

Functionalization of C_nH_{2n+2} Alkanes: Supercritical Carbon Dioxide Enhances the Reactivity towards Primary Carbon–Hydrogen Bonds

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The functionalization of the primary sites of alkanes is one of the more challenging areas in catalysis. In this context, a novel effect has been discovered that is responsible for an enhancement in the reactivity of the primary C–H bonds of alkanes in a catalytic system. The copper complex $Tp^{(CF_3)_2,Br}Cu(NCMe)$ ($Tp^{(CF_3)_2,Br}$ =hydrotris{[3,5-bis(trifluoromethyl)-4-bromo]-pyrazol-1-yl}borate) catalyzes the functionalization of C_nH_{2n+2} with ethyl diazoacetate upon inserting the CHCO₂Et unit into C–H bonds. In addition, the selectivity of the reaction toward the primary sites significantly increased relative to that obtained in neat alkane upon using supercritical carbon dioxide as the reaction medium. This was attributed to the effect of the carbon dioxide molecules that withdraw electron density from the fluorine atoms of the ligand, which enhances the electrophilic nature of the metal center. DFT studies validated this proposal.

The catalytic selective functionalization of nonactivated alkanes C_nH_{2n+2} remains one of the challenges in current chemistry.^[1,2] In spite of decades of effort toward that end, very few examples (e.g., electrophilic activation,^[3] dehydrogenation,^[4] silylation,^[5] and borylation^[6]) of metal-catalyzed transformations of these compounds into value-added products have been described (Scheme 1). This lack of success can be explained not

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	http://dx.doi.org/10.1002/cctc.201500610.

only in terms of their inertness (mainly because of their poor σ nucleophilicity, their high bond dissociation energies,^[7] and their low polarity) but also in terms of the unavailability of further subsequent transformations that provide neat functionalization. Moreover, functionalization of the primary sites in a preferential manner is even more difficult to achieve. In fact, only the alkane borylation catalytic system developed by Hartwig and co-workers^[6] could be considered as selective toward the terminal C–H bonds of alkanes.





There is a factor that is common to the examples shown in Scheme 1: the interaction of the reacting C-H bond with the metal center. Actually, this is the origin of the small number of catalytic systems for alkane functionalization: in many cases, the formation of very stable metal-carbon and/or metal-hydride bond(s) precludes the intermediate from going further into the functionalization step. An alternative approach consists of the design of catalytic systems in which the C-H bond interacts with an X ligand, very often as part of an in situ generated unsaturated M=X bond, and not with the metal center.^[8] This is the basis of a series of catalytic systems in which $C_n H_{2n+2}$ molecules have been functionalized by the neat, formal insertion of carbene, nitrene, or oxo units into their C-H bonds (Scheme 2). Group 11 metal based catalysts have been found as efficient catalysts for those transformations,^[9] particularly if they contain pyrazolylborate ligands. In an example of the potential of this strategy, we first described silver-based catalysts containing highly fluorinated trisindazolylborate ligands that promoted the functionalization of methane with ethyl diazoacetate as the carbene (CHCO₂Et)



Scheme 2. Functionalization of alkanes by formal insertion of carbene, nitrene, or oxo units.

source by using supercritical carbon dioxide ($scCO_2$) (Scheme 3).^[10] The use of such a medium ensured that no other, more reactive C–H bond than those of methane could be available in the reaction mixture. Very recently, we extended this methodology to the use of a copper-based catalyst, with the ligand hydrotris{[3,5-bis(trifluoromethyl)-4-bromo]-pyrazol-1-yl}borate ($Tp^{(CF_3)_2,B'}$), introducing this metal for methane activation.^[11]



Scheme 3. Functionalization of methane with copper- or silver-based catalyst.

The above transformation takes place through the intermediacy of a metallocarbene intermediate, electrophilic in nature, that interacts with the C–H bond of methane, which acts as a (weak) nucleophile (Scheme 3). This strategy suffers with other alkanes from the disadvantage of the lack of selectivity: these carbene-transfer reactions follow the bond dissociation energy trend, and the primary sites are less prone to activation, in contrast with organometallic activation that is known to favor primary sites over secondary and tertiary sites.^[12] Thus, with alkanes having available different types of C–H bonds, mixtures of products are obtained, and the primary sites are usually the less reactive. In this contribution, we

report the results obtained during the development of the catalytic system based on $Tp^{(CF_3)_2Br}Cu(NCMe)$ (1): we found that this catalyst enhances the functionalization of the primary sites of alkanes relative to that observed in the neat alkane as the reaction medium if the reaction was performed in $scCO_2$. The discovery of this completely unprecedented behavior opens up new perspectives to improve the selectivity in alkane chemistry.

The preliminary study performed with complexes Tp^{(CF₃)₂,BrCu(NCMe) (1) and Tp^{(CF₃)₂,Br}Ag(thf) (2) showed their cata-} lytic potential toward the insertion of the carbene CHCO₂Et groups into the C-H bonds of C1-C4 alkanes, that is, the methane-butane series.^[11] An intriguing observation was made with propane and butane as the substrates. In these cases, the regioselectivity toward the functionalization of primary and secondary sites was nearly identical with both the copper and silver catalysts (Scheme 4). This was in clear contrast with previously described catalytic systems with these metals by our group and others in which for the same type of Tp^xML catalysts, the Cu-based catalyst was nearly ineffective toward primary sites, whereas the Ag-containing catalyst provided a certain degree of functionalization at those sites. However, these precedents correspond to reactions performed with pentane, hexane, or other liquid alkanes (Scheme 5) under homogeneous conditions and by using the alkane as the reaction solvent.^[13] The reactions with propane or butane by using catalysts 1 and 2 were performed in scCO₂ as the reaction medium, and therefore, the differences in the alkane nature, concentration, and reaction phase do not allow appropriate direct comparison.^[14]

We performed a series of experiments with alkanes that could be functionalized both in homogeneous phase (alkane as solvent) and in $scCO_2$; pentane, 2-methylbutane, and hexane were chosen as representative examples of nonactivated C–H bonds of linear and branched alkanes. The $Tp^{(CF_3)_2,Br}Cu(NCMe)$ (1) and $Tp^{(CF_3)_2,Br}Ag(thf)$ (2) complexes were employed as catalysts in their reactions with ethyl diazoacetate. Scheme 6 displays the results obtained with these three model alkanes in a series of catalytic experiments performed under identical conditions with the sole difference of the reaction medium. Data available clearly show the different behaviors of both catalysts. Functionalization of the primary sites



Scheme 4. Previous propane and butane functionalization with ethyl diazoacetate and $Tp^{(Cr_{3})_{2},Br}M$ -based catalysts (M=Cu, Ag).

N ₂ CH	CO ₂ Et,			
	N ₂	~~~	t + ~~~~	+ ~~~~
Tp [×] I neat	ML alkane		CO	₂ Et CO ₂ E
$Tp^x = Tp^{Br3}$	M = Cu M = Ag	not detected 22%	76% 51%	24% 21%
$Tp^x = Tp^{F21}$	M = Cu M = Ag	6% 20%	72% 45%	22% 35%

Scheme 5. Reported functionalization of *n*-hexane with Cu and Ag catalysts containing trispyrazolylborate Tp^x ligands: distinct behavior toward primary sites depends on the metal.



ture (therefore out of the supercritical conditions region), the regioselectivity observed was similar to that in the absence of carbon dioxide (Scheme 6, bottom). This experiment suggests that the dramatic change observed in the product distribution by increasing the amount of carbene insertion into the primary sites should be attributed to an effect of the supercritical phase conditions.

A second issue deals with the plausible involvement of free carbenes in this case. The mechanism of this metal-based carbene transfer from diazo compounds (see Scheme 3) is well es-

tablished to occur through the intermediacy of metallocarbene intermediates that in some cases have been detected and/ or isolated.^[15-17] However, it can be thought that the observed reactivity could be related to the dissociation of the carbene ligand and that the reaction takes place through free carbenes.^[18] Previous contributions from our laboratories showed that the regioselectivity of hexane functionalization depends on the catalyst structure and the size of the catalytic pocket,^[19] excluding the involvement of free carbenes. However, to reinforce this proposal, we performed a series of reactions in scCO₂ with hexane as the substrate and with complex 1 or 2 as the catalyst or catalyst-free experiments, the latter under irradiation conditions, thus to generate the free carbene. The results are shown in Scheme 7, from which the involvement of free carbenes can be excluded on the basis of the distinct regioselectivity observed with or without the catalysts.

The results presented here in-

with silver catalyst **2** remained nearly identical upon moving from the neat alkane as the reaction solvent to s_cCO_2 . On the contrary, with the use of copper catalyst **1** in s_cCO_2 the insertion of the carbene group into the primary sites increased five times with respect to that observed with silver catalyst **2** in neat alkane. Given that all the experiments were performed at 40 °C, the observed behavior cannot be related to temperature.

At this stage, several questions may be raised about this unprecedented performance. First, it could be thought that the mere presence of a high pressure of carbon dioxide could be responsible of the change in regioselectivity. However, upon performing the reaction in neat hexane under an atmosphere of carbon dioxide [100 atm (10.1 MPa)] but at room temperagioselectivity of the alkane functionalization reaction with the copper-based catalyst but not with its silver analogue. Previous

dicate that the supercritical phase induces a change in the re-



Scheme 7. Functionalization of *n*-hexane under catalytic or photochemical conditions. Data refer to relative reactivity corrected with the number of H of each type.

by 1 or 2.



studies showed that increasing the electrophilicity at the metal center (and subsequently at the carbene ligand) correlates well with a certain enhancement in the functionalization at the primary sites with this methodology.^[10,20] Diminishing electron density at the carbene carbon atom must be related to the lowering of π backdonation from the metal center to the carbene ligand, as a result of a decrease in the donation capabilities of the trispyrazolylborate ligand (Figure 1). A plausible ex-



Figure 1. Decrease in the electron density of the copper catalyst is due to an electronic flux from the fluorine atoms to carbon dioxide, which pulls electron density from the ligand and therefore decreases π backbonding from copper to the carbene ligand.

planation for that picture would be based on the already described,^[21] so-called "CO₂-philicity" of fluorocarbons, which, in this case, would consist of the interaction of the CF₃ groups with carbon dioxide molecules (at very high concentrations in the supercritical phase). In *sc*CO₂, donation of electron density from the fluorine atoms to the carbon atom of CO₂ would decrease the electron-donating capabilities of the Tp[×] ligand and would subsequently enhance the electrophilicity of the carbene ligand. The lack of this effect in the silver system could be attributed to the diminished π backdonation of this complex, which eventually reaches the limit of electrophilicity.

This effect could be observed with other electronegative substituents in the Tp^x ligands. In one of the first examples of the potential of these Tp^xCu complexes to catalyze this transformation, alkanes were functionalized upon treating them with ethyl diazoacetate by using the Tp^{Br3}Cu(NCMe) complex as the catalyst.^[13a] Insertion of the carbene group took place exclusively into secondary and/or tertiary sites and no reactivity was observed at the primary C-H bonds. We have now explored the catalytic capabilities of this complex in scCO₂ in the reaction of ethyl diazoacetate and *n*-hexane. Although the complex is not very soluble, a certain degree of hexane functionalization was observed (yield < 5%). Interestingly, the product derived from functionalization of the primary sites was not observed. This finding assesses that the enhancement in the selectivity toward primary sites with complex 1 as the catalyst is due to the presence of the fluorine atoms.

Accordingly, we should explain the change that occurs at the copper center if catalyst 1 is dissolved in $scCO_2$. For this reason, we decided to perform a computational study with the B3LYP-D3 functional. As modeling of the supercritical carbon dioxide environment is not common in DFT calculations of

transition-metal compounds, a computational procedure had to be devised. From the point of view of dielectric constant, the medium is very similar to hexane, as dielectric constants between 1.1 and 1.5 have been reported. The experimental data, however, point to a potential involvement of carbon dioxide molecules in the inner coordination sphere of the carbene complex. We represented this by including three explicit carbon dioxide molecules. The number of molecules was selected from the optimized structure in preliminary calculations with a single carbon dioxide molecule, which suggests the placement of three molecules because of the C_3 symmetry of the ligand. We confirmed through preliminary calculations that the observed variations do not depend critically on the number of solvent molecules. For technical reasons, the three carbon dioxide molecules were introduced in a constrained optimization for which the structures of the minima and transition states were kept frozen at the geometries in the continuum calculation (without explicit solvent) and only the placement of the solvent molecules was optimized. The frequency corrections were also taken from the continuum calculation. The reason for this procedure was purely technical. The potential energy surfaces are shallow and the transition states are difficult to locate; the addition of three weakly bound molecules made the geometry optimization extremely troublesome. We checked that the results from the constrained and full optimization were very similar in one example. So, we computed the reaction of the $Tp^{(CF_3)_2,Br}Cu(CHCO_2Et)(CO_2)_3$ and Tp^{(CF₃)₂,Br}Ag(CHCO₂Et)(CO₂)₃ complexes derived from catalysts 1 and 2, respectively, with the primary and secondary C-H bonds of propane. The results are summarized in Figure 2 and Table 1. The barriers reported in Table 1 are very low, which is consistent with a very fast reaction between the carbene complex and the alkane and is in agreement with previous computational studies.^[22] The fact that one of the barriers was negative in terms of free energy is a simple consequence of the fact that the geometries were optimized in potential energy, and the chemical meaning is that the barrier, if it exists, is very low for this process. In the presence of such low barriers, the diffusion of reactants for the bimolecular process has to be taken into account. It is in particular relevant that the self-diffusion activation energy of hexane was reported experimentally



Figure 2. Optimized structure of the transition state of the primary C–H activation of propane by $Tp^{(CF_3)_2BT}Cu(CHCO_2Et)(CO_2)_3$.

Table 1. Computed activation energies and C_{carb} –H bond lengths in the transition state for the Cu and Ag catalysts under both reaction conditions (neat hexane and *sc*CO₂).

Metal complex ^[a]	$\Delta G_{ m act prim}$ [kcal mol ⁻¹]	C _{carb} —H [Å]	$\Delta G_{ m act\ sec}$ [kcal mol ⁻¹]	C _{carb} —H [Å]
Tp ^x Cu Tp ^x Cu(CO ₂) ₃	3.8 2.7	1.657	0.1 _ ^[b]	1.212
Tp ^x Ag Tp ^x Ag(CO ₂) ₃	0.8 0.2	1.878	_[c] _[c]	_[c] _[c]
[a] $Tp^{x} = Tp^{(CF_{3})_{2}}$	^{,Br} . [b] The barrier	for this pro	cess disappears	because of

[a] $P = P^{-22}$. [b] The barrier for this process disappears because of free energy correction. The computed free energy of the transition state is 0.4 kcalmol⁻¹ below the free energy of the reactants. [c] Structure could not be optimized, barrierless process.

to be 2.18 kcal mol⁻¹.^[23] Only two of the eight barriers reported in Table 1 are above the diffusion limit, and both of them correspond to primary C-H activation by the Tp^{(CF₃)₂,Br}Cu complex with values of 3.8 and 2.7 kcalmol⁻¹ in alkane medium and scCO₂ medium, respectively. This fits well with our experimental observation that the secondary/primary ratio for systems with a silver catalyst is independent from the medium. The regioselectivity for these silver systems does not depend on the electronic nature of the metal but on the physical phenomena (e.g., diffusion, transport) that are more likely independent of the complex. If the process is controlled by diffusion, the competition between the different C-H bonds is no longer ruled by the very low C-H activation barriers. Instead, it depends on the orientation of the approaching molecules. As a first approach, we associate the probability of competing C-H activations to statistical considerations, and the more abundant C-H bonds are thus more likely to be activated. This agrees with the experimental results.

Regardless of what diffusion limits allow us to observe experimentally, it is clear from Table 1 that the presence of CO₂ reduces the activation barrier in all cases. The C_{carb}—H distances in the transition states are also presented in the table. There is some electronic control in the case of the primary carbon atoms, and the C–H distance is longer (1.878 vs. 1.657 Å) in the case of the silver complex with a lower barrier. For the case of the secondary carbon atom, the distance is shorter because the process is controlled by steric effects rather than electronic effects. The C_{carb}–H values are the same in alkane and $scCO_2$ media, because we froze them in the $scCO_2$ calculations, as indicated above.

We present the optimized structure of one of the transition states in Figure 2. The carbon dioxide molecules do not favor the process by getting close to the reaction center but instead by interacting through rather long distances with the Tp^{(CF₃)₂,Br ligand. There is one C_{CO2}—F contact in the 2.75/2.95 Å range for each carbon dioxide, and the shortest contacts between the carbon dioxide and the pyrazolyl rings are in the 3.3 Å range. Although the distances are long, the effect in the energy is clear and reproduces well the experimental observation. It seems that electrophilic carbon dioxide is able to abstract some density from the Tp^{(CF₃)₂,Br ligand, which ultimately leads to diminished electron density at the carbon atom,}}

and this renders the C–H bond more reactive. We hypothesize that the low barriers involved in these processes make them especially sensitive to these seemingly subtle interactions.

Why is this acceleration phenomenon not observed in reactions below the critical temperature? After all, there will be some solubility of carbon dioxide in the alkane reaction media. The explanation is that the low availability of carbon dioxide makes the concentration of the "activated" catalyst much lower, which thus results in a negligible effect on the reaction rate.

Interestingly, the picture emerging from the calculations fits well with the already-described^[21] "CO₂-philicity" of fluorocarbons, which in this case would consist of the interaction of the CF₃ groups with the carbon dioxide molecules. In *sc*CO₂, donation of electron density from the fluorine atoms to the CO₂ carbon atom exists. Such donation would decrease the donating capabilities of the ligand and would subsequently result in an enhancement in the electrophilicity of the carbene ligand. The non-observance of the same effect in the experiments on the silver system is due to the fact that the barriers are already below the diffusion limit for these complexes, which are no longer sensitive to electronic enhancements.

We found that functionalization of the nonactivated primary C–H bonds of alkanes by copper-catalyzed carbene insertion can be enhanced with the aid of supercritical CO_2 as the reaction medium. This is the result of the increasing electrophilicity of the carbene complex owing to the decreased flux of electron density from the fluorinated hydrotris{[3,5-bis(trifluoro-methyl)-4-bromo]-pyrazol-1-yl}borate ($Tp^{(CF_3)_2,B'}$) ligand to the metal in carbon dioxide. This effect was not observed with the silver analogue, as this complex has already reached an optimal electronic situation for C–H activation. Thus, this finding provides a new perspective in the design of selective catalysts toward the primary sites of alkanes, a goal we have already targeted in our laboratories. Also, it opens a new window in the effect of the reaction medium in the catalytic outcome in all systems based on an electrophilic metal center.

Experimental Section

General methods

Preparations and manipulations of metal complexes were performed under an oxygen-free nitrogen atmosphere by using conventional Schlenk techniques. Ethyl diazoacetate (EDA) and the liquid alkanes were purchased from Aldrich or Alfa Aesar and were employed without further purification, whereas the gaseous alkanes were purchased from Air Liquide. Complexes **1** and **2** were prepared according to literature procedures.^[11] The experiments under supercritical conditions were performed in a commercial THAR Technologies R100SYS supercritical plant or in a Phenomenex 33 mL HPLC column (21.2 mm ID×25 mm OD×100 mm) L-connected to a HIP valve through 1.59 mm stainless-steel tubes. NMR spectroscopy experiments were run with Agilent Technologies 400 and 500 MHz spectrometers. Chemical shifts for ¹H and ¹³C are reported as δ values (ppm) relative to the deuterated solvent. GC studies were performed by using a Varian 4500.



Reactions performed with neat alkanes as the reaction media with complexes 1 and 2

In a Schlenk flask, complex 1 or 2 (0.005 mmol) was dissolved in the alkane (pentane, hexane, or 2-methylbutane; 5 mL). With the copper catalyst, a solution of EDA (57 μ L) in the alkane (5 mL) was then added over 8 h with the aid of a syringe pump. In the silver case, EDA (57 μ L) was added in one portion, and the mixture was stirred for 3 h. The conversions and yields were determined by GC analysis by using calibration curves. Experiments at room temperature or 40 °C (oil bath) gave the same results.

Catalytic experiments with liquid alkanes under \mbox{CO}_2 pressure

Inside a 100 mL high-pressure reactor, the catalyst (0.005 mmol) was placed in a polypropylene container with permeable caps at both ends, and EDA (0.5 mmol) was added to a second open container. The alkane was added (10 mL), and the reactor was filled with CO_2 (100 atm). The mixture was stirred for 8 h at either room temperature or 40 °C, the latter ensuring supercritical conditions, and then the system was depressurized before analyzing the mixture by GC.

Experiments under irradiation conditions

With hexane as the substrate, the experiments were identical to those above, either in hexane as the solvent or in $scCO_2$, but lacking the catalyst and by using a UV lamp (340 nm) attached either to the Schlenk flask or to the high-pressure reactor through the sapphire window.

Computational details

All calculations were performed with the Gaussian09 program package^[24] by using density functional theory. We select the hybrid B3LYP functional^[25] including the empirical dispersion correction of Grimme (B3LYP-D3)^[26] and including the solvation through the SMD model^[27] with hexane as solvent ($\varepsilon =$ 1.8819). The nature of all stationary points as minima (no imaginary frequencies) or transition states (one imaginary frequency) was confirmed through frequency calculations. Connectivity between minima and transition states was confirmed by relaxation from the transition state. Two different basis sets were used. For geometry optimizations and frequency calculations, basis set I was used: 6-31G(d) was used for C, N, H, B, F, and $\text{Br},^{\text{[28]}}$ whereas the LANL2DZ basis $\text{set}^{\text{[29]}}$ with its associated pseudopotential was used for Cu and Ag including f polarization functions in both cases (exponents of 3.525 and 1.611, respectively). Basis set II was used to refine the potential energies by using 6-31G(d,p) for light atoms^[15] and LANL2TZ(f) for Cu and Ag.^[30] The full experimental system was used in the calculations except for the substrate, for which hexane was replaced by propane, and the reason was that the conformational complexity associated to the pending alkane chains would likely have little chemical relevance.

Acknowledgements

Support for this work was provided by the Ministerio de Economía y Competitividad (MINECO) (CTQ2014-52769-C3-1-R, CTQ2014-52769-C3-2-R, CTQ2014-57761-R and Severo Ochoa Excellence Accreditation 2014–2018 SEV-2013-0319), the Junta de Andalucía (P10-FQM-06292, P12-FQM-01765), the EU COST Action CM1205, the Intecat Network (CTQ2014-52974-REDC), and the ICIQ foundation. R.G. and A.O. thank MINECO for FPI and Juan de la Cierva fellowships. I.F-A. thanks the Severo Ochoa predoctoral training fellowship (Ref: SVP-2014-068662).

Keywords: C–H activation \cdot carbene transfer \cdot copper \cdot silver \cdot supercritical fluids

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Received: May 31, 2015 Revised: July 8, 2015 Published online on September 11, 2015