

On the Mechanism of the Copper-Catalyzed Cyclopropanation Reaction

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Abstract: The selectivity-determining step in enantioselective copper-catalyzed cyclopropanation with diazo compounds has been studied by experimental and computational methods. The addition of the very reactive metallacarbene intermediate in an early transition state to the substrate alkene is concerted but strongly asynchronous, with substantial cationic character on one alkene

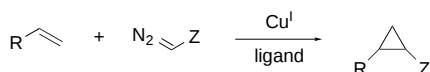
carbon in the neighborhood of the transition state. Evidence from isotope effects and Hammett studies supports the nature of the transition state. For-

mation of a metallacyclobutane intermediate by a [2+2] addition is kinetically disfavored. Ligand–substrate interactions influencing the enantio- and diastereoselectivity have been identified, and the preferred orientation of the alkene substrate during the addition is suggested.

Keywords: asymmetric catalysis • copper • cyclopropanation • density functional calculations • reaction mechanisms

Introduction

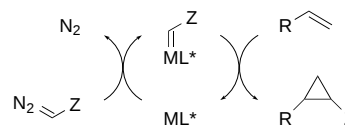
In recent years, much effort has been devoted to the development of methods for metal-catalyzed diastereo- and enantioselective cyclopropanation of olefins with diazo compounds.^[1] One of the most appealing catalytic systems relies on a copper complex together with a C_2 -symmetric ligand, such as a semicorrin^[2] or a bis(oxazoline)^[3] (Scheme 1). These ligands, particularly the bis(oxazolines), which are easily available and induce high levels of enantioselectivity for a range of olefinic substrates, are currently the favorite ones for Cu-catalyzed



Scheme 1. Copper-catalyzed cyclopropanation.

asymmetric cyclopropanation. However, as is often the case for metal-mediated asymmetric catalysis, detailed mechanistic understanding has lagged behind empirical catalyst development. Since better mechanistic insight should aid in the development of even more efficient catalysts, we now present kinetic and computational studies of the copper-catalyzed cyclopropanation of styrenes involving bis(oxazoline) ligands.

For the title reaction two points of mechanistic detail are widely accepted: that the actual catalyst is a Cu^I species,^[1–4] even if Cu^{II} is used, and that a short-lived electrophilic copper–carbene intermediate is involved (Scheme 2).^[1–6] We



Scheme 2. Proposed catalytic cycle for the asymmetric cyclopropanation.

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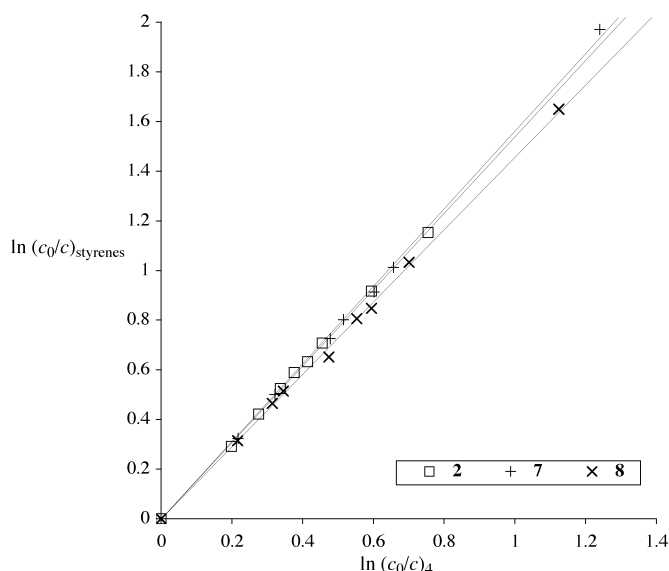


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have used a combination of Hammett-type kinetic studies, isotopic labeling, and high-level computational methods to investigate two of the points of contention, namely the nature of the step which controls the stereochemistry of the reaction^[2, 4, 7] and the participation of a metallacyclobutane intermediate.^[4]

Results and Discussion

Kinetic studies: The relative rates of cyclopropanation of the substituted styrenes (**3–8**) used in the Hammett and isotope



studies are shown in Table 1. All experimental procedures are available as Supporting information. In calculations of rate constants we assumed pure first-order kinetics in substrate,

Substrate	Substituent	σ	σ^+	k_{rel}
3	<i>p</i> -MeO	− 0.28	− 0.78	2.52
4	<i>p</i> -Me	− 0.14	− 0.31	1.54
5	<i>p</i> -CF ₃	0.53	0.61	0.49
6	<i>p</i> -NO ₂	0.81	0.79	0.42 ^[a]
7	α -[D]	−	−	1.02 $\pm$ 0.02 ^[b]
8	β,β -[D ₂]	−	−	0.95 $\pm$ 0.02 ^[b, c]

Figure 1 is a scatter plot showing the correlation between $\log(k_{\text{rel}})$ (y-axis) and σ or σ^+ (x-axis). The y-axis ranges from -0.5 to 0.5, and the x-axis ranges from -1 to 1. Data points for σ (open circles) and σ^+ (plus signs) are plotted. A linear regression line is shown with the equation $\log(k_{\text{rel}}) = -0.51 \sigma^+$ and $r^2 = 0.999$. A legend indicates that open circles represent σ and plus signs represent σ^+ .

that is, $\ln([A]_0/[A]) = kt$ where $[A]$ is any styrene concentration. To avoid influences from other steps in the catalytic cycle (such as formation of the metal carbene), relative rate constants were obtained from competition experiments according to Equation (1). The slopes in Figure 1 for isotopi-

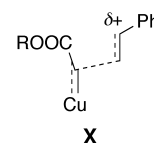
$$\ln([A]_0/[A]) = k_{re} \ln([B]_0/[B]) \quad (1)$$

cally substituted styrenes in competition with *p*-methylstyrene (**4**) give rates relative to that standard, whereas Table 1 has been recalibrated to show rates relative to unsubstituted styrene (**2**). The Hammett results are plotted as $\log(k_{rel})$ versus σ or σ^+ in Figure 2.

It is clear from Figure 2 that the data fit better to σ^+ than to σ values. In combination with the modest $\rho = -0.51$, this indicates an early transition state with substantial positive charge being developed at the benzylic position and is in qualitative agreement with studies of Si-H insertion, showing that the postulated copper carbene is a very reactive electrophile.^[8] In an earlier Hammett study of cyclopropanation employing an anionic ligand a correlation with σ and a more negative ρ value were found.^[9] This difference is understandable, since the neutral Cu complex should be less electrophilic than the cationic complexes employed here.

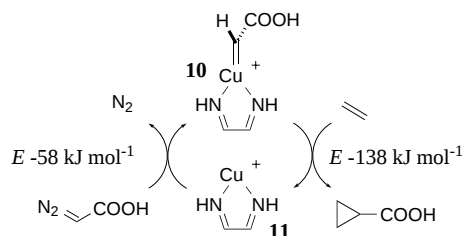
The isotope effects indicate that the β -carbon has been somewhat rehybridized in the transition state (TS), whereas no significant effect can be seen at the α -position (Table 1). There can be many reasons for the absence of observable

isotope effects, but the data are consistent with the concerted but asynchronous transition state **X**, where the new bond to the β -carbon is formed well before the bond to the α -carbon.



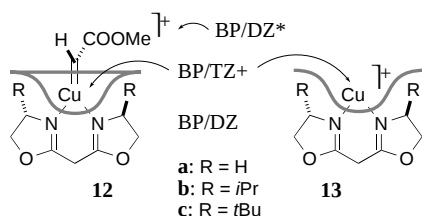
Initial computational studies: Our first goal was to characterize the species in the postulated catalytic cycle (Scheme 2) for a small model system.^[10] We selected the model reaction of ethene with diazoacetic acid catalyzed by the Cu^I complex of 1,4-diazabutadiene. For the initial studies, we employed the B3LYP functional^[11] in Gaussian98^[12] together with the 6-311 + G all-electron basis set for Cu and 6-31G set for the remaining elements. The B3LYP level generally gives a good performance for transition metal complexes,^[13] and has previously been shown to yield good bond energies for copper compounds.^[14] Both reactions in the catalytic cycle are

exothermic (Scheme 3), which is one of the requirements for an efficient catalytic cycle. The geometries and raw energies are available as Supporting information. Other important factors which can influence catalytic efficiency include side paths and the nature of the rate-limiting step,^[10] but in this work we were mainly concerned with factors affecting the selectivity of the reaction.



Scheme 3. Computational small model system, with reaction energies.

Experimentally relevant models (**12** and **13**) of the two metal complexes were also investigated utilizing the BP functional^[15] in ADF.^[16] Most of the system is described by a



double- ζ Slater-type basis (DZ). For the heavy atoms in the carbene moiety, we added a polarization function (DZ*), whereas the copper atom was described by a triple- ζ basis with added diffuse functions, TZ+ (types II, III, and IV in ADF, respectively). The geometries and raw energies are available as Supporting Information.

The geometries of the catalyst complexes **11** and **13** are unsurprising, being near-planar and with the coordination geometry determined by the ligand. Thus, in the small model system **11** the N–Cu–N bond angle is constrained to 83° , whereas the same angle in the more realistic model systems **13** is $110^\circ \pm 2^\circ$. Similarly, the Cu–N bond is $2.033 \text{ \AA}$ in **11** and decreases to $1.90\text{--}1.91 \text{ \AA}$ in **13**, very close to the observed value ($1.88 \text{ \AA}$) for an oxazoline– Cu^I bond.^[17]

The calculated metallacarbenes **10** and **12** display some less intuitively obvious features (Figure 3). The carbenoid carbon is almost planar, with the Cu=C–C plane orthogonal to the N–Cu–N plane. The plane of the carboxylate moiety is in turn orthogonal to the plane through the carbenoid carbon, minimizing conjugation. This is consistent with a strong cationic character on the carbenoid carbon. The force counteracting conjugation is quite strong; in **12c**, in which the *tert*-butyl group interacts closely with the carboxylate, the crowding is minimized mainly by distortion of the bis(oxazoline) ligand, not of the carboxylate.

A population analysis reveals that the d functions of Cu do not participate to any significant degree in the bond between

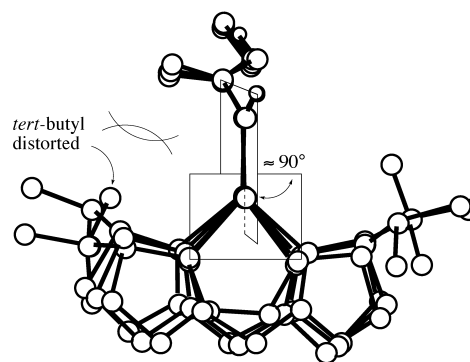


Figure 3. Overlay of the Cu=C–C moieties of **10** and **12a–12c**.

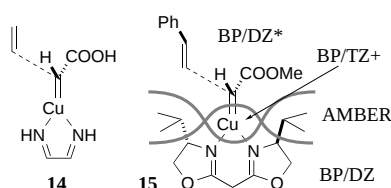
Cu and C, so it should more properly be drawn as $\text{Cu}-\text{C}^+$, corresponding to the lone pair of a singlet carbene coordinated to a Cu^I cation. Again, this corresponds well with the observed electrophilic character of **10/12**. The analysis also points to a slight donation from the carbonyl oxygen to the carbene carbon as the major source of the strong orthogonal preference of the carboxylate moiety.

The selectivity-determining step must be the addition of the metallacarbene (**10** or **12**) to the substrate alkene, even though formation of the metallacarbene has been shown to be turnover-limiting.^[5, 10] We have therefore focused our attention on reaction of the metallacarbene with alkene. Early in our studies it became clear that investigation of this step posed some severe problems. In all our model systems, the reaction between the metal carbene and alkene displays a monotonic downhill energy profile, with no transition state on the potential-energy surface. This is apparently in violation of the experimental evidence that there is a real transition state for the addition, since a substrate-dependent selectivity was observed in the competition studies. In a diffusion-controlled reaction, substrate properties should have no influence on the relative rates of reaction. There can be several reasons for the apparent failure to find a TS in the calculations, each of which can be addressed by computation.

- 1) The real free-energy transition state could exist without a corresponding TS on the potential energy surface. A TS may be located by direct calculation of the free-energy surface.
- 2) The small model system **10** may not reflect the true reaction closely enough. However, **12a–12c** correspond to experimentally tested systems.
- 3) It may be necessary to include the effect of solvation to find a TS.^[18]
- 4) The level of theory may be insufficient.

We do not have sufficient computational resources to address all of these points in one calculation. Instead, we implemented a combination method that has been successful in earlier cases.^[18] Several points on the path were located by scanning along the reaction coordinate, whereupon all contributions to the final energy were calculated at each point and added together to form a composite high-level free energy. We expect this method to yield barriers of sufficient accuracy to allow correlation with experimental data and to serve as a starting point for future development of a Q2MM predictive model.^[19]

To achieve the smooth energy surface, without sudden jumps in unconstrained coordinates, which is necessary for the combination procedure to be successful, the scanning coordinate(s) must be chosen with care and should also be as few as possible to avoid the added complication of a multidimensional surface. When the distance from the carbene carbon to the approaching alkene was chosen as first scanning coordinate, a discontinuous surface was obtained at which the bond to the unconstrained carbon was formed suddenly between one scanning point and the next. This problem could be overcome by taking the angle of the alkene to the approach vector as a second constrained coordinate. However, the alternative of scanning the distance from the carbene carbon to the alkene centroid was found to be more efficient, yielding a smooth surface without application of additional constraints. This latter method was employed for the model systems reported here. For the small model **14** (reaction of **10** with



ethene), we could employ high levels of theory and calculate the most relevant contributions to the total free energy profile. The more realistic model **15** (reaction of **12b** with styrene) was too large to allow direct evaluation of high-level contributions, but is closely related to the system employed in our kinetic studies. We believe that a combination of the results from the two model systems will allow a meaningful comparison with the experimental results. The close correspondence between **10** and **12b** (the overlay in Figure 3 gave an r.m.s. deviation of only 0.008 Å) lends credence to the expectation that the reaction paths will be similar.

As a basis for our computational investigation, we chose an IMOMM-like^[20] QM/MM approach^[21] for the model system **15**, utilizing the same functional and basis set combination as for metallocarbene **12b**, with one exception; the steric interaction is better described at the MM level (which includes dispersion forces^[22]). The isopropyl groups and their interactions with the remainder of the system were therefore described by AMBER,^[23] with the QM/MM^[21] method implemented in ADF.^[16]

The effect of contributions beyond the BP gas-phase calculations were explored in Gaussian98^[12] using the small model system **14**. Geometry optimization was performed by using B3LYP^[11] together with the LANL2DZ^[24] basis set (to correspond to the high-level correlation which was limited to this basis set; vide infra). The geometries were optimized with the same Z-matrix setup as in the ADF calculations, scanning the distance from carbene carbon to alkene centroid. All further contributions were calculated as single-point corrections at the constrained B3LYP/LANL2DZ geometries. Vibrational contributions for nonstationary points were evaluated at the same level by using the projection method of Handy and co-workers, reducing the degrees of freedom by

seven to remove the influence of the residual gradient along the reaction coordinate in addition to translations and rotations.^[25] The B3LYP wavefunction was tested for triplet instability. At all scan points, the energy required for vertical excitation to the triplet exceeded 150 kJ mol⁻¹.

Solvation corrections for **14** were evaluated by using B3LYP/LACVP^[26] together with the PB-SCRF solvation model^[27] in Jaguar.^[28] A continuum solvation treatment similar to the one employed here is both necessary and sufficient for correctly describing an ionic organometallic reaction coordinate.^[18]

Corrections for higher levels of theory were evaluated by using CCSD(T)/LANL2DZ. Correlated calculations require fairly large basis sets,^[29] certainly larger than LANL2DZ. Our computational resources were insufficient to go beyond this basis set at the CCSD(T) level, but the effect of using a larger basis can be estimated at a lower correlated level. Thus, we calculated a basis set correction (ΔE_{basis}) at the MP2 level as the difference between MP2 with SDD on Cu and 6-311G** on the remaining atoms, and MP2/LANL2DZ. Combining the basis set correction with the CCSD(T) energy, we obtained a high-level potential energy E for the model system [Eq. (2)], our best estimate of what the potential energy would be if we could perform the calculations at the CCSD(T) level with a TZVP basis set. With E as a foundation, the total free energy along the reaction path was calculated according to Equation (2). The geometries and all relevant single-point energies are available as Supporting information.

$$G = E + \Delta G_{\text{therm}} + \Delta G_{\text{Solv}} \quad (2)$$

$$\begin{aligned} E &= \text{CCSD(T)/LANL2DZ//B3LYP/LANL2DZ} + \Delta E_{\text{basis}} \\ \Delta G_{\text{therm}} &: \text{vib, rot, and trans at B3LYP/LANL2DZ, 298 K, } 3N - 7 \text{ harmonic vibrations} \\ \Delta G_{\text{Solv}} &= \Delta G_{\text{PB-SCRF}}(\text{B3LYP/LACVP})//\text{B3LYP/LANL2DZ} \\ \Delta E_{\text{basis}} &= (\text{MP2}/[\text{SDD,6-311G**}] - \text{MP2}/\text{LANL2DZ})//\text{B3LYP/LANL2DZ} \end{aligned}$$

To obtain the appropriate correction factor, all constrained geometries of **14** were also calculated at the BP level with the same combination of basis sets that was employed for model system **15**, that is, TZ+ for Cu, DZ* for all atoms close to the reaction center, and DZ for the bidentate imine ligand. A correction term ΔG was calculated as the difference between G [Eq. (2)] and BP.

For all energies, we are interested only in the *relative* contributions along the reaction path. To best illustrate the effects of the various contributions, they were adjusted by the value at an arbitrary zero point, set to the longest scan distance used for the small system **14**, $r_0 = 3.284$ Å. Thus, the relative correction $\Delta\Delta G$ was calculated as shown in Equation (3).

$$\Delta\Delta G_r = \Delta G_r - \Delta\text{BP}_r \quad (3)$$

$$\Delta X_r = X(r) - X(r_0), X = G, E, \text{B3LYP, BP}$$

A third-order polynomial expansion around r_0 was fitted to the total correction energies $\Delta\Delta G_r$ and used to interpolate to points on the finer scan employed for the large system **15**. The regression yielded a very good fit ($r^2 = 0.9999$), with a 95 % confidence interval of only 0.6 kJ mol⁻¹ for interpolated

values. In no case was the polynomial used for extrapolations beyond the range of the scan for system **14**.

Analysis of the results in Figure 4, which shows the relative potential energies at appropriate levels, together with the correction energies and the corresponding polynomial $\Delta\Delta G(r)$, demonstrates that the two DFT functionals agree well, but differ slightly from the high-level potential energy E . In no case can a transition state be located on the potential energy surface (PES), but inclusion of the free energy terms indicates a TS at around $r = 2.5$ Å.

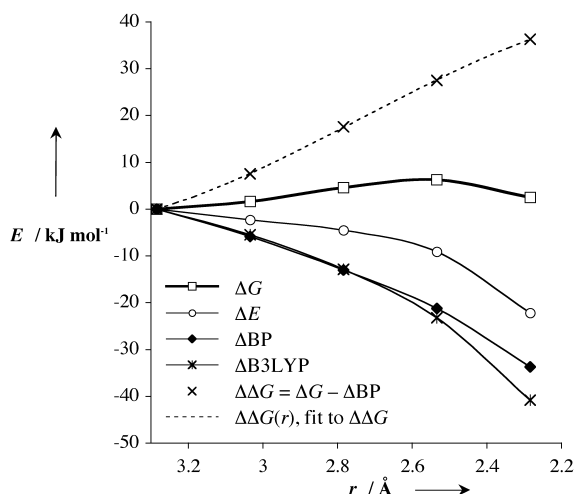


Figure 4. Energies and correction ($\Delta\Delta G$) from model system **14**.

All four correction terms are of similar magnitude, and follow the expected trend (Figure 5). Going along the reaction coordinate towards the product, six degrees of freedom are converted from rotations/translations to vibrations, increasing the total free energy. The surface area decreases, which lessens the stabilization by solvent. The basis set superposition error (BSSE) is worsened by increased overlap, so correcting for this by extending the basis set will also increase the energy

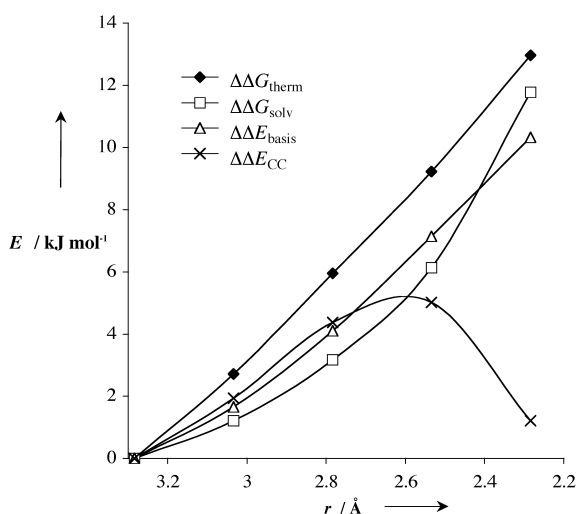


Figure 5. Contributions to the relative free energy correction, Equation (2). The last term, $\Delta\Delta E_{CC}$, is the difference between CCSD(T)/LANL2DZ and BP.

along the reaction path. Finally, the difference between CCSD(T) and BP maximizes around the TS. This is consistent with the concept of the TS being an avoided crossing of reactant and product states, requiring extensive correlation for an accurate description. A T1 test gave a value of 0.033,^[30] indicating that the system is borderline even for CCSD(T) and might be better described by a multideterminant wavefunction, but such a calculation was unfortunately beyond our resources.

With a well-behaved correction term $\Delta\Delta G(r)$ in hand, we initiated an extensive investigation of the larger model system **15**. First, since the ligand is C_2 -symmetric, only one ligand orientation needs to be considered. Inverting the carbene substituent is exactly equivalent to rotating the entire carbene complex by 180° around the Cu=C axis. We have chosen to illustrate the reaction by always using an approach from the left. Figure 6 shows attack from the two faces of the carbene. Upon alkene approach, the carbene will bend as a result of becoming more sp^3 -hybridized. For attack from the *Si* face, this will bring the carboxylate into close proximity with the ligand isopropyl group.

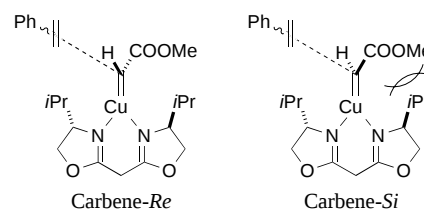


Figure 6. Two possible approaches to a carbene with a C_2 -symmetric ligand.

The approach vectors depicted in Figure 7 differ qualitatively: the open approach corresponds to a concerted but very asynchronous addition, whereas the cyclic path leads to initial formation of a metallacyclobutane, in analogy with known

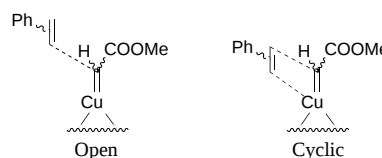


Figure 7. Two addition mechanisms.

metathesis catalysts.^[1] The two approaches are identical beyond approximately 2.7 Å, but separate into two distinct paths at shorter distances. To differentiate the paths, energy scans were started at a point to which the two approaches are clearly different (approximately 2.3 Å) and conducted in both directions to complete the reaction profiles.

Finally, a monosubstituted alkene may approach with four different orientations (Figure 8). One might envision other orientations in which the alkene has been rotated around the approach vector, and at long distances the alkene will orient to achieve the optimum nonbonded distance between the phenyl and the ligand. On closer approach following the open mechanism, the alkene will orient to avoid eclipsing the

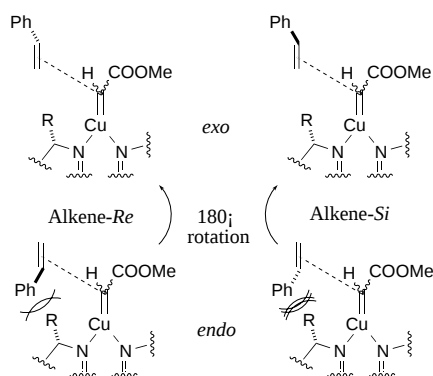


Figure 8. Alkene approach orientations.

carbene substituents, whereas the cyclic mechanism can only be realized when the two reacting bonds are parallel.

The relationship between the orientation of approach and the configuration of the final product is not immediately evident. The configuration of the phenyl-substituted cyclopropyl carbon depends only on which alkene face is attacked, with the *Re* alkene always leading to 2*S* configuration. However, the final configuration of the carbene carbon depends on both the carbene face selectivity and the alkene approach; a switch from *exo* to *endo* attack changes the final configuration. Thus, the carbene-*Re*/*exo* and the carbene-*Si*/*endo* combinations both lead to 1*R* configuration in the product.

In general, the *endo* approach is disfavored. For the open type of TS, the phenyl group can stabilize the developing charge only in an *exo* orientation. For the cyclic TS, the steric interaction with the ligand becomes severe. Most scan attempts for *endo* approaches would be converted spontaneously to the corresponding *exo* orientation by a 180° rotation of the alkene around the approach vector (Figure 8). However, exceptions to this rule were observed (vide infra).

Free-energy surface for model system 15: All free energies were obtained by adding the correction function $\Delta\Delta G(r)$ to the QM/MM potential energies. We first compared the direct addition to the initial formation of a metallacyclobutane intermediate using *exo* approaches (Figure 9).

For the open TS, the QM/MM potential energy decreases monotonically, but the free energy reaches a maximum around 2.5 Å. The curvature is very gentle, and at longer distances there is almost free rotation around the approach vector. At short distances, the alkene bond has to align with the Cu=C bond to form the final product, and the decrease in the rotational freedom provides one reason why the vibrational component of the free energy increases along the reaction path (Figure 5), but at the TS there is still a certain amount of flexibility in the orientation.

Some of the geometrical changes along the reaction path are depicted in Figure 10. The hybridization of the alkene carbons can be measured by the improper torsional angle $R-C=C\cdots H$, where the last H is the second substituent on the first carbon. A completely planar system has an improper torsion of 180°, whereas for an idealized sp^3 carbon it is 120°, and the cyclopropyl carbons lie around 147°. The rehybrid-

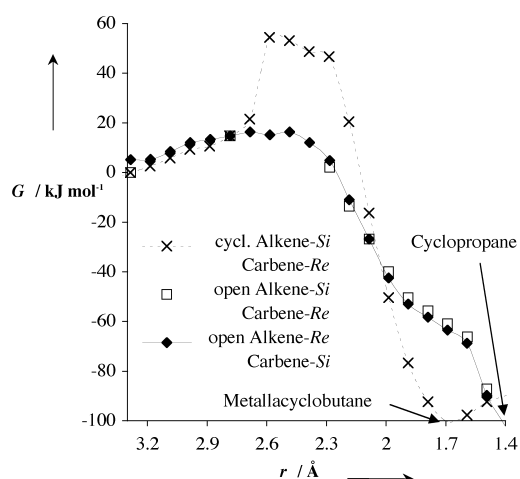


Figure 9. Comparison of the open and cyclic *exo* paths (compare Figure 7). To avoid extrapolation, a constant value of $\Delta\Delta G(r) = \Delta\Delta G(2.284) = 36.26 \text{ kJ mol}^{-1}$ was used for short scan distances, $r < 2.284 \text{ Å}$.

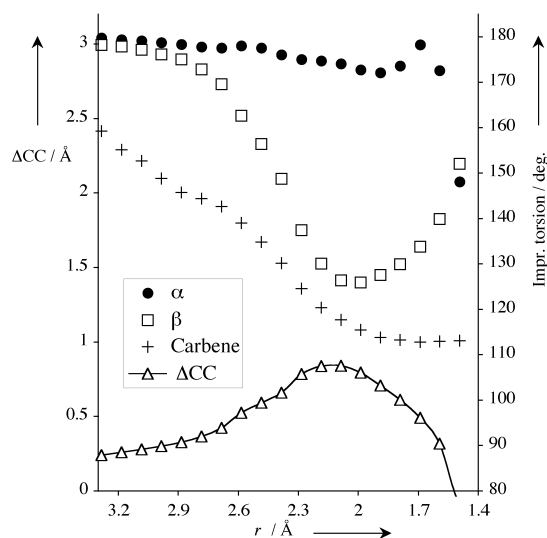


Figure 10. Asynchronicity of the concerted addition, exemplified by the open *exo*-alkene-*Re*/carbene-*Si* path. The improper torsions correspond to the $R-C=X\cdots R$ dihedrals of the three $R_2C=X$ moieties, $sp^2 = 180^\circ$, $sp^3 = 120^\circ$.

ization of the β -carbon starts at approximately 2.8 Å, and this carbon atom is already essentially completely sp^3 -hybridized around 2.0 Å. Over most of the range, the substituents on the α -carbon show a very slight bending towards the reaction center. At $r = 1.7 \text{ Å}$ it becomes completely planar and then rapidly forms the second C–C bond. The pyramidalicity of the carbene carbon can likewise be measured as the $C-C=Cu\cdots H$ improper torsion, at least for as long as a significant Cu–C bond ($r > 1.5 \text{ Å}$) exists. The bending away from planarity has already started beyond $r = 3 \text{ Å}$, and ends at complete sp^3 character around $r = 2 \text{ Å}$. The degree of asynchronicity is also shown by the difference (ΔCC) between the lengths of the C–C bonds that are forming, which reaches a maximum of approximately 0.84 Å at $r = 2.1 \text{ Å}$. The small model system **14** is much more synchronous (maximum $\Delta CC = 0.39 \text{ Å}$). This is probably due to the lack of stabilization of the developing

cationic charge on the primary carbon in the small model system.

There is a significant barrier to formation of a metallacyclobutane, even on the potential-energy surface. In an absolute sense the barrier is still fairly low, and in the absence of alternatives this would have been a feasible path. However, as the direct addition through the open TS is about 40 kJ mol^{-1} lower in energy, the possibility of an *exo*-metallacyclobutane intermediate can be excluded, in agreement with our observed isotope effects.

We concentrated on the open *exo* approaches. The four possible vectors (Figure 11) were compared at one common scan point, reaction coordinate $2.284 \text{ \AA}$, at the the free-energy curve turns sharply downward after a long, flat region. The

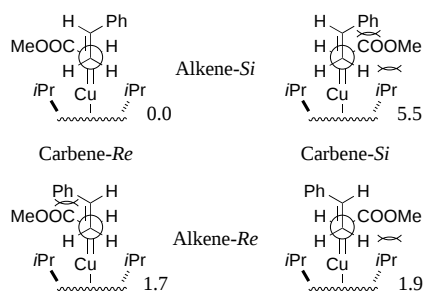


Figure 11. The four possible open *exo* approaches. Energies [kJ mol^{-1}] are relative to the most favorable form (alkene-*Si*, carbene-*Re*).

geometries and raw energies at this distance are available as Supporting Information. At this point the addition is very asynchronous, the length of the bond forming to the β -carbon being $1.92\text{--}1.99 \text{ \AA}$ and the carbene- α -carbon distance still $2.73\text{--}2.78 \text{ \AA}$. The β -carbon is partially rehybridized towards the sp^3 form, whereas the α -carbon is essentially planar (sp^2) (Figure 10).

The structures are not properly converged transition states, so the energy differences should be interpreted only qualitatively. For this scan point, the results are in good agreement with the model proposed by Pfaltz and co-workers.^[2] The path leading to the observed major diastereomer (*1R,2R*) is indeed lowest in energy. The enantioselectivity at the carboxylate substituent arises from the hindered distortion of the *Si* carbene. This penalty is more severe in the *tert*-butyl-substituted ligand **12c** (Figure 3), in perfect agreement with the higher experimental enantioselectivities observed with this ligand. The alkene substituent does not interact significantly with the ligand in any *exo* path; the *cis*–*trans* selectivity is solely an effect of the relatively weak steric repulsion between carboxylate and alkene substituent in the transition state. This is not true, however, for a 1,2-disubstituted alkene, in which one substituent should be strongly affected by direct interaction with the ligand.^[7]

One additional low-energy path was found in the investigation of an *endo* approach. This path has all the characteristics of the open mechanism, in that the bond to the styrene β -carbon is formed first, but the alkene enters in a *gauche*-like orientation which collapses to a metallacyclobutane intermediate (Figure 12). Formation of the cyclopropane from this intermediate is facile and exothermic. At the common

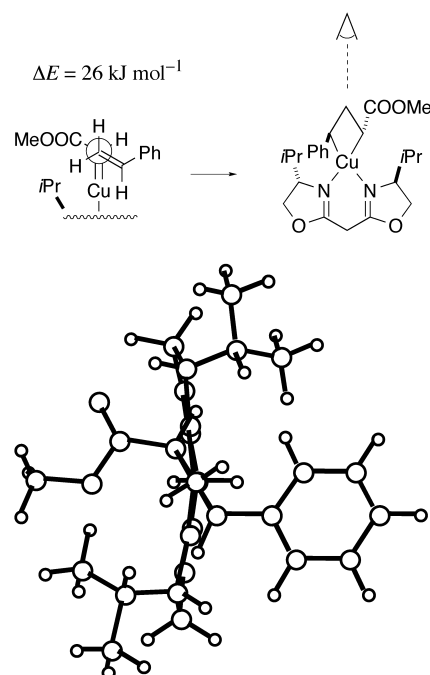


Figure 12. *Gauche* addition with collapse to a metallacyclobutane intermediate. The ball-and-stick figure is viewed from the metallacyclobutane apex (Cu hidden), as indicated on the right.

comparison point ($r = 2.284 \text{ \AA}$), this path is 26 kJ mol^{-1} higher in energy than the most favored mechanism shown in Figure 11, so for this substrate it should not contribute significantly to product formation. This is also indicated by the fact that it would produce the observed minor enantiomer. However, this asynchronous path to the metallacyclobutane, with an *endo* substituent, is substantially lower in energy than the direct $[2+2]$ addition found for the cyclic *exo* path. It also has a steric profile that differs substantially from the other open paths. It is quite clear that the *tert*-butyl substituent (**12c**) would prohibit the metallacyclobutane formation completely, but with less hindered ligands and other alkene substituent patterns the *gauche* path cannot be excluded with absolute certainty. The hybridization changes and degree of bond formation along the reaction path closely parallels that for the open mechanism, so the two mechanisms are not expected to be distinguishable by the type of kinetic studies we employed in this study. The only valid mechanistic indicator in this case seems to be the product pattern to be expected from the different paths.

Conclusion

The selectivity-determining step in the copper-catalyzed cyclopropanation proceeds by a concerted but very asynchronous addition of a metallacarbene to the alkene. For styrene substrates, the bond to the β -carbon is formed early in the reaction, with final ring closure to the cyclopropane product occurring late but still in a concerted manner. In the neighborhood of the free-energy TS, the α -carbon develops substantial cationic character. For the monosubstituted styrenes studied here, a parallel orientation of the $\text{C}=\text{C}$ and $\text{Cu}=\text{C}$

bonds is preferred, with the phenyl group in an *exo* orientation (not interacting with the ligand). The enantioselectivity is determined by a direct repulsive interaction between the carbene substituent and the ligand, whereas the diastereoselectivity for monosubstituted alkenes is determined only by a relatively weak interaction between the carbene and alkene substituents.^[2] However, an alkene with substituents on both carbon atoms could certainly interact directly with the ligand.^[7]

Metallacyclobutane formation through a direct [2+2] addition is kinetically disfavored, but if the approaching alkene adds in a *gauche*-like orientation, the second bond may be formed to Cu, leading to a metastable metallacyclobutane. The *gauche* orientation is disfavored for the styrenes studied here, but cannot be excluded for more highly substituted alkenes. The question of whether a metallacyclobutane is an intermediate in the reaction is of no importance to selectivity predictions, since the selectivity is fully determined in the initial addition, which is irreversible. However, a *gauche* addition would yield a stereoselectivity quite different from the regular open *exo* addition.

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