

Kinetics of the BpCu-Catalyzed Carbene Transfer Reaction (Bp = Dihydrindobis(1-pyrazolyl)borate). Is a 14-Electron Species the Real Catalyst for the General Copper-Mediated Olefin Cyclopropanation?

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Received April 16, 1999

Kinetic studies of the ethyl diazoacetate (EDA) decomposition reaction in the presence of BpCu (**1**) and in the presence or absence of olefin have led to the determination of several kinetic and thermodynamic parameters, and a consistent mechanism has been proposed for the olefin cyclopropanation reaction. Related studies with the complexes [Cu(bipy)₂]I (bipy = bipyridine) and [Cu(bis(oxazoline))₂]OTf have shown strong similarities with the results obtained with **1**. A general mechanism covering the copper-based systems reported in the literature has been proposed, the real catalyst (i.e., the species to be reacted with EDA) in all cases being a neutral, 14-electron fragment of composition (L–L)Cu (L–L = Bp- and Tp-like ligands, semicorrins, salicylaldehyde derivatives) or, alternatively, the isoelectronic, cationic [(L–L)Cu]⁺ (for L–L = bis(oxazoline), bipyridine).

Introduction

In the past decade, the use of copper-based systems as catalysts in the asymmetric olefin cyclopropanation reaction has provided enantiomeric excesses (ee's) higher than 99%.¹ Table 1 displays some of the ligands that induced the aforementioned high ee's. Seminal work by Nozaki² in 1966 presented the asymmetric cyclopropanation of styrene, in the first example of an enantioselective reaction under homogeneous conditions. A few years later, Aratani³ modified Nozaki's catalysts using chiral salicylaldehyde–amino acid derivatives (entry 1). In the early 90's, several groups moved to the use of C₂-symmetry ligands, containing two nitrogen donor atoms. Pfaltz⁴ reported high enantiomeric excesses using semicorrins (entry 2), later Evans⁵ and Masamune⁶ independently employed bis(oxazoline) ligands to achieve the highest ee's obtained with copper-based

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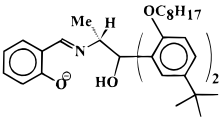
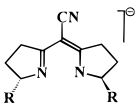
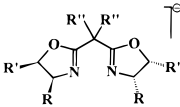
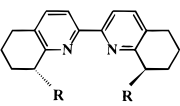



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Table 1. Ligands Employed in the Cu(I)-Catalyzed Olefin Cyclopropanation

Entry	Ligand	Reference
1		3
2		4
3		5, 6
4		7, 8
5		9a, 10
6		9a
7		9b

systems. The use of chiral bipyridines by Katsuki⁷ and Kwong⁸ is also remarkable (entry 4).

Polypyrazolyl ligands have also been employed to induce a significant degree of asymmetry in the cyclopropanation reaction. Tolman et al. have reported a

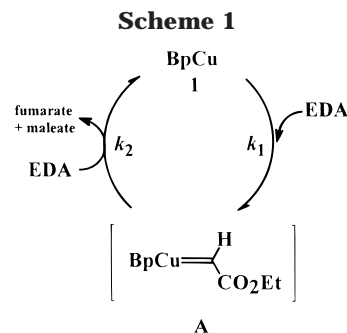
series of hydridotris(pyrazolyl)borate–copper complexes where the pyrazole ring provides the chirality.^{9a} Similar results were presented by Brunner et al. (entry 5).¹⁰ Bis-(pyrazolyl)borate–copper compounds have also been employed as the precatalyst (entry 6),^{9a} as well as related ligands with a phosphorus oxide group instead of the B–H moiety (entry 7).^{9b} In any case, the enantiomeric excesses obtained with this class of ligands are slightly inferior to those in entries 2–4.

On the basis of the previous results, one could think that further studies on the copper-based cyclopropanation reaction might be unnecessary since the ee's are close to the maximum. However, the industrial use of this strategy, i.e., the catalytic addition of carbene units to the carbon–carbon double bond, is still rare despite the plethora of compounds containing the cyclopropane function.^{11,12} This fact might be related to the instability of Cu(I) complexes or to the use of homogeneous conditions that avoids good rates in the recovery and reuse of the catalyst. The heterogenization of the catalyst would solve these problems, a simple system based on copper being recently reported from this laboratory.¹³

We have focused our attention to the study of the cyclopropanation reaction using poly(pyrazolyl)borate ligands such as hydridotris(3,5-dimethyl-1-pyrazolyl)borate (Tp)¹⁴ and dihydridobis(1-pyrazolyl)borate (Bp).¹³ Previous studies carried out with the complex BpCu (**1**) indicated that this formally 14-electron species could be the catalytic species, the real catalyst in the olefin cyclopropanation reaction.¹³ Could it be possible that, despite the differences in the electronics, sterics, and geometries of the systems referred in Table 1, a generic 14-electron catalytic species could be responsible for the catalytic transformation in all cases? If so, this would open new ways to design copper-based catalyst precursors under this premise, probably avoiding the aforementioned drawbacks even under homogeneous conditions.

Results and Discussion

Our recent report of a series of Bp–copper(I) complexes (Bp = dihydridobis(1-pyrazolyl)borate) as catalyst precursors for the olefin cyclopropanation reaction included the proposition of the electronically and coordinatively unsaturated, 14-electron fragment BpCu as the real catalyst in those transformations.¹³ The complex BpCu (**1**), previously prepared, isolated, and characterized, constitutes an excellent starting material to study the kinetic behavior of the diazo compound



decomposition in the absence or in the presence of olefin, as well as with a series of different ligands added as inhibitors. To establish the kinetic equations that govern the mechanism of the olefin cyclopropanation reaction, it is better to divide it into isolated cases: (a) the sole EDA decomposition in the presence of **1**, alone or in the presence of added ligands, and (b) the effect of added olefin, i.e., the kinetics of the cyclopropanation reaction.

A. EDA Decomposition in the Presence of BpCu (1). Although this simplest case has been briefly discussed in a previous contribution,¹³ we present it herein for the sake of completeness. Scheme 1 summarizes this situation, in which EDA is catalytically converted into a mixture of diethyl fumarate and maleate. According to this, the rate of EDA consumption is given by

$$-\frac{d[\text{EDA}]}{dt} = k_1[\mathbf{1}][\text{EDA}] + k_2[\mathbf{A}][\text{EDA}] \quad (1)$$

Assuming the steady-state approximation for the copper–carbene species **A**, we have

$$-\frac{d[\mathbf{A}]}{dt} = k_1[\mathbf{1}][\text{EDA}] - k_2[\mathbf{A}][\text{EDA}] = 0 \quad (2)$$

and, subsequently

$$[\mathbf{A}] = \frac{k_1[\mathbf{1}]}{k_2} \quad (3)$$

From eqs 1 and 3 it follows that

$$-\frac{d[\text{EDA}]}{dt} = 2k_1[\mathbf{1}][\text{EDA}] \quad (4)$$

Since $[\text{Cu}]_{\text{tot}} = [\mathbf{1}] + [\mathbf{A}]$ and $[\mathbf{A}] \ll [\mathbf{1}]$ (steady state), eq 4 can be written in the following manner:

$$-\frac{d[\text{EDA}]}{dt} = 2k_1[\text{Cu}]_{\text{tot}}[\text{EDA}] \quad (5)$$

The value for the observed rate constant, k_{obsd} , is given by eq 6.

$$k_{\text{obsd}} = 2k_1[\text{Cu}]_{\text{tot}} \quad (6)$$

A plot of k_{obsd} vs $[\text{Cu}]_{\text{tot}}$ for a set of experiments gave a k_1 value¹³ of $51.9 \pm 5.4 \text{ M}^{-1} \text{ min}^{-1}$.

The use of the complex BpCu(bipy) (**2**) as the precatalyst for the cyclopropanation reaction provides more information from a kinetic point of view. First, the reaction rate slows down compared with complex **1** as the catalyst ($k_{\text{obsd}} = 0.057 \pm 0.004 \text{ min}^{-1}$ for **2**; $k_{\text{obsd}} =$

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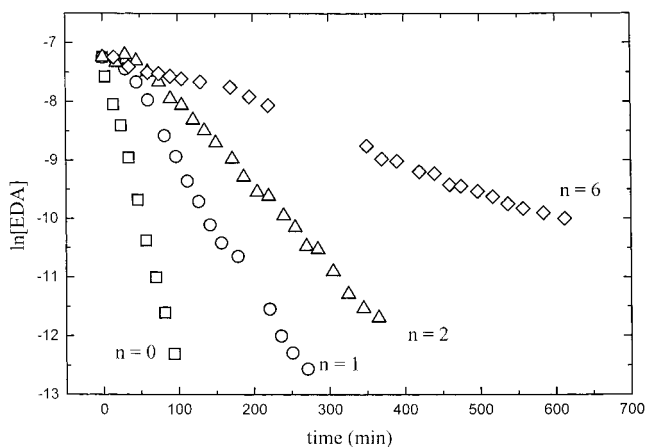
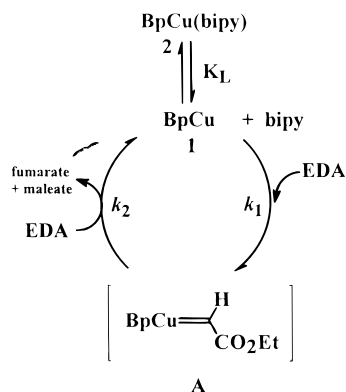


Figure 1. Effect of added bipyridine to the styrene cyclopropanation reaction catalyzed by BpCu(bipy) (**2**): variation of $\ln[\text{EDA}]$ vs time.

Scheme 2



$0.078 \pm 0.005 \text{ min}^{-1}$ for **1**). More interesting is the effect of added bipy ligand to the catalytic mixture. Figure 1 shows the variation of $\ln[\text{EDA}]$ with time for several equivalents of bipy added, a decrease in the reaction rate being clearly observed when the concentration of free bipy is increased. This can be interpreted in terms of a ligand dissociation preequilibrium previous to the copper–EDA interaction. This inhibition by nitrogen-donor ligands has been observed in other systems during diazocarbene decomposition.¹⁵ A mechanistic interpretation, in accord with the experimental data, is depicted in Scheme 2. The disappearance of EDA is still given by eq 4, but now **1** cannot be directly substituted by $[\text{Cu}]_{\text{tot}}$: the amount of copper as **2** has also to be considered. Thus, we can write that $[\text{Cu}]_{\text{tot}} = [\mathbf{1}] + [\mathbf{2}]$, again assuming the steady state for **A**. The aforementioned preequilibrium between **1** and **2** would be



for which K_L is the corresponding equilibrium constant. When adding free bipy in $n[\text{Cu}]_{\text{tot}}$ portions, the concentration of BpCu (**1**) is given by eq 8:

$$[\mathbf{1}] = \frac{K_L[\text{Cu}]_{\text{tot}}}{n[\text{Cu}]_{\text{tot}} + K_L} \quad (8)$$

where it has been assumed that $[\mathbf{1}] \ll n[\text{Cu}]_{\text{tot}}$. Substi-

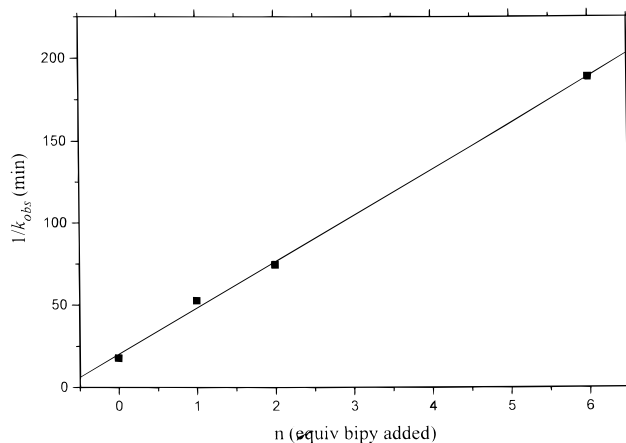


Figure 2. Plot of $1/k_{\text{obsd}}$ vs the number of equiv of bipy added (relative to Cu) for the styrene cyclopropanation reaction. The slope provides the value (see eq 11) for K_L as $(3.43 \pm 0.65) \times 10^{-4}$. Errors are given at 95% confidence limits.

tution of this value in eq 4 gives

$$\frac{-d[\text{EDA}]}{dt} = \frac{2k_1K_L[\text{Cu}]_{\text{tot}}}{n[\text{Cu}]_{\text{tot}} + K_L} [\text{EDA}] \quad (9)$$

the expression of the observed rate constant being given by eq 10:

$$k_{\text{obsd}} = \frac{2k_1K_L[\text{Cu}]_{\text{tot}}}{n[\text{Cu}]_{\text{tot}} + K_L} \quad (10)$$

Equation 10 can be converted into a linear relationship between $1/k_{\text{obsd}}$ vs the number of equivalents of bipy added (eq 11). In good accord with this, a linear plot is obtained (Figure 2), the slope providing the value of the equilibrium constant K_L as $(3.43 \pm 0.65) \times 10^{-4}$.

$$\frac{1}{k_{\text{obsd}}} = \frac{1}{2k_1[\text{Cu}]_{\text{tot}}} + \frac{n}{2k_1K_L} \quad (11)$$

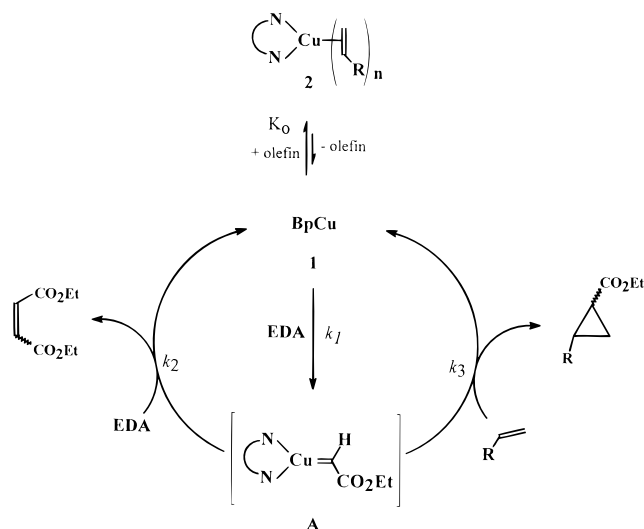
An alternative route to obtain the value of K_L comes straightforwardly from the equilibrium represented in eq 7. Thus, when a dichloroethane solution of **2** is stirred until the equilibrium is reached, dissociated bipy can be detected and measured by GC, leading to the K_L value of 4.5×10^{-4} . This is in good agreement with the kinetically obtained value of 3.43×10^{-4} , considering the approximations established in the previous paragraphs. On this basis, it is possible to assess the steady-state situation for the metal–carbene **A**, its formation being the rate-determining step. This is in good accord with Kochi's observation of first-order behavior in the nitrogen evolution during the reaction of EDA and CuOTf.¹⁶

In our previous contribution,¹³ we had also reported the use of several copper–phosphine complexes such as BpCu(PCy₃) (**3**) and BpCu(PPh₃)₂ (**4**) as the catalyst precursors for the cyclopropanation reaction. We have since learned that under catalytic conditions, due to a bipy-like dissociation preequilibrium, the free phosphine ligand also undergoes a copper-mediated reaction with EDA, with the corresponding formation of ylide-type

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Scheme 3



compounds. This results in the disappearance of the initial phosphine–copper species and the concomitant conversion of all the copper in solution in BpCu (**1**). Thus, the use of phosphine complexes must be avoided and will not be considered from now on.

B. EDA Decomposition in the Presence of Olefin.

When olefin is added, the situation appears to be more complicated. Under the same conditions, the reaction rate decreased with olefin added, as inferred from the k_{obsd} values of $(4.9 \pm 0.2) \times 10^{-3}$ and $(5.7 \pm 0.4) \times 10^{-2} \text{ min}^{-1}$, in the experiments carried out with and without olefin, respectively.¹³ The role of the olefin has been extensively studied by Kochi et al.: the copper center presents a high affinity for the olefin, promoting the coordination of this reagent and therefore inhibiting the diazocarbene decomposition.¹⁶ As shown in Scheme 3, the formation of a copper–olefin complex (**3**) is also invoked herein to account for the observed rate retardation. Equation 1 expresses the rate for EDA consumption, the application of the steady-state approximation to the intermediate **A** leading, in this case, to

$$\frac{-d[\mathbf{A}]}{dt} = k_1[\mathbf{1}][\text{EDA}] - k_2[\mathbf{A}][\text{EDA}] - k_3[\mathbf{A}][\text{olefin}] = 0 \quad (12)$$

and then

$$[\mathbf{A}] = \frac{k_1[\mathbf{1}][\text{EDA}]}{k_2[\text{EDA}] + k_3[\text{olefin}]} \quad (13)$$

Equation 1 is now converted in eq 14:

$$\frac{-d[\text{EDA}]}{dt} = k_1[\mathbf{1}][\text{EDA}] + \frac{k_1 k_2 [\mathbf{1}][\text{EDA}]^2}{k_2[\text{EDA}] + k_3[\text{olefin}]} \quad (14)$$

But now

$$[\text{Cu}]_{\text{tot}} = [\mathbf{1}] + [\mathbf{3}] \quad (15)$$

the amounts of **1** and **3** depending on the equilibrium constant K_0 :

$$[\mathbf{1}] + \text{olefin} \xrightleftharpoons{K_0} [\mathbf{3}] \quad (16)$$

The concentration of BpCu (**1**) in the equilibrium can be expressed in terms of $[\text{Cu}]_{\text{tot}}$, K_0 , and $[\text{olefin}]$ as

$$[\mathbf{1}] = \frac{[\text{Cu}]_{\text{tot}}}{1 + K_0[\text{olefin}]} \quad (17)$$

and the rate of EDA disappearance is obtained from eqs 14 and 17:

$$\frac{-d[\text{EDA}]}{dt} = \frac{k_1[\text{Cu}]_{\text{tot}}[\text{EDA}]}{1 + K_0[\text{olefin}]} \left(1 + \frac{[\text{EDA}]}{[\text{EDA}] + \frac{k_3}{k_2}[\text{olefin}]} \right) \quad (18)$$

On the other hand, it is also possible to obtain the expression for the consumption of the olefin for the sequence of reactions depicted in Scheme 3

$$\frac{-d[\text{olefin}]}{dt} = k_3[\mathbf{A}][\text{olefin}] \quad (19)$$

and from eqs 13, 17, and 19

$$\frac{-d[\text{olefin}]}{dt} = \frac{k_1 k_2 [\text{Cu}]_{\text{tot}} [\text{EDA}] [\text{olefin}]}{(1 + K_0[\text{olefin}])(k_2[\text{EDA}] + k_3[\text{olefin}])} \quad (20)$$

Integration of eqs 18 and 20 would provide the explicit dependence of EDA and olefin concentrations on time, although no analytical solutions have been found for these differential equations. However, it is possible to simplify this kinetic study by considering two limiting situations: (a) the catalytic experiment carried out in the excess of olefin with respect to $[\text{EDA}]$ and (b) the opposite case, i.e., an excess of $[\text{EDA}]$ over the olefin present in the catalytic reaction.

Limiting Case 1: Olefin Excess. When an excess of olefin is employed, then it is reasonable to assume that $k_3[\text{olefin}]/k_2 \gg [\text{EDA}]$ and subsequently eq 18 is transformed as

$$\frac{-d[\text{EDA}]}{dt} = \frac{k_1[\text{Cu}]_{\text{tot}}[\text{EDA}]}{1 + K_0[\text{olefin}]} \quad (21)$$

The amount of olefin can be considered constant due to the large excess employed; thus, k_{app} can be defined as in eq 22

$$k_{\text{app}} = \frac{k_1[\text{Cu}]_{\text{tot}}}{1 + K_0[\text{olefin}]} \quad (22)$$

and a linear dependence of the inverse of k_{app} and $[\text{EDA}]$ would be given by

$$\frac{1}{k_{\text{app}}} = \frac{1}{k_1[\text{Cu}]_{\text{tot}}} + \frac{K_0}{k_1[\text{Cu}]_{\text{tot}}}[\text{olefin}] \quad (23)$$

We have carried out several catalytic experiments in which an excess of olefin with respect to the ethyl diazoacetate has been employed ($[\text{EDA}]:[\text{styrene}] = 1:10$) at several olefin concentrations. Monitoring the disappearance of the carbene precursor for a set of different olefin concentrations, we obtain the values of k_{app} shown in Table 2. As expected from eq 23, a plot of

Table 2. Observed Rate Constants for the Cyclopropanation of Styrene in the Presence of 1 (1:10 [EDA]:[styrene]) at Different Styrene Concentrations^a

k_{app} (min ⁻¹)	[olefin] (M)
$(3.2 \pm 0.47) \times 10^{-3}$	0.2500
$(5.13 \pm 0.13) \times 10^{-3}$	0.1250
$(8.01 \pm 0.57) \times 10^{-3}$	0.0937
$(8.51 \pm 0.29) \times 10^{-3}$	0.0625
$(2.40 \pm 0.29) \times 10^{-2}$	0.0312

^a Errors are given at 95% confidence limits.

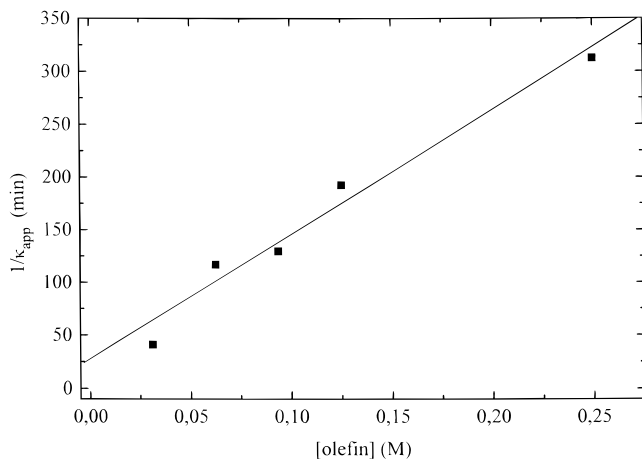


Figure 3. Dependence of $1/k_{\text{app}}$ on the concentration of olefin (styrene). A 77 ± 29 value for K_0 is calculated from the slope. Errors are given at 95% confidence limits.

$1/k_{\text{app}}$ vs [olefin] (Figure 3) is linear. The slope gives the value for $K_0/k_1[\text{Cu}]_{\text{tot}}$; therefore, K_0 can be determined as 77 ± 29 . This result, which supposes a noticeable amount of copper in an olefin-bonded form, explains the decrease of the reaction rate with added olefin, since the concentration of the catalytic species **1** is greatly diminished upon olefin coordination.

The K_0 value of 77 ± 29 can be compared with that calculated from an experiment similar to that employed for K_L . When a solution of **2** and 300 equiv of styrene in dichloroethane reached equilibrium, the concentration of dissociated bipy was measured by GC (see Experimental Section), leading to a K_0 value of 56. This value falls in the range of the kinetically calculated K_0 , as an indication that, again, the approximations employed in the previous kinetic studies are very close to reality.

Limiting Case 2: Ethyldiazoacetate Excess. The use of a high [EDA] to [olefin] ratio implies that $k_3[\text{olefin}] \ll k_2[\text{EDA}]$, eq 20 being converted in

$$\frac{-d[\text{olefin}]}{dt} = \frac{k_1 k_3 [\text{Cu}]_{\text{tot}} [\text{olefin}]}{1 + K_0 [\text{olefin}]} \quad (24)$$

Integration of eq 24 gives

$$\ln[\text{olefin}] + K_0 [\text{olefin}] = \ln[\text{olefin}]_{\text{in}} + K_0 [\text{olefin}]_{\text{in}} - \frac{k_1 k_3 [\text{Cu}]_{\text{tot}}}{k_2} t \quad (25)$$

where $[\text{olefin}]_{\text{in}}$ represents the initial concentration of olefin. For the range of concentrations employed, $\ln[\text{olefin}] + K_0 [\text{olefin}] \approx \ln[\text{olefin}]$; thus, eq 25 is simplified into eq 26:

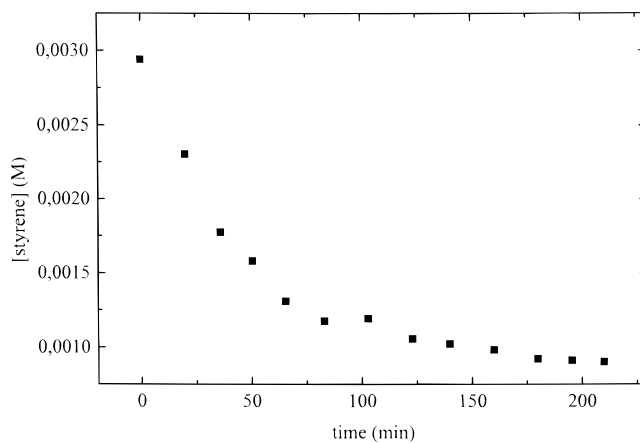


Figure 4. Variation of styrene consumption with time for the BpCu-catalyzed cyclopropanation reaction carried out with an excess of EDA (relative to olefin).

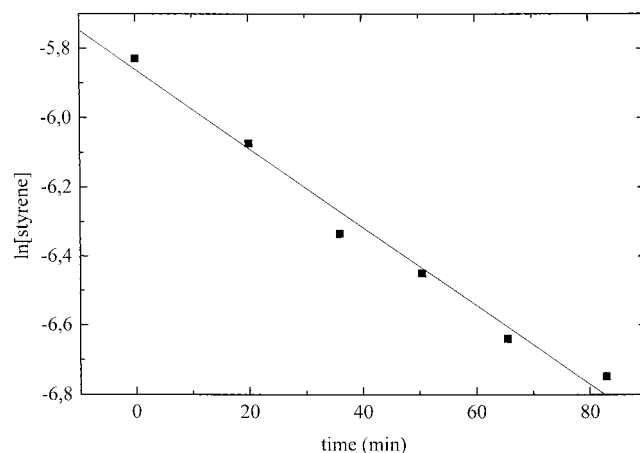


Figure 5. Plot of $\ln[\text{styrene}]$ vs time for the BpCu-catalyzed styrene cyclopropanation reaction (EDA excess). The slope provides the value of k_2/k_3 shown in Table 3, derived from eq 26.

Table 3. k_2/k_3 Values Obtained from Eq 26 at Different [Cu]:[EDA]:[Olefin] Ratios^a

[Cu]:[EDA]:[olefin] (M)	k_2/k_3
$(0.0294:2.94:0.294) \times 10^{-2}$	1.35 ± 0.17
$(0.00713:12.5:1.25) \times 10^{-2}$	1.48 ± 0.80
$(0.00294:2.94:0.147) \times 10^{-2}$	1.62 ± 0.20
$(0.0294:2.94:0.294) \times 10^{-2}$	1.59 ± 0.40

^a Errors are given at 95% confidence limits.

$$\ln[\text{olefin}] = \ln[\text{olefin}]_{\text{in}} - \frac{k_1 k_3 [\text{Cu}]_{\text{tot}}}{k_2} t \quad (26)$$

When a large [EDA] to [olefin] ratio is used, the variation of the concentration of olefin can be easily monitored by GC. Figure 4 shows the observed decreasing of [olefin] with time. As inferred from eq 26, the representation of $\ln[\text{olefin}]$ vs time must fit a linear plot. However, to ensure the applied approximation ($k_3[\text{olefin}] \ll k_2[\text{EDA}]$), only the earlier points must be taken into account. This has been represented in Figure 5, from which a k_2/k_3 value can be obtained. Several experiments carried out with excess of EDA have been performed, leading to the set of k_2/k_3 values displayed in Table 3. The average value of 1.51 ± 0.12 clearly indicates that the EDA dimerization reaction is favored

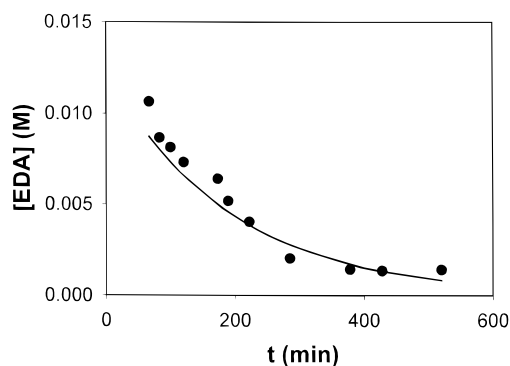


Figure 6. Experimental (●) and simulated (—) data for the EDA consumption in the presence of excess of styrene and BpCu (**1**) as the precatalyst.

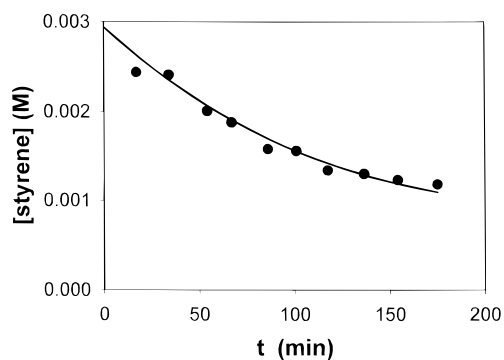
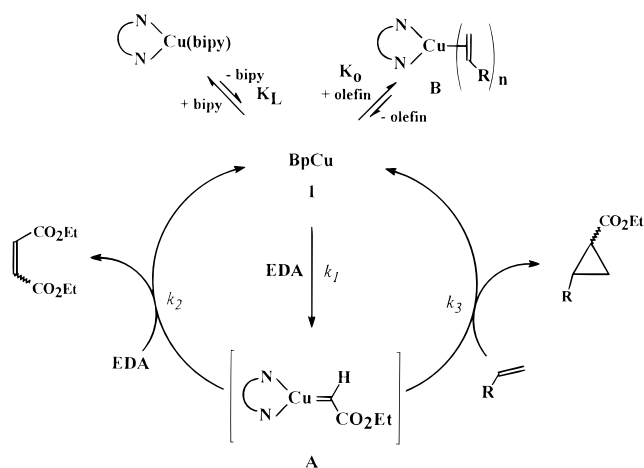


Figure 7. Experimental (●) and simulated (—) data for styrene consumption in the presence of excess of EDA and BpCu (**1**) as the precatalyst.

over the cyclopropanation reaction for similar initial EDA and olefin concentrations. This fact explains the need for a large excess of olefin in the catalytic reactions when high yields of cyclopropanes are desired.

It must be noted that both limiting cases involve several assumptions that could originate slightly erroneous values for the kinetic and thermodynamic parameters obtained from the analysis. To confirm the applicability of those limiting cases and to obtain more precise values for K_0 and k_2/k_3 , eqs 18 and 20 have been solved using a numerical procedure based on the fourth-order Runge–Kutta method,¹⁷ optimizing the set of K_0 and k_2/k_3 values that provides a better agreement with the experimental data. For example, for the disappearance of EDA in the presence of complex **1** and an excess of styrene ([Cu]:[EDA]:[styrene] = 1:10:100), a theoretical curve can be fitted to the experimental data using this procedure, iterating the values of K_0 and k_2/k_3 to minimize deviations (Figure 6). The best agreement with the experimental results was found for $K_0 = 101.3$ and $k_2/k_3 = 1.50$. The value of k_1 was not iterated and maintained as $51.9 \text{ M}^{-1} \text{ min}^{-1}$. On the other hand, the experiment carried out with an excess of olefin ([Cu]:[EDA]:[styrene] = 1:100:10) has also been simulated, leading to the fitted curve shown in Figure 7, which has been obtained with $K_0 = 97$ and $k_2/k_3 = 1.73$ ($k_1 = 51.9 \text{ M}^{-1} \text{ min}^{-1}$). The excellent agreement between the experimental and the simulated data clearly indicates that the proposed model as well as the approximations presumed in the kinetics represent well the mechanism

Scheme 4



of the styrene cyclopropanation reaction catalyzed by the complex BpCu (**1**) or its bipy adduct **2**.

It is clear from the experimental as well as from the computer-simulated data that the 14-electron complex **1** can be unambiguously assigned as the catalytic species in such a transformation. The presence in the reaction mixture of nitrogen-donor ligands clearly diminishes the amount of the catalytic species, the same effect being observed when large amounts of olefins are present: i.e., under catalytic conditions. These facts have to be taken into account in the design of a new catalyst for this reaction, since the kinetics are usually a major problem in the scale-up to pilot plants or to industrial scale. The overall mechanism for the olefin cyclopropanation reaction is shown in Scheme 4. The rate constant k_1 and the ratio k_2/k_3 as well as the equilibrium constants K_L and K_0 have been determined. The ratio $k_2/k_3 > 1$ indicates that the carbene transfer toward a second molecule of EDA is kinetically favored over the cyclopropanation reaction. This is consistent with the need for excess olefin and the use of EDA slow addition techniques to improve the yields in cyclopropanes.

According to this mechanistic proposition, it is also feasible to obtain the relative rate constants k_3 for several olefins. When equimolar mixtures of two different olefins are employed in the cyclopropanation experiment, the ratio of cyclopropane products gives the k_3/k_3' ratio. We have performed these experiments with styrene, *cis*-cyclooctene (COE) and 1-hexene, leading to the following ratios and using styrene as the reference: $k_3(1\text{-hexene})/k_3(\text{styrene}) = 0.35$ and $k_3(\text{cis-COE})/k_3(\text{styrene}) = 1.22$. The calculated $k_3(1\text{-hexene})/k_3(\text{cis-COE})$ value of 0.28 matches with the experimental values of 0.29 (see Experimental).

C. EDA Decomposition Catalyzed by $[\text{Cu}(\text{bipy})_2]\text{X}$ ($\text{X} = \text{I}$, **4a; $\text{X} = \text{TfO}$, **4b**).** Previous work by Evans,⁵ Masasume,⁶ and Katsuki⁷ have shown that the use of N–N chiral ligands such as bis(oxazolines) and bipyridines induces high enantiomeric excesses. The catalytic species is usually generated in situ upon mixing CuOTf and the corresponding ligand. To compare those systems with the BpCu-based system presented herein, we have first studied the kinetic behavior of the EDA decomposition reaction in the presence of $[\text{Cu}(\text{bipy})_2]\text{I}$ (**4a**),¹⁸ a complex in which the metal center is bonded to neutral N–N ligands. This is a good catalyst for the decomposi-

(17) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*, 2nd ed.; McGraw-Hill: New York, 1995.

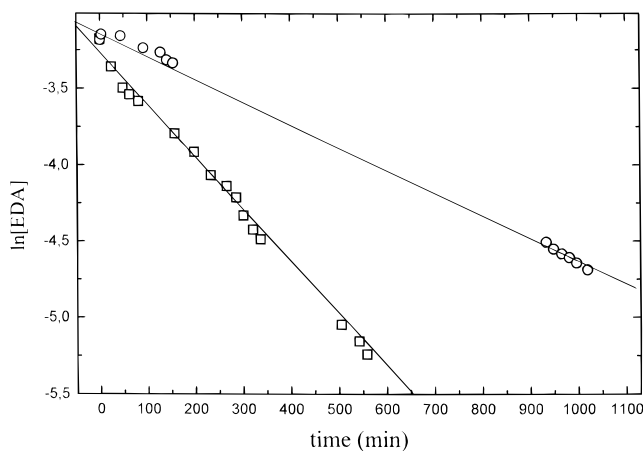
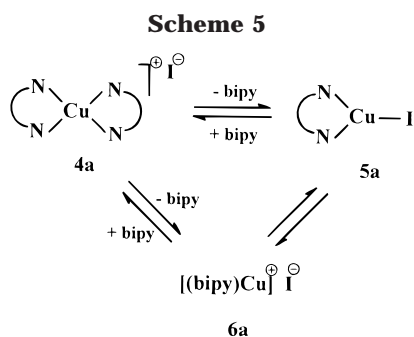


Figure 8. Plots of $\ln[\text{EDA}]$ vs time for the EDA decomposition in the presence of $[\text{Cu}(\text{bipy})_2]\text{I}$ (**4**): (□) in the absence of added iodide; (○) with added iodide.



tion of the diazo reagent, the yield in cyclopropanes when olefin is added being moderate. We have monitored the disappearance of the carbene precursor in the presence of **4a**, leading to a value of k_{obsd} of $(3.46 \pm 0.10) \times 10^{-3} \text{ min}^{-1}$ (see the Experimental Section). A related experiment carried out in the presence of added iodide has shown that the reaction rate for EDA decomposition is retarded upon halide addition. Figure 8 displays the plots of $\ln[\text{EDA}]$ vs time using **4a** as the catalyst precursor in the absence and in the presence of added iodide.

When complex **4a**, isolated and crystallized, is dissolved in dichloroethane, it is possible to detect and quantify by GC the amount of free bipy in solution. In a $1.2 \times 10^{-3} \text{ M}$ solution of **4a**, more than 95% of the complex is in a dissociated form, as a consequence of the decoordination of the bipy ligand from the coordination sphere of copper (Scheme 5). We believe that the dissociated copper species might exist in two different forms: the neutral, formally 16-electron complex **5a** and the cationic, 14-electron complex **6a**, the latter being isoelectronic with complex **1**. As mentioned above, most of the copper in solution exists as **5a** or **6a**; therefore, it is reasonable to assume that one or the other or both of them are responsible for the catalytic decomposition of the diazo compound. Since the equilibrium between **5a** and **6a** consists of the dissociation of the iodide ligand from the metal center, the addition of free iodide anion would favor an increase of [**5a**] and the concomitant

Table 4. Observed Rate Constants for the Styrene Cyclopropanation Reaction in the Presence of Mixtures of CuOTf and Bidentate Ligands (Bipyridine and Bis(oxazoline))

equiv of ligand/equiv of CuOTf	k_{obsd} (min^{-1})	
	bipy	bis(oxazoline)
0	2.16	2.16
0.5	1.22	1.24
1	0.989	1.12
1.5	0.254	0.220
2	0.0135	0.0138

decrease of [**6a**]. This fact would also be in accord with **6a** as the active catalytic species, since the addition of halide displaces the equilibrium toward **5a**, therefore decreasing the amount of **6a** in the mixture and retarding the already mentioned reaction rate. These facts confirm that when complex $[\text{Cu}(\text{bipy})_2]\text{I}$ (**4a**) is used as the catalyst precursor, again a formally 14-electron species is responsible for the catalytic decomposition of the ethyl diazoacetate. Additional information has been gained from cyclopropanation competition experiments of para-substituted styrenes using **4a** as the catalyst precursor. A Hammett plot provides $\rho = -2.2 \pm 0.11$, a value significantly different from those obtained with the complexes BpCu^{13} and $\text{Tp}'\text{Cu}(\text{C}_2\text{H}_4)^{14b}$ (-1.19 and 0.85 , respectively), which could be explained in terms of the cationic nature of the carbene intermediate that would be formed from the interaction of **6a** and EDA.

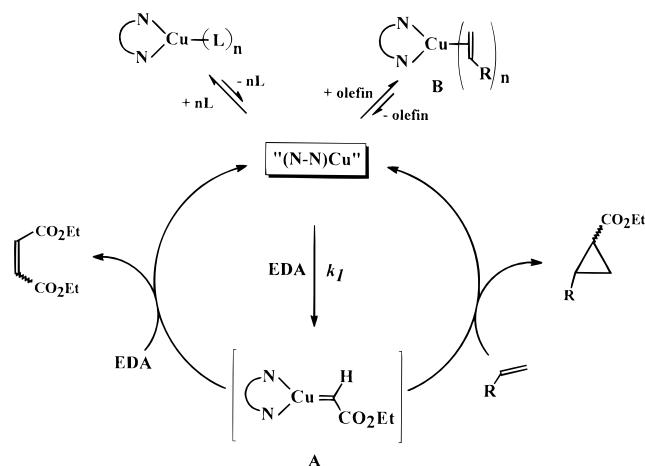
Monitoring of the EDA consumption when using a nonstoichiometric mixture of Cu(OTf) and bipy leads to the set of k_{obsd} values shown in Table 4. In the absence of bipy, CuOTf catalyzes the decomposition of EDA with $k_{\text{obsd}} = 2.16 \text{ min}^{-1}$. The addition of 0.5, 1, or 1.5 equiv of bipy/equiv of Cu(OTf) induces the retardation in the reaction rate. However, in the presence of 2 equiv of bipy, i.e., the conditions for the formation of complex **4b**, a noticeable decrease in the reaction rate takes place. Under that stoichiometric limit, the amount of CuOTf in solution governs the reaction rate, whereas the 2:1 [bipy]:[Cu] ratio ensures the existence of Cu–bipy interaction for the total amount of copper in solution.

D. EDA Decomposition Catalyzed by CuOTf–Bis(oxazoline). A similar set of results has been obtained for the CuOTf–bis(oxazoline) system,^{19a} i.e., with Evans' catalyst.⁵ Mixtures of CuOTf and the chiral ligand were used, without further workup, as the catalyst precursor. In good agreement with the bipy–Cu system, the reaction rate for the ideal stoichiometry that would correspond to $[\text{Cu}(\text{bisox})_2]\text{OTf}$ is 1 order of magnitude below that of 1:1.5, and 2 orders with respect to 1:1. We believe that the chiral system behaves similarly to the bipyridine–Cu one, the copper complex containing 2 equiv of the bis(oxazoline) ligand being formed under the reaction conditions,^{19b} in a fashion similar to that proposed for the bipy system in Scheme

(19) (a) The bis(oxazoline) ligand employed in these studies was 2,2-bis[2-(4*R*)-1-methyl-1,3-oxazolin-2-yl]propane.⁵ (b) The original method of Evans⁵ consisted of the in situ generation of the catalyst by mixing CuOTf and the corresponding ligand in a 1:1 ratio. After it was stirred, this mixture was passed through glass wool, the possible excess of CuOTf being retained in this material. This procedure has also been employed by Katsuki et al.⁷ (c) When NaOTf is added to the catalytic mixture, the reaction with adventitious water (despite the efforts to dry the solvent) produces HOTf that further reacts with EDA to give an unidentified product.

(18) (a) Hathway, B. J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Guillard, R. D., McCleverty, J. K., Eds.; Pergamon Press: Oxford, U.K., 1987; Vol. 5, Chapter 53, p 533. (b) Jardin, F. H. *Adv. Inorg. Chem. Radiochem.* **1975**, *17*, 115.

Scheme 6



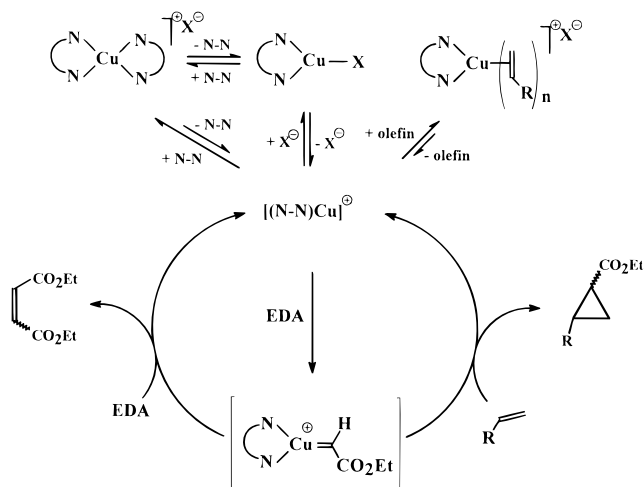
5. Unfortunately, we have not been able to study the effect of excess triflate ligand in the reaction mixture due to the hygroscopic nature of the alkaline salts of such an anion.^{19c} However, when a weak donor such as tetrahydrofuran is added to the catalytic reaction, the k_{obsd} value decreases to $(7.12 \pm 0.4) \times 10^{-2} \text{ min}^{-1}$ ($(1.35 \pm 0.01) \times 10^{-2} \text{ min}^{-1}$ when dichloroethane is the sole solvent; Table 4).²⁰ This retardation could be interpreted as the consequence of the formation of a new copper species of composition $[\text{Cu}(\text{bisoxazoline})(\text{THF})_n]^+$, therefore diminishing the concentration of the active species $[\text{Cu}(\text{bisoxazoline})]^+$.

E. General Mechanism for the Cu-Mediated EDA Decomposition. Despite the differences in the nature of the ligands bonded to the copper center, data available suggest that a 14-electron species could be the real catalyst for the conversion of ethyl diazoacetate and olefins in cyclopropanes, with diethyl fumarate and maleate as byproducts. The chemical systems depicted in Table 1 can be distributed in two groups, depending on the global charge of the ligand: (i) the anionic semicorrins, salicylaldehyde–amino acid derivatives, and bis- and tris(pyrazolyl)borate ligands and (ii) the neutral bis(oxazolines) and bipyridines. Scheme 6 shows a possible mechanism for the former group. The corresponding Cu(I) complexes are neutral. The L ligands can be solvent molecules, an internal hydroxyl group, or the third pyrazole ring in a Tp' ligand (the η^3 – η^2 fluxionality is a well-documented process for this type of ligand).²¹ Alternatively, the 14-electron complexes containing bis(pyrazolyl)borate anions of general composition Bp'Cu can be used directly.

Dissociation of the L groups leads to the generation of the 14-electron fragment (N–N)Cu, still neutral, which could undergo two different reactions: the formation of olefin complexes (B), and the subsequent inhibition of the diazocarbene decomposition reaction, or the interaction with ethyl diazoacetate, with the concomitant formation of the copper–carbene intermediate. The latter might react with either a second molecule of EDA or with the olefin, to finally afford the organic products and regenerate the catalytic species.

When neutral ligands are employed, the situation is slightly different, as shown in Scheme 7. The kinetic

Scheme 7



studies presented herein have demonstrated that in this case, 2 equiv of the ligand is required to avoid the existence of free $\text{Cu}(\text{OTf})$ in the reaction mixture, therefore maximizing the asymmetric induction by the catalyst. The $[\text{bis}(\text{ligand})\text{Cu}]^+$ cationic species equilibrates with two complexes as a consequence of the dissociation of one of the ligands (bipyridine, bis(oxazoline)). Inhibition experiments have shown that the 14-electron, cationic complex $[(\text{N}-\text{N})\text{Cu}]^+$ seems to be responsible for the attack of the ethyl diazoacetate, a related, cationic copper–carbene intermediate being also proposed in the route to cyclopropanes and/or fumarate and maleate.

Thus, it seems clear to us that these 14-electron species are the active catalysts. One aspect that has not been taken into consideration is the existence of a coordinated olefin in the metal–carbene intermediate. Although we do not have any evidence to support this, it might be possible that this coordination would be required for the reaction to occur since the aforementioned 14-electron species have two vacant sites that could be further occupied by the carbene moiety and by the olefin molecule.

Conclusions

The available data have led to a proposition for the copper-mediated olefin cyclopropanation reaction. The real catalyst in this type of transformation seems to be a 14-electron species, independent of the nature of the ligand attached to the copper center. This fact, along with several considerations regarding the required Cu–ligand and Cu–olefin stoichiometry, could constitute the starting point in the design of novel catalysts for the EDA decomposition to afford cyclopropanes.

Experimental Section

General Methods. All preparations and manipulations were carried out under an oxygen-free nitrogen atmosphere using conventional Schlenk techniques. The solvent employed for all preparations (1,2-dichloroethane) was degassed before use. The complexes BpCu, BpCu(bipy), $[\text{Cu}(\text{bipy})_2]\text{I}$, and the bis(oxazoline) ligand 2,2-bis[(4R)-1-methyl-1,3-oxazolin-2-yl]propane were prepared according to literature methods.^{5,13,18} Olefins, ethyl diazoacetate, and CuOTf were purchased from Aldrich and employed without further purification. GC data were collected with a Varian Model GC-3350 instrument.

(20) See the Supporting Information.

(21) For the examples of η^3 – η^2 fluxionality in Tp–metal derivatives see: Trofimenko, S. *Chem. Rev.* **1993**, *93*, 943–980.

Kinetic Experiments. All the kinetics experiments reported in this contribution were carried out by following the same procedure: the required amount of the precatalyst was dissolved in 1,2-dichloroethane, and then the olefin and EDA were added to the stirred solution in the appropriate ratio. The consumption of EDA or olefin was monitored at 25 °C by GC. The concentration vs time tables and the corresponding plots are given in the Supporting Information.

GC Determination of K_L and K_o . (a) A solution of **2** (11.3 mg, 0.03 mmol) in 25 mL of 1,2-dichloroethane was stirred until equilibrium was reached. The amount of free bipy was detected by GC (by means of a calibration graph),²⁰ leading to $[bipy] = 5.44 \times 10^{-4}$ M and a K_L value of 4.5×10^{-4} M⁻¹min⁻¹.

(b) BpCu(bipy) (11.3 mg, 0.03 mmol) was dissolved in 25 mL of 1,2-dichloroethane, and 300 equiv of styrene was added. The mixture was stirred until equilibrium was reached, and the concentration of bipy was determined by GC as 1.034×10^{-3} M.²⁰

Cyclopropanation Competition Experiments with Several Olefins. Complex **1** (10.5 mg, 0.05 mmol) was dissolved in 30 mL of 1,2-dichloroethane, and 300 equiv (15 mmol) of an equimolar mixture of styrene and *cis*-cyclooctene (*cis*-coe) was added to the stirred solution. Ethyl diazoacetate (0.171 g, 1.5 mmol) was immediately added, in one portion, to the above solution. The ratio of products cyclopropane (*cis*-coe):cyclopropane(styrene) = 1.22 was determined by GC after total consumption of EDA. Following the same procedure using equimolar mixtures of 1-hexene/styrene and 1-hexene/*cis*-coe gave the respective ratio of products 0.35 and 0.29.

EDA Decomposition Catalyzed by [Cu(bipy)₂]I. (a) **Absence of Olefin.** [Cu(bipy)₂]I (25.1 mg, 0.05 mmol) was dissolved in 30 mL of 1,2-dichloroethane, and ethyl diazoacetate (142.5 mg, 1.25 mmol) was added. The consumption of the ethyl diazoacetate at 25 °C was monitored by GC until the reaction was complete (no EDA observed). A 20:80 ratio of [fumarate] to [maleate] of products was obtained.

(b) **Cyclopropanation of Styrene.** In a standard cyclopropanation experiment, a 1:50:250 [**4a**]:[EDA]:[styrene] mixture afforded 46% of cyclopropanes (27:73, syn:anti ratio).

(c) **Inhibition with Iodide.** To a solution of 0.05 mmol of [Cu(Bipy)₂]I in 30 mL of 1,2-dichloroethane was added KI (0.25 mmol). Then, the mixture was stirred and 1.25 mmol of EDA was added to the above suspension (the KI does not dissolve completely). The consumption of EDA at 25 °C was monitored by GC until the reaction was complete (no EDA observed).²⁰

Cyclopropanation Competition Experiments with Para-Substituted Styrenes and **4a.** [Cu(bipy)₂]I (25.1 mg, 0.03 mmol) was dissolved in 40 mL of 1,2-dichloroethane, and 150 equiv of an equimolar mixture of styrene and the corresponding para-substituted styrene were added to the stirred red solution. Ethyl diazoacetate (25 equiv, 0.75 mmol) was also added, in one portion, to the above solution. The ratio of products was determined by GC after total consumption of the ethyl diazoacetate. A Hammett plot provides²⁰ a value of -2.2 for ρ .

Determination of k_{obsd} for the EDA Decomposition Reaction in the Presence of Copper Species. (a) **Absence of Olefin.** EDA (142.5 mg, 1.25 mmol) was dissolved in 45 mL of 1,2-dichloroethane, and CuOTf (10.6 mg, 0.05 mmol) was added to the stirred solution. After 3 min, the relative concentration of EDA with respect to the initial solution was determined and the value of k_{obsd} was calculated as 2.16 min⁻¹ according to first-order kinetics.²² Similar experiments carried out in the presence of added ligands (bipy or bis(oxazoline)) gave the set of k_{obsd} values shown in Table 4. For the particular case of a 1:2 ratio of Cu to ligand, the complete kinetics experiments were run.²⁰

(b) **Inhibition with THF.** To a solution of CuOTf (10.6 mg, 0.05 mmol) and 2 equiv of bis(oxazoline) in 45 mL of 1,2-dichloroethane was added 2 mL of tetrahydrofuran (THF). The mixture was stirred, and EDA (142.5 mg, 1.25 mmol) was added to the solution. The consumption of EDA at 25 °C was monitored by GC until the reaction was complete (no EDA observed).²⁰

Acknowledgment. We are grateful to the Universidad de Huelva (Plan Propio de Investigación) and Ministerio de Educación for the financial support. M.M.D.-R thanks the Junta de Andalucía for a research studentship.

Supporting Information Available: Concentration vs time tables, plots, and calculations for the kinetic and/or competition experiments cited in the text. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(22) k_{obsd} values were calculated by means of $k_{obsd} = (1/t) \ln([EDA]_0/[EDA])$.¹⁷