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# Synthesis and Application of Stereoretentive Ruthenium Catalysts on the Basis of the M7 and the Ru-Benzylidene-Oxazinone Design

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Supporting Information

ABSTRACT: A series of new stereoretentive ruthenium catalysts bearing the dithiocatecholate ligand was synthesiszed on the basis of the M7 and Ru-benzylidene-oxazinone design. The activity of the catalysts was tested in ring-opening cross-metathesis reactions, ring-closing metathesis reactions, cross-metathesis reactions, and self-metathesis reactions using Z- and E-configured starting materials. The desired metathesis products were obtained with moderate to high yields and with excellent stereoselectivities (>95%). Substrate-dependent reactivity was found by carrying out kinetic studies on internal and terminal olefins.

#### INTRODUCTION

Carbon-carbon double bonds reside within a large number of molecules. Control of the stereochemistry of alkenes is of utter importance, given that changing the configuration of a double bond can significantly alter the biological and physical properties of a molecule.

Historically, stereoselective synthesis of olefins has relied on reactions producing stoichiometric amounts of waste material, such as the renowned Wittig olefination.<sup>1</sup> In the early 1950s transition-metal-catalyzed olefin metathesis emerged as a powerful tool for the generation of olefins, creating only ethylene or other olefins as side products.<sup>2</sup> Despite the many advances in this field, the stereocontrol of the double bond has been elusive until recently.<sup>3</sup> Early studies of cross-metathesis reactions revealed that certain substrates such as acrylates and styrenes favor the thermodynamically more stable E doublebond isomer whereas others, e.g. acrylonitrile, enynes, and vinylsiloxanes, favor the Z-configured product.<sup>4</sup> Moreover, several examples of ring-closing metathesis reactions were reported where the substrate can exert high levels of stereocontrol, favoring one double bond isomer over the other.5

The first well-defined stereoselective metathesis catalyst was reported by Schrock and Hoveyda in 2009.<sup>6</sup> Since then several stereoselective metathesis catalysts based on Mo, W, and Ru have been discovered and applied to ring-opening metathesis polymerization (ROMP), ring-closing metathesis (RCM), and cross-metathesis (CM) reactions.<sup>7,8</sup> Importantly, many of the reported methodologies require an electronic or stereochemical



predisposition of the substrate in combination with a specific metathesis catalyst to achieve high levels of stereoselectivity.

A structurally simple catalyst based on the selective synthesis of (Z)-olefins was introduced in 2013 by Hoveyda (Scheme 1).<sup>9a</sup> Electronically modified catalyst **Ru-1**, obtained by simple





substitution of the chloride ligands of Hoveyda-Grubbs catalyst Ru-0 by a dithiocatecholate ligand, was subsequently shown to promote various types of metathesis reactions of stereochemically pure olefins with very high levels of Z or Eselectivity (Scheme 2).<sup>9,8f,j-m</sup>

Catalyst Ru-1 was initially described as a stereoselective catalyst.<sup>9</sup> However, subsequent work by Grubbs and co-workers

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clearly showed that **Ru-1** is a stereorententive catalyst capable of transforming (*E*)- or (*Z*)-alkenes into the corresponding *E* or *Z* products without significant loss of the stereochemical information on the starting olefins (Scheme 2).<sup>7d,8k,1</sup>

In contrast to the parent catalyst **Ru-0**, the dithiocatecholatesubstituted catalyst **Ru-1** shows much lower activity and high catalyst loadings (5–10 mol %) are typically required for crossmetathesis reactions. It is well-known that replacing the chloride ligands on ruthenium by more electron donating ligands leads in general to less active catalysts.<sup>10</sup> Furthermore, Hoveyda attributed the low turnover number (TON) to premature degradation of catalyst **Ru-1** via a 1,2-sulfur shift.<sup>9e</sup> In addition to the limited catalyst lifetime, another reason for the low efficiency of catalyst **Ru-1** was identified by Grubbs and Ahmed.<sup>81</sup> <sup>1</sup>H NMR studies demonstrated that the initiation rate of catalyst **Ru-1** is very slow, requiring more than 24 h for full initiation. Therefore, only small amounts of precatalyst enter the catalytic cycle, thus requiring a high catalyst loading.

To overcome the lack of reactivity of dithiocatecholate catalysts, scientists at Materia Inc. and the Grubbs group studied a series of new ruthenium catalysts relying on the 2isopropoxy-3-phenylbenzylidene motif, a structural modification introduced by Blechert in 2000.<sup>8k,l,11</sup> These studies showed the following. (a) (Z)-Alkenes react considerably more quickly in comparison to their (E)-alkene counterparts in the presence of dithiocatecholate catalysts such as Ru-1. (b) Strategies to increase the initiation rate of catalyst Ru-0 seem also to apply to the derived dithiocatecholate catalysts. In other words, the Blechert modification which was previously shown to increase the initation rate of Ru-0 also improved the reactivity of Ru-1. (c) Replacement of the SIMes NHC ligand by the SIPr motif resulted in strong rate enhancement for (Z)-alkenes.<sup>8k,1</sup> In contrast, no significant rate increase was observed with (E)alkenes when catalyst Ru-4 was used (Figure 1). The lower reactivity of bulky Ru-4 catalyst with (E)-alkenes is in agreement with the proposed models for Z and E selectivity reported by Grubbs and Pederson.<sup>8k</sup> Grubbs actually demonstrated that sterically less demanding NHC ligands increased the reaction rates for stereoretentive cross-metathesis with (E)-alkenes. Hoveyda and co-workers also prepared a library of dithiocatecholate ligands and assessed their reactivity for the ROMP of norbornene in a qualitative study.<sup>8j</sup> They found that the dithiocatecholate-substituted Grela catalyst<sup>12</sup> Ru-2 and Zannan catalyst Ru-3<sup>13</sup> were among the most active catalysts (Figure 1), in apparent agreement with the previous finding by Grubbs that modifications for the rate enhancement of Ru-0 also apply to Ru-1.

Complementarily to the work carried out by Grubbs and Hoveyda, our group was interested in the introduction of the dithiocatecholate ligand to aminocarbonyl-group-containing Hoveyda–Grubbs-type complexes, typically referred to as the M7 series (Figure 1).<sup>14</sup> These in-house-developed catalysts were recently commercialized by Umicore and are available on



**Ru-3**; NHC = SIMes,  $R^1 = H$ ,  $R^2 = SO_2NMe_2$  (Hoveyda 2016) **Ru-4**; NHC = SIPr,  $R^1 = H$ ,  $R^2 = H$  (Grubbs 2016) **Ru-5**; NHC = SIPr,  $R^1 = Ph$ ,  $R^2 = H$  (Grubbs 2017)



Figure 1. Recently reported bisthiolate Ru catalysts and new catalysts presented herein.

a kilogram scale.<sup>15</sup> The M7 series benefits from fast initiation due to an electron-withdrawing group in the para position of the benzylidene moiety similarly to the Grela or Zannan catalyst (**Ru-2** and **Ru-3**).<sup>12a-c</sup> Furthermore, we modified Ru– benzylidene–oxazinone catalysts, which we reported recently.<sup>14</sup> In contrast to the M7 series the benzylidene–oxazinone type catalysts rely on a combination of electronic and steric activation.

# RESULTS AND DISCUSSION

Herein, we report the synthesis and application of new stereoretentive ruthenium catalysts on the basis of the M7 and the benzylidene–oxazinone design series. We set out by synthesizing several bis-thiolate ligands following the straightforward protocol reported by Hoveyda and co-workers shown in Scheme 1 (Figure 2). The yields obtained by this procedure are very high, typically ranging between 93 and 99% for the five isolated complexes **Ru-6–Ru-10**.<sup>16</sup> Complexes **Ru-8–Ru-10** contain two stereocenters (see Figure 2). A racemic mixture of the benzylidene moiety was used for complex preparation. Hence, complexes **Ru-8–Ru-10** were obtained as mixtures of diastereoisomers (see the Supporting Information for further details).

Furthermore, we were able to obtain X-ray crystal structures for **Ru-7** and **Ru-8** (Figure 3). Both complexes show relatively short Ru–S<sub>2</sub> bond distances in comparison to **Ru-1** (2.276 and 2.260 Å vs 2.283 Å in **Ru-1**). The shortening of the Ru–S<sub>2</sub> bond distance is probably due to the electron-withdrawing subsitutents on the opposite benzylidene, which minimize the trans influence. Hence, these complexes should rank within the most active complexes in comparison to the ranking recently reported by Hoveyda.<sup>8</sup>

First, we tested our catalysts to the stereoretentive ringopening cross-metathesis (ROCM) of norbornene (Table 1).<sup>9a</sup>

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Figure 2. Synthesized dithiocatecholate-substituted Ru catalysts based on the M7 and Ru–benzylidene–oxazinone motifs.



Figure 3. X-ray structures of dithiocatecholate Ru complexes Ru-5 and Ru-7. H atoms and the solvent molecules are omitted for clarity.

We found that all catalysts are highly stereoretentive, furnishing the products in good to excellent yields. In particular, SiMessubstituted catalysts (**Ru-6** and **Ru-9**) showed greater activity in comparison to their SiPr-substituted derivatives (**Ru-7** and **Ru-10**).<sup>8k,1</sup> Next, we tested a selection of stereoretentive catalysts for the Z-stereoretentive cross-metathesis of *cis*-butendiol and 1-dodecene as reported by Hoveyda and co-workers (Table 2).<sup>9e</sup> Again the SiMes-substituted catalysts showed better performance in comparison to their SiPr-substituted counterparts with only minor erosion of stereoselectivity (Table 2). It is noteworthy that the high Z selectivity varies very little among the ruthenium catalysts tested.





"NMR yield detetermined with anthracene as standard. <sup>b</sup>Yields refer to isolated yields after column chromatography. <sup>c</sup>Z:E ratios were determined by <sup>1</sup>H NMR analysis of purified compounds.

 Table 2. Stereoretentive Cross-Metathesis of cis-Butenediol

 with 1-Dodecene in the Presence of Bisthiolate-Substituted

 Catalysts

ноон 4					
(2 equ	iiv.) Ru-c	Ru-cat. (5 mol%)			
+	Т	THF, rt, 4 h $^{9}$			
947	5		6		
[Ru]	conversn (%) <sup>a</sup>	yield (%) <sup>a</sup>	Z:E ratio <sup>b</sup>		
Ru-1	81	72	96:4		
Ru-4	53	42	95:5		
Ru-6	80	76	98:2		
Ru-7	62	51	98:2		
Ru-8	60	55	98:2		
Ru-9	71	67	98:2		
Ru-10	60	50	97:3		

<sup>*a*</sup>Conversions and NMR yield were determined from the crude mixture by <sup>1</sup>H NMR analysis with 1,1,2,2-tetrachloroethane as standard. <sup>*b*</sup>*Z*:*E* ratios were determined by <sup>1</sup>H NMR analysis of purified compounds (see the Supporting Information).

In order to test the functional group tolerance and the generality of the newly developed catalysts, we chose the highly active ruthenium catalyst **Ru-6** to explore the scope of the CM reaction with *cis*-2-butene-1,4-diol (4) and *cis*-1,4-diacetoxy-2-butene (7) (Figure 4). We were delighted to observe excellent Z selectivity for almost all cases of cross-metathesis with *cis*-2-butene-1,4-diol (>97:3), except for cross-metathesis with allyl butyl ether, which afforded poor Z:E ratios (12).<sup>9e</sup> It appears that unhindered alkenes bearing a remote electron-withdrawing group such as bromo-substituted compound 11 and carboxylic acid 13 react particularly well. Lower yields were observed with  $\alpha$ -branched alkene starting materials (15, 16, and 18).<sup>17</sup> Cross-metathesis with *cis*-1,4-diacetoxy-2-butene (7) furnished 18 and 19 in good yields and excellent selectivity.

We also tested the activity and selectivity of the M7 catalysts for Z-stereoretentive macrocylization (Scheme 3). **Ru-7** provided yuzu lactone **21**, a camphor-like and minty-odored substance,<sup>16</sup> in almost identical yields and selectivity in comparison to **Ru-4**, previously reported by Grubbs (with **Ru-4**: 68% yield, 95:5 Z:E).<sup>8m</sup>

#### **Organometallics**



**Figure 4.** Further examples of CM of various alkenes with *cis*-2butene-1,4-diol (4) or *cis*-1,4-diacetoxy-2-butene (7). Conversions were determined by <sup>1</sup>H NMR analysis of the crude mixture with 1,1,2,2-tetrachloroethane as standard. The *Z*:*E* ratios were determined by <sup>1</sup>H NMR analysis of purified compounds. Legend: (a) 12 h reaction time.



Furthermore, we tested several ruthenium catalysts for the self-metathesis of methyl (E)-9-octadecenoate (E-MO, >99%) to produce dimethyl 9-octadecenedioate (DE) and 9octadecene (HC) (Figure 5). The parent ruthenium complex Ru-1 showed the fastest kinetics, achieving equilibrium in almost 9 h. Ru-9 and Ru-4 also performed well, leaving all other catalysts tested behind. Interestingly, the activity of ruthenium catalyst **Ru-6** dropped significantly in a change from a Z- to an E-configured substrate (Table 2 vs Figure 5).<sup>18</sup> It is noteworthy that Ru-bisthiolate catalysts are stable in the presence of internal alkenes for more than 24 h (Figure 5). In contrast, Hoveyda reported that terminal alkenes lead to full catalyst degradation in less than 4 h.9e On the other hand, while the SiMes-substituted catalysts showed highly stereoretentive reactions (Table 3, entries 1, 3, and 6), most of the SiPrsubstituted catalysts provided the diester DE with lower stereochemical purity (Table 3, entries 2, 4, and 7), with the exception of catalyst Ru-8.

To get further insight concerning the initiation rate of our bisthiolate catalysts, we followed the reaction of a selection of



Figure 5. Self-metathesis of methyl (E)-9-octadecenoate (MO). There was an equilibrium among MO, hydrocarbon HC and diester DE. Product distribution and selectivity were analyzed by GC using tetradecane as internal standard.

Table 3. Self-Metathesis of Methyl (*E*)-9-Octadecenoate (MO): *E*:*Z* Ratios after 24 h

MO		<u>1 mol% [Ru]</u> THF (0.1 M), rt MeO	HC + O (1) 7 (1) 7 OMe DE
entry	[Ru]	MO (%) (E:Z)	DE (%) (E:Z)
1	Ru-1	50 (>99:1)	25 (>99:1)
2	Ru-4	52 (>99:1)	24 (90:10)
3	Ru-6	66 (>99:1)	17 (>99:1)
4	Ru-7	46 (89:11)	23 (88:12)
5	Ru-8	60 (>99:1)	19 (>99:1)
6	Ru-9	50 (>99:1)	25 (>99:1)
7	Ru-10	74 (>99:1)	13 (94:6)

<sup>*a*</sup>Methyl (*E*)-9-octadecenoate of >99% GC purity was used as starting material. Product distribution and selectivity analyzed by GC using tetradecane as internal standard. Note: We were unable to separate the stereoisomers of the hydrocarbon component.

catalysts with ethyl vinyl ether with <sup>1</sup>H NMR spectroscopy (Figure 6). SiPr-substituted catalysts showed high initiation rates even at -20 °C (Figure 6a). In contrast, reactions with SiMes-substituted catalysts were much slower, necessitating higher temperatures (10 °C; Figure 6b). Values of  $k_{init}$  are highest for catalysts **Ru-8** and **Ru-10** in the SiPr series, whereas parent catalyst **Ru-1** initiates significantly more quickly in comparison to **Ru-9** and **Ru-6** in the SiMes series. We also determined the initiation rates in tetrahydrofuran at 45 °C for **Ru-6** and **Ru-7** with *trans*-2-hexenyl acetate (Figure S30),<sup>81</sup> which contains an internal double bond. The initiation rates are significantly lower in comparison to those observed for ethyl



a) SiPr-substituted catalysts (-20 °C)



b) SiMes-substituted catalysts (+10 °C)



Figure 6. Plot of  $ln([Ru]/[Ru]_0)$  versus time for initiation experiments conducted with a selection of bisthiolate catalysts. The disappearance of the benzylidene signal was monitored by <sup>1</sup>H NMR spectroscopy.

vinyl ether, indicating that the initiation kinetics are highly substrate dependent. Interestingly, in this case the calculated values for  $k_{\rm init}$  were found to be very similar for the SiMessubstituted catalyst **Ru-6** (1.42 × 10<sup>-5</sup> s<sup>-1</sup>) and the SiPr-substituted complex **Ru-7** (1.10 × 10<sup>-5</sup> s<sup>-1</sup>).<sup>19,20</sup>

#### CONCLUSIONS

Though we did not achieve the original set goal to develop a significantly more active stereoretentive catalyst, our study has nevertheless added to the knowledge concerning bisthiolate-modified catalysts. First, we were able to show that the bisthiolate modification to obtain stereoretentive catalysts is quite general and the high selectivity is conserved even upon significant electronic and steric modification of the benzylidene moiety. Second, this study further testifies to the stability of ruthenium bisthiolate complexes in the presence of internal olefins, while degradation of these complexes appear to mainly occur in the presence of terminal olefins.<sup>9e</sup> Third, our studies

with methyl (E)-9-octadecenoate showed that SiMes-substituted catalysts not only increase the reaction rate in comparison to their SiPr-substituted congeners but are also crucial for highly stereoretentive metathesis reactions with (E)-olefins. Further studies concerning highly practical stereoretentive catalysts are currently being pursued in our laboratories and will be reported in due course.

#### EXPERIMENTAL SECTION

[add experimental section here]

## ASSOCIATED CONTENT

#### **S** Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organo-met.7b00836.

Experimental procedures and characterization data for all products and catalysts, including <sup>1</sup>H and <sup>13</sup>C, NMR spectra and X-ray structures (PDF)

Cartesian coordinates for calculated structures (XYZ) Cartesian coordinates for calculated structures (XYZ)

#### **Accession Codes**

CCDC 1562960–1562961 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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#### Notes

The authors declare no competing financial interest.

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(17) We were unable to fully attribute the difference of yield and conversion to other products. Approximately 5% of self-metathesis of the alkene was typically observed. We suspect that some of the more volatile starting materials evaporated during the reaction and during workup.

(18) We attribute the lower performance of our catalyst in comparison to **Ru-1** to the more facile attack of the trans to NHC thio ligand at the electron-poor benzylidene moiety as previously described by Hoveyda.<sup>9e</sup>

(19) We also carried out a stability study with the complexes shown; see the Supporting Information for details.

(20) The initiation rates were determined as described by Ahmed and Grubbs; see ref 81 and the Supporting Information for details.