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# Intermolecular Copper-Catalyzed Carbon−Hydrogen Bond Activation via Carbene Insertion

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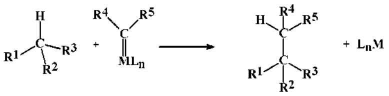
Carbon−hydrogen bond activation by transition metal complexes has been a major theme in organometallic chemistry over the last two decades, and a plethora of contributions regarding this topic has appeared.[1,2] Most studies report reactions which, at some stage, involve oxidation addition of a C−H bond to the metal center.[3] As noted by Davies,[4,5] the transition metal-catalyzed reactions of diazocompounds with alkanes can also be regarded as a C−H bond activation process. A highly reactive, transient metal carbene complex inserts the carbene moiety into a C−H bond, and the unsaturated metal complex is regenerated (eq 1). This methodology, unlike most reactions based an C−H oxidation addition, presents the advantage of operating catalytically.

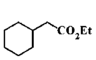
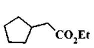
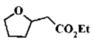
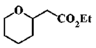
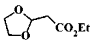
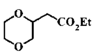


(1)

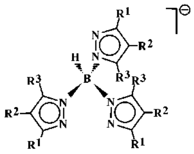
Scott et al.[6] described for the first time the reaction of ethyldiazoacetate (EDA) or diazoacetophenone with cyclohexane in the presence of copper sulfate or copper chloride to give the corresponding insertion products in 9−25% yield. Similar results were presented by Wulfman using $Cu(acac)_2$ or $P(OMe_3)CuCl$ as the catalysts and dimethyl malonate as the carbene source with similar, low yields of C−H activation products being obtained.[7] However, copper was replaced as a valuable catalyst for this transformation after the introduction of rhodium-based catalysts. Seminal work by Noels and co-workers[8] reported the conversion of ethyl diazoacetate and cyclohexane into ethylcyclohexyl acetate in 78% yield at room temperature using $Rh_2(CF_3COO)_4$ as the catalyst. Other cycloalkanes were converted into the corresponding acetate derivatives in lower yields. Callot[9] also described moderate conversions of EDA and linear alkanes into linear monoesters using rhodium(III) porphyrins as catalysts. Very recently, Davies and co-workers[4,5,10] have reported a significant advance in this alternative C−H activation process by employing rhodium-based chiral catalysts together with aromatic- or vinylidene-substituted diazoacetates. They have found this system catalyzes the conversion of many substrates (alkanes, cyclic ethers, cyclic amines) into the corresponding insertion products in moderate-to-high yields and with high enantiomeric excesses.

Employing EDA as the carbene source, we have recently described the use of homoscorpionate-copper(I) catalysts of composition $Tp^XCu$ for olefin cyclopropanation reactions which give very high yields as well as very high diastereoselectivity toward the *cis* isomer.[11] We have now tested the catalytic capabilities of this copper-based system toward the activation of cycloalkanes and cyclic ethers and have found moderate-to-high degrees of conversion under very mild conditions.

**Table 1.** Intermolecular C−H Activation Using EDA and Catalyzed by $Tp^{Ms}Cu^a$

| Substrate | Product | Yield[c] | Relative Reactivity[b] |
|---|---|---|---|
| Cyclohexane |  | 54[d] | 1.0 |
| Cyclopentane |  | 50[d] | 0.34 |
| Tetrahydrofuran |  | 95[e] | 36 |
| Tetrahydropyran |  | 84[f] | 2.78 |
| Dioxolane |  | 95[e] | 18 |
| Dioxane |  | 20[f] | 0.12 |

[a] For experimental details, see ref 13. [b] Cyclohexane as reference. [c] Percentage of insertion product at the end of the reaction (diethyl fumarate and maleate accounted for 100% of EDA). Determined by GC after total consumption of EDA. [d] Addition time: 20 h. [e] Addition time 2 h. [f] Addition time 10 h.



$Tp^X$

The first catalyst employed was generated in situ upon reacting the thallium salt of the hydrotris(3-mesityl)pyrazolylborate[12] ligand ($Tp^{Ms}$) with copper iodide. After workup, the catalyst was dissolved in the corresponding substrate, and EDA was slowly added (5 h) with the aid of a syringe pump. Table 1 shows the results obtained with several substrates containing five- and six-membered rings. In all cases, the reaction was very selective, only one product being observed for each substrate. Although we have not yet optimized yields, we have found that the addition rates of the carbene precursor were crucial for the less reactive substrates. Whereas cyclohexane was converted in 54% yield after 20 h of slow EDA-addition, 95% yields for reactions of tetrahydrofuran and dioxolane were obtained using 2 h of automatic addition. In the case of these more reactive substrates, a longer addition time resulted in the appearance of side products, probably derived from further activations. The yields in cycloalkane activation were lower than those reported by Noels et

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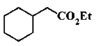
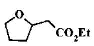
***Table 2.*** C−H Insertion into Cyclohexane and Tetrahydrofuran with EDA and Percentage of *cis* Isomer in the Styrene Cyclopropanation Reaction Catalyzed by Tp$^{\text{X}}$Cu$^{a,b}$

| Ligand | R$^1$ |  |  | % *cis* cyclop.$^c$ |
|---|---|---|---|---|
| Tp | H | --$^d$ | 27 | 42 |
| Tp$^*$ | $CH_3$ | 3 | 39 | 55 |
| Tp$^{\text{Np}}$ | $CH_2C(CH_3)_3$ | 9.5 | --$^d$ | 62 |
| Tp$^{\text{Cy}}$ | $C_6H_{11}$ | 19 | 72 | 77 |
| Tp$^{\text{Ph}}$ | $C_6H_5$ | 20 | 82 | 80 |
| Tp$^{\text{Ms}}$ | 2,4,6-$Me_3C_6H_2$ | 29 | 98 | 98 |

[a] For experimental details, see ref 13. [b] Percentage of the insertion product at the end of the reaction (diethyl fumarate and maleate accounted for 100% of EDA), determined by GC after total consumption of EDA. [c] Reference 11. [d] Not determined.

al.[8a] with the aforementioned rhodium catalyst (78 and 50% for cyclohexane and cyclopentane, respectively). The almost quantitative conversion[13] of THF into the acetate derivative compares well with Davies' results[4,5] with this cyclic ether (70−90%), in our case with EDA as the carbene source. For tetrahydrofuran and tetrahydropyran, the α-carbon−hydrogen bond was the preferred reaction site, whereas for dioxolane the only product observed was that derived from insertion into the C−H bond of the singular methylene group between the oxygen atoms. These results are in accord with those from Adams and co-workers[14] who showed the preferential insertion of carbenoids into C−H bonds adjacent to ether oxygens.

The relative reactivities of the substrates employed have also been determined by means of competition experiments. The results displayed in Table 1 show that the cycloalkane substrates were less reactive than the cyclic ethers, with the exception of dioxolane. Regarding the cyclic ethers, two trends are clearly observed (i) five-membered rings are more reactive than six-membered rings, and (ii) those with one oxygen atom are more reactive than the two-oxygen-containing cycles.

We have also tested the influence of the groups attached to the Tp$^{\text{X}}$-pyrazolyl rings on the activity of the corresponding Tp$^{\text{X}}$Cu catalysts. Several catalysts have been employed under the same experimental conditions, using cyclohexane or tetrahydrofuran as the substrates. The results are shown in Table 2. For THF, the aforementioned mesityl derivative provided the highest degree of conversion, whereas the unsubstituted Tp ligand only gave 27% yield. The Tp$^{\text{Ph}}$ ligand also afforded a good yield (82%), very close to that of the cyclohexyl derivative, Tp$^{\text{Cy}}$ (72%). Regarding the cycloalkane, the same order in reactivity was observed although yields were considerably lower, as expected from Table 1. Thus, it seems that the activation of these carbon−hydrogen bonds is achievable in a general way for this family of Tp$^{\text{X}}$Cu catalysts, with the mesityl-derived catalyst being the most active of them. Since a metal−carbene has been proposed to be the key intermediate in both processes, that is, the C−H activation and the cyclopropanation reaction,[3] some information could be gained comparing experimental data of both reactions with the same catalysts. Figure 1 displays the plot of the yields in C−H insertion products for THF and cyclohexane versus the percentage of the *cis* isomer obtained in the styrene cyclopropanation reaction with those catalysts (Table 2).[11] There is clearly a correlation between the *cis* diastereoselection and the yields of C−H activation products. Somewhat similar results were reported by Callot et al. for rhodium porphyrins as the catalyst.[9b] This observed correlation may be related to the existence of a limited catalytic pocket that would be responsible of the *cis* diastereoselection and suggests that other *cis*-selective cyclopropanation catalysts[3] should be revisited to test their capabilities toward the activation of carbon−hydrogen bonds via carbene insertion.

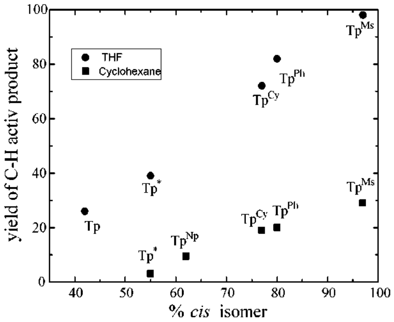


***Figure 1.*** Plot of the yield of the C−H insertion products vs percentage of the *cis* isomer in the styrene cyclopropanation reaction.

In conclusion, we have presented a series of catalysts of general formula Tp$^{\text{X}}$Cu that, by using ethyl diazoacetate as the carbene source, catalyze the insertion of :$CHCO_2Et$ into the carbon−hydrogen bonds of cycloalkanes and cyclic ethers in moderate-to-high yield, and efficient use of Cu for this transformations should rekindle interest in this inexpensive metal for these synthetically useful reactions.

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(13) Experimental Section: (a) 0.05 mmol of CuI and an equimolar amount of the TlTp$^{\text{Ms}}$ salt were dissolved in $CH_2Cl_2$, and the mixture was stirred for 2−3 h. Volatiles were removed under vacuum, and the residue was extracted with 15 mL of cyclohexane. To the resulting filtrate, a solution of 1.25 mmol of EDA (50 equiv relative to Cu) dissolved in 5 mL of cyclohexane was slowly added at a 1 mL/h rate (total time 5 h). No EDA was detected at the end of the reaction by GC. (b) Relative reactivities: after catalyst generation, it was dissolved in an equimolar mixture of substrates (e.g., cyclohexane and THF). EDA (1 mmol) was dissolved in 10 mL of dichloroethane and added at a 1 mL/h (total time 10 h). (c) Tp$^{\text{X}}$Cu (0.05 mmol, generated as above) was dissolved in 10 mL of THF, and a solution of EDA (1.25 mmol, 25 equiv relative to Cu) in THF (10 mL) was added at a 2.5 mL/h (total time 4 h). The cyclohexane experiments were nearly identical (total time 20 h) but required a 1:1 mixture of the cycloalkane and $CH_2Cl_2$ due to the insolubility of some catalysts in neat $C_6H_{12}$. No reaction was observed in a control experiment carried out with $CH_2Cl_2$ as the solvent, with only diethyl fumarate and maleate being obtained in this case.

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