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A General Mechanism for the Copper- and Silver-Catalyzed Olefin Aziridination Reactions: Concomitant Involvement of the Singlet and Triplet Pathways

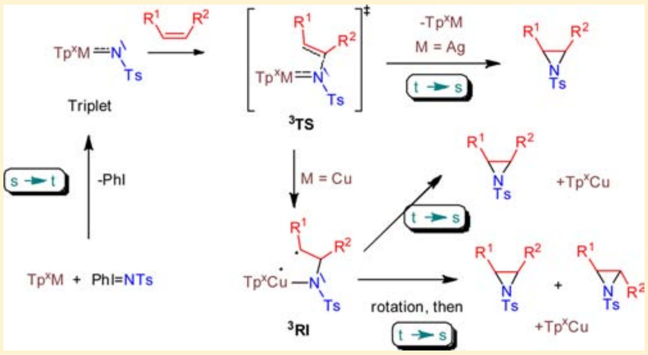
Lourdes Maestre,[†] W. M. C. Sameera,[‡] M. Mar Díaz-Requejo,*[,†] Feliu Maseras,*[,‡,§] and Pedro J. Pérez*[,†]

[†]Laboratorio de Catálisis Homogénea, Departamento de Química y Ciencia de los Materiales, Unidad Asociada al CSIC, Centro de Investigación en Química Sostenible (CIQSO), Universidad de Huelva, Campus de El Carmen, 21007 Huelva, Spain

[‡]Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans 16, 43007 Tarragona, Spain

[§]Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain

Supporting Information

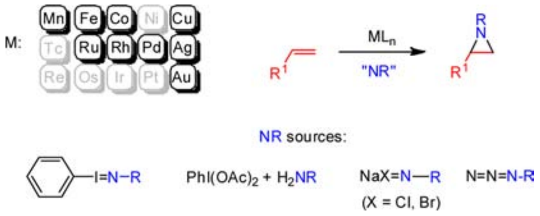


ABSTRACT: The olefin aziridination reactions catalyzed by copper and silver complexes bearing hydrotris(pyrazolyl)-borate (Tp^x) ligands have been investigated from a mechanistic point of view. Several mechanistic probe reactions were carried out, specifically competition experiments with *p*-substituted styrenes, stereospecificity of olefins, effects of the radical inhibitors, and use of a radical clock. Data from these experiments seem to be contradictory, as they do not fully support the previously reported concerted or stepwise mechanisms. But theoretical calculations have provided the reaction profiles for both the silver and copper systems with different olefins to satisfy all experimental data. A mechanistic proposal has been made on the basis of the information that we collected from experimental and theoretical studies. In all cases, the reaction starts with the formation of a metal−nitrene species that holds some radical character, and therefore the aziridination reaction proceeds through the radical mechanism. The silver-based systems however hold a minimum energy crossing point (MECP) between the triplet and closed-shell singlet surfaces, which induce the direct formation of the aziridines, and stereochemistry of the olefin is retained. In the case of copper, a radical intermediate is formed, and this intermediate constitutes the starting point for competition steps involving ring-closure (through a MECP between the open-shell singlet and triplet surfaces) or carbon−carbon bond rotation, and explains the loss of stereochemistry with a given substrate. Overall, all the initially contradictory experimental data fit in a mechanistic proposal that involves *both* the singlet and the triplet pathways.

INTRODUCTION

The conversion of olefins into aziridines by the metal-catalyzed addition of a nitrene NR group to the C═C bond constitutes a useful tool in the preparation of these three-member rings (Scheme 1).[1] Nine out of the fifteen metals from groups 7−11 have been reported to induce such transformation.[2−9] Among them, rhodium-, ruthenium-, and copper-based catalysts have been the most frequently employed, and undergo highly selective transformations with good yields.[1] Isolated or in situ generated hypervalent iodine reagents are the common nitrene sources (Scheme 1) with azides being the other preferred reactant. There are still uncertainties concerning the mechanism that governs this transformation. It has been suggested that the metal−nitrene intermediate is the active intermediate for this reaction, which is electrophilic in nature. Further, such species have been isolated or spectroscopically detected in a few cases: Che and co-workers developed a ruthenium-based system capable of promoting the nitrene transfer reaction to olefins with a diimido complex shown in Scheme 2a.[3] In the case of copper, Warren and co-workers isolated[10a] a nitrene-bridged dinuclear compound, and is active in nitrene transfer reactions (Scheme 2b), whereas the group of Ray has recently trapped a copper nitrene intermediate with scandium(III)

Scheme 1. The Metal-Catalyzed Olefin Aziridination Reaction



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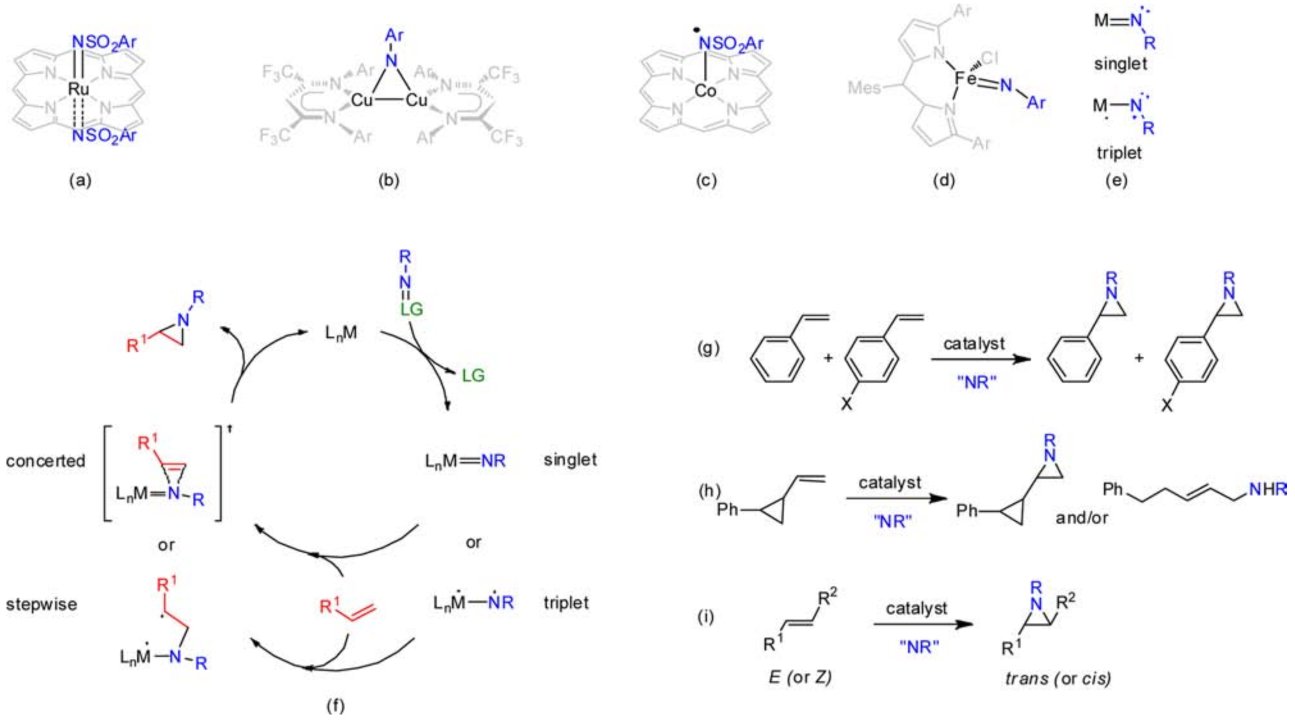
Scheme 2. Metal-Nitrene Complexes and Reactions Involving Them[a]



[a](a–d) Metal–nitrene complexes relevant to olefin aziridination reaction. (e) The singlet and triplet states of the metal-nitrenes. (f) A simple vision of the two commonly proposed pathways for this transformation. (g–i) Mechanistic probes.

triflate.[10b] Zhang, de Bruin, and collaborators have recently reported the EPR detection of paramagnetic cobalt nitrene species that are responsible for both olefin aziridination and C–H amidation (Scheme 2c).[11] Also, an iron–imido complex, active for nitrene transfer reactions, has been isolated by Betley and co-workers (Scheme 2d).[12] The metal–nitrene intermediate plays a crucial role in the subsequent catalytic steps. Two electronic states, singlet and triplet (Scheme 2e) are possible for the "M-NR" species (Scheme 2f shows a deceptively simple representation of both). The triplet species has been usually associated to a stepwise mechanism, whereas a concerted pathway has been frequently assigned as a consequence of the singlet state (Scheme 2f). The presence of the radical or the concerted paths were established on the basis of a series of model experiments, from which a typical behavior is expected depending on the nature of the nitrene intermediate. Thus, competition experiments with *p*-substituted styrenes (Scheme 2g) have provided either linear dependence with the plain Hammett's equation (concerted) or with a dual-parameter equation, involving radical constants (stepwise). The use of radical clocks as substrates (Scheme 2h) or the addition of radical inhibitors have also been employed as probes. However, most frequently performed experiments considered olefins with a given stereochemistry (*Z* or *E*) to study the stereospecificity of the reaction (Scheme 2i), where retention of the initial geometry of the olefin supported a concerted mechanism, while the observance of a certain loss of stereoselectivity indicated a stepwise mechanism.

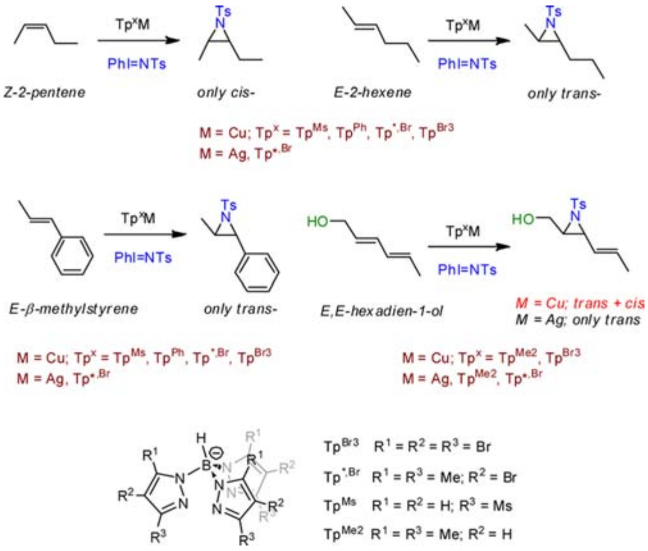
The aforementioned experimental observations implied that the concerted or radical pathways could be explained straightforwardly, which is not always true. For example, it is common to observe that stereoselection depends on the olefin. Several systems have been described to induce a certain degree of loss of stereochemistry with aryl-substituted olefins.[2,3,7–9,13,14] With some of those catalysts, alkyl-substituted olefins performed aziridination in a stereospecific manner,[7a,14] whereas other systems showed a partial loss of stereochemistry during the catalytic reaction.[15,16] On the other hand, rhodium-based catalysts induced a complete retention of the initial geometry with both aryl- and alkyl-containing olefins.[17] With this metal, competition experiments with 3- and 4-substituted styrenes gave a good correlation with the Hammett equation. The same behavior was described for a series of cinnamate esters with copper-based catalysts.[18] However, Hammett studies were contradictory with the results obtained from stereospecificity experiments.[3,19] This diversity has led for years to propose that the mechanism of this reaction is highly system-dependent and is always under the influence of the concerted *or* stepwise routes.

Computational studies of transition metal-catalyzed olefin aziridination reactions have been reported in the literature,[13,18,20] but the description of a mechanistic picture compatible with all experimental observations is yet undescribed. The metal–nitrene complexes have been suggested as the active intermediates for two-electron transfer aziridination, but questions remain on the spin multiplicity (singlet or triplet) of the species throughout the reaction. Density functional approaches (DFT) indicated that the ground state of the metal–nitrene is a triplet,[20a–c] while complete active space self-consistent-field (CASSCF) calculations suggested a singlet ground state, with only a small energy gap between the singlet and triplet.[20d] Previous studies on reactivity seem to favor a stepwise mechanism through a triplet state. Andersson and Norrby demonstrated the involvement of singlet and triplet biradical species in the aziridination of alkenes catalyzed by the (N–N)Cu=NSO$_2$Ar (N–N = chelating diamine) system.[20a]

Comba and co-workers performed experimental and theoretical studies of the aziridination reaction catalyzed by (bispidine)-copper complexes,[13] where formation of metal−nitrene is the key for efficient catalytic aziridination *via* the stepwise mechanism, involving a radical metal−nitrene intermediate. Zhang and de Bruin reported a cobalt−nitrene intermediate in the Co-porphyrin-mediated aziridination of alkenes that occurs through the stepwise mechanism.[20c] The radical mechanism would be seemingly at odds with the experimental observation of retention of configuration in a number of cases. In the presence of a low-energy gap between the singlet and triplet states, the aziridination reactions may proceed through the both singlet and triplet energy profiles, which is a common scenario in two-state reactivity (TSR) or multistate reactivity (MSR).[21] Spin crossover between both surfaces is likely feasible through spin−orbital coupling at the metal.[22]

Our group has some experience in the development of copper-[23] and silver-based[24] catalysts containing trispyrazolylborate ligands (Tp^x, see Scheme 3) for the olefin aziridination reaction. To date, we have mainly focused on the catalytic activity, with a scarce incursion in the mechanism, and more specifically, on a comparison between the olefin aziridination and cyclopropanation reactions catalyzed by the complex Tp^{Me2}Cu(C_2H_4) (Tp^{Me2} = hydrotris(3,5-dimethyl-1-pyrazolyl-borate).[23b] On the basis of the lack of a general mechanistic perspective of this relevant reaction, we have now performed a complete study (60 different experiments) in which a series of copper- and silver complexes of composition Tp^{x}M (M = Cu, Ag) has been exhaustively tested in the probe reactions shown in Scheme 2. Thus, six different catalysts have been employed for Hammett studies and stereoretention experiments with four olefins. A radical clock has been employed with representative copper and silver catalysts and the effect of a radical inhibitor such as *t*-butylhydroxytoluene (BHT) has also been investigated with both metals. From all these experiments we have collected contradictory data that, in principle, cannot support an unambiguous mechanistic pathway, intended as concerted or stepwise. But DFT studies have shown that all those data, albeit contradictory at the first sight, are the consequence of *a reaction mechanism that explains all of them*. This is the first case, to the best of our knowledge, in which with such an array of experimental data that seems to be inconsistent, *a mechanistic picture that involves both the singlet and triplet pathways is proposed.*

Scheme 3. Stereospecificity of the Olefin Aziridination Reaction



RESULTS AND DISCUSSION

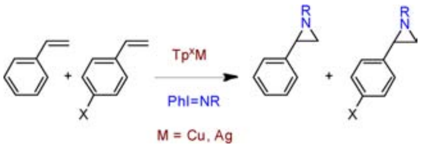
Experimental Studies. To collect a full set of data that could be used to propose a pathway for the nitrene transfer reaction, we have performed the following experiments with a series of Tp^{x}M complexes (M = Cu, Ag, Scheme 3): (i) study the stereospecificity of the reaction with several aryl- and alkyl-substituted olefins; (ii) competition experiments with *p*-substituted styrenes, (iii) effect of the addition of radical inhibitors, and (iv) use of a radical clock.

Aziridination of Z- or E-Olefins: Study of the Stereospecificity of the Reaction. Retention or certain loss of stereochemistry of olefin substituents in the aziridines (Scheme 2h) have been usually invoked to propose either a concerted or a stepwise mechanism, respectively. To check this issue, we have carried out several experiments with a series of Tp^{x}M (M = Cu, Ag) complexes and four different olefins. As shown in Scheme 3, *Z*-2-pentene, *E*-*β*-methyl-styrene, and *E*-2-hexene were converted into the corresponding aziridines with complete retention of the stereochemistry. This was observed with several catalysts bearing quite different Tp^x ligands. These results are in contrast with those previously reported with *E,E*-hexadien-1-ol when copper- or silver-based catalysts were employed.[24] The latter gave the *trans*-aziridine in an exclusive manner, whereas in the copper case, a certain loss of the stereochemistry was observed (*ca.* 2:1 favoring the *trans*-aziridines). Therefore, the group of olefins now tested, initially *Z* or *E*, with alkyl or aryl-containing groups, indicate that the retention of stereochemistry was observed with the exception of that containing an additional hydroxylic functional group. Further, this group seems to be noninnocent in the nitrene transfer reaction with the copper-based catalyst.

In the seminal work of this area,[7a] Evans and co-workers observed that alkyl-substituted olefins lead to stereospecific aziridinations, whereas nonstereospecific reactions were observed with aryl-containing olefins with simple copper salts as catalyst precursors. This is the common pattern with copper-based catalysts, with some exceptions, as that in our system in which we observed retention with alkyl and aryl-substituted olefins (excluding the OH case). Therefore, any plausible mechanism for this transformation should contain an explanation for the distinct behavior of different olefins in their aziridination *with the same catalyst*

Competition Experiments with p-Substituted Styrenes: The Dual-Parameter Hammett Equation. As mentioned above, the fitting of experimental data obtained upon competition reactions with substituted styrenes with the Hammett equation is a common probe in this area. Negative values of ρ are indicative of the existence of a transition state with a certain positive charge. As a result of this, the styrenes bearing electron withdrawing groups in the aromatic ring are less reactive than those with electron-donating substituents. The reported data[17b,18,19] show small values for ρ within the range of −0.38 to −0.65.[25] We have already reported the comparison of these competition studies for the styrene cyclopropanation and aziridination reactions with the complex Tp^{Me2}Cu(C_2H_4).[24b] We found that the cyclopropanation reaction data could be nicely fitted to the Hammett equation

Table 1. Ratio of Aziridines (X/H) Obtained from Competition Experiments with *p*-Substituted Styrenes



entry	Tp^{x}M	OMe	Me	Ph	F	H	Cl	NO_2
1	$Tp^{Me2}Cu$	2.10	1.44	1.38	1.03	1.00	1.11	1.01
2	$Tp^{*,Br}Cu$	2.31	1.46	1.41	0.89	1.00	1.06	0.90
3	$Tp^{Ms}Cu$	1.78	1.57	1.33	1.08	1.00	1.06	0.96
4	$Tp^{Br3}Cu$	2.18	1.38	1.25	1.00	1.00	0.87	0.82
5	$Tp^{Me2}Ag$	3.20	1.48	1.73	0.84	1.00	0.90	0.75
6	$Tp^{*,Br}Ag$	3.06	1.57	1.42	0.75	1.00	1.00	0.60

Table 2. Values of ρ^+, $\rho^\bullet$ and $\rho^+/\rho^\bullet$ Obtained Using the Hammett's Dual-Parameter Equation in the Aziridination Reaction of *p*-Substituted Styrenes

entry	catalyst	ρ^+	$\rho^\bullet$	R^2	$\rho^+/\rho^\bullet$
1	$Tp^{Me2}Cu$	−0.250 ± 0.024	0.272 ± 0.045	0.9666	0.925
2	$Tp^{*,Br}Cu$	−0.314 ± 0.043	0.309 ± 0.082	0.9310	1.016
3	$Tp^{Ms}Cu$	−0.224 ± 0.021	0.212 ± 0.040	0.9659	1.066
4	$Tp^{Br3}Cu$	−0.318 ± 0.030	0.248 ± 0.057	0.9653	1.282
5	$Tp^{Me2}Ag$	−0.475 ± 0.065	0.416 ± 0.122	0.9308	1.141
6	$Tp^{*,Br}Ag$	−0.499 ± 0.074	0.307 ± 0.140	0.9179	1.625
7	CuI	−0.283 ± 0.014	0.172 ± 0.019	0.9978	1.645

(eq 1). However, the attempts to fit the data from the related aziridination reaction failed, since the electron-withdrawing groups, −Cl or $-NO_2$ for instance, led to aziridines in such amounts that the correlation expected from eq 1 was lost. Actually, this behavior was previously observed by Evans and co-workers,[7a] when they described nearly 1:1 mixtures of the aziridines derived from styrene and *p*-nitrostyrene in dichloromethane using plain $CuClO_4$ as catalyst precursor, although a full set of competition experiments was not given. We found that the experimental data could be fitted to a dual-parameter equation containing both polar and radical contributions (eq 2). After our report, Che and co-workers applied[3] the same idea to the experimental results obtained in stoichiometric nitrene transfer reactions from bis(imido)ruthenium complexes to olefins.

$$\log \frac{K_X}{K_H} = \rho\sigma \tag{1}$$

$$\log \frac{K_X}{K_H} = \rho^+\sigma^+ + \rho^\bullet\sigma^\bullet \tag{2}$$

We have now carried out an extensive study (Tables 1 and 2, entries 2−6 and 2−7, respectively) with a series of copper and silver complexes to evaluate the validity of our previous study (referred to single example), and to check the effect of the Tp^x ligand and the metal in this transformation. In a general experiment, 1:1 mixtures of styrene and a *p*-substituted styrene were reacted with PhI═NTs, in the presence of catalytic amounts of Tp^{x}M (M = Cu, Ag) as the catalyst, with a 1: 20:100:100 ratio of catalyst, PhI═NTs, and both styrenes. After 12 h of stirring at room temperature, the solvent was removed and the residue was investigated by ^1H to provide the relative ratio of aziridines (overall yields in aziridines were within the interval 60−80%, and the remaining initial PhINTs was converted into $TsNH_2$). Table 1 shows the relative ratios of products, from which it can be concluded that styrenes bearing electron donating groups favored the aziridination reaction in all cases. However, a distinct behavior was observed in the case of electron-withdrawing groups, particularly with *p*-NO_2. Different degrees of deviation from the expected linear correlation (according to Hammett's equation) were found for the series of catalysts employed (Table 1). Once the generality of this behavior was assessed for a group of different ligands (with distinct electronic and steric properties) and both metals, we applied the dual parameter equation (eq 2) using the three scales for $\sigma^\bullet$ proposed by Jiang and Ji,[26] Jackson,[27] and Fischer.[28] The best fitting was so far obtained with Jackson's scale (see Supporting Information for all fitting data and plots), from which the series of values of $\rho^\bullet$ and ρ^+ shown in Table 2 were obtained. Figure 1 displays the plot of the experimental $\log(K_X/K_H)$ versus calculated $\rho^+\sigma^+ + \rho^\bullet\sigma^\bullet$ for $Tp^{*,Br}M$ (M = Cu, Ag). These correlations evidence that both polar and radical effects must be taken into account to explain this transformation. The negative value of ρ^+ indicates an

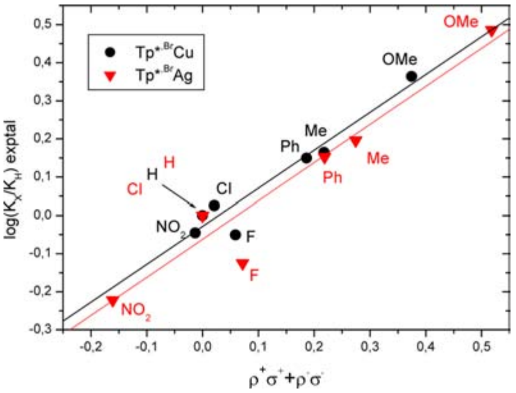


Figure 1. Plot of experimental $\log(K_X/K_H)$ vs calculated $\rho^+\sigma^+ + \rho^\bullet\sigma^\bullet$ (from Table 2) for $Tp^{*,Br}M$ (M = Cu, Ag).

Table 3. Values of ρ^+, $\rho^\bullet$, and $\rho^+/\rho^\bullet$ Obtained Using the Hammett's Dual-Parameter Equation in the Cyclopropanation Reaction of p-Substituted Styrenes

entry	catalyst	ρ^+	$\rho^\bullet$	R^2	$\rho^+/\rho^\bullet$
1	$\mathrm{Tp^{Br3}Cu}$	−0.406 ± 0.076	−0.048 ± 0.144	0.9189	8.45
2	$\mathrm{Tp^{*,Br}Cu}$	−0.623 ± 0.04	0.022 ± 0.075	0.9891	28.3
3	$\mathrm{Tp^{Ms}Cu}$	−0.333 ± 0.069	0.007 ± 0.131	0.8984	47.5

electrophilic attack of the olefin and the development of a positive charge, but very early in the reaction pathway, as inferred from the small value (−0.25 to −0.49). The same reason can be applied for the radical $\rho^\bullet$ contribution: radical species must be located at a certain early stage of the reaction coordinate.[26−28] The positive value indicates that *all substituents* contribute to spin delocalization. It is worth mentioning that the observation of both contributions was also observed with CuI as the catalyst precursor (Table 2, entry 7), as a model for the array of simple copper salts described by Evans and co-workers.[7a]

The relative parameter $\rho^+/\rho^\bullet$ also provides some interesting information. First, this ratio is close to unity (0.96−1.60) in all cases. This is at variance with data obtained for a well-known transformation that occurs in a concerted manner, the copper−catalyzed cyclopropanation reaction. From similar competition studies with p-substituted styrenes and ethyl diazoacetate as the carbene source, we have also fitted the collected data with the dual parameter eq 2 (Table 3). The $\rho^+/\rho^\bullet$ values appear within the range 8.45−47.5, largely favoring the polar contribution, as expected. Actually, fitting to the classical Hammett eq 1 gave nearly the same ρ^+ values (see Supporting Information). The appearance of a small radical contribution in the carbene transfer reaction to olefins could be associated with the existence of an asynchronous step in the cyclopropanation reaction, as recently proposed by Echavarren and co-workers.[29]

We have also found that the relative ratio $\rho^+/\rho^\bullet$ also correlates with two magnitudes: (a) the electron density located at the metal center (evaluated with the aid of FTIR data obtained from a series of $\mathrm{Tp^xCu(CO)}$ complexes) and (b) the Cu(I)/Cu(II) oxidation potential, measured as $E^0_{1/2}$.[30] Figure 2 shows both correlations for the series of four copper catalysts, from which it is concluded that the polar contribution is enhanced by electron-poor metal centers, that are more difficult to oxidize; that is, the radical contribution decreases when the redox potential increases.

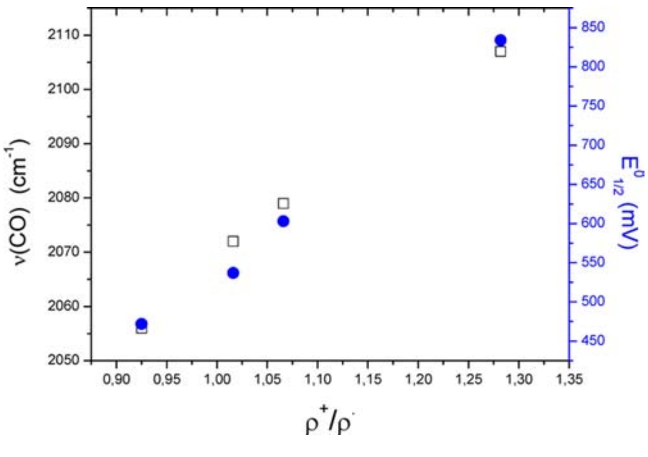
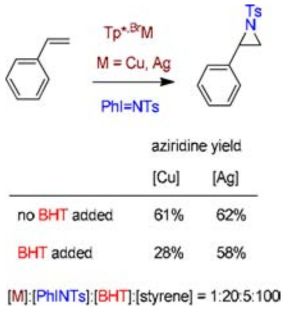


Figure 2. Plot of $\rho^+/\rho^\bullet$ vs ν(CO) and $E^0_{1/2}$ of a series of $\mathrm{Tp^xCu}$ complexes.

Effect of the Presence of BHT as the Radical Inhibitor. A set of experiments has been performed for twin styrene aziridination reactions catalyzed by $\mathrm{Tp^{*,Br}M}$ (M = Cu, Ag) as the catalysts that only differ in the presence or absence of t-butylhydroxitoluene (BHT) as the radical inhibitor. Scheme 4 shows the results obtained: the copper-based catalyst showed a drastic decrease (by 50%) of the aziridine yield. However, nearly identical yields were obtained in the case of the silver-based system (within experimental error) with or without BHT. This observation has important implications for the mechanistic proposal. Further, the Ag-based systems may not form the radical intermediate or if achieved, it would be a short-lived species that could not be intercepted by the radical inhibitor. In contrast, radical intermediate formation and interception to a certain degree seems to be possible in the case of the Cu-based system.

Scheme 4. Effect of the Presence of a Radical Inhibitor

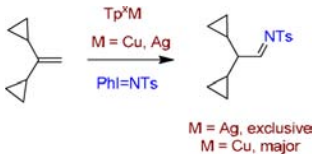


	aziridine yield [Cu]	aziridine yield [Ag]
no BHT added	61%	62%
BHT added	28%	58%

[M]:[PhINTs]:[BHT]:[styrene] = 1:20:5:100

Aziridination of Dicyclopropylethylene as Radical Clock. The use of a radical clock to gain mechanistic insights in the copper-catalyzed olefin aziridination reaction was described by Evans and co-workers.[7a] With $\mathrm{CuClO_4}$ as catalyst, the reaction in Scheme 2h only provided the aziridines, with no evidence of any product derived from the radical-induced aperture of cyclopropyl substituent. We have now employed 1,1-dicyclopropylethylene as the substrate for the aziridination reaction in the presence of $\mathrm{Tp^xM}$ (M = Cu, Ag) catalysts, an olefin that has been described as a radical clock to assess the implication of carbon radical intermediates.[31] Interestingly, we have observed with $\mathrm{Tp^{Br3}Cu}$ and $\mathrm{Tp^{*,Br}Ag}$ (the most active catalysts) the preferential formation of the imine shown in Scheme 5. With the silver catalyst no other product was

Scheme 5. Aziridination of the Radical Clock Probe 1,1-Dicyclopropylethylene



detected, whereas with the copper-based catalyst minor amounts of other species showing olefinic protons were detected by NMR. Although the mechanistic interpretation of these results will be provided later in this contribution, at this stage we can comment on them in a parallel manner with those in the above paragraph on the use of BHT: a certain degree of involvement of radical species is inferred from both sets of experiments for the copper system (BHT and radical clock), whereas the silver-based catalyst does not seem to involve those species on the basis of our experiments.

Summary of Experimental Results. Table 4 shows in brief the results collected and discussed in the previous sections.

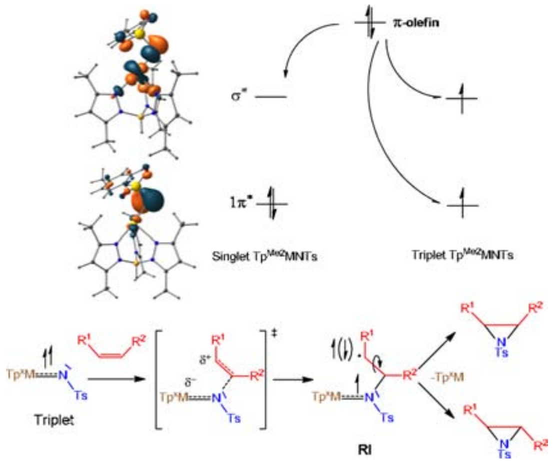
Table 4. Summary of Experimental Results

catalysts	stereochemistry studies	Hammett studies	radical inhibitor	radical clock[b]
Tp^{x}Cu	retention[a]	polar and radical contribution	affected	affected
Tp^{x}Ag	retention	polar and radical contribution	unaffected	unaffected

[a]With the exception of *E*,*E*-hexadien-1-ol. [b]No aziridines formed; see Scheme 5 for products.

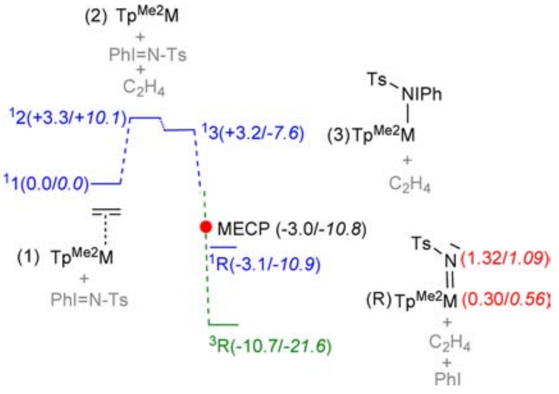
With both families of catalysts (Cu- or Ag-based), the results are somewhat contradictory in terms of unambiguously pointing toward one pathway, either concerted or stepwise. Thus, the concerted pathway, such as that similar to the cyclopropanation reaction in which both C–N bonds are formed synchronously, would not be in accord with the observance of a radical contribution in the Hammett studies. But the observance of the retention of stereochemistry, either with aryl- or alkyl-substituted olefins with both metals could be interpreted (as it has been in the past when using this probe only) in the opposite sense, as the prevalence of a concerted pathway. The formation of the imine from the radical clock (Scheme 5) has also important implications, since it could be the result (as explained below) of a stepwise mechanism in which the second C–N bond cannot form. Therefore, a first sight to the overall picture points toward the lack of any general explanation for *all* these results. It is worth mentioning at this stage that most previously proposed pathways have been supported on the basis of just one of the above experiments, and that the biunivocal correlations concerted-singlet nitrene and stepwise-triplet nitrene have also been invoked to propose corresponding pathways.

Scheme 6. Mechanistic Picture of the Olefin Aziridination Reaction Catalyzed by Tp^{x}M═NTs (M = Cu, Ag)[a]



[a]The two Kohn–Sham orbitals, σ^* are $1\pi^*$, are the singly occupied molecular orbitals (SOMO) of the triplet state of Tp^{Me2}MN–Ts.

Scheme 7. Free Energy Profiles for the Formation of the Active Metal-Nitrene Intermediate, Tp^{Me2}MN–Ts (M = Ag, Cu)[a]



[a]Free energies (kcal mol^{-1}) and spin densities (in red) of the Ag-based system are in full text and Cu-based systems are in italic.

Computational Studies. With the aim of providing a general mechanistic explanation accounting for all the above experimental data, DFT studies have been carried out. Current experimental and previous[13,20] theoretical studies have anticipated two mechanistic proposals for transition metal-catalyzed aziridination reactions, namely, the concerted and stepwise (or radical) mechanisms (Scheme 6). We have the Tp^{Me2}M (M = Cu, Ag) as the model systems in the present study. The triplet state of the active metal–nitrene intermediate, Tp^{Me2}MN–Ts (M = Ag, Cu), holds two unpaired electrons on the $1\pi^*$ and σ^* orbitals (SOMO, Scheme 7). We follow the orbital labeling of Phillips and co-workers[20b] in their analogous Ru-based system. In the simplified mechanistic picture, the triplet state would follow the stepwise mechanism: the first step consists of the transfer of one electron from an olefin-π orbital to the metal–nitrene $1\pi^*$ orbital, giving rise to a triplet biradical intermediate (**RI**, Scheme 6). The presence of this intermediate is consistent with the observation of inversion of the stereochemistry of the olefin, as a rotation around the carbon–carbon bond may take place before the second electron transfer from the olefin–π orbital to the metal–nitrene σ^* orbital. The alternative pathway from the (closed-shell) singlet electronic state of Tp^{Me2}MN–Ts would perform the two-electron transfer from the olefin π orbital to the σ^* orbital of Tp^{Me2}MN–Ts, and this concerted process leads to complete retention of the stereochemistry of the olefin. An additional electronic state that could be present is the open-shell singlet, with an antiparallel occupation of the same open-shell orbitals of the triplet. This open-shell singlet should behave similarly to the triplet in terms of stereochemistry.

However, experimental results described in the previous section cannot be directly fitted within this mechanistic picture. A concerted mechanism, through a singlet spin state, can be proposed for the retention of configuration in the reaction of *Z*-2-pentene, *E*-*β*-methyl-styrene, and *E*-2-hexene with both Tp^{x}Ag and Tp^{x}Cu systems, as well as in the reaction of *E,E*-hexadien-1-ol with Tp^{x}Ag. On the other hand, observed loss of stereochemistry in the aziridination of *E,E*-hexadien-1-ol with the Tp^{x}Cu system supported for the radical mechanism. Finally, correlations of the experiments carried out with *p*-substituted styrene indicated a contribution of both radical and concerted mechanisms with both metals. Herein we present a detailed computational study to rationalize these puzzling observations of aziridination reactions catalyzed by Tp^{x}Ag and Tp^{x}Cu complexes.

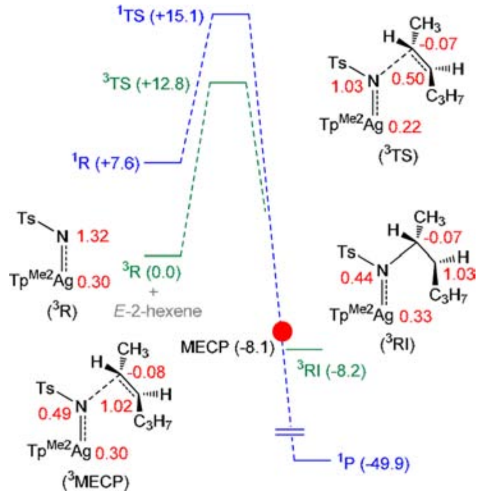
Formation of the Metal−Nitrene Intermediate. We have first focused on calculated free energy profiles for the active metal−nitrene intermediate (Tp^{Me2}MN−Ts) formation (Scheme 7). The catalytic cycle starts from Tp^{Me2}M (**2**), which is initially mixed with C_2H_4 (as the model olefin in this step), leading to the reversible formation of Tp^{Me2}M(C_2H_4) complex (**1**). Adducts of composition Tp^{Me2}M(L) are known in the literature as catalyst precursors, and dissociation pre-equilibrium of the ligand (L) is well-established.[32] Dissociation of ethene from Tp^{Me2}M(C_2H_4) needs 3.3 and 10.1 kcal mol^{-1} for Ag- and Cu-based systems, respectively. The next step consists of PhINTs coordination on Tp^{Me2}M, giving rise to a Tp^{Me2}M−N(PhI)−Ts complex (**3**) with the calculated nitrogen−iodine bond lengths in Tp^{Me2}Ag−PhIN−Ts of 3.16 Å and in Tp^{Me2}Cu−N(PhI)−Ts of 2.99 Å. In the presence of weak nitrogen−iodine bond, PhI dissociation would be easier (we were unable to locate transition states for this step), leading to the singlet metal−nitrene (^{1}**R**). However, the existence of a minimum energy crossing point (MECP) between the singlet and the triplet profiles allows the formation of the triplet metal−nitrene, ^{3}**R**.

The optimized triplet state of Tp^{Me2}AgN−Ts intermediate holds spin densities on nitrogen of 1.32 and silver of 0.30, showing the two unpaired electrons are mainly localized on the nitrogen atom (see section S5, Supporting Information). Despite several attempts, we were unable to locate the open-shell singlet state of this system. The closed-shell singlet state (^{1}**R**) of Tp^{Me2}AgN−Ts is 7.6 kcal mol^{-1} higher than the triplet state. In the analogous Tp^{Me2}CuNTs system, triplet state (^{3}**R**) is 10.6 kcal mol^{-1} more stable than the closed-shell singlet state (^{1}**R**). Moreover, this triplet state holds the calculated spin densities on nitrogen of 1.09 and copper of 0.56, which denotes significant spin density delocalization over the metal center. This electronic nature helps us to locate an open-shell singlet state, ^{1}**R**$_{\mathbf{UKS}}$, which is 5.6 kcal mol^{-1} above the triplet state. In this open-shell singlet state, the calculated spin density on the metal−nitrene unit, $\rho(\mathrm{Cu}) = -0.65$ and $\rho(\mathrm{N}) = +0.79$, indicated that the spin vectors are antiparallel, and the calculated spin contamination, $\langle S^2 \rangle$, is 1.00. The two unpaired electrons are located in similar orbitals in the triplet (parallel spins) and open-shell singlet (antiparallel spin) states. On the basis of our calculations, the electronic structure of the copper−nitrene intermediate is rather Tp^{Me2}Cu^{II}N$^{\bullet}$Ts, while the silver−nitrene intermediate holds the two unpaired electrons mainly localized on nitrogen.

We must admit that the relative energies of states with different multiplicities depend heavily on the functional used. We have included in the Supporting Information (see section S6) a comparison of the performance of the M06 and BP86 functionals for this structure, as well as a justification that our preferred M06 is more appropriate for this system.

Aziridination of E-2-Hexene. Computed free energy profiles for aziridination of *E*-2-hexene catalyzed by Tp^{Me2}AgN−Ts are shown in Scheme 8. The first part of the reaction takes place through the triplet energy surface, where the first nitrogen−carbon bond formation occurs *via* ^{3}**TS** with a barrier of 12.8 kcal mol^{-1} above the separate reactants. The closed-shell singlet transition state, ^{1}**TS**, has a relative energy of 15.1 kcal mol^{-1}, and therefore is a minor contributor for the overall rate. We searched for the open-shell singlet electronic transition state, but we were unable to locate it. On the basis of our DFT calculations, aziridination of *E*-2-hexene occurs through the radical mechanism, where the favored transition state for the reaction is ^{3}**TS** that leads to the triplet radical intermediate (^{3}**RI**), which is −8.2 kcal mol^{-1} below the reactants. However, this intermediate may not be observed, because there is a spin crossing between the triplet and closed-shell singlet energy profiles (MECP at −8.1 kcal mol^{-1}). After spin crossover to the singlet surface, the product (^{1}**P**) is reached with a high stability of −49.9 kcal mol^{-1}. Therefore, Tp^{Me2}Ag system performs aziridination of *E*-2-hexene with retention of stereochemistry, because radical intermediate ^{3}**RI**, where the scrambling could occur, is not formed.

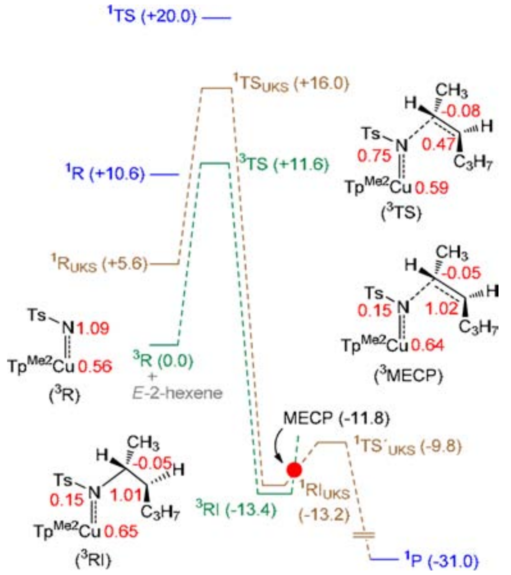
Scheme 8. Computed Free Energy Profiles for the Aziridination of *E*-2-Hexene Catalyzed by Tp^{Me2}AgN−Ts^a



^{a}Free energies are in kcal mol^{-1} and spin densities are in red.

Scheme 9 shows the computed free energy profile for the analogous copper-based system. In a very similar way to the silver-analogue, the reaction starts from the triplet metal−nitrene intermediate, and the formation of the radical intermediate, ^{3}**RI**, has a barrier of 11.6 kcal mol^{-1} (^{3}**TS**). In this case, we were able to locate the open-shell singlet transition state (^{1}**TS**$_{\mathbf{UKS}}$), which is 4.4 kcal mol^{-1} above the ^{3}**TS**, while the closed-shell singlet transition state (^{1}**TS**) is a further 4.0 kcal mol^{-1} higher in energy. The open-shell singlet replaces thus the closed-shell singlet as an alternative to the triplet in the copper system. This open-shell singlet plays however no role before intermediate ^{3}**RI**, as it remains always higher in energy than the

Scheme 9. Computed Free Energy Profiles for Aziridination of *E*-2-Hexene Catalyzed by Tp$^{\mathrm{Me2}}$CuN−Ts[a]

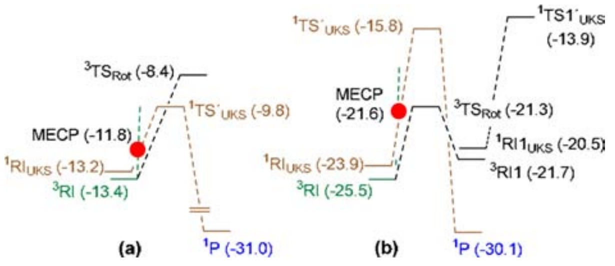


[a]Free energies are in kcal mol^{-1} and spin densities are in red.

triplet. There is a significant qualitative difference between the energy profiles of the silver- and copper-based systems. Despite several attempts, we were unable to locate a MECP between the triplet and closed-shell singlet (or open-shell singlet) energy profiles before the triplet energy profile reaches to the radical intermediate ($^{3}\mathbf{RI}$), which is −13.4 kcal mol^{-1} below the entry channel. The open-shell singlet from of the radical intermediate ($^{1}\mathbf{RI}_{\mathrm{UKS}}$) is only 0.2 kcal mol^{-1} above the $^{3}\mathbf{RI}$. We have also searched the closed-shell singlet form of this species, which is however not a minimum that ultimately converged to the product, $^{1}\mathbf{P}$ (see section S7, Supporting Information for details).

Once this radical intermediate $^{3}\mathbf{RI}$ is formed on the triplet profile, inversion of the stereochemistry of olefin may take place, but we need to consider a new competition between ring closure (toward the product) and bond rotation (toward the scrambling). The reaction toward the product (Scheme 9 and Scheme 10a) proceeds through a MECP between triplet and open-shell singlet profiles (11.8 kcal mol^{-1} below reactants) and transition state $^{1}\mathbf{TS}'_{\mathrm{UKS}}$ (relative energy, −9.8 kcal mol^{-1}),[33] which is the highest energy point before reaching the final product, $^{1}\mathbf{P}$ (−31.0 kcal mol^{-1}). The path toward scrambling involves rotation around the carbon−carbon bond through the transition state $^{3}\mathbf{TS}_{\mathrm{Rot}}$, which has a relative energy of −8.4 kcal mol^{-1}. Transition state $^{1}\mathbf{TS}'_{\mathrm{UKS}}$ is 1.3 kcal mol^{-1} below $^{3}\mathbf{TS}_{\mathrm{Rot}}$, and thus the triplet intermediate, $^{3}\mathbf{RI}$, would mostly evolve to the products before it has time to scramble. Therefore, *both silver- and copper-based systems lead to retention of stereochemistry, but there are two different pathways to account for such behavior.*

Scheme 10. Computed Free Energy Profiles (kcal mol^{-1}) for the Second Electron Transfer Process of the Radical Mechanism with (a) *E*-2-Hexene and (b) *E,E*-Hexadien-1-ol Catalyzed by Tp$^{\mathrm{Me2}}$CuN−Ts



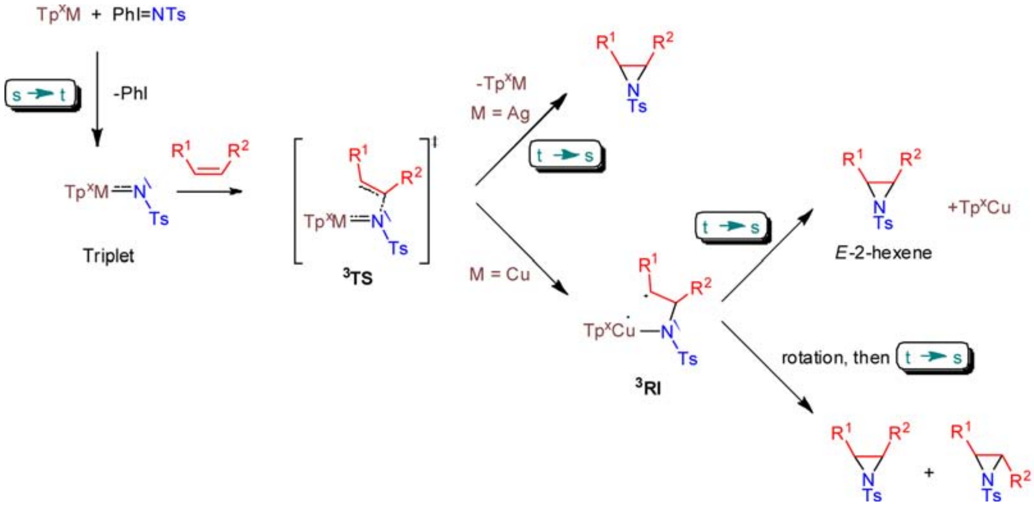
Aziridination of E,E-2,4-Hexadien-1-ol. Computed free energy profiles for aziridination of *E,E*-2,4-hexadien-1-ol are qualitatively similar to those of *E*-2-hexene as can be seen in Figure S3 (section S8, Supporting Information). The analysis of the profile for the reaction with the silver-based catalyst (Supporting Information, Figure S3a) produces the same conclusions for *E*-2-hexene described above; specifically the reaction starts on the triplet state, but the scrambling cannot take place because the system moves to the closed-shell singlet state before reaching the radical intermediate, $^{3}\mathbf{RI}$.

In the case of the copper-based complex (Figure S3b, section S8, Supporting Information), a significant qualitative difference appeared which we highlight in Scheme 10b. The ordering between the relative energies of the two competing paths from intermediate $^{3}\mathbf{RI}$ is opposite, and the transition state ($^{1}\mathbf{TS}'_{\mathrm{UKS}}$) leading to the ring closure has a relative energy of −15.8, which is 5.5 kcal mol^{-1} higher than the transition state leading to scrambling ($^{3}\mathbf{TS}_{\mathrm{Rot}}$). As a result, rotation can take place around the C−C bond before the ring closure takes place, and both *cis*- and *trans*-aziridines can be formed. The proportion between the two aziridines will depend on the relative energies of the corresponding ring-closure transition states, $^{1}\mathbf{TS}'_{\mathrm{UKS}}$ (leading to *trans*-aziridine) and $^{1}\mathbf{TS1}'_{\mathrm{UKS}}$ (leading to *cis*-aziridine). According to our calculations, $^{1}\mathbf{TS}'_{\mathrm{UKS}}$ is 1.9 kcal mol^{-1} more stable than $^{1}\mathbf{TS1}'_{\mathrm{UKS}}$, and therefore *trans*-aziridine can be formed as the major product.

Therefore, the lack of scrambling cannot be used as *unambiguous* evidence for the nonradical mechanism, because even the reaction with retention of configuration starts from the triplet state. For scrambling to take place, two conditions are necessary. The first of them is the formation of triplet radical intermediate ($^{3}\mathbf{RI}$), where only one N−C bond has to be formed. This is not achieved for the silver-based systems that we have tested, due to the presence of a direct crossing to the singlet surface, leading to the products after the first transition state ($^{3}\mathbf{TS}$). Therefore, the electronic properties of the silver−nitrene intermediate prevent scrambling. The second condition for scrambling is that once the $^{3}\mathbf{RI}$ intermediate is reached, the rotation around the C−C bond leading to inversion has to be faster than the product formation. This intermediate is reached for the copper-based catalysts, but the rotation is only fast enough in the case of *E,E*-hexadien-1-ol. This could be explained as the result of a conjugation between the double bonds in this species stabilizing the open ring radical intermediate, and increasing the barrier for the ring closure.

Mechanistic Proposal. At this point, unification of experimental data and theoretical calculations is required. As shown in Scheme 11, the reaction starts in all cases with the formation of a metal−nitrene intermediate in the triplet state. Further, copper−nitrene intermediate is rather Tp^{x}Cu$^{\mathrm{II}}$N$^{\bullet}$Ts, whereas the silver−nitrene displays a biradical character on the nitrogen atom. Their formation takes place by means of a singlet-to-triplet spin crossover characterized by a MECP. This metallonitrene species can attack the olefin through a transition state ($^{3}\mathbf{TS}$) leading to the first carbon−nitrogen bond formation. From here, two different routes seem to operate. In the silver case, the triplet route intercepts with that of the

Scheme 11. Mechanistic Proposal Based on Experimental and Theoretical Data from This Work



singlet before a true intermediate (^{3}**RI**) is formed, leading to the aziridines product. Because of this, retention of stereochemistry is observed with all the olefins, in a process that if not purely synchronous, can be considered at least as concerted. Since the radical intermediate is out of the most probable reaction pathway, there is no effect of the presence of radical traps. However, the lack of fitting to the plain Hammett equation and the proposal of a radical character must be related to the triplet nature of the transition state ^{3}**TS** previous to ring closing. This affects both copper and silver, in an early stage of the reaction as already discussed.

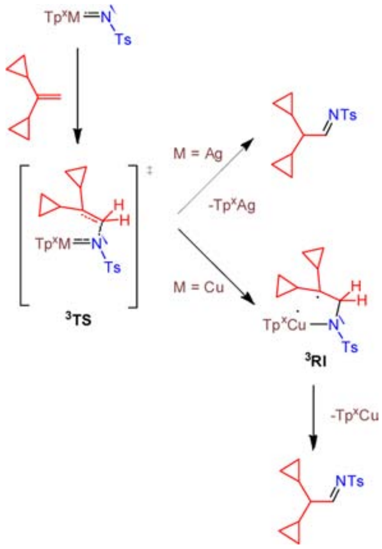
For the copper-based system the radical intermediate ^{3}**RI** is reached, explaining the decrease of the reaction outcome with a radical inhibitor. Now, the crossing of the triplet and singlet pathways takes place beyond that intermediate, and the relative value of the corresponding MECP for such crossing and the barrier for rotation around the C−N bond will control the stereochemistry.

A piece of information is yet to be explained, namely the lack of formation of aziridines when 1,1-dicyclopropylethylene was employed as the substrate. Scheme 12 shows a plausible explanation for this issue. Assuming that a similar transition state is formed (^{3}**TS**), it is very likely that the steric pressure exerted by the two cyclopropyl groups disfavors the aziridine ring closure and leads to the imine as an alternative product. Either with (for copper) or without (for silver) formation of the radical intermediate, the imine could be formed in one step by a 1,2-hydrogen shift. The observance of small amounts of cyclopropyl-opening product with the copper catalyst would proceed from the ^{3}**RI** intermediate as proposed by Evans and co-workers,[7a] this intermediate being only formed in the case of copper.

CONCLUSIONS

On the basis of our experimental data and theoretical calculations, we have developed a mechanistic proposal for the olefin aziridination reaction catalyzed by Tp^{x}M (M = Cu, Ag; Tp^x = hydrotrispyrazolylborate ligand). With both metals, the reaction is triggered by the formation of a metal−nitrene intermediate in the triplet state, holding radical character. The reaction profile is characterized by the presence of minimum energy crossing points (MECPs), where a change from the triplet to the singlet surface takes place. The relative energy of these MECPs compared with those of radical intermediates and transition states involved in ring closing or C−C bond rotation account for the experimental observations in all cases, allowing us to propose a general mechanism. As the result of it, the generally accepted proposal that the retention of the stereochemistry of the olefin is indicative of a concerted pathway based on a singlet nitrene seems to be no longer valid. Herein we have demonstrated that a stepwise pathway, involving triplet copper−nitrene species can also lead to stereospecific aziridination. Also we have shown that even in the case of a concerted (albeit asynchronous) step such as in the case of silver, the initial metallonitrene is a biradical species, not the usually assumed singlet. We believe our findings can be extended to the other reported catalytic systems for the aziridination reaction that could be worth revisiting from a mechanistic point of view.

Scheme 12. Plausible Explanation for the Cu- or Ag-Catalyzed Nitrene Transfer to 1,1-Dicylopropylethylene



EXPERIMENTAL SECTION

General Methods. All preparations and manipulations were carried out under a oxygen-free nitrogen atmosphere using conventional Schlenk techniques or inside a drybox. All the olefins were purchased from Aldrich. Olefins and solvents were rigorously dried before use. The copper and silver complexes employed as catalysts were prepared according to the literature.[23,24,30,34] PhINTs was also prepared following the reported methods.[35] NMR experiments were run in a Varian Mercury 400 MHz spectrometer. GC data were collected with a Varian GC-3900.

General Catalytic Aziridination Reaction. The copper or silver complex (0.01 mmol) and the olefin (1 mmol) were dissolved in CH_2Cl_2 (10 mL). After 5 min of stirring, PhINTs was introduced in one portion (0.2 mmol), and the mixture was stirred overnight at room temperature. No solid PhINTs was observed in the reaction mixture after that time. Volatiles were removed under vacuum, and the aziridines were identified by ^{1}H NMR spectroscopy of the reaction crude in $CDCl_3$ and comparison with the reported data (see Supporting Information).

Catalytic Competition Experiments. These experiments were done by following the above procedure, but using mixtures of styrene and the corresponding *p*-substituted styrene (0.5 mmol of each). Solid PhINTs was not observed in the reaction mixture after stirring overnight. Volatiles were removed under vacuum and the relative ratio of aziridines was estimated by ^{1}H NMR spectroscopy of the reaction crude in $CDCl_3$ (see Supporting Information).

Effect of Radical Inhibitor. This experiment was set up in an identical manner to that described above, with the addition of 5 equiv (with respect to the catalyst) of *t*-butylhydroxytoluene (BHT) to the reaction mixture, and with the use of $Tp^{*,Br}M$ (M = Cu, Ag) as the catalyst. Yields shown in Scheme 4 were calculated by ^{1}H NMR spectroscopy in $CDCl_3$ (see Supporting Information).

1,1-Dicyclopropylethylene as Radical-Clock Probe. 1,1-Dicyclopropylethylene was prepared by means of a typical Wittig reaction, from dicyclopropylketone and Ph_3PCH_3Br. Once isolated, 0.5 mmol of the olefin was reacted with 0.5 mmol of PhINTs in 10 mL of dried CH_2Cl_2 in the presence of 0.025 mmol of either $Tp^{Br3}Cu$ or $Tp^{*,Br}Ag$ as the catalyst. After the mixture was stirred overnight, the volatiles were removed under vacuum and the residue was investigated by NMR. In both cases the major product was identified as *N*-(2,2-dicyclopropylethylidene)-4-methylbenzenesulfonamide. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 8.57 (d, 1H, J = 6.2 Hz), 7.68 (d, 2H, J = 8.2 Hz), 7.37 (d, 2H, J = 8.2 Hz), 2.41 (s, 3H), 1.24 (dt, 1H, J = 6.2, 8.5 Hz), 0.88 (m, 2H), 0.58 (m, 2H), 0.45 (m, 2H), 0.28 (m, 2H), 0.16 (m, 2H). $^{13}C\{^1H\}$ NMR (400 MHz, CD_2Cl_2): 179.8 (iminic CH), 129.8, 127.8 (aromatic CH), 53.5 (CH_3), 21.4 (CH), 11.6 (CH), 3.3 (CH_2), 2.0 (CH_2).

Computational Methods. Gas phase structure optimizations were carried out using DFT as implemented in the Gaussian 09 package[36] with the M06 functional.[37] The BP86 functional was considered as a nonhybrid alternative, but the results collected (in the Supporting Information) indicate it performs worse for this particular problem. The SDD basis set was used for silver, copper, and iodine.[38] The 6-31G* basis sets were considered for the remaining atoms.[39] Final energies were obtained by doing single-point calculations on the optimized structures, where silver, copper, and iodine were still described with SDD, and the remaining atoms were treated with the 6-311++G** basis sets. All geometry optimizations were full with no restrictions, and vibrational frequency calculations performed in order to establish the stationary points were minima or transition states. Further, the connectivity of the transition states was confirmed by relaxing the transition state geometry toward both the reactant and the product. Free-energy corrections at 298.15 K and 10^5 Pa pressure were used, including zero-point energy corrections. Minimum energy crossing points (MECP) were calculated with the MECP program of J. H. Harvey and co-workers.[22] Open-shell electronic configurations were obtained by using the broken symmetry methodology,[40] and calculated total spin density distributions of selected open-shell stationary points are summarized in the Supporting Information (see section S9). This method struggles in the description of the transition from open-shell to closed-shell singlets, as happens in the ring closure transition states $^1\mathbf{TS}'_{\mathrm{UKS}}$ and $^1\mathbf{TS1}'_{\mathrm{UKS}}$ Because of that, the structure and energy of these transition states had to be estimated through a relaxed scan of the N–N–C bond angle, in a procedure analogous to that used by Norrby and co-workers.[20a] Real energy of the open-shell singlet electronic states ($\in_s$) were evaluated by considering the energy $\in_0$ of the optimized broken-symmetry solution and energy $\in_1$ from separate spin-unrestricted m_s = 1 calculation at the same geometry, considering the following formula:[41]

$$\in_s \approx \frac{S_1^2 \in_0 - S_0^2 \in_s}{S_1^2 - S_0^2}$$

where S_0 and S_1 are spin contaminations of the open-shell singlet and the triplet states, respectively.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of the experiments cited in the text, computed structures of metallonitrene complexes, comparison of M06 and BP86 functionals, calculated spin density distribution of open-shell states, total energies and Cartesian coordinates of the computed structures. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

mmdiaz@dqcm.uhu.es; fmaseras@iciq.es; perez@dqcm.uhu.es

Notes

The authors declare no competing financial interest.

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