

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

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S Supporting Information

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.¹ Since its discovery in the 1950s, metathesis has been employed with great success in a number of fields, including biochemistry,² materials science,³ and green chemistry.⁴ However, an ongoing challenge in cross-metathesis reactions has been the control of stereoselectivity, as metathesis catalysts generally favor formation of the thermodynamically preferred *E*-olefin.⁵ Many natural products and pharmaceutical targets, on the other hand, contain *Z*-olefins.⁶ 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.⁷

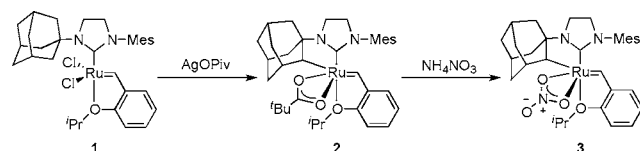
More recently, we reported on the synthesis and activity of a comparable class of *Z*-selective ruthenium metathesis catalysts (**2**, **3**) containing a chelating *N*-heterocyclic carbene (NHC) ligand.⁸ The Ru–adamantyl bond of the chelate was formed via an intramolecular C–H activation induced by 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 hetero-cross-products, stereoregular polymers, and a variety of insect pheromones and macrocyclic musks.^{8c,9}

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.¹⁰ However, as detailed in a previous report, attempts to make significant alterations to the NHC substituents, both to the chelating group and to the *N*-aryl group, mostly resulted in decomposition upon exposure to AgOPiv.¹¹ 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.¹² 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 h.^{13,14} 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 *N*-2,6-diisopropylphenyl (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).

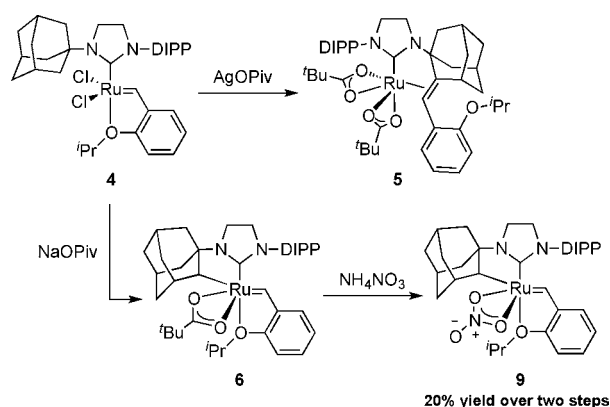
Scheme 1. Synthetic Route to Previously Reported C–H Activated Metathesis Catalysts



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Scheme 2. Decomposition and C–H Activation Pathways of 4



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 ^1H 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.^{8c,15} 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.

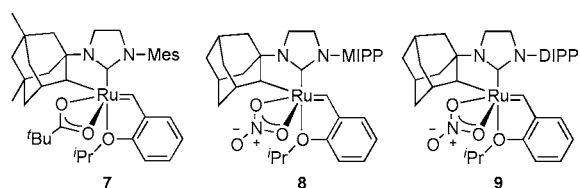


Figure 1. Catalysts 7–9: Mes = 2,4,6-trimethylphenyl (7); MIPP = 2,6-methylisopropylphenyl (8); DIPP = 2,6-diisopropylphenyl (9).

To look at the efficacy of these new complexes for metathesis, we first evaluated their performance in the homodimerization of allylbenzene (10, see Table 1). While a relatively facile substrate for homodimerization, allylbenzene 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.¹⁶ 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%.¹⁷ Excellent conversions and near-perfect *Z*-selectivities (>95%) were seen by ^1H NMR spectroscopy with 7–9, with 8 and 9 being the most selective for the homodimer 11 over the olefin isomerization product 12.

Table 1. Homodimerization of Allylbenzene (10)

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

^aDetermined by ^1H NMR spectroscopy. ^bDCE was used in place of THF.

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.¹⁸ Reactions were run utilizing the standard conditions described above. Of the three catalysts, 9 gave the best results (see Table 2), providing the

Table 2. Homodimerization of 10-Methyl Undecenoate (13) and 4-Pentenol (14)

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

^aDetermined by ^1H NMR spectroscopy. ^bDCE was used in place of THF.

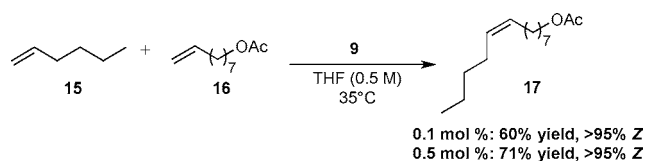
homodimerization products in high conversions (>95% and 77% for 13 and 14, respectively) with >95% *Z*-selectivity for both substrates. Catalyst 8 also demonstrated excellent selectivity (>95% *Z* for both substrates) but low conversions, particularly in the homodimerization of 14 (7%). The almost exclusive 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.¹⁰ 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 maintain-

ing >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.^{8c} 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 %).^{8c} 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

Scheme 3. Synthesis of Pheromone 17 Using Catalyst 9

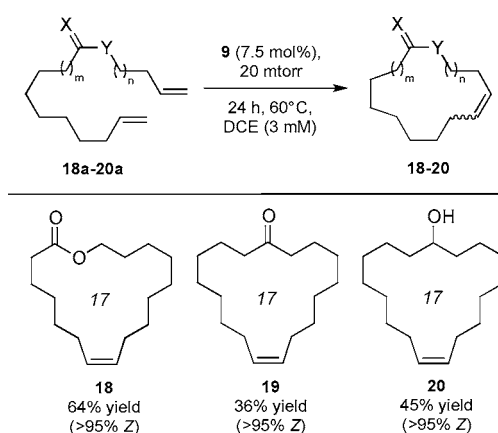


more complicated cross products with presumably total *Z*-selectivity should further enable its widespread use in the synthesis of *Z*-olefin-containing pheromones and other natural products.

We next evaluated catalyst **9** in macrocyclic ring-closing metathesis.^{5,6,19} Although W- and Mo-based systems exhibit *Z*-selectivities as high as 97% for these reactions,²⁰ the Ru-based systems on average only result in ca. 85% *Z*-selectivity.^{9c} 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 ¹H and ¹³C 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.^{5,6,19,21} In fact, **18** and **19** are both currently in demand by the perfume industry (marketed as ambrettolide and civetone, respectively).²¹

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 metathesis reactions. Near-perfect selectivity for the *Z*-olefin (>95%) and unmatched TONs of up to

Table 3. *Z*-Selective Macrocyclizations Employing Catalyst **9**^a



^aIsolated yields (*E/Z* ratios determined by ¹H or ¹³C NMR spectroscopy).

7400 were observed while retaining the ease of use associated with the ruthenium family of metathesis catalysts.

■ ASSOCIATED CONTENT

Supporting Information

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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Notes

The authors declare no competing financial interest.

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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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