Computational Study on the Selectivity of Donor/Acceptor-Substituted Rhodium Carbenoids
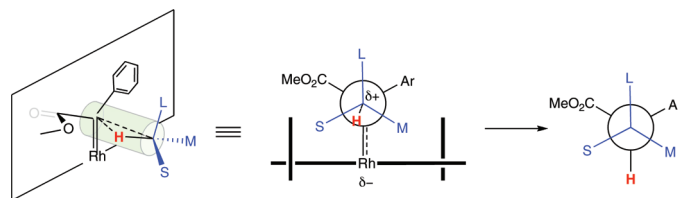
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The mechanism of rhodium-catalyzed cyclopropanation and C−H functionalization reactions with methyl phenyldiazoacetate and methyl diazoacetate has been studied computationally with DFT. In accordance with experimental data, it has been demonstrated that donor/acceptor rhodium carbenoids display potential energy activation barriers consistent with the much higher selectivity in cyclopropanation and C−H insertion chemistry compared to the traditionally used acceptor carbenoids derived from unsubstituted diazo esters. Significantly higher potential energy barriers were found for transformations of donor/acceptor carbenoids than for those of acceptor systems, primarily due to the inherent stability of the former. Analyses of transition state geometries have led to the development of a rational model for the prediction of the stereochemical outcome of intermolecular C−H insertions with donor/acceptor rhodium carbenoids.

Introduction

Transient metal carbenoids, derived from reactions of diazo compounds with a variety of metal complexes, are versatile intermediates in organic synthesis.[1] For several years we have explored the rhodium-catalyzed reactions of donor/acceptor-substituted carbenoids and found that they display much greater chemoselectivity when compared to the more conventional acceptor-substituted carbenoids.[2] A clear example of this effect is seen in a Hammett study of intermolecular cyclopropanation of para-substituted styrenes (Scheme 1).[3] The relative rates of reaction of methyl phenyldiazoacetate with various styrenes are strongly influenced by the electronic character of the styrene (ρ value of -0.9 (σ^+ scale)) while ethyl diazoacetate shows virtually no selectivity.[3]

The greater chemoselectivity of the donor/acceptor carbenoids has opened up a number of reactions that were previously not viable with conventional carbenoids. In particular, the effectiveness in a number of intermolecular C−C bond forming reactions such as cyclopropanation,[4] cyclopropenation,[5] and [4+3] cycloaddition[6] is greatly enhanced with donor/acceptor-substituted carbenoids. A very promising application of donor−acceptor carbenoids has been in intermolecular C−H insertion, which is arguably the most versatile catalytic enantioselective method for C−H functionalization reported to date.[2b,2d,7] Effective methods have also been developed for enantioselective intermolecular Si−H,[8] N−H,[9] and O−H[9a,10] insertions as well as various ylide transformations.[11] The

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SCHEME 1. **Competition Reactions with Styrene, Using Metal Carbenoids**[3]
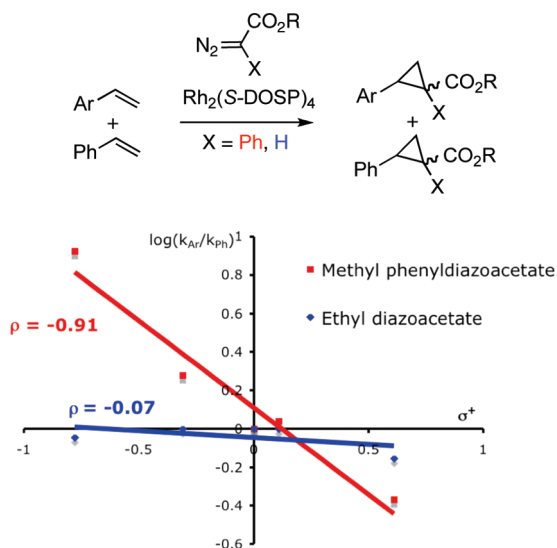
enhanced stability of donor/acceptor carbenoids allows them to be efficiently applied to solid phase synthesis.[12] In addition, selective methods for tagging of complex natural products[13] and functionalization of proteins[14] have been developed that rely on the use of donor/acceptor carbenoids. Even though a qualitative picture is emerging, that these carbenoids are more stabilized than the conventional systems lacking the donor group, studies to quantify the extent of this stabilization are still relatively limited.[7a,15] The significantly enhanced synthetic potential of these species warrants a closer examination of how they behave differently from classical systems at the microscopic level in this chemistry.

This paper describes a computational study directed toward understanding why donor/acceptor carbenoids are more selective than the conventional acceptor carbenoids. Several computational studies have been conducted on the acceptor carbenoids,[15,16] but only one has included a comparison with a donor/acceptor carbenoid (a vinylcarbenoid model).[15] The recent studies related to dirhodium catalysis have been conducted at the B3LYP level of theory, using a composite basis set consisting of LANL2DZ on Rh and 6-31G* on smaller atoms.[15,16a,17] The first portion of this paper will analyze the formation of the reactive carbenoid intermediates with subsequent cyclopropanation reactions with use of a more flexible basis set for Rh[18] and relate the results to previous calculations. An analysis of the impact of carbenoid structure on C−H functionalization chemistry will then follow. A new model for prediction of absolute and relative stereochemistry in intermolecular C−H insertions of donor/acceptor rhodium carbenoids has been developed based on the computational analyses.

Computational Methods

All calculations were performed with the Gaussian '03 software package.[19] Density Functional Theory was employed with the 3-parameter hybrid functional B3LYP[20] to locate stationary points on the potential energy surface (PES).[19] The structures were subjected to full geometry optimization with a basis set consisting of the 1997 Stuttgart relativistic small-core effective core-potential [Stuttgart RSC 1997 ECP][18a−c] for Rh, augmented with a 4f-function (ζ_f(Rh) = 1.350).[18d] This basis offers more flexibility in the valence shell ((8s,7p,6d) → [6s,5p,3d]) compared to LANL2DZ ((5s,6p,4d) → [3s,3p,2d]). 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 hereafter abbreviated 6-31G*-[Rh-RSC+4f]. Stability of the SCF solution was confirmed by stability analyses for selected stationary points at this level.[21a,21b] The LANL2DZ basis on Rh will be abbreviated [Rh-LA2]. The main discussion is based on single-point energies calculated at the B3LYP/6-311G(2d,2p)[Rh-RSC+4f]//B3LYP/6-31G*[Rh-RSC+4f] level. Heavy atom basis set definitions and corresponding pseudopotential parameters were obtained from the EMSL basis set exchange library.[21c,21d] All stationary points were characterized by normal coordinate analysis at the

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6-31G*[Rh-RSC+4f] level of theory.[22] Transition states were confirmed to have only one imaginary vibrational mode corresponding to the reaction coordinate.[22] Equilibrium structures were confirmed to have zero imaginary vibrational modes.[22] Transition states were further characterized by intrinsic reaction coordinate (IRC) analysis to confirm that the stationary points were smoothly connected to each other.[22] The calculated harmonic zero-point vibrational energies (ZPVE) are reported unscaled. Wiberg bond indices were calculated from NBO theory as implemented in Gaussian '03.[19] Calculated structures have been visualized by using Mercury.[23] In this work, only potential energies (E) have been studied. It should be mentioned that entropy effects are not expected to be completely negligible, particularly since dirhodium complexes always have some labile axially coordinating ligands associated.[24] The free energy surface may therefore deviate from the PES.[15,16a] However, earlier computational studies on kinetic isotope effects in carbenoid systems support that transition structures located on the PES are close to the physical reality.[15,16a]

Basis set effects were studied in detail and we include a discussion of this in the Supporting Information. The main findings were that the flexibility of the rhodium basis set and the added 4f-polarization function are important for the description of barriers in this chemistry. Furthermore, it was found that a triple-ζ quality basis with added polarization functions should be used for smaller atoms to obtain more accurate energies.

Results and Discussion

Cyclopropanation Reactions. Previous studies on the mechanism of reactions of diazo compounds with dirhodium complexes[25] demonstrated that the calculated energies of the reaction were fairly consistent with their experimentally available values, including kinetic isotope effects.[15,16a] Singleton, Davies, and co-workers analyzed both methyl diazoacetate and methyl vinyldiazoacetate as models for acceptor and donor/acceptor systems, respectively.[15] It was found that the unsubstituted carbenoid derived from methyl diazoacetate had no potential energy barrier for cyclopropanation with styrene, whereas the vinylcarbenoid displayed a barrier of 0.5 kcal/mol (E + ZPVE). It was argued that the small energy barrier in combination with entropic factors resulted in the high selectivity observed in the cyclopropanation chemistry of donor/acceptor carbenoids.[15] As we continued to study the chemistry of donor/acceptor carbenoids, we became concerned that the calculated small potential energy barrier was not consistent with a large amount of experimental data that suggests that donor/acceptor carbenoids are very selective species.[2b,2d,3,4c] For example, the relative rates obtained in the Hammett studies indicate that the barrier for the reaction with various styrenes must have a difference of at least ~1.8 kcal/mol in order to display measured substituent effects.[3] We hypothesized that an

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SCHEME 2. Reaction Pathway for Carbenoid Formation and Cyclopropanation of Styrene
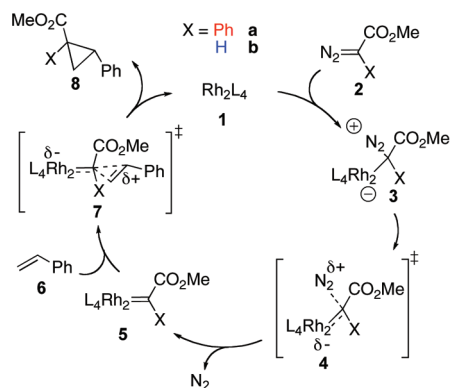
insufficient basis set for rhodium could be the cause for this discrepancy, and hence, the previously used [Rh-LA2] basis set was not appropriately describing rhodium in the system. This became the impetus for the current study, which uses a more flexible basis for Rh, further augmented with a 4f polarization function, along with a different pseudopotential to more accurately describe interactions with rhodium.

The study began with a comparison of the cyclopropanation chemistry of methyl phenyldiazoacetate **2a** and methyl diazoacetate **2b** (Scheme 2). Dirhodium formate, Rh$_2$-(O$_2$CH)$_4$ (**1**), has been shown to be a suitable model for rhodium carboxylates[15,16a] and was employed as the catalyst for simplicity. Styrene (**6**) was used as the alkene trap. The reaction pathway was calculated relative to free reactants. Solvent effects have not been considered in this work since our interests lie mainly in the intrinsic effects of the substituents on the reaction pathway, but also because the chemistry in practice often is carried out in hydrocarbon solvents, which have very small dielectric constants.

The currently accepted pathway for carbenoid formation and subsequent trapping used in the calculations is shown in Scheme 2.[1,16a,25,27] Figure 1 shows the potential energy surfaces for reactions of methyl phenyldiazoacetate (red) and methyl diazoacetate (blue) as one proceeds along the reaction coordinate. Coordination of phenyldiazoacetate **2a** to the dirhodium catalyst is predicted to be exothermic by −7.4 kcal/mol (Figures 1 and 2). The same process for methyl diazoacetate **2b** is significantly more exothermic (−10.7 kcal/mol, Figures 1 and 3). The phenyldiazoacetate−rhodium complex **3a** must overcome a potential energy barrier of 11.3 kcal/mol for nitrogen extrusion to form the metal carbenoid intermediate **5a**, which is stabilized relative to the free reactants (**1**, **2**, and **6**) by −16.5 kcal/mol. The methyl diazoacetate−rhodium adduct undergoes nitrogen extrusion with a 11.9 kcal/mol energy barrier. This value is reasonably close to the experimental value obtained in a study with rhodium acetate and ethyl diazoacetate by Teyssié and co-workers,[26] who determined the enthalpic barrier to be $\Delta H^{\ddagger} =$ 15.0 kcal/mol. Furthermore, the energies are consistent with the observation of Michaelis−Menten kinetics in such systems by Pirrung and co-workers.[27] They estimated the

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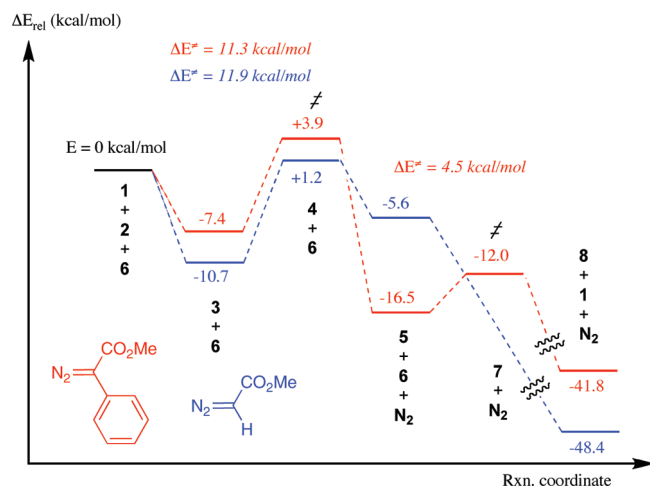
FIGURE 1. Calculated relative energies on the potential energy surface for phenyldiazoacetate and methyl diazoacetate in the cyclopropanation reaction with styrene. The energy barriers are indicated in italics for all elementary reactions.

free energy barrier for nitrogen extrusion of a diazo-ketone system to be 13.3 kcal/mol.[27] Previous computational studies give similar values.[15,16a] The high energy of the resulting carbenoid complex **5b** renders the nitrogen extrusion step endothermic by +5.3 kcal/mol. A transition structure for the cyclopropanation of styrene could not be located on the potential energy surface for this carbenoid species. Singleton and Davies reported similar results and indicated that the step probably is enthalpically barrierless.[15] They reported an approximate transition structure, located on the free energy potential surface, which was lower in energy than the carbenoid intermediate complex on the PES.[15] This is in agreement with the observations from the Hammett analysis.[3] These studies confirm that the carbenoid trapping step is without an enthalpic barrier in this case. The donor/acceptor carbenoid **5a**, however, displays a barrier of 4.5 kcal/mol for the cyclopropanation step. It is clear from the figure that the existence of this barrier is mainly due to the high stability of the carbenoid intermediate **5a**, which renders the nitrogen extrusion process (**3a** → **5a**) exothermic overall by −9.1 kcal/mol.

Figure 2 shows calculated structures of the intermediates involved in the cyclopropanation by methyl phenyldiazo-acetate **2a**. Figure 3 shows the calculated structures for the intermediates in the cyclopropanation by methyl diazoacetate **2b**. One striking geometrical feature of the donor/acceptor carbenoid **5a** vs. the acceptor carbenoid **5b** is the difference in preference for alignment on the rhodium active site (compare Figures 2 and 3). Whereas the acceptor carbenoid prefers the eclipsed conformation, the donor/acceptor carbenoid adopts the staggered arrangement. There appears to be an electronic preference for the eclipsed conformation

for both the acceptor system and the vinylcarbenoid model. The more sterically bulky nature of the phenyl group does not permit the eclipsed conformation. This may have major implications for the current models for enantioinduction that have been developed for chiral dirhodium complexes[1,2b,4d,15,16b,28] since the two carbenoids will orient themselves differently relative to a given chiral ligand environment. The significance of the carbenoid orientation will be explored further in future studies.

As discussed above, the enhanced stability of the donor/acceptor carbenoid intermediate leads to a significant potential energy barrier for cyclopropanation of 4.5 kcal/mol. This result is of great interest, particularly since the previously reported zero-point corrected potential energy barrier for the vinylcarbene model was much smaller ($\Delta(E + ZPVE)_{rel} = 0.5$ kcal/mol).[15] The pathway for cyclopropanation with the vinyldiazoacetate model (**9**, Figure 4) was therefore re-evaluated with the 6-31G*[Rh-RSC+4f] composite basis set.[18d] A zero-point corrected barrier of 2.4 kcal/mol for the cyclopropanation step was found (Figure 4, black pathway), about 2.0 kcal/mol higher than previously reported.[15] Evaluation of this barrier at the B3LYP/6-311G-(2d,2p)[Rh-RSC+4f]//B3LYP/6-31G*[Rh-RSC+4f] level gave a value of $\Delta E^{\ddagger} = 3.0$ kcal/mol. These higher values are more consistent with experimentally observed selectivity profiles for donor/acceptor carbenoids in this chemistry.[3] The remaining pathway, coordination to form **10**, nitrogen extrusion via transition state **11** to generate the carbenoid intermediate **12**, was in good agreement with the previous calculations.[15]

C−H Functionalization. Selective C−H functionalization is one area of widespread current interest due to the strategic versatility of the corresponding retrosynthetic disconnection.[2d,7b,7c] Methods based on directed, oxidative addition of C−H bonds onto active metal complexes have been known for many years.[7b,29] Intramolecular carbenoid C−H insertions have also been developed extensively.[30] It was with the appearance of donor/acceptor carbenoids, however, that selective, intermolecular C−H functionalization was realized,[7a,28f] and consequently, this method has been developed extensively and found applications in several complex molecule syntheses.[2b,7c,31] Computational analyses of rhodium carbenoid C−H insertions published to date do not offer detailed insights into the differential nature of donor/acceptor vs. acceptor systems or the reactivity of these carbenoids toward different C−H bonds.[15,16]

The C−H insertion reactions of rhodium donor/acceptor and acceptor carbenoids with cyclopentane[28f] were investigated with our model systems (Figure 5). Cyclopentane is known to be a relatively unreactive system that requires slow addition of the carbenoid precursor under rigorously dry and degassed conditions.[28f] The transition states are correspondingly high in energy. The phenylcarbenoid intermediate **5a**

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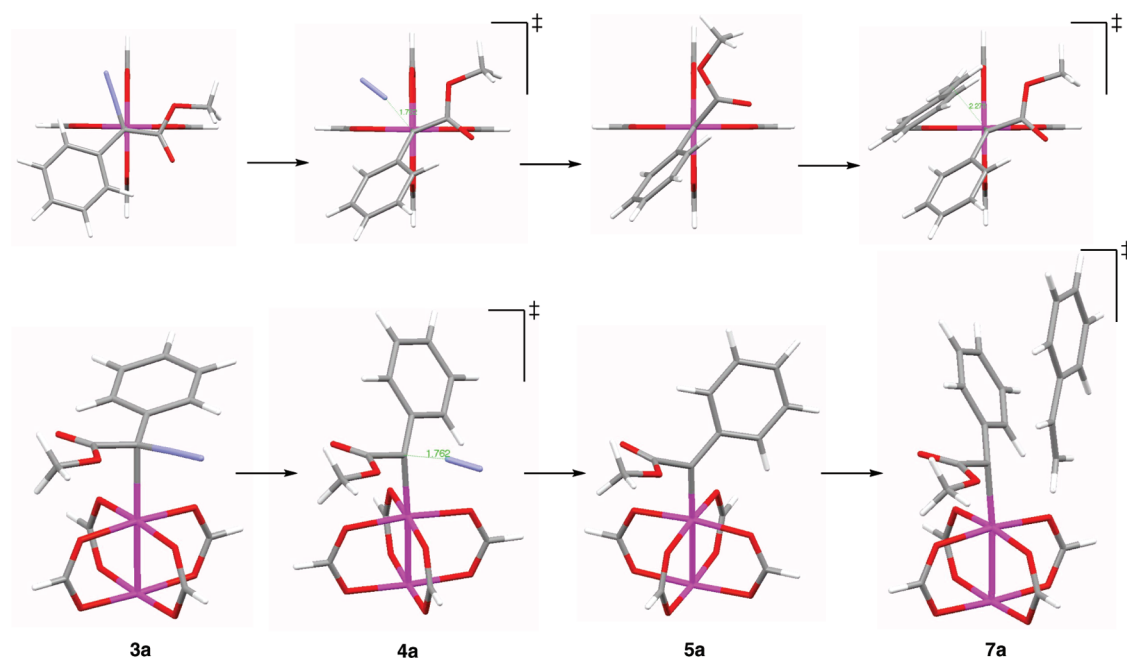
FIGURE 2. Calculated structures for the donor/acceptor system, top and side views: C = gray, H = white, O = red, N = blue, and Rh = purple.
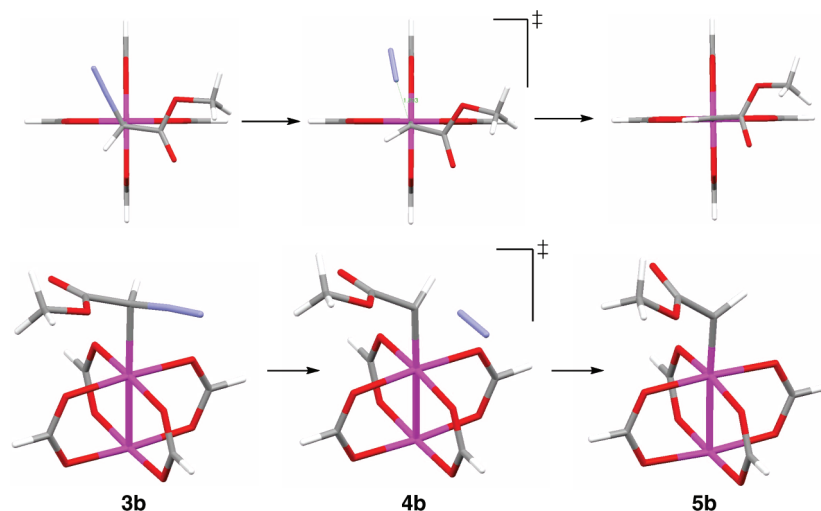

FIGURE 3. Calculated structures for the acceptor system, top and side views.

undergoes the C−H insertion step with a potential energy barrier of 17.4 kcal/mol, whereas for the acceptor carbenoid, the barrier is only 3.5 kcal/mol. In comparison, Nakamura reported a potential energy barrier of +0.2 kcal/mol for insertion into a methylene C−H bond of propane for this acceptor carbenoid at the B3LYP/631G*[Rh-LA2] level of theory.[16a] Both the donor/acceptor and acceptor carbenoid reactions are overall very exothermic (−50.1 and −56.2 kcal/mol, respectively). There are two factors that predominantly determine the difference in selectivity between the two carbenoids: (1) the intermediate **5a** is much more stable than the acceptor system **5b** and (2) because of the later transition state and its bulkier nature, more steric interactions are involved between the substrate and the carbenoid substituents. The high stability leads to a much

later transition state with significantly higher charge buildup than the acceptor system. For the donor/acceptor system, positive charge buildup (Mulliken charges) on the carbon to be functionalized increases from −0.27 in free cyclopentane to −0.17 in the transition state (+0.10 units more positive). In comparison, positive charge buildup is only +0.05 for the acceptor system, indicating an earlier transition state.[16a] Interestingly, the calculation predicts that for the donor/acceptor system, the carbenoid trapping step will have a higher potential energy barrier (17.4 kcal/mol) than the nitrogen extrusion (11.3 kcal/mol). Activation free energies calculated at the B3LYP/631G*[Rh-RSC+4f] level of theory were 32.3 kcal/mol (C−H insertion) and 10.4 kcal/mol (nitrogen extrusion), confirming that the C−H insertion step is rate limiting. This
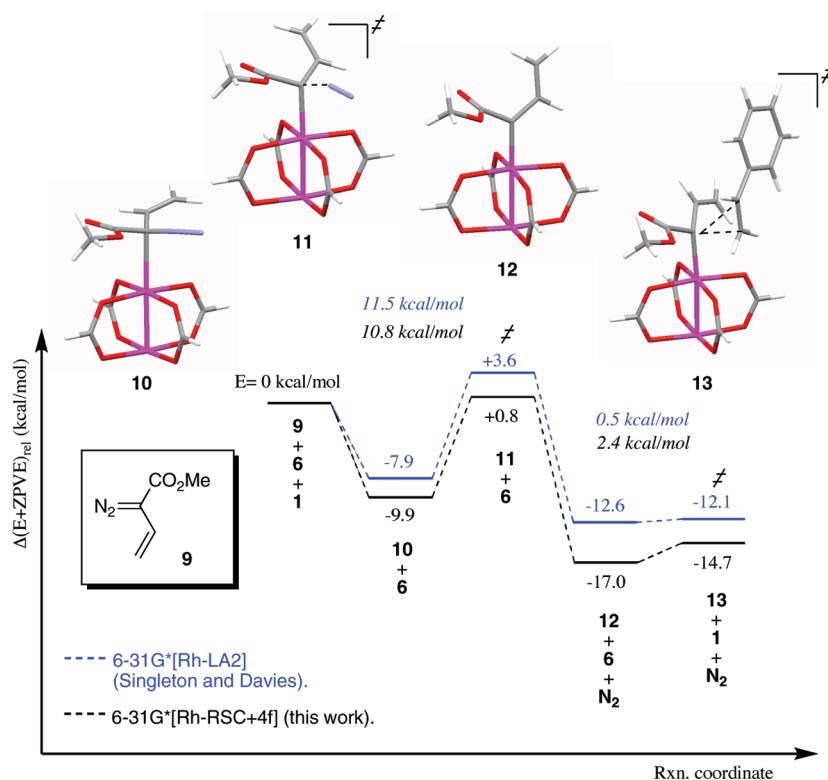
FIGURE 4. Comparison of metal basis set influence on reaction pathway. Energies (B3LYP+ZPVE) are given in kcal/mol. Structures of key intermediates 10−13 are shown above.
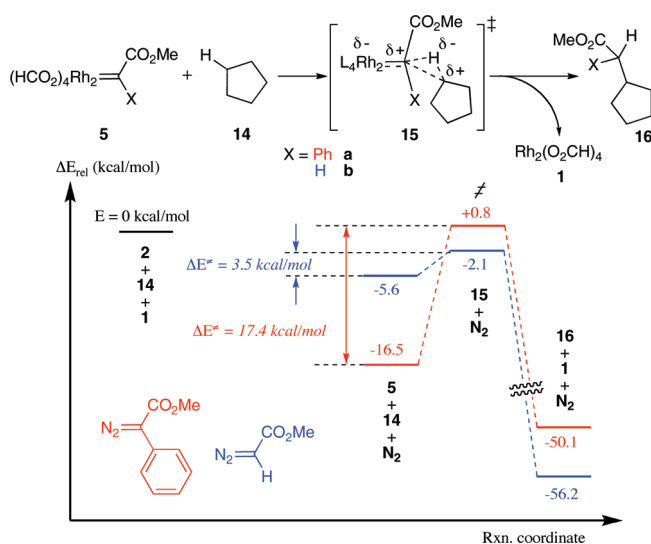

FIGURE 5. Relative energies on the potential energy surface for C−H functionalization of cyclopentane. Values are given in kcal/mol.

means that such carbenoid complexes could potentially be isolated.

A significantly more activated C−H bond is found in 1,4-cyclohexadiene (**17**, Figure 6), where the methylene groups are each flanked by two double bonds. The doubly allylic system is a remarkable substrate for donor/acceptor carbenoid C−H insertions.[32] Transition structures were found for

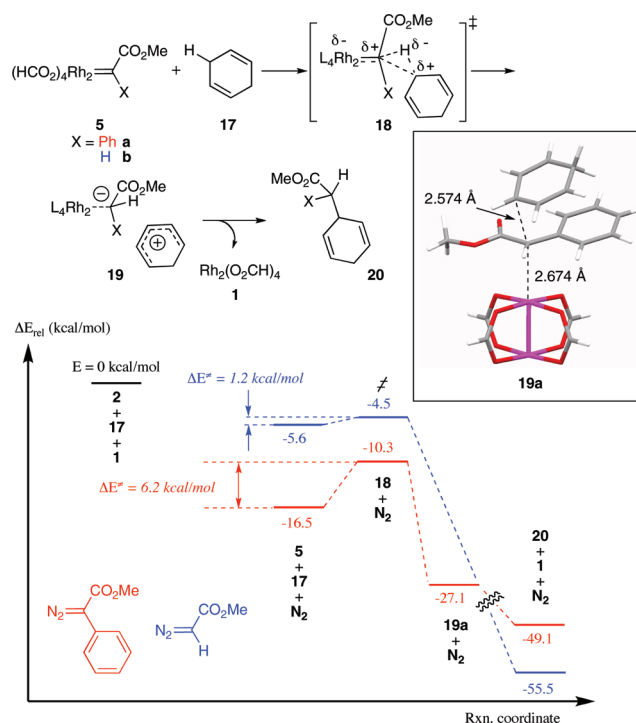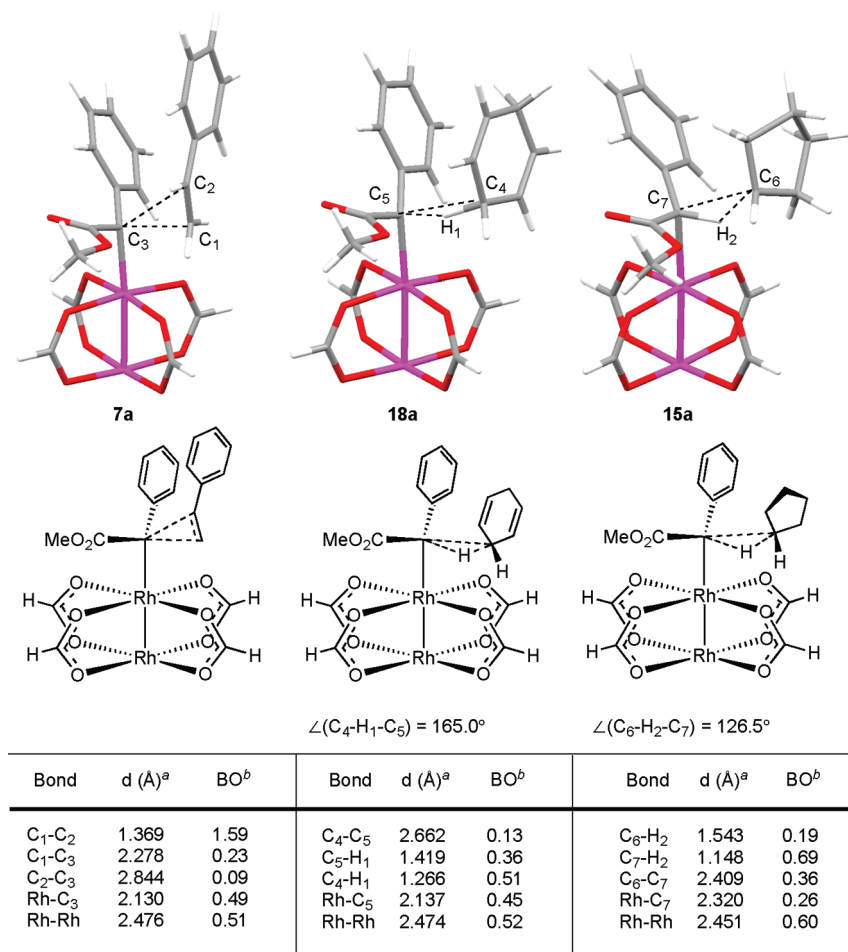(32) Davies, H. M. L.; Nikolai, J. _Org. Biomol. Chem._ **2005**, _3_, 4176–4187.

FIGURE 6. Relative energies on the potential energy surface for C−H functionalization of 1,4-cyclohexadiene. Values are given in kcal/mol.

insertion of both the acceptor and donor/acceptor carbenoid models. In accordance with the significantly more reactive nature of the methylene C−H bond in this substrate versus

7a   18a   15a

∠(C₄-H₁-C₅) = 165.0°   ∠(C₆-H₂-C₇) = 126.5°

Bond	d (Å)[a]	BO[b]		Bond	d (Å)[a]	BO[b]		Bond	d (Å)[a]	BO[b]
C_1-C_2	1.369	1.59		C_4-C_5	2.662	0.13		C_6-H_2	1.543	0.19
C_1-C_3	2.278	0.23		C_5-H_1	1.419	0.36		C_7-H_2	1.148	0.69
C_2-C_3	2.844	0.09		C_4-H_1	1.266	0.51		C_6-C_7	2.409	0.36
Rh-C_3	2.130	0.49		Rh-C_5	2.137	0.45		Rh-C_7	2.320	0.26
Rh-Rh	2.476	0.51		Rh-Rh	2.474	0.52		Rh-Rh	2.451	0.60

[a] Bond length. [b] Wiberg bond indices. [c] For comparison, in the free carbenoid complex **5**, d(Rh-C) = 2.010 Å, BO(Rh-Rh) = 0.47, d(Rh-Rh) = 2.476 Å, BO(Rh-C) = 0.69.

FIGURE 7. Structural characteristics and selected bond orders in calculated transition state structures for donor/acceptor carbenoid C−H insertions and cyclopropanation.

cyclopentane, both activation energies are much lower. With the donor/acceptor carbenoid **5a**, a predicted potential energy barrier of 6.2 kcal/mol is present for the C−H insertion versus only 1.2 kcal/mol for **5b**. The models presented here are qualitatively in good agreement with experimental results that indicate that 1,4-cyclohexadiene (**17**) and styrene (**6**) are much more reactive substrates than cyclopentane (**14**) toward aryldiazoacetates in this chemistry.[7a]

The forward intrinsic reaction coordinate drive from the transition state for the donor/acceptor system did not yield the insertion product directly. The optimization converged to a zwitterionic structure **19a** (Figure 6), with an enolate moiety coordinated to rhodium and a cyclohexadienyl cation closely associated with it (C−C distance of 2.574 Å). Although this structure was shown to be a minimum on the PES by vibrational frequency analysis, a relaxed scan of the C−C bond formation coordinate (see Supporting Information) demonstrated that the pathway toward the insertion product had no potential energy barrier. Stability of the wave function was also confirmed by stability analyses for **18a** and **19a**.[21a,21b] As **19a** is in a very flat region of the potential energy surface, this can be problematic for the optimization algorithm, which may have caused the job to converge. However, structure **19a** shows that systems with good stabilization of the positive charge buildup proceed with a very large hydride transfer component relative to C−C bond formation. Complete hydride transfer has been reported in the literature for certain systems.[33] The acceptor system did not have a similar zwitterionic structure, but went directly to the insertion product **20b**.

In terms of overall reaction energy, the least stable diazoacetate gives the highest exotherm of −55.5 kcal/mol. The reaction of methyl phenyldiazoacetate has a predicted exotherm of −49.1 kcal/mol. Once again, the energy diagram shows that the high reactivity of the acceptor carbenoid is mainly due to its low kinetic stability. The stabilization of the donor/acceptor carbenoid leads to a significant barrier with a much later transition state.

Transition States. The calculated transition state structures for both the cyclopropanation and C−H insertion reactions of donor/acceptor carbenoids are shown in Figure 7 along with selected bond lengths and bond orders. All the transition states are highly asynchronous. The cyclopropanation transition state is relatively early, with a bond order C_1−C_3 of only 0.23. C_2 and C_3 have very slight bond

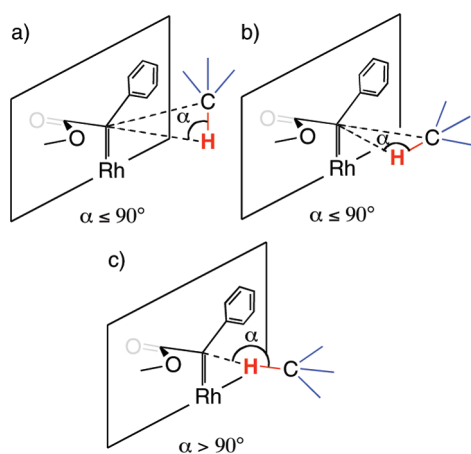(33) Clark, J. S.; Wong, Y.-S.; Townsend, R. J. *Tetrahedron Lett.* **2001**, *42*, 6187–6190.

FIGURE 8. Possible approach angles between the C−H bond vector and the carbenoid plane: (a) parallel with the Rh−C bond, (b) perpendicular to the Rh−C bond, parallel to carbenoid plane, and (c) orthogonal to the carbenoid plane.

formation at this stage (BO = 0.09), which is consistent with a concerted, highly asynchronous transition state. This is also supported by experimental kinetic isotope effects.[15] The Rh−C bond is significantly elongated relative to the free carbenoid complex (2.130 Å vs. 2.010 Å respectively). The transition state for insertion with 1,4-cyclohexadiene is also somewhat early, with only hydride transfer occurring (BO(C$_5$−H$_1$) = 0.36). C−C bond formation is not detectable (BO = 0.13) in the transition state. Also, the C−H−C bond angle of 165° supports this. For the cyclopentane system, significant differences are observed. This transition state is much later than for the other two substrates, with considerably more Rh−C bond breakage occurring (2.320 Å, BO = 0.26). The hydride transfer is almost complete in this transition state (BO(C$_7$−H$_2$) = 0.69) and a relatively high degree of C−C bond formation is evident from the structure (BO = 0.36). This analysis is in agreement with that of Nakamura[16a] for C−H insertions with methyl diazoacetate and diazomethane, in which a hydride transfer component was also found to be dominant in the transition state. The results show that C−C bond formation is significantly more progressed in the transition state for less activated C−H bonds. Activated systems such as styrene and 1,4-cyclohexadiene proceed much more asynchronously. The latter system displayed only a hydride transfer component in the transition state, although this is likely to be followed by rapid C−C bond formation because the C−H functionalization of 1,4-cyclohexadiene with chiral dirhodium catalysts can be highly enantioselective.[34]

Predictive Model for C−H Insertion Stereoselectivity. The C−H functionalization chemistry of the donor/acceptor-substituted carbenoids can occur with high levels of diastereo- and enantiocontrol.[2b−d] Insertion into a methylene site, in which the other two groups have size differentiation, can lead to highly diastereoselective processes.[2b−d] To predict this stereoselectivity, it is crucial to have an understanding of how the substrates approach the carbenoid complex. In particular, the orientation of the C−H bond undergoing the insertion is a critical issue, especially as these
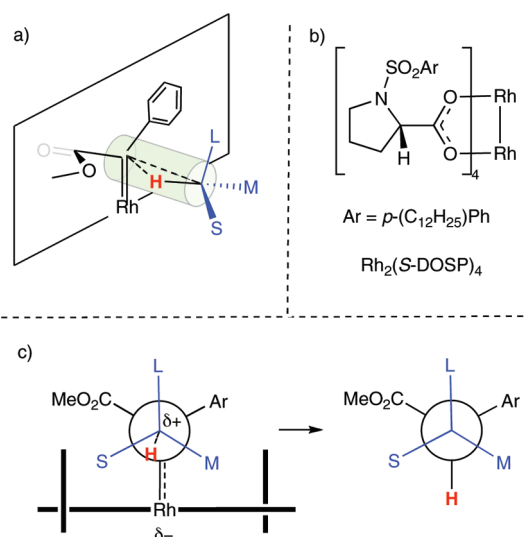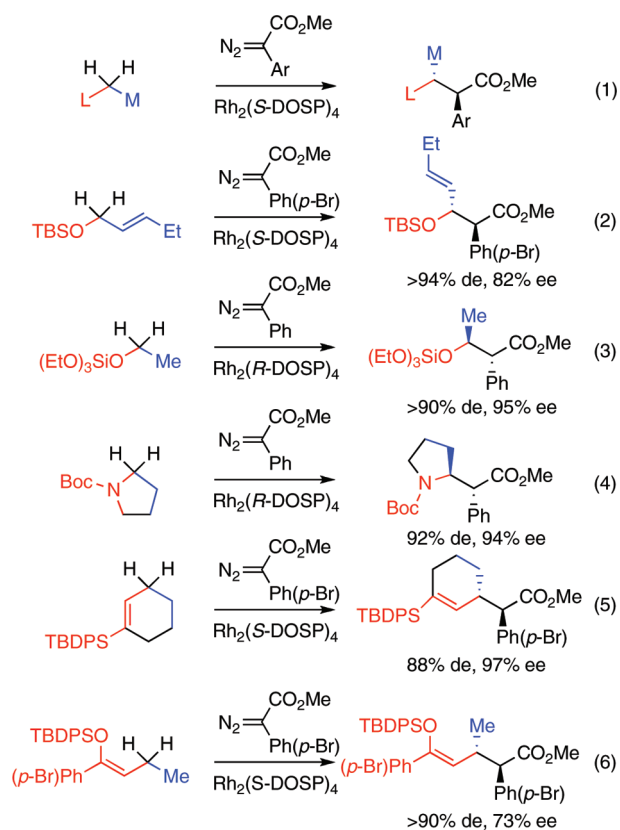
(34) Muller, P.; Tohill, S. *Tetrahedron* **2000**, *56*, 1725–1731.

FIGURE 9. (a) Newman-projection model for C−H insertion; (b) standard chiral catalyst; and (c) prediction of absolute stereochemistry by using the projection model.

reactions occur without prior coordination to the metal. The theoretical studies presented in this paper give an informative view on how the substrate reacts with the carbenoid. Considering that the C−H insertion has been viewed as a concerted nonsynchronous process, it would have been reasonable to assume that the C−H bond undergoing insertion needs to be almost parallel to the carbenoid plane in order to make the transition state three-centered, as shown for approaches a and b in Figure 8.[28f,2b] The C−H−C angle would ideally be ≤90° if this was the case. The calculations, however, demonstrate that the C−H functionalization event begins with considerable hydride transfer character. In the case with 1,4-cyclohexadiene as substrate, the C−H−C angle is 165°, while with cyclopentane, it is 127°. The C−H bond is nearly orthogonal to the carbenoid plane as illustrated in Figure 8c. C−H−C angles in the range 117−128° were also found computationally by Nakamura and co-workers for insertion reactions between simple alkanes and diazomethane and methyl diazoacetate.[16a]

The large C−H−C angle in the substrate approach has led to a revised perspective on how the C−H insertion transition state should be analyzed. The three remaining groups at the insertion site exist in essentially a staggered relation to the three groups around the carbenoid center, presumably adopting the least crowded orientation preferentially. The ester group acts as a sterically demanding substituent since the O−C−O plane is almost perpendicular to the carbenoid plane. The smallest group on the insertion site is therefore oriented "gauche" to both the ester substituent and the rhodium catalyst. On the basis of this analysis, the Newman projection can be proposed as a simple predictive model, as shown in Figure 9a. The projection is along the C−C bond that is formed in the process. This model provides a simple rationale for the relative orientation of the large (L), medium (M), and small substituent (S) in the substrate during the insertion event and therefore allows for prediction of the relative stereochemistry in the product. A standard chiral catalyst, such as Rh$_2$(S-DOSP)$_4$ (Figure 9b), is considered to be D_2-symmetric.[4d,28h] The chirality inherent in the catalyst can be taken into account by adding blocking

SCHEME 3. Predicted Stereocenters with Use of the Newman Projection Model[35]

With *N*-Boc-pyrrolidine, the *N*-Boc portion of the ring is considered as the large group (Scheme 3, eq 4).[35c,35d] Highly diastereoselective, allylic C−H functionalization of cyclohexenes is only achieved when the bulky *tert*-butyldiphenylsilyl group is introduced onto the ring (Scheme 3, eq 5).[35e] Similarly, highly diastereoselective allylic C−H functionalization of acyclic structures is only obtained when highly functionalized vinyl groups are used (Scheme 3, eq 6).[35f]

Conclusions

The computational analysis presented herein shows that donor/acceptor rhodium carbenoids, derived from aryl- and vinyldiazoacetates, are significantly more stabilized than the conventionally used acceptor carbenoids. This intrinsic stability, imparted by the donor group, leads to relatively late transition states with significant charge build-up occurring. The resulting energy barrier implies that steric interactions also become very important. A consequence of these factors is that the activation energies for the product determining steps are much greater for donor/acceptor carbenoids than for acceptor systems, which renders the former system able to display selectivity between substrates based on their electronic character. In sterically demanding trapping agents, however, the electronic control is a secondary factor.[2d,31a,32] The computed transition state geometries revealed that the C−H insertion mechanism initially has a dominant hydride transfer component, and that this propensity increases with more stabilized positive charge build-up. The substrates transiently possess significant carbocationic character. This study also demonstrates that using a more flexible, polarized basis set for rhodium as well as a higher basis set than 6-31G* on small atoms in the calculations provides activation energy barriers for the product determining steps that are more consistent with experimental data.

Calculated transition state geometries have led to the development of a new predictive model for stereoselectivity in donor/acceptor rhodium carbenoid C−H insertions. The model provides a more accurate picture of the substrate orientation during the insertion event and a significantly enhanced understanding of factors controlling the stereochemical outcome of such reactions.

groups as indicated by bold lines in Figure 9c.[4d] The proposed model can then be used to predict the absolute configuration of the two stereocenters that are formed.

The new model predicts that insertion into methylene groups will occur with predictable diastereoselectivity as indicated in eq 1 (Scheme 3). If there is good size differentiation between the two substituents (L and M) at the insertion site, the reaction proceeds with high diastereoselectivity. This can be readily understood from the model, since a very large group will prefer to point away from the rhodium complex. Less size difference between L and M leads to less preference for the orientation indicated in Figure 9c. Systems that give low diastereoselectivity can also therefore be understood in the context of this model. Some of the most highly diastereoselective C−H functionalizations are indicated in eqs 2−6 in Scheme 3.[35] In each case, the large group is marked in red and the medium group is marked in blue. In the case of silyl enol ethers and tetraalkoxysilanes, the siloxy group is considered to be the large group (Scheme 3, eqs 2[35a] and 3[35b]).

Supporting Information Available: Input file details, calculated geometries and energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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