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## Ru-Based Z-Selective Metathesis Catalysts with Modified Cyclometalated Carbene Ligands†

Sarah M. Bronner, Myles B. Herbert, Paresma R. Patel, Vanessa M. Marx, and Robert H. Grubbs\*

### Abstract

A series of cyclometalated Z-selective ruthenium olefin metathesis catalysts with alterations to the *N*-heterocyclic carbene (NHC) ligand were prepared. X-Ray crystal structures of several new catalysts were obtained, elucidating the structural features of this class of cyclometalated complexes. The metathesis activity of each stable complex was evaluated, and one catalyst, bearing geminal dimethyl backbone substitution, was found to be comparable to our best Z-selective metathesis catalyst to date.

### Introduction

The olefin metathesis reaction is arguably one of the most well-studied and useful tools in organic synthesis.<sup>1</sup> The utility of this powerful methodology is demonstrated by its prevalence in numerous applications, including natural product synthesis,<sup>2</sup> materials science,<sup>3</sup> and biochemistry.<sup>4</sup> Recent metathesis endeavors have addressed the challenge of stereoselectivity, as productive metathesis reactions may construct carbon–carbon double bonds with either *Z*- or *E*-stereochemistry. As a result of the reversible nature of the olefin metathesis reaction, the thermodynamically favored *E*-olefin is generally formed.<sup>5</sup> In contrast, selective generation of the *Z*-olefin, a motif found in many natural products and pharmaceutical targets,<sup>2b</sup> via olefin metathesis has only recently been enabled by the development of novel metathesis catalysts. The Schrock and Hoveyda groups have achieved highly *Z*-selective metathesis utilizing monoaryloxide pyrrolide (MAP) molybdenum and tungsten catalysts, and have applied their systems to perform the *Z*-selective homodimerization and cross-metathesis of terminal olefins,<sup>6</sup> ring-opening metathesis polymerization,<sup>7</sup> as well as macrocyclic ring-closing metathesis.<sup>8</sup>

Recently, our group has developed *Z*-selective ruthenium-based catalysts with cyclometalated *N*-heterocyclic carbene (NHC) ligands.<sup>9,10</sup> The general synthetic strategy used to access these complexes involves *in situ* generation of a carbene and subsequent metalation (e.g., **1** ⇌ **4** and **2** ⇌ **5**, Scheme 1).<sup>11</sup> The resulting NHC-ligated complex then undergoes carboxylate-driven C–H activation enabled by metal-bound carboxylates.<sup>12</sup> In our

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Arnold and Mabel Beckman Laboratories of Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California, 91125, USA. rhg@caltech.edu; Fax: +1 626-564-9297.

early reports, it was discovered that while pivalate-ligated catalyst **6** was highly *Z*-selective,<sup>9a,b</sup> nitrate catalyst **7** had increased stability and selectivity with turnover numbers (TONs) approaching 1000 and *Z*-selectivity of approximately 90%.<sup>9c</sup> An analogous C–H activation strategy could not be used on complexes containing more sterically demanding NHCs; for example, treatment of **5**, containing a *N*-2,6-diisopropylphenyl (DIPP) group, with silver pivalate (AgOPiv) led to complex mixtures.<sup>11</sup> By employing the milder sodium pivalate (NaOPiv) in place of AgOPiv, it was discovered that C–H activation of **5**, as well as other challenging complexes, could occur cleanly to generate catalyst **8**.<sup>12a</sup> Gratifyingly, catalyst **8** was found to perform a number of homodimerization and cross-metathesis reactions with near perfect *Z*-selectivity (>95%) and unmatched TONs (>7400). The power and industrial relevance of this class of cyclometalated ruthenium compounds has since been illustrated via applications in the synthesis of insect pheromone natural products<sup>13</sup> and macrocyclic musks,<sup>14</sup> in addition to more complicated natural products.<sup>15</sup>

Computational studies provide a model for the *Z*-selectivity exhibited by cyclometalated metathesis catalysts **7** and **8**, and also provide guidance for further catalyst development. The Houk group has previously shown that steric crowding over the ruthenium center forces the forming side-bound metallacycle into all-*cis* geometry (**11**, Figure 1), resulting in selective formation of the *Z*-isomer (**12**) via kinetic control.<sup>16</sup> In the case of cyclometalated catalysts **7** and **8**, the 5-membered imidazoline NHC holds the *N*-aryl group in close proximity to the intermediate metallacycle, thus explaining why the sterically more hindered *N*-DIPP group imparts greater selectivity than the *N*-Mes analogue.

Despite the recent advances in catalyst development, there remains a need for more *Z*-selective ruthenium metathesis catalysts with expanded substrate scopes. In previous generations of ruthenium metathesis catalysts, modification of the NHC ligand has been well explored and has led to insights on the relation of structure, activity, and stability,<sup>19</sup> however, modifications to the NHC ligand<sup>17</sup> of cyclometalated catalysts have been largely unexplored, although proposed transition states suggest that this group is critical in imparting stereochemistry to the forming metallacycle.<sup>16</sup> We hypothesized that modification to the identity of the NHC ligand could potentially lead to more active and more *Z*-selective metathesis catalysts.

## Results and discussion

### Selection and Synthesis of Catalysts

Herein, we report the preparation, characterization, and metathesis activity of seven new cyclometalated ruthenium metathesis catalysts with varying carbene ligands. While modifying the identity of the cyclometalated carbene, other features of the catalyst were left unaltered for the purpose of consistency. Although alternative *X*-type ligands have been explored, the nitrate ligand was selected for our catalyst series because it has been shown to impart exceptional stability and selectivity.<sup>9c</sup> In the past, we have seen that the *N*-1-adamantyl chelate is most stable,<sup>12a</sup> and for the purposes of this study this feature was left unchanged. Finally, our previous most promising *Z*-selective metathesis catalysts have possessed either *N*-Mes or *N*-DIPP substituents.

Cyclometalated complexes **16–22**, bearing a number of unique carbene motifs, were selected as catalyst targets for our studies (Figure 2). Complex **16**, possessing a 6-membered NHC, was of interest because crystal structures of similar non-cyclometalated ruthenium complexes have revealed that the *N*-aryl component exerts a larger steric influence on the benzyldiene than with the 5-membered NHC analogue,<sup>18</sup> thus implying that **16** may display improved *Z*-selectivity. Furthermore, increasing the ring size of the NHC could result in additional degrees of freedom, relieving ring strain of the NHC and leading to a more stable catalyst.

Backbone-substituted ruthenium complexes **17–19** were expected to display extended catalyst lifetimes and increased *Z*-selectivity.<sup>19</sup> It was hypothesized that the geminal dimethyl substitution on compound **17** could push the *N*-adamantyl group closer to the metal center, resulting in a more stable chelate, thereby disfavoring common decomposition pathways.<sup>11</sup> Alternatively, it was expected that the same substitution above the *N*-aryl group (e.g., **18** and **19**) could prevent *N*-aryl rotation from occurring, and also position the aryl substituent closer to the forming metallacyclobutane; both effects could result in improved *Z*-selectivity.

In the past, metathesis catalysts with unsaturated NHC ligands have been found to be less active than their saturated analogues.<sup>20</sup> While it was expected that they would be less active, backbone unsaturated ruthenium complexes **20** and **21** were identified as synthetic targets. Finally, we decided to pursue ruthenium cyclic (alkyl)(amino)carbene (CAAC) complex **22**, bearing a 2,6-diethylphenyl (DEP) substituent. In addition to being structurally interesting with a unique spiro-binding mode, CAAC ligands have been shown to impart a unique reactivity to catalysts of previous generations.<sup>21</sup> In the case of each target shown in Figure 2, the carbene was synthesized using modifications of previously reported procedures.<sup>22</sup> Elaboration to the cyclometalated complex was accomplished using strategies analogous to those shown in Scheme 1, involving metal-carboxylate mediated C–H activation, followed by ligand exchange with the addition of ammonium nitrate.<sup>23</sup>

A number of formamidinium salts were synthesized that could not be elaborated to the desired cyclometalated ruthenium complexes (Figure 3). Previously, non-cyclometalated metathesis catalysts with acyclic diaminocarbenes have provided metathesis products with lower *E:Z* ratios than analogous catalysts containing NHC ligands.<sup>24</sup> Based on these observations, it was anticipated that C–H activation of these acyclic diaminocarbene ruthenium complexes might lead to improved *Z*-selective metathesis catalysts. However, acyclic formamidinium salts **23** and **24** underwent metalation to produce an unstable dichloride that could not be isolated without substantial decomposition. We also attempted to synthesize a DIPP analogue to catalyst **16** with a 6-membered NHC, but found that the corresponding formamidinium salt (**25**) did not undergo successful metalation. Cyclometalated ruthenium complexes with 7-membered NHCs were also targeted because, like the 6-membered NHC complex, the *N*-aryl component was expected to have an increased steric effect on the forming metallacyclobutane. However, attempts to metalate 7-membered formamidinium salts **26** and **27** were unsuccessful, as was the metalation of previously reported CAAC salt **28**.<sup>25</sup>

## Structural Analyses

To probe the steric and electronic effects of cyclometalated carbene modification, crystals of **19**, **21**, and **22** were grown and their molecular structures were confirmed by single-crystal X-ray crystallographic analysis (Figures 5, 6, and 7, respectively). For comparison purposes, a crystal structure of **8**, which previously had not been reported, was also obtained (Figure 4). The crystal structure of **8** did not vary significantly from the previously disclosed structure of **7**.<sup>9c</sup> A comparison between structures reveals that the distance between Ru and the chelating adamantyl-carbon does not change significantly, with the exception of CAAC-ligated **22**, which possesses a slightly longer bond length. Other key structural features are summarized in Table 1. Of note, catalyst **8**, bearing a 5-membered saturated NHC, has the ability to kink its backbone, as shown by the N(1)–C(2)–C(3)–N(2) torsional angle of 23.33°. This kinked geometry relieves ring strain and allows for a more stable catalyst. Interestingly, catalyst **19** possesses an approximately equal but opposite torsional angle (–23.66°). As expected, unsaturation of the NHC results in a nearly planar geometry, as indicated by **21**'s torsional angle of 1.16°. Furthermore, from the crystal structure of CAAC-ligated **22**, it is apparent that the *N*-aryl ring is situated further away from the benzyldiene moiety. This structural feature may explain the diminished *Z*-selectivity observed in metathesis studies, along with the fact that **22** is a less stable complex.

## Homodimerization Metathesis Activity

To probe the metathesis ability of each new cyclometalated complex, homodimerization studies were performed using three standard substrates. Allyl benzene (**29**) was selected for our initial studies because this substrate is prone to double bond migration and the extent of isomerization to form **31** is a good litmus test to assess the overall stability of new metathesis catalysts.<sup>26</sup> All homodimerization reactions were performed in tetrahydrofuran (THF) at 35 °C with an olefin concentration of 3.35 M and 0.1 mol% catalyst loading. Aliquots were removed at 1-, 3-, 7-, and 12-hour time points, and conversion as well as *Z*-selectivity were calculated by analysis of the <sup>1</sup>H NMR spectra of the unpurified reaction mixtures (Table 2). Complexes **7** and **8** were able to catalyze the homodimerization of allyl benzene with excellent conversions and high selectivities, and were in good agreement with previously published data.<sup>12a</sup> A number of catalysts were found to homodimerize allyl benzene with similar efficacy. While catalysts **17**, **20**, and **21** demonstrated erosion of *Z*-selectivity over time, catalyst **19**, bearing geminal dimethyl substitution on the NHC backbone, displayed higher *Z*-selectivities than **8** (98% conversion, 92% *Z*-selectivity vs. >99% conversion, 83% *Z*-selectivity at 12 h of reaction time). The efficacy of **19** at preserving *Z*-selectivity highlights this new catalyst structure's unique attributes. However, complex **16**, with a 6-membered NHC, was not metathesis active, while CAAC-ligated **22** was found to be highly unstable under the reaction conditions.

Next, the efficacy of our new complexes was further examined using two more challenging homodimerization substrates. 10-Methyl undecenoate (**32**, Table 3) was selected because the ester functionality is far removed from the double bond, while 4-pentenol (**34**, Table 4) has been linked to decomposition pathways of prior generations of Ru-metathesis catalysts.<sup>27</sup> Furthermore, pronounced *Z*-content degradation has been observed in the homodimerization

of 4-pentenol with previous *Z*-selective metathesis catalysts **7** and **8**. Metathesis reactions were executed utilizing the standard conditions described above. Catalyst **19** effected the homodimerization of 10-methyl undecenoate with approximately the same conversions and near-perfect selectivities as catalyst **8** (96% vs. 97% conversion at 12 h for **19** and **8**, respectively), and **21** showed a similar level of *Z*-selectivity and efficiency. As expected, 4-pentenol was a difficult substrate and erosion of *Z*-selectivity was observed for all catalysts. Of note, **20** and **21** have improved solubility compared to **7** and **8**, and could perform neat, homogeneous homodimerizations of allylbenzene (**29**), 10-methyl undecenoate (**32**), and pentenol (**34**) without reduced activity.

### Cross-Metathesis Activity

Based on the results of the homodimerization studies, our two most active and selective new catalysts **19** and **21** were selected to be evaluated in more complicated cross-metathesis reactions. Cross-metathesis with allylic-substituted olefins is a particularly difficult transformation because increased steric bulk further destabilizes the *Z*-geometry of the cross product.<sup>28</sup> However, the utility of *Z*-selective cyclometalated metathesis catalyst **8** has previously been illustrated in the cross-metathesis of vinyl pinacol boronate (**36**) with 1-dodecene (**37**).<sup>29</sup> In the case of catalyst **8**, the reaction proceeds with 81% yield and 92% *Z*-selectivity. Catalyst **19** performed with comparable yields and selectivities, while unsaturated catalyst **21** displayed low activity under these conditions.

Chemoselective cross-metathesis of dienes is another underdeveloped reaction<sup>30</sup> that can be accomplished by cyclometalated ruthenium metathesis catalysts. Previously, **8** was demonstrated to catalyze the *Z*-selective cross-metathesis of **39** and **40** with complete chemoselectivity.<sup>31</sup> Under identical reaction conditions, the catalytic abilities of **8**, **19**, and **21** were compared (Table 6). Catalysts **8** and **19** afforded cross-product in similar yields (77% and 64%, respectively), with near perfect *Z*-selectivities, while **21** was again found to be an ineffective catalyst.

### Conclusions

A variety of new cyclometalated ruthenium alkylidene complexes have been prepared that exhibit high *Z*-selectivity. The use of NaOPiv to perform C–H activation has allowed access to a number of unique structures. This approach was used to synthesize seven new cyclometalated species, which were evaluated in a number of metathesis reactions. As expected, it was found that *N*-DIPP-substituted catalysts were more *Z*-selective than the analogous *N*-Mes-substituted complexes. One catalyst in particular, **19**, was found to be comparable to the best *Z*-selective metathesis catalyst to date in this series (**8**) in homodimerizations and more complicated cross-metathesis reactions. Future studies into catalyst development will focus on investigating modification of the X-type ligand, *N*-chelate, and the chelating isopropoxy styrene group.

### Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

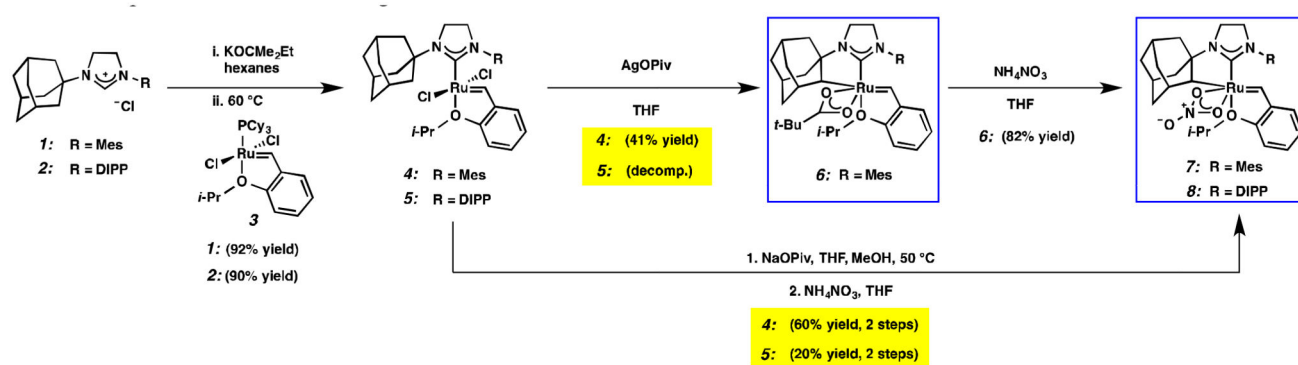
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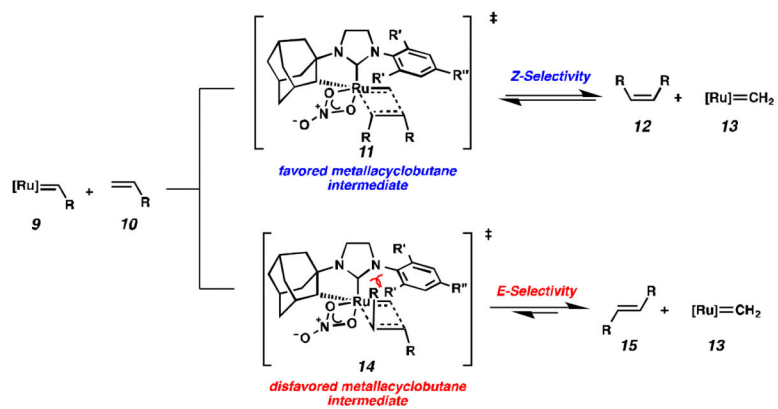
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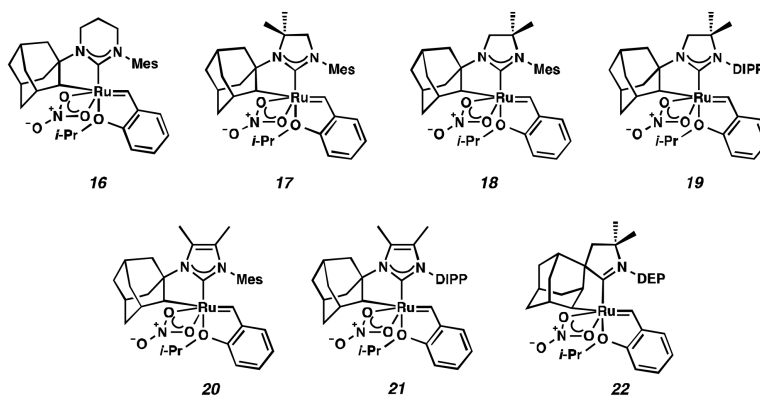


**Scheme 1.**  
 Synthetic Route to Previously Reported C–H Activated Metathesis Catalysts.

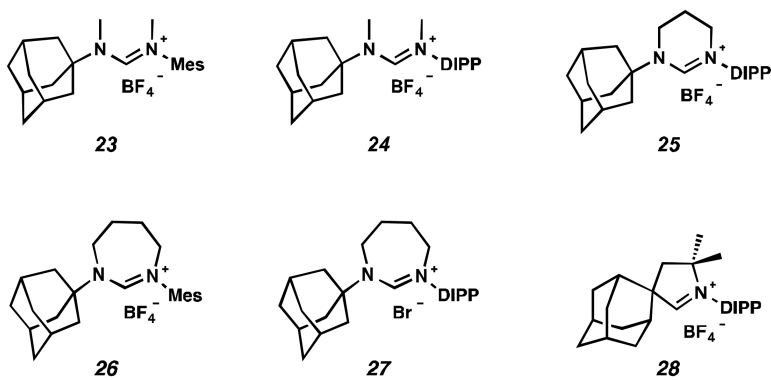




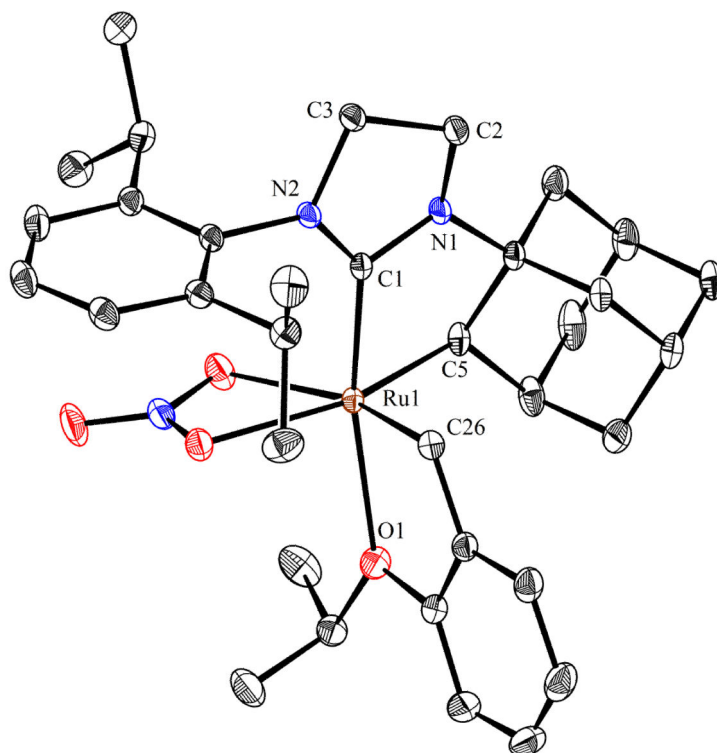
**Figure 1.**  
Steric crowding of metallacycle enforces Z-stereochemistry.



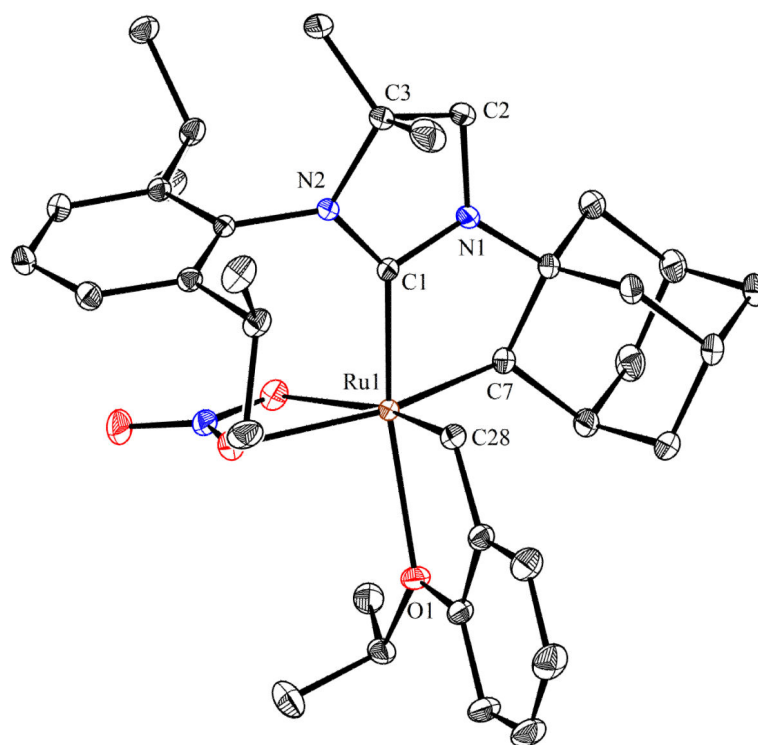
**Figure 2.**  
New ruthenium complexes with modified cyclometalated carbene ligands.



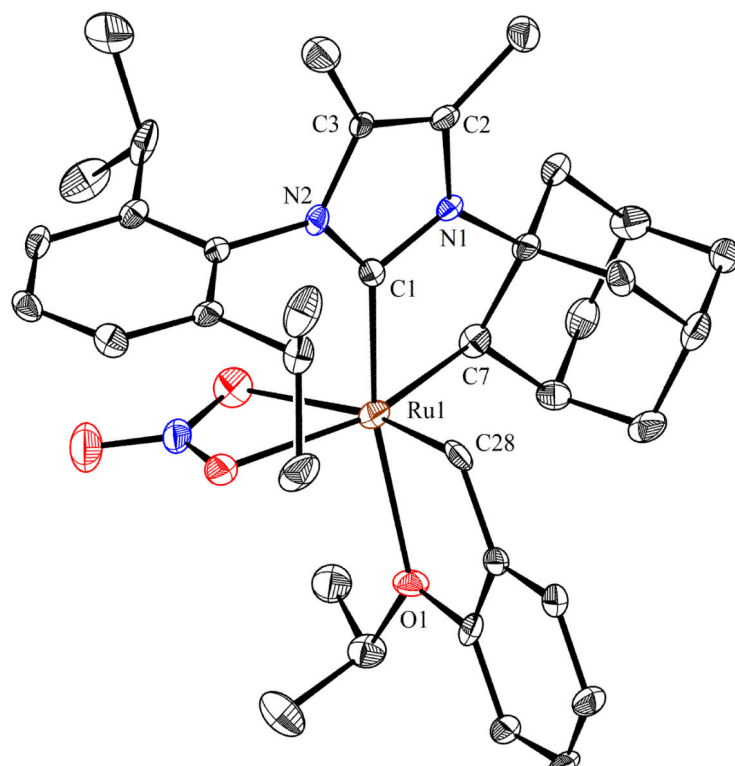
**Figure 3.** Formamidinium salts that could not be elaborated to cyclometalated ruthenium metathesis catalysts.



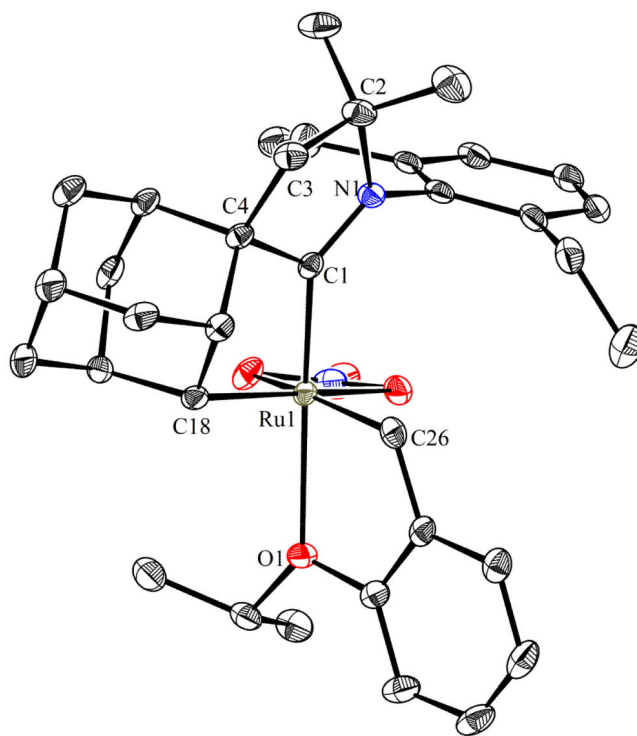
**Figure 4.** ORTEP drawing of **8**. Displacement ellipsoids are drawn at 50% probability. For clarity, hydrogen atoms have been omitted.



**Figure 5.** ORTEP drawing of **19**. Displacement ellipsoids are drawn at 50% probability. For clarity, hydrogen atoms have been omitted.



**Figure 6.** ORTEP drawing of **21**. Displacement ellipsoids are drawn at 50% probability. For clarity, hydrogen atoms have been omitted.



**Figure 7.**  
ORTEP drawing of **22**. Displacement ellipsoids are drawn at 50% probability. For clarity, hydrogen atoms have been omitted.

**Table 1**Selected X-Ray Data for **8**, **19**, **21**, and **22**.

	<b>8</b>	<b>19</b>	<b>21</b>	<b>22</b>
Bond Lengths (Å)				
Ruthenium-NHC Carbene Carbon Ru(1)–C(1)	1.954	1.974	1.965	1.939
Ruthenium-Chelating Isopropoxy Group Ru(1)–O(1)	2.311	2.320	2.317	2.329
Ruthenium-Chelating Adamantyl Carbon Ru(1)–C(5)	2.062	2.064	2.060	2.096
Ruthenium Alkylidene Styrene Carbon Ru(1)–C(26)	1.849	1.851	1.841	1.852
	Ru(1)–C(26)	Ru(1)–C(28)	Ru(1)–C(28)	Ru(1)–C(26)
Torsional Angle (deg)				
N(1)–C(2)–C(3)–N(2)	23.33	–23.66	1.16	n/a

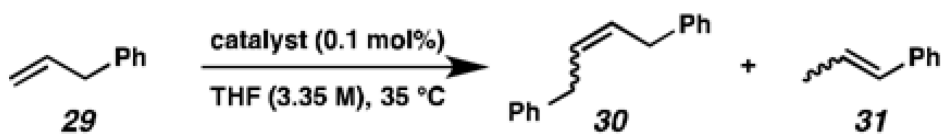


Table 2

Homodimerization of allyl benzene (**29**).

Reaction scheme showing the homodimerization of allyl benzene (**29**) to (E)-1,5-diphenylpent-2-ene (**30**) and (Z)-1,5-diphenylpent-2-ene (**31**). The reaction conditions are catalyst (0.1 mol%), THF (3.35 M), and 35 °C.

catalyst	time (h)	conversion (%) <sup>a</sup>	Z-selectivity (%) <sup>a</sup>	30/31 <sup>a</sup>
<p><b>7</b></p>	1	93	92	>50
	3	98	84	>50
	7	>99	66	>50
	12	>99	45	>50
<p><b>8</b></p>	1	92	>95	>50
	3	98	>95	>50
	7	>99	91	>50
	12	>99	83	>50
<p><b>16</b></p>	1	0	n/a	n/a
	3	0	n/a	n/a
	7	0	n/a	n/a
	12	0	n/a	n/a
<p><b>17</b></p>	1	72	>95	>50
	3	92	95	>50
	7	97	72	>50
	12	99	53	>50
<p><b>18</b></p>	1	82	>95	>50
	3	94	95	>50
	7	97	90	>50
	12	99	79	>50



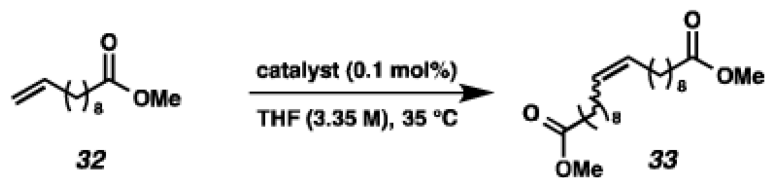
catalyst	time (h)	conversion (%) <sup>a</sup>	Z-selectivity (%) <sup>a</sup>	30/31 <sup>a</sup>
 <b>19</b>	1	75	>95	>50
	3	91	>95	>50
	7	97	>95	>50
	12	98	92	>50
 <b>20</b>	1	84	97	>50
	3	95	90	>50
	7	>99	54	>50
	12	>99	25	>50
 <b>21</b>	1	13	>95	>50
	3	75	>95	>50
	7	95	>95	>50
	12	98	93	>50
	25	>99	74	>50
 <b>22</b>	1	4	50	17
	3	6	49	2
	7	10	49	1
	12	15	49	0.6

<sup>a</sup>Determined from analysis of the <sup>1</sup>H NMR spectrum.

Table 3

Homodimerization of 10-methyl undecenoate (**32**).

catalyst	time (h)	conversion (%) <sup>a</sup>	Z-selectivity (%) <sup>a</sup>
<b>7</b> 	1	85	92
	3	94	89
	7	96	88
	12	97	83
<b>8</b> 	1	70	>95
	3	91	>95
	7	96	>95
	12	97	>95
<b>16</b> 	1	0	n/a
	3	0	n/a
	7	0	n/a
	12	0	n/a
<b>17</b> 	1	18	>95
	3	56	>95
	7	79	94
	12	86	91



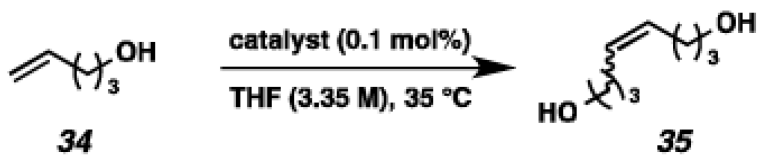
catalyst	time (h)	conversion (%) <sup>a</sup>	Z-selectivity (%) <sup>a</sup>
 <b>18</b>	1	35	>95
	3	65	>95
	7	78	>95
	12	82	94
 <b>19</b>	1	68	>95
	3	88	>95
	7	94	>95
	12	96	>95
 <b>20</b>	1	28	>95
	3	56	92
	7	75	85
	12	82	78
 <b>21</b>	1	5	>95
	3	27	>95
	7	65	>95
	12	81	>95
	25	85	>95
 <b>22</b>	1	0	n/a
	3	0	n/a
	7	0	n/a
	12	0	n/a

<sup>a</sup>Determined from analysis of the <sup>1</sup>H NMR spectrum.

Table 4

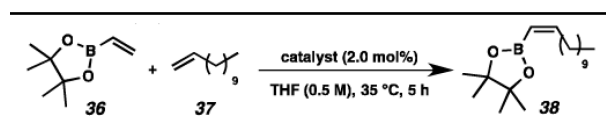
Homodimerization of 4-pentenol (**34**).

catalyst	time (h)	conversion (%) <sup>a</sup>	Z-selectivity (%) <sup>a</sup>
	1	52	>95
	3	92	88
	7	96	58
	12	99	24
	1	37	>95
	3	87	80
	7	94	33
	12	97	21
	1	0	n/a
	3	0	n/a
	7	0	n/a
	12	0	n/a
	1	6	>95
	3	55	88
	7	73	78
	12	85	76



catalyst	time (h)	conversion (%) <sup>a</sup>	Z-selectivity (%) <sup>a</sup>
 <b>18</b>	1	20	>96
	3	63	95
	7	71	82
	12	81	63
 <b>19</b>	1	14	>95
	3	63	82
	7	79	30
	12	86	29
 <b>20</b>	1	22	n/a
	3	84	75
	7	95	35
	12	significant isomerization	
 <b>21</b>	1	0	n/a
	3	10	>95
	7	49	72
	12	65	47
	25	88	27
 <b>22</b>	1	0	n/a
	3	0	n/a
	7	0	n/a
	12	0	n/a

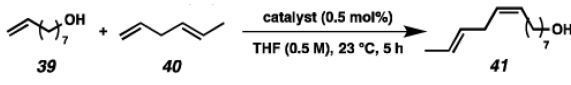
<sup>a</sup>Determined from analysis of the <sup>1</sup>H NMR spectrum.

**Table 5**Cross-metathesis of vinyl pinacol boronate (**36**) and 1-dodecene (**37**).

catalyst	yield (%) <sup>a</sup>	Z-selectivity (%) <sup>b</sup>
8	81	92
19	81	>95
21	<5	n/a

<sup>a</sup> Isolated yields.<sup>b</sup> Z-Selectivity determined by analysis of the <sup>1</sup>H NMR spectrum of the purified product.



**Table 6**Chemoselective cross-metathesis of 8-nonenol (**39**) and *trans*-1,4-hexadiene (**40**).


catalyst	yield (%) <sup>a</sup>	Z-selectivity (%) <sup>b</sup>
8	77	>95
19	64	>95
21	<5	n/a

<sup>a</sup> Isolated yields.<sup>b</sup> Z-Selectivity determined by analysis of the <sup>1</sup>H NMR spectrum of the purified product.