

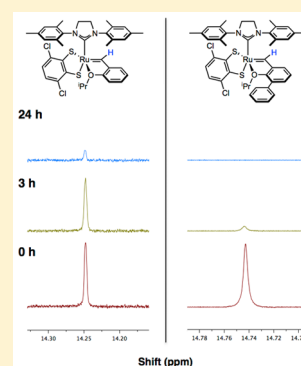
Fast-Initiating, Ruthenium-based Catalysts for Improved Activity in Highly *E*-Selective Cross Metathesis

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S Supporting Information

ABSTRACT: Ruthenium-based olefin metathesis catalysts bearing dithiolate ligands have been recently employed to generate olefins with high *E*-selectivity (>99% *E*) but have been limited by low to moderate yields. In this report, ¹H NMR studies reveal that a major contributing factor to this low activity is the extremely low initiation rates of these catalysts with *trans* olefins. Introducing a 2-isopropoxy-3-phenylbenzylidene ligand in place of the conventional 2-isopropoxybenzylidene ligand resulted in catalysts that initiate rapidly under reaction conditions. As a result, reactions were completed in significantly less time and delivered higher yields than those in previous reports while maintaining high stereoselectivity (>99% *E*).



BACKGROUND

Given its robustness and general ease of implementation, transition metal-catalyzed olefin metathesis has become an increasingly ubiquitous method for generating C–C double bonds in a wide variety of fields including organic synthesis, green chemistry, and biochemistry.¹ Over the last several years, olefin metathesis has been significantly advanced through the synthesis of well-defined catalysts, where methodical tuning of catalyst architecture has allowed for the development of different catalysts that can each achieve a specific purpose including enantioselectivity,² stereoselectivity,³ or increased activity.⁴

Achieving high selectivity for 1,2-disubstituted olefinic products with a particular stereochemistry (*E* or *Z*) was a longstanding challenge in olefin metathesis until discrete Ru-,^{3e–h} Mo-, and W-based^{3b–d} catalysts were developed in recent years for the metathesis of terminal olefins to produce high levels of *cis* olefins. Each of these catalysts exploits steric impedances within the catalyst structure to favor the *syn* over the *anti* metallacyclobutane pathway.⁵

Until very recently, methods of achieving high kinetic *trans* selectivity through olefin metathesis had remained elusive. Selectivity for *trans* product in olefin metathesis can often be achieved by allowing the reaction to reach equilibrium so that the thermodynamically favored product, often *trans*, is present in higher quantities.⁶ However, the difference in energy between some *cis* and *trans* isomers may be insignificant; hence, this method is not reliable for obtaining all *trans* products in high selectivity. Other methods for preparing *trans* olefins with high stereoselectivity include *Z*-selective ethenolysis of *E*/*Z*-olefin mixtures,⁷ Wittig reactions of stabilized ylides,⁸ Julia olefinations,⁹ and Peterson olefinations.¹⁰ In addition, alkyne metathesis followed by Na/NH₃ reduction,¹¹

catalytic *trans*-hydrosilylation/protodesilylation,¹² or semihydrogenation¹³ can also furnish *trans* olefins. These methods, however, are either harsh or require multiple steps to reach the desired *trans* product.

The first demonstration of highly kinetically *trans*-selective transition metal-catalyzed olefin cross metathesis was reported this year with the unexpected discovery that ruthenium-based catalysts bearing chelated dithiolate ligands are able to perform cross metathesis between two *trans* olefins or between a *trans* olefin and a terminal olefin to generate products with high *trans* selectivity (>98% *E*).^{3l} These catalysts had been previously demonstrated to react with *cis* starting materials to form highly *cis* products.^{3k} Hence, these catalysts are stereoretentive, preserving the stereochemical purity of the starting olefins in the product olefins. The *E*-selectivity of the catalysts is proposed to arise from the two *N*-aryl groups of the NHC forcing the α substituents of a side-bound metallacycle to point down while the β substituent can point into the open space in front of the plane containing the N–C–N bonds of the NHC and between the two *N*-aryl groups (Figure 1). This proposed model was supported by the observation that reducing the size of the *ortho* substituents of the *N*-aryl groups of the NHC led to increased catalyst activity in this transformation. A subsequent report from the Hoveyda and Schrock groups demonstrated a similar approach to achieving *trans*-selective cross metathesis using Mo-based catalysts.^{3m} Steric interactions of the substituents of the metallacycle with surrounding ligands in combination with minimizing unfavorable eclipsing interactions

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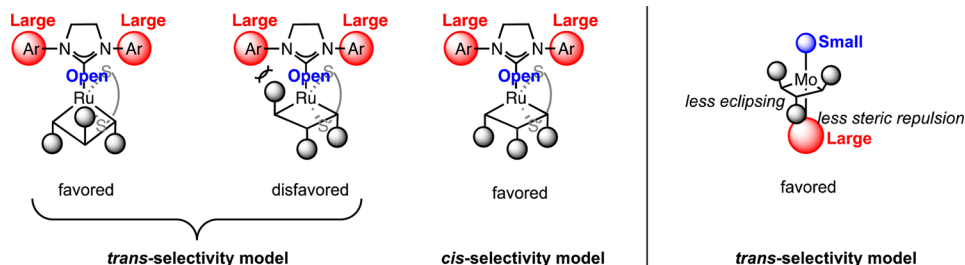


Figure 1. Proposed models for high kinetic *trans* and *cis* selectivity in cross metathesis with ruthenium catalysts³¹ (left) and high *trans* selectivity with molybdenum catalysts^{3m} (right).

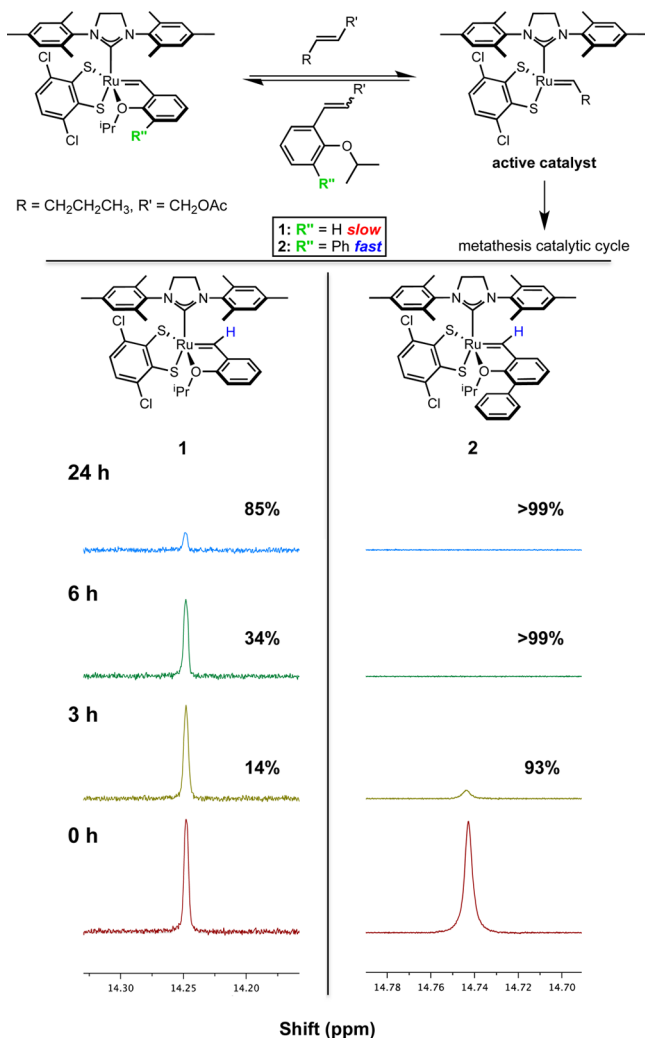


Figure 2. Signals corresponding to the benzylidene protons of each **1** and **2** over the course of the reaction with *trans*-2-hexenyl acetate (0.5 M) in THF-*d*₈ at 45 °C. Percentages shown are percentages of catalyst initiated as determined by the decrease in the benzylidene signal over time upon reaction with substrate.

of these substituents was their proposed rationale for the favorable formation of *anti* metallacycles.

In many instances, the *trans*-selective, Ru dithiolate catalysts generated low yields of products. Two possible reasons for the low activity can be envisioned: slow catalyst initiation and the inherently small “open space” in which the β substituent can place itself. Herein, we establish that poor initiation is indeed a significant factor in the low conversions observed with previous dithiolate catalysts. We address this through the development

of new catalysts with improved initiation efficiency that demonstrate significantly improved conversions and reaction times in comparison to previous catalysts.

RESULTS AND DISCUSSION

When examining the self-metathesis of *trans*-2-hexenyl acetate catalyzed by 1 mol % **1**, uninitiated catalyst was evident in the ¹H NMR after 24 h at 45 °C, at which time only 85% of the catalyst had initiated (Figure 2). Based on this result, new catalyst **2**, bearing a chelating 2-isopropoxy-3-phenylbenzylidene ligand in place of the 2-isopropoxybenzylidene of catalyst **1**, was synthesized. This alteration has been shown to drastically increase rates of initiation in other ruthenium-based metathesis catalysts.^{4c–f} Under the same aforementioned reaction conditions with *trans*-2-hexenyl acetate, 93% of **2** initiated after only 3 h, and **2** was fully initiated within 6 h. For each catalyst, loss of the chelated benzylidene ligand is required prior to entrance into the catalytic cycle of olefin metathesis. Given the poor initiation of **1** even under relatively forcing conditions of elevated temperatures and high *trans*-substrate concentration, the concentration of active catalyst is significantly lower than that expected from the catalyst loading. As a result, the yields of products are diminished, limiting the use of this catalyst. This issue is resolved with catalyst **2**.

Initiation rate constants (k_{init}) were calculated for **1** and **2** under these reaction conditions and were determined to be 2.52×10^{-5} and $1.75 \times 10^{-4} \text{ s}^{-1}$, respectively (Figure 3).

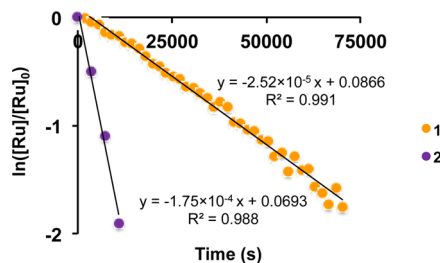


Figure 3. Plot of $\ln([Ru]/[Ru]_0)$ versus time. Plots remain approximately linear over the course of three half-lives of the reaction.

The relative rate constant (k_{rel}) hence has a value of ~ 7 . Thus, one-seventh of the catalyst loading of **1** can be used to achieve the same active catalyst concentration with catalyst **2**. Given the low activity seen in previous studies of **1** in cross metathesis reactions involving *trans* olefins and the inability of this catalyst to initiate efficiently even under forcing conditions, the difference in the ability between **1** and **2** to initiate under normal reaction conditions can make a significant difference in the ability to provide meaningful yields of products.

Scheme 1

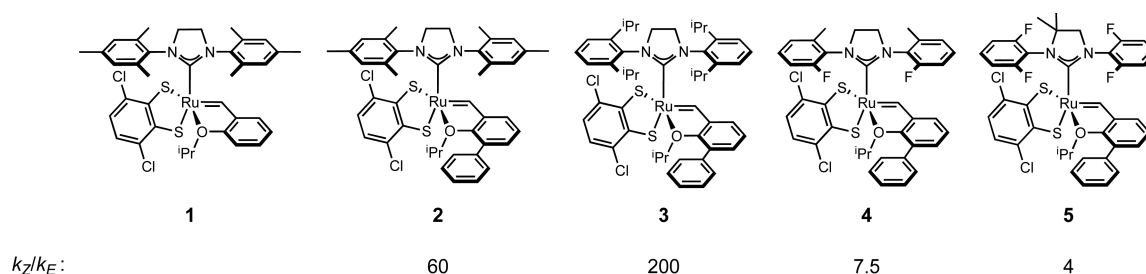
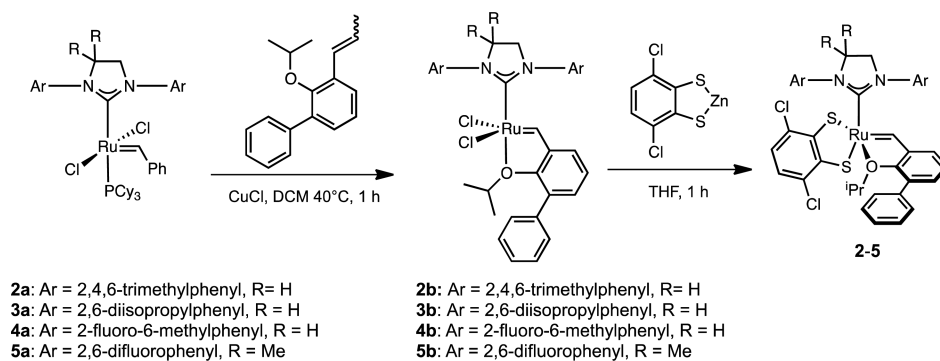


Figure 4. Catalysts examined in this study.

Table 1. Self-Metathesis of Methyl 9-octadecanoate^a

entry	starting material	Ru (mol %)	time	% MO (E/Z)	% DE (E/Z)	% 9C18 (E/Z)
1	E	1 (1.0)	1 h	99 (>99/1)	0.5 (>99/1)	0.5 (>99/1)
			3 h	92 (>99/1)	4 (>99/1)	4 (>99/1)
			11 h	54 (>99/1)	23 (>99/1)	23 (>99/1)
			15 h	50 (>99/1)	25 (>99/1)	25 (>99/1)
2	E	2 (1.0)	1 h	80 (>99/1)	10 (>99/1)	10 (>99/1)
			3 h	50 (>99/1)	25 (>99/1)	25 (>99/1)
3	E	3 (1.0)	30 min	88 (>99/1)	6 (>99/1)	6 (>99/1)
			2.5 h	50 (>99/1)	25 (>99/1)	25 (>99/1)
4	E	4 (1.0)	10 min	84 (>99/1)	8 (>99/1)	8 (>99/1)
			20 min	60 (>99/1)	20 (>99/1)	20 (>99/1)
			30 min	50 (>99/1)	25 (>99/1)	25 (>99/1)
5	E	4 (0.5)	1 h	50 (>99/1)	25 (>99/1)	25 (>99/1)
6	E	5 (1.0)	10 min	62 (>99/1)	19 (>99/1)	19 (>99/1)
			20 min	50 (>99/1)	25 (>99/1)	25 (>99/1)
7	E	5 (0.5)	40 min	50 (>99/1)	25 (>99/1)	25 (>99/1)
8	Z	1 (0.1)	30 min	98 (<1/99)	1 (<1/99)	1 (<1/99)
			1 h	92 (<1/99)	4 (<1/99)	4 (<1/99)
			3 h	54 (<1/99)	23 (<1/99)	23 (<1/99)
			5 h	50 (<1/99)	25 (<1/99)	25 (<1/99)
9	Z	2 (0.1)	15 min	80 (<1/99)	10 (<1/99)	10 (<1/99)
			30 min	50 (<1/99)	25 (<1/99)	25 (<1/99)
10	Z	3 (0.5)	30 s	70 (<1/99)	15 (<1/99)	15 (<1/99)
			60 s	60 (<1/99)	20 (<1/99)	20 (<1/99)
			90 s	50 (<1/99)	25 (<1/99)	25 (<1/99)
11	Z	3 (0.05)	15 min	50 (<1/99)	25 (<1/99)	25 (<1/99)
12	Z	4 (0.1)	15 min	76 (<1/99)	12 (<1/99)	12 (<1/99)
			40 min	50 (<1/99)	25 (<1/99)	25 (<1/99)
13	Z	5 (0.1)	25 min	62 (<1/99)	19 (<1/99)	19 (<1/99)
			50 min	50 (<1/99)	25 (<1/99)	25 (<1/99)

^aProduct distribution and selectivity analyzed by GC using tridecane as an internal standard.

By varying the size of the *ortho* substituents of the *N*-aryl groups of the NHC, a series of other fast-initiating catalysts (3–5) were synthesized (Scheme 1). 2–5 were synthesized from phosphine-bound catalysts 2a–5a. The chelating 2-isopropoxy-3-phenylbenzylidene ligand is installed by reaction of 2a–5a with CuCl and (*E/Z*)-2-isopropoxy-3-(prop-1-en-1-yl)-1,1'-biphenyl to generate 2b–5b. This is followed by the exchange of the two chloride X-ligands with a dithiolate ligand using a zinc transmetalating agent to produce 2–5 (Figure 4).

To observe differences in reactivity of catalysts 1–5, the self-metathesis of the *trans* isomer of the substrate methyl 9-octadecenoate (MO) to produce dimethyl 9-octadecenedioate (DE) and 9-octadecene (9C18) was examined (Table 1, entries 1–7). With 1 mol % 1, this reaction requires 15 h to reach equilibrium, whereas the same reaction with 2 reaches equilibrium in 3 h while maintaining the same high stereoselectivity (>99% *E*). To examine the relationship between the size of the *ortho* substituents of the *N*-aryl group of the NHC and catalyst activity, 3–5 were then studied in this reaction. 3 reaches equilibrium in 2.5 h, whereas it only takes 30 min for 4 and 20 min for 5 to achieve the same distribution while high *trans* selectivity is conserved (>99% *E*). The catalyst loading of 4 and 5 can be dropped to 0.5 mol %, and the reaction still reaches equilibrium within 1 h and 40 min, respectively.

The self-metathesis of the *cis* analogue of this substrate, *Z*-methyl 9-octadecenoate, was also analyzed (Table 1, entries 8–13). These catalysts were markedly more active in this reaction than that of the *E*-isomer. Catalyst 3 (0.5 mol %) is strikingly fast and reaches equilibrium in 90 s, while the products retain the stereochemistry of the starting material (>99% *Z*). The catalyst loading can be reduced 10-fold to 0.05 mol %, and the reaction reaches equilibrium in 15 min. With 0.1 mol % catalyst, the reaction reaches equilibrium in 30 min with 2, 40 min with 4, and 50 min with 5. Catalyst 1, however, requires 5 h at the same loading to achieve equilibrium.

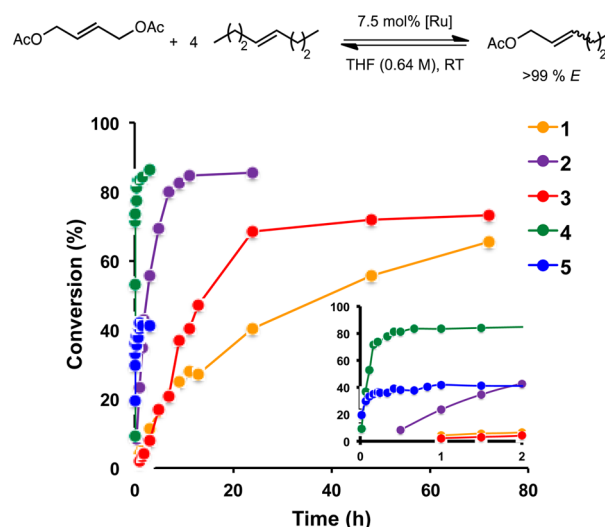
To examine the disparity of the rates of reaction of each of these catalysts with the *E*- and *Z*-isomers of methyl 9-octadecenoate, a relative rate constant (k_Z/k_E) was calculated using the times needed for the reactions to reach equilibrium (t_E and t_Z), assuming first-order kinetics with respect to initial catalyst concentration ($[Ru]_E$ and $[Ru]_Z$).¹⁴

$$k_Z/k_E = [Ru]_E t_E / ([Ru]_Z t_Z) \quad (1)$$

For catalysts 2–5, k_Z/k_E values were determined to be 200, 60, 7.5, and 4. This is in accordance with our proposed model for selectivity, where *E*-olefin formation proceeds through a metallacycle in which the β substituent points into the “open space” between the two *N*-aryl groups. Thus, reducing the size of the *ortho* substituents of the *N*-aryl groups increases the ability of the *E*-olefin to react with the catalysts.

In order to examine the reactivity of these catalysts with substrates bearing functional groups closer to the double bond, cross metathesis between *trans*-4-octene and *trans*-1,4-diacetoxy-2-butene (4:1 mol ratio) was examined (Scheme 2). Using 1 (7.5 mol %), this reaction reaches a conversion of only 4% in 1 h to *trans*-2-hexenyl acetate (>99% *E*). Under identical conditions, 2 achieves 24% conversion in 1 h. After 7 h, the reaction reaches 80% conversion with 2, while parent catalyst 1 requires 3 days to reach 65% conversion. Consistent with the proposed model for selectivity, 3, with bulky *N*-diisopropylphenyl groups of the NHC, has lower activity for these *trans*

Scheme 2. Cross Metathesis of *trans*-1,4-Diacetoxy-2-butene with *trans*-4-Octene^a

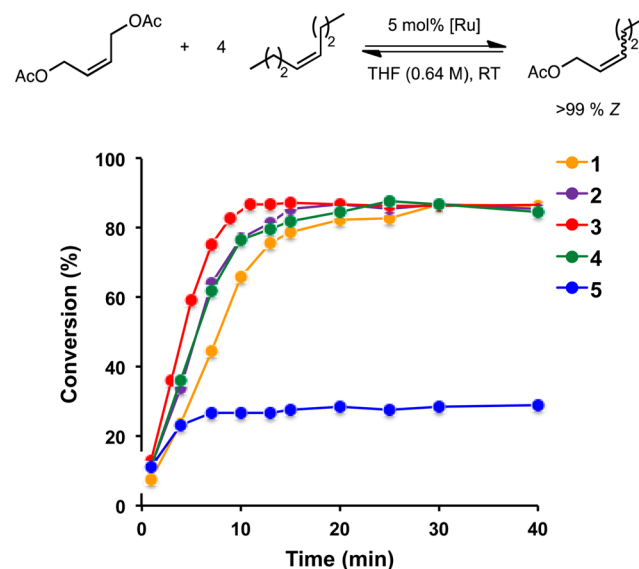


^aConversions determined using ¹H NMR. Stereoselectivity determined by GC. Inset shows early time points.

substrates in comparison to that of 2, but is more active than 1 in this transformation. Catalyst 4 is remarkably fast in this reaction, achieving 80% conversion to the product (>99% *E*) in only 25 min. Also in agreement with the proposed model that suggests increased activity with decreasing *ortho* substituent size of the *N*-aryl groups, 5 demonstrated high initial conversion early in the reaction, but was found to decompose under reaction conditions, only reaching 36% overall conversion.

As seen in the reaction with methyl 9-octadecenoate, the reaction of the *cis* isomers of these substrates, *cis*-4-octene and *cis*-1,4-diacetoxy-2-butene (4:1 molar ratio), was significantly more facile than that of the corresponding *trans* isomers with the catalysts (Scheme 3). 3 was the most active catalyst in this reaction, reaching 86% conversion in 11 min. 2 and 4

Scheme 3. Cross Metathesis of *cis*-1,4-Diacetoxy-2-butene with *cis*-4-Octene^a

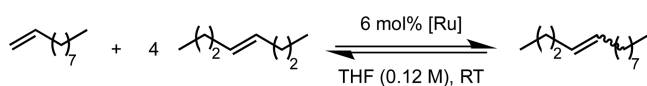


^aConversions determined using ¹H NMR. Stereoselectivity determined by GC.

performed similarly, both reaching 81% conversion in 15 min. **1** reached 80% conversion in this reaction in 20 min. Catalyst **5** again decomposed under reaction conditions, reaching an overall yield of 28%. At the start of the reaction, however, it displayed reactivity less than that of catalysts **2–4** but greater than that of parent catalyst **1**. In this set of reactions, the opposite trend is seen with respect to changing the identity of the *ortho* substituents: As the NHC substituents get smaller, the reactivity with this substrate decreases. Because degradation is seen in both the reaction with the *cis* and *trans* isomers, the decomposition of **5** is likely due to a side reaction with 1,4-diacetoxy-2-butene.

The more challenging reaction of the cross metathesis of a disubstituted olefin, *trans*-4-octene, and a terminal olefin, 1-decene, to generate 4-tridecene was then attempted (Table 2).

Table 2. Cross Metathesis of 1-Decene and *trans*-4-Octene^a



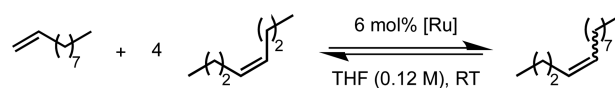
entry	[Ru]	time (h)	yield	E/Z
1	1	0.25	17	>99/1
		1	20	>99/1
		2	20	>99/1
		4	21	>99/1
2	2	0.25	24	>99/1
		1	25	>99/1
		2	26	>99/1
		4	27	>99/1
3	3	0.25	16	90/10
		1	17	90/10
		2	17	90/10
		4	19	90/10
4	4	0.25	47	>99/1
		1	49	>99/1
		2	50	>99/1
		4	49	>99/1
5	5	0.25	51	>99/1
		1	52	>99/1
		2	52	>99/1
		4	52	>99/1

^aProduct distribution and selectivity analyzed by GC using tetradecane as an internal standard.

This reaction proved difficult for all catalysts due to rapid decomposition of these catalysts, likely due to the formation of the unstable ruthenium methylidenes under these conditions. As a result, yields of the product in this reaction for each of these catalysts did not change significantly after 15 min. Catalyst **3** (6 mol %) was the least active, reaching a maximum of 19% yield (90% *E*).¹⁵ **2** generated the product in 27% yield, slightly higher than that of **1** at 21% yield. **4** and **5**, however, were efficient at reaching moderate yields of products with yields of 50 and 52%, respectively, again in agreement with the proposed model by which reducing *ortho* substituent size of *N*-aryl groups is proposed to increase catalytic activity.¹⁶ Catalysts **1**, **2**, **4**, and **5** all delivered high selectivity of the *trans* product (>99% *E*).

In the cross metathesis of *cis*-4-octene and 1-decene, yields were consistent across catalysts **1–4**, ranging from 75–78% with high stereoretention (>95% *Z*) throughout the reaction (Table 3).¹⁷ Catalyst **5** generated the product in a slightly lower 70% yield.

Table 3. Cross Metathesis of 1-Decene and *cis*-4-Octene^a



entry	[Ru]	time (h)	yield	E/Z
1	1	0.25	73	<1/99
		1	74	<1/99
		2	74	<1/99
		4	75	<1/99
2	2	0.25	75	<1/99
		1	75	<1/99
		2	76	<1/99
		4	77	<1/99
3	3	0.25	77	<1/99
		1	77	2/98
		2	77	2/98
		4	78	5/95
4	4	0.25	75	<1/99
		1	75	<1/99
		2	75	<1/99
		4	74	<1/99
5	5	0.25	65	<1/99
		1	70	<1/99
		2	70	<1/99
		4	70	<1/99

^aProduct distribution and selectivity analyzed by GC using tetradecane as an internal standard.

CONCLUSIONS

¹H NMR studies were used to determine that recently reported highly stereoretentive ruthenium-based catalysts bearing dithiolate ligands suffer from poor catalyst initiation in reactions with *trans* olefins. In order to improve initiation characteristics, a series of fast-initiating catalysts **2–5** possessing a 2-isopropoxy-3-phenylbenzylidene ligand in place of the 2-isopropoxybenzylidene ligand were synthesized. These catalysts demonstrate significantly improved initiation compared to that of **1**, resulting in considerably increased activity of these catalysts in reactions of *trans* olefins and demonstrating higher yields at shorter reaction times, while maintaining high stereoselectivity of products (>99% *E*). Some improvement was also observed in reactions with *cis* olefins compared to previously reported catalysts, although the difference was more marginal as the previous catalysts were efficient at catalyzing reactions involving *cis* olefins with high stereoselectivity (>99% *Z*).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11330.

Characterization data, and experimental data (PDF)

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Notes

The authors declare no competing financial interest.

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- (14) By increasing catalyst concentration by a certain factor, reaction rate was increased by the same factor. See [Table S1](#) for data.
- (15) In this case, conversion of 1-decene to a variety of isomers was also seen, and this isomerization process might be responsible for the degraded level of *E*-selectivity.
- (16) Previous studies have shown that Ru---F interactions sometimes occur in particular olefin metathesis systems.¹⁸ Although there is no evidence of this in this system, this type of interaction might play a role in this reaction.
- (17) Lower yields than expected in this reaction could be attributed to the self-metathesis of the product, 4-tridecene, to form 4-octene and 9-octadecene as detected by GC. Degradation of *Z*-content with **3** is likely due to secondary metathesis processes promoted by this very active catalyst.
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