

# The $Tp^xM$ core in $C_{sp^3}\text{-H}$ bond functionalization reactions: comparing carbene, nitrene and oxo insertion processes ( $Tp^x$ = scorpionate ligand; $M = Cu, Ag$ )

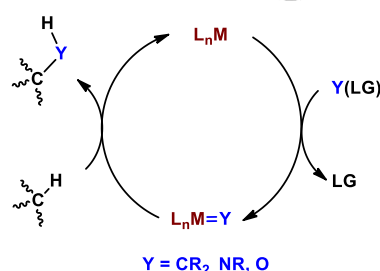
M. Mar Díaz-Requejo,<sup>\*,[a]</sup> Pedro J. Pérez<sup>\*,[a]</sup>

Dedication ((optional))

**Abstract:** A comparison between three  $Tp^xM$ -catalyzed ( $Tp^x$  = scorpionate ligand;  $M = Cu, Ag$ ) reactions leading to the functionalization of non-activated, alkane  $C_{sp^3}\text{-H}$  bonds by carbene, nitrene or oxo insertion is presented. Analogies and differences in these transformations are discussed, including main reactive intermediates, selectivity trends and mechanistic interpretations.

## 1. Introduction

The catalytic functionalization of alkanes yet constitutes an area of tremendous interest due to the lack of efficient procedures, in terms of conversions and selectivities.<sup>[1]</sup> Protocols involving organometallic intermediates frequently require harsh conditions because of the stability of metal-carbon bonds formed during the transformations.<sup>[2]</sup> Alternatively, the strategy of installation of directing groups has emerged in the last years,<sup>[3]</sup> with the drawback of augmenting the synthetic routes and decreasing the atomic selectivity, not to mention that this tactic is far of being useful for alkane  $C_nH_{2n+2}$ , losing the advantage of using such molecules as raw materials. In contrast, catalytic methodologies where the C-H bond interacts with a ligand, particularly those connected to the metal by a multiple bond (Scheme 1), have found application in this area. Thus, the reaction of the appropriate transition metal complex  $L_nM$  with  $Y(LG)$  ( $LG$  = leaving group) leads to the formation of intermediates of type  $L_nM=Y$ , usually electrophilic in nature, which may react with the



**Scheme 1.** Catalytic functionalization of carbon-hydrogen bonds by ligands, avoiding metal-C-H interactions.

nucleophilic C-H bond to give the functionalized product before the cycle is re-started.<sup>[4]</sup> In this context, the most employed X groups are carbene ( $CR_2$ ), nitrene (NR) and oxo (O), generated from diazocompounds, hypervalent iodine reagents of hydrogen peroxide or alkylperoxides, respectively.

Our group has been involved in this area of work for the last two decades, developing group 11 metal-based catalysts for the transfer of the units shown in Scheme 1 to hydrocarbons, with special emphasis to the very low reactive alkanes.<sup>[5]</sup> Along these years, the preferred ancillary ligands employed have been hydrotrispyrazolylborates ( $Tp^x$ ),<sup>[6]</sup> which offer the possibility of modulating electronic and steric properties at the metal center to control the catalytic activity toward the desired target. In this contribution we provide for the first time a direct comparison of these three transformations, i.e. the carbene, nitrene and oxo transfer and insertion into alkane C-H bonds, including catalytic activities, selectivities, intermediates and mechanistic interpretations.

M. Mar Díaz Requejo is Professor of Inorganic Chemistry at Universidad de Huelva, Spain. Her research interests focus on the development of coinage metal catalysts for carbene-, nitrene- and oxo transfer to saturated or unsaturated substrates forming new C-C and C-heteroatom bonds. She has been awarded by the Royal Society of Chemistry of Spain with the Young Researcher Award (2005) and the Lilly Research Award (2008).



Pedro J. Pérez (FRSC) is Professor of Inorganic Chemistry at Universidad de Huelva, Spain. His work is mainly devoted to the development of late transition-metal complexes as catalysts for transformations involving saturated and unsaturated hydrocarbons. He is the founder of the Center for Research in Sustainable Chemistry (CIQSO) at Universidad de Huelva, where he is Leader of the Homogeneous Catalysis Laboratory. He has been recognized by the Royal Society of Chemistry of Spain with the Research Prize and Gold Medal (2016) and the Inorganic Chemistry Award (2007). The Royal Society of Chemistry awarded him with the 2015 Homogeneous Catalysis Award. He is member of the Academia Europaea (2018) and the Royal Academy of Sciences of Spain (2014).

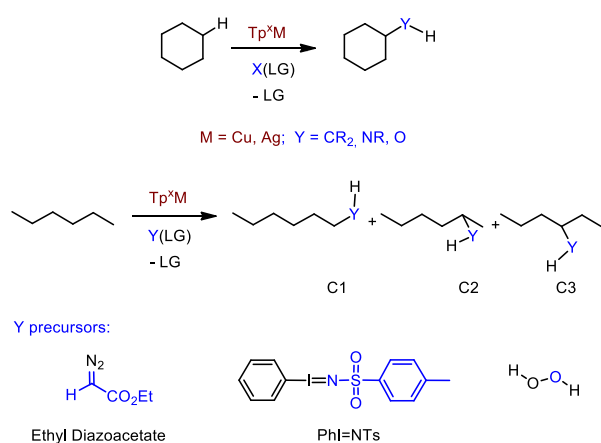


[a] Prof. Dr. M. M. Díaz-Requejo, Prof. Dr. P. J. Pérez  
Laboratorio de Catálisis Homogénea, Unidad Asociada al CSIC, CIQSO-Centro de Investigación en Química Sostenible and Departamento de Química, Universidad de Huelva, Campus de El Carmen 21007 Huelva, Spain.  
E-mail: perez@dqcm.uhu.es, mmdiaz@dqcm.uhu.es

## 2. The model reactions and their selectivities

Two substrates have been chosen as models for comparative purposes, cyclohexane and n-hexane, both being catalytically functionalized with copper or silver catalysts bearing hydrotrispyrazolylborate ligands. Scheme 2 shows the transformations in which the hydrocarbons are converted into esters,<sup>[7]</sup> amines<sup>[8]</sup> or alcohols<sup>[9]</sup> (and ketones due to overoxidation). These experiments are usually carried out using the hydrocarbon as the solvent. Cyclohexane leads to one product for each reaction whereas the existence of three different C-H bonds in n-hexane may originate mixtures of products derived from the insertion into the available reaction sites. As discussed below, the election of the  $\text{Tp}^x$  ligand and the metal (Cu or Ag) become crucial for the reaction outcome in these transformations.

Scheme 2 shows the precursors for the carbene, nitrene or oxo moieties to be inserted in the C-H bonds. The source for the carbene group  $\text{CR}_2$  is a diazo compound  $\text{N}_2=\text{CR}_2$ , with  $\text{N}_2$  being



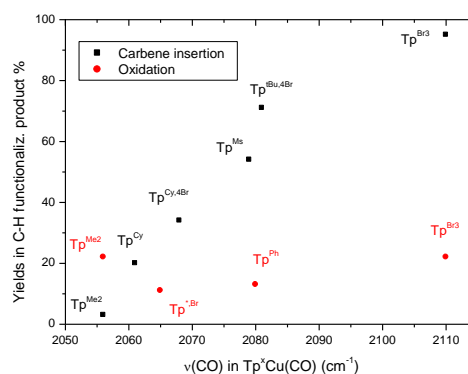
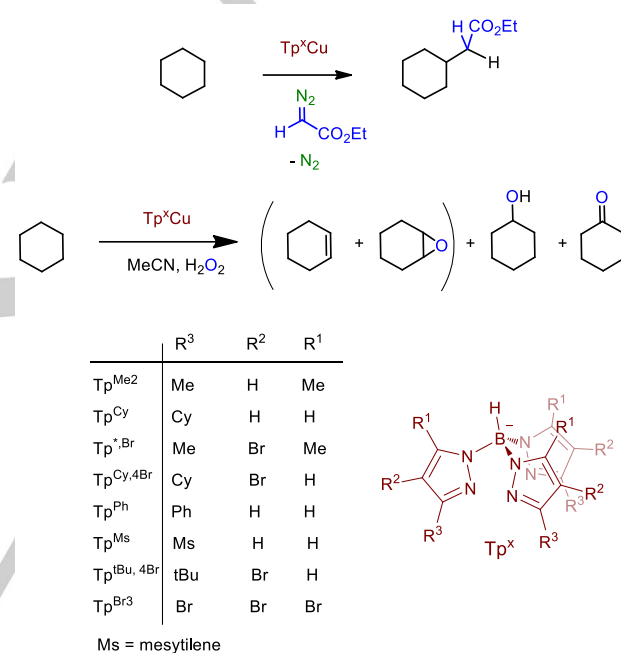
**Scheme 2.** Cyclohexane and n-hexane as model substrates for the comparison of carbene, nitrene and oxo transfer into C-H bonds using  $\text{Tp}^x\text{M}$  cores as catalysts ( $M = \text{Cu, Ag}$ ).

evolved when interacting with the metal center en route to the metalcarbene intermediate. The nitrene analogue is formed in situ from hypervalent iodine compound  $\text{PhI}=\text{NTs}$ , albeit chloramine-T ( $\text{NaClNTs}$ ) can also be employed. Finally, the oxo transfer chemistry induced by the  $\text{Tp}^x\text{Cu}$  core employs hydrogen peroxide as the oxo source. It is worth mentioning that no metal-C-H bond interaction takes place in this class of functionalization reactions, the C-H bond interacting with the coordinated Y fragment. Because of this, the general trend of reactivity  $1^{\text{ry}} \text{C-H} < 2^{\text{ry}} \text{C-H} < 3^{\text{ry}} \text{C-H}$  is commonly observed.

### 2.1 Catalyst effect in reaction yields.

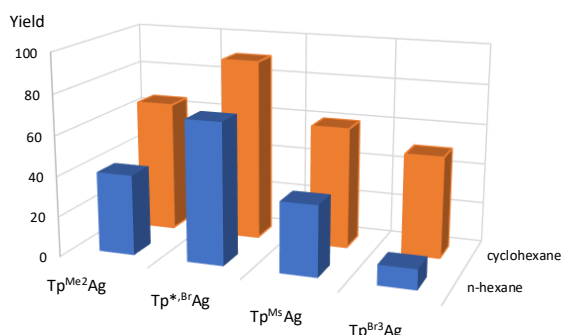
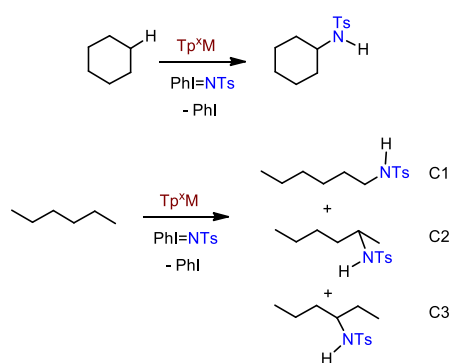
The  $\text{Tp}^x\text{M}$  core has been employed as catalyst for the transformations shown in Scheme 2. Given the large number of different trispyrazolylborate ligands,<sup>[6]</sup> it is not obvious at the first sight to make an election of the appropriate one, in view of the array of different R groups that can be attached to the pyrazolyl rings. The presence of electron-donating or electron-withdrawing

groups affects the three N-donor capabilities whereas the size of the  $\text{R}^3$  group greatly defines the volume available around the metal center. Thus, depending of the nature of the transformation, electronic and/or steric effects play a distinct role in the reaction outcome. In the context of reaction yields into functionalized products we have found interesting differences for the three reactions. With cyclohexane as the substrate, a comparison between the carbene and oxo insertion reaction is shown in Scheme 3. When a series of copper complexes bearing the  $\text{Tp}^x$  ligand were used as the catalyst for the reaction of ethyl diazoacetate (EDA) and cyclohexane, a correlation between the yield into the functionalized product and the  $\nu(\text{CO})$  value of the corresponding  $\text{Tp}^x\text{Cu}(\text{CO})$  complexes was observed: the higher the latter, the more productive the catalytic reaction. This is explained as a consequence of the need of electrophilic metal centers to both form the metal-carbene



**Scheme 3.** The effect of the  $\text{Tp}^x$  ligand in the functionalization of cyclohexane by carbene and oxo transfer reactions.

intermediate and enhance its interaction with the C-H bond. On the other hand, the oxidation reaction of cyclohexane with  $\text{H}_2\text{O}_2$  was also reported with several  $\text{Tp}^x\text{Cu}$  complexes (Scheme 3),<sup>[9]</sup> albeit in this case the overall reaction yield was maintained within the 10–22 % yield (cyclohexane-based) despite the significant differences in electronic and steric properties of the  $\text{Tp}^x$  ligand. Thus,  $\text{Tp}^{\text{Br}3}$  and  $\text{Tp}^{\text{Me}2}$  display similar steric hindrance around copper,<sup>[10]</sup> but a large difference in the electronic effect onto the metal center (ca 51  $\text{cm}^{-1}$  difference in the  $\nu(\text{CO})$  bands of their CO adducts).<sup>[11]</sup> Additionally, the bulkier  $\text{Tp}^{\text{Ph}}$  does not show significant change in catalytic activity when compared with the parent  $\text{Tp}^{\text{Me}2}$ -containing catalyst. These pieces of information support the existence of substantial differences between the carbene and oxo transfer reactions mediated by the same family



**Scheme 4.** Overall yields (%) for amination of cyclohexane and hexane by  $\text{Tp}^x\text{Ag}$  core.

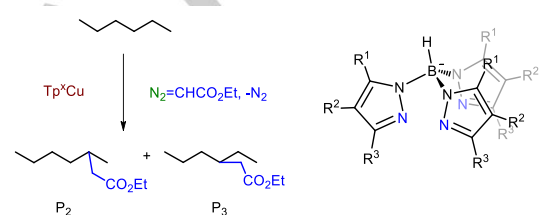
of catalysts.

The nitrene insertion into C-H bonds is better illustrated with silver complexes bearing  $\text{Tp}^x$  ligands as catalysts to achieve significant conversions,<sup>[8a]</sup> since copper analogues were not active enough. The reaction of cyclohexane or n-hexane with  $\text{PhI}=\text{NTs}$  leads to the insertion of the  $\text{NTs}$  moiety into available C-H bonds. Scheme 4 shows yields obtained with both alkanes, showing a similar pattern: the highest values are obtained with  $\text{Tp}^{*,\text{Br}}\text{Ag}$ . The use of  $\text{Tp}^{\text{Ms}}$  or  $\text{Tp}^{\text{Br}3}$  seems to affect negatively the reaction outcome: both are less donating ligands than  $\text{Tp}^{*,\text{Br}}$ . Also the more electron-donating  $\text{Tp}^{\text{Me}2}$ , and sterically similar to  $\text{Tp}^{*,\text{Br}}$  also provides significant yields.

From data presented in this section, it seems that the carbene transfer reaction follows a pattern in which electronic effect appears crucial for catalyst activity. On the other hand, the nitrene and oxo transfer reactions do not show such a clear behavior, leading to the first distinction between these three transformations.

## 2.2 Catalyst effect in regioselectivity.

When more than one reaction site is available at the substrate, catalyst regioselectivity becomes crucial in the reaction outcome. The presence of several distinct C-H bonds in the alkane usually provides a mixture of compounds deriving from the insertion of the carbene, nitrene or oxo moieties. However, it is important to distinguish between the effect of the electronic and steric factors on regioselectivity. To evaluate the latter, it seems

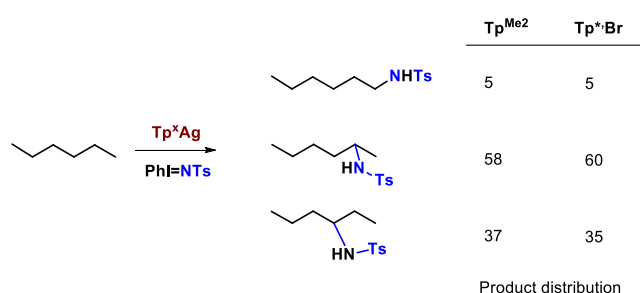


$\text{Tp}^x$	$\text{R}^1$	$\text{R}^2$	$\text{R}^3$	% $\text{P}_2$	% $\text{P}_3$
$\text{Tp}^{\text{Me}2}$	Me	H	Me	75	25
$\text{Tp}^{\text{Br}3}$	Br	Br	Br	76	24
$\text{Tp}^{\text{Ph},4\text{Bn}}$	H	$\text{CH}_2\text{Ph}$	Ph	78	22
$\text{Tp}^{\text{Ph}}$	H	H	Ph	80	20
$\text{Tp}^{\text{Ph},4\text{Pr}}$	H	nPr	Ph	83	17
$\text{Tp}^{\text{Ms}}$	H	H	2,4,6- $\text{Me}_3\text{C}_6\text{H}_3$	86	14

**Scheme 5.** The effect of the catalyst structure in the regioselectivity of the carbene insertion into alkane C-H bond.

appropriate to consider two (or more) C-H bonds of the same type, with similar bond dissociation energies, so regioselection should be mainly influenced by the steric pressure between the C-H bond environment and the  $\text{Tp}^x\text{M}$  core.<sup>[7, 12]</sup> This is the case of the reaction of n-hexane and ethyl diazoacetate in the presence of several  $\text{Tp}^x\text{Cu}$  complexes, as shown in Scheme 5, where only secondary sites are functionalized. The difference in the product distribution is mainly due to the variance in the bulkiness of that  $\text{R}^3$  group: the comparison between  $\text{Tp}^{\text{Ms}}$  and  $\text{Tp}^{\text{Me}2}$  illustrates such difference.

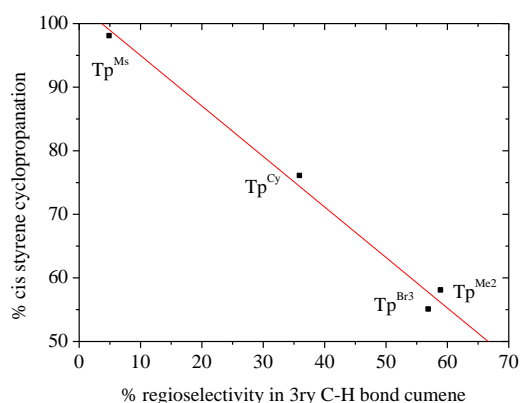
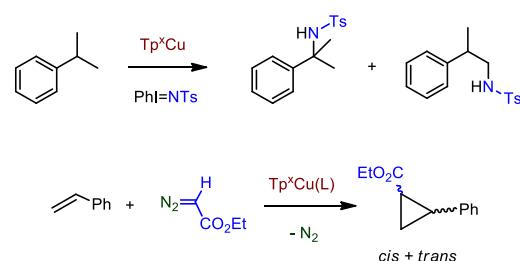
The nitrene transfer to n-hexane shows a comparable behavior. Thus, using the electronically different and sterically similar  $\text{Tp}^{\text{Me}2}\text{Ag}$ - and  $\text{Tp}^{*,\text{Br}}\text{Ag}$ -based catalysts, the product distributions for the insertion into C1, C2 or C3 C-H bonds were quite similar,<sup>[8a]</sup> evidencing the predominant steric effect in this case (Scheme 6).



**Scheme 6.** Amination of n-hexane with silver catalysts.

An interesting correlation between nitrene and carbene transfer reaction can be established when comparing the amination of the tertiary sites of cumene and the cyclopropanation of styrene with ethyl diazoacetate.<sup>[8c]</sup> The use of the bulkier Tp<sup>Ms</sup> ligand provides the highest value of the cis-cyclopropane (98%) but the lowest ratio in tertiary C-H amination. Both findings can be interpreted as the result of the carbene and nitrene transfer reaction occurring near the metal center, which is highly influenced by the steric pressure induced by the Tp<sup>x</sup> ligand.

Besides the above effect of the size, the electronic density at metal is also of interest in these catalytic systems, since it affects in a different manner to the carbene or nitrene transfer. In the former, experimental data available indicates that the decrease of the electron density at the metal originates an increase in the degree of functionalization of the primary sites of



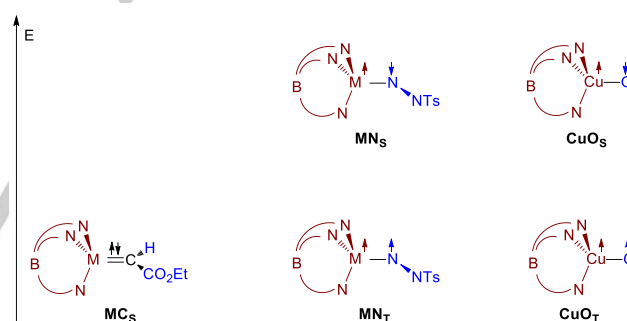
**Scheme 7.** Correlation between carbene and nitrene transfer reaction depending of the Tp<sup>x</sup> ligand.

n-hexane. It is the case of catalysts Tp<sup>Br3</sup>Ag<sup>[7d]</sup> and Tp<sup>(CF<sub>3</sub>)<sub>2</sub>Br</sup>Ag,<sup>[13]</sup> that provide 22% and 36 % of the product derived from the insertion of the CHCO<sub>2</sub>Et group in the methyl group of hexane. The electron densities at the Tp<sup>x</sup>M cores are measured using the carbonyl derivatives of their corresponding  $\nu(\text{CO})$  values (2157 and 2166 cm<sup>-1</sup>, respectively), higher than the corresponding copper partners. However, such effect is not observed in the nitrene case, since the also electronically different Tp<sup>x</sup>Ag and Tp<sup>x</sup>BrAg complexes led to very close regioselectivities (see Scheme 6). This discrepancy between both processes must be related to the existence of different reaction pathways, as will be discussed below.

### 3. The active intermediates Tp<sup>x</sup>M=Y (M = Cu, Ag; Y = carbene, nitrene, oxo)

#### 3.1 Singlet and triplet species intermediates.

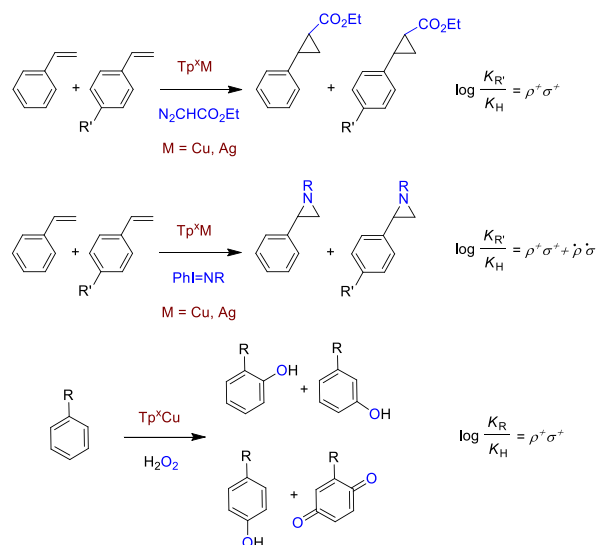
As shown in Scheme 1, the transformations discussed herein are proposed occurring through the intermediates bearing unsaturated metal-ligand bonds, with carbene, nitrene or oxo functionalities. It is well-known that these metal-ligand moieties can present singlet or triplet electronic states. Extensive DFT studies,<sup>[9,14,15,16]</sup> in collaboration with the groups of Maseras, Lledós and Balcells have provided valuable data on this issue.



**Scheme 8.** The intermediate species relevant in the carbene, nitrene and oxo transfer reactions (M = Cu, Ag).

Scheme 8 shows a comparison of the relevant findings, where a clear distinction is made between the carbene reaction, on one side, and the nitrene and oxo reactions, on the other. The interaction of the Tp<sup>x</sup>M (M = Cu, Ag) core with a diazocompound leads to the formation of a Fischer-type metalcarbene (**MC<sub>s</sub>**) with the well-known  $\sigma$  donation-  $\pi$  backdonation bond pattern, a singlet carbene being coordinated to the metal center. The reaction with PhI=NTs or H<sub>2</sub>O<sub>2</sub> leads to metallo-nitrene and -oxo intermediates best defined as a single M-X bond and a significant electron density located at Cu and N or O. The triplet states **MN<sub>t</sub>** and **MO<sub>t</sub>** are significantly more stable (by ca 10 and 33 kcal mol<sup>-1</sup>) than their singlet counterparts (**MN<sub>s</sub>** and **MO<sub>s</sub>**), the reaction with the C-H bond thus starting from the former.

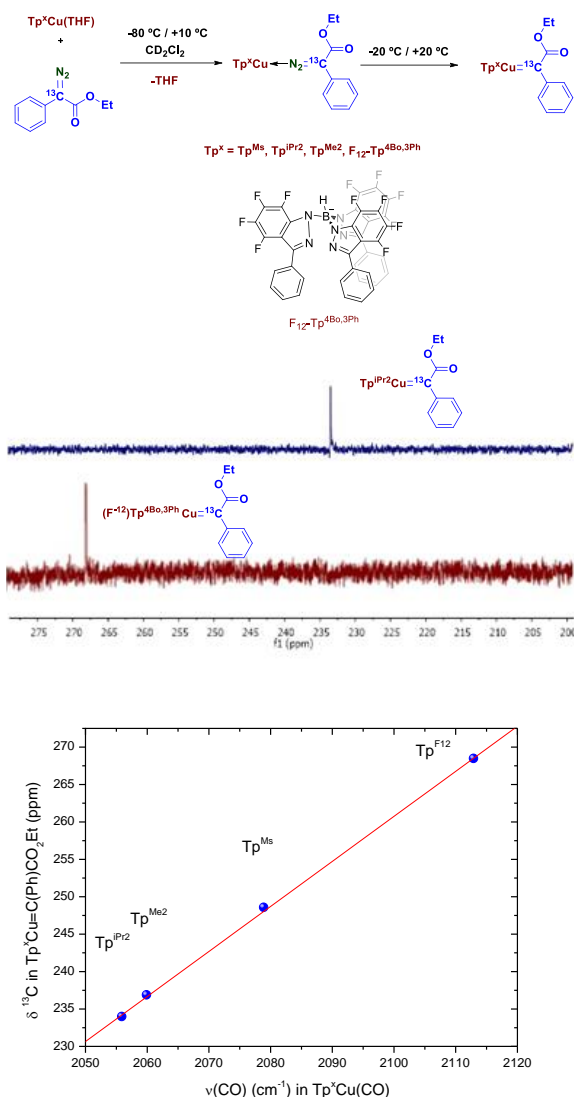
The nature of the  $\text{Tp}^x\text{M}=\text{Y}$  species has been established as electrophilic based on experimental studies carried out on the corresponding transfer of carbene, nitrene or oxo species to substituted styrenes or arenes. Scheme 9 shows the competition experiments and the Hammett equation required for data fitting. In all cases a negative value of  $\rho^+$  was obtained within the range -0.25 to -1.1, evidencing electrophilic nature of the  $\text{Tp}^x\text{M}=\text{Y}$  intermediate. For the nitrene reaction a dual parameter equation involving both polar and radical  $\sigma$  values was required in the context of the olefin aziridination reaction.



**Scheme 9.** Experiments employed to assess the electrophilic nature of the  $\text{Tp}^x\text{Cu}=\text{Y}$  intermediates:  $\rho^+$  values are within the -0.25 and -1.1 range.

### 3.2 Detection of copper-carbene species.

The high catalytic activity of the  $\text{Tp}^x\text{M}$  cores ( $\text{M} = \text{Cu, Ag}$ ) in the transfer of carbene, nitrene or oxo ligands to  $\text{C}_{\text{sp}^3}\text{-H}$  bonds has precluded the isolation or detection of the unsaturated intermediates shown in Scheme 8. However, when the disubstituted diazo reagent  $\text{PhC}(\text{N}_2)\text{CO}_2\text{Et}$  was employed along with the sterically demanding  $\text{Tp}^{\text{Ms}}\text{Cu}$  core, a copper-diazo adduct was isolated and structurally characterized.<sup>[17]</sup> Moreover, NMR studies carried out with  $^{13}\text{C}$ -labelled  $\text{PhC}(\text{N}_2)\text{CO}_2\text{Et}$  showed the conversion of such adduct into the corresponding copper-carbene species for an array of  $\text{Tp}^x\text{Cu}$  complexes (Scheme 10). An interesting correlation between the chemical shift of the carbene ligand in  $\text{Tp}^x\text{Cu}=\text{C}(\text{Ph})\text{CO}_2\text{Et}$  and the  $\nu(\text{CO})$  of the  $\text{Tp}^x\text{Cu}(\text{CO})$  was found, demonstrating that a increasing in the latter is related with less shielded carbene ligand and, consequently, more electrophilic and catalytically active metal centers. Attempts to detect the nitrene or oxo analogs have yet been unsuccessful.



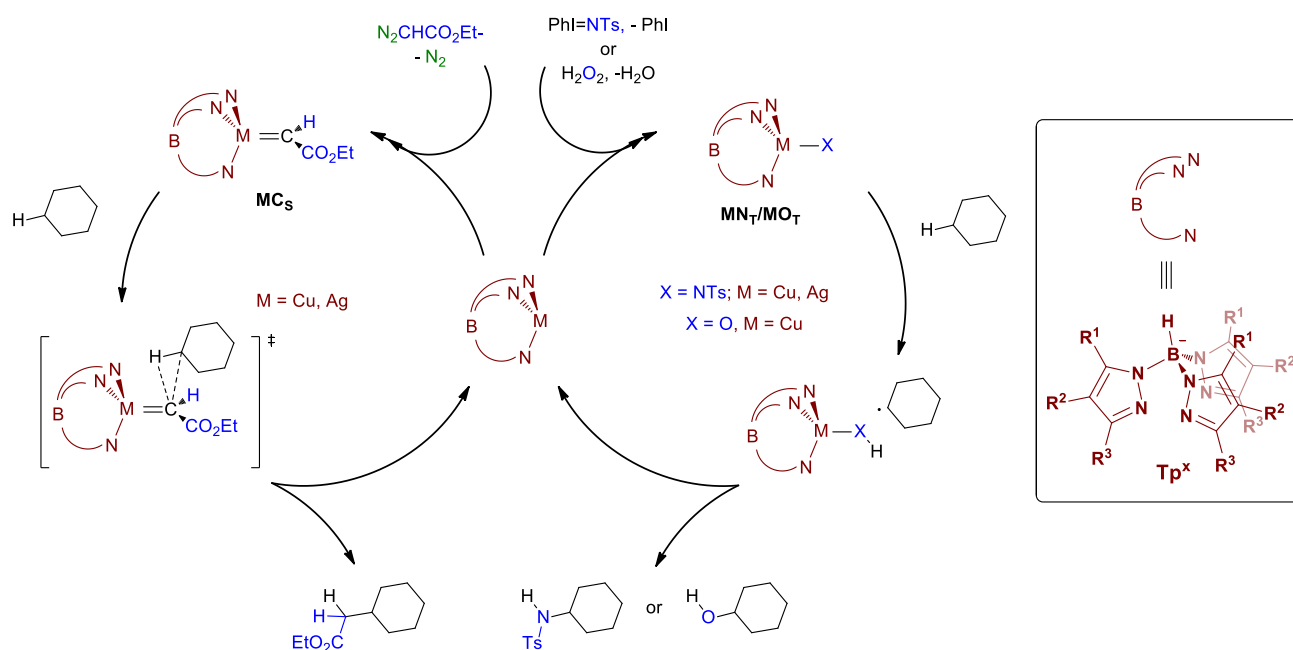
**Scheme 10.** Top: The sequential formation of copper-diazoadducts and copper-carbene species. Middle: carbene region of the  $^{13}\text{C}\{^1\text{H}\}$  NMR spectra for the experiments carried out with  $\text{Tp}^x = \text{Tp}^{\text{PIr}2}$  and  $\text{F}_{12}\text{-Tp}^{\text{4Bo,3Ph}}$ . Bottom: the correlation between the carbene ligand chemical shifts in  $\text{Tp}^x\text{Cu}=\text{C}(\text{Ph})\text{CO}_2\text{Et}$  and the  $\nu(\text{CO})$  of the  $\text{Tp}^x\text{Cu}(\text{CO})$ .

## 4. The comparative mechanistic picture

### 4.1 Evidencing the intermediacy of radical species.

Studies similar to those commented in section 3.1 on the effect of substituents cannot be performed with alkane C-H bonds without affecting the reaction outcome. However, some other experimental data can be added. This is the case of the addition of a radical inhibitor such as 2,6-di-tert-butyl-4-methylphenol (BHT), which induces a decrease of the functionalization process for the nitrene and oxo cases whereas does not affect the carbene reaction.

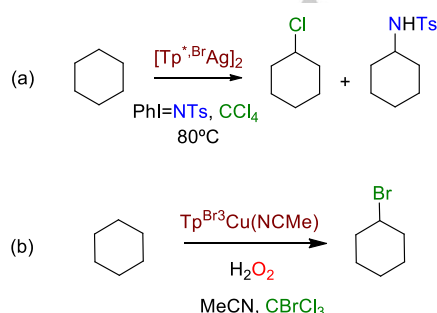




**Scheme 12.** Global mechanistic picture for the alkane (cyclohexane) C-H bond functionalization by carbene, nitrene or oxo insertion.

The addition of a chlorinated solvent such as  $\text{CCl}_4$  or  $\text{CBrCl}_3$  in the nitrene/oxo reactions carried out with cyclohexane originate monohalogenated-cyclohexane products, a consequence of the formation of the cyclohexyl radical through the reaction pathway (Scheme 11).<sup>[18]</sup> Such trapping is not observed in the carbene transfer reaction, albeit it is worth mentioning that with  $\text{Tp}^x\text{Ag}$  catalysts the carbene moiety inserts not only in the alkane C-H bonds but also in the C-X bonds ( $X = \text{halogen}$ ).<sup>[19]</sup> These data indicate that the transfer of the X group to the C-H bond takes place in a concerted manner for the carbene reaction, and via step-wise mechanisms for nitrene and oxo reactions, involving hydrogen abstraction and carbon-centered radicals.

alkane functionalization by carbene, nitrene and oxo insertion. The  $\text{Tp}^x\text{M}$  core reacts with a diazocompound,  $\text{PhI}=\text{NTs}$  or  $\text{H}_2\text{O}_2$  to form the transient intermediates  $\text{MC}_s$ ,  $\text{MN}_T$  and  $\text{MO}_T$ , respectively. The former interacts with the C-H bond of cyclohexane, as the representative hydrocarbon, in a concerted manner, where the new C-C and C-H bonds are formed while the alkane C-H bond is broken. On the other hand, the metal-nitrene and -oxo species attack the C-H bond inducing the C-H abstraction, with the concomitant formation of the  $\text{Tp}^x\text{M}-\text{N}(\text{H})\text{Ts}$  and  $\text{Tp}^x\text{M}-\text{OH}$  and the cyclohexyl radical. From here, the so-called rebound mechanism takes place, in which the radical reacts with such species forming the new C-N and C-O bonds, and releasing the product to re-start the catalytic cycle.



**Scheme 11.** Radical trapping experiments.

#### 4.2 The bimodal reaction pathway.

With all the information collected, Scheme 12 displays the mechanistic interpretation for the three reactions involving

#### Conclusions.

The use of the same family of catalysts including the  $\text{Tp}^x\text{M}$  core ( $M = \text{Cu}, \text{Ag}$ ) for the functionalization of non-activated C-H bonds of alkanes by carbene, nitrene or oxo insertion provides valuable data to compare the three reactions. They proceed through unsaturated electrophilic  $\text{Tp}^x\text{M}=\text{Y}$  intermediates, which have been proposed as Fischer carbenes, on one side, and radical, triplet state species in the case of nitrene and oxo. When transferring carbenes to alkanes, the reaction is not affected by radical scavengers, at variance with the inhibition induced in nitrene/oxo reactions. Another feature regarding activity and selectivities is that catalysts seem to be more active as well as more selective toward primary sites when increasing electrophilicity at the metal center. Such feature finds no parallelism in the nitrene/oxo case, where the involvement of free radicals also influences the reaction outcome. The steric

pressure of the  $Tp^xM$  core is of interest particularly when distinguishing between two or more reaction sites with similar bond strength, as it is the case of secondary sites in n-hexane. Future challenges within this area of work includes the induction of enantioselection in the C-H bond functionalization by nitrene or oxo insertion as well as the development of more selective catalysts toward the different reaction sites (distinct C-H bonds) in the alkane chain.

## Acknowledgments

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**Keywords:** trispyrazolylborate ligands • copper and silver catalysts • carbene nitrene oxo • C-H functionalization • alkane catalysis

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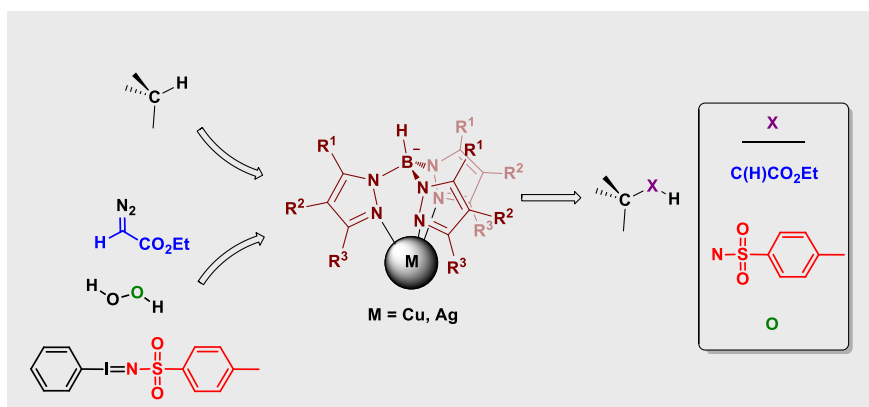
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Alkane functionalization

M. Mar Díaz-Requejo,\* Pedro J. Pérez\*

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The  $Tp^xM$  core in  $C_{sp^3}$ -H bond functionalization reactions: comparing carbene, nitrene and oxo insertion processes ( $Tp^x$  = scorpionate ligand; M = Cu, Ag)



A comparison of three reactions involving alkane C-H functionalization by carbene, nitrene and oxo insertion using trispyrazolylborate complexes of copper or silver is presented. The effect of the ligand scaffold, both steric and electronic, in the reaction outcome is discussed toward a global overview for future catalytic design.