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Substituent Effects on the Reaction Rates of Copper-Catalyzed Cyclopropanation and Aziridination of *para*-Substituted Styrenes[†]

M. Mar Díaz-Requejo,[‡] Pedro J. Pérez,*[,‡] Maurice Brookhart,[§] and
Joseph L. Templeton[§]

Departamento de Química y Ciencia de Materiales, Universidad de Huelva, Carretera de Palos de la Fra., 21819-Huelva, Spain, and Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290

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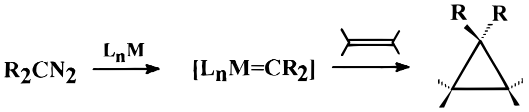
Relative rates of cyclopropanation and aziridination of a series of *para*-substituted styrenes have been determined using $Tp'Cu(C_2H_4)$ (Tp' = hydridotris(3,5-dimethyl-1-pyrazolyl)borate) as the copper precatalyst in combination with $N_2CHCO_2CH_2CH_3$ and $C_6H_5INSO_2C_6H_4CH_3$ (PhI═NTs), respectively. For the cyclopropanation reaction, a linear plot of the experimental data is obtained by means of the Hammett equation, $\log(k_X/k_H) = \rho\sigma$ ($\rho = -0.85 \pm 0.07$). This correlation supports earlier mechanistic proposals of an electrophilic metal−carbene complex intermediate. In the case of the aziridination reaction, the experimental data can be fit with a two term equation of the type $\log(k_X/k_H) = \rho^+\sigma^+ + \rho^\bullet\sigma^\bullet$ ($\sigma^\bullet$ are Jackson's radical substituent constants) leading to the values $\rho^+ = -0.28 \pm 0.06$ (polar contribution) and $\rho^\bullet = +0.34 \pm 0.13$ (radical contribution). A paramagnetic copper nitrene species which behaves as an electrophilic, nitrogen-centered radical is proposed as the intermediate for the aziridination reaction.

The development of new transition-metal-based catalysts capable of transferring carbene, nitrene, and oxo groups to unsaturated substrates has received the attention of a number of research groups.[1] Rhodium and copper complexes are the most efficient catalysts developed to date for carbene transfer from diazo compounds to olefins and alkynes to give cyclopropanes and cyclopropenes, respectively.[2] For aziridination of olefins using PhI═NTs (Ts = $-SO_2C_6H_4CH_3$), copper-based catalysts are presently the systems of choice.[3,4] The mechanism that governs each of these transformations has not been examined with the same attention. For the cyclopropanation reactions, several studies support a pathway involving the intermediacy of an electrophilic metal−carbene complex (eq 1).[5] In contrast, few studies have addressed the nature of the intermediate in metal-catalyzed aziridinations.[3,4]



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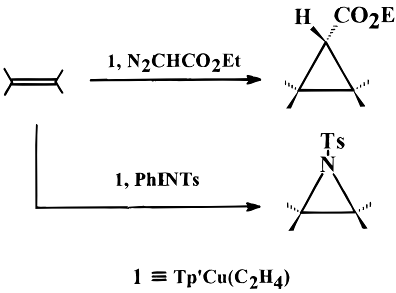
We have recently reported that the complex $Tp'Cu(C_2H_4)$ (Tp' = hydridotris(3,5-dimethyl-1-pyrazolyl)borate) (**1**) catalyzes carbene transfer from ethyl diazoacetate (EDA) to olefins, yielding cyclopropanes, as well as nitrene transfer from PhI═NTs to olefins to give aziridines (eqs 2 and 3).[6] This complex thus provides the possibility of comparing the catalytic behavior of the same catalyst precursor in both the cyclopropanation and aziridination reactions.[7] We report here a study of the relative rates of cyclopropanation and aziridination of a series of *para*- substituted styrenes employing **1** as the precatalyst with EDA and PhI═NTs, respectively.



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[†] Dedicated to Professor J. Carlos Vílchez Martín on occasion of his 60th birthday.

[‡] Universidad de Huelva.

[§] University of North Carolina at Chapel Hill.

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(1) (a) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, U.K., 1995; Vol. 12, p 387. (b) Doyle, M. P. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993. (c) Jacobsen, E. N. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, U.K., 1995; Vol. 12, p 1097.

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(4) (a) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889. (b) Zhang, W.; Lee, N. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 425. (c) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326.

(5) (a) Maxwell, J. L.; Brown, K. C.; Bartley, D. W.; Kodadek, T. *Science* **1992**, *256*, 1544. (b) Brown, K. C.; Kodadek, T. *J. Am. Chem. Soc.* **1992**, *114*, 8336. (c) Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53.

(6) Pérez, P. J.; Brookhart, M. S.; Templeton, J. L. *Organometallics* **1993**, *12*, 261.

(7) Jacobsen and co-workers[4a] have directly compared the enantioselectivities of cyclopropanation and aziridination reactions catalyzed by a series of copper diimine complexes.

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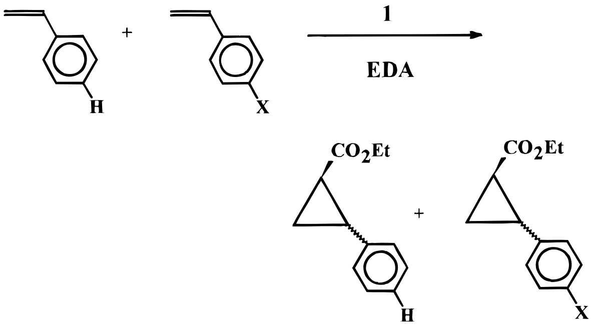
Quite different responses to substituents were observed for these systems, which lend insight into the differing nature of the intermediates in the transfer reactions.

Results and Discussion

Cyclopropanation of *para*-Substituted Styrenes. The relative rates of catalytic cyclopropanation of a series of *para*-substituted styrenes using **1** with ethyl diazoacetate (EDA) were determined through pairwise competition experiments (eq 4). Equimolar mixtures of styrene and a *para*-substituted styrene derivative were treated with EDA in the presence of catalytic amounts of the copper complex **1** (**1**:EDA:styrenes = 1:100:300). The ratios of the resulting cyclopropanes **2a,b**:**3a,b** were determined by ^{1}H NMR spectroscopy (see Experimental Section). The results are summarized in Table 1. The observed *cis:trans* ratio for the cyclopropanes is not substantially influenced by the nature of the *para* substituent. This ratio varies in a range from 1:1 to 1:1.5. For example, styrene is catalytically converted into a 45:55 *cis:trans* mixture of the corresponding cyclopropanes, whereas for the *p*-CF_3 and *p*-OMe styrenes, 50:50 and 42:58 ratios are observed.



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2a (cis) **2b (trans)** **3a (cis)** **3b (trans)**

Table 1. Product Ratios for the Cyclopropanation Competition Experiments (*p*-X-C_6H_4−CH═CH_2 vs C_6H_5−CH═CH_2) Using Tp′Cu(C_2H_4) (1) as the Precatalyst and $N_2CHCOOCH_2CH_3$ in $ClCH_2CH_2Cl$ at 25 °C

	product ratios
X	([**3a**] + [**3b**])/([**2a**] + [**2b**])
OMe	2.00
H	1.00
Cl	0.80
CF_3	0.46
NO_2	0.22

Several observations suggest that the oxidation state of copper remains as Cu(I) during carbene transfer employing **1**. First, as earlier reported,[6] the Cu(I) species Tp*Cu(CH_2═CHPh) is spectroscopically observed as the catalyst resting state during carbene transfer. Secondly, treatment of the reaction solution with ethylene following catalysis results in quantitative (by NMR) regeneration of **1**.[6] In addition, no color changes indicative of Cu(II) (see below) occur during catalysis. These observations are consistent with earlier suggestions[8] that Cu(I) salts are the active species in carbene transfer employing various diazo compounds and that, when Cu(II) salts are employed, diazo compounds effect reduction to Cu(I) prior to the catalytic carbene transfer reaction.

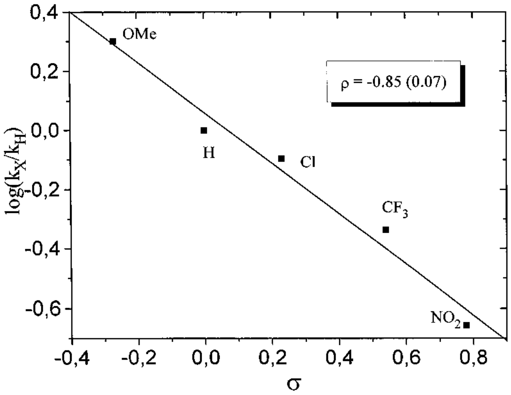
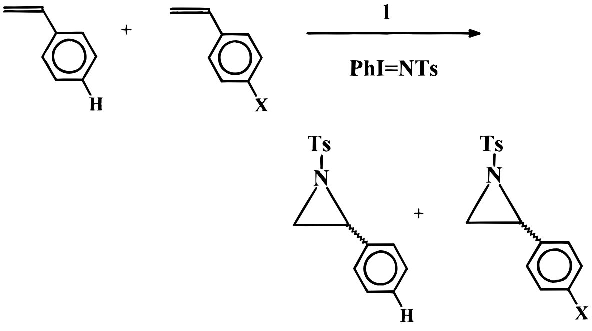


Figure 1. Hammett σρ correlation for relative rates of cyclopropanation, $\log(k_X/k_H)$.

The results in Table 1 indicate that styrenes with electron-withdrawing groups are less reactive than those with electron-donating substituents. A Hammett plot of $\log(k_X/k_H)$ versus σ is shown in Figure 1. A reasonable $\sigma\rho$ correlation is obtained with $\rho = -0.85 \pm 0.07$. This value is similar to that reported by Kodadek and Woo et al. for the cyclopropanation of substituted styrenes using an EDA/iron (II) phorphyrin system ($\rho = -0.68 \pm 0.07$).[9] A substantially larger ρ value of −2.2 was determined for the stoichiometric reaction of the cationic, highly electrophilic iron carbene complex Cp-$(CO)_2Fe$═$CH(CH_3)^+$ with *para*-substituted styrenes.[10]

The satisfactory Hammett $\sigma\rho$ correlation with a negative value for ρ further supports the earlier mechanistic proposals[1] of an electrophilic metal−carbene complex intermediate. The small negative value of ρ suggests only a moderate positive charge build-up at the benzylic carbon in the transition state.

Aziridination of *para*-Substituted Styrenes. In experiments analogous to the cyclopropanation reactions, the relative rates of catalytic aziridination of a series of *para*-substituted styrenes using **1** and PhI═NTs were established through competition experiments (eq 5). The results are summarized in Table 2. Similar to the cyclopropanation reaction, styrenes with electron-donating substituents are more reactive than unsubstituted styrene. However, in contrast, electron-with-



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4 **5**

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[9] Wolf, J. R.; Hamaker, C. G.; Djukic, J.-P.; Kodadek, T.; Woo, L. K. *J. Am. Chem. Soc.* **1995**, *117*, 9194.

[10] Brookhart, M.; Studebaker, W. D. *Chem. Rev.* **1987**, *87*, 411.

Table 2. Product Ratios for the Aziridination Competition Experiments (p-X-C_6H_4−CH=CH_2 vs C_6H_5−CH=CH_2) Using Tp′Cu(C_2H_4) (1) as the Precatalyst with PhI=NTs in CH_2Cl_2 at 25 °C

X	product ratios [**5**]/[**4**] exptl	product ratios [**5**]/[**4**] calcd[a]
OMe	2.43	2.33
Me	2.13	1.67
Ph	1.36	1.56
H	1.00	1.00
Cl	1.21	1.07
CF_3	1.02	*b*
NO_2	1.15	1.08

[a] Calculated using the dual-parameter equation $\log(k_X/k_H) = \rho^+\sigma^+ + \rho^\bullet\sigma^\bullet$, where $\rho^+ = -0.28$, $\rho^\bullet = +0.34$, σ^+ are Hammett constants, and $\sigma^\bullet$ are Jackson's constants.[10a] [b] No $\sigma^\bullet$ parameter available (ref 11a).

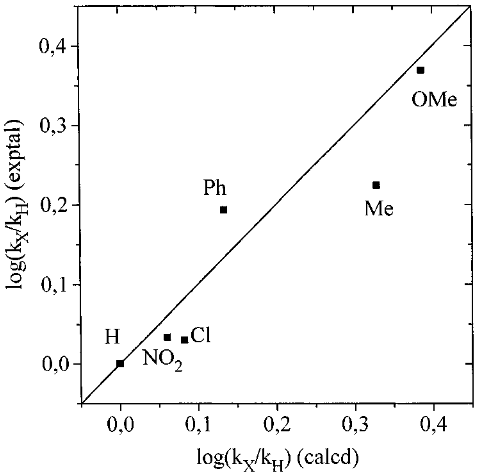


Figure 2. Plot of experimentally determined $\log(k_X/k_H)$ versus the calculated $\log(k_X/k_H)$ using eq 6 (see text). The line (slope = 1) represents an ideal fit of the experimental data to eq 6.

drawing substituents do not retard rates of aziridination and, in fact, are slightly accelerating as seen in the 1.15:1 reactivity ratio of p-nitrostyrene:styrene. Overall, the relative rates of aziridination are much less sensitive to substituent effects than are catalytic cyclopropanations employing **1**. Similarly, Evans, Faul, and Bilodeau have noted relatively little rate difference between aziridination of p-nitrostyrene and styrene employing $CuClO_4$/PhI=NTs in CH_2Cl_2.[3a]

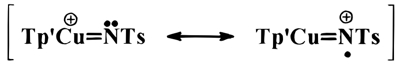
Jacobsen[4a] has established that enantioselectivities observed in the catalytic aziridinations employing chiral diimine ligands are independent of aryl substituents on ArI=NTs precursors and that these selectivities match those obtained using $TsN_3/h\nu$ as the nitrene source. These results argue for a discrete copper nitrene intermediate in which ArI is fully dissociated from the active species. A copper(III)−nitrene species, L*Cu=NTs$^+$ (L* = chiral diimine ligand), has been proposed.[4a]

Evans has suggested that Cu(II) is the catalytically active oxidation state in nitrene transfer employing PhI=NTs.[3a] He has shown that PhI=NTs oxidizes Cu(I)OTf/bis(oxazoline) to a Cu(II) complex and that, beginning with either Cu(I)OTf of Cu(II)$(OTf)_2$ salts as precursors, identical relative reactivities toward various pairs of olefins were observed. In the transfers reported here, treatment of **1** in CH_2Cl_2 with PhI=NTs resulted in immediate formation of a green solution; UV−vis spectral analysis of the solution (λ_{max} = 350 nm) was consistent with the formation of Cu(II). Furthermore, no characterizable Cu(I) species can be isolated following the catalytic aziridination reactions. These results are consistent with those of Evans and suggest that Cu(II) is the catalytically competent oxidation state in the aziridination reactions.

Attempts to quantitatively fit the relative reactivity data in Table 2 to any set of Hammett-type σ scales have been unsuccessful. Since the complex responsible for nitrene transfer likely involves a paramagnetic Cu(II) species, we have attempted to fit the data using a radical-based $\sigma^\bullet$ scale.[11] Since radical reactions often have a polar character, quantitative analysis of substituent effects on most such reactions usually involve a two-parameter fit employing Hammett-type σ parameters together with $\sigma^\bullet$ parameters. A moderate fit of the data in Table 2 can be obtained employing Jackson's $\sigma^\bullet$ substituent constants[11a] and Hammett σ^+ constants in eq 6. The best fit is obtained for $\rho^\bullet = +0.34$ and $\rho^+ =$

$$\log(k_X/k_H) = \rho^\bullet\sigma^\bullet + \rho^+\sigma^+ \tag{6}$$

-0.28. Column 2 in Table 2 shows the predicted ratios calculated using these values of $\rho^\bullet$ and ρ^+. The fit is graphically illustrated in Figure 2. The negative value of ρ^+ suggests that the intermediate species which attacks styrene possesses some electrophilic character. A reasonable proposal for this intermediate is a paramagnetic copper nitrene species, **6**, which behaves as an electrophilic, nitrogen-centered radical.[12]



$$\left[\mathrm{Tp'}\overset{\oplus}{\mathrm{Cu}}{=}\ddot{\mathrm{N}}\mathrm{Ts} \longleftrightarrow \mathrm{Tp'Cu}{=}\overset{\oplus}{\underset{\bullet}{\mathrm{N}}}\mathrm{Ts}\right]$$

6

Experimental Section

General Methods. All preparations and manipulations were carried out under an oxygen-free nitrogen atmosphere using conventional Schlenk techniques. Solvents were dried and degassed before use. The *para*-substituted styrenes were purchased from Aldrich and Pfaltz and Bauer and were employed without further purification. The complex Tp′Cu(C_2H_4) (**1**) and the nitrene precursor PhI=NTs were prepared according to literature methods.[6,13]

Cyclopropanation Competition Experiments. Complex **1** Tp′Cu(C_2H_4) (20 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 the corresponding *para*-substituted styrene was added to the stirred colorless solution. Ethyl diazoacetate (0.57 g, 5 mmol) was dissolved in 20 mL of 1,2-dichloroethane

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(11) (a) Dinçtürk, S.; Jackson, R. A. *J. Chem. Soc., Perkin Trans. II* **1981**, 1127. (b) Jiang, X.-K.; Ji, G.-Z. *J. Org. Chem.* **1992**, *57*, 6051. (c) Fischer, T. H.; Meierhoefer, A. W. *J. Org. Chem.* **1978**, *43*, 224.

(12) As a reviewer has noted, the results by Evans *et al.*[3a] concerning the aziridination of 1-phenyl-2-vinylcyclopropane using $CuClO_4$ in CH_3CN provided no evidence for a radical intermediate and suggested a concerted mechanism, while Jacobsen's experiments on aziridination of *cis*-β-methylstyrene using a copper complex of a chiral diimine support a stepwise pathway.[4b] Thus, the mechanism of aziridination may be system dependent. We have no evidence concerning a concerted or stepwise pathway in the Tp′-based catalyst examined here. However, we note that the nature of the copper ligands in a species such as **6** will affect the charge distribution and spin densities and thus could influence the timing of the two C−N bond-forming steps.

(13) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361.

and slowly added to the above solution over 18 h with a syringe pump. When the addition was completed, the volatiles were removed under vacuum and the oily residue was investigated by ^{1}H NMR spectroscopy. The ratio of the products was as follows (NMR integration, average of at least two runs): *p*-OMe/H = 2.0; *p*-Cl/H = 0.80; *p*-CF_3/H = 0.46; *p*-NO_2/H = 0.22. These ratios were obtained by integrating the methylene ester and/or methyl ester proton resonances. Previously, each cyclopropane was independently prepared and their NMR spectral data compared with the values reported in the literature.[9] The observed *cis:trans* ratios were 45:55 for styrene, 50:50 for *p*-CF_3−styrene, and 42:58 for *p*-OMe−styrene. For the Cl and NO_2 derivatives, this ratio was not calculated due to the overlap of resonances, although they were not far from 50:50.

Aziridination Competition Experiments. Complex **1** Tp′Cu(C_2H_4) (20 mg, 0.05 mmol) was dissolved in 60 mL of rigorously dried methylene chloride, and 60 equiv (3 mmol) of an equimolar mixture of styrene and the corresponding *para*-substituted styrene was added to the stirred colorless solution. Upon addition of 0.185 g (0.5 mmol) of PhI═NTs, the resulting solution immediately acquired a light green color, and gradually the nitrene precursor dissolved. When no more solid PhI═NTs remained, the reaction mixture was passed through a plug of silica gel (1.5 cm thick; 1 cm diameter) and then taken to dryness. The residue was dissolved in $CDCl_3$ and was investigated by ^{1}H NMR spectroscopy.[4a] The ratio of the products was as follows (NMR integration, average of at least two runs): *p*-OMe/H = 2.43; *p*-Me/H = 2.13; *p*-Ph/H = 1.36; *p*-Cl/H = 1.21; *p*-CF_3/H = 1.02; *p*-NO_2/H = 1.15. Each aziridine was previously prepared, and their NMR spectra were compared with those reported previously in the literature. For the integrals, the resonances of the >C*H*−C_6H_4X and/or the methylene proton that resonate around 3.7 and 3.0 ppm, respectively, were employed.

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