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Discovering Copper for Methane C−H Bond Functionalization

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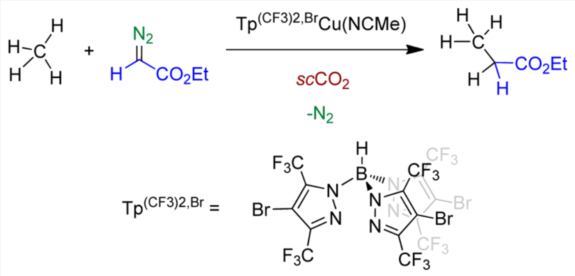
Ⓢ *Supporting Information*

ABSTRACT: The copper complex Tp$^{(CF3)2,Br}$Cu(NCMe) (**1**, Tp$^{(CF3)2,Br}$ = hydrotris((3,5-bis(trifluoromethyl)-4-bromo)-pyrazol-1-yl)borate) catalyzes the insertion of the $CHCO_2Et$ group (from ethyl diazoacetate N_2CHCO_2Et, EDA) into the C−H bonds of methane, in a homogeneous process that uses supercritical carbon dioxide ($scCO_2$) as the reaction medium. Other light alkanes such as ethane, propane, and butane have been also functionalized with this copper-based catalyst, in the first example of the derivatization of the series of C_1−C_4 alkanes with this metal and a soluble catalyst.



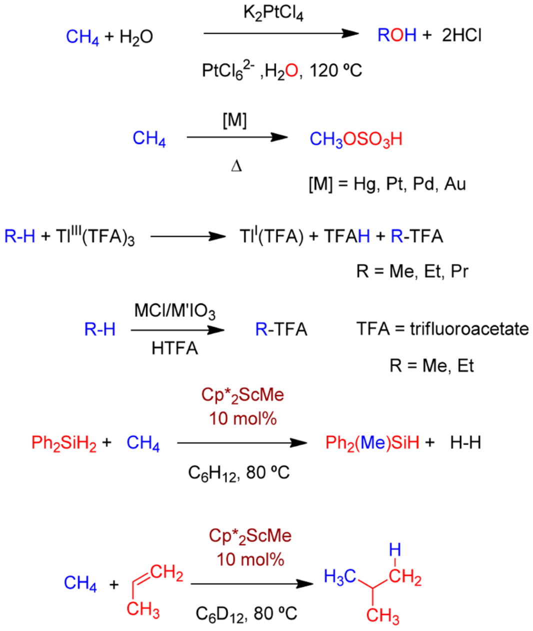
KEYWORDS: *methane activation, copper catalysis, C−H activation, carbene insertion, supercritical carbon dioxide*

Natural and shale gas currently constitutes the main source of methane, along with ethane and other light hydrocarbons.[1] The main uses of methane are restricted to fuel source and to the preparation of syngas,[2] a mixture of carbon monoxide and molecular hydrogen from the complete cleavage of the methane molecule. In addition, methane is difficult and expensive to transport, and therefore, its conversion into liquid derivatives that surpass such drawback is highly desirable.[3] The development of practical catalytic systems that would employ methane as C1-source for synthetic purposes constitutes one of the challenges of modern chemistry.[4]

There are only a few catalytic systems that have been described for the chemical transformation of methane into functionalized products in the homogeneous phase (Scheme 1).[5] The so-called electrophilic activation was initiated in the late 60s by Shilov using platinum salts as catalyst and oxidant to promote the oxidation of the C−H bonds of methane.[6] From that basis, the group of Periana has provided the most active catalysts in this area, with different metal complexes or salts based on mercury,[7] platinum,[8] palladium[9] or gold[10] in superacidic media. Main group elements such as Tl or Pb have also been described to oxidize methane in a stoichiometric manner, in the absence of acid medium.[11] Also, the use of hypervalent iodine compounds as the oxidant has been described by several groups, leading to the conversion of methane into the corresponding trifluoroacetate[12] or methyl esters derivatives.[13]

Tilley and co-workers employed the classical organometallic activation of methane by a scandium-based system for the catalytic conversion of methane in two different ways: the

Scheme 1. Catalytic Systems Described for the Homogeneous Functionalization of Methane



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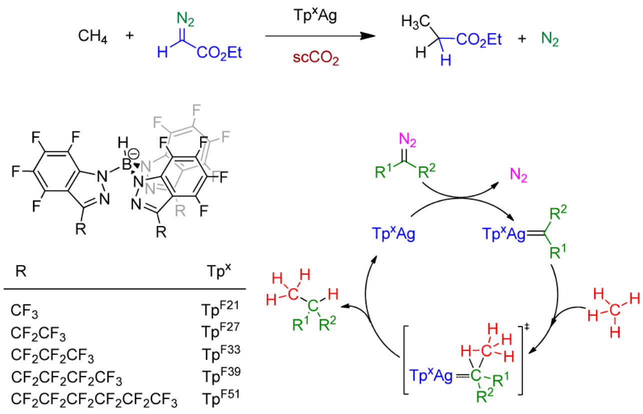
methane dehydrosylation[14] and the hydromethylation of propene.[15] In addition, the H/D exchange of methane with a deuterium source has also been described with several transition-metal complexes.[16]

The above examples of methane activation and functionalization display a common intermediate in which the C–H bond of methane interacts with the metal center, either by sigma-bond coordination or by sigma-bond metathesis. An alternative approach,[17] in which such feature does not occur, has been described by our groups with silver catalysts which promote the formation of a transient, highly electrophilic silver-carbene intermediate from ethyl diazoacetate and the subsequent transfer of such carbene $\mathrm{CHCO_2Et}$ group to the C–H bond of methane (Scheme 2). It is worth mentioning that this transformation takes place in supercritical carbon dioxide ($\mathrm{scCO_2}$) as the reaction medium to ensure that methane is the sole reactant (in terms of C–H bonds) in the reaction mixture. The use of the hydrocarbon as the reaction medium is precluded due to the insolubility of the catalyst as well as of the diazo compound.

Scheme 2. Methane Functionalization by Carbene Insertion with Silver Catalysts

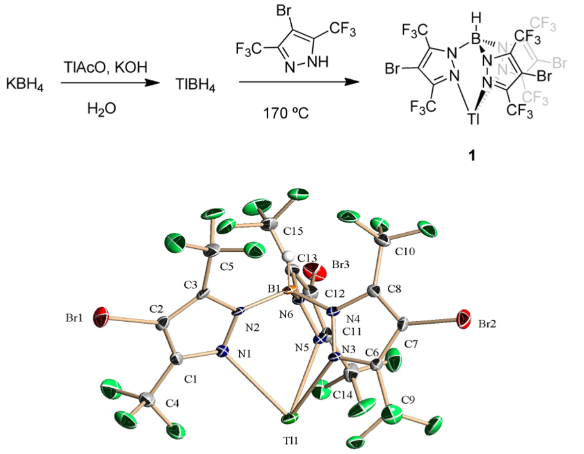


R	$\mathrm{Tp^x}$
$\mathrm{CF_3}$	$\mathrm{Tp^{F21}}$
$\mathrm{CF_2CF_3}$	$\mathrm{Tp^{F27}}$
$\mathrm{CF_2CF_2CF_3}$	$\mathrm{Tp^{F33}}$
$\mathrm{CF_2CF_2CF_2CF_3}$	$\mathrm{Tp^{F39}}$
$\mathrm{CF_2CF_2CF_2CF_2CF_2CF_3}$	$\mathrm{Tp^{F51}}$

Thus, the metal-based reported catalytic systems for methane functionalization (all of them yet far from practical applications) are based on Hg, Sc, Pd, Pt, Ag, or Au, most of them precious metals, some with high toxicities. Because of this, we have focused in the use of a less toxic and expensive metal such as copper. We have previously employed complexes of this element for the alkane C–H bond funcionalization by carbene insertion,[18] but to date, we have not found a copper catalyst capable of inducing the aforementioned methane functionalization. In fact, the copper analogues to the series of silver-based catalysts shown in Scheme 2 did not induce such transformation. In this contribution, we report the synthesis of a new ligand of the trispyrazolylborate class that, when bonded to copper, promotes the catalytic transfer of the $\mathrm{CHCO_2Et}$ group (from ethyl diazoacetate, EDA) to methane in $\mathrm{scCO_2}$ as the solvent, in the first example of the use of this metal for $\mathrm{CH_4}$ activation under homogeneous conditions.

We have previously employed highly fluorinated $\mathrm{Tp^x}$ ligands with the aim of increasing the solubility of the corresponding silver complexes in $\mathrm{scCO_2}$,[17] given the well-known capabilities of fluorine-containing complexes to dissolve in such medium.[19] Despite this, they were only soluble to a certain extent, the solubility being even lower for the copper complexes when compared to the silver ones, a feature that could explain the lack of catalytic activity toward methane. Thus, we decided to build a new trispyrazolylborate ligand containing trisubstituted pyrazolyl rings bearing two $\mathrm{CF_3}$ and one bromine groups. Some of us, in an earlier contribution,[20] demonstrated that the $\mathrm{Tp^{Br3}Cu(NCMe)}$ complex partially dissolved in a fluorous phase, and therefore, we expected that the combination of fluorine and bromine substituents in a ligand could improve the solubility of its complexes in $\mathrm{scCO_2}$. With this idea in mind, the new thalium complex $\mathrm{TlTp^{(CF3)2,Br}}$ (**1**) was synthesized upon direct reaction of the 3,5-bis(trifluoromethyl)-4-bromo-pyrazole and $\mathrm{TlBH_4}$ (previously prepared from TlAcO and $\mathrm{KBH_4}$).[21] This method avoids the isolation of the potassium salt and the low-yielding transmetalation step with thalium nitrate, described for other $\mathrm{TlTp^x}$ ligands.[22] This complex has been characterized on the basis of spectroscopic and analytical data, as well as from X-ray studies (Scheme 3; see Supporting Information for complete characterization data).

Scheme 3. Synthetic Route to Complex $\mathrm{TlTp^{(CF3)2,Br}}$ (1) and Its Solid-State Structure



Once the new ligand was isolated, the copper and silver derivatives were prepared by transmetalation reactions with CuI or AgOTf in acetonitrile or tetrahydrofuran (thf), at room temperature, respectively (Scheme 4). In this manner, the complexes $\mathrm{Tp^{(CF3)2,Br}Cu(NCMe)}$ (**2**) and $\mathrm{Tp^{(CF3)2,Br}Ag(thf)}$ (**3**) were isolated and characterized. Scheme 4 shows the molecular structures for both complexes, where the ligand is bonded to the metal center in a tricoordinated fashion, with bond distances and angles similar to those found in other related complexes of these metals with trispyrazolylborate ligands.[23] It is worth noting that these metal centers are electrophilic in nature, as inferred from the ν(CO) values (in solution) of the corresponding carbonyl adducts $\mathrm{Tp^{(CF3)2,Br}M(CO)}$ of 2125 $\mathrm{cm^{-1}}$ (M = Cu) and 2167 $\mathrm{cm^{-1}}$ (M = Ag). The latter value is nearly identical to those obtained for an array of five complexes of silver with fluorinated tris(indazolyl)borate ligands bearing fluorine atoms,[17] or to that of the related $\mathrm{Tp^{(CF3)2}Ag(CO)}$ (2162 $\mathrm{cm^{-1}}$ in solution, 2178 $\mathrm{cm^{-1}}$ in the solid state),[24] and constitutes another example of a nonclassical silver–carbonyl complex.[25]

The next step consisted of the study of the catalytic potential of complexes **2** and **3** toward the reaction of methane with ethyl diazoacetate (EDA) in $\mathrm{scCO_2}$. The reaction was performed with a 1:50 ratio of the catalyst precursor (0.005 mmol of **2** or **3**) and EDA (0.25 mmol) in a mixture of carbon dioxide (90

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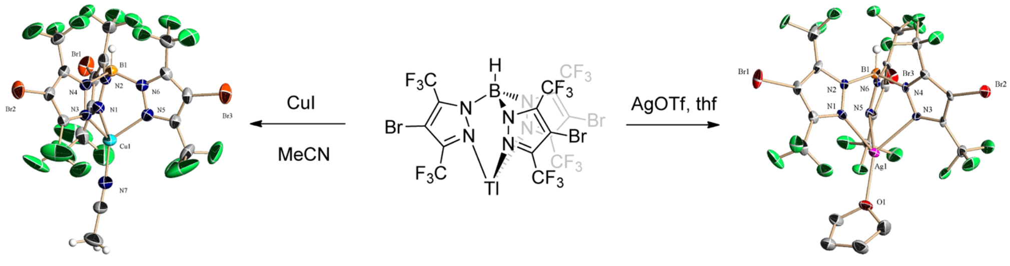
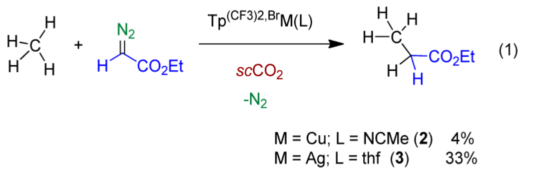
Scheme 4. Synthesis of the Copper- and Silver-Based Catalysts 2 and 3



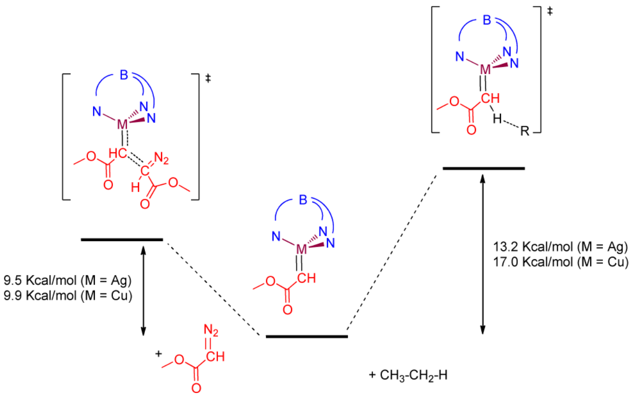
2 **1** **3**

atm) and methane (160 atm), at 40 °C. These values of pressure and temperature ensured reaching supercritical conditions. It is worth noting that, at variance with the partial solubility of the previously described fluorinated trisindazolylborate derivatives, complexes **2** and **3** completely dissolved in all cases, the combination of CF_3 and Br resulting effective to that purpose. After 8 h, the reaction mixture was analyzed with a GC directly connected to the pressure vessel, showing the formation of ethyl propionate (eq 1), the product resulting



from the insertion of the $CHCO_2Et$ moiety into the methane C–H bond. Albeit in low yield (4% with respect to initial EDA), the results observed with the copper-based catalyst represent the first example of the catalytic modification of methane with this metal under homogeneous conditions. Moreover, the remaining 96% of initial EDA was converted into a mixture of diethyl fumarate and maleate,[26] the products derived from the metal-catalyzed carbene coupling.[27] It is well-known that the formation of the latter can be minimized by maintaining a low concentration in the reaction mixture, using slow addition devices. At the present stage, we have not been able to do so, due to the use of high pressure conditions. However, we envisage that with the appropriate engineering design, the enhancement of the yields into the methane derivative would be achievable. Increasing the relative amount of catalyst with respect to EDA is not a solution, because we demonstrated that such strategy favors the formation of the formal carbene-coupling products, diethyl fumarate and maleate.[28]

Scheme 5. Comparison of the Relative Barriers of the Interaction of the Metallocarbene Intermediate with a Second Molecule of Diazo Compound (Left) or Ethane (Right)[a]



[a]Data from ref 26b.

The silver catalyst **3** was more efficient with methane in terms of yields, and it is similar to those reported with the aforementioned fluorinated trisindazolylborate silver catalysts.[17] The difference between both metals stand on the relative barriers of C–H insertion and carbene coupling. Previous work provided a computational model,[26b] showing that this reaction occurs through the intermediacy of a metallocarbene intermediate, which very recently has been detected with this family of catalysts.[29] The relative barriers of the steps involving the interaction of such intermediate with a second molecule of diazo reagent or with the alkane govern the reaction outcome. For copper-based catalysts, that difference is higher (Scheme 5) than those calculated for the silver counterpart. This is in agreement with the observation of, under the same experimental conditions, larger amounts of the alkane-functionalized product with the silver catalyst.

Table 1 displays the catalytic results obtained for the series of ethane, propane, and *n*-butane. To the best of our knowledge, there is no previous report on the use of copper catalysts for the functionalization of these light alkanes by carbene insertion, the already described catalytic systems being limited to alkanes ranging from pentane to polyolefins.[18]

Complex **2** catalyzes the functionalization of those C_2-C_4 alkanes at a larger extent than with methane: 15% with ethane, 23% with propane, and 53% with butane (EDA-based yields). Complex **3** also catalyzes the functionalization of this group of three alkanes, at higher yields. The use of silver-based catalysts for this transformation with C_2-C_4 has been previously described by us,[17] as well as by the groups of Caulton and Mindiola.[30] As expected, the silver catalyst is more active than the copper analogue, due to the already mentioned tendency of the latter to favor carbene coupling, a reaction that is disfavored with the former.

The existence of two different C–H bonds in the molecules of propane and butane originates the formation of a mixture of compounds derived from the metal-catalyzed insertion of the carbene moiety into both sites. Previous catalytic systems based on Tp^xM (M = Cu, Ag) cores have shown that the copper derivative provides none or very low functionalization of the primary sites, whereas the silver analogue does effectively promote it.[17,31] Thus, the regioselectivity observed with the C_3-C_4 alkanes can be considered as unexpected, because we have found that under the reaction conditions, that is, the reaction of the alkane and EDA in $scCO_2$, both metal catalysts

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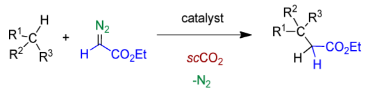
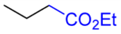
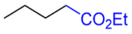
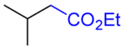
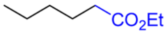
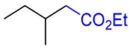
Table 1. Catalytic Functionalization of Alkanes C2−C4 with Ethyl Diazoacetate and Complexes 2 and 3 as Catalysts[a,b]



		Catalyst 2		Catalyst 3	
Alkane	Products	Yield (%)[c]	Regio (%)	Yield (%)	Regio (%)
Ethane		15	--	99	--
Propane		23	44	75	44
			56		56
Butane		53	42	99	44
			58		56

[a]0.005 mmol of catalyst and 0.5 mmol of EDA; 20 g of CO_2 and 3−5 g of the alkane with a total pressure of 250 atm. Reaction time 8 h at 40 °C. [b]Data quantified by GC using calibration curves. See Supporting Information for complete description of the experiments. [c]Remaining of initial EDA was converted into a mixture of diethylfumarate and maleate.

behave in a very similar manner in terms of regioselectivity. We are currently studying this effect that could be of interest from the point of view of exerting a certain control of the nature of the metal in the regioselectivity of the reaction.

As a conclusion, the synthesis of the new ligand hydrotris((3,5-bis(trifluoromethyl)-4-bromo)-pyrazol-1-yl)borate ($Tp^{(CF_3)2,Br}$) and its copper complex $Tp^{(CF_3)2,Br}Cu(NCMe)$ have led to the first example of the use of a homogeneous catalyst based on this metal for the functionalization of methane, with the methodology of the metal-catalyzed carbene insertion into the C−H bonds of the alkane, and using ethyl diazoacetate as the carbene source and $scCO_2$ as the reaction medium. The same catalyst promoted the functionalization, for the first time, of the ethane, propane and butane with this methodology. When comparing the catalytic results with those of the silver analogue $Tp^{(CF_3)2,Br}Ag(thf)$, an interesting feature has been observed: the distribution of products derived from the insertion into primary or secondary C−H bonds of propane and butane were similar to both metals, at variance with the lack of reactivity toward the primary sites with the copper-based catalysts reported to date.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00718.

X-ray data (CIF)
General methods, synthetic procedures, and catalytic experiments (PDF)

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Notes

The authors declare no competing financial interest.

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