

# Functionalization of Carbon–Hydrogen Bonds of Hydrocarbons and Ethers via Carbene Insertion with Copper(I)–Homoscorpionate Catalysts

Ana Caballero,<sup>†</sup> M. Mar Díaz-Requejo,<sup>†</sup> Tomás R. Belderrain,<sup>†</sup>  
M. Carmen Nicasio,<sup>†</sup> Swiatoslaw Trofimenko,<sup>‡</sup> and Pedro J. Pérez\*<sup>\*,†</sup>

Departamento de Química y Ciencia de Materiales, Universidad de Huelva,  
Campus de El Carmen, 21007-Huelva, Spain, and Department of Chemistry and Biochemistry,  
University of Delaware, Newark, Delaware 19716

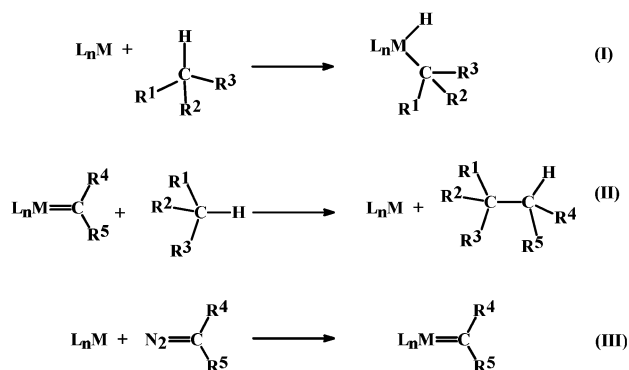
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Complexes of general formula  $Tp^x Cu$  ( $Tp^x$  = homoscorpionate ligand) have been employed as catalysts for the insertion of ethyl diazoacetate into C–H bonds of a variety of hydrocarbons and ethers, in moderate to high yields: tertiary, secondary, and primary C–H bonds have been functionalized by this methodology. Particularly interesting is the homologation of O-methyl groups in ethers, which has been achieved for a group of substrates. The existence of electron-withdrawing groups in the  $Tp^x$  ligand seems to be crucial for the activity and the selectivity of the catalyst.

## Introduction

In the beginning of the 21st century, one of the most challenging areas of research consists of the development of efficient chemical systems capable of the conversion of affordable carbon sources such as hydrocarbons into more valuable products.<sup>1</sup> Despite years of work in the field of carbon–hydrogen bond activation, the number of known catalytic processes for this kind of transformation is still quite small.<sup>2,3</sup> This fact can be explained on the basis of the following: first, the bond energy required for the cleavage of a C–H bond is quite high, and second, most of the effort in the past decades has been concentrated in what could be named the “classical” C–H activation reaction, which supposes the formal insertion of the metal center into the carbon–hydrogen bond, with the formation of  $\sigma$ -organyl derivatives (Scheme 1, (I)). But once a metal complex has been found to react in such way, very frequently the strength of the new metal–carbon and metal–hydrogen bonds provided a somewhat stable organometallic compound, therefore preventing subsequent transformations. On the other hand, the interaction of a transient metal-carbene intermediate with a C–H bond would lead to the formation of a new C–C bond from a formal insertion of the carbene unit into the carbon–hydrogen bond, the metal center being released to re-enter the catalytic cycle (Scheme 1, (II)). This transient metal-carbene species could be easily generated in situ by the

## Scheme 1. Carbon–Hydrogen Bond Activation: (I) Classical Approach; (II) Carbene Insertion Alternative; (III) Generation of the Metalcarbene Intermediate



appropriate transition metal complex and a diazo compound (Scheme 1, (III)).<sup>4</sup>

The above alternative method for the intermolecular C–H bond functionalization reaction was first reported by Scott using copper inorganic salts as catalysts for the insertion of the  $:CH(CO_2Et)$  fragment into the C–H bond of cyclohexane.<sup>5</sup> Similar results were later presented by Wulffmann<sup>6</sup> with  $Cu(acac)_2$ . In the early 1980s, Theyssié, Noels, and co-workers published a series of articles focusing on the use of the complex  $Rh_2(O_2CCF_3)_4$  as the catalyst for this type of transformation.<sup>7</sup> The yields were quite good when compared with the above copper-based systems. Other related rhodium catalysts were later employed to functionalize alkanes and ethers

<sup>†</sup> Universidad de Huelva.

<sup>‡</sup> University of Delaware.

\* Corresponding author.

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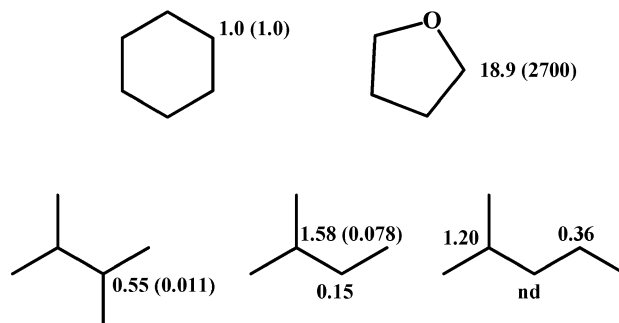
by means of this methodology,<sup>8–10</sup> which has been considered for many years without synthetic utility.<sup>11</sup> Recently, Davies' work with chiral rhodium-based catalysts and vinyl and aryl diazoacetates as the carbene source has provided a synthetic tool for the functionalization of many substrates: alkanes and cyclic ethers,<sup>12</sup> pyrrolidines,<sup>13</sup> allylic alkenes,<sup>14</sup> alkoxy silanes,<sup>15</sup> N-BOC protected amines,<sup>16</sup> allyl silyl ethers,<sup>17</sup> or silyl enol ethers.<sup>18</sup> Very recently, an immobilized catalyst has also been reported to operate under heterogeneous conditions.<sup>19</sup>

Our group has recently entered this area of research, following our previous work in the general olefin cyclopropanation reaction<sup>20</sup> with copper-based catalysts containing homoscorpionate ligands.<sup>21</sup> Preliminary work<sup>22</sup> described the use of the complex  $\text{Tp}^{\text{Ms}}\text{Cu}$  (**1**) as a good catalyst for the insertion of ethyl diazoacetate into the C–H bond of cycloalkanes and cyclic ethers, thus rediscovering copper for this kind of transformation. Very recently,<sup>23</sup> functionalization of low-reactive hydrocarbon molecules has been achieved with the complex  $\text{Tp}^{\text{Br}^3}\text{Cu}(\text{NCMe})$  (**2**). In this contribution, we report a full study in which the catalytic properties of this family of catalysts have been determined. These findings led to metal-controlled insertion of carbene moieties into tertiary, secondary, and primary C–H bonds of a variety of substrates.

## Results and Discussion

**Functionalization of Hydrocarbons.** Our first contribution in the area of C–H bond activation through carbene insertion was performed with the complex  $\text{Tp}^{\text{Ms}}\text{Cu}$  (**1**) as the catalyst. Cycloalkanes and cyclic ethers were transformed into the acetate derivatives in

**Scheme 2. Relative Reactivity of Hydrocarbons toward Carbene Insertion (from EDA) into C–H Bonds Using  $\text{Tp}^{\text{Br}^3}\text{Cu}(\text{NCMe})$  as the Catalyst (values in brackets are for  $\text{Rh}_2(\text{S-DOSP})_4$  and  $\text{N}_2\text{C}(\text{Ph})\text{CO}_2\text{Et}$  as the carbene source<sup>12a</sup>)**



moderate and high yields, respectively, using the commercially available ethyl diazoacetate (EDA) as the carbene source. But catalyst improvement was needed in order to achieve the functionalization of a broader range of substrates. It is generally accepted that the decomposition of diazo compounds in the presence of metal–carbene complexes occurs with the intermediacy of a transient electrophilic metalcarbene species,<sup>4</sup> which has been recently detected by Hoffman et al. in a copper-based system.<sup>24</sup> The use of transient copper–carbene species in catalysis has been nicely reviewed by Kirmse.<sup>25</sup> The electrophilic character of such intermediates has been proposed in previous work from these laboratories for the  $\text{Tp}^x\text{Cu}$  family of catalysts in the olefin cyclopropanation reaction.<sup>20</sup> Since the use of electron-withdrawing ligands in rhodium-based systems was related to the enhancement of the yields in the C–H activation reaction, we decided to apply such knowledge to our copper system. The novel complex  $\text{Tp}^{\text{Br}^3}\text{Cu}(\text{NCMe})$  (**2**) was prepared, and its catalytic capabilities toward carbene insertion (from EDA) into C–H bonds were tested, leading to moderate to high conversions of linear and branched hydrocarbons.<sup>23</sup> In addition, that preliminary study with **2** and several hydrocarbons showed the order of regioselectivity tertiary > secondary >> primary, similar to those observed with several rhodium systems.<sup>12</sup>

After those preliminary results, we have performed intermolecular competition experiments, with several hydrocarbons and **2** as the catalyst, to obtain the relative reactivity toward this carbene insertion process, with the results displayed in Scheme 2. Again, the well-known order for bond energies  $1^\circ > 2^\circ > 3^\circ$  was observed, as inferred from the opposite order of reactivities  $3^\circ > 2^\circ > 1^\circ$ . However, the values are clearly influenced by the nature of the catalyst employed. Tertiary C–H bonds in 2-methylbutane and 2-methylpentane were more reactive than cyclohexane, in contrast with data presented by Davies et al., for which a 1:0.078 cyclohexane:2-methylbutane ( $3^\circ$ ) ratio was reported.<sup>12a</sup> 2,3-Dimethylbutane was found to be less reactive than 2-methylbutane by a factor of 3, whereas Davies' work gave a ca. 1:6 ratio of relative reactivity. When using thf as the substrate, the rhodium system

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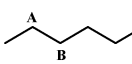
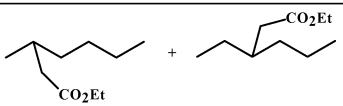
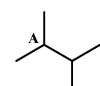
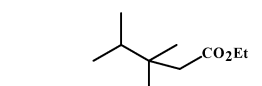
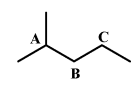
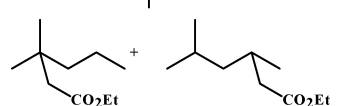
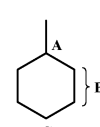
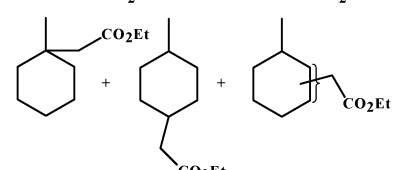
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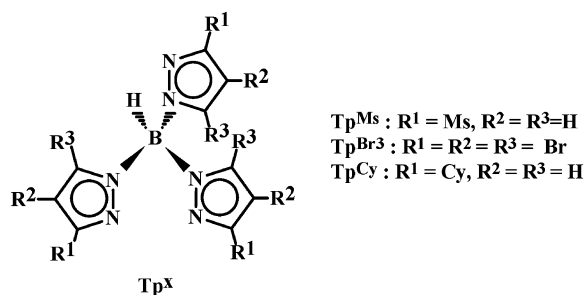
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**Table 1. Intramolecular Relative Reactivity of Hydrocarbons vs Catalyst Structure**

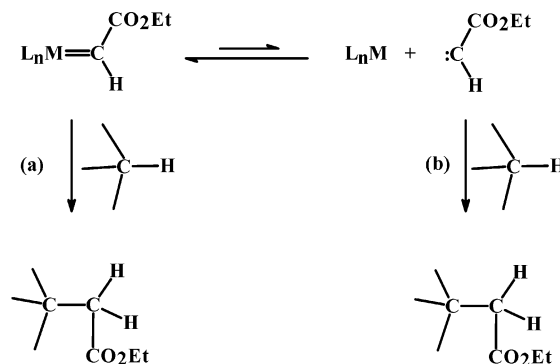
Substrate	Products	Tp <sup>Ms</sup>		Tp <sup>Br3</sup>		Tp <sup>Cy</sup>	
		% Regioselect. <sup>a,b</sup>	Yield <sup>b</sup>	% Regioselect. <sup>a,b</sup>	Yield <sup>b</sup>	% Regioselect. <sup>a,b</sup>	Yield <sup>b</sup>
		A	86	A	76	A	80
		B	14	B	24	B	20
		A	>99	A	>99	A	nd
		B	30	B	56	B	nd
		A	83	A	77	A	91
		B	nd	B	nd	B	nd
		C	44	C	73	C	9
		A	19	A	30	A	59
		B	5	B	5	B	2
		C	60	C	97	C	10
		C	76	C	65	C	39

<sup>a</sup> Values normalized by the number of C–H bonds. <sup>b</sup> Determined at the end of the reaction by GC after total consumption of EDA. Diethyl fumarate and maleate accounted for 100% of EDA.

**Chart 1**

was found to be more reactive toward this molecule in comparison with our copper-based system. Overall, we can conclude that the Tp<sup>Br3</sup>Cu(NCMe) catalyst displays a different chemoselectivity toward nonactivated C–H bonds, i.e., for hydrocarbon molecules other than the rhodium system.

**Regioselectivity: Influence of the Catalyst.** Several, distinct hydrocarbon molecules have been reacted with EDA in the presence of three representative catalysts: Tp<sup>Ms</sup>Cu (1), Tp<sup>Br3</sup>Cu (2), and Tp<sup>Cy</sup>Cu (3) (Chart 1). We have chosen hexane, 2,3-dimethylbutane, 2-methylpentane, and methylcyclohexane to evaluate different types of electronic and steric environments for the C–H bonds suitable for reaction with EDA. The results are shown in Table 1, from which two general trends can be obtained: (a) the existence of a catalyst-dependent regioselectivity and (b) the lack of detectable amounts of primary (CH<sub>3</sub>) functionalization. The latter is in accord with Davies' work with Rh<sub>2</sub>(S-DOSP)<sub>4</sub>,<sup>12a</sup> whereas other authors<sup>7,8b</sup> have reported minor amounts of products resulting from the activation of this site, also with rhodium-based catalysts. Noels et al. have proposed the existence of an equilibrium between the metallocarbene and the free carbene species (Scheme 3), which could be responsible in some degree for the methyl C–H functionalization.<sup>7e</sup> In our case, we believe that the catalyst dependence of the distribution of products clearly evidences that such equilibrium, if it exists, should be displaced toward the metallocarbene species.

**Scheme 3. Equilibrium between the Metallocarbene Species and the Free Carbene. Route (a): Metal-Controlled Reaction. Route (b): Free Carbene Reaction**

Nakamura has very recently reported,<sup>26</sup> for rhodium-based catalysts, a theoretical work that has demonstrated the differences in energies between the activation of distinct C–H bonds: the activation of a secondary C–H bond seems to be spontaneous with respect to the carbene complex ( $\Delta E < 0$ ), whereas the corresponding activation of a primary C–H bond presents an energy value higher than that of the metallocarbene intermediate. In terms of C–H bond energies, the order CH<sub>4</sub> > 1° > 2° > 3° has been derived from the respective values of 105, 101, 99, and 97 kcal/mol.<sup>27</sup> On the basis of the intermediacy of a copper–carbene transient species as the crucial step in this transformation, the regioselectivity of the insertion reaction into a given C–H bond must obviously depend on the steric interaction and the electronic effects of the catalyst–substrate couple. From a steric point of view, the rational order of reactivity should be primary > secondary > tertiary. On the other hand, the cleavage of the C–H bond will be easier in the opposite way, that is, tertiary > secondary > primary.<sup>1</sup>

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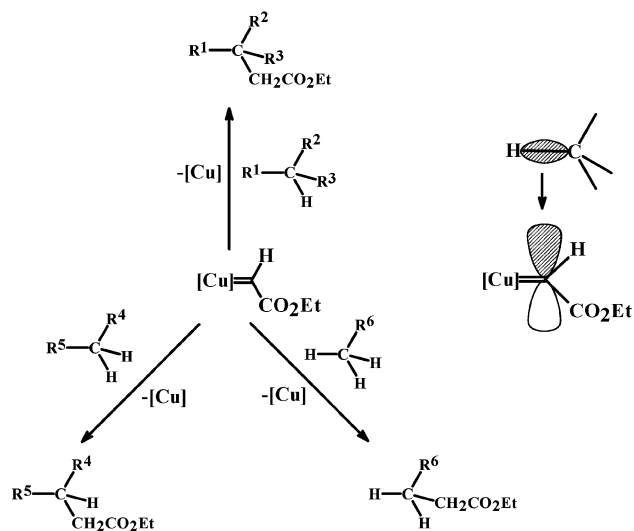
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**Table 2.** Activation of C–H Bonds of Ethers via Carbene Insertion with  $\text{Tp}^{\text{Br}^3}\text{Cu}$  as the Catalyst<sup>a</sup>

Entry	Substrate	Product	Yield <sup>a</sup>	Entry	Substrate	Product	Yield <sup>a</sup>
1			>99	5			>99
2		 + 	80	6			20
3			41	7			>99
4		---	nd	8			47

<sup>a</sup> Determined at the end of the reaction by GC after total consumption of EDA. Diethyl fumarate and maleate accounted for 100% of EDA. <sup>b</sup> Distribution of products.

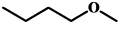
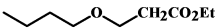
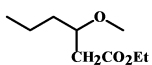


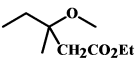

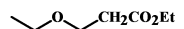
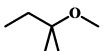


If we consider hexane, the two different, secondary C–H bond reaction sites present similar bond energies and different steric hindrance, the activation at C2 sites being more favored for the three catalysts. No methyl activation was observed with this or any other substrate. In good accord with this, the reaction with 2,3-dimethylbutane gave only the product derived from the activation of the tertiary C–H bond. However, the case of 2-methylpentane has afforded interesting data about the relative intramolecular reactivity of tertiary and secondary C–H bonds. In all cases, the higher selectivity corresponded to the tertiary site. Among the secondary sites **B** and **C**, only the latter has been functionalized, with no observation of detectable amounts (by NMR) of the **B**-derived product. We believe this is due to the steric effect, which discriminates between both sites. The observation of mixtures of products from the activation at the **A** and **C** sites reveals that both processes are energetically available, with a small energy barrier from one to another. In addition, the fact that the ratio of product varies with the catalysts supports this explanation. The lack of observation of any functionalization at the methyl groups indicates that the energy gap between this and those processes is too high to be accessible by these catalysts. This is in accord with the already mentioned results by Nakamura et al.<sup>26</sup> Scheme 4 displays the three possible activation processes that might occur with a given substrate: primary, secondary, and/or tertiary C–H sites are suitable for functionalization. The observation of different ratios of secondary- and tertiary-derived products supposes that both processes are energetically available for the catalysts employed. We can assume that the reaction of the metalcarbene intermediate with the C–H bond occurs by the interaction of the empty p-carbene orbital and the  $\sigma$ -filled MO of the C–H bond (Scheme 4). An increase in the electrophilicity of the carbene would imply an increase in the preference for electron-rich bonds, and this could explain the enhancement in the secondary site-derived products, since electron density at tertiary C–H bonds must be lower than at secondary ones. Additional evidence for this proposal rests on the lack of reactivity of 3-methyl-1-bromobutane with EDA in the presence of **1** or **2**: the bromine atom completely deactivates the C–H bonds (tertiary and secondary), only fumarate and maleate being observed. At this point, we can partially conclude

**Scheme 4.** Interaction of Primary, Secondary, and Tertiary C–H Bonds with the Copper–Carbene Intermediate

that (i) the existence of electron-withdrawing groups in the  $\text{Tp}^x$  ligand favors the chemoselectivity toward the C–H activation reaction and (ii) the use of those groups also influences the regioselectivity, favoring the activation of C–H bonds with a higher electron density, despite their higher bond energy. These findings support the following prediction: decreasing the electron density of a given C–H bond could confer it a somewhat chemical inertness toward this transformation, and therefore other bonds, formally less reactive from an electronic point of view (e.g., methyl groups), could be transformed.

**Functionalization of Ethers: Activation of Methyl C–H Bonds.** Our first report<sup>22</sup> in this area showed the capabilities of complex  $\text{Tp}^{\text{Ms}}\text{Cu}$  to catalyze the insertion of the  $:\text{CHCO}_2\text{Et}$  group (from EDA) into the C–H bonds of cyclic ethers in high yield. One common feature was observed in those transformations: only the C–H bonds located on the  $\alpha$ -carbon (with respect to the oxygen atom) were functionalized. We have now employed the perbromo derivative with those and other ethers, with the results shown in Table 2. In all cases, only activation of the  $\alpha$ -C–H bonds has been observed. For example, 2,2,5,5-tetramethyltetrahydrofuran does not react at all, since the available secondary C–H

**Table 3. Regioselectivities in the Activation of C–H Bonds of Alkyl Methyl Ethers via Carbene Insertion with  $\text{Tp}^x\text{Cu}$  as the Catalyst<sup>a</sup>**

Entry	Substrate	Product <sup>ab</sup>	$\text{Tp}^{\text{Br}^3}$	$\text{Tp}^{\text{Ms}}$	$\text{Tp}^{\text{Cy}}$
1			23	41	9
			(70)	(26)	(25)
2			65	77	21
			(50)	(16)	(7)
3			>99	c	c
4			(75)	c	c
			>99	(25)	c

<sup>a</sup> Values are for distribution of products. Normalized regioselectivities are given in the text. <sup>b</sup> Values in brackets are overall yields, determined at the end of the reaction by GC after total consumption of EDA. Diethyl fumarate and maleate accounted for 100% of EDA. <sup>c</sup> Not performed.

bonds are as sterically hindered as those in 2,5-dimethylhexane, for which only tertiary activation was observed.<sup>23</sup> These findings are in agreement with the seminal work by Adams and co-workers<sup>9</sup> showing that the insertion of diazocarbonyl compounds, in the presence of rhodium acetate, takes place preferentially at the C–H bonds adjacent to the ether oxygen. This behavior must be related with the values of the bond energy of such bonds: in the case of methanol, a value of 96 kcal/mol for the H–CH<sub>2</sub>OH bond has been obtained,<sup>28</sup> which is very similar to that of a tertiary, aliphatic C–H bond (97 kcal/mol).

At variance with Adams' and other reports, the  $\text{Tp}^{\text{Br}^3}\text{Cu}$  catalyst displays an exceptional activity toward ethers, in such a way that even diethyl ether has been functionalized in high yield. It is worth pointing out that diethyl ether has been extensively employed as the solvent for carbene-transfer reactions due to its inertness toward C–H activation and oxonium ylide formation reactions.<sup>28</sup> The EDA-based yields (ethers were used in excess) were moderate to high in almost all cases, with the exception of dioxane. The latter was an intriguing result since all the C–H bonds are in the vicinity of an oxygen atom. To explain this behavior, we must invoke a contribution from Nakatani's group<sup>29</sup> that demonstrated the deactivation of the C–H bonds located at the  $\beta$ -position with respect to an electron-withdrawing group. Thus, two opposite effects coexist in the molecule of dioxane, activation in  $\alpha$  and deactivation in  $\beta$ , the overall effect being an unreactive substrate. This explanation also accounts for the dioxolane ring, for which quantitative functionalization at the position between both oxygen atoms was observed. These carbon–hydrogen bonds should present lower electron densities than those of the ethylene bridge. However, these are located in an environment similar to the dioxane case, and only the singular methylene group was found to be reactive toward carbene insertion.

The existence of methyl groups at the  $\alpha$ -carbon (to oxygen) suppresses a decrease in the yield, due to the steric effect of such groups. This is in agreement with

the results obtained with 2-methyltetrahydrofuran, a substrate with two types of  $\alpha$ -C–H bonds relative to oxygen. Both sites were activated, with a distribution of products of 38:62 (see Table 3), which leads to a 55:45 tertiary:secondary regioselectivity (normalized by the number of C–H bonds). These values show a slight preference for the tertiary activation, but with a noticeable conversion at the secondary sites. On the basis of these results, it seems that a combination of the appropriate groups at both sides of such oxygen and a given  $\text{Tp}^x\text{Cu}$  catalyst could control the regioselectivity of the reaction. In addition, the unprecedented reactivity of these C–H bonds in diethyl ether led us to wonder about the reactivity of primary C–H bonds located at this position. We have examined the reaction of several methyl alkyl ethers, with different degrees of branching in the alkyl side, and with the three representative catalysts employed throughout this work. The results are shown in Table 3. For those substrates with a quaternary carbon bonded to oxygen, only activation of methyl C–H bonds was observed (entries 3 and 4). Only in the aforementioned Adams' work has methyl *tert*-butyl ether been functionalized with EDA, but in very low yields. When other secondary or tertiary C–H bonds competed with the methyl ones, the situation varied, with mixtures of products being obtained from the insertion at both sides of the oxygen atom. In the case of *n*-butyl methyl ether, the major product obtained was that from the insertion into the secondary site, with a 23:77 primary:secondary ratio for the distribution of products (normalized regioselectivity, 17:83). However, that ratio reverses when using *sec*-butyl methyl ether, which gave a 65:35 ratio of products and a 38:62 regioselectivity for primary:tertiary sites, respectively. These values can be modified upon changing the catalyst, therefore demonstrating that the use of the appropriate  $\text{Tp}^x$  ligand allows the control of the regioselectivity. For example, in the case of methyl *sec*-butyl ether, the regioselectivity can be reversed by employing  $\text{Tp}^{\text{Ms}}$  (77:23 primary:tertiary) or  $\text{Tp}^{\text{Cy}}$  (21:79 primary:tertiary distribution of products). To our knowledge, the

(28) Reference 4b, pp 377–378.

(29) Stork, G.; Nakatani, K. *Tetrahedron Lett.* **1988**, *29*, 2283.

levels of C–H methyl functionalization reported with this copper-based system find no precedent in the literature.

In conclusion, the family of complexes of general formula  $\text{Tp}^x\text{Cu}$  can be used as catalysts for the insertion of carbene units, from ethyl diazoacetate, into carbon–hydrogen bonds of hydrocarbons and ethers. Our present studies have demonstrated the potential of this system to be tuned toward a given substrate or a given C–H unit in a substrate. The activity of the catalyst in terms of overall yields is governed by the existence of electron-withdrawing groups on the pyrazolyl rings. The regioselectivity can be tuned by modifying the electronic density at the metallocarbene and/or by the steric hindrance of the groups attached to the pyrazolyl rings. These findings will allow the design of new  $\text{Tp}^x$  ligands that comply with those requirements for a better control of the C–H activation reaction via carbene insertion. Work focused on this idea as well as on the mechanistic differences between hydrocarbon and ether activation is already in progress in our laboratories.

### Experimental Section

**General Procedures.**  $^1\text{H}$  NMR spectra were run at 400 MHz and  $^{13}\text{C}$  NMR at 100 MHz, using as solvent  $\text{CDCl}_3$ . Mass spectra were carried out in a Varian Saturn 2100T. GC analyses were recorded on a Varian CP-3800. Solvents were dried and degassed before use. All the hydrocarbons and ethers were purchased and employed without any further purification. Syntheses of the copper catalysts (**1–4**) were carried out as reported previously.<sup>23</sup>

**General Catalytic Experiment.** A 0.05 mmol sample of  $\text{Tp}^x\text{Cu}$  was dissolved in a mixture of  $\text{CH}_2\text{Cl}_2$  (5 mL) and the substrate (15 mL). A solution of EDA (1 mmol) in the substrate (10 mL) was slowly added for 2–4 h with the aid of a syringe pump, at room temperature. No EDA was detected at the end of the reaction by GC, only the activation product(s) as well as diethyl fumarate and maleate being detected by this technique. Reported yields correspond to, at least, an average of three runs and were determined in the following manner. After removal of volatiles, the crude product was investigated by  $^1\text{H}$  NMR spectroscopy, with a standard compound being added (tosyl chloride, styrene) to ensure that all the initial EDA was converted in the observed products. The observed ratios were compared to those from GC analysis, to establish the response factors. The following experiments were checked by GC using such factors. The specific reaction conditions for each substrate and their characterization by NMR and GC–MS are given in the Supporting Information.

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**Supporting Information Available:** Syntheses and characterization of the catalysts, catalytic experiments, and spectroscopic data for the monoester compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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