

Favoring Alkane Primary Carbon-Hydrogen Bond Functionalization in Supercritical Carbon Dioxide as Reaction Medium

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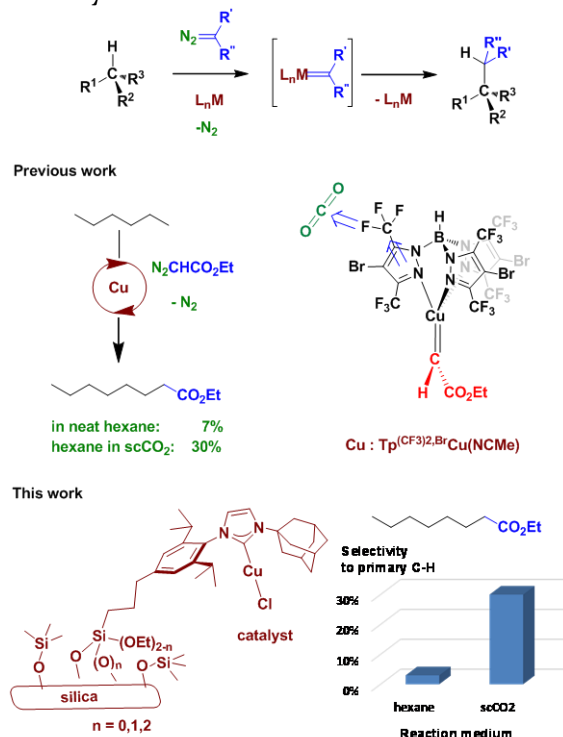
ABSTRACT: The selectivity of a catalytic alkane functionalization process can be modified just changing the reaction medium from neat alkane to supercritical carbon dioxide (scCO₂). A silica supported copper complex bearing an N-heterocyclic carbene ligand promotes the functionalization of carbon-hydrogen bonds of alkanes by transferring the CHCO₂Et group from N₂=CHCO₂Et (ethyl diazoacetate, EDA). In neat hexane only 3% of the primary C-H bonds (ethyl heptanoate being the product) are functionalized in that manner, whereas the same reaction carried out in scCO₂ provides a 30% yield in this linear ester. Such effect seems to be induced by an electronic density flux from the NHC ligand to the surrounding carbon dioxide molecules.

INTRODUCTION

The vast field of homogeneous catalysis remains in continuous expansion providing novel transformations or improving known reaction in terms of yields or selectivities.¹ Toward that end, the election and/or design of the catalysts seems to be the main tool, albeit the reaction conditions also play a significant role. Among them, the solvent employed may exert a certain influence in the reaction outcome, particularly when polar reactants or products are involved.² On the other hand, when low polar as well as low reactive molecules such as those of alkanes are targeted for catalysis, the substrate is frequently employed as the solvent, and modification of the reaction outcome with this variable is not an option.³ Since alkanes are readily available and affordable raw materials, the development of catalytic systems toward their neat functionalization are highly desirable, particularly with special emphasis in the selectivity within the different C-H bonds existing in their molecules.⁴

One strategy for the catalytic functionalization of alkanes consists of the metal-catalyzed insertion of a carbene group from a diazo compound, with the intermediacy of a metal-carbene species (Scheme 1).^{5,6,7,8} With the appropriate design of the catalyst, high yields (usually diazo-based) as well as selectivities (diastereo and enantio) have been described.⁹ The ultimate example of methane functionalization was reached with the functionalization of the lightest alkane in supercritical carbon dioxide (scCO₂) as the reaction medium.^{10,11} Precisely, the use of this *solvent* led to one rare example of the variation of the regioselectivity of the C-H bonds of alkanes.¹² When

Scheme 1. Carbon-hydrogen functionalization by carbene insertion from diazocompounds, and the effect of the reaction medium in the regioselectivity.



neat hexane (or other liquid alkanes) were reacted with

ethyl diazoacetate in the presence of the copper catalyst $\text{Tp}^{(\text{CF}_3)_2, \text{Br}}\text{Cu}(\text{NCMe})$ ($\text{Tp}^{(\text{CF}_3)_2, \text{Br}} = \text{hydrotris}[\{3,5\text{-bis}(\text{trifluoromethyl})\text{-4-bromo}\}\text{-pyrazol-1-yl}\}\text{-borate}$),¹³ the regioselectivity toward the primary sites was very low (7%, Scheme 1). However, the same reaction performed in scCO_2 led to an increase of such selectivity up to 30%. This change was explained¹² as the result of an interaction of the dissolved catalyst with carbon dioxide through the fluorine atoms of the $\text{Tp}^{(\text{CF}_3)_2, \text{Br}}$ ligands, which made the copper-carbene intermediate more electrophilic and decreased the barrier for primary sites (secondary C-H bonds were nearly barrier less). This was the first example of a reaction in which the regioselectivity is affected by the presence of carbon dioxide under supercritical conditions.¹⁴

After those results, we wondered about the possibility of inducing a similar effect but in the absence of fluorine, to validate the role of scCO_2 . We chose a copper-based, N-heterocyclic carbene ligand-containing catalyst (Scheme 1) in view of previous work showing their capability toward the carbene transfer reaction from diazo compound to alkanes.¹⁵ Herein we describe the observation of the aforementioned effect with that fluorine-free catalyst, with a significant ten-fold increment of the functionalization of the primary sites of n-hexane (Scheme 1) when using this reaction medium. This effect might be due to an electronic flux from the copper center to the carbon dioxide molecules through the electron rich N-C-N moiety.

EXPERIMENTAL SECTION

General. Reactions were carried out under inert atmosphere. Solvents were also purified by distillation or using a MBRAUN SPS system. GC studies were performed with a FINNIGAN FOCUS GC, with a FID detector, using a SGE PBX5 capillary column (30m x 0,25 mm x 0,25 μm). NMR data were collected in a Bruker DPX-300, Bruker 400 AV or Bruker DRX-500 equipment. ^{13}C and ^{29}Si CP-MAS spectra were recorded on a Bruker Avance III 400 WB spectrometer equipped with a 4 mm probe. The organic content (wt% C, H, N) was determined by combustion analysis using an EA-1110 CHNS Fisons elemental organic analyzer. The metal content as measured by ICP-MS in a HP500EI spectrometer (detection limit 0.01 $\mu\text{g}\cdot\text{L}^{-1}$). SEM images were taken on a HITACHI S-4800 field emission scanning electronic microscope with a resolution of 1.4 nm at 1KV, equipped with a Bruker backscattered detector of RX. The IAdPrHCl^{16} 1-(adamantan-1-yl)-3-[2,6-diisopropyl-4-[3-(triethoxysilyl)propyl]phenyl]imidazolium chloride and $\text{NaBAr}^{\text{F}}_4$ (sodium tetrakis(3,5-bis(trifluoromethyl)phenyl)-borate)¹⁷ salts were prepared as previously described. The evaluation of the alkane functionalization reactions was performed following well-established, already reported methods.¹⁸

Synthesis of complex 1. The IAdPrHCl imidazolium salt (1 eq) was reacted with CuCl (0.55 mmol) and K^tBuO

in THF (1 mL) for 7 h at room temperature. The final mixture was filtered through celite and the filtrate was taken to dryness. The residue was purified by column chromatography ($\text{CH}_2\text{Cl}_2:\text{MeOH}$, 10:1) leading to a brownish solid of complex **1** in 72% yield. ^1H NMR (300 MHz, CDCl_3) δ 7.18 (d, $J = 1.8$ Hz, 1H), 6.95 (s, 2H), 6.78 (d, $J = 1.8$ Hz, 1H), 3.78 (q, $J = 7.0$ Hz, 6H), 2.64-2.53 (m, 2H), 2.40 (br s, 6H), 2.26 - 2.20 (5H), 1.74 (br, s, 6H), 1.24 - 1.22 (m, 15H), 1.02 (d, $J = 6.9$ Hz, 6H) 0.74 - 0.58 (m, 3H). $^{13}\text{C}\{^1\text{H}\}$ NMR: (75 MHz, CDCl_3) δ 176.8, 145.3, 144.4, 133.6, 124.2, 121.8, 117.0, 62.8, 58.5, 45.1, 39.5, 35.9, 30.0, 28.4, 24.7, 24.4, 18.4, 10.4.

Immobilization of complex 1 in silica gel (2). Previously dried silica gel (1 g) was added to 100 mL of toluene before 0.12 mmol of complex **1** were incorporated to the mixture, which was placed into a Dean-Stark apparatus to be stirred for 30 min first at room temperature and then refluxed overnight. The solid was separated upon centrifugation, successively washed with toluene and dichloromethane and dried under vacuum until constant weight was observed. The greyish solid thus obtained (**2**) was analyzed by ICP-MS leading to a value of 0.083 mmol of copper per gram of solid. This value corresponds to the calculated elemental analyses of C, 2.7% and N, 0.2 %. Found: C, 3.2%; N, 0.3 %. H is not given since silica is hydroxylated. ^{13}C CP-MAS NMR (75 MHz): δ 163.4, 148.4, 130.2, 125.1, 63.8, 45.0, 37.3, 32.2, 24.8, 13.0. ^{29}Si CP-MAS NMR (80 MHz): δ -49.9, -56.4, -61.2, -91.2, -102.00.

Immobilization of complex 1 in OH-free silica gel (2_{TMS}). Step 1. The previous procedure was repeated but using the imidazolium salt IAdPrHCl instead of complex **1**, leading to the isolation of the heterogeneized salt ($\text{IAdPrHCl}_{\text{het}}$) onto the silica surface as a white solid. ^{13}C CP-MAS NMR (75 MHz): δ 147.3, 129.7, 124.4, 62.7, 44.1, 36.5, 31.3, 23.6, 11.9. ^{29}Si CP-MAS NMR (80 MHz): δ -48.5, -56.8, -61.3, -92.4, -102.0, -111.6.

Step 2. 1 g of dried $\text{IAdPrHCl}_{\text{het}}$ was placed under argon in CH_2Cl_2 (4 mL) and 4 mL of chlorotrimethylsilane were slowly added. The mixture was heated under reflux for 5 h, and then filtered under argon. The solid $\text{IAdPrHCl}_{\text{het-TMS}}$ was sequentially washed with dichloromethane and a 1:1 water:acetone mixture before drying under vacuum until weight was maintained constant. ^{13}C CP-MAS NMR (75 MHz): δ 146.8, 130.2, 125.4, 64.2, 45.2, 37.2, 32.1, 24.2, 15.1, 2.2. ^{29}Si CP-MAS NMR (80 MHz): δ 11.2, -66.6, -92.1, -102.6, -112.0.

Step 3. $\text{IAdPrHCl}_{\text{het-TMS}}$ was reacted with copper as described in the previous paragraph leading to the metallated, heterogeneized material **2_{TMS}**. ICP-MS analysis revealed the presence of copper as 0.126 mmol/g of solid. Elemental analysis found: C, 5.64%; N, 0.24 %. ^{13}C CP-MAS NMR (75 MHz): δ 175.2, 146.8, 136.2, 130.7, 126.7, 124.6, 63.1, 44.0, 36.5, 30.9, 24.4, 14.1, 2.2. ^{29}Si CP-MAS NMR (80 MHz): δ 11.4, -55.8, -67.4, -93.7, -102.6, -111.7.

Alkane catalytic functionalization. In all cases, the catalyst was treated under nitrogen with a three-fold

excess of $\text{NaBAR}_4^{\text{F}}$ in 10 mL of CH_2Cl_2 . The mixture was stirred for 1 h and then the solid was separated upon filtration and dried under vacuum before use.

Method A: alkane as solvent. The solid catalyst was placed in a flask along with 2.5 mL of dichloromethane and 2.5 mL of the alkane. A solution of ethyl diazoacetate (0.5 mmol) and 5 mL of the alkane was slowly added with the aid of a syringe pump for 12 h. At the end of that time, the mixture was filtered, and the solid washed several times with dichloromethane. All the filtrates were collected and evaluated by GC, as previously described, providing EDA consumptions as well as yields into products. In the case of the study of recyclability, the recovered catalyst was reused up to four times following the same protocol.

Method B: supercritical carbon dioxide as reaction medium. A 33 mL stainless steel reactor was filled under argon atmosphere with 1.5 mL of the alkane, 0.02 mmol of the solid catalyst and 0.2 mmol of EDA, the latter into a polypropylene deposit attached to the reactor wall, and opened in the upper part. The reactor was closed and then pressurized with carbon dioxide at the desired pressure and introduced into a bath at a fixed temperature. After 14 h, the reactor was cooled and introduced in a Dewar recipient filled with liquid nitrogen for 20 min. The reactor was open and the frozen cylinder containing all the reactants, catalyst, products and carbon dioxide was introduced into a Schlenk flask, and an argon stream was gently passed until all the carbon dioxide was eliminated. The residue was washed several times with more alkane, the filtrates being collected for GC studies. As an alternative to the freezing of the reactor mixture, similar results were obtained upon passing the stream from the reactor through a cold trap. Once the pressure has been released, the reactor was opened and the residue washed and filtered, the filtrates being added to the amounts in the cold trap.

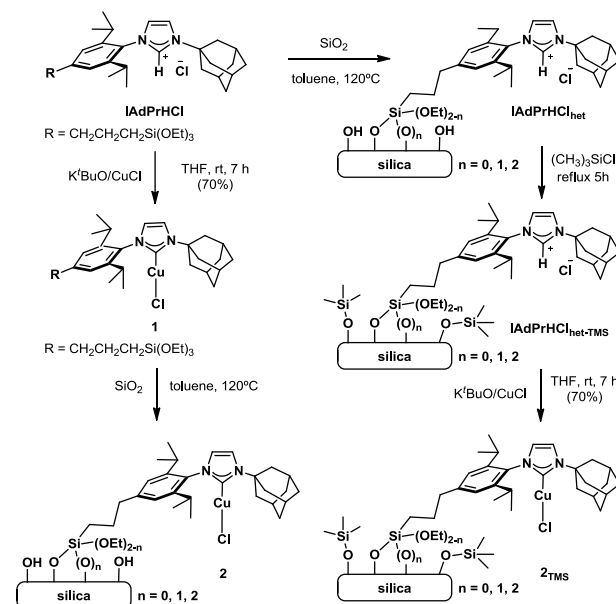
RESULTS AND DISCUSSION

Synthesis of the copper compounds. One of our laboratories reported a few years ago the catalytic capabilities of NHC-Cu complexes for the alkane functionalization by carbene insertion from EDA.¹⁵ Given that we wish to test the effect of scCO_2 in such transformation in the absence of fluorine atoms in the catalyst structure, a catalyst bearing such NHC-Cu core was tested. Also, we have described¹⁶ the synthesis of gold complexes bearing a NHC ligand tethered to silica supports, which showed an impressive catalytic activity for several alkyne functionalization reactions. Based on that, we have targeted the synthesis of the corresponding copper analogs to be employed as catalysts in the aforementioned alkane functionalization reaction. The reaction of the imidazolium salt IAdPrHCl ¹⁶ with copper chloride in the presence of

K^tBuO (Scheme 2) led to the isolation of IAdPrCuCl (**1**). The complex was characterized straightforward based on reported data for a number of similar compounds.¹⁹ The heterogeneous counterpart was prepared following the strategy previously developed for gold derivatives,¹⁶ leading to the silica-supported complex **2**. Such anchoring takes place through the $\text{Si}(\text{OEt})_3$ groups located at the chain tail of the ligand, upon heating a toluene solution of complex **1** with suspended silica gel. After workup, a brownish solid **2** that contains 0.083 mmol of copper per gram of material was obtained (ICP-MS measured).

Since the goal of this work is focused in the use of these copper compounds as catalysts for carbene transfer reactions from diazo compounds, we envisioned that the presence of silanol functionalities onto the silica surface could compete in that transformation, given the well-known capabilities of copper-based catalysts to insert carbene groups into O-H bonds. Thus, in a second route (Scheme 2) the imidazolium IAdPrHCl was first anchored onto silica, affording $\text{IAdPrHCl}_{\text{het}}$, and this material was further reacted with chlorotrimethylsilane to convert the residual -OH into -O-SiMe₃ along the surface of the inorganic material. Isolation of $\text{IAdPrHCl}_{\text{het-TMS}}$ was followed by treatment with a copper source and a base to afford **2**_{TMS} containing 0.126 mmol Cu/g of solid as determined by ICP-MS. Thus, **2** and **2**_{TMS} only differ in the groups attached to the surface-silicon entities: OH in **2** and OSiMe₃ in **2**_{TMS}.

Scheme 2. Synthesis of copper complexes 1, 2 and 2_{TMS}



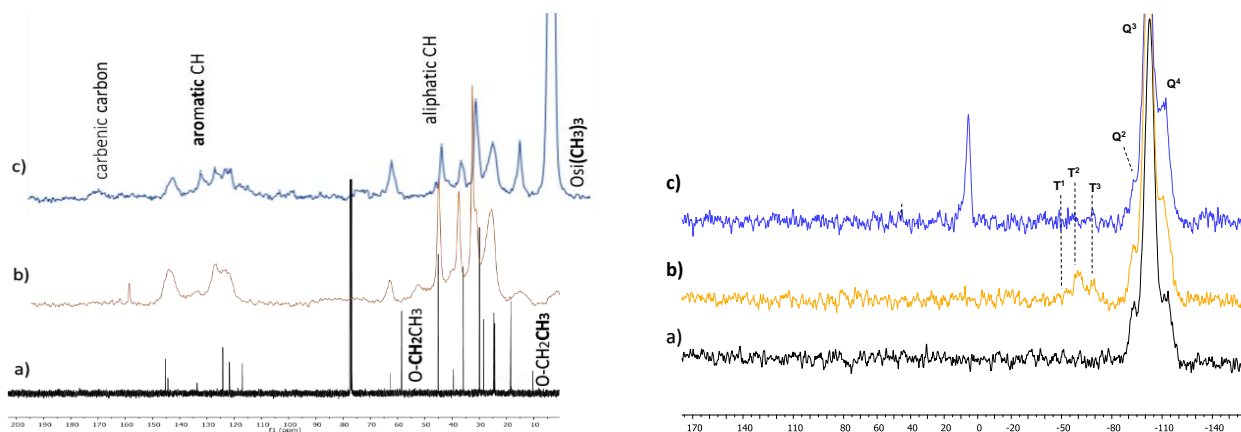
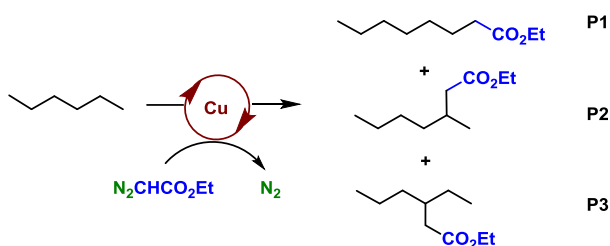


Figure 1. Left: (a) $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of complex **1** in CDCl_3 ; (b) ^{13}C CP-MAS spectrum of **2** and (c): ^{13}C CP-MAS spectrum of **2**_{TMS}. Right: ^{29}Si CP-MAS spectra of (a) silica gel, (b) hybrid material **2** and (c) hybrid material **2**_{TMS}.

Characterization of the solid materials **2** and **2**_{TMS}.

In addition to the measurement of the copper content by ICP-MS, these solids were studied by CP-MAS NMR using ^{13}C and ^{29}Si as the relevant nuclei. As an example, Figure 1 shows a comparison of the $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of soluble complex **1** in CDCl_3 and the ^{13}C CP-MAS spectra of **2** and **2**_{TMS}. A significant concordance between the sets of resonances verifies the anchoring of the copper complex onto the silica surface. Moreover, the resonances of the OCH_2CH_3 groups at the end of the tail in **1** (57.7 and 18.6 for methyl and methylene moieties, respectively) do not find their corresponding bands in the NMR of solid **2**,

Scheme 3. Hexane functionalization with ethyl diazoacetate using IPrCuCl , **2** and **2**_{TMS} as catalyst in the presence of $\text{NaBAR}_4^{\text{F}}$. Values indicate distribution of products P1-P3.



	%P1	%P2	%P3	% EDA consumed	% EDA incorp.	% DEF/DEM
IPrCuCl	3	68	29	47	37	10
2	3	64	32	100	15	3
2 _{TMS}	3	62	35	45	45	0

DEF/DEM = diethyl fumarate and maleate




evidencing their complete or, at least, partial loss due to the anchoring. In the case of **2**_{TMS}, the ^{13}C CP-MAS spectrum shows a band at ca. 175 ppm attributed to the carbenic carbon nucleus, assessing the metalation of the supported imidazolium salt $\text{IAdPrHCl}_{\text{het-TMS}}$. Additionally, an intense band in the proximities of 0 ppm demonstrated the presence of the protecting $-\text{SiMe}_3$ groups (see Supporting Information for NMR spectra).

Complementary and relevant information arises from collected ^{29}Si CP-MAS spectra. As shown in Figure 1, a comparison of the spectra of non-functionalized silica gel with those of **2** and **2**_{TMS} evidences distinct patterns of resonances. Bands for the several $(\text{SiO})_n\text{Si}(\text{OH})_{3-n}\text{R}$ ($n = 1-3$; T_1-T_3) and $(\text{SiO})_n\text{Si}(\text{OH})_{4-n}$ ($n = 2-4$; Q_2-Q_4) have been identified for **2** and **2**_{TMS}. Moreover, the band centered at 11 ppm in the spectrum of the latter corresponds to the SiMe_3 groups, verifying the targeted protection of the initial silanol groups. Overall, CP-MAS data are in agreement with both the anchoring of the copper complex and the protection of the silanol moieties. Additionally, SEM studies were carried out with these solids, showing similarities with the already described gold-based systems (see Supporting Information).¹⁶

Catalytic activity of the copper compounds toward alkane functionalization by carbene insertion: alkane as reaction medium. We first evaluated the catalytic performance of compounds **2** and **2**_{TMS} in the reaction of hexane with ethyl diazoacetate, and compared with that of complex IPrCuCl . The compounds were treated with $\text{NaBAR}_4^{\text{F}}$ as chloride scavenger before use.²⁰ The three catalysts provided in n-hexane solution under the same conditions (rt, 14h, slow addition of EDA, see Experimental), a comparable regioselectivity regarding

the relative functionalization of the three different C-H bonds of n-hexane (Scheme 3). The primary sites were modified in a very low extent (3-4 %) whereas the C-H bond located at C2 showed a significantly higher reactivity than that at C3. The similarities observed for the three catalysts assesses that the transfer of the carbene group from the copper center is not affected by the homogeneous (1) or heterogeneous (2, 2_{TMS}) nature of the catalyst. However, we have found some other features that deserve

Table 1. Alkane functionalization^a with ethyl diazoacetate using 2_{TMS} as catalyst. Study of catalyst recovery.

Cycle	Alkane	% EDA Incorporated ^b	% product distribution ^b		
			1 ^{ry} sites	2 ^{ry} sites C2 C3	3 ^{ry} sites
1		45	3	62	35
2		29	3	67	30
3		25	4	62	34
4		8	4	64	32
1		45	2	72	26
2		37	2	76	22
3		28	2	74	24
4		11	4	76	20
1		50	2		98
2		45	1		99
3		41	3		97
4		19	3		97

^a EDA (0.25 mmol) was added dissolved in a 3:1 mixture of alkane:CH₂Cl₂ with a syringe pump for 12 h, with additional 2 h of stirring at the end of the addition. See Experimental for details. ^b By GC using calibration curves.

some comments. As shown in Scheme 3, both 1 and 2_{TMS} only consumed ca. 50% of EDA in 14 h. Also, the amount of CHCO₂Et incorporated to hexane is very close to that of EDA consumed. With IPrCuCl, 7% of diethyl fumarate and maleate is also formed, in a typically observed non-desired side reaction also induced by the copper center.²¹ It is noteworthy the absence of such dimers with 2_{TMS} as the catalyst, all EDA consumed being incorporated into hexane. On the other hand, the catalytic behavior of 2 shows distinct features. First, all EDA is consumed in 14 h, but only 15% was quantified as hexane derivatives. Additionally, diethyl fumarate and maleate only accounted for 3% of initial EDA. Given that this catalyst contains hydroxyl groups onto the silica surface, it is reasonable assuming that EDA is mostly employed in modifying OH groups by copper-mediated carbene insertion, a well-known as well as highly favored reaction.²² In a blank experiment, silica gel was treated with EDA in the presence of IPrCuCl + NaBAR₄^F as the catalyst, leading to the

appearance of carboxylate units on the surface, as inferred by the observance of a strong absorption in the FTIR centered at 1738 cm⁻¹ (see Supporting Information). Overall, this first set of data indicates that the best catalyst precursor is 2_{TMS}, which we employed for further studies.

Albeit we do not pretend, at this stage of the investigations, the use of this catalytic system for synthetic purposes, we decided to evaluate the potential of catalyst recovery and reuse given the heterogeneous nature of 2_{TMS}, and the lack of examples of such recovery for this type of transformations with anchored metal-based catalysts onto solid supports.⁵ Toward that end, hexane, pentane and 2,3-dimethylbutane were employed as substrates in a study in which the catalyst was recovered and employed four consecutive times. Table 1 displays the results, from which several trends can be extracted. For hexane and pentane the regioselectivity is quite similar, considering the statistic distribution of secondary sites, and with very low functionalization of the primary sites. With 2,3-dimethylbutane the tertiary C-H bond is the main reaction site, primary functionalization being detected below 3% (product distribution). In all cases, the regioselectivity remains unaltered along the four cycles, a fact that we interpret as the maintenance of the same catalytic species (an NHCCu core) as that responsible of alkane functionalization. However, the degree of EDA incorporation into the alkanes significantly decreases along the cycles. ICP-MS studies carried out with the filtrates after each run have shown that the copper leakage is lower than 1% of the supported copper, therefore leaching cannot be invoked to explain such decrease in activity. Diethyl fumarate and maleate were detected in very low amount or were not detected along the cycles. A similar decrease in catalytic activity has been previously observed in the gold analogs in a series of catalytic alkyne transformations.¹⁶ The recovered heterogeneous catalysts were analyzed by SEM. Also in these cases, a significant decrease in the particle size was observed when the mor-

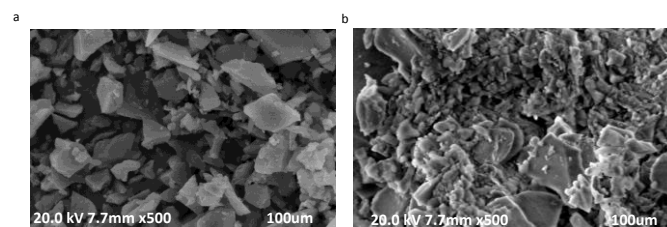


Figure 2. SEM images of 2_{TMS} before (left) and after (right) catalysis.

phology of the solids is compared before and after the catalysis (Figure 2). Such decrease would affect the surface modifying the accessibility to the active sites and thus decreasing the catalytic activity. Nonetheless, neither the copper content nor the catalytic behavior, in

terms of selectivity, are affected in the remaining available catalytic sites.

Supercritical carbon dioxide as reaction medium: effect in the regioselectivity in C-H bond functionalization. In alkane solution the aforementioned degree of functionalization of the primary sites of the alkanes, below 5% of the overall mixture of products, is similar for $\mathbf{2}_{\text{TMS}}$ as the catalyst to that previously reported for the copper-based catalyst $\text{Tp}^{(\text{CF}_3)_2, \text{Br}}\text{Cu}(\text{NCMe})$. It is well-known that the enhancement of this feature (primary sites activation) is favored upon decreasing the electron density at the metal center.⁶ However, that $\text{Tp}^{(\text{CF}_3)_2, \text{Br}}\text{Cu}$ -based system was found to promote such enhancement when using scCO_2 as the reaction medium. Now, we have tested $\mathbf{2}_{\text{TMS}}$ as the catalyst precursor for hexane functionalization and compared its catalytic activity in neat alkane with that observed when carbon dioxide is present below and above the critical point (72.9 atm, 31.1 °C).¹⁴ Table 2 displays the results of this series of experiments carried

(entries 3 and 4) at room temperature, the relative amounts of P1 were 6 and 15% at 75 and 250 atm, respectively. At the latter pressure but 273K, the amount of P1 slightly decreases to 13%. When pressure and temperatures surpassed the critical point of carbon dioxide, regioselectivity toward P1 reached 16 and 30% at 150 and 250 atm (entries 6 and 7). These results mean an overall ten-fold increase in the selectivity from the experiment carried out in neat alkane to that performed in scCO_2 at 313K and 250 atm as reaction medium.

These results demonstrate the existence of an enhancement in the yields of the product derived from primary site functionalization in liquid or scCO_2 solution

Table 2. Effect of the reaction medium in the regioselectivity of hexane functionalization with EDA using $\mathbf{2}_{\text{TMS}}$ as catalyst.^a

Entry	CO ₂ (atm)	T (K)	% EDA incorp.	% DEF + DEM	P ₁	P ₂	P ₃
1	0	rt	45	0	3	62	35
2	50 CO _{2(g)}	313	24	60	9	59	32
3	75 CO _{2(l)}	rt	30	24	6	54	40
4	250 CO _{2(l)}	rt	37	33	15	46	39
5	250 CO _{2(l)}	273	30	15	13	57	30
6	150 scCO ₂	313	25	38	16	46	38
7	250 scCO ₂	313	30	40	30	49	21

^aExperiments in entries 2-7 run with all EDA added in one portion at the beginning of the reaction. See Experimental for details.

out with hexane as the representative alkane. It is worth mentioning that since these experiments are carried out in a vessel under pressure, EDA cannot be added slowly but in one initial portion, although this favors the formation of diethyl fumarate and maleate.²³ Entry 1 Table 2 corresponds to an experiment carried out under nitrogen, at 1 atm, which serves as the reference for the series in this Table.

Use of variable high pressures of carbon dioxide in the reaction mixture modulate the regioselectivity of the carbene insertion reaction. Under 50 atm of CO₂ (entry 2) a slight increase of the percentage of product P₁ was observed. With pressures ensuring liquid carbon dioxide

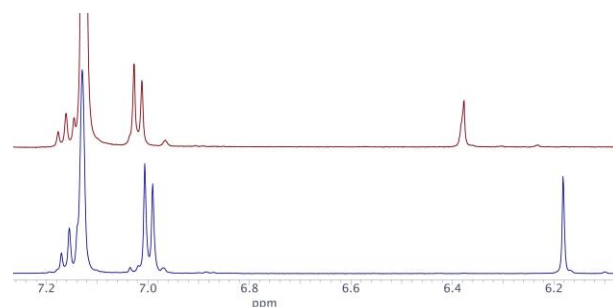


Figure 3. Bottom: ¹H NMR spectrum of IPrCuCl in C₆D₆ at room temperature. Top: ¹H NMR spectrum of the same sample under 72 atm of CO₂.

both with fluorine-containing Tp and NHC catalysts. Since the fluorine-carbon dioxide interaction was invoked as responsible for the decrease of electron density at the catalyst, thus increasing electrophilicity of the copper-carbene intermediate, how can we explain the same behavior in compound $\mathbf{2}_{\text{TMS}}$? We believe that the same reasoning applies in this system; an electronic density flux is taking place from the catalyst to the reaction medium. Actually, data in Table 2 shows that an increase in the amount of CO₂ in the reaction mixture originates an effect in the regioselectivity, even below the critical point (compare entries 1 with 2, 3 with 4 or 6 with 7), albeit the maximum growth is observed under supercritical conditions, where the CO₂ concentration reaches a maximum. To shed light to this proposal, we have investigated the effect of pressure of carbon dioxide on the NMR spectrum of the parent IPrCuCl complex. To our delight, when a solution of IPrCuCl in C₆D₆ at room temperature was exposed to 72 atm of CO₂, the resonance of the backbone C-H nuclei showed a low field shift, because of the deshielding induced by a decrease of the electron density (Figure 3). It is worth noting that such shift is not observed for other resonances (see Supporting Information for full spectroscopic data).

On the basis of the above, and assuming the Lewis acid character of CO₂, we propose that the origin of the electronic flux is located at the N-C-N moiety of the NHC ligand (Figure 4), given the high electron density located

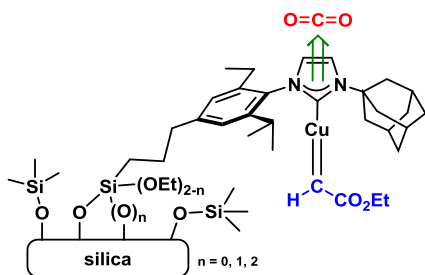


Figure 4. Proposed electronic density flux from NHC ligand to carbon dioxide.

on those three centers-two bonds.²⁴ This flux would decrease the donation from the NHC ligand to the copper center and subsequently the backdonation from Cu to the CHCO₂Et ligand would also decrease, enhancing the electrophilicity of the carbenic carbon atom. However, we cannot rule out the existence of any additional interaction of the catalyst and/or the carbon dioxide with the solid surface that could play a role in the observed catalytic behavior.

CONCLUSION

We have developed a heterogeneous NHC-catalytic system for the functionalization of alkanes by carbene insertion from ethyl diazoacetate. Use of carbon dioxide as the reaction medium, enhances the selectivity of the carbene insertion reactions toward the primary sites up to a ten-fold factor for *sc*CO₂. Based on copper, the NHC ligand directly bonded to the metal seems to be crucial toward that effect, which takes place through the transfer of electronic density of the ligand to the carbon dioxide molecules of the reaction medium. This work should pave the way toward the use of *sc*CO₂ not only as the solvent but also as a potential acceptor of electronic density from catalytic systems that might affect the reaction outcome.

Supporting Information

General information, NMR spectra and SEM data. (PDF)

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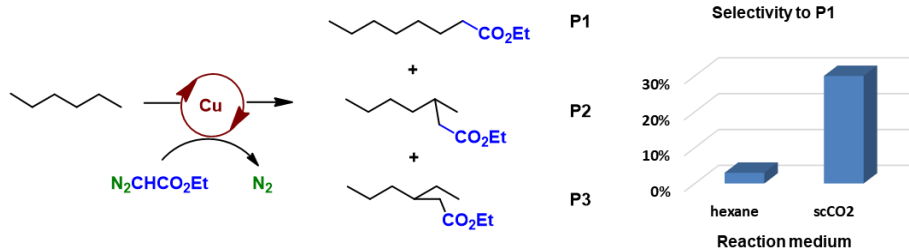
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The use of scCO₂ as renewable reaction medium also originates an effect in the selectivity of the copper-catalyzed alkane C-H functionalization by carbene insertion