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Catalyst versus Substrate Control of Forming (*E*)-2-Alkenes from 1-Alkenes Using Bifunctional Ruthenium Catalysts

Erik R. Paulson, Esteban Delgado, III, Andrew L. Cooksy, and Douglas B. Grotjahn*

San Diego State University, 5500 Campanile Drive, San Diego, California 92182-1030, United States

Supporting Information

ABSTRACT: Here we examine in detail two catalysts for their ability to selectively convert 1-alkenes to (*E*)-2-alkenes while limiting overisomerization to 3- or 4-alkenes. Catalysts **1** and **3** are composed of the cations CpRu(κ^2-PN)(CH_3CN)$^+$ and Cp*Ru(κ^2-PN)$^+$, respectively (where PN is a bifunctional phosphine ligand), and the anion PF_6^-. Kinetic modeling of the reactions of six substrates with **1** and **3** generated first- and second-order rate constants k_1 and k_2 (and k_3 when applicable) that represent the rates of reaction for conversion of 1-alkene to (*E*)-2-alkene (k_1), (*E*)-2-alkene to (*E*)-3-alkene (k_2), and so on. The k_1:k_2 ratios were calculated to produce a measure of selectivity for each catalyst toward monoisomerization with each substrate. The k_1:k_2 values for **1** with the six substrates range from 32 to 132. The k_1:k_2 values for **3** are significantly more substrate-dependent, ranging from 192 to 62 000 for all of the substrates except 5-hexen-2-one, for which the k_1:k_2 value was only 4.7. Comparison of the ratios for **1** and **3** for each substrate shows a 6−12-fold greater selectivity using **3** on the three linear substrates as well as a *>230-fold* increase for 5-methylhex-1-ene and a 44-fold increase for a silyl-protected 4-penten-1-ol substrate, which are branched three and five atoms away from the alkene, respectively. The substrate 5-hexen-2-one is unique in that **1** was more selective than **3**; NMR analysis suggested that chelation of the carbonyl oxygen can facilitate overisomerization. This work highlights the need for catalyst developers to report results for catalyzed reactions at different time points and shows that one needs to consider not only the catalyst rate but also the duration over which a desired product (here the (*E*)-2-alkene) remains intact, where **3** is generally superior to **1** for the title reaction.

KEYWORDS: *alkene, isomerization, monoisomerization, selectivity ratio, E-selective, kinetic control*

INTRODUCTION

The C═C bond is one of the most useful and versatile functional groups in organic chemistry, and alkenes serve as starting materials for a wide variety of classical transformations that provide functionality to everyday products. Alkenes are present in pharmaceutical intermediates,[1] used as feedstocks in the plastic and polymer industry,[2] and found in many food additives and scents in the flavor and fragrance industries.[3−5] The presence, position, and geometry of the C═C bond can all greatly influence polymer structure and texture as well as flavor and fragrance olfactory and sensory properties, to highlight just two important application areas.

While classical alkene transformations have been known since the 1800s, the last 10−20 years have seen a renewed interest in providing transition metal catalysts to expand the diversity of alkene reaction partners. One important goal is selective isomerization of alkenes to produce unique isomeric compounds that expand the scope of other synthetic transformations. An ideal selective alkene isomerization process would produce a single isomer in high yield (>95%) in order to simply purification and minimize waste consisting of unwanted isomers.[6] One of the greatest challenges during catalytic alkene isomerization is avoiding the formation of multiple isomers. In the example of 1-heptene, a nonselective isomerization would provide the thermodynamic ratio of the five possible isomers: 1-heptene (0.43%), (*Z*)-2-heptene (11.7%), (*E*)-2-heptene (48.5%), (*Z*)-3-heptene (6.94%), and (*E*)-3-heptene (32.4%).[7] With heptene and other linear alkene substrates, the considerable challenge of controlling the formation of a single isomer over another is clear. In general, catalytic alkene isomerization processes can be divided into two classes: isomerizations that are allowed to proceed until they are under thermodynamic control and those operating under kinetic control. Under thermodynamic control, the selectivity is entirely governed by the nature of the substrate. Under kinetic control, either the nature of the catalyst or the nature of the substrate may be more important in determining the selectivity between various isomers. Both thermodynamically and kinetically controlled reactions are important for synthetic chemists, but the greatest challenge is developing a selective catalyst for alkene mixtures far away from equilibrium compositions.

For unfunctionalized alkenes, the degree of substitution is the main determinant of thermodynamic stability among positional isomers, with increasing substitution providing more stability and therefore a higher fraction of that isomer in the mixture at equilibrium. Long-chain linear alkenes contain several disubstituted positions of similar stability, but with branched alkenes, the trisubstituted position(s) (e.g., 2-methyl-2-pentene in a 2-methylpentene isomer mixture) will be significantly more prevalent (e.g., 2-methyl-2-pentene constitutes 75−79% of the 2-methylpentene isomeric mixture at equilibrium).[8] The typical *E*/*Z* ratio for unsubstituted linear alkenes is around 4:1 in favor

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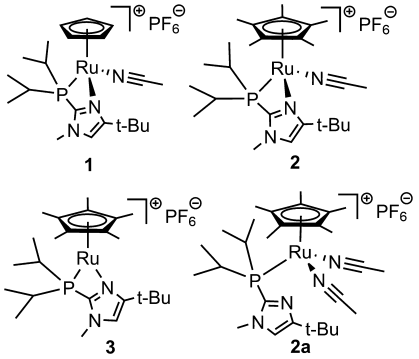
of the *E* isomer (i.e., (*E*)-2-heptene:(*Z*)-2-heptene = 4.14:1). The formation of significant amounts of several positional and geometric isomers at equilibrium for most substrates highlights the need for kinetically controlled isomerization.

Kinetically controlled isomerization occurs when the catalysis produces certain isomers at higher rates than others, leading to an initial ratio that is higher than the equilibrium ratio. The ideal catalyst for kinetically controlled isomerization should rely on specific interactions between the catalyst and substrate (either repulsive steric interactions or attractive binding or dipole interactions) to influence substrate binding and/or a particular step in the catalytic cycle in order to favor one geometric or positional isomer over another.

Although several transition metal catalyst systems have been developed to provide general control over positional and/or geometric selectivity during the isomerization of alkenes, catalysts **1**−**3**[9−11] (Chart 1) have shown unparalleled and general selectivity in the production of (*E*)-alkenes. In particular, **1** has been found to be a very effective partner with other catalysts in sequential and tandem processes to produce a number of high-value compounds. Some examples include the synthesis of (*Z*)-5-decene from (*E*)-3-hexene in a tandem isomerization−metathesis (ISOMET) developed by us in collaboration with the Schrock group,[12] an isomerization−oxidation sequence developed by the Stoltz group to synthesize unnatural amino acids,[13] sequential isomerization−metathesis processes developed by the Fogg and Grela groups to produce cinnamate esters[14] and musk macrocycles,[15] respectively, and an isomerization−allylation sequence developed by the Murakami group to produce *anti*-1,2-oxaborinan-3-enes from aldehydes and 1,1-di(boryl)alk-3-enes.[16] These catalyst systems take advantage of several different features of **1**. The cinnamate syntheses outlined by Fogg and the isomerization−oxidation process reported by Stoltz exploit the high efficiency of catalyst **1**. The isomerization−oxidation process also utilizes the ruthenium metal in **1** in the second step, which upon oxidation by $NaIO_4$ becomes the oxidant. The Murakami isomerization−allylation sequence and the Schrock ISOMET strategy both take advantage of the propensity of **1** to produce *E* isomers, in the former case by influencing the final product selectivity and in the latter case by ensuring that no intermediate *Z* isomers are present prior to metathesis. The isomerization−ring-closing metathesis (RCM) system outlined by Grela uses very low concentrations of **1** and careful monitoring to selectively monoisomerize two long terminal alkene chains, typically in ∼82% yield, that suffer from overisomerization. Subsequent RCM creates the musk macrocycles. The Grela process and other similar applications demand better control over the positional isomerization than catalyst **1** provides, and here **2** and the nitrile-free version **3** would be most useful. Complexes **2** and **3** are more recent additions to the isomerization catalyst literature, and both are capable of maintaining the geometric selectivity of **1** while improving the positional selectivity, resulting in reported (*E*)-2-alkene yields of 95−97% from linear terminal alkenes.[10,11,17] Complexes **2** and **3**, along with an iridium complex recently reported by Huang,[18] offer the highest general combined positional and geometric selectivity for alkene isomerization currently reported in the literature.

Chart 1. Isomerization Catalysts 1−3



Geometric and positional selectivity present different challenges. Starting with a terminal 1-alkene, either the (*E*)-2- or (*Z*)-2-alkene is formed. Because the two geometric products originate from a common starting terminal alkene, the transition state(s) for forming the *E* product must be significantly lower in energy (by >3 kcal mol^{-1}) than the one(s) for forming the *Z* product. Previous studies by our group,[19,20] Fang,[21] and Miller[22] have asserted that pendent heteroatoms, which may also behave as internal bases, can contribute to both high activity and high selectivity in alkene isomerization. Our ongoing comprehensive computational study is expected to clarify the role of the ligand pendent base in facilitating the efficiency and selectivity of **1**, and results will be published in due course.

Positional selectivity, on the other hand, presents a different set of challenges. There is no isomerization reaction that will directly transform the 1-alkene to the 3-alkene; instead, the 2-alkene must first be produced as an intermediate. Importantly, the intermediate 2-alkene will never be consumed completely unless there is some functional group that strongly stabilizes the 3-alkene, since internal unfunctionalized alkenes are generally similar to each other in energy. The consequence is that mixtures of internal isomers will result unless one can "trap" the (*E*)-2- or (*Z*)-2-alkene before it overisomerizes. A successful catalyst for monoisomerization should meet two requirements: (1) a high rate of isomerization of the 1-alkene to the 2-alkene (which we will define as k_1; see below) and (2) a significantly lower relative rate of isomerization of the 2-alkene to the 3-alkene (denoted as k_2; see below) in order to obtain a high yield of the 2-alkene. Previous work has shown that catalyst **1** satisfies the first requirement, whereas the catalyst mixture **2** + **2a** meets both requirements. However, because **2** + **2a** was much slower than **1**, we developed catalyst **3**, which kept the same selectivity of **2** + **2a** but drastically improved the rate of conversion by >400 times.

When catalysts (including **1**−**3**) are touted for their selectivity (or maligned for their lack of selectivity), a single yield is frequently reported. Sometimes the reported yield is the maximum yield produced by the catalyst after monitoring of the reaction at several time points, but the reported yield can also simply be a single number obtained after a set period of time. However, in a kinetically controlled isomerization process, the ratios of isomers are in constant flux. From a practical point of view, it would be useful to observe the isomerization process over time to better understand the catalyst behavior. More rigorous observation and analysis can allow us to more accurately determine not only the maximum yields of various isomers but also their persistence. Chemists can then decide which catalyst best suits their purpose. Our work below describes the monitoring and analysis of a number of substrates subjected to isomerization with catalysts **1** and **3** in an effort to provide a practical quantitative comparison of selectivities for the user.

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EXPERIMENTAL SECTION

All of the reactions were performed under dry nitrogen using a combination of Schlenk line and glovebox techniques. Acetone was purchased from Fisher Chemicals, and acetone-d_6 was obtained from Cambridge Isotope Laboratories. 1-Hexene (99%) was purchased from Oakwood Chemical. 1-Octene, 4-penten-1-ol, 5-hexen-2-one, 9-decen-1-ol, and 5-methyl-1-hexene were purchased from Acros Organics. Catalysts **1** and **3** were synthesized as described in the literature.[9,11] All of the solvents and substrates were deoxygenated prior to use by bubbling nitrogen gas through the liquid. NMR tube reactions were performed in resealable J. Young NMR tubes. All of the NMR data were measured at room temperature (22−25 °C). Varian spectrometers were used: a 500 MHz INOVA (500 MHz listed below for ^{1}H = 499.940 MHz) and a 400 MHz Varian NMR-S (400 MHz listed below for ^{1}H = 399.763 MHz). For all of the reactions, a 2.048 s acquisition time, 10 s relaxation delay, and 15° pulse width were used. ^{1}H chemical shifts are referenced to nonvolatile tetrakis(trimethylsilyl)methane as an internal standard (0.264 ppm). All of the isomerization reactions were carried out at a substrate concentration of 0.500 M. The catalyst loadings relative to substrate were chosen to keep the conversion of the terminal alkene over time relatively consistent among catalysts. For a typical isomerization reaction, 10−11 spectra were acquired at time points spread out over the initial 60 min, followed a gradual increase in time between spectra to reflect the lower reaction rates after consumption of the terminal alkene substrate. The spectra were then processed using the MestreNova processing software. The spectra were manually integrated after an automatic global and metabonomics phase correction and a Whittaker smoother baseline correction. Integrations were referenced to the internal standard (tetrakis-(trimethylsilyl)methane), which was set to 10.0 integral units. One or two signals were chosen to represent each isomer, and their integrations were compared to the initial integration values for the terminal alkene (set to 100%) in order to calculate the percentage of each isomer in the mixture at each time point.

Examples of Reactions. All of the manipulations were conducted in a glovebox. To prepare the stock solution of catalyst **1**, in a 1 dram glass vial fitted with a Teflon-lined cap, **1** (3.0 mg, 0.0050 mmol) was weighed out, and enough acetone-d_6 was added to bring the solution to a total volume of 1.0 mL, forming a 0.0050 M solution of **1**. To prepare the stock solution of catalyst **3**, in a 1 dram glass vial fitted with a Teflon-lined cap, **3** (9.5 mg, 0.015 mmol) was weighed out, and enough acetone-d_6 was added to bring the solution to a total volume of 1.0 mL, forming a 0.015 M solution of **3**.

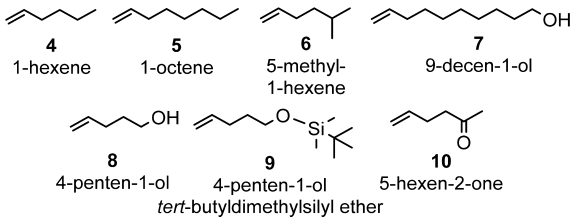
*Substrate **4** and Catalyst **1**.* In a resealable J. Young tube in a glovebox, the internal standard $(Me_3Si)_4C$ (~0.2 mg) and 1-hexene (42.3 mg, 0.503 mmol) were combined in a mixture with enough deoxygenated acetone-d_6 to obtain a total volume of 900 μL, and an initial NMR spectrum was acquired. Back in the glovebox, to this mixture was added an aliquot of the stock solution of **1** (100 μL, 0.000500 mmol). The reaction was kept at room temperature and monitored.

*Substrate **4** and Catalyst **3**.* In a resealable J. Young tube in a glovebox, the internal standard $(Me_3Si)_4C$ (~0.2 mg) and 1-hexene (42.1 mg, 0.503 mmol) were combined in a mixture with enough deoxygenated acetone-d_6 to obtain a total volume of 900 μL, and an initial NMR spectrum was acquired. Back in the glovebox, to this mixture was added an aliquot of the stock solution of **3** (100 μL, 0.00150 mmol). The reaction was kept at room temperature and monitored.

RESULTS AND DISCUSSION

Substrates **4**−**10** (Chart 2) represent a sample of functionalized and unfunctionalized linear and branched alkenes, which were chosen to provide a variety of steric and electronic environments. The unfunctionalized substrates **4** and **5** have different numbers of possible isomers (five for **4** and seven for **5**), but both exhibit no branching or other increased steric constraints that would lead to a strong kinetic bias. *It could be argued that unfunctionalized linear alkenes **4** and **5** are the most challenging substrates to selectively isomerize because all of the selectivity must derive from the catalyst.* Branched substrate **6** introduces steric demand in the form of a methyl group at the 5-position. The other four substrates **7**−**10** contain functional groups that are capable of conjugating with the alkene, which presents a challenge of its own, as the increased stability of the conjugated isomers should in theory lower the kinetic barrier to further isomerization.

Chart 2. Isomerization Substrates 4−10



Isomerizations were carried out for **4**−**10** with each catalyst (**1** or **3**), resulting in a total of 14 runs, all at room temperature. Each isomerization was designed by the choice of an appropriate catalyst loading to give full conversion of the 1-alkene within 30 min. For substrates **4**−**9**, eight or nine spectra were obtained within the first 30 min in order to reliably capture the maximum yield of monoisomerized product and provide sufficient information about the rate of initial isomerization. An effort was made to gather spectra at longer times, in some cases as much as 200 h (8 days) later, in order to allow isomeric mixtures to reach equilibrium, but this was not practically feasible for all of the reactions. Notably, despite the high catalyst loading of **3** (2.0 mol %) for the isomerization of **10**, the reaction still required >200 min for full conversion of the starting alkene. The catalyst loadings and maximum yields of the monoisomerized *E* isomers are indicated in Table 1, and the early reaction profiles (first 120−180 min) for all 14 runs are shown in Figures 1−7 (the full reaction profiles are available in the Supporting Information).

One significant finding shown in Table 1 is that reactions with **4**−**9** reached >90% of monoisomerized product at their maximum with both catalysts. Yields similar to those shown in Table 1 have been reported for catalyst **3** (and the related nitrile complexes **2** + **2a**), but yields of >90% have not been seen in previously published studies with catalyst **1** for substrates that do not contain significant branching or functionality near the isomerization site.[10,17,23] The higher yields encountered here are likely due to the low catalyst loading and higher frequency of data collection early in the reaction.

What is clear from Table 1 is that the level of positional selectivity achievable with catalyst **1** can be higher than what has been reported but that very careful reaction monitoring would be necessary to know when to stop each reaction. For the

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Table 1. Time Points of the Reactions of 4−10 with Catalysts 1 and 3 Where the Percentage of Monoisomerized Alkene Is Highest (Maximum)

Substrate	Catalyst	Catalyst Loading (mol %)	Time (min)	1-alkene[a] (%)	(*E*)-2-alkene[a] (maximum)	(*E*)-3-alkene[a]
4	**1**	0.1	15	1.7	90.5	7.5
	3	0.3	40	2.0	96.1	2.0
5	**1**	0.1	12	3.3	91.3	3.9
	3	0.3	30	2.2	96.1	1.6
6	**1**	0.1	13	1.3	97.8	0.9
	3[b]	0.3	45	1.2	98.7	0.0
7	**1**	0.1	12	5.6	91.3	3.6
	3	0.3	12	2.9	97.1	0.0
8	**1**	0.2	90	2.4	92.1	4.0
	3	0.3	180	2.1	96.8	0.6
9	**1**	0.1	30	2.6	97.1	3.4
	3	0.3	40	4.7	95.7	0.5
10	**1**	0.1	120	5.2	85.2	9.1
	3	2.0	120	11.5	67.9	21.0

[a]For clarity of comparison, all of the terminal alkenes are called 1-alkenes even though some (e.g., 5-hexen-2-one) are numbered differently in the IUPAC system. [b]A second experiment was performed at a catalyst loading of 0.9 mol % and gave similar maximum conversion at 10 min.

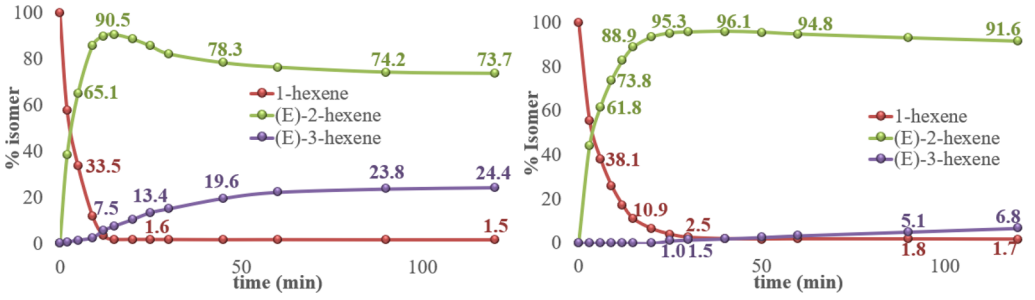

Figure 1. Isomerization of **4** with catalysts **1** (left) and **3** (right).

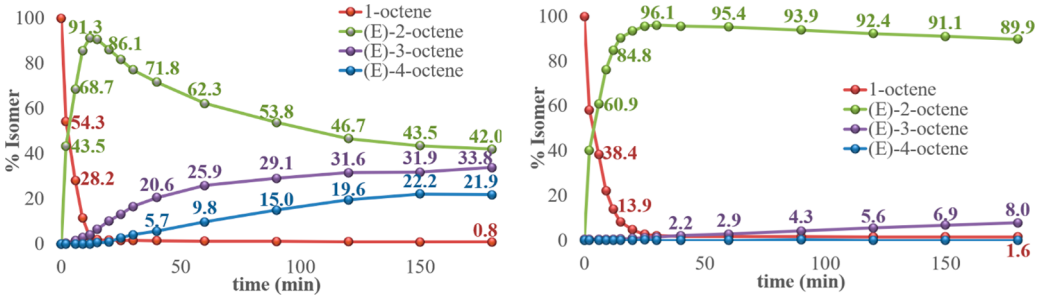

Figure 2. Isomerization of **5** with catalysts **1** (left) and **3** (right).

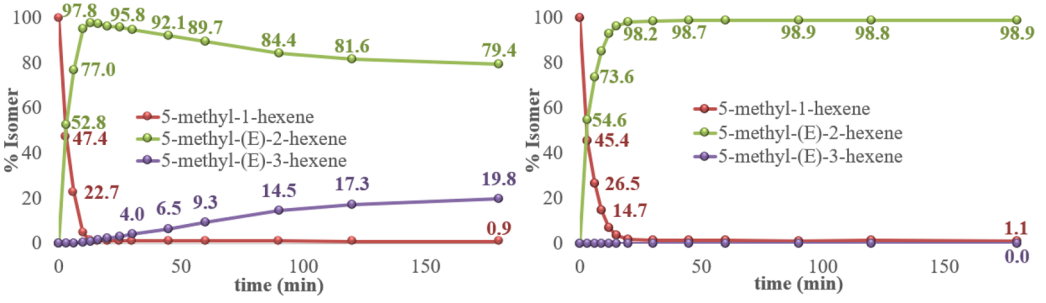

Figure 3. Isomerization of **6** with catalysts **1** (left) and **3** (right)

practical chemist, the variability in product distribution is precisely why a single reported measurement fails to capture the likelihood of isolating the product in a similar yield. Of similar importance as a high maximum yield is the *duration* with which that isomer remains at high yield. Both of these characteristics arise from the relative reaction rates of 1- to 2-alkene conversion and 2- to 3-alkene conversion. With that in mind, our first attempt to compare the selectivities of catalysts **1** and **3** focuses on two parameters: the first is a comparison of the times to reach 50% conversion of the terminal and monoisomerized alkenes, as

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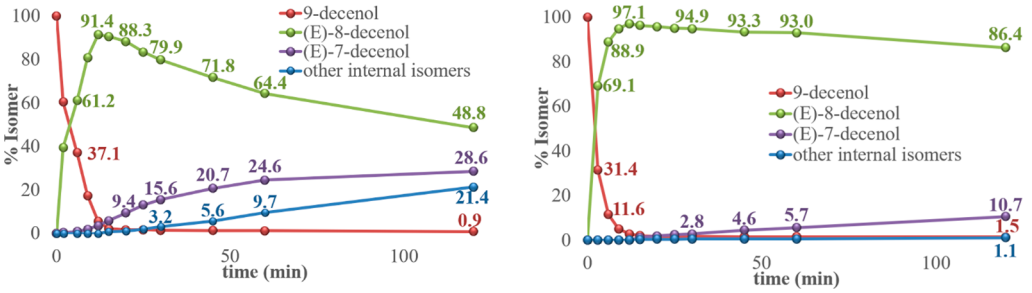

Figure 4. Isomerization of **7** with catalysts **1** (left) and **3** (right).

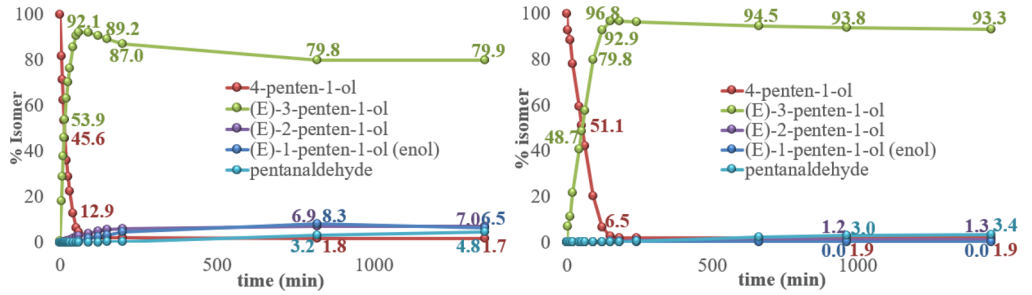

Figure 5. Isomerization of **8** with catalysts **1** (left) and **3** (right).

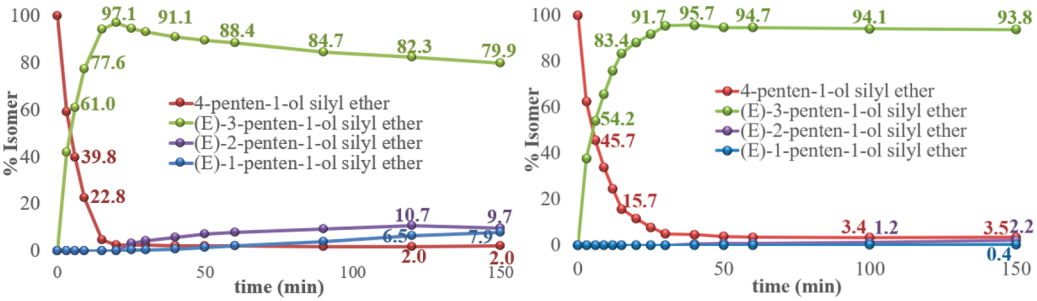

Figure 6. Isomerization of **9** with catalysts **1** (left) and **3** (right).

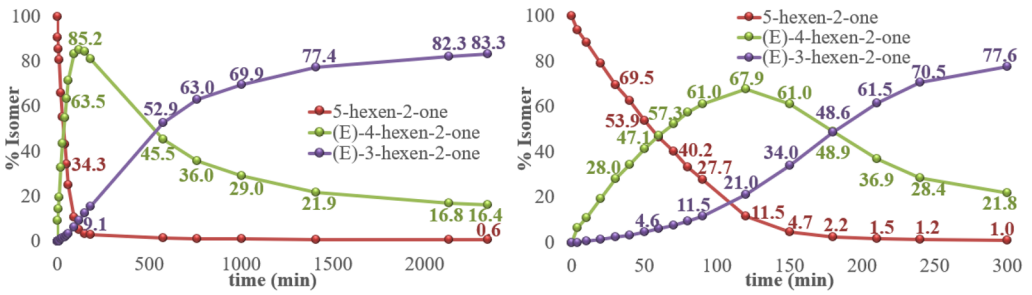

Figure 7. Isomerization of **10** with catalysts **1** (left) and **3** (right).

a way of measuring half-life; the second is the ratio of the time required for the yield to reach 90% to the time that the monoisomerized product remains >90% of the mixture, as both a practical measure and a quantifiable determination of selectivity. Since the ratio is a relative comparison of the two measurements and both measurements scale with catalyst loading, the ratios should remain constant regardless of catalyst loading. The results are shown in Table 2.

Ratios comparing relative 50% conversion times for the first and second isomerizations were calculated for substrates **5**, **7**, **9**, and **10**. Values for 50% conversion times were not determined for substrates **4** and **6** (because of equilibrium position) and **8** (because of likely catalyst deactivation),[24] where deactivation can generally be overcome to complete reactions using higher catalyst loadings. The duration at >90% was not determined for substrate **10** because neither catalyst was selective enough to reach 90%. According to the data presented in Table 2, the selectivity ratios ranged from 6 to 20 in favor of catalyst **3** for all of the substrates except **6** and **10**. Substrates **5**, **7**, and **9** were compared using both ratios, and a significant disparity between the two was seen for all three substrates, indicating one of the several shortcomings of using these two particular parameters for selectivity analysis. Another challenge lies in the fact that none of the time points measured for any of the 14 reactions pinpointed precisely when the reactions reached 50% 1- or 2-alkene or 90% 2-alkene, so estimations had to be made that

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Table 2. Selectivity Ratios with Substrates 4−10: 50% Conversion and 90% Duration (All Times Are in Minutes)

Substrate	Cat.	Time of 50% conv of 1-alkene	Time of 50% conv of (*E*)-2-alkene	50% ratio (*E*)-2:1	Time to reach >90% (*E*)-2	Duration at >90% (*E*)-2	>90% Ratio
4	**1**	~2.5	N/A	-	12	5	0.42
	3	~3	N/A	-	~16	134	8.4
Selectivity	**3:1**			-			**20**
5	**1**	~2.5	~105	42	>9	<11	1.2
	3	~3	~2500	830	~15	~165	11
Selectivity	**3:1**			**20**			**9.1**
6	**1**	~2.5	N/A	-	9	60	6.7
	3	~2.5	N/A	-	3	~4000	1300
Selectivity	**3:1**			-			**194**
7	**1**	~4	~110	28	<12	<11	0.91
	3	~2	~1200	600	~7	~90	13
Selectivity	**3:1**			**21**			**14**
8	**1**	~14	N/A	-	~48	~90	1.9
	3	~52	N/A	-	~110	>4100	>>37
Selectivity	**3:1**			-			**>>20**
9	**1**	4.5	1000	220	~12	~38	3.2
	3	~6.5	~15000 (?)[a]	2300	~23	~470	20
Selectivity	**3:1**			**10**			**6.3**
10	**1**	~33	~500	15	N/A	N/A	-
	3	~55	~170	3.1	N/A	N/A	-
Selectivity	**3:1**			**0.21**			-

[a]See Figure 6. This was a very slow reaction.

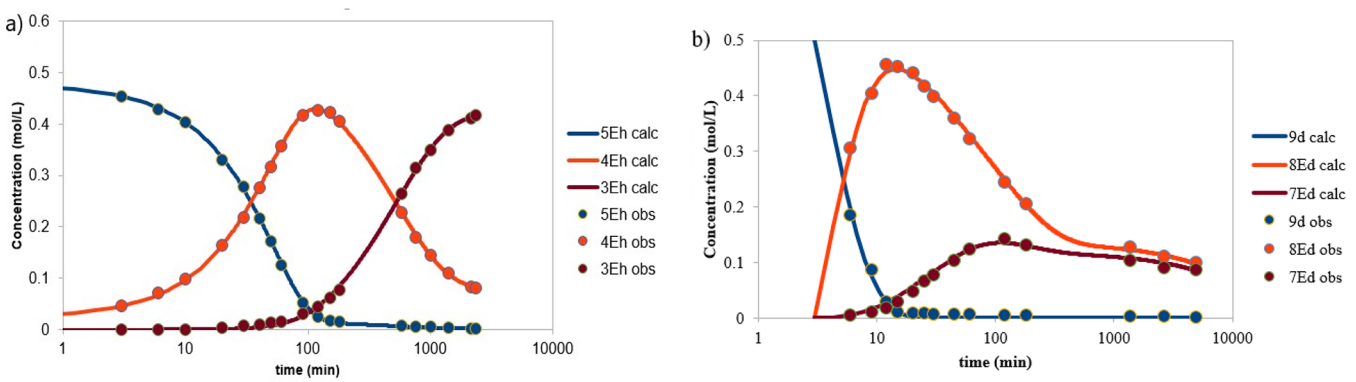

Figure 8. Observed time-dependent concentrations and fitted profiles for the (a) **10**/**1** and (b) **7**/**1** systems. The horizontal time axis is in logarithmic format to more clearly display the evolution of the concentrations in different time regimes.

introduced large sources of error. The error could be mitigated by collecting a larger number of time points, but the long duration of the experiments prohibited that option. Most importantly, both measures are rather arbitrary: half-life can only be legitimately related to the rate if the reaction is first-order, as is often not the case in catalysis by **1** and **3** (see below), and the 90% threshold is only useful if the isomer in question reaches that value in the course of both isomerizations. Therefore, a more sophisticated analysis is required: a direct comparison of rate constants generated from modeling of the kinetics of the reaction.

Rate constants were obtained by least-squares fitting to the time-dependent NMR data using the FORTRAN program *rate.f* developed and used by the Cooksy group. The program employs a fourth-order Runge−Kutta numerical integration scheme[25] to model the kinetics and various numerical recipes for least-squares fitting and uncertainty analysis.[26] More details on the fitting procedure and code are provided in the Supporting Information.

For each system, the data may be sensitive to different functional forms of the reaction rate law, determining which rate constants can be resolved and whether a given step is better modeled as a unimolecular or bimolecular process (further background is provided in the Supporting Information). Therefore, to fit the rate constants, several mechanisms were tried for each system, always beginning with the simplest model of a series of irreversible first-order reaction steps. Reversible steps, the catalyst concentration, and the reaction complex concentration were included in any given mechanism only if they reduced the overall standard deviation of the fit and resulted in well-determined rate constants. The resulting best-fit rate constants and mechanisms are given in Table S16, and results are graphed for two representative cases in Figure 8. We emphasize that more than one mechanism may result in fits of similar quality, and therefore, the uncertainties attached to the values indicate only the quality of the fit for the given mechanism.

The final fits to the data from substrates **4** and **5** are the most straightforward, as they were adequately modeled by first-order steps (some reversible) throughout. For substrate **7**, (*E*)-7-decenol is the last identified alkene in the progression of the reaction, but it continues to react to form several isomers. With

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Table 3. Selectivity Ratios Comparing Relative Rate Constants for Substrates 4−7, 9, and 10 with Catalysts 1 and 3 (k_x Refers to the Conversion of the x-Alkene to the $(x+1)$-Alkene)

Substrate	Cat.	k_1 (min^{-1})	k_2 (min^{-1})	k_1:k_2	k_3 (min^{-1})	k_2:k_3
4	**1**	0.326	0.01126	28.95	N/A	-
	3	0.1292	0.000674	191.69	N/A	-
Selectivity	**3:1**			**6.62**		-
5	**1**	0.407	0.01046	38.91	0.0194	0.54
	3	0.1676	5.54E-4	302.53	7.71E-4	0.72
Selectivity	**3:1**			**7.78**		**1.33**
6	**1**	0.2596	0.001961	132.4		
	3	0.4851*	7.74E-6*	62670		
Selectivity	**3:1**			**473 (>230[a])**		
7	**1**	0.3166	0.00985	32.14	0.0116	0.85
	3	0.3951	0.001015	389.26	5.94E-4	1.71
Selectivity	**3:1**			**12.11**		**2.01**
9	**1**	0.1701	5.22E-3*	32.59	0.0168*	0.31
	3	0.1249	8.7E-5	1435.63	1.53E-3	0.06
Selectivity	**3:1**			**44.06**		**0.18**
10	**1**	0.0991*	1.533E-3	64.64	N/A	-
	3	0.1042*	0.02208	4.72	N/A	-
Selectivity	**3:1**			**0.07**		-

*This is a pseudo-first-order rate constant obtained by multiplying the second-order rate constant by the catalyst concentration. [a]The low rate of formation of (*E*)-5-methyhex-3-ene from **6** using **3** led to differences from the mechanism modeled for **6** and **1**. Hence, the 473-fold increase in selectivity for **6** may be overestimated, though not by more than a factor of 2.

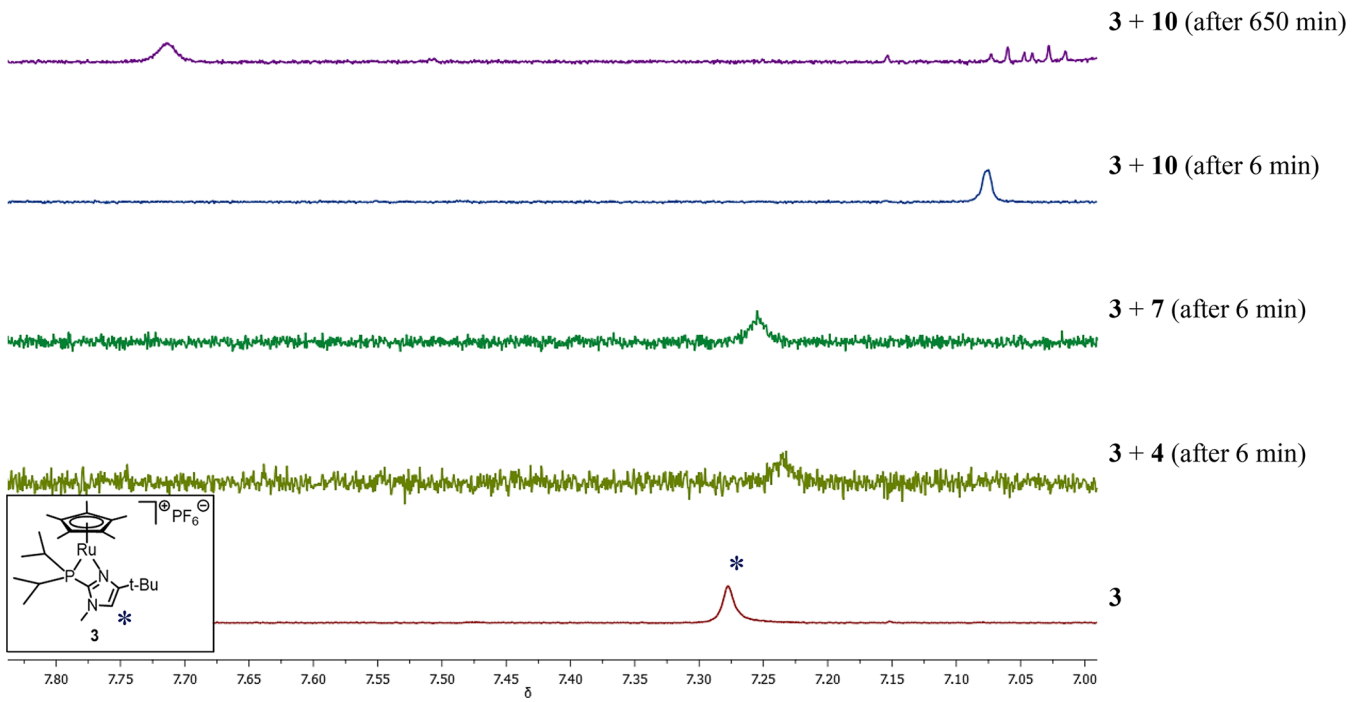

Figure 9. Stacked ^{1}H NMR spectra of catalyst **3** (7.0 to 7.8 ppm) in the presence of substrates **4** (0.3 mol % catalyst loading), **7** (0.3 mol % catalyst loading), and **10** (2.0 mol % catalyst loading).

catalyst **1**, it was necessary to model those subsequent reactions in two steps: formation of one intermediate (presumed to be (*E*)-6-decenol in Table S16), followed by further reaction of that intermediate. The observed decay of the (*E*)-7-decenol concentration could not be fit well otherwise because there are two distinct time scales for the equilibration of these isomers. The separation of these time scales in the **7**/**1** system is apparent from the orders of magnitude of the rate constants k_3 (0.0116 min^{-1} for (*E*)-7-decenol → (*E*)-6-decenol) and the much smaller k_4 (1.25×10^{-4} min^{-1} for (*E*)-6-decenol → other isomers) and results in the late drop in the concentrations of (*E*)-7-decenol and (*E*)-8-decenol in the last few measurements shown in Figure 8b.

Substrate **8** was not subjected to analysis because of failure of the reaction to proceed toward equilibrium; indications of catalyst deactivation were present in both catalyst runs. For the remaining six substrates (Table 3), to provide uniform rate constants for comparison, second-order rate constants were converted to pseudo-first-order rate constants by multiplying them by the catalyst concentration (rate constants calculated from second-order reaction steps are indicated with * in Table 3). In Table 3, k_1 refers to conversion of the 1-alkene to the (*E*)-2-alkene, k_2 to the conversion of the (*E*)-2-alkene to the (*E*)-3-alkene, and so on. Selectivity ratios were then generated by dividing k_1 by k_2 to indicate relative selectivity between the catalysts for the 1- to 2-alkene transformation versus the 2- to 3-

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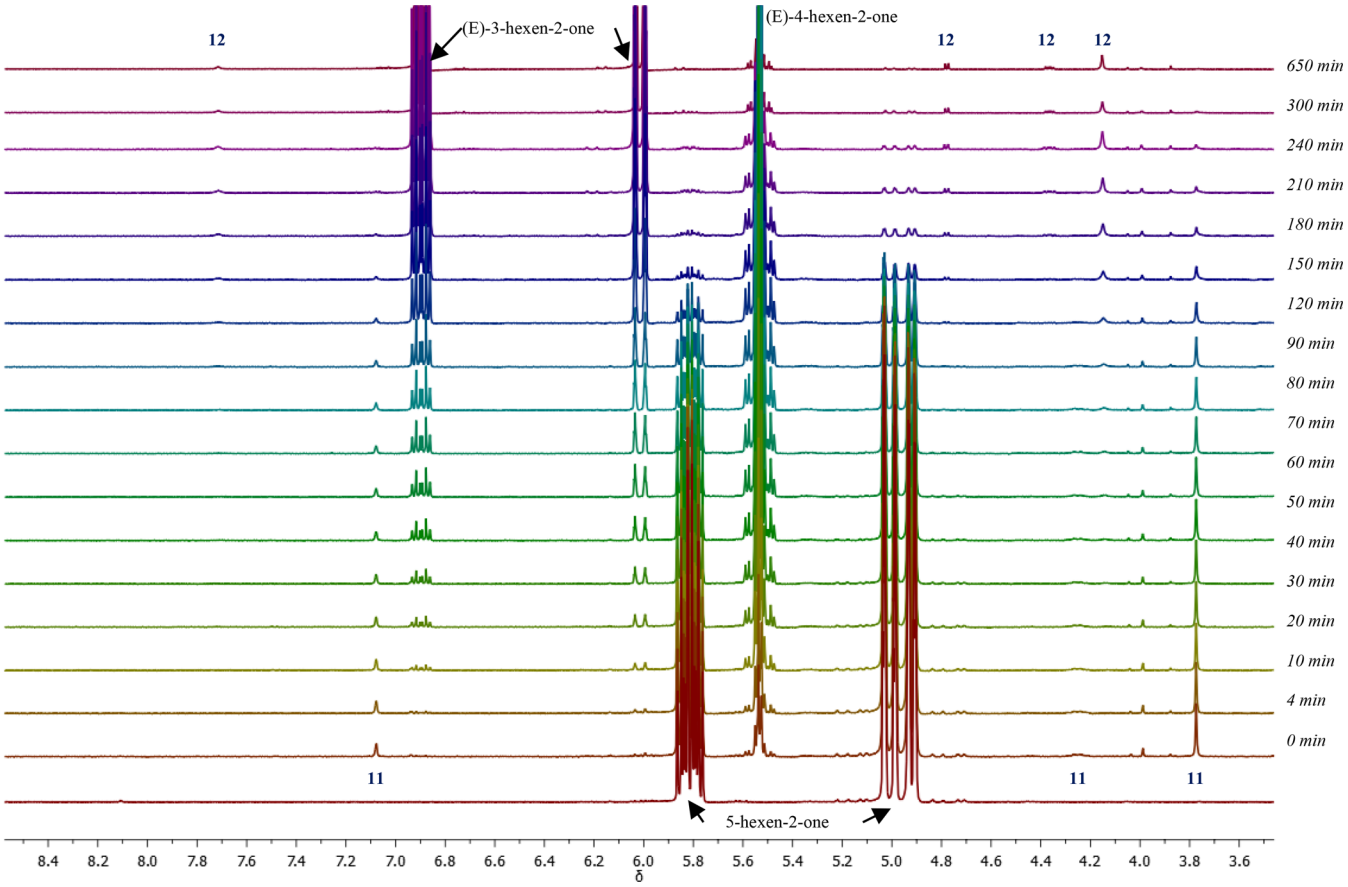

Figure 10. Stacked ^{1}H NMR plots (3.6 to 8.4 ppm) for the conversion of **10** to a mixture of (*E*)-4-hexen-2-one and (*E*)-3-hexen-2-one over 650 min with catalyst **3**.

alkene transformation, or what could be called the "terminal:internal ratio". An "internal:internal" ratio was also calculated by dividing k_2 by k_3.

The k_1:k_2 ratios for catalyst **1** were relatively similar across all of the substrates (28 to 132). The range of ratios for catalyst **3** was much larger (192 to 62 000), with the prominent exception of 4.7 for substrate **10** (discussed in greater detail below). Comparison of the k_1:k_2 ratios for catalysts **1** and **3** shows that for linear unfunctionalized alkenes **4** and **5**, catalyst **3** gives a modest 6−8-fold larger ratio than catalyst **1**; in other words, catalyst **3** is 6−8 times more selective for monoisomerization of shorter-chain linear alkenes than catalyst **1**. For longer-chain alkene **7**, which is functionalized eight carbons away from the alkene, complex **3** provides slightly higher terminal:internal selectivity (ratio of k_1:k_2 values = 12.11) and internal:internal selectivity (ratio of k_2:k_3 values = 2.01). The largest differences in terminal:internal selectivity, however, are seen with substrates **6** and **9**, which feature branching either three carbons away (**6**) or five atoms away (**9**, at the Si of the protecting group) from the alkene. Substrate **6** shows a *>230-fold increase* in terminal:internal selectivity with catalyst **3** over catalyst **1**, whereas for **9** the increase is 44-fold, *consistent with greater discrimination by the bulkier Cp* catalyst 3*.

While branching three or five carbons away from the alkene likely contributed to the increased terminal:internal selectivity in the case of substrates **6** and **9**, the presence in **10** of a carbonyl oxygen five carbons away makes catalyst **3** less selective than **1**. For **10**, the initial isomerization with **3** appears to proceed with a rate constant k_1 similar to that with **1**, which is the case with the other substrates. The second isomerization with **3** proceeds at a higher rate than that with **1**, leading to a selectivity ratio that is 14:1 *in favor* of **1**.

The change in selectivity for **3** with **10** is accompanied by qualitative and quantitative changes in the NMR spectra during isomerization. Catalyst **3** itself possesses a brilliant blue color, and most of the isomerization reactions using **3** (including substrates **4**−**9**) maintain the blue color during the course of the reaction. By contrast, the reaction of **10** with **3** exhibits an orange color, suggesting a stronger interaction between **10** and **3**. This is consistent with **10** being the only substrate which, in combination with **3**, requires the reaction complex to be invoked in order to fit the rate constants reported in Table S16. Likewise, an examination of the ^{1}H chemical shift of the imidazolyl C−H of **3** reveals larger chemical shift changes with **10** than are seen with substrates **4** and **7** (Figure 9). An initial chemical shift of 7.27 ppm without substrate is shifted upfield by 0.03−0.05 ppm upon the addition of **4** and **7**. In contrast, in the early course of the reaction with **10**, the imidazoyl C−H peak is shifted 0.2 ppm upfield, and later, when the system approaches equilibrium, the imidazolyl C−H peak is shifted downfield relative to the catalyst-only peak by ∼0.45 ppm.

Upon closer inspection of the isomerization of **10** with catalyst **3** (Figure 10), the upfield peak remains until complete consumption of **10** has taken place; the disappearance of the upfield peak (assigned to intermediate **11**) is concurrent with the disappearance of **10**. As the upfield peak disappears, the downfield peak (assigned to intermediate **12**) increases in intensity.

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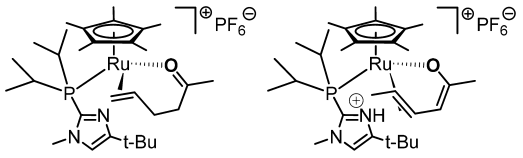
The upfield shift of the imidazolyl C−H in **3** upon exposure to **4**, **7**, and **10** is consistent with reversible binding of the alkene to the catalyst, which may or may not involve opening of the P,N-chelate.[11] The shift is greater with substrate **10**, which could be due to chelation of the carbonyl oxygen (see the structure of intermediate **11** in Chart 3), increasing the stability of alkene binding. The downfield shift that appears later in the reaction is consistent with protonated imidazole,[11] which could come from conjugated enolate **12** (Chart 3), a possible intermediate between (*E*)-4- and (*E*)-3-hexen-2-one. Intermediate **12** appears to be long-lived enough to show vinyl peaks consistent with bound alkene; a partial assignment of peaks is shown in Figure 11. The presence of a strongly bound alkene species during catalysis is in agreement with the fitted second-order kinetics for the formation of both (*E*)-4-hexen-2-one and (*E*)-3-hexen-2-one.

Chart 3. Proposed Intermediates 11 and 12 in the Isomerization of 10 with Catalyst 3



3 + 5-hexen-2-one (proposed complex) (**11**)

3 + (*E*)-4/(*E*)-3-hexen-2-one (proposed intermediate) (**12**)

Binding and chelation of the carbonyl oxygen acidifies the α-protons of the carbonyl, which would make the formation of intermediate **12** easier, thus facilitating the (*E*)-4- to (*E*)-3-hexen-2-one isomerization. Chelation of alkene substrates to $Cp^{R}Ru$ systems has been shown to influence product formation and selectivity by Trost (R = H)[27] and Vidovic (R = Me).[28] In contrast to catalyst **3**, catalyst **1** shows no rate enhancement with respect to the (*E*)-4- to (*E*)-3-hexen-2-one conversion, perhaps because of the presence of the nitrile as a competitive ligand preventing the binding of the carbonyl oxygen.

Practical Considerations in Using These Catalysts. For the practical user of catalyst **1** or **3** as well as any other catalyst for alkene isomerization, the results of the kinetic studies described herein can provide some insights as to how to utilize the catalysts to achieve the highest yield of the desired product. While several experiments with different catalyst loadings and temperatures and gathering multiple time points would be prudent to determine the ideal conditions for each substrate with each catalyst, it is not expected that the user has the time or resources for a detailed kinetic study, so some general conclusions and assertions can be made to simplify and streamline the process. The first clear assertion is that if a positionally unselective isomerization is acceptable or if a thermodynamic sink exists that minimizes the likelihood of multiple positional isomers, catalyst **1** is the clear choice because of its superior efficiency.

Another assertion that can be made is that for positionally selective isomerization reactions with substrates that can generate multiple potential isomers, if catalyst **1** is being used, catalyst loadings should be kept at 0.1 mol % or lower initially. Substrates **4**−**7** all reached the maximum yield of the (*E*)-2-alkene within 15 min using 0.1 mol % **1**. Reactions run at higher loadings or for longer times risk overisomerization and a lower yield of the (*E*)-2-alkene. If reactions are sluggish for a given substrate using 0.1 mol % **1**, then an increase in loading can be made commensurate with the progress of the reaction.

In comparison, for long-chain linear alkenes, catalyst **3** efficiently forms the (*E*)-2-alkenes at loadings of 0.3−0.5 mol % and is the superior choice if positional selectivity is desired

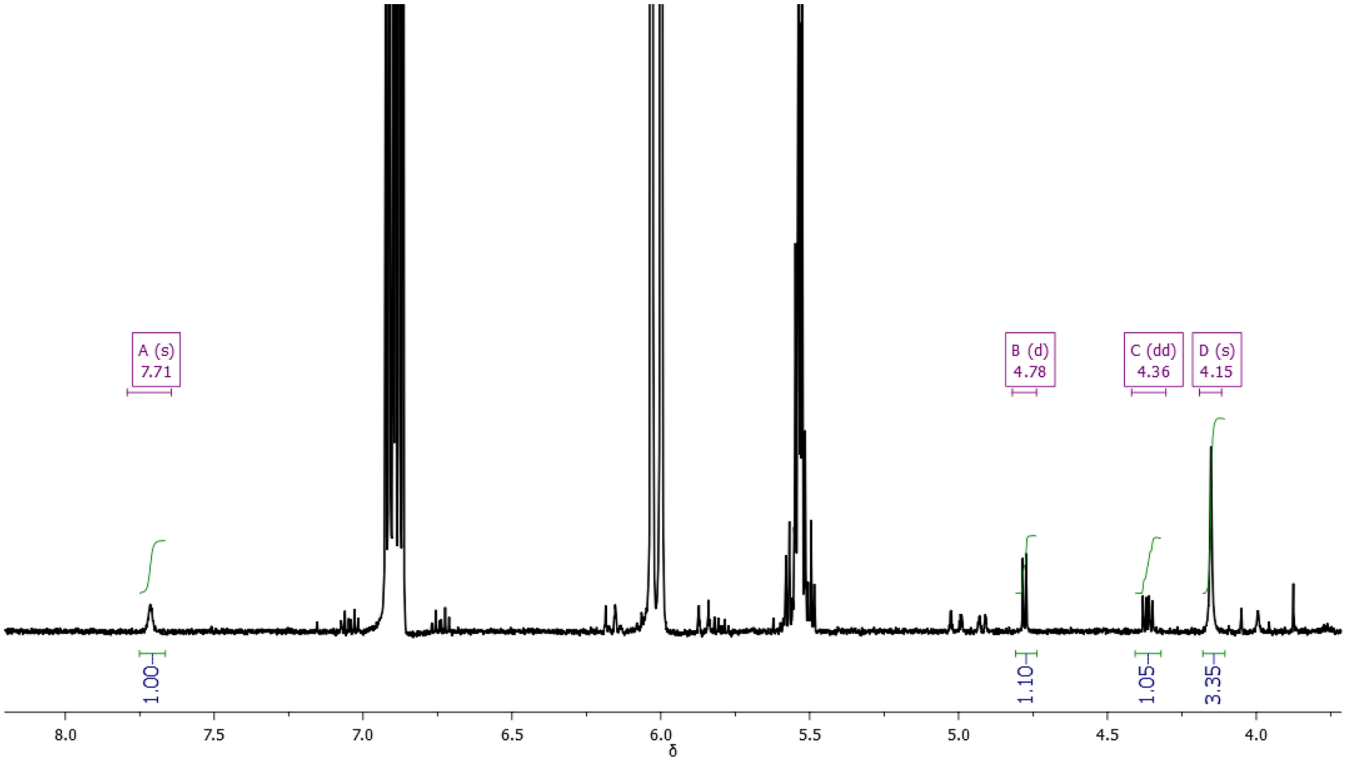


Figure 11. Partial ^{1}H NMR spectrum of **10** with **3** after 650 min. Signals A−D consistent with **12** are identified.

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because of the longer time that the (*E*)-2-alkene product remains at high yield. *The user would not need to monitor the time of the reaction as closely.* As an example, the run described for substrate **5** with catalyst **3** above reached the maximum yield of 96.1% at 30 min, but the yield had eroded by only ∼2% to 93.9% at 90 min. Additionally, if we assume a first-order linear relationship between the catalyst loading and rate, tripling of the catalyst loading to 0.9% mol % should achieve the maximum yield in just 10 min, which would still only erode ∼2% after 30 min.

However, branching or chelating functional groups that are five or fewer carbons away from the alkene can reduce the rate (in some cases requiring higher catalyst loadings), either increasing the positional selectivity in the case of branching (**6**) or potentially reducing the selectivity in the case of chelation (**10**).

The most general point that can be made about isomerization reactions with **1** and **3** is that the choice of catalyst and determination of the catalyst loading are crucial to finding the balance between efficiency and high yield of a desired product, *especially if careful monitoring of the reaction is not performed.*

CONCLUSIONS

For linear unfunctionalized substrates, catalyst **3** provides a 6–12-fold enhancement in selectivity for monoisomerization compared with highly optimized and carefully monitored reactions using **1**, rendering it a superior alternative to catalyst **1** when a single positional isomerism is required and high amounts of *E* isomers are desired. However, branching or coordinating functionality near the alkene can provide a significant positive (**6**) or negative (**10**) influence on the relative selectivity of **3** and **1**, where bulk alone from branching enhances the selectivity of **3** relative to **1** and coordinating functionality seems to erode the selectivity. Future work will focus on expansion of the substrate scope to further understand how position, size, and composition of functional groups and/or branching can affect the relative positional selectivity of **3** compared with **1** and other isomerization catalysts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00315.

Isomerization data, least-squares-fit graphs, and rate constant data (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: dbgrotjahn@sdsu.edu.

ORCID

Douglas B. Grotjahn: 0000-0002-2481-7889

Author Contributions

The manuscript was written through contributions from all of the authors. All of the authors approved the final version of the manuscript.

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Notes

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