

Article

Triazole Modified Ru-Carbene Complexes (TA-Ru): A Valid Olefin Metathesis (OM) Pre-Catalyst for Dynamic Covalent Chemistry via C=C Bond Formation

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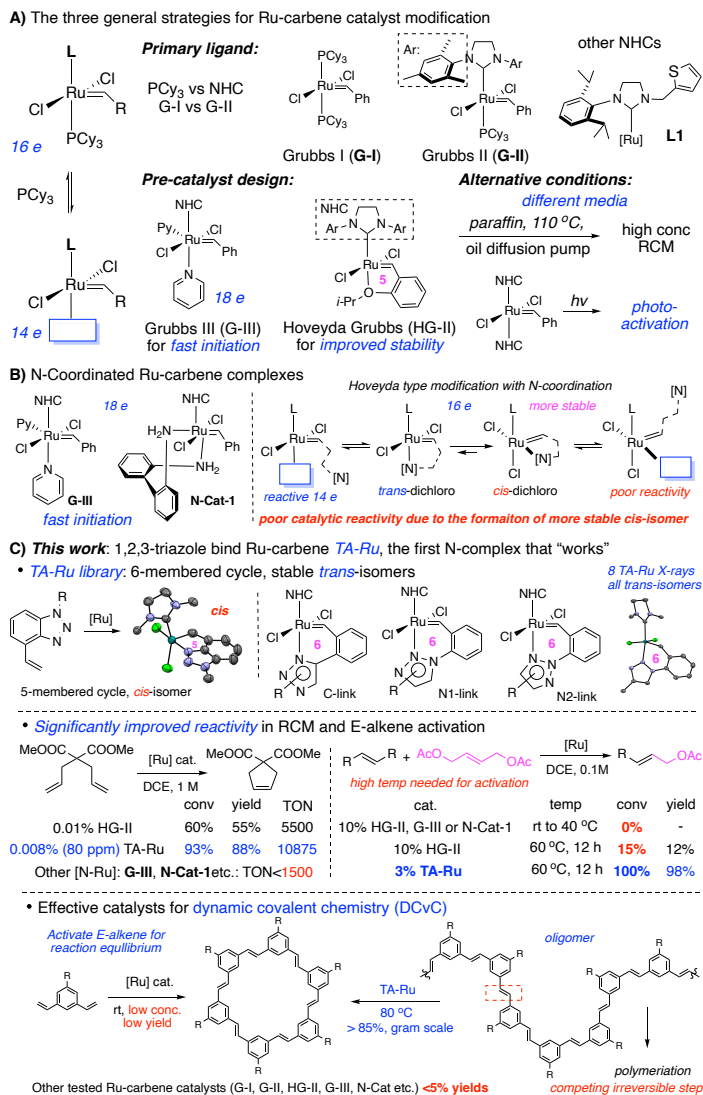
SUMMARY

The 1,2,3-triazole coordinated ruthenium carbene complexes (TA-Ru) were reported for the first time as a new class of modified Grubbs catalyst to achieve challenging olefin metathesis at higher temperatures without catalyst decomposition. Previously reported N-tethered Ru-carbene complexes all suffered from rapid *cis/trans* isomerization, causing significantly reduced catalyst reactivity. These new TA-Ru complexes hold the active *trans*-dichloro conformation even at 80 °C, allowing effective olefin metathesis for challenging substrates. With this new TA-Ru catalyst, cross-metathesis (CM), ring-closing metathesis (RCM) and dynamic covalent chemistry (DCvC) were achieved. Excitingly, the reactivity of TA-Ru prevails all previously reported N-coordinated Ru-carbene pre-catalysts, Grubbs II, and Hoveyda-Grubbs, making the TA-Ru a transformative catalytic system in olefin catalysis.

INTRODUCTION

Olefin metathesis (OM) is widely recognized as one of the most significant developments in synthesis and catalysis over the past three decades. It offers an effective method for construction of complex molecular skeleton through C=C bond formation.¹⁻⁷ The two main categories of metathesis catalysts are Mo-carbene (Schrock catalyst)⁸⁻¹¹ and Ru-carbene (Grubbs catalyst)¹²⁻²⁰, with the latter exhibiting better stability toward air and moisture, allowing for operation under less restricted conditions. Encouraged by the chemo orthogonal reactivity and numerous chemical, material and biological applications, researchers have put tremendous efforts in developing new Ru-carbene complexes systems for improved reactivity with higher TON and TOF, good substrate tolerability (more hindered olefin starting materials), product selectivity (E vs Z alkene)²¹, and more practical operation conditions (tolerability of high temperature and large-scale synthesis at high concentration)²²⁻²⁵ etc. Current modification strategies for Ru-carbene complexes could be broadly classified into three categories: the primary ligand, pre-catalyst design, and alternative operation conditions. As shown in **Scheme 1A**, the investigation on primary ligand led to the discovery of Grubbs I and II catalysts along with various

NHC-modified carbene complexes. Pre-catalysts have been developed to improve catalyst stability and reactivity, including 18 e complexes (i. e. Grubbs III)²⁶⁻²⁸ for fast activation and Hoveyda modification.²⁹⁻³⁴ Recently, some new operation conditions have been developed for improved olefin-metathesis performance, such as the application of paraffin oil as reaction media under vacuum to achieve ring-closing metathesis and photoactivation of bis-NHC precatalyst.^{22,35} Overall, the versatile reactivity of olefin metathesis and its broad applications keep metathesis reactions under the spotlight. New systems that could address the key challenges associated with previous reported OM catalysts are highly desirable.



Scheme 1. Triazole Ru-carbene (TA-Ru) as new olefin metathesis catalyst

- (A) Ru-carbene catalyst modification;
 (B) Limitation of N chelated Ru complexes;
 (C) TA-Ru catalysts with unique reactivity in olefin metathesis

Our research group is interested in developing new OM catalysts to overcome the challenge of poor stability at high temperatures. According to literature, the application of NHC primary ligand (over PR₃) was the first breakthrough, which made

the Grubbs II one of the most widely adopted catalysts for OM in academic and industry research.¹⁸ Although efforts to develop NHC derivatives have led to improved catalyst stability (such as **L1**), the cost of making these new NHC ligands and potential problem on scale-up production raised concerns of this tuning-primary-ligand approach for further catalyst optimization.³⁶ The 18-e pre-catalysts design has received tremendous success in rapid transformation through fast initiation. As the trade-off, these fast-initiating catalysts typically have very poor stability at higher temperature (fast ligand dissociation and complex decomposition). The application of hemi-labile coordination led to the discovery of Hoveyda-Grubbs catalysts, which were considered a breakthrough in OM with balanced reactivity and stability. Higher TON and broader substrate scope have been achieved.³¹ Interestingly, although alternative hemi-labile ligand modifications have been explored over the past decade, especially with the amine and sulfur chelation (Ru-N and Ru-S binding),³⁷⁻⁴¹ HG catalysts are still playing a crucial role in OM. This is likely due to the primary ligand vs *trans*-effect dilemma: while the strong coordinating NHC primary ligand helped the alkene activation through *trans*-effect, the Ru-N complexes (unlike Ru-O) favor the formation of *cis*-dichloride isomers (thermally stable), giving less reactive intermediates with open-coordination site at the *cis* position of NHC primary ligand (**Scheme 1B**).³⁷ Thus, no N-modified Ru-carbene complexes have been identified as one paradigm changing modification, despite stronger Ru-N bond was formed in the process. In this work, we report the triazole-Ru carbene complexes (TA-Ru) as new class of OM catalysts. Unlike other N-modified Ru-carbene complexes, the high kinetic barrier of Ru-TA dissociation grants excellent stability to the active *trans*-dichloro isomers even at high temperatures (80 °C) without isomerization. This makes the TA-Ru a practical N-tethered Ru-carbene catalyst for OM at high temperatures for the first time (**Scheme 1C**). The readily available synthesis, excellent catalyst stability and superior reactivity make the TA-Ru a potentially new catalytic system for many foreseeable applications to come.

RESULTS AND DISCUSSION

One well-known challenge in olefin metathesis is E-alkene activation. As shown in **Figure 1A**, although the 18e pre-catalyst **G-III** could give rapid terminal alkene activation, there was no reaction with E-olefins at rt or 40 °C. To activate sterically more hindered *trans*-alkene, higher temperature (60 °C) was required, which led to the observed poor reactivity (low TON) due to competing catalyst decomposition at higher temperature. Moreover, the Ru-complexes containing simple NHC ligands gave *trans*-alkene as the preferred OM products. As a result, although the OM transformation is considered under reaction equilibrium, the C=C bond is not considered as one practical bond forming strategy in dynamic covalent chemistry (DCvC) due to the high temperature (>60 °C) required for E-alkene activation and rapid catalyst decomposition under this reaction condition (**Figure 1B**). Notably, with the application of Ru-carbene catalysts containing modified NHC primary ligands, Grela and coworkers have reported an interesting process protocol with melted paraffin as reaction media under oil diffusion pump (removal of low bp alkenes), allowing RCM at high temperature (>110 °C).²² Although with limited reaction scope (not working well without ester linkage), this protocol is a representative example to achieve OM at high temperature. Unfortunately, this method has not been applied in the dynamic covalent chemistry, likely due to the poor solubility of oligomer and rapid polymer precipitation, dragging the reaction mixture to polymerization with very low yield of the desired cyclic DCvC products. Therefore, to develop new metathesis catalytic systems that could be achieve in DCvC is not only novel but also highly desirable.

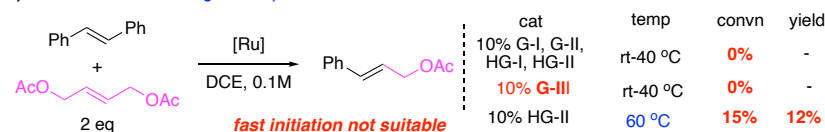
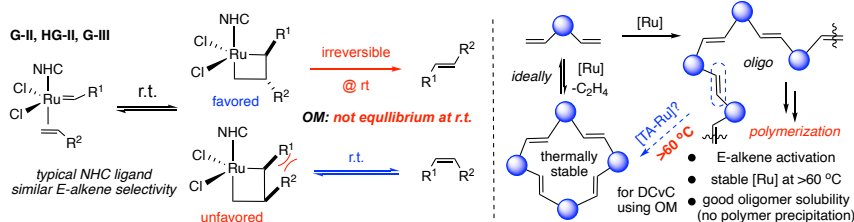
A) E-Alkene activation: *Higher temperature is inevitable*B) Key for dynamic covalent chemistry (DCvC) with OM: *E-alkene activation and no catalyst decomposition*

Figure 1. E-Alkene activation and challenges for DCvC using OM

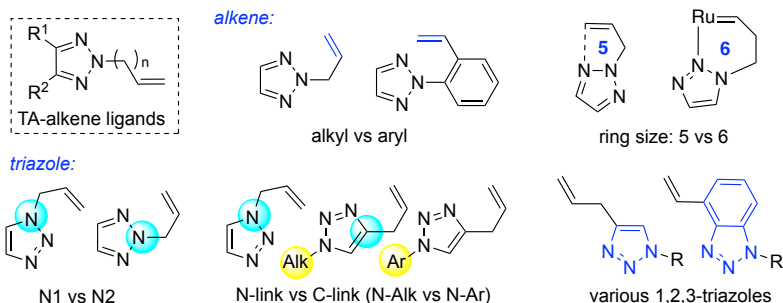
(A) Trans-alkene activation requires high temperature

(B) Design principle for DCvC using OM

Our group has previously investigated 1,2,3-triazole (TA) coordination ability toward various metal cations and we concluded that the high polarity nature (three N on one side of the molecule) makes of TA one dynamic N-ligand with high kinetic activation barrier.⁴²⁻⁴⁶ Thus, we postulate that TA-modified Ru-carbene complexes could serve as new OM catalysts with balanced reactivity and high-temperature stability. Ultimately, it might provide a practical solution to make the long-expected OM-DCvC possible.

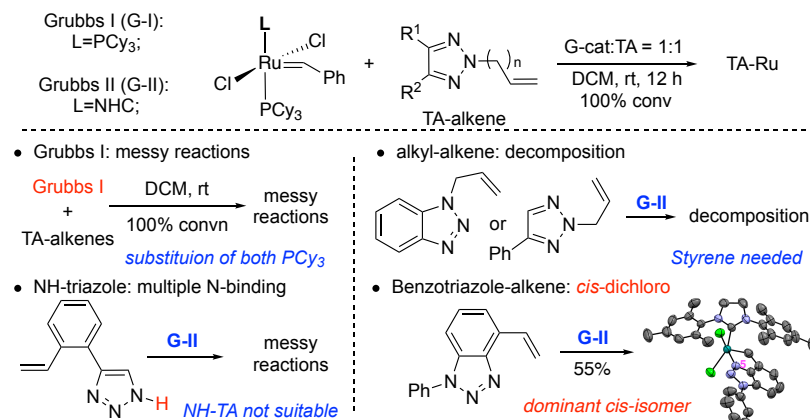
To explore triazole-Ru binding, a library of various triazole derivatives were prepared. Some key factors for ligand design are summarized in Figure 2A. Both alkyl and aryl substituted alkenes are prepared. The linker between TA and alkene gave either 5 or 6-membered metallocycles. The N1 or N2 substituted triazole derivatives could be prepared and purified using our previously reported methods. The linkage between TA and alkene could be either N- or C-link. Both triazole and benzotriazole were used to explore the influence of different TA-cores. Based on this analysis, >30 TA-ligands were prepared (see details in SI) covering the different combinations of the above-mentioned factors. The resulting ligands were applied into the reactions with Grubbs (I and II) catalysts under various conditions. Some representative reactivity of the TA-ligand exchange is summarized in Figure 2B (see details in SI).

A) Key design factors of TA-alkene ligands

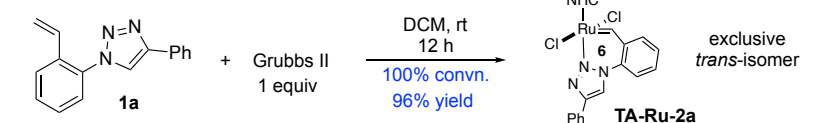


A library with >30 TA-alkene ligands were prepared based on the structural analysis

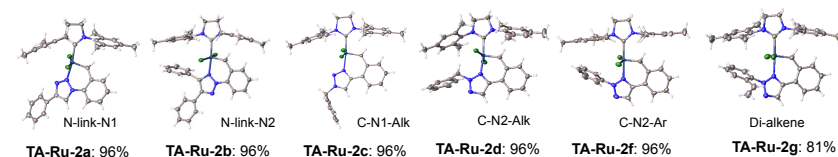
B) Representative TA-Ru synthesis conditions



C) Synthesis of TA-Ru and X-ray crystal structures



X-rays of trans-TA-Ru-2



Literature reported N-Ru complexes

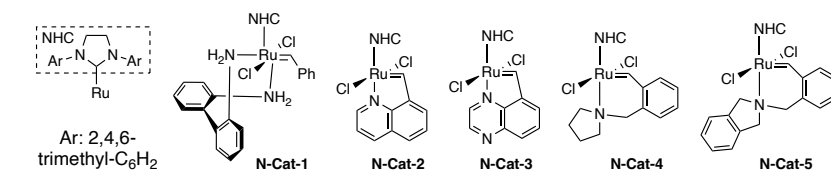


Figure 2. TA-Ru synthesis and X-ray structures.

(A) TA-alkene ligand design

(B) TA-Ru synthesis conditions

(C) X-Ray structures of TA-Ru complexes

Treating TA-alkene (1.0 equiv) with either Grubbs I or II in DCM gave complete ligand conversion in 12 h (rt). Messy reactions were observed with G-I. This is likely due to the TA-substitution of both PCy₃ in Grubbs I, which caused complex decomposition. Reactions of aliphatic alkenes also gave messy reactions, like other literature reports, suggesting the slow complex decomposition with alkyl substituted carbene. Reaction

of NH-triazole gave TA-bridged complex clusters, which decomposed over time. Interestingly, the 4-vinyl-benzotriazole and G-II gave the formation of the designed TA-Ru containing 5-membered metallocycle. However, X-ray crystal structure confirmed the formation of *cis*-dichloro isomers due to rapid isomerization in this 5-member chelating system. Based on these critical reaction insights (see details in SI), triazole-styrene **1a** to **1f** were prepared and applied to react with Grubbs II. Complete conversion of G-II was obtained in 12 h. The desired TA-Ru complexes (**TA-Ru 2a-2f**) were obtained with excellent yields (> 90% in all cases). Notably, the TA-alkenes represent all key structural cases: N-linkage vs C-linkage, N-1 vs N-2 isomers and N-alkyl vs N-aryl derivatives. The structures of TA-Rus were characterized by X-ray crystallography, confirming the exclusive formation of *trans*-dichloro isomers. To make direct reactivity comparison, representative literature reported N-Ru complexes (**N-Cat-1** to **N-Cat-5**) were also synthesized (Figure 2C).³⁷⁻⁴⁰

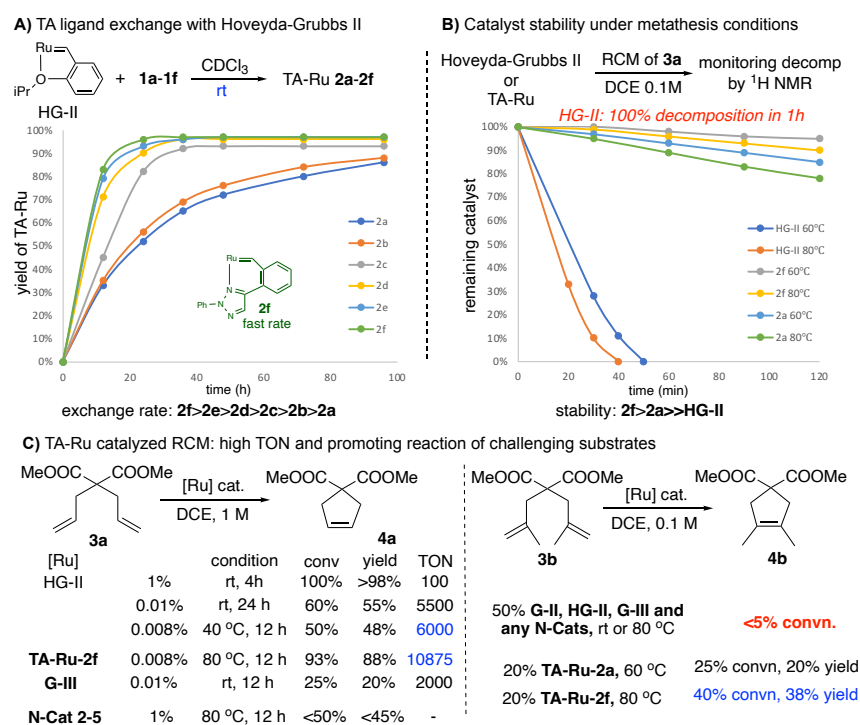


Figure 3. TA-Ru catalyzed OM reactions at high temperature.

- (A) TA ligand exchange process with Hoveyda Grubbs catalysts
 (B) Catalyst stability under metathesis conditions
 (C) TA-Ru Reactivity in RCM

As shown in Figure 3A, treating TA-alkenes with Hoveyda-Grubbs II gave complete ligand exchange (formation of TA-Ru), confirming the stronger coordination ability of TA (N) over ether (O) toward Ru cation. The different exchanging rates observed suggest the tunable binding ability of these TA-ligands. Monitoring the sample decomposition at higher temperature using ¹H NMR provided the direct comparison of catalyst stability under metathesis conditions (Figure 3B). As expected, HG-II gave complete decomposition within 1 hour at either 60 °C or 80 °C. Both **TA-Ru-2a** and **TA-Ru-2f** showed excellent stability at high temperature, giving only slight decomposition even at 80 °C. The thermal stability of all Ru complexes has been tested at various temperatures (40, 60, 80 and 100 °C), and the detailed results are provided in SI.

With the clearly improved thermal stability, the TA-Rus were used in RCM reactions to evaluate their overall reactivity. It is well-known that RCM of mono-substituted diene **3a** could give cyclic alkene **4a** in excellent yields using 1% HG-II at rt. Similarly, the fast-activation catalyst G-III could achieve the same >98% yield with 1% loading if conducting the reaction at rt. To achieve a higher TON, lower loading would be applied, which would require a longer reaction time. In this case, the competing catalyst decomposition became a concern. For example, with 0.01% loading of HG-II, RCM of **3a** could only reach a 60% conversion at rt. Raising reaction temperature to 40 °C could only slightly improve the reaction performance due to faster catalyst decomposition. The excellent thermal stability of TA-Rus makes them ideal catalysts for RCM with high TON and large-scale synthesis. For example, using **TA-Ru-2f**, almost complete conversion could be achieved with only 80 ppm catalyst loading at 80 °C, giving TON > 10,000 (see different TA-Ru RCM reaction details in SI). Alternatively, the ability to promote OM at higher temperature allows TA-Ru as effective catalyst in promoting RCM of tetra-substituted alkenes. While all tested Ru-carbene catalysts, G-II, HG-II, G-III and all other N-Cats, gave almost no reaction for the RCM of **3b** even with 50% loading, **TA-Ru-2f** successfully promoted this challenging transformation at 80 °C, giving **4b** in modest yields. It is important to note that all other N-chelated Ru-carbene catalysts **N-Cat 1-5** gave even worse results than HG-II (see details in SI), which clearly highlights the unique reactivity of TA-Ru beyond any previously reported N-chelated Ru-carbene complexes.

With the confirmation of TA-Ru's excellent reactivity in promoting OM reactions at high temperature, we put our attention to the investigations whether TA-Ru could be applied as the first viable catalytic system for dynamic covalent chemistry (DCvC) through C=C double bond construction.^{47,48} The cross metathesis (CM) between two E-alkenes **5** and **6** were performed. The results are summarized in Figure 4.

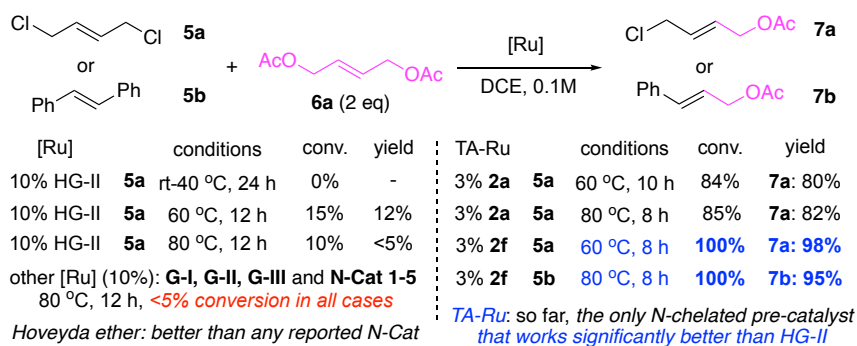
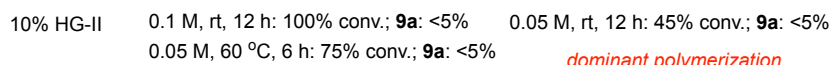


Figure 4. Cross-metathesis (CM) of E-alkenes.

As discussed above, to activate E-alkene with Ru-carbene catalysts containing regular NHC primary ligand (G-II type), higher temperature (>60 °C) is required. Although poor conversion (15%) was observed using 10% HG-II, the Hoveyda ether modification remains the most effective catalyst comparing with other catalysts. In particular, all tested literature reported N-chelated Ru-carbene complexes **N-Cat 1-5** gave poor results (<5% conversion), which explains why no N-chelated catalysts have been adopted by the community (not as good as HG-II). The TA-Ru complexes were all tested (**TA-Ru 2a-2f**). Excitingly, most of the TA-Ru complexes showed improved thermal stability and significantly better reactivity. Screening of TA-Ru revealed complex **2f** showed the optimal reactivity in this cross-metathesis reaction, giving the desired product in excellent yields (see details in SI). To the best of knowledge, this is the first N-chelated Ru-carbene complexes showed significantly improved reactivity over long-time dominant Hoveyda ether modification, which suggested that the TA-

Challenges of using OM in DCvC: A) *trans*-alkene activation; B) polymer precipitation



G-I, G-II, G-III, HG-I, and N-Cat 1-5: <5% **9a in all cases**

5% TA-Ru-2f, 0.05 M, 60 °C: 100% **8a** convn @ 6 h competing polymer
yield of **9a**: 8% @ 6 h; 15% @ 12 h; 20% @ 24 h precipitation



syringe pump addition,
preventing polymer precipitation

cat. TA-Ru, DCE, 80 °C

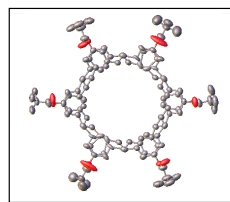
0.5% TA-Ru-2f, DCE, 80 °C,
syringe pump add. over 12 h
gram-scale synthesis

isolated yield
9a: 88%;
9b: 91%;
9c: 89%;

10% HG-II, 60 °C,
syringe pump add.

50% **8a** conv
9a: 12%

G-III and N-Cats: <5% **9a** with syringe pump add.

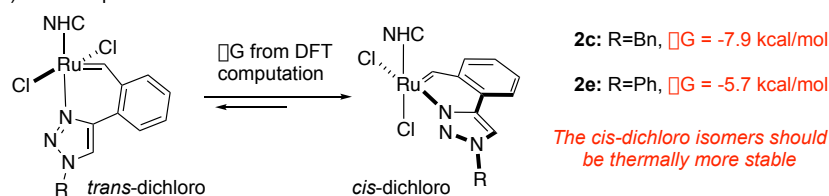


Encouraged by the successful activation of **E-5b** using TA-Ru, dienes **8a-8c** were prepared with the intention to form the hexametric compound **9** as the thermally stable macrocycles. Notably, Zhang group has previously reported this chemistry and claimed that the ortho-divinylbenzene **8** could give macrocyclic compound **9** under olefin metathesis conditions.⁴⁷ With the 120° functional group angle, the hexametric structure is the thermally stable product, if reaction equilibrium could be reached. When we conduct the same reaction in 200 mg scale under the reported identical conditions (10% G-II, 35 °C, 0.005 M in 1,2,4-trichlorobenzene, 16 h), only 7% cyclic compound **9a** was obtained (Schlenk tube or glovebox). Monitoring the reaction with ¹H NMR showed clear catalyst decomposition within the first 8 hours. The HG-II was also applied for this cyclization. At rt, <5% of **9a** was observed with dominant polymerization. Heating reaction to 60 °C did not help due to faster catalyst decomposition. It proved difficult to reproduce this procedure in our hands, pointing the need for a more robust method. Switching catalyst to **TA-Ru-2f** (5%) gave complete conversion of **8a** within 6 h. Interestingly, the amount of **9a** increased over time (6h, 8%; 12 h, 15%; 24 h, 20%), which confirmed the activation of trans-alkene (in the oligomer) under TA-Ru conditions. However, low overall yield (<30%) was received after 72 h. This is due to the polymer precipitation, which drove the oligomer consumed from solution. To overcome this problem, we proposed the slow addition of **8a** into the TA-Ru solution to help the oligomer reaching equilibrium prior to the

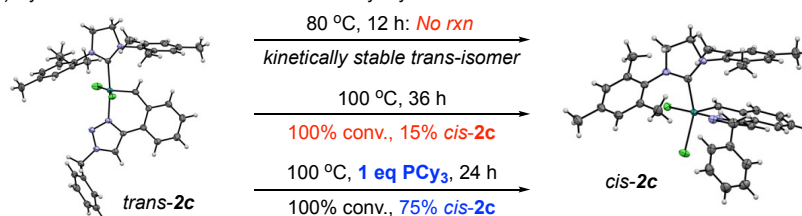
polymer formation. As expected, with the syringe pump addition of **8** (over 12 h) into TA-Ru solution in DCE at 70 °C (0.5 M initial concentration), the desired macrocycles **9a-9c** were all received in excellent isolated yields (>88%) with only 1% TA-Ru loading. The cyclic core structure was identified by XRD, despite the presence of atom disorder. It is important to note that all other tested Ru-carbene catalysts, including those literature reported N-chelated complexes, all gave <5% yields either under the dilution or syringe pump slow addition conditions, confirming the unique reactivity of TA-Ru as the practical good catalyst in DCvC through olefin metathesis.

To understand why 1,2,3-triazole is a unique N-ligand in Ru-carbene coordination, the DFT computational studies were performed. To our surprise, the catalytically less reactive *cis*-dichloro TA-Rus were the thermodynamically more stable isomers, similar to other chelated N-ligands (Figure 6A, see details in SI).

A) DFT computational studies confirmed *cis*-dichloro TA-Ru as the more stable isomers



B) Synthesis of *cis*-dichloro TA-Ru and X-ray crystal structure.



C) Proposed *trans-cis* isomerization mechanism: *L*-ligand coordination at axial position

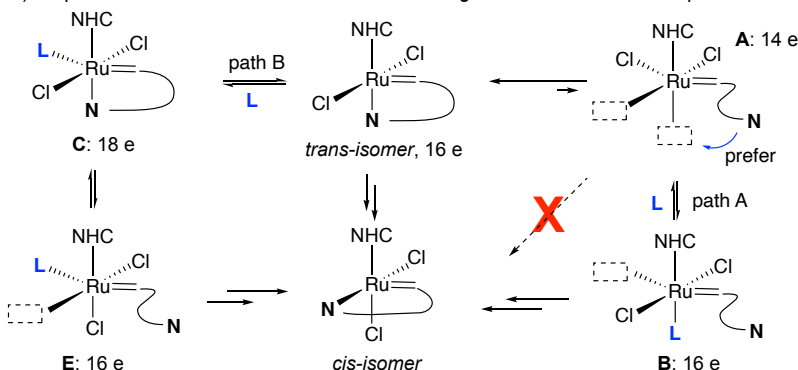


Figure 6. Mechanism for *trans-cis* isomerization

(A) DFT study of complex conformation

(B) Synthesis of *cis*-dichloro TA-Ru and X-ray

(C) Proposed isomerization mechanism

From the synthesis of TA-Ru, all complexes obtained are exclusively *trans*-dichloro isomers and no isomerization even upon heating these complexes to 80 °C for 24 hours. Raising the temperature to 100 °C gave decomposition of TA-Ru, forming complex reaction mixtures. Enlighted by the computational results, we re-evaluated the reaction and *cis* isomers were identified from NMR. Carefully purification gave *cis*-TA-Ru-2c in 15% yield with structure characterized by X-ray (Figure 6B).

Interestingly, after exploring reactivity of *trans* and *cis* TA-Ru, an improved synthesis of *cis*-TA-Ru was identified through addition of 1 equiv of PCy₃ (75% yield of *cis*-TA-Ru-2c). As computational studies predicted, the *cis*-TA-Rus are very stable and will not convert into *trans*-isomers under various conditions. Moreover, applying these *cis*-TA-Ru in the RCM, CM and DCvC discussed above, no reactions were observed at 60 °C, which suggested the high stability (and poor reactivity) of these *cis*-TA-Ru. Two isomerization paths are proposed. Based on the reaction results, 14e intermediate A could not give the formation of *cis*-isomer as no TA-Ru isomerization was observed during the reaction cycle. Considering that NHC could provide strong *trans*-effect in leading the axial bond coordination, the isomerization must occur either through axial coordinated intermediate B or 18e fully coordinated intermediate C. The detailed reaction mechanism and substituted effects of TA-ligands are currently under investigations in our lab and will be reported in due course. Nevertheless, the excellent thermal stability, good catalytic reactivity at high temperature and capability in retaining the catalytic active *trans*-dichloro geometry make the TA-Ru one unique new catalytic system for OM reaction.

CONCLUSIONS

In summary, we disclosed herein the effective use of 1,2,3-triazole-coordinated ruthenium carbene complexes, TA-Ru, as olefin metathesis catalysts for the first time. Unlike previously reported N-chelated Ru-carbene complexes, TA-Ru showed excellent thermal stability and reactivity, and were able to retain their catalytic activity even at high temperatures, owing to their *trans*-dichloro geometry. This sets them apart from all other previously reported N-chelated systems, allowing for *trans*-alkene activation with excellent performance that was previously unachievable. The use of the TA-Ru catalyst, along with the syringe pump addition strategy, has introduced a practical new approach in constructing C=C bonds under dynamic covalent conditions, and offers numerous new opportunities in the future. Overall, this new TA-Ru system has made challenging olefin metathesis transformations. Investigations of Z-alkene synthesis, asymmetric metathesis, and more complex molecular skeletons under the DCvC concept are currently ongoing in our lab to explore these possibilities.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Xiaodong Shi (xmshi@usf.edu).

Materials availability

All materials generated in this study are available from the lead contact without restriction.

Data and code availability

All data supporting this study are available in the manuscript and supplemental information.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at



ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

X.S. and C.W. conceived the project. C.W., S.Z., T.Y., X.H. and M.A. conducted the experiments; X.S. designed the experiments and wrote the paper.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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