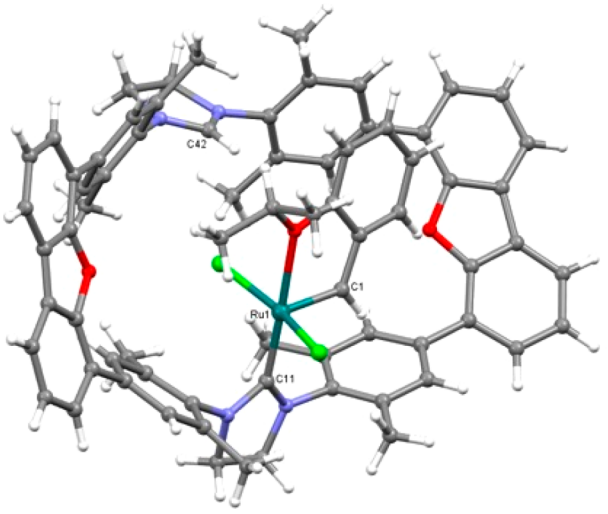
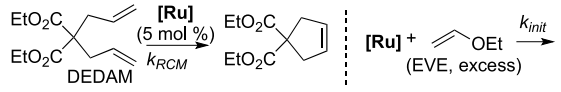


Figure 1. Solid state structure of **Ru1**.

was dissolved in CH_2Cl_2 and layered successively with 50% CH_2Cl_2–benzene and benzene. After standing 2 d in an inert atmosphere glovebox, green crystals had formed. Two Ru carbene complexes were found in the unit cell. Some of the bond lengths are typical of Hoveyda–Grubbs chelates:[7] the Ru=C1 bond length is 1.830(11) Å, Ru–C11 to the NHC was 2.371(3) Å, and the Ru–O bond length was 2.262(7) Å. There was a slight difference in the Ru–Cl bond lengths; the endo Cl–Ru was 2.344(3) Å, and the exo Cl–Ru bond was 2.371(3) Å. The dihydroimidazolium unit bridges the Ru carbene fragment, creating a wall around the backside of the Ru=C bond and a cleft in the front. The presence of a positively charged unit in the macrocycle and its associated counteranion (tetrafluoroborate, not shown in Figure 1) is a unique characteristic of **Ru1**. The bridging azolium ring points its C42–H toward the oxygen atom of the chelating benzylidene.

An evaluation of catalyst reactivity showed that **Ru1** was much less reactive than **HG2**. First, ring-closing metathesis was performed under standard reaction conditions. The apparent second-order rate constants are presented in Table 2. The RCM promoted by **Ru1** took 90 h to reach 85% conversion, or

Table 2. Performance Testing: RCM[8] and Initiation Rates[9]



cat.	k_{RCM}/M^{-1} s^{-1}[a]	k_{rel}(RCM)	k_{init}/M^{-1} s^{-1}(EVE)	k_{rel}(EVE)
HG2	3.00×10^{-2}[b]	160	2.63×10^{-2}[c]	429
Ru1	1.88×10^{-4}	1	6.13×10^{-5}[d]	1

[a]Conditions: [DEDAM] = 0.1 M, CD_2Cl_2, 30 °C (^{1}H NMR). [b]From ref 8. [c]From ref 9. [d]0.1 mM [**Ru**], 3 M EVE, CH_2Cl_2, 25 °C (UV–vis at 379 nm). EVE = ethyl vinyl ether. DEDAM = diethyl diallylmalonate.

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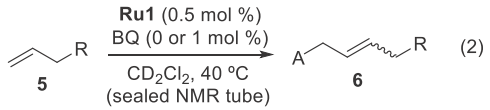
was 160 times slower than **HG2**. The kinetic data for the RCM of DEDAM provides a composite of initiation rate and rate of metathesis. Quantitative measurement of initiation rates with ethyl vinyl ether (EVE) showed an even greater difference between **Ru1** and **HG2**. These data suggest that macrocyclic **Ru1** is sterically bulky and may be useful for discrimination of alkene reactants based on the size of remote substituents.

Initially, alkene dimerization was examined to evaluate the effect of remote steric bulk. We focused on substitution at the homoallylic position since this position generally does not affect alkene reactivity classification for the Grubbs catalyst.[10] Dimerization requires two steps: alkylidenation and cross metathesis. For a hindered catalyst, we hypothesized that bulky alkenes would register slower rates of dimerization. This was tested with macrocyclic **Ru1** by evaluating catalyst activity at low substrate conversion.[11] The unhindered linear alkenes gave highest activities (Table 3, entries 1 and 2). For slow reacting

Table 3. Homodimerization of Various Alkenes Using Ru1



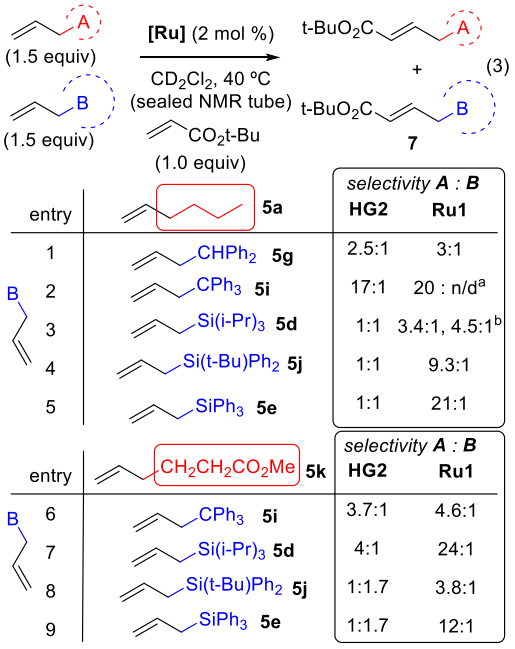
entry			conversion, 1 h[a]	activity[a,b]
1		**5a**	23, (13)	60, (33)[c]
2	CO_2Et	**5b**	29, (16)	200, (43)[c]
3	$SiMe_3$	**5c**	(1)	(2)[d]
4	$Si(iPr)_3$	**5d**	(1)	(2)[d]
5	$SiPh_3$	**5e**	0	NR
6	Ph	**5f**	(14)	(33)[c]
7	CH_2Ph	**5g**	(9)	(18)[d]
8	$CHPh_2$	**5h**	(6)	(12)[d]
9	CPh_3	**5i**	0	NR

[a]Parentheses = includes benzoquinone (BQ), 1 mol %. [b]Activity = turnovers/h at: [c]10% conversion or [d]1 h.

alkenes, we anticipated that alkene isomerization might become problematic. When benzoquinone was included, a 2-fold reduction in rate was observed. Allyl silanes showed the lowest reactivity. Though differing in substituent bulk, iPr_3Si- and Me_3Si- showed similar slow rates. The bulkier Ph_3Si- derivative gave no conversion after 1 h or up to 22 h.[12] Allyl benzene had a similar dimerization rate as alkenes **5a** and **5b** in entries 1 and 2. In the series of substituted homoallylbenzenes, increasing phenyl substitution gave a decreasing reaction rate; the $-CPh_3$ substituent showed no reaction after 1 h or up to 22 h (entries 7–9). These alkenes showed rate variation that correlated with the aggregate size of the allylic substituent. The rate of alkene reaction with a catalyst is not the sole factor determining selectivity in cross alkene metathesis. However, alkene reactivity is important because the Grubbs model classifies alkenes based on their dimerization rates. These rate data show how traditional type 1 alkene reactivity can be separated by a bulky macrocyclic catalyst.

To determine whether there was size differentiation of alkene reactants, an alkene cross metathesis competition experiment was performed between alkene pairs and *tert*-butyl acrylate. The latter alkene is a type 2 alkene. Comparisons were made with the acyclic catalyst **HG2**. The competition results are shown in Table 4. From the

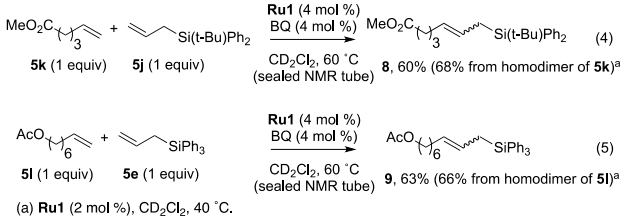
Table 4. Competition Alkene Metathesis



[a]Not detected by ^1H NMR spectroscopy. [b]Contains 4 mol % benzoquinone.

dimerization studies above, unhindered alkenes stood out as type 1 alkenes for **Ru1**. 1-Hexene (**5a**) and **5k** (the homologue of **5b** above) were selected as competitors for the least reactive alkenes. With **5a** (Table 4, entries 1–5), **HG2** surprisingly showed increased selectivity going from $-CHPh_2$ to $-CPh_3$, but not with the allylsilanes. Macrocyclic **Ru1** similarly showed increased selectivity for $-CHPh_2$ and $-CPh_3$ substituents but contrastingly showed increasing selectivity that correlated with the size of silane substituents for the allyl silanes (entries 3–5). The presence of additional phenyl substituents correlated with higher selectivity. For alkene **5k**, **Ru1** showed parallel selectivity for all alkenes (entries 6–9), albeit not as high as seen with alkene **5a**. For example, lower selectivity was seen between **5k** and **5i** ($-CPh_3$ substituent, entry 6) but higher selectivity was seen for **5k** and **5d** ($-Si(iPr)_3$ substituent; entry 7 vs entry 3). The bulkiest silanes gave reversed selectivity with **HG2** (favoring the bulkier cross product), and slightly diminished selectivities were found with **Ru1**.

Last, the homodimerization reactivity studies and the knowledge from the competition experiments led to selective cross alkene metathesis reactions (eqs 4 and 5). Using the



terminal, type 1 alkene reactants, benzoquinone was needed to prevent alkene isomerization. Conducting the reaction in NMR tubes[13] permitted reaction monitoring over several days,

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and cross products **8** and **9** were isolated by chromatography in good yields. In each case, none of the corresponding allylsilane homodimer was detected in the crude reaction. Similar yields were obtained using the type 1 homodimers of alkene **5k** and **5l** using a lower catalyst loading and lower reaction temperatures. In these cases, no benzoquinone additive was required.

In conclusion, a selective cross metathesis has been accomplished with a macrocyclic Ru carbene catalyst. The synthesis was enabled by a macrocyclization step where two bifunctional building blocks formed the macrocyclic ligand. Though much less reactive than the Hoveyda–Grubbs catalyst, **Ru1** displayed a unique reactivity profile with a set of type 1 alkenes in homodimerization. Competition cross metathesis with alkene pairs showed different selectivity than that seen with **HG2**. The reactivity trend in the homodimerization studies and the selectivity in the competition experiments correlated with the aggregate size of the allylic substituent. The ability of a macrocyclic catalyst to differentiate substrates based on size provides a new approach to selective cross alkene metathesis. Future applications to couple different type 1 alkenes by cross metathesis and improvements in catalyst reactivity are foreseeable.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c00081.

Synthetic procedures, characterization data for new compounds, and results of rate and competition studies (PDF)

Crystallographic data for **Ru1** (CIF)

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Notes

The authors declare no competing financial interest.

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(10) In contrast, allylic substitution has a pronounced steric effect and can move allylic alcohols from type 1 to type 2. Unlike substitution at the homoallylic position, allylic substitution is close enough to the alkene to affect reactivity with commercial, acyclic catalysts.

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(12) (a) With or without the benzoquinone additive, no conversion was observed. (b) For comparison, **HG2** gave a TOF of 986 for 1-hexene and 133 for allyltriphenylsilane.

(13) Due to the long reaction times, open vessel reactions resulted in evaporation of solvent. The best results were obtained in CH_2Cl_2; use of dichloroethane gave inferior results.