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Insights on Rh(II) carbenoid reactivity

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ABSTRACT

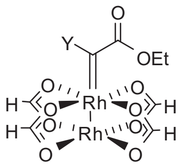
A computational study on a range of Rh(II) carbenoids shows how carbenoid stability and cyclopropanation diastereoselectivity can be affected by certain properties of the carbenoid substituents. The results of the study imply that substituents capable of π-interactions are stabilising and *cis*-directing, and that the *trans*-directing abilities are affected by steric effects as well as the polarity of carbonyl groups.

The role of dirhodium(II) carbenoids as valuable and versatile intermediates in organic synthesis is firmly established. However, as highlighted by the current debate on the mode of stereochemical induction in enantioselective carbenoid reactions,[1] the factors governing the reactivity of Rh(II) carbenoids have yet to be fully understood.

A prevalent theory for explaining the effect of carbenoid substituents on Rh(II) carbenoid reactivity has the substituents divided into either donors or acceptors, with hydrogen being neither.[2] From this classification, three categories of carbenoids result: acceptor-, acceptor/acceptor- and donor/acceptor-substituted carbenoids. The stability of a given carbenoid is explained by which category the carbenoid in question belongs to, the combination of a donor and an acceptor stabilising the donor/acceptor-substituted carbenoids, and the acceptor-substituted carbenoids being the most reactive. The diastereomeric ratios (drs) in cyclopropanation reactions are also rationalised based on these categories, the acceptor-substituted carbenoids all, except for those with extremely bulky ester substituents,[3] giving low drs, and aryl-, vinyl- or alkynyl-substituted donor/acceptor-substituted carbenoids giving high drs. The third category, the acceptor/acceptor-substituted carbenoids, display larger variations.

Some acceptor/acceptor-substituted Rh(II) carbenoids can give very good drs. Recent reports show that certain carbenoid substituents, such as amide groups, display remarkably good '*trans*-directing' abilities, leading to high drs in cyclopropanation reactions of acceptor/acceptor-substituted carbenoids.[4] A proposed explanation of the *trans*-directing abilities of carbonyl substituents is that the carbonyl oxygen is tilted towards the approaching alkene in the transition state stabilising the developing positive charge on the alkene.[4,5] It has been suggested that either the nucleophilicity[5] or polarity[4b] of the carbonyl group of a carbenoid substituent determines the level of a substituent's *trans*-directing ability.

In our recent computational study of cyclopropanation reactions with halodiazoacetates,[6] we examined the carbenoids formed from ethyl bromo-, chloro- and iododiazoacetate in reactions with model catalyst $Rh_2(O_2CH)_4$ carbenoids **2**–**4** (Fig. 1), in order to classify them according to the acceptor versus donor theory. We knew from experimental work[7] that all the three halodiazoacetates react very much alike: they display similar selectivities, stabilities and rates, and they are all *cis*-directing in cyclopropanation reactions. Due to these similarities, the carbenoids formed from these diazo compounds would be expected to belong to the same substituent-category. The net electron-withdrawing or -donating properties of a substituent is reflected in the said substituent's charge: the more positive the charge, the more electron-poor the substituent is, and the more electron-donating it is. Therefore, the natural bond orbital (NBO) charges[8] of the halogens in carbenoids **2**–**4** were calculated and compared to that of hydrogen in carbenoid **1**, as hydrogen is the designated zero-point of the scale from acceptor to donor. The results showed that all three halogens have positive charges, implying that they are net donors. However, iodine has a greater positive charge than hydrogen, chlorine has a lesser positive charge than hydrogen and bromine has a charge very similar to that of hydrogen. Thus, if the halogen substituents were to be classified as donors or acceptors based on their net electron-donating or -withdrawing abilities, iodine would be a donor, chlorine an acceptor and bromine neither.



1 Y = H
2 Y = Cl
3 Y = Br
4 Y = I
5 Y = CH=CHCOOEt
6 Y = Ph[a]
7 Y = CH=CHPh
8 Y = NO_2
9 Y = $SiEt_3$
10 Y = $SiMe_2Ph$
11 Y = $COCH_3$
12 Y = COPh
13 Y = $CONMe_2$
14 Y = COOEt

Figure 1. The Rh(II) carbenoids included in this study. In this carbenoid the ethyl ester group is exchanged for a methyl ester, to match the carbenoid used experimentally.[9]

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Our unexpected findings prompted us to study the properties of a range of carbenoid substituents in order to identify how the substituents affect the properties of the carbenoid. The generalised carbenoid depicted in Figure 1 was our standard system for this computational study; the ethyl ester substituent was kept unchanged while the other substituent (from now on referred to as the Y-substituent) was varied.

We first looked for correlations between the net charge of the Y-substituent of each energy-optimised carbenoid and the reported dr in the cyclopropanation of styrene with the corresponding diazo compound[10] (Table 1),[11] in order to further investigate the acceptor versus donor theory.

The results revealed that there is no correlation between overall substituent charge and dr in cyclopropanation reactions: the net electron-donating or -withdrawing effect of a carbenoid substituent does not determine the reactivity of the carbenoid.[13]

The vinyl- and aryl substituents in carbenoids **5**–**7** are all classified as donors according to the acceptor versus donor theory. From the NBO charges of these substituents it is clear that while the styryl group (carbenoid **7**) is a stronger net donor than hydrogen, both the phenyl group (carbenoid **6**) and the ester substituted vinyl group in carbenoid **5** are overall less electron-donating than hydrogen. However, studying the properties of carbenoids **5**–**7**, we found that they, along with carbenoids **2**–**4**, all share a common feature: the bond order of the carbon-Y-substituent bond in these carbenoids is, at around 1.3, quite high. The higher bond order implies a π-interaction between the Y-substituent and a carbenoid carbon p orbital, most likely in the form of π-donation from the Y-substituent to the electron-deficient carbenoid carbon. This π-interaction is also present in the analogous free carbenes—the carbene-analogues of carbenoids **3** and **6** have carbon-Y-substituent bond orders of 1.4 and 1.3, respectively—but not in the diazo compounds. This further indicates that the higher bond order is the expression of an on-demand π-donation from a polarisable Y-substituent to an unfilled p orbital. Thus, the substituents commonly referred to as donors are not necessarily strongly electron-donating, but they are π-*donors*.

Carbenoids **2**–**7** are all known to be relatively stable compared to many other Rh(II) carbenoids.[6,14] The relative stability of the carbenoids results in a lower tendency for dimerisation as a side-reaction in cyclopropanation reactions, and may also be the reason why these carbenoids give good results in C–H insertion reactions,[7a,15] which are known to be among the more difficult carbenoid reactions. It has also been shown computationally that carbenoids **2**–**4** and **6** have a higher relative stability than carbenoid **1**.[6,14] The higher stability of carbenoids **2**–**7** compared to the other studied carbenoids is nicely explained by the π-donating abilities of their Y-substituents, as an expected result of π-donation from a Y-substituent to the carbenoid p orbital is a more stable carbenoid.

The polarisable nature of the Y-substituents in carbenoids **2**–**7** also provides a rationale for the fact that these carbenoids are the only carbenoids among those studied that give good *cis*-selectivities in cyclopropanation reactions (Table 1). The Y-substituents do not only interact with the carbenoid carbon; they can also be expected to interact with substituents on the alkene in the transition state for cyclopropanation. Halogenated carbenoids **2**–**4** give good diastereoselectivities with styrene and styrene analogues,[7b] and aryl- and vinyl-substituted carbenoids give high drs in reactions with styrene and styrene analogues and vinyl ethers,[2b] and lower drs in reaction with alkyl-substituted alkenes. The Rh(II) carbenoids being electrophilic, it has been assumed that the effect of the substituents on the substrate alkene on the dr in cyclopropanation reactions is merely a matter of more electron-rich alkenes being better substrates, but we believe that the substituents on the alkene have additional, more profound effects. Halogens and aryl and vinyl groups are all moieties that can partake in stabilising π-interactions with the aryl groups on the alkene, the halogens through π-halogen bonding,[16] and the aryl- and vinyl-substituents through π-stacking. The presence of such stabilising interactions in the transition state will make the approach of the alkene with the aryl group *syn* to the Y-substituent more favoured (Fig. 2), resulting in an excess of the diastereomeric cyclopropane which has a *cis* relationship between the Y-substituent and the aryl-ring from the alkene. Similar interactions can be expected between the ether substituent in vinyl ethers and the aryl or vinyl groups of **5**–**7** and analogous carbenoids. The drs in Table 1 imply that the π-stacking interaction is more important for the more electron-rich π-bonds, as seen by the higher dr in the case of styryl (carbenoid **7**) than for the electron-poor vinyl in carbenoid **6**, and that π-stacking is a stronger interaction than π-halogen bonding, resulting in a higher dr for carbenoids **5**–**7** than for **2**–**4**.

Carbenoids **8–13** are all *trans*-directing, and they all, except for **10** and **12**, lack substituents that can be expected to partake in π-interactions. In the case of carbenoids **10** and **12**, the phenyl rings are located farther away from the carbenoid carbon than in carbenoid **6**, and calculations show that the *cis* transition state for cyclopropanation of styrene with carbenoid **12** has the keto substituent in an out-of-plane orientation with the phenyl ring pointing away from the approaching alkene (Rh-C–C=O dihedral angle −85.2°).

Table 1
Properties of carbenoids **1**–**13**

Carbenoid	Y-substituent	NBO charge, Y-subst.	C-Y- subst. bond order	Reported dr, cyclopropanation of styrene[12] (*cis*:*trans*)[a]
1	H	+0.23	0.91	1.6:1
2	Cl	+0.17	1.31	6:1
3	Br	+0.24	1.29	9:1
4	I	+0.35	1.27	14:1
5	CH=CH–COOEt	+0.12	1.26	8:1
6	Ph	+0.19	1.28	>30:1
7	CH=CH-Ph	+0.28	1.36	>30:1
8	NO_2	−0.17	0.93	1:8
9	$SiEt_3$	+0.52	0.72	1:3
10	$SiMe_2Ph$	+0.51	0.71	1:6
11	$COCH_3$	+0.07	1.04	1:4
12	COPh	+0.09	1.04	1:14
13	$CONMe_2$	+0.16	1.03	1:>30
14	COOEt	+0.07	1.02	—

[a] *cis* and *trans* refer to the relationship between the phenyl ring and the Y-substituent in the cyclopropane products.

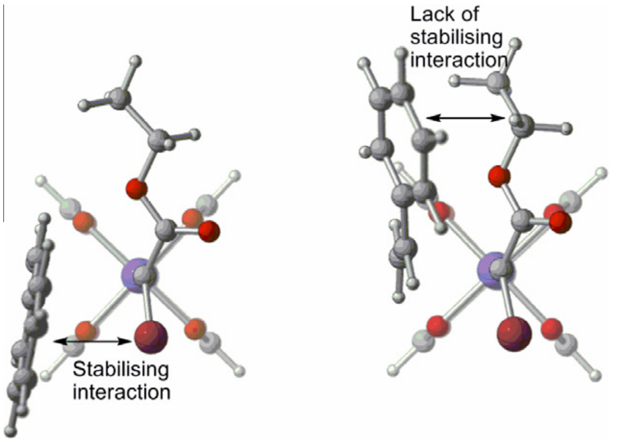
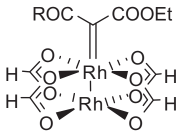


Figure 2. Illustration of presumed stabilising interactions between the carbenoid substituent (here: bromine) and the alkene substituent (here: phenyl) in transition states for cyclopropanation.

We next turned our attention to the *trans*-directing keto and amide substituents in carbenoids **11**–**13**. *trans*-Directing carbonyl substituents are believed to stabilise the developing charge on the alkene in cyclopropanation transition states through an interaction between the carbonyl oxygen and the internal olefinic carbon.[4,5] For this interaction to take place, it is assumed that the substituent adapts an out-of-plane orientation relative to the carbene, with the carbonyl oxygen tilted towards the approaching alkene. This orientation then makes monosubstituted alkenes approach the carbenoid preferably with their substituent *anti* to the Y-substituent, leading to an excess of the diastereomeric cyclopropane which has a *trans* relationship between the Y-substituent and the substituent from the alkene. It has been argued that increasing the nucleophilicity of the carbonyl oxygen in a carbenoid substituent will increase its *trans*-directing ability,[5] and consequently lead to a higher dr in cyclopropanation reactions. We therefore looked for correlations between carbonyl oxygen charge and observed drs (Table 1). We first studied the charges on the carbonyl oxygens in the carbenoids (**11**–**13**) (Table 2).

Our findings showed that there is no correlation between *trans*-directing ability (Table 1) and carbonyl oxygen charge in the carbenoid. We also studied the charges on the carbonyl oxygens in the transition states for the cyclopropanation of styrene with the same carbenoids, **TS-11**–**TS-13** (Table 3), and found that the same was true for the transition states. The most *trans*-directing substituent among those studied, the amide group in carbenoid **13**, does have the most negatively charged carbonyl oxygen among the studied substituents, both in the carbenoid and the transition states. However, the keto oxygens of carbenoids **11** and **12** bear the same charge even though the carbenoids give quite different drs in cyclopropanation reactions. Furthermore, the charge on the carbonyl oxygen of the ethyl ester group is, both in the carbenoids and the transition states, higher than the charge on the carbonyl oxygen in the keto groups. This means that if diastereoselectivity was determined solely by carbonyl oxygen nucleophilicity, the ester would have been more *trans*-directing than the keto groups.

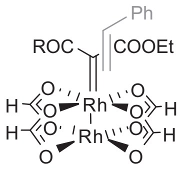
Table 2
Properties of carbenoids **11**–**13**



11: R=Me
12: R=Ph
13: R=NMe$_2$

Carbenoid	Charge, carbonyl O	Charge, ester carbonyl O	IR freq.
11	−0.49	−0.56	1748
12	−0.49	−0.56	1700
13	−0.54	−0.57	1720

Table 3
Properties of the most favoured transition states for cyclopropanation of styrene with carbenoids **11**–**13**



TS-11: R=Me
TS-12: R=Ph
TS-13: R=NMe$_2$

Transition state	Charge, carbonyl O	Charge, ester carbonyl O	IR freq.
TS-11	−0.53	−0.56	1748
TS-12	−0.54	−0.56	1700
TS-13	−0.61	−0.58	1687

The *trans*-directing abilities of carbonyl substituents have also been rationalised based on the polarity of the carbonyls, more polarised carbonyls better stabilising the positive charge on the alkene. Charette and co-workers reported a correlation between *trans*-directing ability and C═O IR stretching frequency of certain substituents.[4b] It is known that this IR frequency may give insight into the polarity of the C═O bond, so the observed correlation was taken to mean that the lower the frequency, the more polar the C═O bond and the better the diastereoselectivity. However, the IR stretching vibrations were taken from a general database, and were not specific for the studied species. We therefore calculated the IR frequencies for C═O stretching in the amide and keto substituents in carbenoids **11**–**13** (Table 2) and in the transition states for the cyclopropanation of styrene with **11**–**13** (Table 3).

We found that there is no correlation between a substituent's *trans*-directing effects and its C═O IR stretching frequency in the carbenoid. The order of stretching frequencies is **12** < **13** < **11**, and the order of dr in the cyclopropanation of styrene is **13** > **12** > **11**. In the transition states, however, the situation is quite different (Table 3). For the keto substituents (carbenoids **11** and **12**), the C═O stretching frequency remains unchanged in going from the carbenoid to the transition state, but the frequency is lowered considerably for the most *trans*-directing of the substituents, the amide group (carbenoid **13**). This results in the amide carbonyl having the lowest frequency. The carbonyl oxygens in all three Y-substituents also become more negatively charged in the transition states. These findings imply that the carbonyls in the *trans*-directing substituents can become more polarised in the transition state for cyclopropanation compared to the carbenoid. The polarity of the carbonyl in the transition state appears to have a determining effect on the *trans*-directing abilities of the substituents: the order of stretching frequencies *in the transition states* is **13** < **12** < **11**, which corresponds directly with the reported order of dr in the cyclopropanation of styrene (**13** > **12** > **11**). The increased carbonyl polarity in the transition states may be the result of an interaction between the *trans*-directing substituents, such as the studied keto and amide substituents, and perhaps also the nitro group in carbenoid **8**, and the alkene.

The structures of the transition states[17] in the cyclopropanation of styrene with carbenoids **11**–**13** indicate that subtle stereoelectronic effects may also be at play. Charette and co-workers postulated that carbenoids with two carbonyl substituents adopt an 'in–out' orientation of the substituents in the transition state,[4] with the most *trans*-directing substituent in an out-of-plane orientation relative to the carbene and the other substituent in the plane. They proposed that an 'out–out' conformation with both substituents in out-of-plane orientations must be unreactive because of steric repulsions with the approaching alkene. Our findings imply that

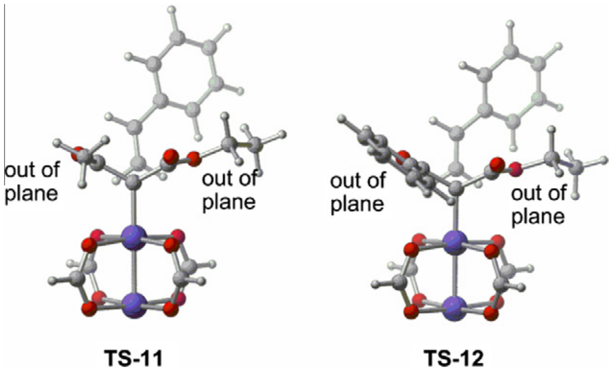
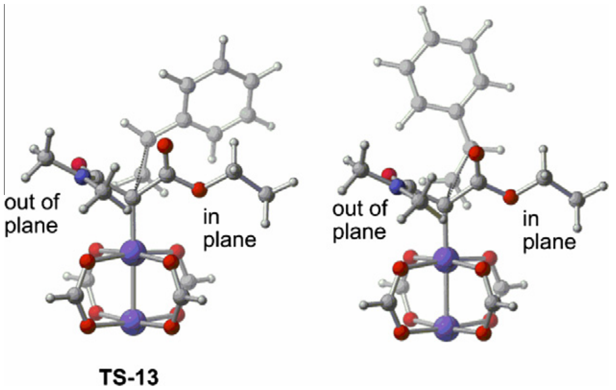


Figure 3. Structures of transition states **TS-11** and **TS-12**. 'Plane' refers to the plane of the carbene.



TS-13

Figure 4. Transition states for cyclopropanation of styrene with **13**, leading to *trans*-substituted (left) and *cis*-substituted (right) cyclopropanes. 'Plane' refers to the plane of the carbene.

this is not the case. The transition states for cyclopropanation of styrene with carbenoids **11** and **12**, **TS-11** and **TS-12**, both have distinct 'out–out' conformations (Fig. 3). This is also the case for the analogous transition state with carbenoid **14**.

The most favoured transition state for cyclopropanation of styrene with carbenoid **13** (**TS-13**), on the other hand, has more of an 'in–out' conformation (Fig. 4); the amide group has an Rh-C-C=O dihedral angle of −151°. The analogous angle in the transition state leading to the *cis*-substituted cyclopropane is −152°, implying that the orientation of the substituent is not affected by the proximity of the styrene phenyl group. The 'in–out' conformation of the transition states contrasts the conformation of the carbenoid (**13**), which has an 'out–out' conformation.

It is not clear why the amide substituent affects the orientation of the ester group in this manner, but the outcome is less steric repulsion between the ester group and the phenyl ring in the transition state leading to the *trans*-substituted cyclopropane (**TS-13**). This steric effect is expected to make the *trans*-transition state more favoured in cyclopropanations with **13** than with other carbenoids, and may be an additional factor that makes the amide substituent *trans*-directing. The reported results from cyclopropanation reactions with carbenoids **9** and **10** further imply that the *trans*-directing effect of a substituent may be affected by the size of the substituent: the Y-substituents in carbenoids **9** and **10** are both large, the $SiMe_2Ph$ group in **10** is larger than the $SiEt_3$ group in **9**, and they are both *trans*-directing, the $SiMe_2Ph$ group more so than the smaller $SiEt_3$ group.

In summary, we have examined computationally the properties of a range of Rh(II) carbenoids. Of the carbenoid substituents studied, all those that are classified as acceptors according to the commonly used acceptor versus donor theory are more electron-withdrawing than hydrogen, which is the designated zero-point of the scale from acceptor to donor. The substituents classified as donors are not necessarily more net electron-donating than hydrogen, but they are donors in the sense that they are π-donors. The π-donors stabilise the carbenoids, and are *cis*-directing in cyclopropanation reactions. For *trans*-directing substituents, carbonyl polarity appears to be of importance, along with steric effects.

Supplementary data

Supplementary data (computational details and energies and full geometries for all structures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.116.

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11. Since the diastereomeric ratio is known to be influenced by the catalyst as well as the carbenoid substituents, only reactions catalysed by $Rh_2(OAc)_4$, $Rh_2(esp)_2$ and $Rh_2(OOct)_4$ were considered. The catalyst in our model system, $Rh_2(O_2CH)_4$, has been shown to be a good model for $Rh_2(esp)_2$ and $Rh_2(OAc)_4$, see: (a) Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181–7192, and (b) Bonge, H. T.; Hansen, T. *Eur. J. Org. Chem.*, manuscript accepted, while $Rh_2(OOct)_4$ typically reacts similarly to $Rh_2(OAc)_4$, see for instance (c) Qu, Z; Shi, W.; Wang, J. *J. Org. Chem.* **2001**, *66*, 8139–8144, and (d) Taber, D. F.; Sheth, R. B.; Tian, W. *J. Org. Chem.* **2009**, *74*, 2433–2437. Following precedence from previous computational studies of carbenoid reactions, solvent effects are not included in this study, so experiments conducted in different solvents could be studied in the future.
12. The diastereomeric ratios for carbenoids **1**, **5**–**8** are taken from Ref. 8, pp 171; **2**–**4** from Ref. 6, **9** and **10** from Müller, P.; Lacrampe, F. *Helv. Chim. Acta* **2004**, *87*, 2848–2859. ; and **11**–**13** from Ref. 4b.
13. The lack of correlation between the net electron-donating or -withdrawing properties of a substituent and the diastereomeric ratios is also evident from the lack of correlation between the substituents' Hammett σ-values and the diastereomeric ratios. For a survey of Hammett substituent constants, see: Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.
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