JOC Article

Epimerization Reaction of a Substituted Vinylcyclopropane Catalyzed by Ruthenium Carbenes: Mechanistic Analysis

Xingzhong Zeng, Xudong Wei,* Vittorio Farina,* Elio Napolitano,† Yibo Xu, Li Zhang, Nizar Haddad, Nathan K. Yee, Nelu Grinberg, Sherry Shen, and Chris H. Senanayake

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877, and Scuola Normale Superiore, Piazza dei Cavalieri 7, 56127 Pisa, Italy

xwei@rdg.boehringer-ingelheim.com

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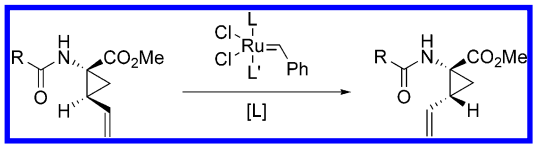

A novel ruthenium carbene-catalyzed epimerization of vinylcyclopropanes is reported. The reaction rate strongly depends on the presence of ruthenium ligands in solution. When the first-generation Grubbs catalyst is employed, a 5.3:1 equilibrium ratio of epimers is established quickly, but when a first-generation Hoveyda catalyst is employed, epimerization is observed only if an additional phosphine or nitrogen ligand is added. NMR and kinetic studies suggest that the isomerization reaction occurs through the intermediacy of a ruthenacyclopentene. The observation suggests that cyclopropylmethylidene ruthenium carbenes of synthetic utility may be accessible via ruthenacyclopentenes obtained via other routes.

Introduction

During the past decade, ruthenium-catalyzed olefin metathesis reactions (CM, RCM, and ROM) have been intensively investigated and widely applied in organic synthesis.[1] Along with the large number of successful metathesis reactions, some nonmetathesis reactions promoted by ruthenium−carbene complexes have been observed, often as side reactions due to special reaction conditions or to decomposition of ruthenium catalysts.[2] Among published examples, notable are the chloroform addition to alkenes,[3] ring contraction during ring-closure metathesis (RCM),[4] alkene isomerization of allyl amines, amides, and ethers,[5] and olefin hydrogenation.[6] Although the mechanisms of these reactions have not been fully elucidated, they represent an interesting synthetic development. Indeed, some of these reactions have been optimized and show some utility in organic synthesis. Coupled with a metathesis reaction, several elegant tandem processes have been developed, such as the tandem metathesis/hydrogenation process developed by Grubbs,[6a] the tandem RCM−alkene isomerization process for glycol synthesis developed by Snapper,[5g] the isomerization−ring closure me-

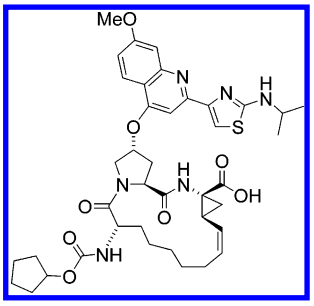

FIGURE 1. BILN 2061 (**1**).

† Scuola Normale Superiore.

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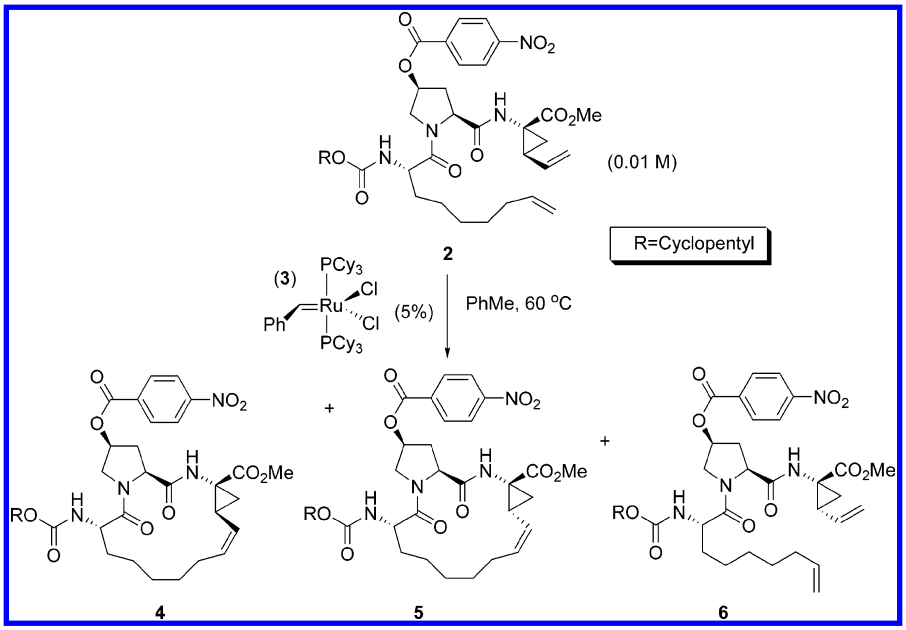
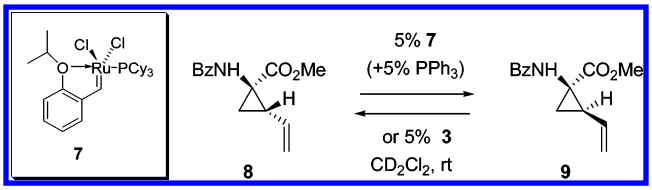
SCHEME 1. RCM and Isomerization of 2



SCHEME 2. Epimerization of 8 Catalyzed by Ru Carbenes



tathesis process for synthesis of indoles[5h] developed by Nishida, and the RCM−double bond migration developed by Schmidt.[7]

Herein we report our recent research on an unprecedented ruthenium carbene-catalyzed vinylcyclopropane epimerization reaction, which was discovered during the first synthesis of BILN 2061 (**1**), a macrocyclic HCV NS3 protease inhibitor (Figure 1),[8] and which had a major impact in our development of a scalable, robust ring-closure metathesis process to produce multi-kilogram amounts of this important new drug prototype.

Results

When tripeptide diene **2** was subjected to the RCM conditions with the first-generation Grubbs catalyst (**3**) in toluene at 60 °C, side product **5** was formed, together with the desired product **4**, in a ratio of ∼1:1 (Scheme 1). A pure sample of **5** was isolated by preparative HPLC and analyzed by NMR and MS, and its structure was assigned as the epimer of **4** at alkenyl-bearing cyclopropyl methine, in agreement with data from Tsantrizos et al.[9] In addition, an isomer of starting material **2** was observed, which is tentatively identified as **6**, because it is slowly converted to **5** on further teatment with the Grubbs catalyst. Interestingly, however, when the first-generation Hoveyda catalyst (**7**, Scheme 2)[10] was used, little or no epimerization (<1% **5** + **6**) was observed.

To characterize this epimerization reaction more fully, vinylcyclopropane aminoester **8** was prepared by standard benzoylation of (1*R*,2*S*)-methyl *trans*-1-amino-2-vinylcyclopropane carboxylate[11] and subjected to 5 mol % of **3** or 5 mol % of **7** plus an extra 5 mol % of PPh_3 or tricyclohexylphosphine (PCy_3). Little metathesis occurred, and a rapid epimerization reaction was instead observed; an apparent equilibrium with K_{eq} = ∼5.3 was reached in about 2 h at 50 °C (Scheme 2). The isomerized product **9** was isolated in 65% yield as a crystalline solid, and its structure was confirmed by comparison with published data.[12] Subjection of pure **9** to the reaction conditions of Scheme 2 re-established the equilibrium composition of 5.3:1 (**9**:**8**).

An authentic sample of **5** was prepared by applying the novel epimerization reaction to substrate (1*R*,2*S*)-**10** (Scheme 3). After deprotection and standard peptide coupling operations, closely following our synthesis of BILN 2061,[13] an authentic sample of diene **6** was obtained, which matched the structure of the side product obtained directly from **2**. Its RCM reaction under our conditions led to **5**.

Because of this isomerization problem with the first-generation Grubbs catalyst **3**, catalyst **7** was used for all of our RCM

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(12) That, indeed, epimerization had occurred at C-2 was unambiguously determined by converting resolved (1*R*,2*R*)-**9** to (1*R*,2*S*)-allocoronamic acid by double-bond hydrogenation and hydrolysis (note: the CIP designation changes from 2*R* to 2*S* upon double-bond hydrogenation). The optical rotation of a recrystallized sample matched the literature value. $[\alpha]^{22}_D$: found +61°, lit. +64°. See: Alcarza, C.; Herrero, A.; Marco, J. L.; Fernandez-Alvarez, E.; Bernabe, M. *Tetrahedron Lett.* **1992**, *33*, 5605.

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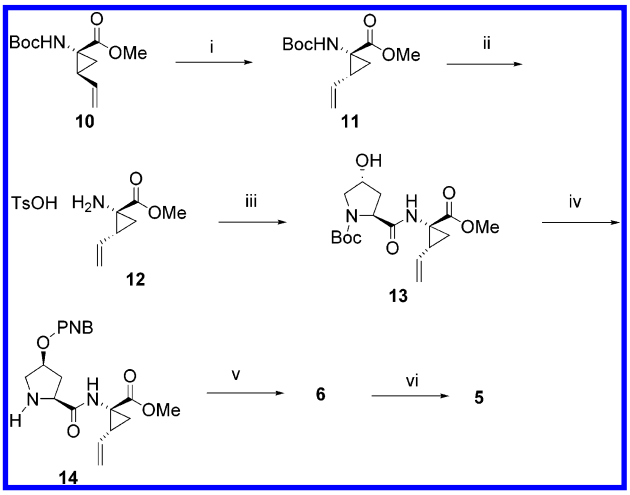
TABLE 1. RCM and Isomerization of 2 as a Function of Additives[a]

no.	**7** (%)	additive (%)	solvent	time (h)	**2** (%)	**4** (%)	**5** (%)	**6** (%)
1	4	none	PhMe	24	0	100	0	0
2	none	**15** (5)	PhMe	5	100	0	0	0
3	none	**16** (5)	PhMe	5	100	0	0	0
4	4	**16** (5)	CH_2Cl_2	15	9	69	6	16
5	4	**16** (5)	PhMe	15	2	78	2	17
6	6	pyrrolidine (12)	PhMe	48	48	34	8	10
7	4	*N*-methylpyrrolidine (12)	PhMe	17	2	82	2	14
8	2	Ph_3P (4)	PhMe	1.5	8	74	5	13
9	5	Cy_3P (5)	PhMe	2	6	54	13	27
10	4	$(n\text{-Bu})_3P$ (5)	PhMe	1.5	9	60	7	24
11	5	Cs_2CO_3 (5)	PhMe	5	10	90	0	0

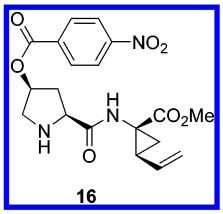
[a] Reactions were carried out at 0.01 M substrate (**2**) concentration, at 60 °C (PhMe) or 40 °C (CH_2Cl_2).

SCHEME 3. Synthesis of Authentic 5[a]



[a] Conditions: (i) 5% **7**, 5% PPh_3, PhMe, 60 °C; (ii) *p*-TsOH, EtOAc, rt; (iii) *N*-Boc-(*trans*)-4-hydroxyproline, EDC, HOBT; (iv) *p*-$NO_2C_6H_4CO_2H$, DEAD, PPh_3, THF, rt; then HCl, dioxane, rt; (v) (*S*)-2-cyclopentyloxycarbonylamino-8-nonenoic acid (**15**), TBTU, *i*-Pr_2NEt, rt; (vi) 5% **7**, PhMe, 0.01M **6**, 60 °C.

reactions. However, it was soon found that, even with **7**, the *epi* RCM product **5** was observed in some batches, with its content being variable from run to run. In some runs, **5** was observed in a proportion of up to 45% of total RCM product, clearly pointing to a reaction variable that was not under control. This is indeed rather common in catalytic reactions, where traces of moisture, air, or solvent impurities can affect the performance of the catalyst. After examining a number of potential variables, the starting materials of the reactions that gave the largest amount of isomerization product were carefully analyzed. By quantitative HPLC analysis, we detected up to 2−4% of compound **16**, i.e. an intermediate en route to **2** that had escaped acylation.[13]



The RCM reaction was then repeated using highly purified **2** in the presence of 5 mol % of **16**; a large amount of *epi* product **5** was indeed obtained, suggesting that **16** is a plausible culprit for the side reaction. Given that **16** is a secondary amine,

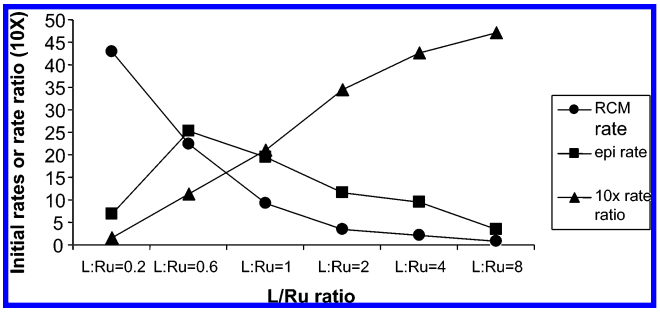


FIGURE 2. Dependence of RCM and the epimerization rates of **2**, and their ratio, upon [PPh_3], using **7** as a catalyst.

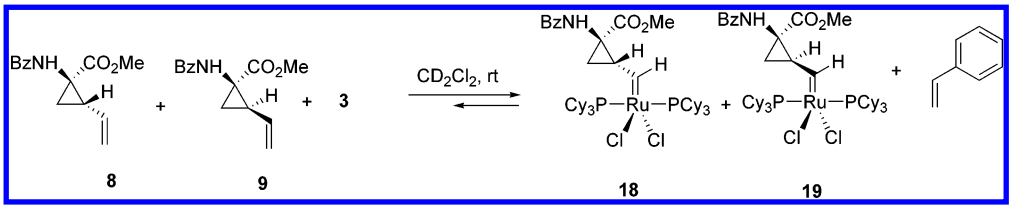
it was hypothesized that such an effect is due to its basicity, and we tested other bases such as pyrrolidine and *N*-methylpyrrolidine for their ability to induce epimerization. We also tested some representative phosphines as potential epimerization inducers. The results are shown in Table 1.

All amines tested promoted the epimerization, and surprisingly, even phosphines such as Ph_3P, Cy_3P, and $(n\text{-Bu})_3P$ led to variable amounts of **5** and **6**. It is clear that both the Ru catalyst and the base/ligand are required for this epimerization reaction (entries 1−3). Entry 11, where an inorganic base failed to cause epimerization, suggests an amine effect and not a general base effect. It should be noted that secondary amines such as pyrrolidine also deactivate the Ru catalyst to a major extent (entry 6).

The epimerization caused by excess PCy_3 is consistent with the observation that the Grubbs catalyst leads to epimerization without the need for further additives. It is known that excess ligand retards the metathesis reaction, because initiation is a dissociative reaction.[14] Therefore, one possible role of the excess ligand may be to slow the RCM reaction while not affecting a pre-existing background epimerization reaction. To determine whether excess ligand in solution affected the relative rate of the epimerization, we then decided to carry out an experiment in which increasing concentrations of ligand were added to a fixed amount of **7** (Figure 2). In this experiment, we monitored (by HPLC) the disappearance of **2**, as well as the formation of **4**, **5**, and **6**, vs time at different ratios of added PPh_3 vs catalyst **7** (5 mol %, 0.01 M initial concentration of **2**). The raw data are reported in the Supporting Information. The kinetics are too complex to allow a quantitative analysis. At this stage, we were satisfied with monitoring the inhibitory effect of excess ligand on the RCM initial rate (as measured by % RCM product after

(14) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

SCHEME 4. Reaction of Vinylcyclopropane Amino Acid Derivatives with Catalyst 3



30 min) and comparing this initial rate with the effect of ligand concentration on the epimerization rate (as measured by % **5** + **6** after 30 min at the same L/Ru ratio).

Figure 2 shows that the initial RCM rate drops as [L] increases, as expected.[15] The initial rate of epimerization increases with [L] up to L/Ru = ~0.6 and then drops in a fashion that is approximately parallel with the rate decrease in the RCM. The third line shows the ratio of the two rates (×10 for better visualization), yielding a sigmoidal curve. With no added L, no epimerization takes place at all. The higher the value of [L], the higher the proportion of epimerization, but the ratio of the rates reaches a plateau around 5 at high L/Ru ratios (>8). At even higher ratios, both reactions became so slow that their conversion was difficult to monitor accurately.

The fact that both processes are inhibited by free ligand suggested to us that the first step of both reactions may be a [2+2] reaction, consisting of a carbene transfer from the catalyst to the substrate. This is well-known to be inhibited by free phosphine.[14] We, therefore, decided to verify the nature of any new Ru carbenes, which may be present in solution during the epimerization, both by ^{1}H and ^{31}P NMR spectroscopy.

NMR Studies. NMR monitoring of the reaction of **8** with 30 mol % of Hoveyda catalyst **7** was not very informative. Very little epimerization to **9** took place, and the precatalyst **7** did not react appreciably. The starting material was slowly consumed, which is consistent with the occurrence of a slow metathesis, producing, at the same time, a poorly reactive Ru carbene CH_2═$Ru(PCy_3)_2Cl_2$ (**17**: ^{1}H NMR, CD_2Cl_2, δ 19.0, 2H, s),[15] which slowly accumulated. Basically, none of the epimerization reaction illustrated in Scheme 2 took place under these conditions, in agreement with the excellent RCM performance of this catalyst.

Treatment of **8** with 30 mol % of Grubbs catalyst (**3**) under similar conditions was, instead, much more informative (Scheme 4). Formation of a second Ru carbene species, **18** (^{1}H NMR, δ 18.5, d, J = 9.9 Hz; ^{31}P NMR, δ 38.4, s), was almost quantitative after 5 min, and its epimer **19** (^{1}H NMR, δ 18.3, d, J = 9.9 Hz; ^{31}P NMR, δ 38.8, s) also slowly formed over about 2−3 h, very likely by direct epimerization of **18,** although this cannot be absolutely established on the basis of the NMR study alone.[16] Formation of **9** also took place rapidly, and this species grew in composition vs **8** until the customary K_{eq} = 5.3 was obtained. Olefins **8** and **9** could be readily quantitated by integration of their allylic methine hydrogen signals at δ 2.30 (m, $J \approx$ 8.8 Hz) and δ 2.54 (m, $J \approx$ 8.8 Hz), respectively.

When the experiment was repeated with 1 equiv of **3**, carbene species **18** and **19** comprised about 90% of the total carbene content, indicating that the equilibrium in Scheme 4 lies very much to the right. To confirm that this reaction is an equilibrium, 2 equiv of d^8-styrene was added. The composition shifted immediately, and the proportion of **3** in the carbenic mixture rose from ~10% to ~20%. In addition, its carbene proton at δ 20.07 (s) in the ^{1}H NMR spectrum was 65% exchanged with D (from the deuterated styrene), which is consistent with a statistical mixture of H and D. The establishment of this equilibrium is consistent with the literature.[1] This initial carbene transfer reaction is indeed involved in the catalytic cycle of metathesis reactions. However, for olefins bearing α-branches, the equilibrium usually lies to the left,[15] and therefore, the quantitative aspects of our study are surprising.

Interestingly, the equilibrium mixture represented in Scheme 4 could be reproduced by using 1 equiv of **7** plus 1 equiv of PCy_3. The product composition was almost identical, with the only exception being 2-isopropoxystyrene replacing styrene. This clearly suggests that it is not the initial catalyst that makes a difference in the rate of the epimerization reaction, but the total amount of ligand present in solution.

The reaction in Scheme 1, i.e. the RCM of interest, was then monitored by ^{1}H and ^{31}P NMR under quasi-stoichiometric conditions to ascertain the site of initiation. Upon treatment with 30 mol % of **3**, most of **2** was consumed (>90%); two new species could be detected and identified as **20** (minor; ^{1}H NMR, δ 19.3, br t; ~4% of carbene mixture) and **21** (major; ^{1}H NMR, δ 18.5, d, J = 9.9 Hz; ~96% of carbene mixture). After the initiation, **21** epimerized to **22** (^{1}H NMR, δ 18.18, d, J = 9.8 Hz), in analogy with our study on the isolated species **8**, and **22** soon predominated (up to a ratio of **22**/**21** of ~7). At the same time, the RCM products **4** and **5** also appeared in a ratio of ~1:1. As the catalyst turned over, a new carbene species, identified by its ^{1}H and ^{31}P NMR spectrum as the methylidene species **17**, also formed (Scheme 5).

Thus, the chemoselectivity of catalyst **3** is surprisingly very high for initiation at *the more hindered site of* the diene. While the selectivity for propagation and the relative cyclization rate of species **20**, **21**, and **22** are not known, the observation of **21** and **22** during the catalytic cycle is a strong indication that the epimerization during the RCM is associated with a bis-ligated (where L = phosphine) Ru−carbene complex, in close analogy with the epimerization of **8**. In contrast, RCM of **2** (0.01 M) in the presence of Hoveyda catalyst **7** (30 mol %) proceeded smoothly at room temperature, but no discrete intermediates could be observed by NMR and no epimerization of **2** took place. Addition of 1 equiv of PCy_3 (vs Ru), under conditions known to lead to epimerization of the substrate, established a reaction composition quite similar to the one in Scheme 5.

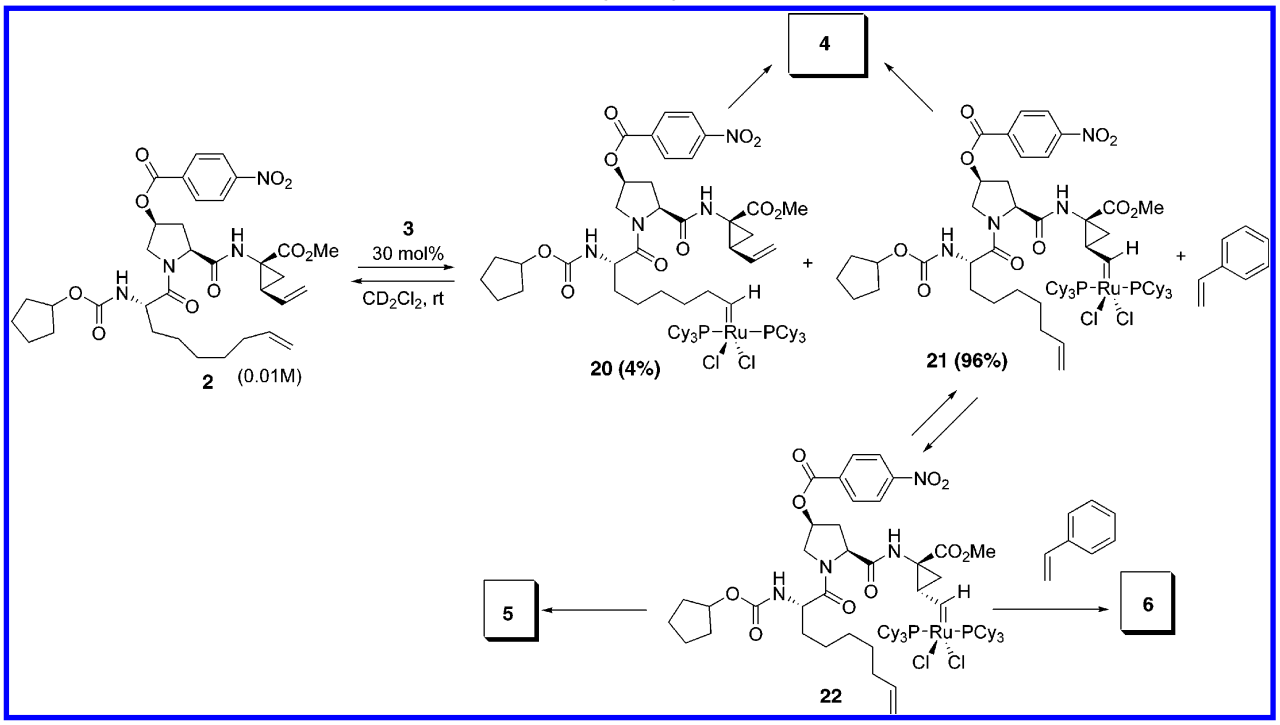
Given the rather facile epimerization of **8**, we became interested in finding out whether a simpler diene bearing an asymmetric center next to a terminal vinyl group may also readily undergo epimerization.

RCM Reaction of (*S*)-Citronellene. With a substrate containing only one stereogenic center, the result of an epimerization

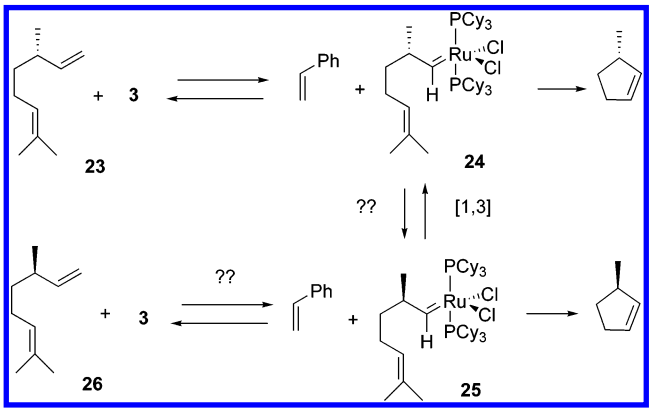
(15) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(16) It was quite surprising to observe that, for both **18** and **19**, the ^{31}P NMR spectrum consists of a singlet, even though the two P centers are diastereotopic. However, the cooling of a solution of **18** and **19** in CD_2Cl_2 to −90 °C evidenced the expected four doublets. The dynamic NMR behavior of these and related complexes will be the subject of a forthcoming study.

SCHEME 5. Intermediates in the RCM Reaction of 2 Catalyzed by 3



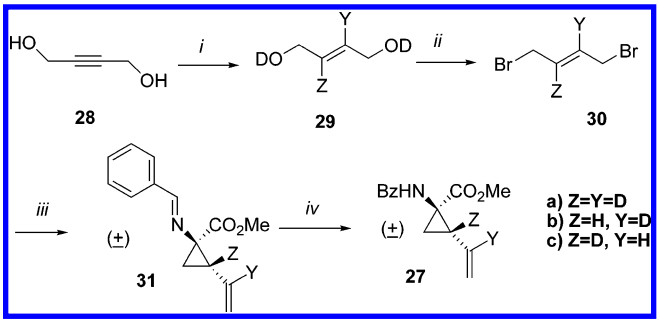
SCHEME 6. Monitoring the Possible Racemization of (*S*)-Citronellene



would be racemization. Given that (*S*)-citronellene (**23**) is available in bulk and its (*R*)-enantiomer **26** is also available, we set out to detect racemization during its known RCM reaction (Scheme 6).[5c] We monitored the reaction by ^{1}H NMR to make sure that a carbene exchange reaction took place, as shown for vinylcyclopropane **8**; we also examined the reaction by chiral phase GC to monitor the enantiometric excess (ee) of the starting material throughout the reaction.

^{1}H NMR monitoring (rt, CD_2Cl_2) using 5−10 mol % of **3** vs **23** showed a rapid (50%) conversion of **23** to **24** (δ 19.2, d; ^{31}P NMR, δ 35.3, s). As the catalyst turned over, the methylidene species **17** also formed. After about 75 min, at the completion of the reaction, the ratio of **3**/**24**/**17** was ∼34:47:19 (^{1}H NMR integration). Thus, as predicted, **24** is an intermediate in the reaction and accumulates to a large extent during the RCM; if a [1,3] hydride shift were a low-energy pathway in these systems, some racemization of **24** to **25** and, consequently, of **23** to **26** would be observed. Therefore, (*S*)- and (*R*)-citronellene were separated on a 50m Chiraldex column (retention times: 61.7 min for the (*S*)-enantiomer; 62.5 for the (*R*)-enantiomer).

SCHEME 7. Synthesis of D-Labeled Substrates 27a,b,c[a]



[a] Conditions: (i) $LiAlD_4$, THF, then D_2O (for **27a**) or H_2O (for **27b,c**); (ii) PPh_3Br_2 (64−70% overall); (iii) PhCH=NCH_2CO_2Me, *t*-BuOLi, PhMe; (iv) HCl, then BzCl, *i*-Pr_2NEt (37−52% overall).

The samples of starting material that were analyzed during the reaction (rt, CH_2Cl_2) consistently showed no trace of **26**. No detectable racemization (<1%) was, therefore, observed in this RCM reaction, demonstrating that equilibration between **24** and **25** under the reaction conditions is not a facile process. This may also explain why this type of epimerization has not been reported in the literature and suggests that there is something unique in our system that is triggering the epimerization.

Labeling and Crossover Studies. To determine whether the base/ligand effect in the epimerization originates from an inter- or intramolecular pathway, a bis-deuterium-labeled substrate, **27a**, was prepared, as shown in Scheme 7. The crystalline racemic **27a** was >99.5% deuterated at both the internal vinylic and the allylic carbon for obvious synthetic convenience. The monodeuterated product could be analogously prepared (Scheme 7). As predicted, it consisted of a 50:50 mixture of **27b** and **27c**. Although not useful in the crossover study, this mixture proved extremely useful for kinetic isotope effect determination (KIE, *vide infra*). Ethyl ester **32** was prepared analogously to **8**. When **27a** and **32** were subjected, in equimolar amounts, to epimerization conditions, there were no crossover products: both

TABLE 2. Observed k_1 for Reaction in Scheme 9 under Different Conditions ($k_1/k_{-1} = 5.3$)

entry	catalyst (mol %)	solvent	temp (°C)	added PCy_3 (mol %)	10^2k_1 (min^{-1})	10^2SD
1	2.5	PhMe	50		1.36	0.098
2	5.0	PhMe	50		2.52	0.048
3	7.5	PhMe	50		3.52	0.021
4	2.5	PhMe	50	2.5	0.70	0.055
5	2.5	PhMe	50	5.0	0.56	0.059
6	2.5	PhMe	50	10.0	0.55	0.024
7	2.5	PhMe	50	15.0	0.45	0.033
8	2.5	PhMe	50	20.0	0.38	0.054
9	2.5[a]	PhMe	50		1.11	0.042
10	10.0	CD_2Cl_2	23.5		0.127	0.005

[a] MeCH═$RuCl_2(PCy_3)_2$ (**33**) used as catalyst.

methyl esters were >99.5% deuterated, and both ethyl esters were <0.5% deuterated (NMR integration). The data conclusively show, therefore, that the epimerization reaction is intramolecular (Scheme 8).

Kinetic Studies. The epimerization of **8** to **9** (Scheme 9), catalyzed by varying amounts of **3** and, in one case, its ethylidene analogue MeCH═$RuCl_2(PCy_3)_2$ (**33**), was studied kinetically both by quantitative HPLC and by ^{1}H NMR. For the HPLC work, reactions were carried out at 0.01 M initial substrate concentration in degassed PhMe at 50 ± 0.2 °C. Samples were withdrawn at suitable intervals and analyzed vs external standards of starting material and product. Concentrations were determined against a standard response line. For the NMR work (0.05 M substrate concentration, CD_2Cl_2, 23.5 ± 0.5 °C), concentration vs time was measured using an internal standard (1,3,5-trimethoxybenzene). Initially, a 2.5 mol % catalyst load was used for the HPLC experiments and 10 mol % was used for the NMR work. In addition, rates at different catalyst concentrations and rates in the presence of added ligand (PCy_3) were measured. The kinetics were equilibrium first-order in **8** and **9**. The observed first-order kinetic constant ($k_1 + k_{-1}$) was derived by plotting $\ln[(C - C_{eq})/(C_0 - C)]$ vs time (where $C = [\mathbf{9}]$). Linear behavior ($R^2 > 0.995$), until at least one half-life, was observed in essentially all experiments (Figure 3).

Typically, data points up to 25−30% conversion were used for better accuracy, because, at higher conversions, small amounts of metathesis products were observed (peaks in HPLC-MS with the correct mass for a dimer minus ethylene). The results are shown in Table 2. The variability reflected by the standard deviation is mainly due to errors in weighing the small quantities of catalyst. Each rate constant represents an average of 2−6 determinations.

The dependence of k_1 on the catalyst concentration is not linear. Thus (entries 1−3), the rate constant does not increase proportionally to the concentration of the Ru catalyst (factors of 1.85 and 2.58, respectively, on doubling and trebling the catalyst load). Added ligand inhibits the reaction (entries 4−8). Once again, the effect is nonlinear, and it appears to saturate at a higher concentration of PCy_3. This is shown graphically in Figure 4.

The rate constant was about 20% lower (entry 9) when the ethylidene analogue of the Grubbs catalyst was used, but the kinetic behavior was otherwise analogous. Finally, the NMR kinetics in CD_2Cl_2 at room temperature were also well-behaved. Given the reduced temperature, the reaction was, not surprisingly, about 10 times slower, although 4 times more catalyst was used (entry 10). This experiment was carried out in order to determine the feasibility of measuring the KIE in the reaction under these conditions.

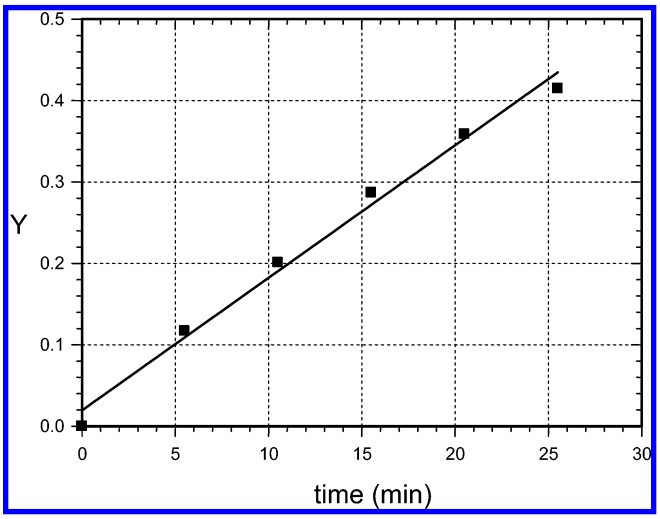


FIGURE 3. Typical kinetic plot for Scheme 9 $\{Y = \ln[(C-C_{eq})/(C_0-C)]\}$.

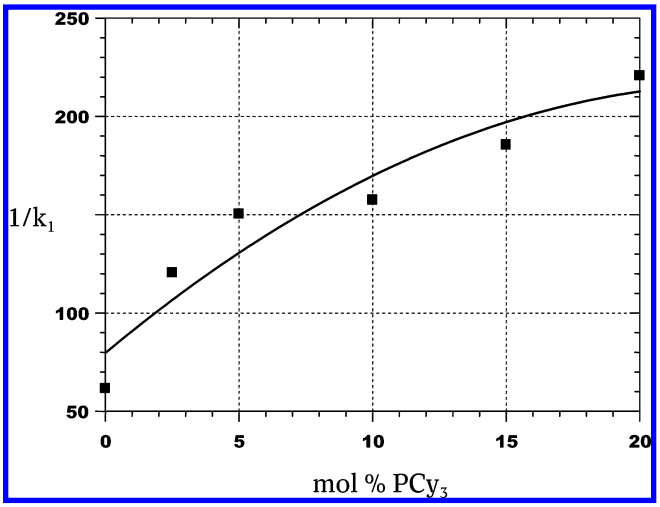


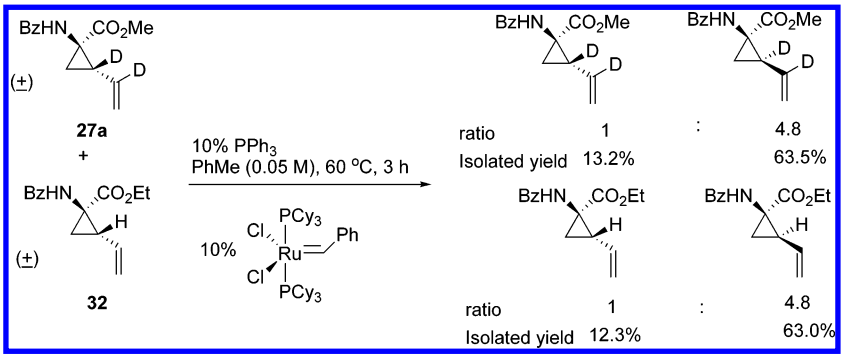
FIGURE 4. Dependence of k_1 on the ligand (PCy_3) in solution.

Kinetic Isotope Effects. To gain information on the nature of the turnover-limiting step (TLS), we determined the KIE for the equilibration of **27a** to **34** (Scheme 9). The main goal for the experiment was to determine whether the C−H bond at the carbon center undergoing the epimerization was being broken in the TLS and, therefore, gain an insight into the mechanism of this novel step. When the reaction was carried out as for the protio substrate (Table 2, entry 1), but with **8** instead of **27a**, the KIE, i.e. k_H/k_D, was 0.96 ± 0.11 (average of six determinations).

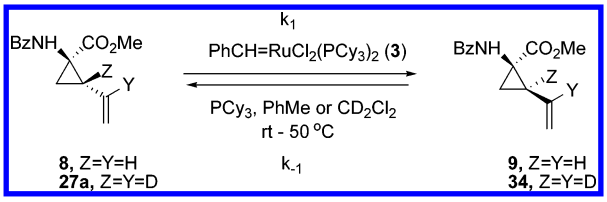
For further verification, the experiment in Table 2, entry 10 (NMR kinetics) was repeated with bis-deuterated substrate **27a**. The KIE, i.e. k_H/k_D, was 1.06 ± 0.12 (average of two determinations). This established that there is no primary KIE in the TLS of the epimerization. This study has two limitations: (1) Substrate **27a** bears two deuterium atoms. Deuterated olefins are known to exhibit a secondary KIE in metathesis reactions, ranging from positive (1.7 for a *trideuterated* primary olefin)[17]

(17) Ulman, M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 2484.

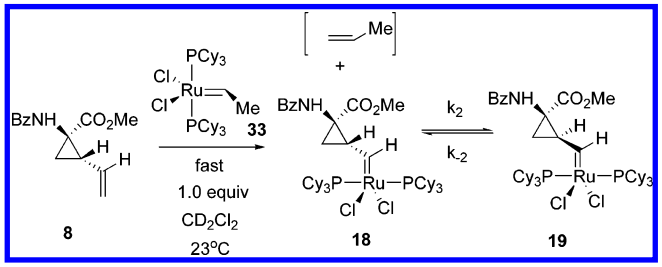
SCHEME 8. Results of the Crossover Study



SCHEME 9. Equilibration Experiments



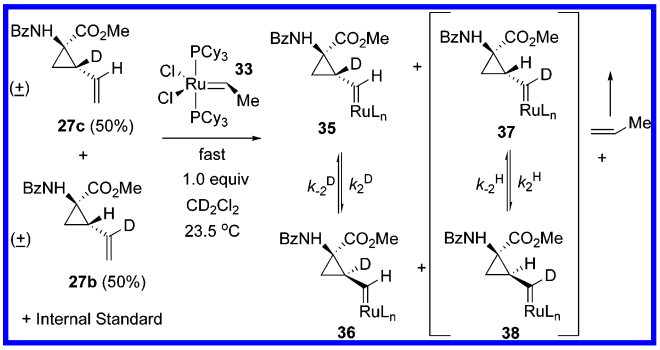
SCHEME 10. Measuring the Rate of Carbene Epimerization by ^{1}H NMR Kinetics



to negative (0.86),[18] depending on the substrate and the nature of the TLS. Thus, the olefinic D atom complicates the interpretation of the above results. (2) If the mechanism of the epimerization involves, as suggested by the above NMR study, direct epimerization of the carbene complexes **18** and **19** (Scheme 4), but not as a TLS, then it would be most informative to study the primary KIE in this isolated step, because the steps leading to the formation of **18** are those of a typical metathesis reaction and are already fairly well understood. If such steps are partially rate-determining, we are simply measuring the KIE of well-precedented and well-characterized steps.

What is needed, therefore, is a way to prepare **18** *in situ* and to directly study its epimerization to **19**. This would also unequivocally prove that the epimerization does actually proceed through these carbene complexes and that they are not merely observable depot forms. To begin with, the epimerization of **18** was carried out stoichiometrically (Scheme 10). When **8** was treated with 1 equiv of **33** in CD_2Cl_2 at room temperature for 10 min and the content of the flask was allowed to evaporate *in vacuo*, only complex **18** (plus small amounts of **19** and **33**) was left. The purity of the **18**/**19** mixture was assessed as ~97% by NMR vs the internal standard (1,3,5-trimethoxybenzene). In this case, the use of **33** as the carbene source is of great importance, because it is the evaporation of the olefin byproduct, propene, which drives the equilibrium all the way to the right. In this way, the back-reaction was eliminated, and the spontaneous equilibration of **18** to **19** could be monitored by ^{1}H NMR by integration of the signals of the carbene methine hydrogens. The concentrations of **18** and **19** vs time were determined by integration vs the standard and yielded first-order equilibrium kinetics ($k_2/k_{-2} = 7.0$). In this case, k_2 was determined to be 1.36×10^{-2} min^{-1} (five determinations; SD $= 7.6 \times 10^{-4}$) at 23.5 °C in CD_2Cl_2.

SCHEME 11. Measuring the Rate of D-Carbene Epimerization by ^{1}H NMR Kinetics



For the kinetic study on the monodeuterated substrate **27b**,**c**, this equimolar mixture was used directly. Addition of 1 equiv of **33** produced the two carbene complexes **35** and **37** (Scheme 11), which epimerize at rates that are, in principle, different. Rather than trying to determine both rate constants and deriving the KIE from a single competition experiment, we chose to ignore **37**, due to the difficulty of obtaining reliable integration on all relevant signals (Scheme 11), and focus only on **35**. By focusing on the low-field signals of the carbene methines of **35** and **36**, we could ignore **37** and **38**, determine the rate constant for the epimerization of **35** to **36**, and then compare it with that of the reaction in Scheme 9. Using this protocol, the KIE for this epimerization was found to be $k^H_2/k^D_2 = 1.19 \pm 0.21$ (average of three determinations).

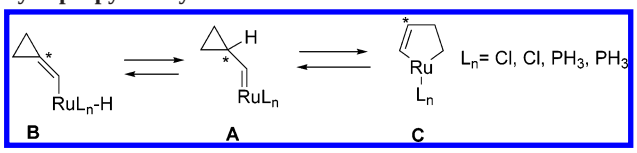
Thus, the experiments with isolated carbenes **18**, **19**, **35**, and **36** confirm that the catalytic epimerization reaction observed with substrate **8** proceeds through these intermediates and that the C−H bond of the center undergoing epimerization is not broken during the process (no primary KIE). To shed further light on the nature of this key step, we probed the coordination state of the reactive intermediates in the conversion of **18** to **19** by conducting the NMR kinetics in the presence of increasing amounts of added ligand (PCy_3). The data are summarized in Table 3. The data show that the epimerization of **18** to **19** *is neither inhibited nor promoted by added ligand*. Within experimental error, the kinetic constants of entries 2−4 are identical. These rate constants are, however, slightly, but

(18) Adlhart, C.; Hinderling, C.; Baumann, H.; Chen, P. *J. Am. Chem. Soc.* **2000**, *122*, 8204.

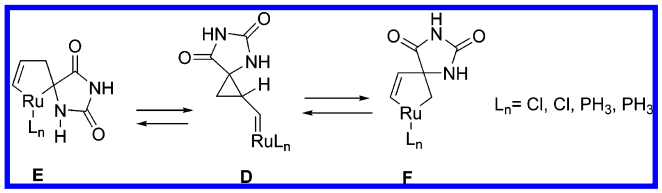
TABLE 3. Effect of Added Ligand on the Epimerization Rate of 18 to 19 in CD_2Cl_2 at 23.5 °C

entry	added PCy_3 (equiv vs Ru)	10^2k_1 (min^{-1})	10^2SD
1	0	1.36	0.08
2	1	2.14	0.08
3	2	2.59	0.31
4	4	2.30	0.22

SCHEME 12. Potential Sigmatropisms of Cyclopropylmethylidene Carbenes



SCHEME 13. Potential Sigmatropies with Substituted Cyclopropylmethylidene Ru Carbenes



significantly, enhanced with respect to those obtained in the absence of excess ligand.

Density Functional Theory (DFT) Calculations. It was of considerable interest to submit to theoretical calculations the mechanism involving breakage of the allylic C−H bond (e.g. a [1,3] shift);[19] faced with our KIE observations, we also decided to test a pathway that did not involve cleavage of the allylic C−H bond, but rather of the C−C bond. Both pathways are shown in Scheme 12. In particular, we wanted to compare the energy profiles of the H-shift, leading from the Ru carbene **A** to the cyclopropylidenemethyl−ruthenium−hydride complex **B**, vs the C-shift, leading from **A** to the ruthenacyclopentene complex **C**. In both cases, the consequence of the rearrangement is the transformation of the methine carbon of species **A** to a planar center; both pathways would account for the loss of diastereomeric purity through epimerization of the starred carbon center in **A**. Species **A** was selected as a model for the ruthenium−carbene intermediates **18** and **19**, and the ligand sphere was selected as consisting of two Cl and two PH_3 ligands in order to simplify calculations. Spirohydantoins **D**, **E**, and **F** (Scheme 13) were also investigated; these species were meant as improved models for **18** and **19** in the attempt to evaluate how nitrogen and oxycarbonyl substitution at the cyclopropane ring could affect the ease and regiochemistry of the C-shift in the interconversion of **18** and **19** via ruthenacyclopentenes.

All calculations were carried out using the Gaussian 98 program package.[20] In particular, the DFT approach was followed for all optimizations, using Becke's three-parameter hybrid method with LYP correlation (B3LYP)[21] and the LanL2DZ basis set (using Hay and Wadt's ECP with the corresponding DZ basis set for Ru, P, and Cl[22] and Dunning−Huzinaga's DZ basis set for C, H, N, and O[23]). The B3LYP/LanL2DZ combination has proved to be quite reliable in energy and geometry computations in systems containing transition metals.[24] Transition states were searched without symmetry constraints, following the method of Schlegel (as implemented in the "TS" option of Gaussian Input), starting with the approximate geometries of transition states found by empirical exploration of the potential energy surface along hypothetical reaction coordinates. For the optimized transition states, a normal-mode analysis was performed in order to confirm that only one imaginary frequency was present and that it was associated with the transition state of the reaction coordinate under investigation. The three-dimensional structures of all species calculated are shown in Figures 5 and 6.

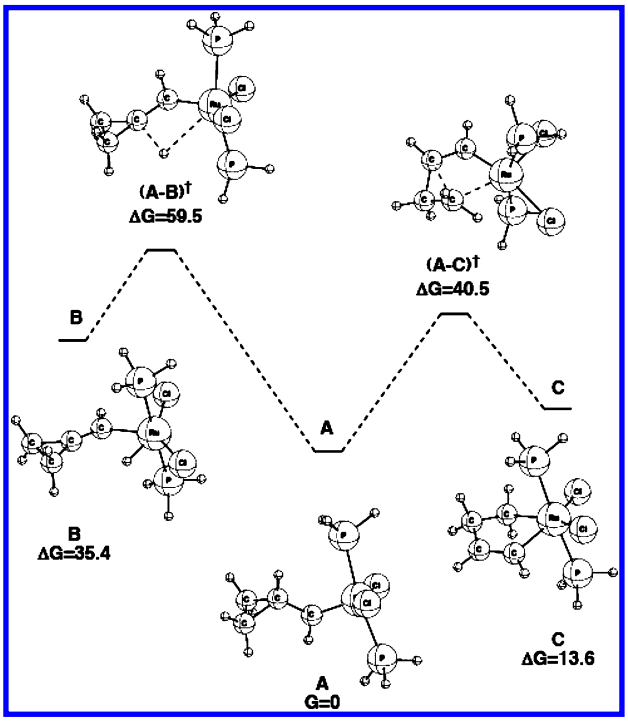


FIGURE 5. Calculated energetics (DFT) of postulated sigmatropic shifts.

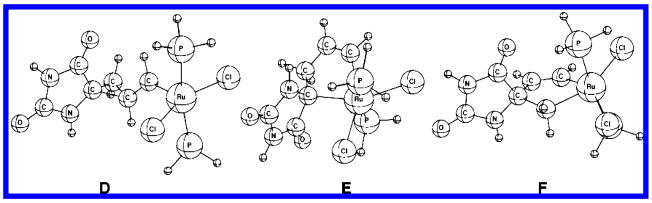
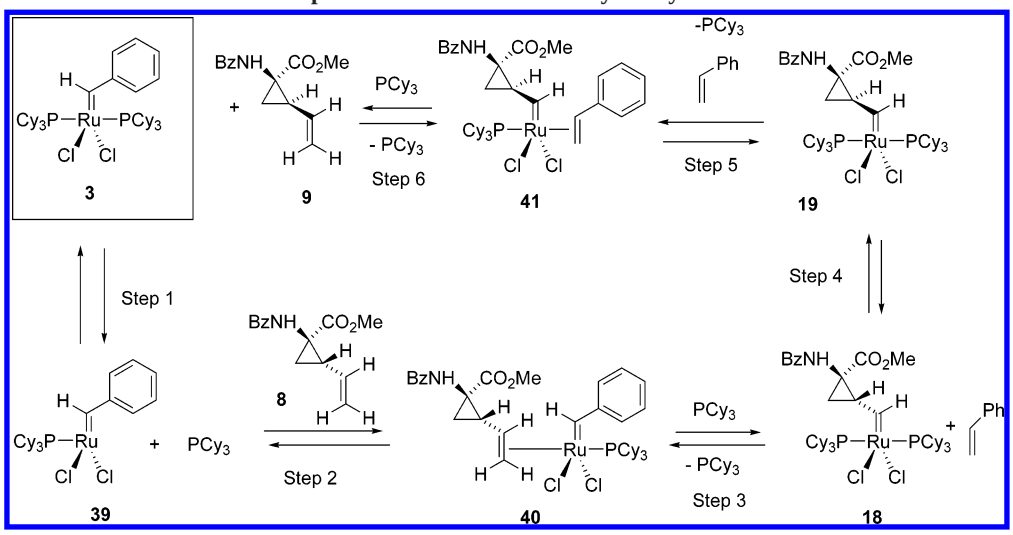


FIGURE 6. Calculated structures for species **D**, **E**, and **F**.

In all of the complexes, the P−Ru−P angle is very close to 180°. The carbene complex **A** is a substantially distorted square pyramid in which the carbene carbon atom occupies the apical position; the C−Ru−Cl and Cl−Ru−Cl angles are 105.5° (rather than 90°) and 154.2° (rather than 180°), respectively; these values are quite different from 120°, which would

(19) Gurjar, M. K.; Yakambram, P. *Tetrahedron Lett.* **2001**, *42*, 3633.
(20) Frisch, M. J.; et al. *Gaussian 98*, Revision A.6; Gaussian Inc.: Pittsburgh, PA, 1998. For a practical guide, see: Foresman, J. B.; Frisch, A. *Exploring Chemistry with Electronic Structure Methods*; Gaussian Inc.: Pittsburgh, PA, 1996.
(21) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter* **1988**, *37*, 785.
(22) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270.
(23) Dunning, T. H.; Hay, P. G. In *Modern Theoretical Chemistry*; Schaefer, H. F., III, Ed.; Plenum: New York, 1976; Vol. 3, p 1.
(24) Niu, S.; Hall, M. B. *Chem. Rev.* **2000**, *100*, 353. Dedieu, A. *Chem. Rev.* **2000**, *100*, 543.

SCHEME 14. Mechanistic Scheme for the Epimerization of 8 to 9 Catalyzed by 3



characterize the complex as a trigonal bipyramid with phosphines in the apical positions. The cyclopropylidenemethyl ruthenium hydride **B** can be described as a distorted octahedron or a square pyramid in which the H and C substituents share the apical position (the Cl−Ru−Cl angle is 143°). The ruthenacyclopentene complex **C** can also be described as a distorted octahedron with the phosphines occupying two *trans* positions; the value of the Cl−Ru−Cl angle (129°, larger than 120°) still shows the tendency of the Ru complex to assume a square pyramidal structure. Transition structures (**A**→**B**)$^{\#}$ (Cl−Ru−Cl angle 144.6°) and (**A**→**C**)$^{\#}$ (Cl−Ru−Cl angle 144.2°) bear a closer resemblance to the respective product than to the reactant **A**, thus suggesting a late transition state in both cases. As to the energy profile (Figure 6), the H-shift leading from **A** to **B** (ΔG = 35.4 kcal/mol, $\Delta G^{\#}$ = 59.5 kcal/mol) is distinctly more difficult than the C-shift leading from **A** to **C** (ΔG = 13.6 kcal/mol, $\Delta G^{\#}$ = 40.5 kcal/mol). This difference is partially due to an increased strain in the cyclopropyl ring, which must now accommodate an exocyclic double bond. The presence of a spirocondensed hydantoin at the cyclopropane ring of the Ru−carbene complex **A** appears to facilitate the C-shift to a ruthenacyclopentene (Scheme 13); the rearrangement of **D** into the two isomeric rearranged species **E** (ΔG = 9.9 kcal/mol) or **F** (ΔG = 9.7 kcal/mol) is, in fact, energetically more favorable than the similar rearrangement involving the parent species **A** and **C**. Quite surprisingly, considering the different substitution pattern at the carbon bound to the metal atom, the two isomeric species **E** and **F** are very similar in free energy. No attempt was made to compute the transition states leading from **D** to either **E** or **F**, and we also did not attempt to fine-tune the system for the extra steric hindrance that is caused by the bulky PCy_3 (vs PH_3).

Discussion

Interestingly, there are scattered examples in the literature that describe metathesis reactions of vinylcyclopropanes, and these reactions have been reported to proceed uneventfully.[25] We were unable, therefore, to find any precedent for the reaction described in this paper. Olefin isomerizations or migrations, on the other hand, have been detected often in metathesis reactions. Several mechanisms may be responsible for these side processes: allylic activation pathways[26] and the action of Ru−H species[27] formed by decomposition of the primary catalyst[28−30] have been invoked as possible rationales. Clearly, the epimerization of **8** to **9** cannot be explained with these mechanisms. The smooth first-order kinetics and the lack of a preactivation period show that no Ru−H species are responsible for the epimerization and that the catalyst is **3** itself. The experiments with isolated **18** and **19** strongly suggest that these compounds, observed by NMR spectroscopy as the predominant Ru-containing species throughout the reaction, are the intermediates on the pathway for the epimerization of **8** to **9**. The kinetic constant for the stoichiometric epimerization reaction (CD_2Cl_2, 23.5 °C), i.e. $k_2 = 1.36 \times 10^{-2}$ min^{-1}, is quite consistent with the catalytic rate constant for the epimerization reaction of **8** measured under the same conditions (10 mol % of catalyst, i.e. 10 times less Ru), which is $k_1 = 1.27 \times 10^{-3}$. Unfortunately, because the dependence of k_1 on the Ru catalyst concentration is nonlinear, it is not possible to say that the epimerization reaction is the TLS in k_1, but rather that the two rate constants are qualitatively consistent with such an explanation. All of our observations, coupled with the ample literature background for these reactions, allow us to propose a tentative mechanistic scheme for the Ru-catalyzed epimerization of **8** to **9** (Scheme 14).

Ruthenacyclobutanes as potential intermediates have been removed from the scheme for simplicity. Overall, steps 1−3, 5, and 6 are well-precedented by the work of Grubbs[15,17] and are steps en route to a typical olefin metathesis reaction. What is perhaps surprising is the extent to which the equilibrium in

(25) (a) Yang, Z.-Q.; Geng, X.; Solit, D.; Pratilas, C. A.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 7881. (b) Yamamoto, K.; Biswas, K.; Gaul, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2003**, *44*, 3297. (c) Barrett, A. G. M.; Hamprecht, D.; James, R. A.; Ohkubo, M.; Procopiou, P. A.; Toledo, M. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2001**, *66*, 2187. (d) Verbicky, C. A.; Zercher, C. K. *Tetrahedron Lett.* **2000**, *41*, 8723.

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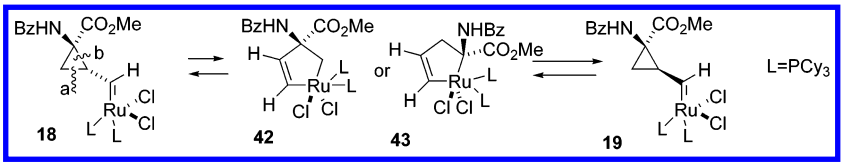
(27) McGrath, D. V.; Grubbs, R. H. *Organometallics* **1994**, *13*, 224.

(28) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414.

(29) Dinger, M.; Mol, J. C. *Organometallics* **2003**, *22*, 1089.

(30) Schmidt, B. *Chem. Commun.* **2004**, 742.

SCHEME 15. Proposed Mechanism for the Epimerization Reaction of 18 and 19



Scheme 4 lies to the right, making it extremely favorable for the carbene transfer step.

It is tempting to speculate about the possibility of an extra coordination imposed on the Ru atom, by the ester carbonyl in **18** and the amide carbonyl in **19**, as being responsible for the relative stability of **18** and **19**. The effect of such coordination would be to stabilize these carbene complexes and retard the metathesis reaction. These effects by basic carbonyl groups have been postulated often in the literature,[31] although, in our case, this coordination would create a hexacoordinated Ru center. In fact, intermediates **18** and **19** bear two phosphine ligands, as evidenced by the absence of the signal due to free phosphine in the ^{31}P NMR. Also noteworthy is the fact that our RCM reaction is rather smooth despite this stabilizing coordination and is not appreciably affected by Ti(*i*-PrO)$_4$ (data not shown).[32] The kinetic law for such a scheme is too complex to be solved in detail, and we can only make a qualitative assessment of its features. The nonlinear dependence of k_1 vs [**3**] could indicate the involvement of catalyst dimers (which is extremely unlikely for a catalytic system that is so well-characterized) or simply a complex, multistep kinetic scheme in which the Ru resides in a variety of discrete environments at any given time, as we propose in Scheme 14.

The inverse dependence of k_1 vs [L] is typical of metathesis reactions. Were the initial dissociation (step 1) the only TLS, such a dependence would be of the linear type.[14] Instead, the relationship is complex, indicating the presence of another TLS, which is L-promoted. Indeed, the presence of such a step is predicated on the initial observation that free ligand in solution is absolutely instrumental in bringing about this epimerization. Such a step must clearly be step 3. Whereas the metathesis reaction is inhibited by the ligand because its initiation step is dissociative, the epimerization process must contain an associative step, and it is probably the interplay between these two steps vs [L] that yields the "saturating" behavior, depicted in Figure 4 and by the unusual curve in Figure 2.

Clearly, the values of the "catalytic" k_1 and the stoichiometric k_2 are compatible with step 4 being turnover-limiting. In addition, entry 9 in Table 2 shows that the ethylidene analogue (**33**) of the Grubbs catalyst **3** catalyzes the epimerization at a reduced rate (~80%) vs **3**. In carbene transfer reactions, alkylidene Ru carbenes instead react more readily than **3** due to a faster initial ligand dissociation from Ru(II).[14] This confirms that step 1 cannot be the sole TLS.

However, rather than a detailed kinetic scheme for the novel catalytic cycle, what is of the utmost interest is the mechanism of the novel and extremely smooth transformation between **18** and **19**. Clearly, the lack of a primary KIE rules out any type of [1,3] hydride shift. Given the limited precision of the KIE measurements, it is not possible to say whether a small secondary isotope effect is at play.

A rather simple and attractive way to account for the transformation of **18** to **19** is through the intermediacy of a cyclic Ru(IV) intermediate, a ruthenacyclopentene (Scheme 15).[33] This intermediate (**42** or **43**) is consistent with the KIE data and with the kinetics of the epimerization of isolated **18**. It is also supported by our preliminary DFT calculations. Interestingly, the two potential isomeric ruthenacyclopentenes, **42** and **43**, are predicted to have similar free-energy (*vide supra*), and it is, therefore, not possible to be more specific and postulate which of the two intermediates is the one on the epimerization pathway. A limitation of the DFT calculation is the use of a hydantoin surrogate for the amide and ester groups in **18** and the use of PH_3 as a surrogate for PCy_3. Clearly, steric effects may tilt the balance in favor of the less crowded isomer (probably **42**), but it is difficult to be more precise at this stage.

For the formation of **42**, the C−C bond (a) in **18** (Scheme 15) would have to break, and this has no stereochemical consequences. If the C−C bond (b) breaks (through **43**), then the ring expansion would have to take place with retention of configuration (twice) at the migrating carbon. Consistent with the kinetics, the sigmatropic shift leading from **18** to **19** through **42** or **43** (Scheme 15) is not affected, within experimental error, by free ligand in solution (Table 3); that is, the reaction proceeds directly through the 16-electron intermediates shown, without the intervention of ligand dissociation or association. If the reaction were dissociative, inhibition by added ligand would be observed. If the reaction required the association of a third phosphine equivalent to promote the epimerization (through an admittedly unlikely 18-electron intermediate), then the observed rate constant would systematically increase with [L]. Still uncertain is the origin of the slightly lower epimerization rate in the absence of added ligand (Table 3, entry 1). This could be due to partial self-dissociation of any of the species involved in the equilibration, such as **18**, **19**, **42**, or **43**. Whereas appreciable dissociation of **18** and **19** was not detected by ^{31}P and ^{1}H NMR in solution, dissociation of high-energy intermediates **42** and **43** would not be detectable but would have kinetic consequences.[34]

Intermediates such as **42** and **43** are extremely intriguing. It is rather surprising that, given the abundance of metallacyclopentenes as intermediates in cycloaddition reactions, their transformation to cyclopropylmethylidene complexes has not been documented before. Ruthenacyclopentenes are likely intermediates, i.e. in Ru-catalyzed alkene/alkyne addition,[35] in catalytic Pauson−Khand reactions,[36] and in Ru-catalyzed enyne cycloaddition.[37] In one case, the conversion of a ruthenacyclopentene into a cyclopropylmethylidene Ru carbene has been

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(33) This possibility was first proposed by Tsantrizos et al.; see ref 10.

(34) In fact, small amounts of the phosphine oxide are detected in the ^{31}P NMR spectrum as the reaction progresses, and they are probably due to slow oxidation of the very sensitive PCy_3 by adventitious oxygen.

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(36) Itami, K.; Mitsudo, K.; Fujita, K.; Ohashi, Y.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2004**, *126*, 11058.

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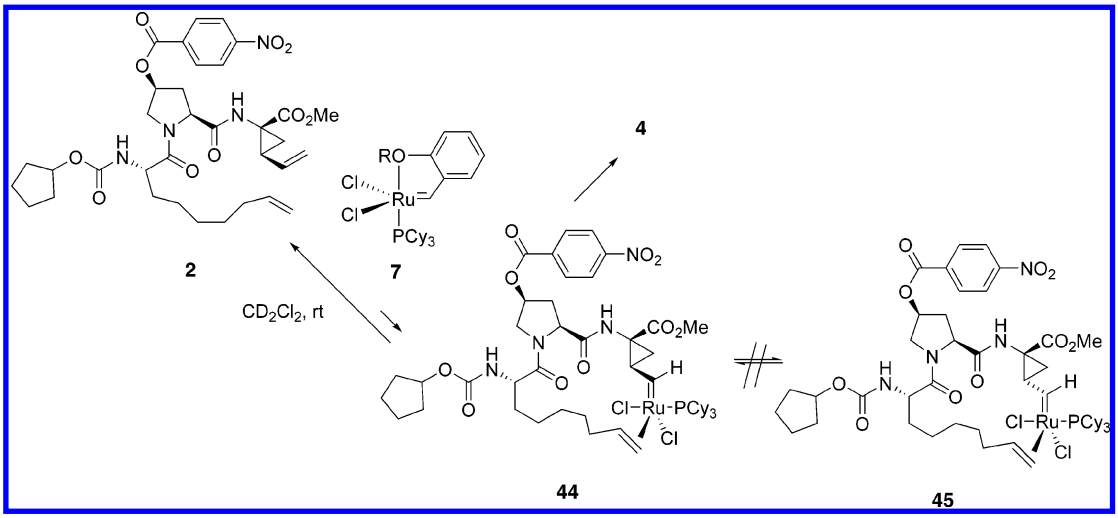
SCHEME 16. Mechanistic Rationale for Clean Formation of 4 Using Hoveyda Catalyst 7



suggested.[38] In other metal systems, cycloisomerization of enynes is known to give a variety of products, some originating from metallacyclopentenes and others from cyclopropylmethylidene carbenes, and the relationship between these and other intermediates has been thoroughly discussed.[39]

Admittedly, although we have ruled out a number of reasonable mechanisms for the epimerization of **8** to **9**, the evidence for the ruthenacyclopentene mechanism is only indirect. The theoretical calculations suggest that our proposal is energetically reasonable. Our work also suggests that these intermediates, obtained through other means, could enter a vinylcyclopropane manifold, giving rise to novel processes. This intriguing possibility remains to be verified experimentally. For the original RCM that stimulated the mechanistic studies described here, the implications of this mechanism seem rather clear: the epimerization process requires a bis-phosphino−Ru complex (or perhaps an amino−phosphino complex)[40] to proceed, and therefore, only catalysts that do not form these intermediates stoichiometrically will yield epimer-free RCM products.

Given the lack of observable intermediates during the RCM of **2** catalyzed by the Hoveyda catalyst (Scheme 16), it is reasonable to assume that this reaction proceeds through the intermediacy of steady-state species (not observable by NMR), such as **44**, while the bulk of Ru is observed in its resting state, i.e. precatalyst **7**. Species **44** apparently cannot epimerize directly to **45** but requires the addition of a second strong σ-donor as a ligand. Indeed, addition of PCy_3 leads to observable formation of species **21** (Scheme 5) and subsequent epimerization to **22**. Although we have not verified this possibility experimentally, amines may also act as Ru ligands and direct the RCM toward epimers **5** and **6**.

It is also possible, although in our opinion much less likely, that with the Hoveyda catalyst the RCM initiates and propagates at the aminononenoic acid moiety, i.e. through intermediate **20** (Scheme 5), and no interaction with the vinylcyclopropane moiety takes place at any time. This possibility, although rather remote, should be considered and probed further.

Conclusions

The impetus for this study arose from the need to understand the intrinsic abilities of two very similar RCM catalysts to promote the reaction of diene **2** along two stereochemically divergent pathways, and to understand the impact of low levels of impurities on the reaction course. This led to the discovery of a novel epimerization reaction of vinylcyclopropanes, which is efficiently catalyzed by the Grubbs catalyst **3** but not by the Hoveyda catalyst **7**. This discrepancy was ascribed to the ligand (σ-donor) content of the two catalysts.

In addition, the unusual observation was made that diene **2**, contrary to our previous assumptions, reacts with **3** at the more hindered olefin terminus and with excellent regioselectivity (>20:1). A possible explanation for this observation may be an internal "soft" coordination of the carboxylate group of **21** to the Ru center. This remains to be verified experimentally. Although it is not known whether **20** or **21** is catalytically more active, these observations suggest the possibility of directing the RCM initiation and propagation site in a diene at will[41] and, in such a way, minimizing unwanted side reactions such as epimerization (or others). This avenue is under active investigation.

In conclusion, we have proposed a novel ruthenacyclopentene as an intermediate en route to cyclopropylmethylidene−Ru complexes. This new manifold, if accessible from other precursors (e.g. enynes), could lead to a variety of new synthetic avenues. A recent example of Ru-catalyzed enyne cyclization to produce vinylcyclopropanes may be an early realization of this possibility.[42]

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(39) (a) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431. (b) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863. (c) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654.

(40) Secondary aliphatic amines are rare as the Ru ligand in metathetical processes, but mixed piperidino/phosphino−Ru−carbene complexes have been implicated in the ROMP of norbornene: (a) Matos, J. M. E.; Lima-Neto, B. S. *J. Mol. Catal. A: Chem.* **2004**, *222*, 82. Pyridine−Ru−carbene complexes are well-known as rapid initiators: (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *Organometallics* **2001**, *20*, 5314. (c) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103. (d) Bai, C.-X.; Zhang, W.-Z.; He, R.; Lu, X.-B.; Zhang, Z.-Q. *Tetrahedron Lett.* **2005**, *46*, 7225.

(41) For a novel relay strategy, see: (a) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210. See also: (b) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912 and references therein.

(42) Eckert, M.; Monnier, F.; Shchetnikov, G. T.; Titanuyk, I. D.; Osipov, S. N.; Toupet, L.; Dérien, S.; Dixneuf, P. H. *Org. Lett.* **2005**, *7*, 3741.

Finally, tandem RCM−epimerization, as exemplified in the (undesired, in this case) production of macrocycle **5**, could be exploited as a synthetically useful operation. It is hoped that our mechanistic insight may help to plan such synthetic operations. We are currently pursuing these and other strategies.

Experimental Section

General. All experiments were conducted under Ar or N_2 atmosphere. Anhydrous THF, CH_2Cl_2, and toluene were degassed with Ar before use. All of the reagents and catalysts used in this paper were commercially available and used as received. (1*R*,2*S*)-1-Amino-2-vinylcyclopropane carboxylic acid methyl ester tosylate salt (99% ee) and its *tert*-butyloxycarbonyl derivatives were prepared as previously described.[11] The ethylidene species MeCH=$RuCl_2$-$(PCy_3)_2$ (**33**) was prepared according to the literature procedure.[15]

NMR Studies. Representative Example. (1*R*,2*S*)-Methyl 1-benzoylamino-2-vinylcyclopropane carboxylate (**8**) (12.3 mg, 0.05 mmol) and Grubbs catalyst (**3**) (12.3 mg, 0.015 mmol) were added to a dry vial under Ar. CD_2Cl_2 (1.00 mL, degassed with Ar bubbling through at rt for 1 h) was added to dissolve the two compounds, and a purple homogeneous solution resulted, which was then transferred to an NMR tube with a screw cap and septum under Ar. The sample was monitored by NMR at 303 K (500.1 MHz, ^{1}H; 202.5 MHz, ^{31}P) until epimerization reached equilibrium (2−3 h).

Crossover Study. A mixture of racemic methyl 1-benzoylamino-2-deuterium-2-(1-deuteriumvinyl)cyclopropane carboxylate (**27a**) (124 mg, 0.5 mmol), racemic ethyl 1-benzoylamino-2-vinylcyclopropane carboxylate (**32**) (130 mg, 0.5 mmol), Grubbs catalyst (41.1 mg, 0.05 mmol), and Ph_3P (13.1 mg, 0.05 mmol) in toluene (20 mL) was stirred at 60 °C for 3 h and then concentrated. Flash chromatography (silica gel, ethyl acetate/hexanes = 2/3) gave recovered racemic ethyl 1-benzoylamino-2-vinylcyclopropane carboxylate (**32**) (16.0 mg, 12.3%), *epi*-racemic methyl 1-benzoylamino-2-deuterium-2-(1-deuteriumvinyl)cyclopropane carboxylate (78.5 mg, 63.5%), and a mixture of racemic methyl 1-benzoylamino-2-deuterium-2-(1-deuteriumvinyl)cyclopropane carboxylate (**27a**) and *epi*-racemic ethyl 1-benzoylamino-2-vinylcyclopropane carboxylate. The mixture was separated by preparative HPLC to give recovered racemic methyl 1-benzoylamino-2-deuterium-2-(1-deuteriumvinyl)-cyclopropane carboxylate (**27a**) (16.4 mg, 13.2%) and *epi*-racemic ethyl 1-benzoylamino-2-vinylcyclopropane carboxylate (81.8 mg, 63.0%). Preparative HPLC conditions: mobile phases, water with 0.05% trifluoroacetic acid and acetonitrile with 0.05% trifluoroacetic acid; column, Phenomenex Luna C18(2) 30 × 250, 10 μm; flow rate, 25 mL/min; collection by UV at 220 nm. Identification data for *epi*-racemic methyl 1-benzoylamino-2-deuterium-2-(1-deuteriumvinyl)cyclopropane carboxylate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.82 (m, 2H), 7.47−7.53 (m, 1H), 7.37−7.44 (m, 2H), 6.80 (bs, 1H), 5.28 (s, 1H), 5.20 (s, 1H), 3.69 (s, 3H), 2.00 (d, J = 5.5 Hz, 1H), 1.40 (d, J = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.02, 168.38, 134.07, 132.75 (t, J = 24.2 Hz, 1C), 131.72, 128.42 (2C), 127.03 (2C), 118.45, 52.55, 38.74, 30.71 (t, J = 24.2 Hz, 1C), 22.31. Identification data for *epi*-racemic ethyl 1-benzoylamino-2-vinylcyclopropane carboxylate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.8 (m, 2H), 7.48−7.54 (m, 1H), 7.38−7.47 (m, 2H), 6.75 (bs, 1H), 5.57−5.66 (m, 1H), 5.31 (dd, J = 17.1 and 0.9 Hz, 1H), 5.23 (dd, J = 10.3 and 1.1 Hz, 1H), 4.16 (q, J = 7.1, 2H), 2.50 (q, J = 8.0 Hz, 1H), 2.04 (dd, J = 10.5 and 5.4 Hz, 1H), 1.41 (dd, J = 7.5 and 5.6 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H).

Kinetic Studies. HPLC Kinetics. A mixture of (1*R*,2*S*)-Methyl 1-benzoylamino-2-vinylcyclopropane carboxylate (**8**) (123 mg, 0.5 mmol) and Cy_3P (1.0 M in toluene, 0, 2.5, 5, 10, 15, or 20 mol %) in toluene (degassed with Ar at 50 °C for 2 h, 0.01 M) was stirred at 50 ± 0.2 °C under Ar for 30 min. A stock solution of Grubbs catalyst PhCH=$RuCl_2(PCy_3)_2$ (**3**) (2.5, 5.0, or 7.5 mol %, 0.025 M stock solution in toluene) or ethylidene catalyst[2] MeCH=$RuCl_2$-$(PCy_3)_2$ (**33**) was added, and timing was initiated. Samples (100 μL) were withdrawn at 5 min intervals and analyzed by HPLC vs external standards of starting compound (**8**) and its epimer (**9**). The concentrations of **8** and **9** were determined against quantitative HPLC calibration curves. Each experiment was repeated 1−5 times. Each rate constant represents the average of 2−6 determinations.

NMR Kinetics. A. Grubbs Catalyst PhCH=$RuCl_2(PCy_3)_2$ (3). (1*R*,2*S*)-Methyl 1-benzoylamino-2-vinylcyclopropane carboxylate (**8**) (36.9 mg, 0.15 mmol), internal standard 1,3,5-trimethoxybenzene (26.8 mg, 99%, 0.158 mmol), and Grubbs catalyst PhCH=$RuCl_2$-$(PCy_3)_2$ (**3**) (12.3 mg, 0.015 mmol) were added to a dry vial under Ar. CD_2Cl_2 (3.00 mL, degassed with Ar bubbling through at rt for 1 h) was added to dissolve the three components, and the resulting purple homogeneous solution was transferred to an NMR tube with a screw cap and septum under Ar. The sample was monitored by NMR at 23.5 ± 0.5 °C (500.1 MHz ^{1}H; 202.5 MHz ^{31}P). ^{1}H and ^{31}P NMR were recorded at 15−20 min intervals. The concentrations of **8** and **9** were determined based on integrations against the internal standard. Each experiment was repeated 1−2 times.

B. Ethylidene Catalyst MeCH=$RuCl_2(PCy_3)_2$ (33). (1*R*,2*S*)-Methyl 1-benzoylamino-2-vinylcyclopropane carboxylate (**8**) (12.3 mg, 0.05 mmol), internal standard 1,3,5-trimethoxybenzene (18.3 mg, 99%, 0.108 mmol), and ethylidene catalyst[2] MeCH=$RuCl_2$-$(PCy_3)_2$ (**33**) (38.0 mg, 0.05 mmol) were added to a dry vial under Ar. Degassed CD_2Cl_2 (1.00 mL) was added, and the resulting purple homogeneous solution was stirred at rt for 10 min and evaporated *in vacuo* to dryness (∼10 min). Another 1.00 mL of degassed CD_2-Cl_2 was added, followed by the addition of a Cy_3P solution in toluene (1.0 M; 0.05, 0.1, or 0.2 mL; corresponding to 1, 2, or 4 equiv of Cy_3P relative to the substrate). The resulting homogeneous mixture was transferred to an NMR tube with a screw cap and septum under Ar. The sample was monitored by NMR at 23.5 ± 0.5 °C (500.1 MHz ^{1}H; 202.5 MHz ^{31}P). ^{1}H and ^{31}P NMR were recorded at 15−20 min intervals. The concentrations of **8** and **9** were determined based on integrations against the internal standard. Each experiment was repeated 1−4 times.

Kinetic Isotope Effects. The HPLC and NMR kinetics experiments were performed following the above example except that (1*R*,2*S*)-methyl 1-benzoylamino-2-vinylcyclopropane carboxylate (**8**) was replaced with racemic methyl 1-benzoylamino-2-deuterium-2-(1-deuteriumvinyl)cyclopropane carboxylate (**27a**). The NMR kinetics experiments were also performed on (1*R*,2*S*)-methyl 1-benzoylamino-2-vinylcyclopropane carboxylate (**8**) and an equimolar mixture of racemic methyl 1-benzoylamino-2-(1-deuteriumvinyl)cyclopropane carboxylate (**27b**) and racemic methyl 1-benzoylamino-2-deuterium-2-vinylcyclopropane carboxylate (**27c**), using 1 equiv of the ethylidene catalyst[2] MeCH=$RuCl_2(PCy_3)_2$ (**33**) instead of 10 mol % of the Grubbs catalyst PhCH=$RuCl_2(PCy_3)_2$ (**3**).

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Supporting Information Available: Complete refs 13 and 20. Detailed experimental procedures and characterization of all compounds, plus energies and coordinates for all ground states and transition states described in the paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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