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## Highly Active Ruthenium Metathesis Catalysts Exhibiting Unprecedented Activity and Z-Selectivity

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### Abstract

A novel chelated ruthenium-based metathesis catalyst bearing an *N*-2,6-diisopropylphenyl group is reported and displays near-perfect selectivity for the *Z*-olefin (>95%), as well as unparalleled TONs of up to 7400, in a variety of homodimerization and industrially relevant metathesis reactions. This derivative and other new catalytically-active species were synthesized using an improved method employing sodium carboxylates to induce the salt metathesis and C-H activation of these chelated complexes. All of these new ruthenium-based catalysts are highly *Z*-selective in the homodimerization of terminal olefins.

The transition-metal catalyzed olefin metathesis reaction has emerged as an indispensable methodology for the construction of new carbon-carbon double bonds.<sup>1</sup> Since its discovery in the 1950s, metathesis has been employed with great success in a number of fields, including biochemistry,<sup>2</sup> materials science,<sup>3</sup> and green chemistry.<sup>4</sup> However, an ongoing challenge in cross metathesis (CM) reactions has been the control of stereoselectivity, as metathesis catalysts generally favor formation of the thermodynamically preferred *E*-olefin.<sup>5</sup> Many natural products and pharmaceutical targets, on the other hand, contain *Z*-olefins.<sup>6</sup> Recent groundbreaking work by Schrock and Hoveyda *et al.* resulted in the development of the first *Z*-selective metathesis catalysts using molybdenum and tungsten, allowing for the effective synthesis of *Z*-olefins via metathesis for the first time and opening the door to the development of new and improved *Z*-selective catalysts.<sup>7</sup>

More recently, we reported on the synthesis and activity of a comparable class of *Z*-selective ruthenium metathesis catalysts (**2**, **3**) containing a chelating *N*-heterocyclic carbene (NHC) ligand.<sup>8</sup> The Ru-adamantyl bond of the chelate was formed via an intramolecular C-H activation induced by the addition of silver pivalate (AgOPiv) (Scheme 1). Prior to this report, nitrate-catalyst **3** was the best *Z*-selective ruthenium-based metathesis catalyst, with turnover numbers (TONs) approaching 1000 and *Z*-selectivity on average around 90%. This catalyst has been shown to be effective for the synthesis of homo- and heterocross products, stereoregular polymers, and a variety of insect pheromones and macrocyclic musks.<sup>8c,9</sup>

Based on computational data, we hypothesized that increasing the steric bulk of the *N*-aryl group of **3** would further destabilize the *E*-selective transition state, thereby enhancing *Z*-selectivity.<sup>10</sup> However, as detailed in a previous report, attempts to make significant

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Experimental details and characterization data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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alterations to the NHC substituents, both to the chelating group and to the *N*-aryl group, mostly resulted in decomposition upon exposure to AgOPiv.<sup>11</sup> In order to access stable chelated species with various modifications to the NHC substituents, we sought to develop a milder approach to form this ruthenium-carbon bond. Herein, we report on an improved method to induce the salt metathesis and C-H activation of ruthenium alkylidene complexes employing mild and economically viable sodium carboxylates, and explore the superior activity and selectivity of several new chelated metathesis-active catalysts. Through the use of this improved approach, we have uncovered the highly active catalyst **9**, which on average gives >95% *Z*-selectivity and TONs of up to 7400 in the homodimerizations of terminal olefin substrates. In contrast, recently reported molybdenum- and tungsten-based systems reach TONs of up to 500 with comparable *Z*-selectivities for the same reactions.<sup>12</sup> As such, the turnover numbers reported herein are the highest for any *Z*-selective metathesis catalyst to date.

We initiated our studies by first employing sodium pivalate (NaOPiv) in place of AgOPiv during the C-H activation step. It was quickly discovered that exposing the unactivated dichloride catalyst **1** to excess NaOPiv in a 1:1 mixture of THF and MeOH resulted in the clean formation of the desired chelated catalyst **2** after heating at 40°C for 6 hours.<sup>13,14</sup> In order to explore the utility and mildness of this new approach, we revisited a number of ruthenium complexes containing a variety of *N*-aryl and *N*-carbocyclic groups that had decomposed when using AgOPiv. Attempts to replace the *N*-mesityl group of **3** with a bulkier DIPP group, as in **4**, for example, had resulted in substantial decomposition to **5** during the C-H activation step. Using NaOPiv, however, we were able to cleanly form the stable *N*-adamantyl, *N*-DIPP pivalate precursor (**6**) of catalyst **9** (Scheme 2).

We were also able to generate activated *N*-3,5-dimethyladamantyl, *N*-mesityl (**7**) and *N*-adamantyl, *N*-2,6-methylisopropylphenyl (MIPP) (**8**) derivatives via this improved method. More extreme alterations to the chelating group, however, including exchanging the *N*-adamantane for an *N*-cyclohexyl or *N*-1-methylcyclohexyl group, resulted in the formation of chelated catalysts that were inherently unstable. When these reactions were monitored by <sup>1</sup>H NMR spectroscopy, these complexes were seen to either decompose immediately to a ruthenium-hydride species upon introduction of NaOPiv or form a metastable activated complex that was unisolable without noticeable decomposition.

Complexes observed to form a stable chelated architecture were subsequently converted to the nitrate form via ligand exchange with the pivalate (Scheme 2), as past experience with catalyst **3** suggested that the nitrate-complexes would be more stable and show increased activity.<sup>8c,15</sup> While this seemed to be the case for complexes possessing a chelating *N*-adamantyl group, catalyst **7** was more stable and more easily isolated in the pivalate form. Catalysts successfully synthesized using the NaOPiv method are depicted in Figure 1.

To look at the efficacy of these new complexes for metathesis, we first evaluated their performance in the homodimerization of allyl benzene (**10**). While a relatively facile substrate for homodimerization, allyl benzene is also prone to olefin isomerization to form **12**. Importantly, the extent of this side reaction depends heavily on the identity and stability of the catalyst, making **10** a good benchmark substrate.<sup>16</sup> Homodimerization reactions were generally run in THF at 35°C with a high substrate concentration (3.3 M in **10**) and a catalyst loading varying between 0.1 and 2 mol%.<sup>17</sup> Excellent conversions and near-perfect *Z*-selectivities (>95%) were seen by <sup>1</sup>H NMR spectroscopy with **7–9**, with **8** and **9** being the most selective for the homodimer **11** over the olefin isomerization product **12**.

In order to differentiate between these very active catalysts, we turned to two more challenging homodimerization substrates, methyl 10-undecenoate (**13**) and the primary

alcohol 4-pentenol (**14**), the latter of which has been indirectly implicated in the decomposition of previous generations of ruthenium metathesis catalysts.<sup>18</sup> Reactions were run utilizing the standard conditions described above. Of the three catalysts, **9** gave the best results, providing the homodimerization products in high conversions (>95% and 77% for **13** and **14**, respectively) with >95% *Z*-selectivity for both substrates. Catalyst **8** also demonstrated excellent selectivity (>95% *Z* for both substrates) but low conversions, particularly in the homodimerization of **14** (7%). The almost exclusive selectivity for the *Z*-olefin observed with **8** and **9** is likely a result of the steric bulk of the *N*-MIPP or *N*-DIPP group positioned over the alkylidene, which ensures that any approach of the terminal olefin in a manner that would produce an *E*-olefin is extremely disfavored.<sup>10</sup> Previously, the homodimer of **14** was isolated in 67% yield with only 81% selectivity for the *Z*-olefin using catalyst **3**; thus the development of **9** represents a significant improvement in the field of *Z*-selective metathesis.

In order to further quantify the activity of the highly *Z*-selective catalyst **9**, we assayed its performance at room temperature and lower concentration (1 M in substrate). Under these conditions, similar conversions and *Z*-selectivities were observed compared to those recorded under standard conditions, although significantly longer reaction times were necessary. We additionally tested **9** at 0.01 mol % and were pleased to discover that it performed exceptionally well, reaching turnover numbers as high as 5800 and 7400 in the homodimerizations of **14** and **10**, respectively, while maintaining >95% *Z*-selectivity. This is in comparison to previously reported TONs of up to 1000 for catalyst **3** in conjunction with on average 90% *Z*-selectivity.<sup>8c</sup> Finally, isolated yields were obtained for all reactions employing catalyst **9**, including those run using the standard conditions (see Supporting Information).

Having established the effectiveness of **9** in homodimerization reactions, we set about to further evaluate its activity and *Z*-selectivity by exploring more complex transformations. The reaction of 1-hexene (**15**) and 8-nonenyl acetate (**16**) to form the pheromone derivative **17** was previously described using catalyst **3**, and proceeded in good yield (67%) with high *Z*-selectivity (91%) at a low catalyst loading (0.5 mol %).<sup>8c</sup> Catalyst **9** was able to catalyze this transformation with no observable formation of the *E*-isomer and in slightly higher yield (71%) at the same catalyst loading. Additionally, the catalyst loading could be lowered to 0.1 mol % and still provide a good yield of **17** (60%) while maintaining >95% *Z*-selectivity (Scheme 3). The expansion of this methodology to produce more complicated cross products with presumably total *Z*-selectivity should further enable its widespread use in the synthesis of *Z*-olefin-containing pheromones and other natural products.

We next evaluated catalyst **9** in macrocyclic ring-closing metathesis (RCM).<sup>5,6,19</sup> Although W- and Mo-based systems exhibit *Z*-selectivities as high as 97% for these reactions,<sup>20</sup> the Ru-based systems on average only result in *ca.* 85% *Z*-selectivity.<sup>9c</sup> Particularly problematic for the Ru-based system are substrates containing ketone or alcohol functionality, in which it is observed that the *Z*-isomer is readily degraded at high conversions. Thus, we were delighted to find that when dienes **18a–20a** were exposed to catalyst **9**, macrocycles **18–20** were all obtained in modest yields and with only trace amounts of the *E*-isomer evident by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy (Table 3). It is expected that this methodology will have application to a variety of natural products and pharmaceuticals, as well as for the synthesis of a unique class of olfactory compounds, termed macrocyclic musks. Many of these compounds contain a macrocyclic backbone either featuring a *Z*-olefin, or bearing functionality stereospecifically installed using a *Z*-olefin.<sup>5,6,19,21</sup> In fact, **18** and **19** are both currently in demand by the perfume industry (marketed as ambrettolide and civetone, respectively).<sup>21</sup>

In summary, we have developed a new method to effect the salt metathesis and C-H activation of *Z*-selective ruthenium-based metathesis catalysts using sodium carboxylates. This approach has been used to synthesize several new stable chelated species, all of which were found to be *Z*-selective in the homodimerizations of terminal olefin substrates. Notably, installation of an *N*-2,6-diisopropylphenyl group on the NHC led to significant improvements in activity and selectivity in both the homodimerization reactions of terminal olefins and industrially relevant products. Near-perfect selectivity for the *Z*-olefin (>95%) and unmatched TONs of up to 7400 were observed while retaining the ease of use associated with the ruthenium family of metathesis catalysts.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

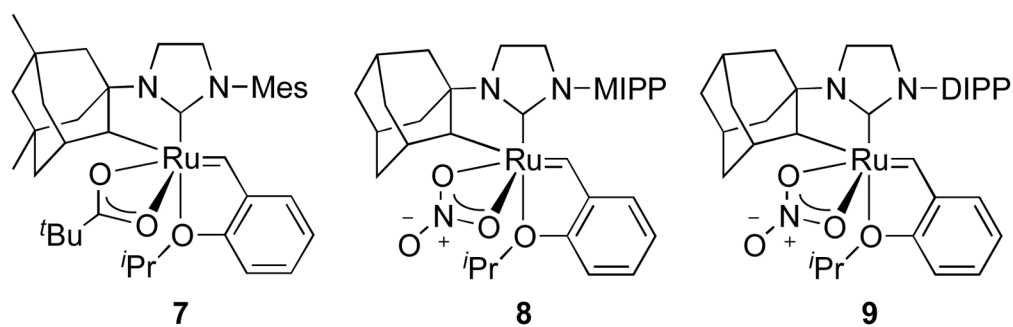
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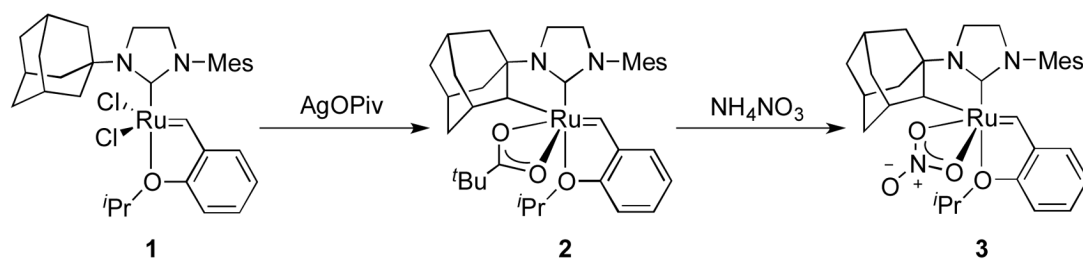
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13. The two-step synthesis of **3** using AgOPiv proceeded in 48% overall yield, whereas the same sequence using NaOPiv provided **3** in 60% overall yield.
14. Reaction of **1** with excess sodium acetate also resulted in complete conversion to **2**, but with some catalysts the C-H activation failed to reach full conversion. Reducing the steric bulk of the carboxylate even further by using sodium formate or sodium bicarbonate results in no discernible conversion to the desired chelated product.
15. Complex **6** and the pivalate analogue of catalyst **8** were isolated and assayed. As expected, they exhibited decreased activity and stability compared to the corresponding nitrate-complexes.
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17. Catalyst **8** was not soluble in THF, thus all reactions using **8** were run in 1,2-dichloroethane (DCE). Experimentation with catalyst **9** showed that using DCE in place of THF provided analogous results (see Table 2).
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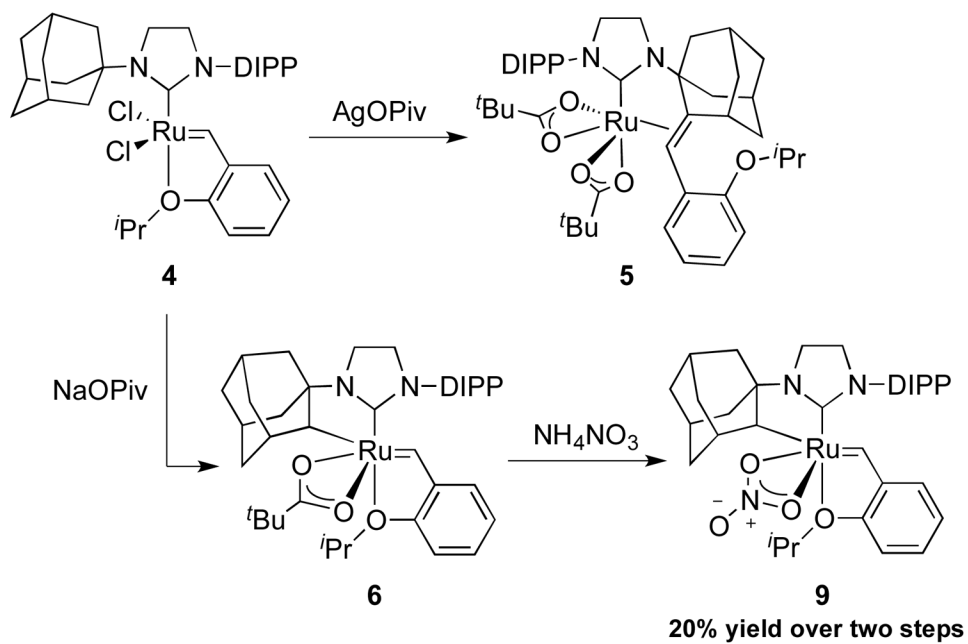
**Figure 1.**

Catalysts **7–9**: Mes = 2,4,6-trimethylphenyl (**7**); MIPP = 2,6-methylisopropylphenyl (**8**)

DIPP = 2,6-diisopropylphenyl (**9**).

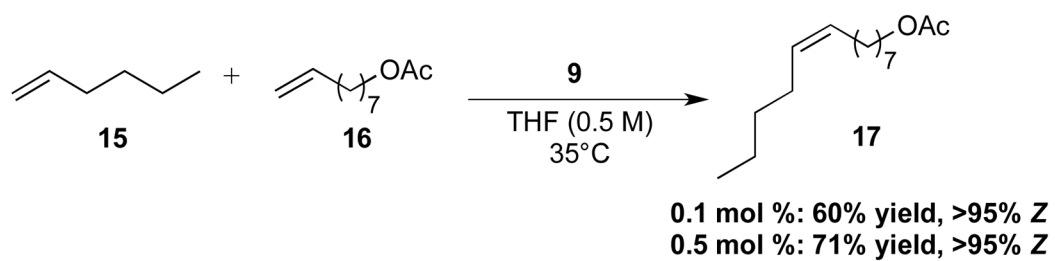


**Scheme 1.**  
Synthetic Route to Previously Reported C-H Activated Metathesis Catalysts.



**Scheme 2.**  
Decomposition and C-H Activation Pathways of 4.

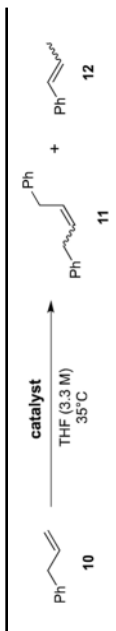




**Scheme 3.**  
Synthesis of Pheromone 17 Using Catalyst 9.

Table 1

Homodimerization of Allyl Benzene (10).



catalyst	loading, mol %	time, h	conv, % <sup>a</sup>	Z-11, % <sup>a</sup>	11/12 <sup>a</sup>
7	2	1.5	94	>95	16.6
8 <sup>b</sup>	0.1	2	78	>95	50
9	0.1	2	>95	>95	50

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy.<sup>b</sup>DCE was used in place of THF.

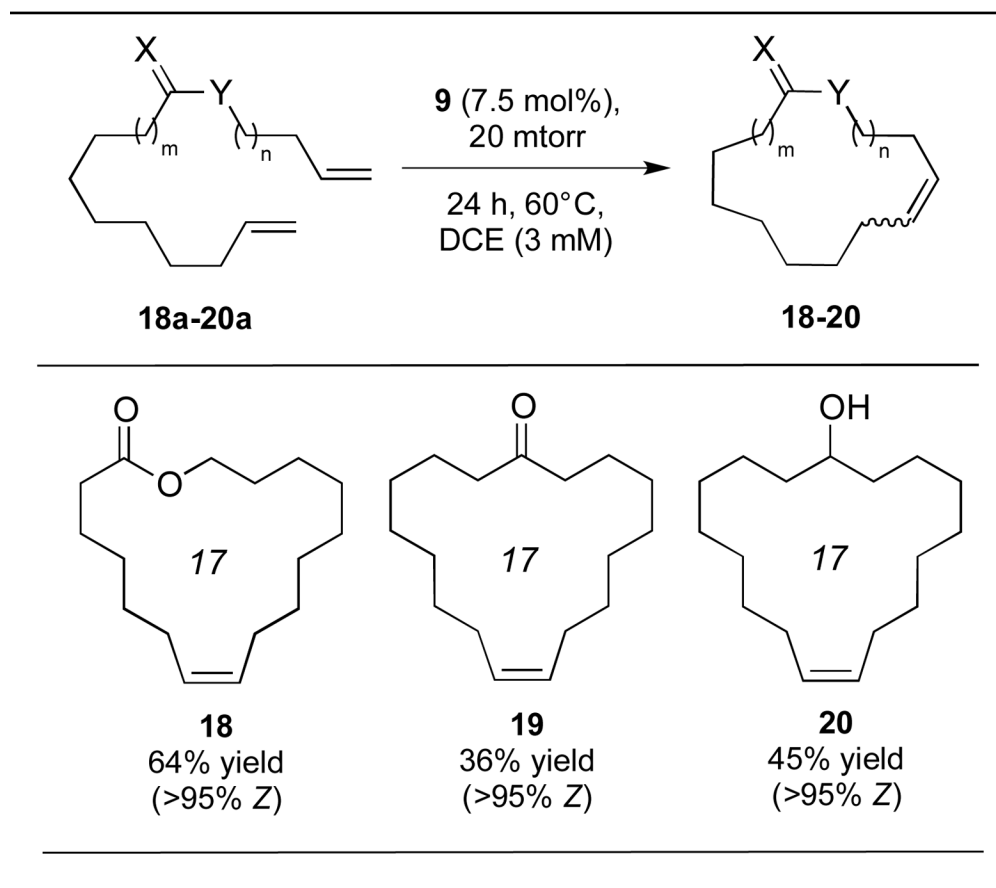
Table 2

Homodimerization of 10-Methyl Undecenoate (13) and 4-Pentenol (14).

substrate	catalyst	loading, mol %	time, h	conv, % <sup>a</sup>	Z, % <sup>a</sup>
13	7	2	3	77	91
	8 <sup>b</sup>	0.1	6	65	>95
	9	0.1	6	>95	>95
14	7	2	1.5	83	80
	8 <sup>b</sup>	0.1	2	7	>95
	9	0.1	2	77	>95
	9 <sup>b</sup>	0.1	2	79	92

<sup>a</sup>Determined by <sup>1</sup>H NMR spectroscopy.<sup>b</sup>DCE was used in place of THF.

Table 3

*Z*-Selective Macrocyclizations Employing Catalyst 9.<sup>a</sup><sup>a</sup> Isolated yields (*E/Z* ratios determined by <sup>1</sup>H- or <sup>13</sup>C-NMR spectroscopy).