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The Effect of Catalyst Loading in Copper-Catalyzed Cyclohexane Functionalization by Carbene Insertion

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A study of the variables that affect the insertion of the $:CHCO_2Et$ group (formed from ethyl diazocetate, EDA) into the C–H bonds of cyclohexane in the presence of a Tp^xCu complex as the catalyst (Tp^x = trispyrazolylborate ligand) has demonstrated an anomalous effect of the catalyst loading. The use of low concentrations of catalyst produces an increase in the yield of the C–H activation product ethyl cyclohexaneacetate. This effect has also been found in the case of other less elaborated catalysts such as $[Bp^{Br3}Cu]$ or $[(bipy)_2Cu][I]$.
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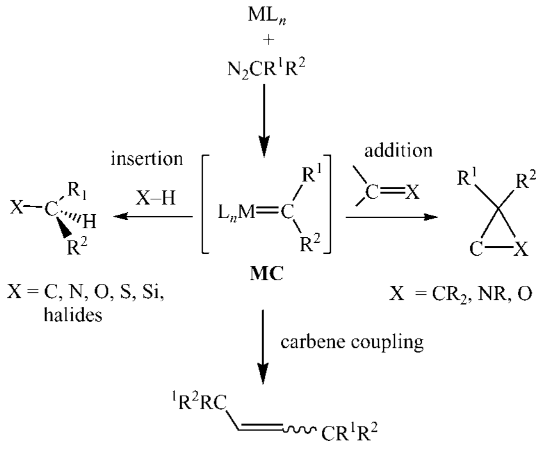
Introduction

Diazo reagents have been employed extensively as a carbene source, initially under thermal or photochemical conditions and in the last decades with the aid of transition-metal complexes as catalysts for several transformations[1] for the transfer of the carbene unit to many saturated and unsaturated substrates (Scheme 1). Besides the desired addition or insertion products, the undesired carbene coupling side-reaction has usually been observed in the vast majority of reported systems.



Scheme 1. Transition-metal-catalyzed carbene transfer from diazo compounds.

It is well established that the transformations depicted in Scheme 1 take place through the intermediacy of a metallocarbene species $L_nM{=}CR^1R^2$, which is generated from the direct reaction of the catalyst ML_n and the diazo compound,[1] and that this constitutes the rate-determining step of the overall process.[2,3] The transient metallocarbenoid species (MC) usually displays an electrophilic behavior,[4] which explains its reactivity towards the nucleophiles available in solution – the diazo compound or the target substrate to be functionalized. Due to its high reactivity, there are few reports in the literature in which these intermediates have been detected or isolated. In the case of copper, the first observation of one of these species under catalytic conditions is due to Straub and Hofmann.[5] Later, Warren and Dai described the preparation and structural characterization of the copper carbene complex $[(N\text{–}N)Cu{=}CPh_2]$ from the reaction of a diketiminatocopper(I) complex and Ph_2CN_2.[6]

In recent years we have described the potential of a family of complexes of general formula $[Tp^xCu(NCMe)]$ (Tp^x = homoscorpionate ligand) toward the two processes mentioned above: the addition of $:CHCO_2Et$ from ethyl diazoacetate (EDA) to multiple carbon–carbon bonds (alkenes,[7] alkynes,[8] aromatics[9]) or its insertion into single X–H bonds (alkanes,[10] amines,[11] alcohols[12]). All these transformations are accompanied by the copper-catalyzed carbene coupling reaction, which leads to the formation of diethyl fumarate and maleate in variable yields [Equation (1)]. In this contribution, we present the results obtained during the course of our investigations focused on the study of the variables that could affect the formation of these undesired by-products with the aim of its decrease or suppression. We

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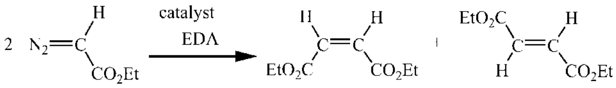
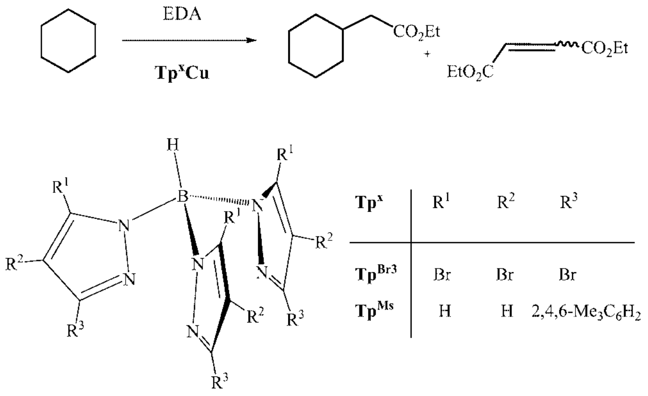
have found an unexpected effect of the catalyst loading that affects the chemoselectivity of these transformations not only in the case of the [Tp^{x}Cu(NCMe)] catalysts but also with other less elaborated catalysts. This knowledge has allowed the enhancement of the yields of the desired products.



(1)

Results and Discussion

We have previously reported[10] that the complexes [Tp^{Br3}Cu(NCMe)] (**1**) and [Tp^{Ms}Cu] (**2**) catalyze the insertion of EDA into the C–H bonds of cyclohexane (Scheme 2), leading to the formation of ethyl cyclohexaneacetate as well as diethyl fumarate (DEF) and maleate (DEM). Under the same conditions (1:20:2000 for [catalyst]:[EDA]:[C_6H_{12}], 0.05 mmol of catalyst) **1** and **2** gave 90 and 54% yield of ethyl cyclohexaneacetate, respectively, with DEF and DEM accounting for the remaining EDA. In order to diminish such amounts of non-desired products, we studied the effect of the following variables that could affect the chemoselectivity induced by a given catalyst: (a) the addition rate of EDA, (b) the concentration of EDA, and (c) the catalyst loading.



Tp^x	R^1	R^2	R^3
Tp^{Br3}	Br	Br	Br
Tp^{Ms}	H	H	2,4,6-$Me_3C_6H_2$

Scheme 2. [Tp^{x}Cu]-catalyzed cyclohexane functionalization by EDA insertion.

Effect of EDA Concentration and Addition Time

The traditional experimental methodology in metal-catalyzed diazo compound decomposition usually employs a large excess of substrate with respect to the diazo compound, as well as slow addition devices to add the latter to the solution containing the catalyst and the substrate.[1,13] With this experimental design, the [diazo compound]/[catalyst] ratio in the reaction mixture can be maintained at low values, thereby minimizing the formation of DEF and DEM. To verify this common behavior, we have run a series of five experiments for the reaction of cyclohexane and EDA in the presence of **1** or **2** in which only the time employed for the addition of EDA was varied. Figure 1 (left) shows the conversion into ethyl cyclohexaneacetate obtained at the end of each experiment (determined from the NMR spectra of the crude reaction mixture). Those carried out at t = 0 h were performed by adding the diazo compound in one portion, whereas the others were run with the aid of a syringe pump programmed to add the EDA (1 mmol dissolved in 10 mL of cyclohexane) over 1, 3, 6 and 12 h. An increase in the yields of the desired product was observed upon lengthening the addition time, although for the Tp^{Ms}-containing catalyst this increase was not as high as with the Tp^{Br3} catalyst. The use of the latter in a series of experiments in which only the concentration of EDA in the feed solution was varied gave the results shown on the right-hand side in Figure 1: the lower the value of [EDA], the higher the yield of the desired product. Overall, both sets of experiments are in agreement with the mentioned effect of the [EDA]:[catalyst] ratio in the reaction mixture: a low value of this ratio enhances the yield of the desired product and decreases the yields of DEF and DEM.

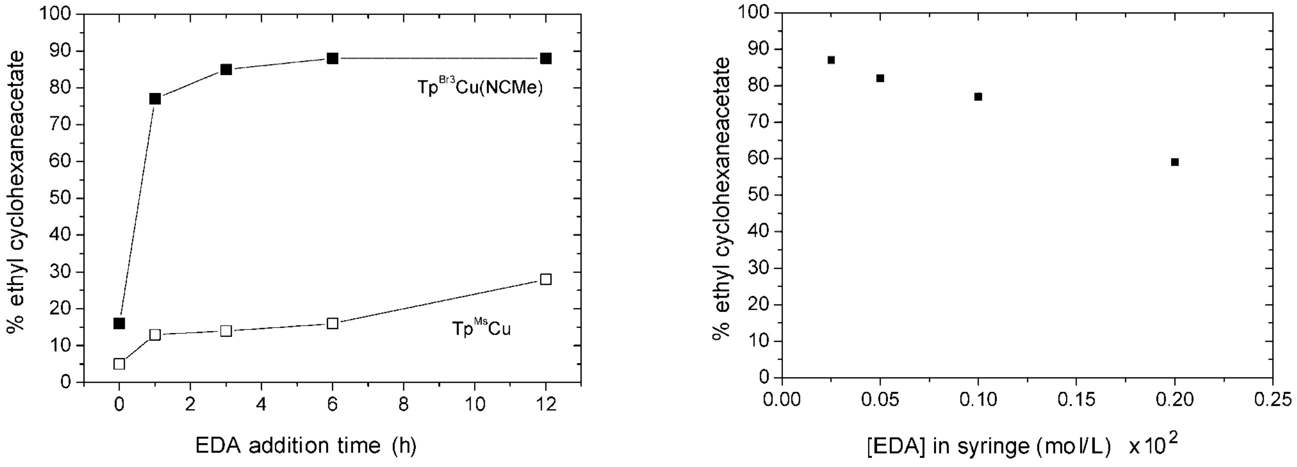


Figure 1. Variation of the yield of ethyl cyclohexaneacetate with EDA addition time (left) and the EDA concentration added from the syringe pump {[Tp^{Br3}Cu(NCMe)] as the catalyst}.

Effect of the Catalyst Loading

Another approach to ensure the above conditions, i.e., a low [EDA]:[catalyst] ratio is to employ a higher catalyst loading at a fixed EDA concentration and addition time (6 h). Surprisingly, when we employed a fivefold amount of the catalyst (0.25 mmol instead of the 0.05 mmol in the previous experiments), we did not observe any increase in the yields of ethyl cyclohexaneacetate *but the opposite effect*. As shown in Figure 2, a certain decrease occurred with **1** (from 88 to 70%) as the catalyst, whereas no response to this variable was obtained from the experiment with **2** and the same catalyst loading (ca. 16% in both cases). We then explored the use of different catalyst loadings in the range 0.002 to 0.25 mmol, with the results displayed in Figure 2. An unexpected increase in the degree of conversion of cyclohexane and EDA into ethyl cyclohexaneacetate took place when the catalyst concentration was decreased in both cases. No EDA was detected by GC shortly after the addition was completed, which is an indication of the ease with which catalysts **1** and **2** consume the diazo compound. The main yield enhancement in the case of the $Tp^{Ms}Cu$ catalyst appeared on going from 0.01 to 0.002 mmol as the catalyst loading, which corresponds to an increase of nearly 45% (from 25 to 70%). This is a completely unexpected behavior since such an increase takes place in the direction in which the [EDA]:[catalyst] also increases, which is exactly the contrary to that found above when EDA addition time or EDA concentration were studied. It is also worth mentioning that this anomalous effect is not observed with styrene as the substrate. In this case, a similar study was carried out but no effect of the catalyst loading was observed. This is in good agreement with the fact that styrene is much more reactive than a cyclohexane C–H bond, and there is no real competition between cyclopropanation and the EDA decomposition toward diethyl fumarate and maleate.

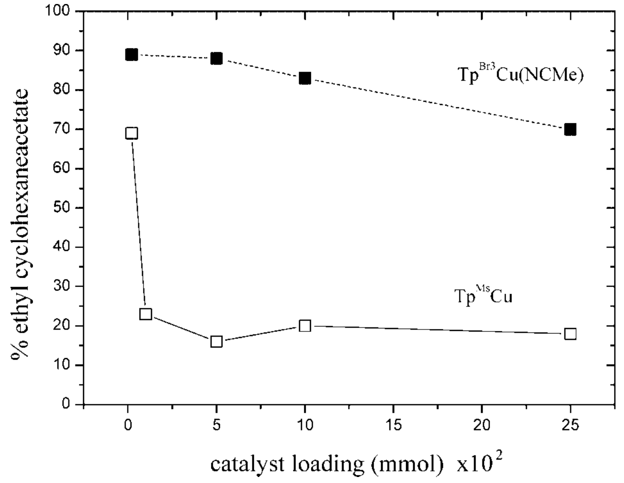


Figure 2. Effect of the catalyst loading on the yields in ethyl cyclohexaneacetate.

Scope of this Methodology

We have not been able to find a reasonable explanation for this behavior[14] as our experimental methodology, which is based on the use of slow addition devices for EDA, prevents us from carrying out reliable kinetic studies. However, the importance of the discovery of the effect of the catalyst loading in this transformation, which gives a noticeable enhancement in the yields simply by decreasing the amount of catalyst, should be pointed out. At this point, we wondered about the extension of this proposal to other copper-based catalysts. The number of catalytic systems based on copper for the intermolecular insertion of diazo compounds into C–H bonds is very limited,[15] the highest conversions thus far being obtained with our Tp^xCu system.[10] In contrast, there are more examples for the intramolecular version, including chiral catalysts that have led to moderate to high degrees of enantioselectivity.[16] The ligands bound to the copper center in these cases were preferentially bis-oxazolines and bis-imines, i.e., ligands with two nitrogen donor atoms. However, there are no reports of the use of these catalysts for the intermolecular, asymmetric insertion of diazo compounds into C–H bonds. In the search for model complexes for the above chiral systems, we decided to study the catalytic properties of the complex $[Bp^{Br3}Cu]$ (**4**), which is similar to the $[Bp^xCu]$ complexes already reported by other authors.[17] Table 1 shows the results obtained for the reaction of EDA and cyclohexane in the presence of **4**. In one-portion addition reactions, only an 8% yield of ethyl cyclohexaneacetate was observed with a 0.05 mmol catalyst loading. This yield was improved up to 13% when performing the slow addition of EDA over 3 h (entry 2). Although modest, it is worth pointing out that these data compare well with those shown in Figure 1 for **2** as the catalyst under the same conditions. Following the strategy learnt from the previous sections, we used a lower catalyst loading (0.002 mmol) of **4** and observed the desired effect: the yields were enhanced up to 36 and 49% with EDA addition times of 4 and 17 h, respectively. We find these results quite remarkable in two ways: first, they demonstrate the catalytic capability of a copper complex with a bidentate, not tridentate, Bp^x ligand, with yields similar to those obtained with **2**, and secondly, they demonstrate that the steric protection assumed for the Tp^xCu system seems not to be as crucial as initially supposed, and that other factors, such as the electron-withdrawing nature of the ligand and catalyst loading, could be very important at this point.

Complex **4** could be a good model for anionic chiral ligands (semicorrines, some bisoxazolines), but many others, including those referred to above, are neutral in nature. In order to check the validity of our proposal, we ran a few experiments using $[(bipy)_2Cu][I]$ (**5**) as the catalyst for the insertion of EDA into the C–H bonds of cyclohexane. We anticipated a very low catalytic activity for this complex in this reaction since (a) no electron-withdrawing groups are bonded to the metal center and (b) it appears to be coordinatively and electronically saturated. However, previous studies with this complex for the cyclopropanation of styrene have shown that bipy de-coordination takes place easily.[3a] Under our standard conditions (0.05 mmol of **5**, 1 mmol of EDA, one portion addition of the diazo ester),

Bp^{Br3}

$R^1 = R^2 = R^3 = Br$

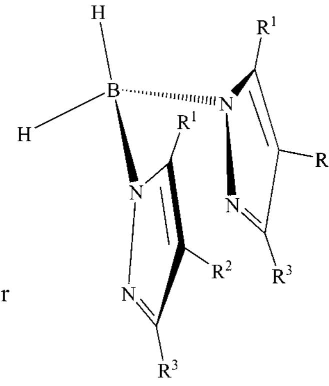


Table 1. Use of [Bp^{Br3}Cu] (**4**) and [$(bipy)_2$Cu][I] (**5**) as catalysts for the reaction of ethyl diazoacetate and cyclohexane.[a]

Catalyst loading [mmol]	EDA addition time [h]	[Bp^{Br3}Cu][b]	[$(bipy)_2$Cu][I][b]
0.05	one portion	8	nd
0.05	3	13	–
0.002	4	36	10
0.002	12	–	18
0.002	17	49	–

[a] See Experimental Section. [b] Yields calculated by NMR spectroscopy, with DEF and DEM formation accounting for 100% of EDA.

no ethyl cyclohexaneacetate was observed, with only DEF and DEM being detected at the end of the reaction. This could be enough to discard **5** (or any other complex) as a potential catalyst. However, based on our proposal, we ran two experiments with a lower catalyst loading and, with the aid of a syringe pump, with a total addition time of 4 and 12 h, the yields of the desired product increased up to 10 and 18%, respectively. Again, these results indicate that, even for very low activity and non-elaborated catalysts, the catalyst loading affects the chemoselectivity of the reaction.

Conclusions

We have discovered that the formation of diethyl fumarate and maleate in the presence of [Tp^xCu] is influenced by the catalyst loading in the opposite sense that would normally be expected. The use of very low concentrations of the [Tp^xCu] catalysts causes a decrease in the formation of DEF and DEM and a concomitant increase in the yields of the desired C–H-functionalized product. These findings have been extended to copper complexes with bidentate ligands as models for other already known catalysts. We believe that these results could be extended to many already known systems for the copper-catalyzed carbene transfer from diazo compounds, thereby opening up a new perspective in the copper-catalyzed insertion of diazo compounds into C–H bonds.

Experimental Section

General: ^{1}H NMR spectra were run at 400 MHz and ^{13}C NMR at 100 MHz, with $CDCl_3$ as solvent. Mass spectra were recorded with a Varian Saturn 2100T. GC analysis was performed with a Varian CP-3800. Solvents were dried and degassed before use. All reagents were purchased from Aldrich and employed without any further purification. The synthesis of the copper catalysts[7–10] was carried out as reported previously.

General Catalytic Experiment: [Tp^xCu] (0.05 mmol) was dissolved in a mixture of CH_2Cl_2 (10 mL) and cyclohexane (10 mL). A solution of EDA (1 mmol) in cyclohexane (10 mL) was slowly added during the programmed time with the aid of a syringe pump, at room temperature. No EDA was detected at the end of the reaction by GC, only ethyl cyclohexaneacetate and diethyl fumarate and maleate. Other experiments were performed by adding the pure diazo compound in one portion. For those experiments carried out without cyclohexane, dichloromethane were employed as the sole solvent.

The reported yields correspond to an average of at least of two runs, and were determined in the following manner. After removal of volatiles, the crude product was investigated by ^{1}H NMR spectroscopy, with a standard compound being added (tosyl chloride or styrene) to ensure that all the initial EDA was converted in the observed products. The observed ratios were compared to those from GC analysis in order to establish the response factors, which were later employed in the subsequent experiments to determine the yields. The products were identified by comparison with commercial samples (ethyl cyclohexaneacetate, diethyl fumarate and maleate) or with data already reported.

Acknowledgments

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[13] In some cases the diazo compound has been added in one portion at the beginning of the reaction. See, for example, ref.[7]

[14] The experimental data available have not been fitted into a mechanistic proposal that accounts for all them. A referee has noted that radical species could perhaps be involved in this transformation. A previous study concerning the use of [Tp*Cu] as the catalyst for carbene and nitrene transfer has shown that radicals could be responsible for the transfer only in the latter case. See: M. M. Díaz-Requejo, P. J. Pérez, M. Brookhart, J. L. Templeton, *Organometallics* **1997**, *16*, 4399–4402.

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