

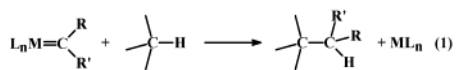
Highly Regioselective Functionalization of Aliphatic Carbon–Hydrogen Bonds with a Perbromohomoscorpionate Copper(I) Catalyst

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Despite the many advances made in the past 20 years concerning the stoichiometric activation of C–H bonds by transition-metal complexes, there are few examples of catalytic transformations incorporating these activation reactions.¹ Saturated hydrocarbons, currently the most abundant feedstock, are particularly difficult to functionalize using a C–H oxidation addition reaction.² One alternative methodology to functionalize alkanes consists of the insertion of a transient metalcarbene species into the carbon–hydrogen bond (eq 1)³

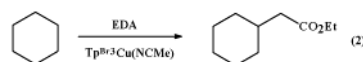


with the subsequent formation of a new carbon–carbon bond and catalyst release to restart the catalytic cycle. The metalcarbene species can be generated in situ by addition of a diazo reagent to an appropriate transition-metal complex. Although the intramolecular version of this reaction has been widely applied in organic synthesis,³ the intermolecular counterpart has not been studied as much. The reaction between ethyl diazoacetate (EDA) and cyclohexane was first reported by Scott et al.⁴ wherein low yields of the insertion product with copper salts as the catalyst were obtained. The allylic C–H bond functionalization of cyclohexene induced by Cu(acac)₂ was later reported by Wulfman, again with very low conversions.⁵ To our knowledge, no more Cu-based catalytic systems for this transformation have been reported until our recent contribution describing the use of complexes of general formula Tp^XCu (Tp^X = homoscorpionate ligand) as catalysts for the insertion of ethyl diazoacetate into C–H bonds of cycloalkanes and cyclic ethers.⁶ The decay of copper for this and other metalcarbene-based reactions³ was mainly due to the work by Noels and co-workers, that described Rh₂(OAc)₄ as the catalyst of choice for those transformations.⁷ Related rhodium catalysts, later employed by Callot,⁸ Adams,⁹ and Müller,¹⁰ provided interesting results with a range of substrates from hydrocarbons to cyclic ethers. However, no doubt this alternative for C–H bond functionalization has gained much interest in the past few years after the work from Davies and co-workers with their chiral rhodium-based catalysts: in addition to the insertion of aryldiazoacetates into alkanes and cyclic ethers,¹¹ the functionalization of C–H bonds of pyrrolidines,^{12a} allylic alkenes,^{12b} alkoxysilanes,^{12c} *N*-BOC-protected amines,^{12d} allyl silyl ethers,^{12e} or silyl enol ethers^{12f} has been achieved in preparative yields and with high degrees of asymmetric induction. However, the application of this methodology to very unreactive alkane substrates finds few reports in the literature.^{4,5,7,8,11} The development of catalytic systems that allow the functionalization of those C–H bonds could provide a new method for converting inexpensive

feedstocks into valuable chemicals. Particularly interesting could be the use of this procedure to functionalize hydrocarbon-based polymers. This method would allow installation of a functional group after polymer formation, avoiding the well-known problems in the use of functionalized monomers.¹³

In our previous contribution,⁶ the yields were high in the case of cyclic ethers but moderate (50%) in the case of cycloalkanes (cyclohexane and cyclopentane). Low conversions (<10%) were observed when using acyclic alkanes. In search of a better catalyst for such substrates, we have chosen to examine the novel perbromo ligand Tp^{Br3},¹⁴ that contains nine bromine atoms in the Tp framework. This choice was based on the previous proposal by several authors that the existence of electron-withdrawing groups on ligands in the coordination sphere could favor the insertion reaction, due to the enhancement in the electrophilicity of the metal–carbene intermediate.^{7,8,12} The new complex Tp^{Br3}Cu(NCMe) (**1**) was prepared by the direct reaction of CuI and TITp^{Br3} in acetonitrile. Evidence for the decrease in electron density at the metal center comes straightforwardly from the monocarbonyl adduct Tp^{Br3}Cu(CO) (**2**) that displays a value of 2110 cm⁻¹ for ν (CO). The related derivative Tp^{M5}Cu(CO) complex showed a ν (CO) frequency of 2060 cm⁻¹.¹⁵

The expected enhancement of the catalytic activity with **1** was demonstrated upon reacting EDA and cyclohexane (eq 2):



ethyl 2-cyclohexyl acetate was obtained in 90% yield (based in EDA, [Cu]:[EDA]:[C₆H₁₂], 1:20:1000). But, as mentioned above, acyclic substrates present more interest from the functionalization point of view. A series of experiments¹⁶ have been carried out with such molecules; the results are summarized in Table 1. The chemoselectivity induced by **1** with EDA as the carbene source is higher than that reported with other copper^{4,5} and rhodium^{7,8} systems. This activity is somewhat unexpected, particularly after a recent theoretical study by Nakamura et al.¹⁷ that predicted values for the activation energy of this type of C–H insertion reaction: the +5.7 kcal/mol calculated for the rhodium case is quite distinct from the +15.6 kcal/mol estimated for copper. Thus, tuning of the metal center with the Tp^{Br3} ligand seems to be decisive in improving the catalytic activity in the copper system.

Several trends can be inferred from the data in Table 1. First, no primary C–H insertion has been observed, at least in the NMR detection limit. This is in contrast with the previous reports of both Noels⁷ and Callot,⁸ but similar to Davies' results.¹² The use of 2-methylbutane provided a direct measure of the relative reactivities between primary, secondary, and tertiary C–H bonds. NMR studies showed a 80:20 tertiary:secondary molar ratio of products. A

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Table 1. Insertion of Ethyl Diazoacetate into C–H Bonds of Alkanes Catalyzed by $\text{Tp}^{\text{Br}^3}\text{Cu}(\text{NCMe})$ (**1**)^a

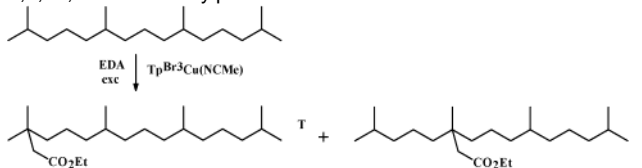
Alkane	Products ^b	Yield ^c	Select ^d
		53	91 ^d
		73	87 ^d
		56	>99 ^d
		71	>99 ^d
		50	64 ^e
		60	76 ^e

^a See ref 16 for experimental details. ^b Product distribution observed by ¹H NMR spectroscopy. ^c EDA-based, determined after total consumption of EDA. Diethyl fumarate, maleate, and ethyl glycidate account for 100% of EDA. ^d Selectivity for tertiary sites, normalized for the relative number of hydrogen atoms. ^e Selectivity for C2 secondary sites, also normalized.

statistical factor must be included to estimate the regioselectivity per C–H bond,^{7d} the tertiary selectivity for 2-methylbutane reaching 91%. Other branched alkanes such as 2-methylpentane, 2,3-dimethylpentane, and 2,5-dimethylhexane have also been studied, with the respective values for the tertiary selectivities of 87, >99, and >99% being observed. This tertiary reaction site displays the weakest C–H bond as well as the highest steric hindrance, and thus electronic effects appear to dominate in this system. Additional support came from a competition reaction between 2-methylbutane and 1-bromo-3-methylbutane, for which only products derived from the former were observed; the bromine atom deactivated both tertiary and secondary sites in this substrate. This effect has also been observed by Callot using rhodium–porphyrin catalysts.⁸

The situation varies when comparing the degree of functionalization for methylene groups. Given the similarities in electronics, steric factors must be crucial. The methylene groups adjacent to terminal methyl groups undergo activation in all cases, whereas internal CH₂ groups were activated to a lesser extent in linear alkanes or did not react at all when directly bonded to branched carbons. As a result of this trend, high control of the selectivity was achieved for 2,5-dimethylhexane, with no secondary activation in the central CH₂–CH₂ unit being observed. To our knowledge, the level of regioselectivity displayed by this system with the readily available EDA finds no precedent in the literature.

The catalytic properties of complex **1** toward the preferential functionalization of tertiary C–H bonds can be expanded to more elaborate substrates. We have explored the application of such capabilities to higher alkanes such as 2,6,10,14-tetramethylpentadecane (TMPD). This molecule models the potential activation sites of branched polymers with different tertiary as well as secondary C–H bonds available. In this experiment, the diazo reagent has been employed in excess. Thus, when 1 mmol of TMPD was reacted^{16b} with a 10-fold excess of EDA, 85% of the alkane was converted into mono-inserted derivatives (Scheme 1); only tertiary sites were activated with no secondary activation being observed within the NMR detection limit. Two isomers **T** (terminal) and **I** (internal) have been isolated and characterized in a 60:40 ratio favoring the former. The activation of tertiary sites and the lack of

Scheme 1. Selective Functionalization of 2,6,10,14-Tetramethylpentadecane with EDA

insertion into the methylene groups are in good agreement with the trends presented above.

In conclusion, we have found that the complex $\text{Tp}^{\text{Br}^3}\text{Cu}(\text{NCMe})$ (**1**) is an excellent catalyst for the regioselective carbene-transfer reaction to tertiary C–H bonds of hydrocarbons. Applications to other substrates, such as hydrocarbon polymeric chains, are currently underway in our laboratories.

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Supporting Information Available: Syntheses and characterization of complexes **1** and **2**, and spectroscopic data for the monoesters compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (16) Experimental: (a) All the operations were carried out inside a drybox. **1** (0.05 mmol) was dissolved in CH₂Cl₂ (5 mL) and the alkane (20 mL). A solution of EDA (1 mmol) in the same alkane (10 mL) was added for 5 h with the aid of a syringe pump. No EDA was detected at the end of the reaction by GC. After removal of volatiles, the crude product was investigated by ¹H NMR spectroscopy. (b) In the case of TMPD, 1 mmol of the alkane was dissolved in 20 mL of CH₂Cl₂, and 10 mmol of EDA was added (10 mL of CH₂Cl₂) over 5 h with the syringe pump.
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