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On the Mechanism and Selectivity of the Combined C−H Activation/Cope Rearrangement

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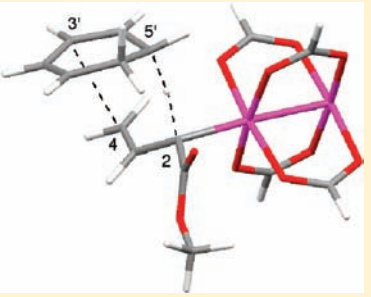
Supporting Information

ABSTRACT: The combined C−H activation/Cope rearrangement (CHCR) is an effective C−H functionalization process that has been used for the asymmetric synthesis of natural products and pharmaceutical building blocks. Up until now, a detailed understanding of this process was lacking. Herein, we describe a combination of theoretical and experimental studies that have resulted in a coherent description of the likely mechanism of the reaction. Density functional studies on the reactions of rhodium vinylcarbenoids at allylic C−H sites demonstrate that the CHCR proceeds through a concerted, but highly asynchronous, hydride-transfer/C−C bond-forming event. Even though most of the previously known examples of this process are highly diastereoselective, the calculations demonstrate that other transition-states and stereochemical outcomes might be possible by appropriate modifications of the reagents, and this was confirmed experimentally. The calculations also indicate that there is a potential energy surface bifurcation between CHCR and the competing direct C−H insertion.

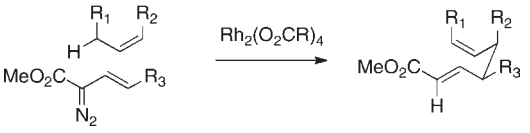


INTRODUCTION

New C−H functionalization methods offer exciting strategies for the synthesis of complex organic architectures.[1,2] Since our original communication in 1997,[3] we have been actively engaged in exploring the use of donor/acceptor-substituted rhodium carbenoids as intermediates for stereoselective intermolecular C−H functionalization.[2e−g,4] One of the most impressive variants of this chemistry is the reaction between vinyldiazoacetates and allylic C−H bonds, which has been called the "combined C−H activation/Cope rearrangement" (CHCR) (Scheme 1).[2g,4−7] This reaction occurs with remarkable stereoselectivity, and many examples have been reported in which the products contain two new stereocenters formed in >50:1 dr and >98% ee.[2g,5−11]

The CHCR has been demonstrated to be a powerful tool in organic synthesis.[12] It has been applied as a key reaction in the formation of medicinally interesting molecules[7,9,13] as well as natural products.[12,14−16] The most impressive examples of the synthetic power of the CHCR are in its application to complex natural product synthesis.[12,14−17] A general approach toward marine natural products isolated from *Pseudopterogorgia elisabethae* has been reported, using the CHCR to incorporate traditionally challenging motifs.[12,14−17] This was highlighted in the total syntheses of (−)-colombiasin A,[17] (−)-elisapterosin B,[17] and several other related natural products.[14−16] The key step involved in the combined C−H activation/Cope rearrangement is an enantiodivergent process from a racemic dihydronaphthalene substrate.[16] This led to enantiocontrol over three crucial stereocenters present in these natural products (Scheme 2).[12,14−17]

Scheme 1. Combined C−H Activation/Cope Rearrangement (CHCR)



Even though the CHCR reaction is a powerful transformation, with many substrates, a competing reaction is the direct C−H insertion, as illustrated in Scheme 3.[5] The Rh_2(*S*-DOSP)$_4$-catalyzed reaction of styryldiazoacetate **3** with 1-methylcyclohexene generates a 1.6:1 mixture of the CHCR product **4** and the direct C−H insertion product **5**.[5] On first glance, it would be reasonable to assume that the CHCR occurs by a C−H insertion followed by a Cope rearrangement, but it has been shown on several occasions that the C−H insertion products are thermodynamically more stable and thus are not viable intermediates in the CHCR process.[6,7,18,19] A challenge in this chemistry is to understand what factors control whether a CHCR or a direct C−H insertion is the favored transformation.

A model has been proposed to rationalize the stereochemical outcome of this chemistry, in which the reaction is believed to be initiated by a C−H insertion process, but this is interrupted by a Cope rearrangement occurring through a chairlike transition

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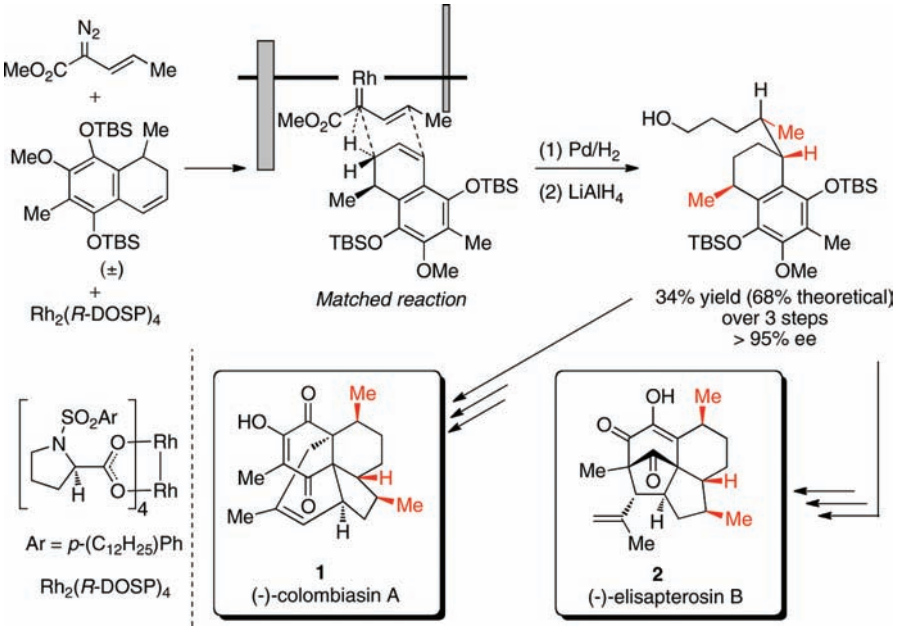
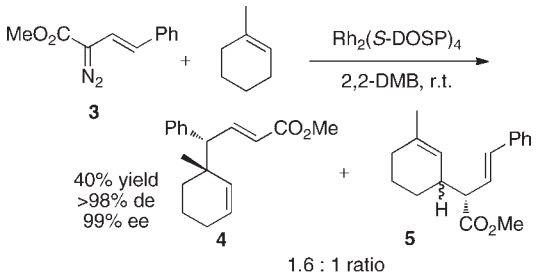
Scheme 2. Application of the Enantiodivergent CHCR in Natural Product Total Synthesis[17]



Scheme 3. Competing C−H Insertion and CHCR.[5]



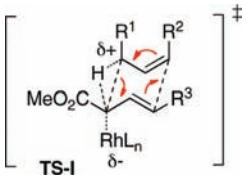
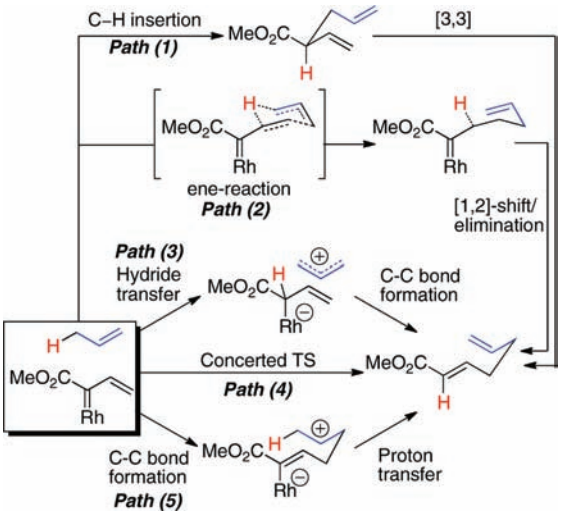


Figure 1. Current "chair" transition-state hypothesis.[5,10]

state **TS-I** (Figure 1).[5,10] This model successfully predicts the observed major stereoisomer. Although the model illustrated in Figure 1 is predictive of the stereochemical outcome of the reaction, to date, it has not been rigorously evaluated.

Since its discovery in the late 1990s,[7] several mechanistic hypotheses have been put forth for the CHCR process. Five proposals currently exist (Scheme 4): (1) a direct C−H insertion, followed by a thermal Cope rearrangement,[2d] (2) an ene-type reaction, in which the vinylcarbenoid acts as a 2π-enophile,[7] followed by hydride shift/elimination, (3) a hydride transfer, followed by vinylogous C−C bond formation, (4) a concerted, synchronous transition state[5] involving seven atoms or, (5) initial attack of the vinyl group onto the vinylogous position of the carbenoid complex, followed by proton transfer. The latter three lie on a mechanistic continuum, as indicated in Scheme 4.

Scheme 4. Mechanistic Proposals for the CHCR Reaction.[2d,5,7]



Mechanism (1) can be eliminated, since, in several cases, the CHCR reaction has been demonstrated to produce the thermodynamically less stable (kinetic) product.[6,7,18,19] The C−H insertion product can therefore not be an intermediate in this process. Mechanism (2) is also an unlikely pathway, particularly since hydride shift/elimination in alkyl-substituted rhodium carbenoids is well precedented and is known to form the *Z*-product preferentially.[20] In the CHCR reaction, the *E*-product is typically observed. Mechanisms (3) and (4) are both consistent with the observed chemistry. The latter pathway has served as the basis of the currently used stereochemical predictive model for this reaction.[5] Pathway (5) may also occur, since vinylogous reactivity leading to C−C bond formation is known.[21] However, in 1,3-diene-like systems, this would imply that an internal position of

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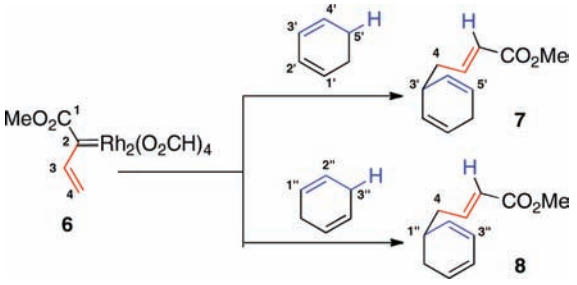
Scheme 5. Model Reactions for the Computational Studies



the sp^2-system must initiate the reaction, which is inconsistent with the HOMO electron density distribution.[22]

In this paper we have undertaken a detailed computational analysis of the CHCR process. In particular, the likely mechanism of the reaction has been interrogated in order to evaluate whether a process that seems to combine the C−H insertion and the Cope rearrangement is feasible. Second, a conformational analysis of rhodium vinylcarbenoids and its implications for the stereochemical outcome of the reaction has been investigated. Third, studies have been conducted to determine what controls whether a reaction proceeds by a direct C−H insertion or the CHCR, because in many instances these reactions compete with each other. Finally, experimental studies have been conducted to test the predictions that arose from the computational studies.

CHEMICAL MODELS

The CHCR reaction is often highly stereoselective. The most successful substrates in this chemistry have been cyclic 1,3-diene-like systems such as 1,3-cyclohexadienes,[7] cycloheptatriene,[6] and particularly 1,2-dihydronaphthalenes.[8,10,19,23] In this work, we have studied two model catalytic reactions between vinylcarbenoids and allylic C−H sites using dirhodium tetrakis(formate), $Rh_2(O_2CH)_4$, as a dirhodium carboxylate model[24,25] (Scheme 5)—the reaction between the unsubstituted vinylcarbenoid complex **6**[24,25] and either (1) 1,3-cyclohexadiene to produce **7** or (2) 1,4-cyclohexadiene, to produce **8**. Although the unsubstituted vinylcarbenoid has not been used for synthetic utility of the CHCR reaction, it was employed herein for computational simplicity. These model reactions serve to study the fundamental mechanism and to analyze the stereochemical outcome of the transformation. The vinylcarbenoid model **6** has been described in previous computational studies on cyclopropanation chemistry.[24,25c] This study is focused on an analysis of how the rhodium carbenoid reacts with the substrates. For detailed discussions on the formation of the reactive vinylcarbenoid complex, see refs 24 and 25c.

COMPUTATIONAL METHODOLOGY

All calculations were performed with the Gaussian '09 software package.[26] Density functional theory was employed with the three-parameter hybrid functional B3LYP[27] to locate stationary points on the potential energy surface (PES). Some of the structures were initially located at the B3LYP/Lanl2DZ level of theory but were then subjected to full geometry optimization with a basis set consisting of the 1997 Stuttgart relativistic small-core effective core-potential and basis set [Stuttgart RSC 1997 ECP][28] for Rh, augmented with a 4f-function (ζ_f(Rh) = 1.350).[24] The split valence basis set 6-31G* was used in the optimization and frequency calculations for all other atoms (C, H, N, and O). This composite basis set is abbreviated 6-31G*[Rh-RSC+4f].[24] The main discussion is based on single-point energies calculated at the B3LYP/6-311+G(2d,2p)[Rh-RSC+4f]//B3LYP/6-31G*[Rh-RSC+4f] level of theory, with zero-point energy corrections calculated at the B3LYP/6-31G*[Rh-RSC+4f] level and Gibbs free energies calculated at the B3LYP/6-31G*[Rh-RSC+4f] level of theory. Stability of the SCF-solution was confirmed by stability analyses for selected stationary points at the same level.[29a,b] This analysis was conducted since it is well-known that the transition state for the Cope rearrangement itself has a considerable triplet-character.[29c−e] Heavy-atom basis set definitions and corresponding pseudopotential parameters were obtained from the EMSL basis set exchange library.[30] All stationary points were characterized by normal coordinate analysis at the B3LYP/6-31G*[Rh-RSC+4f] level of theory. Transition states were confirmed to have only one imaginary vibrational mode corresponding to movement along the reaction coordinate. Equilibrium structures were confirmed to have zero imaginary vibrational modes. Transition states were further characterized by either full intrinsic reaction coordinate (IRC) analysis using maxpoints = 100 or more, or by using default parameters in Gaussian'09, followed by geometry optimization to confirm that the stationary points were smoothly connected. The calculated harmonic zero-point vibrational energies (ZPVE) are reported unscaled. Calculated structures have been visualized using Mercury.[31]

Solvent effects have not been considered in this work because the C−H functionalization chemistry in practice often is carried out in hydrocarbon solvents such as hexanes, pentane, or 2,2-dimethylbutane, which have very small dielectric constants.

RESULTS AND DISCUSSION

Stereochemical Considerations. The CHCR reaction is usually highly selective for one stereoisomeric outcome. However, stereochemical issues exist that could have crucial impact on the reaction outcome for a given vinylcarbenoid/substrate combination.[21a] The two main variables in this regard are associated with: (1) the vinylcarbenoid conformation and (2) the substrate orientation. The vinylcarbenoid may exist in both *s-cis* and *s-trans* conformations, which can readily interconvert (Figure 2a).[21a] When the vinylcarbenoid is substituted at the terminus, which is the case for most synthetically useful systems, reactions via the two conformers will result in two stereochemically distinct pathways. With two possible orientations of the substrate, this leads to four possible approach combinations as shown in Figure 2b. The combinations can be considered to be boatlike or chairlike, in analogy to the corresponding Cope rearrangement, and are therefore classified based on this in addition to the orientation of the vinylcarbenoid (*s-cis*/chair etc.). In the following section, we will describe a conformational analysis of rhodium vinylcarbenoids and show how substituents on the vinyl group influence the preferred conformation. This would be a valuable tool for assessing reactions with more complex vinylcarbenoid systems. A detailed evaluation of reactions through all four possible transition-state combinations of substrate orientation and vinylcarbenoid conformation will then follow.

Conformational Analysis. Considering the vital importance the vinylcarbenoid conformation can have on the stereochemical outcome of the CHCR reaction, we decided to investigate the equilibrium between the *s-trans* and *s-cis* vinylcarbenoid conformations using differentially substituted vinyl groups. By considering gas-phase Gibbs free energies from B3LYP/6-31G*[Rh-RSC+4f] calculations (Table 1), the equilibrium constants for the *s-cis* to *s-trans* isomerization process were calculated for substituted vinylcarbenoids. The unsubstituted vinylcarbenoid **6** has

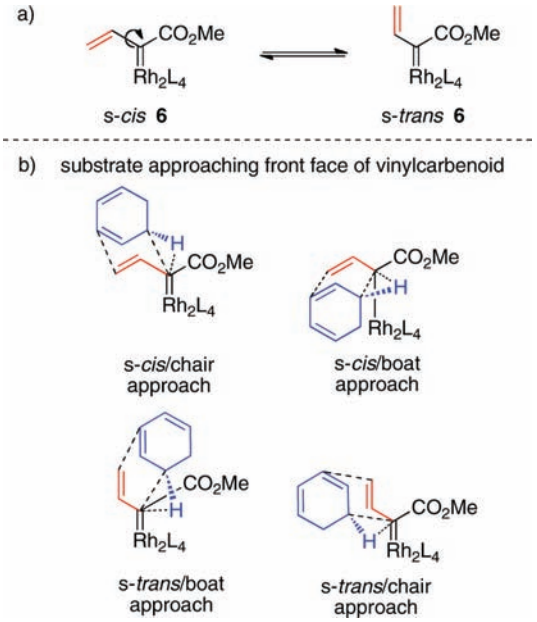
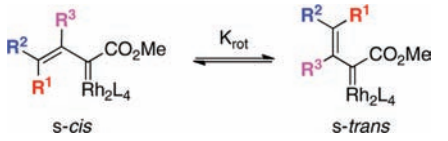


Figure 2. (a) Vinylcarbenoid conformations. (b) Combinations of substrate approaches and vinylcarbenoid conformations.

a slight preference for the *s-trans* conformer (−0.59 kcal/mol). In comparison, previously described calculations at the B3LYP/6-31G*[Rh-LA2] level of theory give $\Delta G_{rot} = -0.47$ kcal/mol for this system.[25c] By introducing a methyl group at the (*E*) position, R^2 (**9**), a commonly used vinylcarbenoid in synthesis, there is still a small preference for the latter conformer of −0.20 kcal/mol. When the methyl group is introduced at the internal position (R^3), a stronger preference for the *s-cis* conformation of **10** is observed by +1.78 kcal/mol. This is related to the unfavorable steric interactions involved between the internal substituent and the catalyst "wall" in the *s-trans* conformation. This effect is more pronounced when introducing a (*Z*)-substituent (R^1 = Me) in vinylcarbenoid **11**, which strongly prefers the *s-trans* conformer by −3.63 kcal/mol. The (*Z*)-substituent (R^1) is very close to the catalyst structure in the *s-cis* conformer and leads to a somewhat distorted geometry. Another system, often used in synthesis, is the (*E*)-styrylcarbenoid **12**. Similar to entries 1 and 2, there is a slight preference for the *s-trans* conformer by −0.12 kcal/mol. The general trends appear to be: (1) for vinylcarbenoids with only an (*E*)-substituent (other than hydrogen), there is no strongly preferred conformer, and hence, both potentially have to be considered in reactions involving the vinyl group. For most such systems, however, the *s-cis* conformer appears to be the more reactive. (2) For vinylcarbenoids with an internal substituent, the *s-cis* conformation is preferred. Most likely, this is the only conformer present for the commonly used vinylcarbenoids, as the group is usually much larger than methyl (usually siloxy-, aryl-, or alkyl group). (3) If the vinylcarbenoid has a (*Z*)-substituent, the *s-trans* conformer is strongly preferred. These results will serve as a foundation for evaluation of specific carbenoid systems in this chemistry. However, when considering reactions with the vinylcarbenoid, a Curtin-Hammett situation is likely to occur.[32] The barrier for rotation of the unsubstituted carbenoid **6** is $\Delta G^{\ddagger} = +8.8$ kcal/mol (*s-trans* to *s-cis* **6**), much smaller than the free energy barriers for the CHCR process ($\Delta G^{\ddagger} > 16$ kcal/mol), so that conditions for a Curtin-Hammett system are present.[32] The least stable conformer may be predominantly involved in the reaction. However, for carbenoids such as **10** and **11**, and especially for systems with even bigger substituents than methyl, reactions are more likely to be controlled by the major available conformer. The free energy barrier for vinyl group rotation in carbenoid **10** is $\Delta G^{\ddagger} = +6.5$ kcal/mol (*s-cis* to *s-trans* **10**), while for the *Z*-vinylcarbenoid **11** it is $\Delta G^{\ddagger} = +9.1$ kcal/mol (*s-trans* to *s-cis* **11**).

Table 1. Influence of Substitution on Conformational Preference



Entry	Carbenoid	R^1	R^2	R^3	ΔG_{rot} (kcal/mol)	K_{rot}
1	**6**	H	H	H	-0.59	2.74
2	**9**	H	Me	H	-0.20	1.40
3	**10**	H	H	Me	+1.78	0.049
4	**11**	Me	H	H	-3.63	462
5	**12**	H	Ph	H	-0.12	1.22

Reaction with 1,3-Cyclohexadiene. Transition structures were next sought for all the combinations of substrate orientation and carbenoid conformation in the reaction between the vinylcarbenoid model **6** and 1,3-cyclohexadiene. None of the located transition states indicated a concerted, synchronous process involving all seven atoms, as previously hypothesized.[5] The most stable transition structure, **TS-II**, was the *s-cis*/chair combination of vinylcarbenoid and substrate (Figure 3). All the located transition states were characterized by an almost perpendicular approach of the allylic C−H bond of the substrate toward the carbenoid, with C−H−$C_{carbenoid}$ angles of ∼170°. When animated in their imaginary vibrational modes, the transition states displayed lengthening of the substrate C−H bond with motion toward the carbenoid carbon. These observations strongly indicate a predominant hydride-transfer process—consistent with what has been observed in direct C−H insertion chemistry.[24,25a,25b] However, the hydride-transfer component appears to be more pronounced for the allylic C−H bonds. The terminal carbons ($C_{3'}$ and C_4) are separated by 3.188 Å and display no signs of rehybridization (unchanged bond lengths and angles), which indicates that no C−C bond forming interactions have developed in the TS.

When moving forward on the reaction coordinate from **TS-II** (IRC), the potential energy surface following the hydride-transfer transition state is relatively flat; however, C−C bond formation between the terminal positions occurs before a zwitterionic intermediate can form. These observations indicate that the CHCR reaction proceeds through a concerted, but highly asynchronous, hydride-transfer/C−C bond-formation event. These results are consistent with previous DFT studies of direct C−H insertion.[24,25a,25b] The more accurate picture of the mechanism is shown in Figure 4a, with the hydride-transfer component occurring first. From this, a simple predictive model for the sense of

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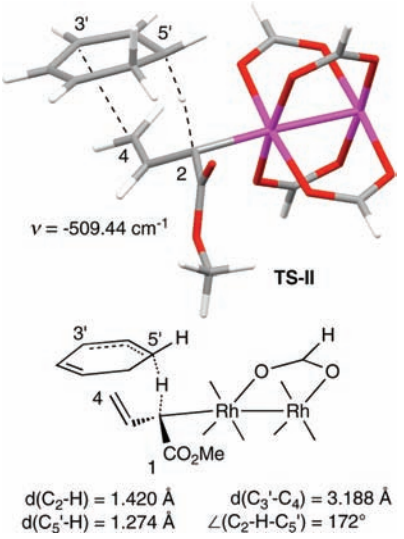

Figure 3. Most stable TS structure and geometrical characteristics.

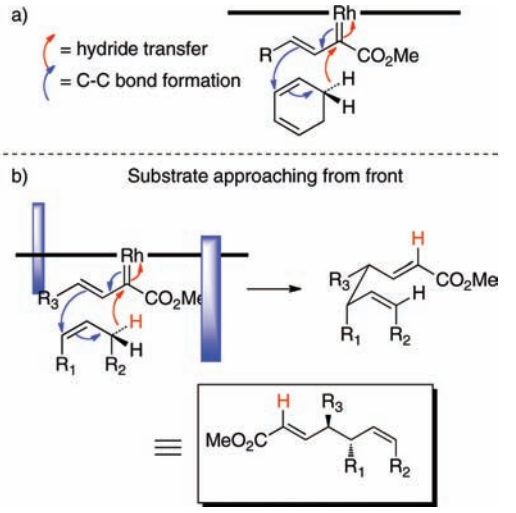

Figure 4. (a) Concerted, yet highly asynchronous mechanism for the CHCR reaction. (b) Predictive model for asymmetric induction by Rh_2(*S*-DOSP)$_4$.

absolute asymmetric induction can be introduced when considering the chiral influence of the commonly used catalyst, Rh_2(*S*-DOSP)$_4$. This catalyst is proposed to exist in a D_2-symmetric conformation[33] in nonpolar media, and the chiral influence can be represented by steric blocking groups as indicated in Figure 4b—allowing for reaction to occur at the carbenoid *Re*-face.[24,33] This model can now successfully predict the stereochemical outcome for this reaction. For a detailed discussion of the D_2-symmetry model for the dirhodium prolinates, see refs 33a and 33c.

A given combination of vinylcarbenoid conformation (*s-cis*/*s-trans*) and substrate orientation (boat/chair) gives rise to a distinct pathway in the CHCR reaction. Scheme 6 shows all the transition-state combinations for our model system, their energies (*E*+ZPE) and Gibbs free energies relative to free carbenoid and 1,3-cyclohexadiene as well as results of forward intrinsic reaction coordinate analyses. We have added two unspecified groups R and R′ (R = R′ = H in the calculations) to demonstrate the stereochemical implications of each pathway, as this would be important to synthetically relevant reaction systems. The *s-cis*/chair transition state **TS-II** ($(E+ZPE)_{rel}$ = +4.2 kcal/mol) corresponds to the basic model for the CHCR reaction and gives a predicted product consistent with the experimentally observed stereoselectivity.[5,7] This is also the most stable transition structure. The *s-cis*/boat combination **TS-III** ($(E+ZPE)_{rel}$ = +6.2 kcal/mol) would give CHCR product **14**, which would have one inverted stereocenter compared to **13**. However, this stereoisomer has not been observed for the CHCR reaction. The *s-trans*/boat transition structure **TS-IV** ($(E+ZPE)_{rel}$ = +5.8 kcal/mol) led to a different product **15**. As the hydride transfer proceeds toward completion, the carbonyl oxygen of the ester group deprotonates the adjacent position on the substrate (presumably due to a significant cationic character at this point), leading to an enol **15** and aromatization of the substrate. Finally, the *s-trans*/chair structure **TS-V** ($(E+ZPE)_{rel}$ = +4.4 kcal/mol) undergoes the CHCR reaction to form **16**, with totally opposite stereocenters to that of **13**. A more interesting feature here is the formation of a *Z*-double bond, a feature set by the *s-trans* orientation of the initial vinylcarbenoid.[21a] A *Z*-CHCR product has only been observed as a minor product with this substrate when a very electron-deficient catalyst, $Rh_2(TFA)_4$, was used in the reaction.[34] Although the most stable transition structure **TS-II** corresponds to the experimentally observed outcome of the CHCR reaction, the variation in relative potential energies (+4.2−6.2 kcal/mol) and Gibbs free energies (+16.4−18.5 kcal/mol) for the four combinations is relatively small. This leads to the exciting possibility that, even though the examples of the CHCR reactions reported to date have proceeded through the *s-cis*/chair approach, other stereochemical outcomes may be accessible by using the appropriate combination of carbenoid precursor and substrate.

We decided to test the hypothesis that other transition-state combinations may be accessible in the CHCR reaction by experiments with specific carbenoid precursors. As a test substrate, we decided to use 1-methyldihydronaphthalene **17**, as such 1,3-diene-like compounds are known to be effective in the CHCR reaction.[10,19,23] By performing the reactions with an established chiral catalyst, Rh_2(*S*-DOSP)$_4$, valuable stereochemical information would also result from the experiments (Scheme 7). The *E*-vinylcarbenoid derived from diazo compound **18** would undergo a CHCR reaction predicted by the established model (*s-cis*/chair TS) to form **19** with excellent stereocontrol.[10] It has been demonstrated experimentally that the use of a *Z*-vinyldiazoacetate results in reactions derived from an intermediate *s-trans* vinylcarbenoid[21a]—consistent with our above conformational analysis showing that just a methyl group is required to totally control the *Z*-vinylcarbenoid conformation (*s-trans* only). A CHCR reaction using the *Z*-vinyldiazoacetate **20** would consequently be forced to go through either the *s-trans*/chair or *s-trans*/boat transition states—totally unprecedented pathways. Stereochemical analyses of the products from these reactions would reveal what transition state is pertinent.

The reaction between **18** and **17**, catalyzed by Rh_2(*S*-DOSP)$_4$, in hexanes at 0 °C led to two isolated products, the predicted CHCR product **19** and the C−H insertion product **21** in a 6:1 ratio (Scheme 8). The CHCR product was formed in 53% yield and in excellent 98% ee, and with stereochemistry consistent with the *s-cis*/chair predictive model.[10] Even though the C−H insertion product **21** can be derived from a CHCR reaction to form **19**, followed by a Cope rearrangement,[10] in this case, **21** is considered to be formed from a direct C−H insertion. Typically more vigorous conditions are required to induce the Cope

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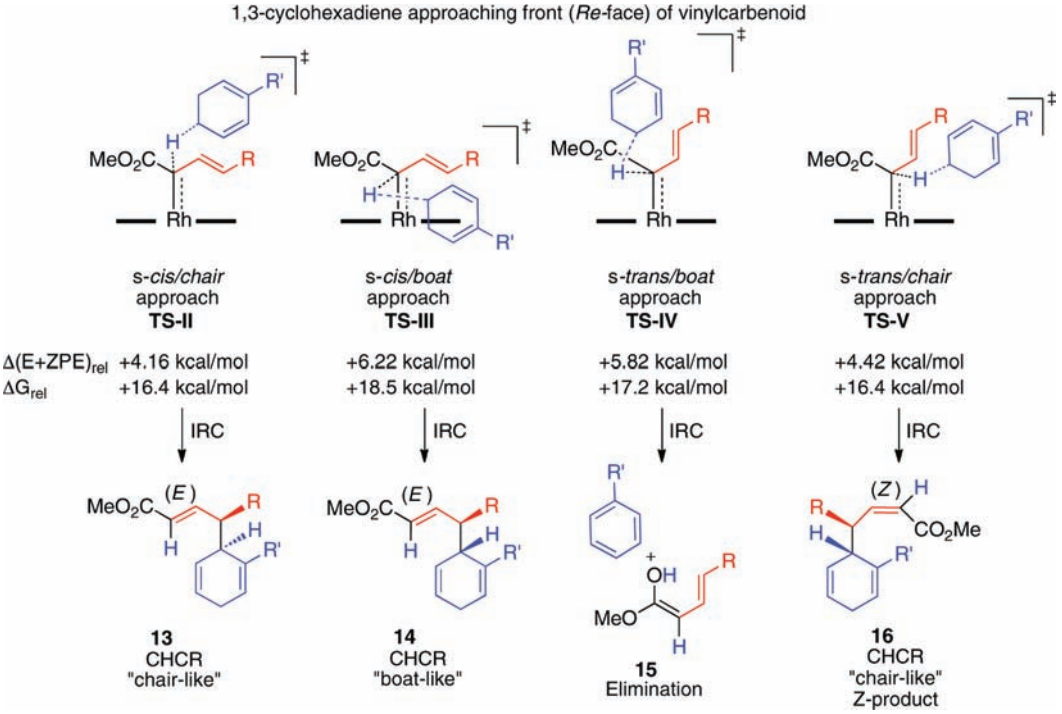
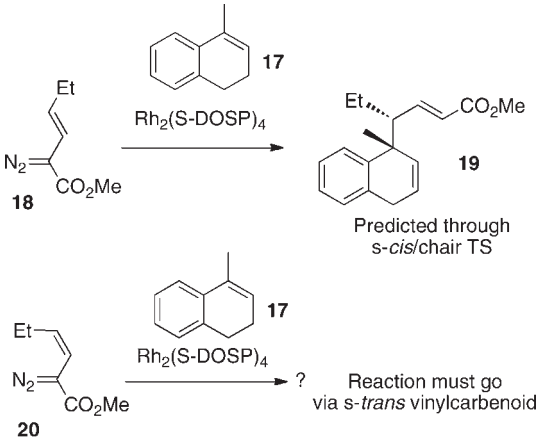
Scheme 6. Forward Intrinsic Reaction Coordinate Analysis and Stereochemical Implications[a]



[a] Gibbs free energies and ZPE were calculated at the B3LYP/6-31G*[Rh-RSC+4f] level of theory. Potential energies were calculated at the B3LYP/6-311+G(2d,2p)[Rh-RSC+4f]//B3LYP/6-31G*[Rh-RSC+4f] level of theory. The energies are reported relative to *s-trans* carbenoid **6** + 1,3-cyclohexadiene.

Scheme 7. Experimental Probe of Vinylcarbenoid Conformational Control



rearrangement in this substrate. Furthermore, the difference in the enantiomeric excess of the two products and the lack of change in the product ratio on allowing the reaction to stand is not consistent with the formation of the C−H insertion product **21** from **19**. Reaction with the *Z*-vinyldiazoacetate led to a 1:2.5 ratio of CHCR product **22** (14% yield, 91% ee)[35] and direct C−H insertion product **23** (44% yield, 10:1 dr, 84% ee of major diastereomer). In this case, the latter product is indeed derived from a direct C−H insertion process, as the attenuated diastereo- and enantioselectivity relative to the CHCR product is consistent with previous findings in C−H insertion chemistry.[4c] Interestingly, the CHCR product has a *Z*-double bond, but has retained the same stereogenic centers as in the reaction with the *E*-vinyldiazoacetate. This would only be consistent with a reaction proceeding through the *s-trans*/boat transition state (**TS-IV**). The *s-trans*/chair TS may be disfavored for dihydronaphthalene substrates as the aromatic moiety would be expected to have more steric interference with the catalyst structure compared to in the *s-trans*/boat-approach. Nevertheless, we have demonstrated that, through appropriate vinylcarbenoid conformational control, a "non-traditional" transition state for the CHCR reaction can be favored—consistent with our hypothesis. Furthermore, the results suggest that a given substrate may have a preference for a specific approach and, hence, a different diastereomeric outcome of the CHCR reaction may be possible by subtle changes in substrate. Another interesting observation is that the reaction through an *s-trans* vinylcarbenoid appears to slightly favor direct C−H insertion chemistry over the CHCR reaction. This will be discussed below.

Direct C−H Insertion versus CHCR. 1,3-Diene-like compounds are excellent substrates for the CHCR reaction. However, it is not fully understood how the substrate structure controls whether a system undergoes direct C−H insertion or the CHCR process. The success of dihydronaphthalenes and 1,3-dienes in the CHCR chemistry, as well as our enhanced understanding of the mechanistic details presented herein and in previous works,[24] prompted us to investigate what intrinsic factors of the substrate could control this delicate balance. In accordance with our mechanistic description of the CHCR, as the hydride-transfer stage of the highly asynchronous process becomes advanced, there would be a strong carbocationic character developing in the conjugated system of the substrate, as well as carbanionic character at the vinylcarbenoid portion. For a 1,3-diene-like substrate, the

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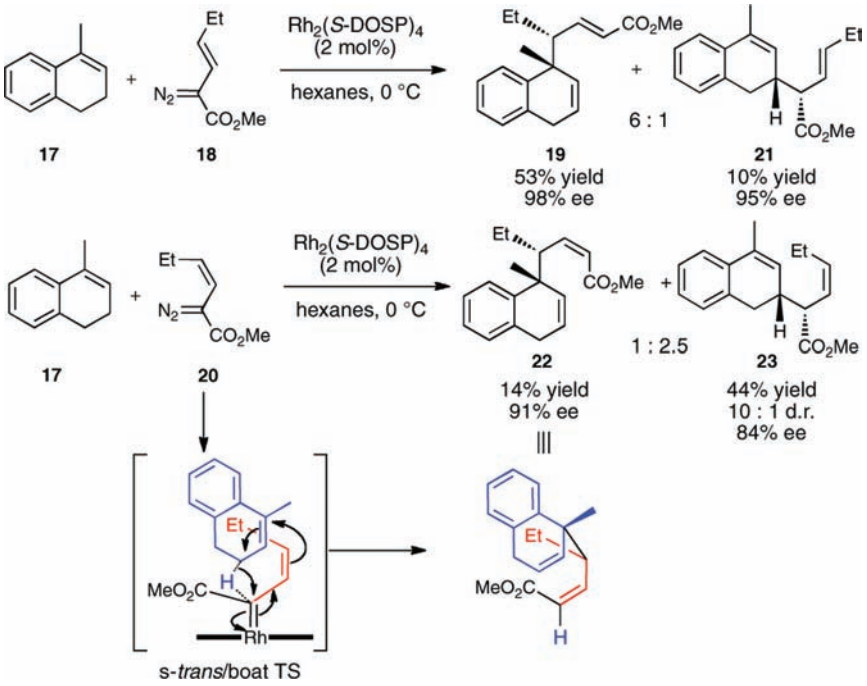
Scheme 8. *E* vs *Z*-Vinylcarbenoids in the CHCR Reaction



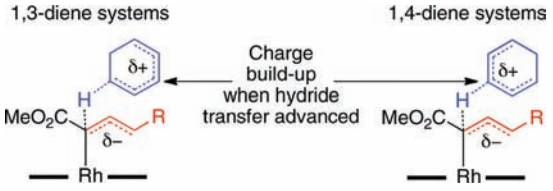


Figure 5. Charge stabilization in dienyl substrates.

majority of positive charge buildup would localize onto the central carbon of the cyclohexadienyl system (Figure 5), consistent with charge distribution in pentadienyl cation systems.[22] For dihydronaphthalenes, this position would also be benzylic, providing even better positive charge stabilization. One hypothesis is that this charge stabilization during the reaction progress in 1,3-diene systems favors the CHCR reaction to occur as the carbanionic vinylcarbenoid moiety prefers to form a C−C bond between the vinyl terminus and the internal position of the substrate. In order to support this idea we hypothesized that, in closely related substrates such as 1,4-cyclohexadienes, the same charge-localization would occur as the hydride transfer becomes advanced. However, as the internal position of the cationlike system would be at the site of hydride transfer in this case, C−C bond formation would preferably occur at this position and, hence, reduce the propensity of the CHCR process to occur.

To test the above hypothesis, we decided to carry out experiments with 1,4-cyclohexadiene as a substrate in the reaction with methyl styryldiazoacetate **24**, catalyzed by Rh_2(*S*-DOSP)$_4$ (see Scheme 9). The reaction afforded the CHCR product **25** as the major product in 72% relative yield and in 93% ee. The product derived from a direct C−H insertion (**26**) was also formed in 26% relative yield in 85% ee. This was shown to be the thermodynamically most stable product. A minor amount of another CHCR product **27** (2% relative yield), containing a *Z* double bond and inverted stereogenic centers relative to **25**, was produced in 79% ee.[36] This product is quite unusual in this chemistry. The absolute and relative configuration of **25** is consistent with the established *s-cis*/chair model for the CHCR reaction (Figure 4). Furthermore, the direct C−H insertion to form **26** is in agreement with the predictive model developed for C−H insertion chemistry.[24] Consistent with our previous considerations, the formation of a *Z*-product (**27**) must occur through a vinylcarbenoid in the *s-trans* conformation, and the absolute and relative configurations suggest that it is formed through an *s-trans*/chair TS. The observation of direct C−H insertion does indeed lend support to our hypothesis on the electronic factors that influence the CHCR reaction in 1,3-diene-like systems. For 1,3-cyclohexadienes, no C−H insertion has been reported.[7]

Considering our hypothesis on the electronic factors influencing the CHCR reaction, as well as the above experimental results indicating a higher propensity of direct C−H insertion, we decided to carry out a detailed computational analysis using the 1,4-cyclohexadiene system as substrate. Transition states were located for the approach of 1,4-cyclohexadiene toward our vinylcarbenoid model **6**. Because of the symmetry, only one hydride-transfer TS was found for each vinylcarbenoid conformer (Scheme 10). Both transition structures had very similar potential energies (relative to free carbenoid plus 1,4-cyclohexadiene), +5.06 kcal/mol for **TS-VI** and +5.17 kcal/mol for **TS-VII**. The IRC analysis showed that reaction through **TS-VI** proceeded by a hydride-transfer/C−C bond-forming reaction, consistent with our previous findings, and ultimately led to CHCR product **28**, derived from an *s-cis*/chair TS. This is in agreement with the existing stereochemical model and the experimental results. The IRC analysis from **TS-VII**, however, led to the direct C−H insertion product **29** with stereochemistry in agreement with the existing model for this chemistry.[24] These results suggest that reaction via the *s-trans* vinylcarbenoid may have a preference for direct C−H insertion

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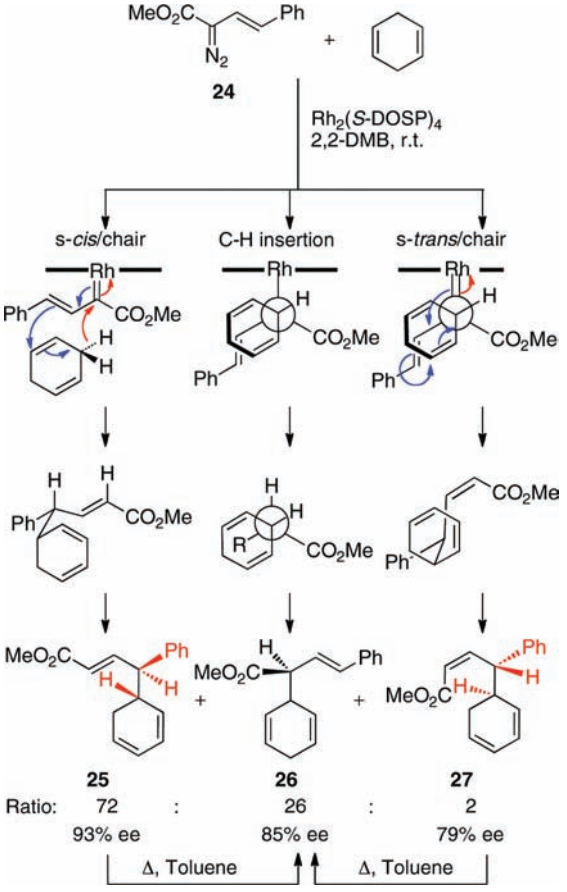
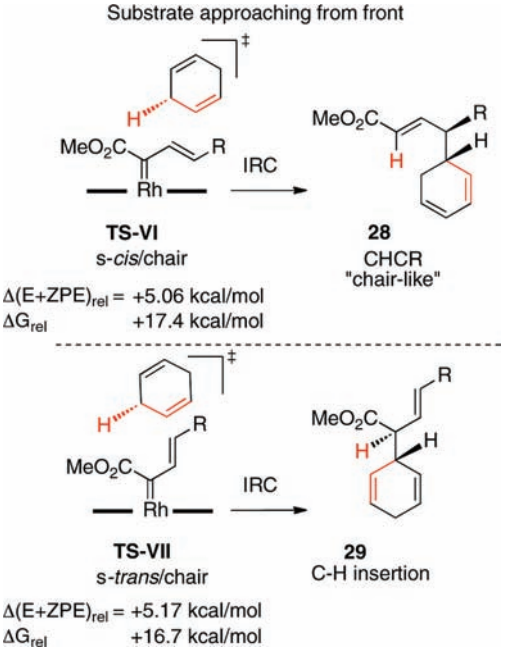
Scheme 9. Reaction between Styryldiazoacetate 24 and 1,4-Cyclohexadiene



Scheme 10. IRC Analyses of Both Combinations of 1,4-Cyclohexadiene and Vinylcarbenoid 6[a]



[a] Gibbs free energies and ZPEs were calculated at the B3LYP/6-31G*[Rh-RSC+4f] level of theory. Potential energies were calculated at the B3LYP/6-311+G(2d,2p)[Rh-RSC+4f]//B3LYP/6-31G*[Rh-RSC+4f] level of theory. The energies are reported relative to *s-trans* carbenoid **6** + 1,4-cyclohexadiene.

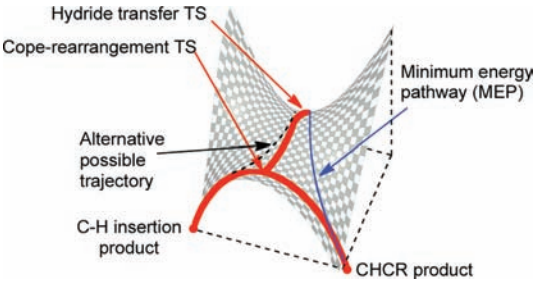


Figure 6. Model potential energy surface bifurcation.

rather than the CHCR reaction. Evidence for this was also noted in the experimental results in the reaction between a *Z*-vinylcarbenoid and 1-methyldihydronaphthalene (Scheme 8), which favored direct C−H insertion even though the substrate was considered to be "optimal" for the CHCR reaction. The results are puzzling, because how does direct C−H insertion occur through the same transition state that would have to be invoked to explain the existence of the minor *Z*-CHCR product **27** observed in experiments?

The issue of competition between direct C−H insertion and the CHCR process is complex, since we have shown that the latter reaction proceeds initially through a transition state with hydride-transfer character— the same transition state that would be expected to lead to direct C−H insertion, according to our previous studies.[24] The idea that both reactions may occur through the same initial transition state, without an intervening intermediate, is consistent with a *potential energy surface bifurcation* (Figure 6).[37] This phenomenon is characterized by two sequential transition states that are not connected via a minimum. Although the minimum energy pathway (MEP), from the initial transition state leads to one product (for example the CHCR product), alternative reaction trajectories over the initial hydride-transfer transition-state ridge may lead to a second product (direct C−H insertion).[37c] In retrospect, it is sensible that the transition-state valley of the hydride transfer ultimately must be connected with the Cope rearrangement transition-state ridge, which again connects the two products. Bifurcations of potential energy surfaces of organic reactions are well-known and have received much attention in recent years because of several examples of this phenomenon in synthetically important reaction systems.[37c,38] Unfortunately, no simple, general predictors of the selectivity in such systems can be formulated,[38d] as it will be governed by the potential energy surface shape and Newtonian dynamic effects, rather than traditional TST considerations.[37c,38d]

In order to gather evidence of whether direct C−H insertion and the CHCR reaction are related through a bifurcated potential energy surface, it was decided study the reaction coordinate potential energy profile for the model reaction with 1,4-cyclohexadiene, generated from the above analysis, more closely. Figure 7 shows the reaction coordinate potential energy surface when moving forward from the hydride-transfer transition state **TS-VII**, following the minimum energy path toward the direct C−H insertion product **29**. As the initial hydride-transfer component is almost complete, the potential energy surface becomes

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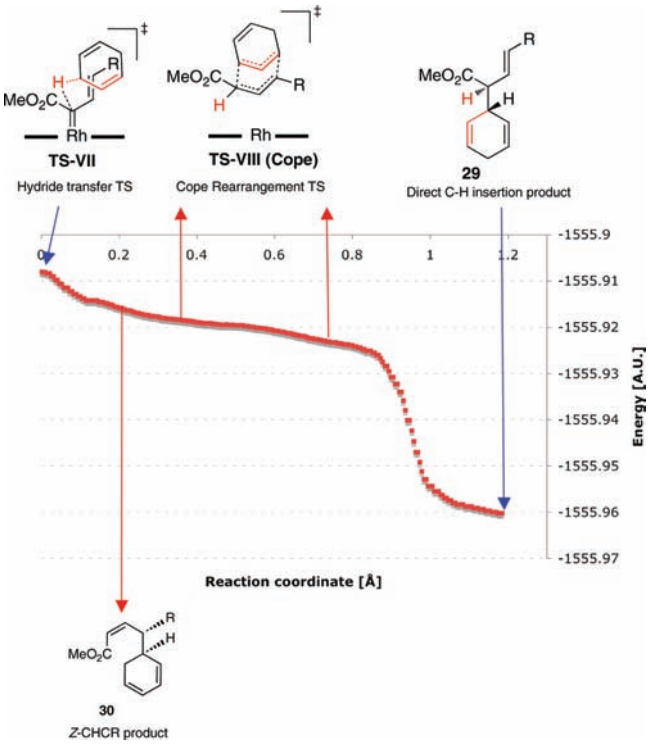

Figure 7. Forward IRC for reaction of 1,4-cyclohexadiene with *s-trans* **6**. Upward red arrows represent transition-state optimizations. Downward red arrows represent geometry optimizations.

relatively flat (~0.2−0.85 Å) and then follows a steep path toward product **29** as the C−C bonding occurs. Such flat portions of the potential energy surface are characteristically observed for bifurcating systems.[38e] Furthermore, by inspecting geometries from the flat region, they are found to have features that resemble those of [3,3]-sigmatropic rearrangement transition states. Indeed, by choosing two random geometries and then subjecting these to transition-state optimization procedures, both led to transition state **TS-VIII**, which is that of a Cope rearrangement. An even more interesting observation was that, by subjecting an intermediate geometry from the potential energy surface to geometry optimization, a different CHCR product **30** was obtained rather than the direct C−H insertion product **29**. **30** has a *Z*-double bond geometry, and would have opposite stereogenic centers to the normal *s-cis*/chair product **28**—in excellent agreement with the experimental results described before. These results show that the hydride-transfer transition structure **TS-VII** is connected to CHCR product **30**, the direct C−H insertion product **29**, and the Cope rearrangement transition state **TS-VIII** on the same potential energy surface. In conjunction with experimental results, this demonstrates that a potential energy surface bifurcation can exist in the reaction between vinylcarbenoids and allylic C−H sites.

Although we have demonstrated that a bifurcation exists for the reaction between *s-trans* vinylcarbenoid **6** and 1,4-cyclohexadiene, this would also extend to the reaction through the *s-cis* vinylcarbenoid with similar properties. When considering the 1,3-cyclohexadiene model, all four possible transition-state combinations may also have bifurcating potential energy surfaces. Using the tools presented herein, we can now analyze and rationalize the outcome of any given vinylcarbenoid/substrate combination in terms of C−H insertion or CHCR processes.

CONCLUSIONS

In conclusion, we have conducted extensive DFT studies in combination with experiments on the mechanism of the combined C−H activation/Cope rearrangement and have found that the reaction proceeds through a concerted, but highly asynchronous, hydride-transfer/C−C bond-forming process. A delicate balance exists, governed by the detailed structures of substrate and vinylcarbenoid, between different possible diastereomeric outcomes in this reaction. However, the absolute and relative stereochemical outcome is predictable from models described herein. We have demonstrated that direct C−H insertion and the CHCR process can proceed through the same initial transition state through a potential energy bifurcation. The studies presented herein have revealed the crucial importance of vinylcarbenoid conformation and substrate structure in this chemistry and have provided the tools for a thorough assessment of stereochemical issues related to rhodium vinylcarbenoid chemistry. Future studies, guided by these computational results, will explore the utilization of modified carbenoid precursors and substrates to achieve different stereochemical outcomes.

ASSOCIATED CONTENT

Supporting Information. Complete reference 26. Computational details, theoretical structures, calculated quantities, and experimental details.This material is available free of charge via the Internet at http://pubs.acs.org.

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(35) The crystal structure of **22** has been deposited at the Cambridge Crystallographic Data Centre, and the deposition number CCDC 795283 has been allocated.

(36) Description of the stereochemical determination of **25**−**27** is given in the Supporting Information.

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