Synthesis and Reactivity of Olefin Metathesis-Catalyzing Ruthenium Complexes with a Selenoether Moiety in the Benzylidene Ligand

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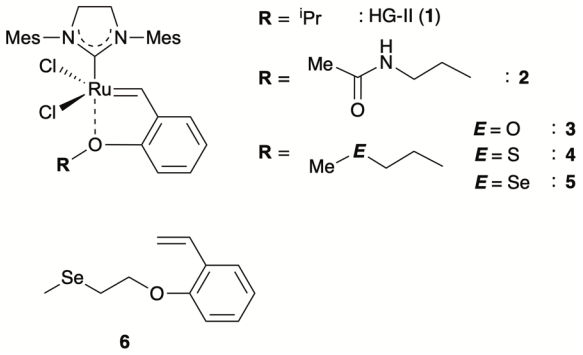
Abstract. A Hoveyda-Grubbs (HG)-type olefin metathesis complex with a selenoether moiety at the terminal of phenoxy moiety was synthesized. The complex showed a *Se*-coordination to the ruthenium center, resulting in its higher thermostability than the parent HG catalyst. The *Se*-coordinative property enhanced product yields in the ring-closing metathesis of *N*-tosyldiallylamine in the presence of methanol. The large activation enthalpy observed in the reaction with butyl vinyl ether indicated an increased contribution of "dissociative mechanism" during the initiation of the catalytic cycle. Introducing coordinative atoms or functional groups at the terminal of the phenoxy moiety is a useful strategy to regulate the thermostability of HG-type olefin metathesis catalysts.

KEYWORDS. Olefin metathesis; Hoveyda-Grubbs catalyst; selenium; chalcogen atom

Olefin metathesis (OM) catalyzed by transition metal complexes is a useful method for constructing new olefin moieties through the rearrangement of C=C double bonds in both laboratory and industrial scale syntheses, because OM reactions are highly selective in olefins among various functional groups.[1-4] Hoveyda-Grubbs 2nd generation complex (HG-II (**1**)[5]; Chart 1) is the most widely used OM catalyst due to its higher thermostability than other OM transition metal catalysts and ease of functionalization through structural modifications of the *N*-heterocyclic carbenoid (NHC) and benzylidene ligand moieties. These characteristics have led some researchers to investigate the applicability of **1** and its derivatives to reactions involving biomolecules in aqueous media.[6, 7] Furthermore, several studies have shown that the reactivity of HG-II can be modulated by introducing functional groups at the terminal of phenoxy moiety in the complex ("R" part in the structure of **1**)[8-10] Coordinative functional groups, such as imide,[11,12] carbonyl,[13,14] sulfonamide[15] can directly influence the reactivity of the metal center. Additionally, complex **2** regulates the reactivities of the metal center through second coordination sphere (SCS) effect (*i.e.*, amide NH ••• Cl interaction).[16] Replacing the amide group with an ether moiety (complex **3**) led to higher initial velocities in OM reactions compared to HG-II (**1**). This is due to electrostatic repulsion between the oxygen and chlorido ligand, which accelerated the benzylidene ligand dissociation.[17] However, the complex durability is low. On the other hand, the sulfur atom in complex **4** directly coordinates to the metal center with an apparent 18-electron coordination fashion.[17] Despite this, the complex achieves similar final yields in OM reactions to those observed in complexes **1** and **3**. Moreover, complex **4** showed higher durability in the presence of protic solvents than complex **1**. These observations highlighted different modes of reactivity regulation by chalcogen atoms (*O* and *S*) at the terminus of the phenoxy moiety. Expecting that heavier chalcogen atoms might reveal new modes of reactivity regulation for HG-II-type complex, we

investigated the effects of selenium (Se) atoms on the reactivities of HG-II-type complexes using a ruthenium complex containing a selenium atom at the terminus of the phenoxy moiety (complex **5**).

Chart 1. Structures of ruthenium complexes (**1**–**5**) and selenoether ligand (**6**)



Complex **5** was synthesized through ligand exchange between Grubbs 2nd generation complex (G-II) and selenoether benzylidene ligand **6** in the presence of CuCl as a phosphine scavenger[5,18] (Scheme 1) and characterized using nuclear magnetic resonance (NMR) spectroscopy (Figures S1–S3) and mass analysis. The ^{1}H-NMR spectrum of complex **5** (Figure S1) showed the benzylidene proton signal at 16.3 ppm and the *Se*-methyl proton signal at 1.63 ppm. The *Se*-methyl proton signal was shifted upfield by 0.45 ppm compared to the *Se*-methyl protons in ligand **6**. These spectral features are similar to those observed in *S*-containing complex **4**,[17] suggesting that complex **5** has a *trans*-configuration with *Se*-coordination to the metal center, akin to complex **4**. The *Se*-coordination was also suggested by the ^{77}Se-NMR spectrum with a signal at 114.2 ppm (Figure S3), which was shifted downfield from the signal observed in ligand **6** (79.5 ppm). The X-ray crystallographic structure of complex **5** (Figure 1 and Table S1) confirmed the *Se*-coordination with a Ru(1)–Se(1) bond distance of 2.8784(4) Å. The bond length is larger than the typical Ru–Se distances (~ 2.45 Å) recorded in the Cambridge Crystallographic Data Center (CCDC) database, indicating a relatively weak *Se*-coordination in complex **5**.

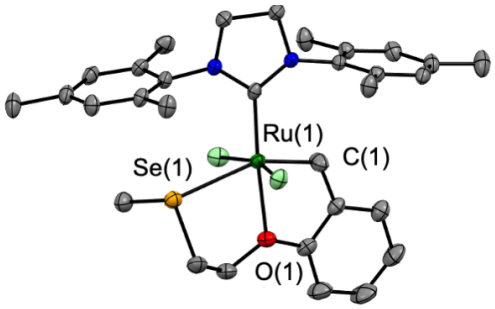
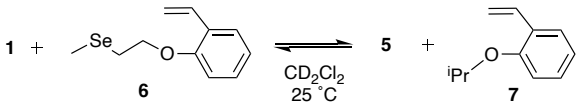


Figure 1. X-ray crystallographic structure of selenoether complex **5**. Thermal ellipsoids are drawn at a 50% possibility level. Selected bond lengths: Ru(1)-Se(1) 2.7874(4) Å; Ru(1)-C(1) 1.866(3) Å; Ru(1)-O(1) 2.236(1) Å.

Next, we investigated the effect of *Se*-coordination on the thermostability of complex **5** using the stoichiometric ligand exchange reactions between HG-II(**1**) and ligand **6** (Scheme 1).[16,17] Yields of over 50% for complex **5** are equivalent to higher stability of the complex than the parent HG-II(**1**). Monitoring the reaction using ^{1}H-NMR over 48 h (Figures S4 and S5; Table S2) showed the formation of complex **5** in 95% yield, indicating that the *Se*-coordination occurs in solution and enhances the thermostability of complex **5**.

Scheme 1. Ligand exchange between HG-II(1) and ligand 6.

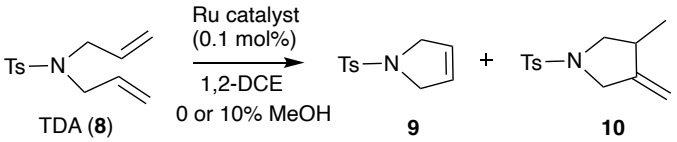


Our previous report showed that sulfur-coordinated complex **4** exhibits the catalytic reactivity of olefin metathesis despite a saturated coordination structure around the metal center.[17] Furthermore, its catalytic activity in the presence of protic solvents is higher than that of HG-II(**1**). Accordingly, we investigated the OM catalytic activity of complex **5** using the ring-closing metathesis (RCM) of *N*-tosyldialliylamine (TDA, **8**), a commonly used benchmark reaction for

evaluating the reactivities of OM catalysts (Tables 1 and S3). The RCM reaction in 1,2-dichloroethane (1,2-DCE) was monitored by ^{1}H-NMR spectroscopy (Figures S6 and S7). To examine the tolerance of complex **5** to protic media, the reactions were also conducted in the presence of methanol (Figures S8 and S9).

In the absence of methanol, the complex **5**-mediated RCM reaction proceeded with a slower rate compared to other complexes (as seen by the yields at 0.3 h), although the RCM product **9** ultimately reached a yield of *ca*. 90% at 48 h without forming cycloisomerized by-product **10**. All investigated catalysts displayed a final RCM product yield of over 90%. Additionally, in the presence of methanol, the **5**-catalyzed RCM reaction was slower than those mediated by other complexes. However, the final RCM product yield was higher than that in **1**- or **3**-catalyzed reactions (47% for **5**; 38% for **1**; 19% for **3**). The higher tolerance of complex **5** to methanol compared to complexes **1** and **3** was attributed to the *Se*-coordination. The coordinative selenoether ligand can protect the reactive intermediate from catalyst deactivation during the catalytic cycle as a release–return ligand (*i.e.*, so-called "boomerang effect").[19] On the other hand, *Se*-coordinated complex **5** showed a lower RCM product yield compared to *S*-coordinated complex **4**. The by-product yield increased slightly (7.3% for **4** and 9.6% for **5**). The reactivities of chalcogen atom-containing catalysts (*i.e.*, complexes **3** (*O*-containing), **4** (*S*-containing), and **5** (*Se*-containing)) do not simply follow the order of the periodic table. However, the high tolerance of complexes **4** and **5** to methanol demonstrates the utility of coordinative atoms at the terminus of phenoxy moiety for increasing the final yields of RCM products in the presence of protic solvents.

Table 1. Reactions of TDA (**8**) mediated by ruthenium catalysts[a]



TDA (**8**) **9** **10**

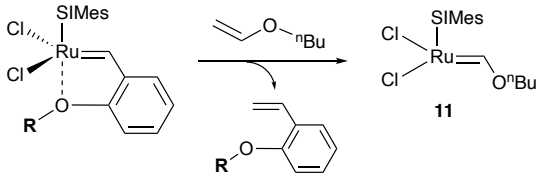
catalyst	MeOH (%(v/v))	yield(%)	
		9	**10**
1	0	93 (0.3 h)[b] , >99 (6 h)[b,c]	N.D.[d]
3	0	89 (0.3 h)[b], >99 (6 h)[b,c]	N.D.[d]
4	0	53 (0.3 h)[b], 86 (6 h)[b,c]	N.D.[d]
5	0	12 (0.3 h), 95 (48 h)[c]	N.D.[d]
1	10	38 (12 h)[b,c]	trace (12 h)
3	10	19 (12 h)[b,c]	trace (12 h)
4	10	59 (48 h)[b,c]	7.3 (48 h)
5	10	47 (48 h)[c]	9.6 (48 h)

[a]reaction conditions: [**8**] = 42 mM in 1,2-DCE; 0.1 mol% catalyst load; at 40 ˚C. [b]ref. 17. [c]yields when reactions reached have plateaued. [d]Not detected.

The chalcogen atom coordination to the metal center in complexes **4** and **5** may influence the initial phase of the OM catalytic cycle, as the dissociation of the chalcogen atom is involved in the activation of the pre-catalyst form. To evaluate the effects of chalcogen atom coordination on the initiation of OM catalytic cycles, we performed kinetic analyses of the reaction of OM catalysts with butyl vinyl ether (BuVE)[20-22] (Table 2; Figures S11 and S12)), where the reaction produces a Fischer-type complex **11**, a catalytically inactive form, and enables us to analyze the initial step of the catalytic cycle. The pseudo-first-order rate constants (k_{init}) at 25 ˚C for the reaction of Ru complexes with BuVE indicated smaller values for complexes **4** and **5** compared to complexes **1**

and **3**. This is because the unligation of the sulfur or selenium atom in the ligand is necessary for BuVE to access the metal center. The activation parameters of the reaction of Ru complexes with BuVE were determined using Eyring plots shown in Figure S12. Complexes **1** and **3** exhibited more negative activation entropy ($\Delta S^{\ddagger}$) values compared to complexes **4** and **5**. HG-II(**1**) is known to mainly initiate OM catalytic cycles via "interchange mechanism" (*i.e.*, substrate-binding along with the dissociation of the benzylidene ligand in the transition state).[21-23] Since complex **3** which contains an oxygen in the ligand moiety but no *O*-metal coordination), showed similar activation parameters to HG-II(**1**), the "inter-change mechanism" is the predominant pathway in the initial phase of **3**-catalyzed OM reactions. In contrast, complexes **4** and **5** displayed larger $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values, reflecting the increased contribution of ligand dissociation in the initial step of OM catalytic cycles. This fact indicates that the introduction of a sulfur or selenium atom at the terminusof the phenoxy moiety shifts the favorable mechanism in this step from the "interchange" pathway to a "dissociative" pathway.

Table 2. Rate constants (k_{init}) at 25 ˚C and activation parameters for the reaction of butyl vinyl ether (BuVE) with ruthenium complexes.[a]



complex	$k_{initial}$[b] ($M^{-1}s^{-1}$)	$\Delta H^{\ddagger}$ ($kJmol^{-1}$)	$\Delta S^{\ddagger}$ ($Jmol^{-1}$)
1	$(1.6 \pm 0.1) \times 10^{-2}$	64 ± 4[c] (59 ± 5[d])	-90 ± 10[c] (-78 ± 20[d])
3	$(4.6 \pm 0.3) \times 10^{-2}$	59 ± 6[c]	-96 ± 15[c]
4	$(3.2 \pm 0.2) \times 10^{-4}$	79 ± 3[c]	-51 ± 9[c]
5	$(1.8 \pm 0.1) \times 10^{-4}$	80 ± 8[c]	-50 ± 9[c]

[a]reaction conditions: [Ru complex] = 100 μM; in 1,2-dichloroethane (DCE). [b]rate constants obtained by pseudo-first-order kinetic analysis under excess BuVE ([BuVE] > 500 × [Ru complex]) at 25 ˚C. [c]average of three repeating expriments. [d]values in CH_2Cl_2 (quoted from ref. 21; converted into joule unit).

In conclusion, the HG-II-type complex with a selenoether moiety in the benzylidene ligand exhibits the *Se*-coordination in its pre-catalyst form. The structural features result in the enhanced complex thermostability and grater durability in the presence of protic solvents compared to HG-II(**1**). A series of experimental results indicate that introducing coordinative atoms at the phenoxy moiety allows for the optimization of OM reactivity, particularly in protic media, and effectively regulates the reaction pathway in catalytic cycles. Since the solubilities of HG-type complexes in protic solvents can be increased by introducing ionic groups into the NHC ligand,[8, 9, 24, 25] the findings of this study indicate the potential of HG-type complexes with a coordinative group in the phenoxy moiety as experimental tools for chemical modification of biomolecules in protic media.

ASSOCIATED CONTENT

Supporting Information.

Experimental details, X-ray crystallographic data, NMR spectra of complex **5**, NMR spectral changes during ligand exchange, time-courses of RCM reactions, UV-vis spectra, and kinetic analyses (PDF).

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Takashi Matsuo :

Conceptualization; Funding acquisition; Investigation; Project administration; Resources;

Supervision; Visualization; Writing – review & editing

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Grubbs, R. H.; Trnka, T. M. Ruthenium-Catalyzed Olefin Metathesis. In *Ruthenium in Organic Synthesis*, Wiley‐VCH Verlag GmbH & Co. KGaA, 2004; pp 153–177

(2) Ravindar, L.; Lekkala, R.; Rakesh, K. P.; Asiri, A. M.; Marwani, H. M.; Qin, H.-L. Carbonyl–Olefin Metathesis: A Key Review. *Org. Chem. Front.* **2018**, *5* (8), 1381–1391. DOI: 10.1039/C7QO01037K

(3) Hughes, D.; Wheeler, P.; Ene, D. Olefin Metathesis in Drug Discovery and Development—Examples from Recent Patent Literature. *Org. Proc*cess *Res. Dev.* **2017**, *21* (12), 1938–1962. DOI: 10.1021/acs.oprd.7b00319

(4) Lecourt, C.; Dhambri, S.; Allievi, L.; Sanogo, Y.; Zeghbib, N.; Ben Othman, R.; Lannou, M. I.; Sorin, G.; Ardisson, J. Natural Products and Ring-Closing Metathesis: Synthesis of Sterically Congested Olefins. *Nat. Prod. Rep.* **2018**, *35* (1), 105-124. DOI: 10.1039/C7NP00048K

(5) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. Efficient and Recyclable Monomeric and Dendritic Ru-Based Metathesis Catalysts. *J. Am. Chem. Soc.* **2000**, *122* (34), 8168–8179. DOI: 10.1021/ja001179g

(6) Ingram, A. A.; Wang, D.; Schwaneberg, U.; Okuda, J. Grubbs-Hoveyda Catalysts Conjugated To a β-Barrel Protein: Effect of Halide Substitution on Aqueous Olefin Metathesis Activity. *J. Inorg. Biochem.* **2024**, *258*, 112616. DOI: 0.1016/j.jinorgbio.2024.112616

(7) Blanco, C. O.; Ramos Castellanos, R.; Fogg, D. E. Anionic Olefin Metathesis Catalysts Enable Modification of Unprotected Biomolecules in Water. *ACS Catal.* **2024**, 11147–11152. DOI: 10.1021/acscatal.4c02811

(8) Szczepaniak, G.; Kosiński, K.; Grela, K. Towards "Cleaner" Olefin Metathesis: Tailoring The NHC Ligand of Second Generation Ruthenium Catalysts to Afford Auxiliary Traits. *Green Chem^.* **2014**, *16* (10), 4474–4492. DOI: 10.1039/C4GC00705K

(9) Matsuo, T. Functionalization of Ruthenium Olefin-Metathesis Catalysts for Interdisciplinary Studies in Chemistry and Biology. *Catalysts*, **2021**, *11* (3), 359(1)–359(25). DOI: 10.3390/catal11030359

(10) Nadirova, M.; Zieliński, A.; Malinska, M.; Kajetanowicz, A. Fast Initiating Furan-Containing Hoveyda-Type Complexes: Synthesis and Applications in Metathesis Reactions. *Chemistry* **2022**, *4* (3), 786-795. DOI: 10.3390/chemistry4030056

(11) Czarnocki, S. J.; Czeluśniak, I.; Olszewski, T. K.; Malinska, M.; Woźniak, K.; Grela, K. Rational and Then Serendipitous Formation of Aza Analogues of Hoveyda-Type Catalysts Containing a Chelating Ester Group Leading to a Polymerization Catalyst Family. *ACS Catal.* **2017**, *7* (6), 4115–4121. DOI: 10.1021/acscatal.7b00843

(12) Hejl, A.; Day, M. W.; Grubbs, R. H. Latent Olefin Metathesis Catalysts Featuring Chelating Alkylidenes. *Organometallics*, **2006**, *25* (26), 6149-6154. DOI: 10.1021/om060620u

(13) Bieniek, M.; Bujok, R.; Cabaj, M.; Lugan, N.; Lavigne, G.; Arlt, D.; Grela, K. Advanced Fine-Tuning of Grubbs/Hoveyda Olefin Metathesis Catalysts: A Further Step toward an Optimum Balance between Antinomic Properties. *J. Am. Chem. Soc.* **2006**, *128* (42), 13652–13653. DOI: 10.1021/ja063186w

(14) Gawin, R.; Makal, A.; Woźniak, K.; Mauduit, M.; Grela, K. A Dormant Ruthenium Catalyst Bearing a Chelating Carboxylate Ligand: In Situ Activation and Application in Metathesis Reactions. *Angew. Chem. Int. Ed.* **2007**, *46* (38), 7206–7209. DOI: 10.1002/anie.200701302

(15) Pump, E.; Fischer, R. C.; Slugovc, C. Halide Exchange in Second-Generation *cis*-Dihalo Ruthenium Benzylidene Complexes. *Organometallics*, **2012**, *31* (19), 6972–6979. DOI: 10.1021/om300785t

(16) Jatmika, C.; Goshima, K.; Wakabayashi, K.; Akiyama, N.; Hirota, S.; Matsuo, T. Second-Coordination Sphere Effects on the Reactivities of Hoveyda-Grubbs-Type Catalysts: A Ligand Exchange Study Using Phenolic Moiety-Functionalized Ligands. *Dalton Trans.* **2020**, *49* (33), 11618–11627. DOI: 10.1039/d0dt02353a

(17) Kinugawa, T.; Matsuo, T. Reactivity Regulation for Olefin Metathesis-Catalyzing Ruthenium Complexes with Sulfur Atoms at the Terminal of 2-Alkoxybenzylidene Ligands. *Dalton Trans.* **2023**, *52* (27), 9499-–9508. DOI: 10.1039/d3dt01471a

(18) Ledoux, N.; Linden, A.; Allaert, B.; Mierde, H. V.; Verpoort, F. Comparative Investigation of Hoveyda–Grubbs Catalysts Bearing Modified *N*-Heterocyclic Carbene Ligands. *Adv. Synth. Catal.* **2007**, *349* (10), 1692–1700. DOI: 10.1002/adsc.200700042

(19) Bates, J. M.; Lummiss, J. A. M.; Bailey, G. A.; Fogg, D. E. Operation of the Boomerang Mechanism in Olefin Metathesis Reactions Promoted by the Second-Generation Hoveyda Catalyst. *ACS Catal*. **2014**, *4* (7), 2387–2394. DOI: 10.1021/cs500539m

(20) Vorfalt, T.; Wannowius, K.-J.; Plenio, H. Probing the Mechanism of Olefin Metathesis in Grubbs–Hoveyda and Grela Type Complexes. *Angew. Chem. Int. Ed*. **2010**, *49* (32), 5533–5536. DOI: 10.1002/anie.201000581

(21) Ashworth, I. W.; Hillier, I. H.; Nelson, D. J.; Percy, J. M.; Vincent, M. A. What is The Initiation Step of the Grubbs-Hoveyda Olefin Metathesis Catalyst? *Chem. Commun*. **2011**, *47* (19), 5428–5430. DOI: 10.1039/C1CC11230A.

(22) Thiel, V.; Hendann, M.; Wannowius, K.-J.; Plenio, H. On the Mechanism of the Initiation Reaction in Grubbs–Hoveyda Complexes. *J. Am. Chem. Soc*. **2012**, *134* (2), 1104–1114. DOI: 10.1021/ja208967h

(23) Nelson, D. J.; Manzini, S.; Urbina-Blanco, C. A.; Nolan, S. P. Key Processes in Ruthenium-Catalysed Olefin Metathesis. *Chem. Commun*. **2014**, *50* (72), 10355–10375. DOI: 10.1039/C4CC02515F

(24) Jordan, J. P.; Grubbs, R. H. Small-Molecule *N*-Heterocyclic-Carbene-Containing Olefin-Metathesis Catalysts for Use in Water. *Angew. Chem. Int. Ed*. **2007**, *46* (27), 5152–5155. DOI: 10.1002/anie.200701258.

(25) Hong, S. H.; Grubbs, R. H. Highly Active Water-Soluble Olefin Metathesis Catalyst. *J. Am. Chem. Soc*. **2006**, *128* (11), 3508–3509. DOI: 10.1021/ja058451c

SYNOPSIS

A Hoveyda-Grubbs-type complex with a selenoether moiety in the phenoxy group exhibited direct selenium-to-ruthenium coordination, which enhanced the complex thermostability and tolerance to protic solvents. Thermodynamic parameters in the initial step of the catalytic cycle for the selenium-containing complex highlight the contribution of "dissociative mechanism" in the initiation of catalysis.

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