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High *Trans* Kinetic Selectivity in Ruthenium-Based Olefin Cross-Metathesis through Stereoretention

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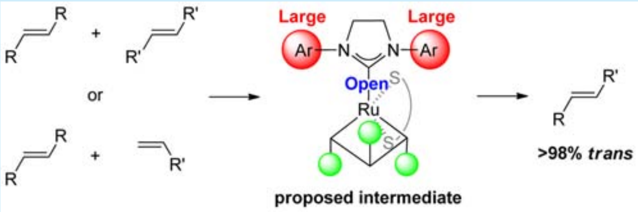
Ⓢ *Supporting Information*

ABSTRACT: The first kinetically controlled, highly *trans*-selective (>98%) olefin cross-metathesis reaction is demonstrated using Ru-based catalysts. Reactions with either *trans* or *cis* olefins afford products with highly *trans* or *cis* stereochemistry, respectively. This *E*-selective olefin cross-metathesis is shown to occur between two *trans* olefins and between a *trans* olefin and a terminal olefin. Additionally, new stereoretentive catalysts have been synthesized for improved reactivity.



Transition-metal-catalyzed olefin metathesis is widely accepted as a powerful synthetic methodology for the construction of carbon–carbon double bonds.[1] Broad functional group tolerance and straightforward implementation have allowed for the application of this technology to a variety of fields.[1a] In recent years, syntheses of well-defined catalysts and detailed mechanistic studies have resulted in Ru-,[2] W-, and Mo-based[3] complexes capable of *Z*-selective olefin metathesis. Mechanistically similar, each complex is posited to afford *cis*-olefins by sterically controlling the geometry of substituents decorating the key metallacyclobutane intermediate (Figure 1).[4]

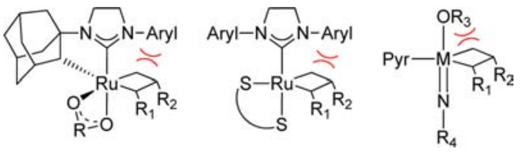


Figure 1. Key steric interactions in theorized metallocyclobutane intermediates resulting in *Z*-selectivity.

Though *trans*-olefins are usually thermodynamically preferred to *cis*-olefins, kinetically *E*-selective olefin metathesis remains challenging.[5] Allowing metathesis reactions to achieve equilibrium affords *trans*-enriched olefins that can subsequently be "purified" by *Z*-selective ethenolysis/alkenolysis to afford *trans*-olefins in high stereopurity (Figure 2).[6] While products are accessible in high purity, utilizing an equilibrium mixture of olefin as starting material limits the overall yield of the transformation. Furthermore, alkenolysis/ethenolysis introduces an additional purification step.

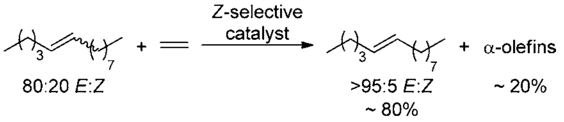


Figure 2. Stereoselective ethenolysis affording *E*-olefins.

Alternate methods for the stereoselective preparation of *trans*-olefins include well-established organic transformations (e.g., Birch-type reductions[7] and Wittig olefinations with stabilized ylides[8]), but most suffer from limited substrate compatibility, the need for specialized substrates, or the generation of stoichiometric amounts of waste. An important advance was the discovery of an efficient two-step transformation composed of catalytic *trans*-hydrosilylation of an alkyne followed by mild protodesilylation.[9] Subsequent improvements have afforded the direct semihydrogenation of alkynes to *E*-alkenes catalyzed by a frustrated Lewis pair,[10] an acridine-based PNP iron complex,[11] or an in situ mixture of Cp*Ru(COD)Cl/AgOTf.[12] Though each of these systems require an appropriate alkyne, Cp*Ru(COD)Cl/AgOTf has been demonstrated to tolerate a variety of reducible functionalities.

During the course of internal investigations with dithiolate-ligated ruthenium complexes (Figure 3), we observed that they were competent for transformations with *E*-olefins in contrast to other *Z*-selective catalysts. In fact, reactions of *E*-olefins afforded *E*-products in high stereopurity. Herein we report the first kinetically controlled, highly *trans*-selective olefin cross-metathesis.

Catalyst **1**[2g] was reacted with *cis* and *trans* isomers of 5-tetradecene (5C14) independently (Table 1). Unexpectedly, after 2 h at 40 °C, reactions of each starting material (>98%

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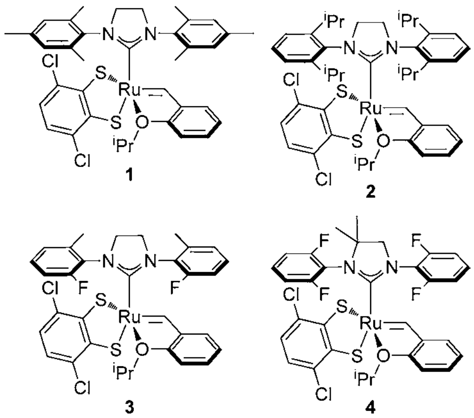
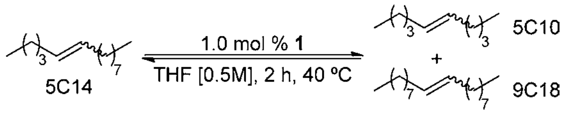


Figure 3. Ruthenium-based metathesis catalysts in this study.

Table 1. Self-Metathesis of 5-Tetradecene[a]



5C14	% 5C14 (*Z*/*E*)	%5C10 (*Z*/*E*)	%9C18
>98% cis	50 (97/3)	25 (97/3)	25
>98% trans	54 (4/96)	23 (5/95)	23

[a] General conditions: 5-tetradecene (0.150 mL, 0.588 mmol), **1** (4.5 mg, 0.0059 mmol), 1 mL of THF, 40 °C, 2 h. Yields and stereoselectivities were determined by gas chromatography.

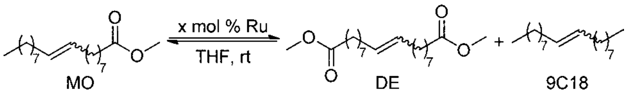
stereoisomerically pure) catalyzed by 1 mol % of **1** reached a near-equilibrium distribution of products while retaining the stereochemistry of the starting material in high fidelity.

Interested in expanding the substrate scope and improving catalyst activity, the self-metathesis of methyl 9-octadecenoate (MO) catalyzed by **1** and **2** (the sIPr analogue of **1**) was subsequently examined (Table 2). Catalyst **2** was remarkably efficient at catalyzing the self-metathesis of *cis*-methyl 9-octadecenoate as a 0.01 mol % (100 ppm) loading afforded an equilibrium distribution of product within 2 h with excellent stereoretention (>99% *Z*) (entry 1). Under these same conditions, no reaction was observed with *trans*-methyl 9-octadecenoate (entry 2). Catalyst **1** (0.5 mol %) only afforded 20% conversion of *cis*-methyl 9-octadecenoate and failed to afford any reaction with *trans*-methyl 9-octadecenoate after 2 h (entries 3 and 4). Fortunately, increasing the catalyst loading restored reactivity with *trans*-methyl 9-octadecenoate (entries 5−7), and after 20 h, **1** (7.5 mol %) afforded a near-equilibrium distribution of products with good stereoretention (96% *E*).[13] The small amount of erosion in *E*-selectivity after prolonged reaction times may be attributed to catalyst decomposition.

The disparity in the reactivity between the *cis* and *trans* isomers was also observed during investigations into the cross-metathesis of matched stereoisomers of 4-octene and 1,4-diacetoxy-2-butene (Table 3). Contacting a mixture of *cis*-1,4-diacetoxy-2-butene and *cis*-4-octene (4:1) with **1** (3.0 mol %) afforded *cis*-2-hexenyl acetate in 91% yield (>99% *Z*) (entry 1). Reactions between *trans*-1,4-diacetoxy-2-butene and *trans*-4-octene were considerably slower (entries 2 and 3), but after 72 h, a mixture of *trans*-1,4-diacetoxy-2-butene and *trans*-4-octene (4:1) with **1** (7.5 mol %) afforded *trans*-2-hexenyl acetate in 47% yield (>99% *E*).

Though transformations possessed high levels of stereoretention, the prolonged reaction times and elevated catalyst loadings required for substrates with *trans* stereochemistry warranted an improved catalyst. Inspired by the lack of reactivity between **2** and *trans* substrates,[14] and in accord with the proposed model (vide infra), we sought to examine the effect of reducing the steric bulk of the NHC ligand. Catalysts **3** and **4** were prepared, providing examples where *o*-methyl groups on the mesityl ring of the NHC ligand in **1** have been replaced with smaller fluorine atoms.

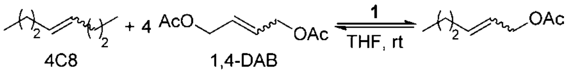
Table 2. Self-Metathesis of Methyl Oleate[a]



entry	Ru (mol %)	MO[c]	time (h)	% MO[c] (*Z*/*E*)	% DE[d] (*Z*/*E*)	% 9C18[e] (*Z*/*E*)
1	**2** (0.01)	>99% *Z*	0.5	64 (>99/1)	18 (>99/1)	18 (>99/1)
			1.5	53 (>99/1)	23 (>99/1)	24 (>99/1)
			2	51[b] (>99/1)	24[b] (>99/1)	24[b] (>99/1)
2	**2** (0.01)	>97% *E*	0.5	100 (<1/99)	ND[f]	ND[f]
			1.5	100 (<1/99)	ND[f]	ND[f]
			2	100 (<1/99)	ND[f]	ND[f]
3	**1** (0.5)	>99% Z	0.5	90 (>99/1)	5 (>99/1)	5 (>99/1)
			1.5	84 (>99/1)	8 (>99/1)	8 (>99/1)
			2	80 (>99/1)	10 (>99/1)	10 (>99/1)
4	**1** (0.5)	>97% *E*	2	100 (<1/99)	ND[f]	ND[f]
5	**1** (2.5)	>97% *E*	4	98 (<1/99)	1 (<1/99)	1 (<1/99)
			20	92 (<1/99)	4 (<1/99)	4 (<1/99)
6	**1** (5.0)	>97% *E*	4	93 (<1/99)	3 (<1/99)	3 (<1/99)
			20	72 (1/99)	14 (3/97)	14 (3/97)
7	**1** (7.5)	>97% *E*	4	80 (<1/99)	10 (<1/99)	10 (<1/99)
			20	51[b] (4/96)	24[b] (4/96)	24[b] (4/96)

[a] General conditions: methyl-9-octadecenoate (0.150 mL, 0.442 mmol), 1 mL of TMF, rt. Yields and stereoselectivities were determined by GC. [b] Isolated yield (stereoselectivity determined by GC). [c] MO = methyl-9-octadecenoate. [d] DE = "diester" = dimethyl 9-octadecenedioate. [e] 9C18 = 9-octadecene. [f] Not detected.

Table 3. Cross-Metathesis of 4-Octene and 1,4-Diacetoxy-2-butene[a]

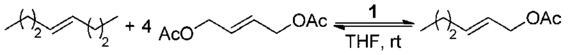


entry	1 (mol %)	4C8[b]/1,4-DAB[c]	time (h)	% conv	% yield	Z/E
1	3.0	cis/cis	0.25	54	49	>99/1
			1.5	94	91	>99/1
			2.5	95	91	>99/1
			5	95	91 (83)	>99/1
2	5.0	trans/trans	1	9	6	<1/99
			2	15	11	<1/99
			4	19	17	<1/99
			5	22	20	<1/99
			72	33	31	<1/99
3	7.5	trans/trans	1	15	11	<1/99
			2	21	19	<1/99
			4	30	27	<1/99
			5	33	31 (25)	<1/99
			72	50	47	<1/99

[a] General conditions: 4-octene (0.100 mL. 0.32 mmol), 1,4-diacetoxy-2-butene (0.406 mL. 2.55 mmol), 0.5 mL of THF, rt. Yields and stereoselectivities were determined by gas chromatography (isolated yields in parentheses). [b] 4C8 = 4-octene. [c] 1,4-DAB = 1,4-diacetoxy-2-butene.

To evaluate these new catalysts, a mixture of *trans*-1,4-diacetoxy-2-butene and *trans*-4-octene (4:1) was combined with ruthenium catalyst (3.0 mol %) to yield *trans*-2-hexenyl acetate (Table 4). After 72 h, **1** afforded 13% yield of *trans*-2-hexenyl acetate (entry 1), whereas **3** and **4** afforded improved yields of 24 and 28%, respectively (entries 2–4).

Table 4. Cross Metathesis of *trans*-4-Octene and *trans*-1,4-Diacetoxy-2-butene[a]

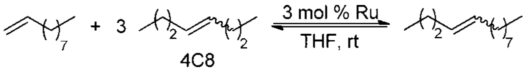


entry	Ru	time (h)	% conv	% yield	Z/E
1	**1**	1	0	0	ND[b]
		2	2	2	<1/99
		4	5	4	<1/99
		72	15	13	<1/99
2	**3**	1	2	2	<1/99
		2	5	5	<1/99
		4	12	11	<1/99
		72	25	24	<1/99
3	**4**	1	4	4	<1/99
		2	7	7	<1/99
		4	15	14	<1/99
		72	29	28	<1/99

[a] General conditions: *trans*-4-octene (0.050 mL. 0.32 mmol), *trans*-1,4-diacetoxy-2-butene (0.203 mL, 1.27 mmol), Ru (0.0096 mmol, 3 mol %), 1 mL of THF, rt. Yields and stereoselectivities were determined by gas chromatography. [b] Not determined.

Additionally, this family of catalysts was evaluated for the more demanding cross-metathesis of 1-decene and 4-octene. Mitigating catalyst decomposition in the presence of terminal olefin in addition to outpacing the self-metathesis of the desired product was challenging. Reactions were conducted by combining a mixture of 1-decene and *cis*-4-octene (1:3) with **1**–**4** (3.0 mol %) in tetrahydrofuran (2.0 mL) (Table 5). After 1 h, **2** afforded a 75% yield of *cis*-4-tridecene with >98% *Z* (entry 1). Prolonged exposure to reaction conditions eroded the observed selectivity. Catalysts **1**, **3**, and **4** were less active but afforded 54–58% yield of *cis*-4-tridecene with exceptional stereoretention (>99% *Z*) (entries 3, 5, and 7). Self-metathesis of *cis*-4-tridecene to afford 9-octadecene and 4-octene was the major contributor to the fact that conversions were on average 25–30% higher than observed yields. As previously observed, reactions with *trans*-4-octene were less productive. Unlike reactions of *cis*-4-octene, the disparity between conversion and yield is largely attributed to isomerization of 1-decene. After 4 h, catalyst **2** afforded 4% yield but managed to convert 92% of the starting 1-decene (entry 2). Stereoretention is likely poor due to the significant amount of isomerization observed. Catalyst **1** afforded a marginally better 7% yield with significantly less isomerization though stereoretention was excellent (>99% *E*) (entry 4). Yields were noticeably better in reactions conducted with catalysts **3** and **4**, affording 29 and 31% yield of *cis*-4-tridecene, respectively, with excellent stereoretention (>99% *E*) (entries 6 and 8).

Table 5. Cross-Metathesis of 1-Decene and 4-Octene[a]



entry	Ru	4C8[b]	time (h)	% conv	% yield	Z/E
1	**2**	*cis*	1	90	75	98/2
			2	90	75	97/3
			4	89	74	96/4
2		*trans*	1	90	3	12/88
			2	91	4	12/88
			4	92	4	13/88
3	**1**	*cis*	1	84	55	>99/1
			2	85	55	>99/1
			4	84	58	>99/1
4		*trans*	1	36	7	<1/99
			2	36	7	<1/99
			4	36	7	<1/99
5	**3**	*cis*	1	82	58	>99/1
			2	87	59	97/3
			4	88	57	97/3
6		*trans*	1	50	21	<1/99
			2	54	26	<1/99
			4	53	29	<1/99
7	**4**	*cis*	1	66	42	>99/1
			2	74	49	>99/1
			4	79	54	>99/1
8		*trans*	1	43	19	<1/99
			2	51	25	<1/99
			4	53	31	<1/99

[a] General conditions: 1-decene (0.050 mL, 0.26 mmol), 4-octene (0.125 mL. 0.79 mmol), Ru (0.0078 mmol), 2 mL of THF, rt. Yields and stereoselectivities were determined by GC. [b] 4C8 = 4-octene.

Maintaining the side-bound geometry of the metallocyclobutane requisite for these catalysts to facilitate *Z*-selective transformations, the observed *E*-selectivity is proposed to arise from the ability of the substituent at the β position of the metallacycle to point “up” into the “open” space located in front of the plane containing the N–C–N bonds of the NHC and between the two *N*-aryl groups (Figure 4). Due to steric repulsion, substituents at the α positions are forced down, away

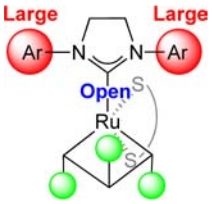


Figure 4. Proposed metallacyclic intermediate in *trans*-selective cross-metathesis.

from the NHC. Provided the disubstituted olefin used for cross-metathesis initially has *trans* stereochemistry, the kinetic product should also have *trans* stereochemistry. Comparison of the reactivities of catalysts **1**−**4** supports this model. As the size of the *ortho* substituents of the *N*-aryl groups decreases (F < Me < iPr), conversions tend to increase, presumably due an increase in "open" space.

In summary, we have demonstrated the first kinetically controlled, highly *trans* selective system for olefin cross-metathesis. Catalysts **1**, **3**, and **4** react with either *E* or *Z* olefins stereoretentively to yield *E* and *Z* products, respectively, with high stereopurity. Reactions of *E*-olefinic hydrocarbons proceeded more rapidly than reactions of *E*-olefins bearing ester functionalities; however, both substrate classes afforded high stereoselectivities. The reaction of *E*-olefins with terminal olefins was also demonstrated to occur with high *E*-selectivity. For each reaction examined, *cis* olefins reacted more quickly than their *trans* analogues. Catalysts **3** and **4**, bearing smaller *ortho* substituents on the *N*-aryl group of the NHC, were prepared, and catalytic reactions resulted in improved yields while retaining high *E*-stereoselectivity. These findings support the proposed model whereby *trans*-olefinic substrates are increasingly compatible with catalysts as steric encumbrance is reduced.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00031.

Experimental procedures, preparations for complexes **2**−**4** and compound characterizations (PDF)

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Notes

The authors declare no competing financial interest.

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(13) Results similar to those in Table 2, entry 7, were attainable by conducting the reaction with 1 mol % of **1** at 45 °C for 5 h.

(14) The self-metathesis of *trans*-methyl-9-octadecenoate conducted in the presence of 7.5 mol % **2** did not afford any desired product.