Copper-Catalyzed Carbene Insertion into O−H Bonds: High Selective Conversion of Alcohols into Ethers

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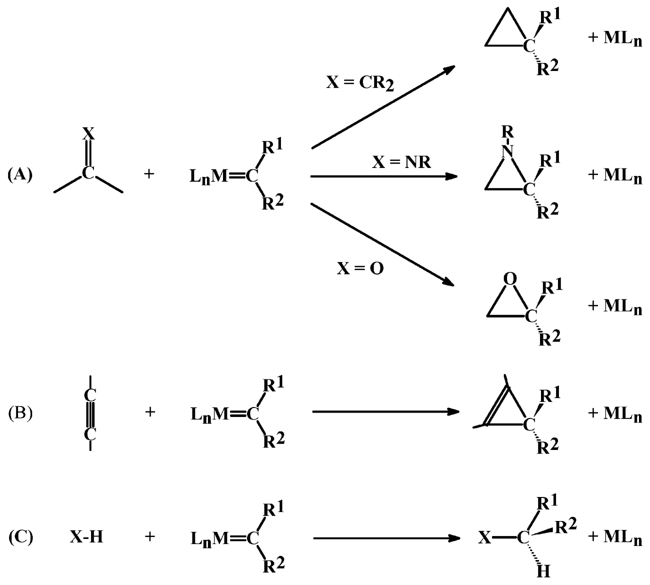
The complexes Tp^XCu (Tp^X = homoscorpionate ligands) efficiently catalyze the insertion of the carbene fragment $:CHCO_2Et$, generated from ethyl diazoacetate, into the OH bond of saturated and unsaturated alcohols, under mild conditions. In the case of unsaturated alcohols, the reaction proceeds selectively toward the insertion product, and in no case has the addition product been observed.

Introduction

The decomposition of diazo compounds in the presence of transition metal complexes as catalysts has allowed the controlled transfer of carbene units into organic substrates.[1,2] Usually these reactions formally consist of (i) the addition of such fragment to an unsaturated bond (Chart 1, A and B) or (ii) its insertion into an X−H bond (Chart 1, C). The latter process has been reported for X = C, Si, N, P, O, S, Se, and halides.[1] Particularly interesting is the case of the insertion into hydroxylic bonds,[3] since it provides a new carbon−oxygen bond, and the subsequent conversion of the alcohol into an ether. The syntheses of several natural products as well as of cyclic ethers have been achieved using this methodology at a certain stage of the synthetic pathway.[4]

Chart 1



Since its discovery in the late 1970s, $Rh_2(OAc)_4$ has been the catalyst of choice for the above transformations.[5] This complex catalyzes the insertion of several diazo compounds[6,7] into the O−H bond of saturated alcohols at room temperature and in high yield. Other metals such as Ru,[8] Cu,[9] Ni,[9c] or Sc[10] have also been employed as catalysts, but their activities were quite far from those obtained with the rhodium catalyst. However, there is still a drawback with $Rh_2(OAc)_4$ as the catalyst when unsaturated alcohols are employed. Although the O−H insertion products are the major products, the addition derivatives are also obtained in such amounts that this catalyst cannot be considered as selective from a synthetic point of view.[5] Given the importance of this reaction, a high selective catalyst for the O−H etherization would be very convenient. Very recently, a platinum-based system[11] has been developed, providing high yields of the O−H insertion product for the reaction of allyl alcohol with ethyl diazoacetate

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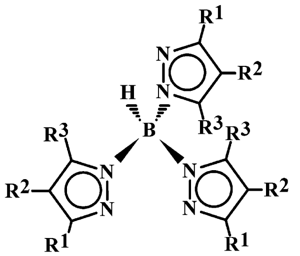
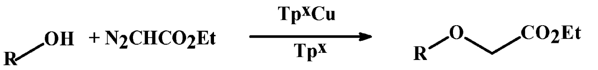
(EDA), with minor amounts of cyclopropanes being detected. The system operates at 45 °C, with a somewhat high alcohol:EDA ratio employed (20:1). In this contribution we present the catalytic capabilities of a series of complexes of general formula Tp^{X}Cu (Tp^X = homoscorpionate ligand)[12] as catalysts for the insertion of carbene units derived from EDA into the O−H bond of saturated and unsaturated alcohols.



Results and Discussion

Saturated Alcohols. We have studied in recent years the use of copper(I) complexes containing homoscorpionate ligands as catalysts for diazoester decomposition. Addition to olefins[13] and alkynes[14] as well as insertion into C−H[15] and N−H[16] bonds have been achieved in high yields, and under very mild conditions. We also decided to investigate the potential of this system toward the O−H bond functionalization, with this goal in mind: to develop a catalyst showing the activity of rhodium, the selectivity of platinum (in the case of allyl alcohol), and the added value of the low cost of copper. In a first series of experiments, we have tested the catalytic capabilities of the complex Tp*Cu[17] (**1**) (Tp* = hydrotris(3,5-dimethylpyrazolyl)borate) for the reaction of ethyl diazoacetate and a series of saturated, lineal, and branched alcohols. The reactions were performed at room temperature and with a 2:1 alcohol to EDA ratio (eq 1). The results are shown in Table 1. After completion, almost quantitative conversion of the initial alcohols into the corresponding ethers was observed in all cases. The other products detected were diethyl fumarate and maleate as well as ethyl glycidate, the latter as the result of water functionalization (alcohols were employed from commercial samples without any purification). To our knowledge, the degree of transformation shown in Table 1 finds no precedent for copper as the catalyst. Although the first examples of carbene insertion into O−H bonds were reported with this metal,[9] the yields were low to moderate and high alcohol:diazo reagent ratios were employed. In addition, the reactions were usually performed at higher than ambient temperatures. Moreover, the results presented herein with **1** as the catalyst are very similar to those originally reported by Noels and co-workers for $Rh_2(OAc)_4$.[5] Since these were obtained using a ca. 17:1 alcohol:EDA ratio, we have now performed twin reactions to directly compare the efficiency of both catalysts, and we have observed a slight difference in activity favoring the copper-based catalyst. As an example, two experiments were set following the conditions employed in Table 1, using 2-propanol as the substrate and **1** and $Rh_2(OAc)_4$ as the catalysts. The yields of $i\text{-}C_3H_7OCH_2CO_2Et$ obtained were 96% and 91% (average of two runs), respectively. Thus, we can conclude at this stage that complex Tp*Cu (**1**) is an excellent catalyst for the insertion of EDA into O−H bonds of saturated alcohols. It is worth mentioning that complex **1** can be prepared very easily from copper iodide and the potassium salt of the Tp* ligand,[17] which can also be readily prepared in multigram scale within a few hours.[12]



(1)

Table 1. Catalytic Conversion of R−OH and Ethyldiazoacetate (EDA) in the Presence of Complex Tp*Cu (1)[a]

alcohol	product	yield[b] (%)
C_2H_5OH	$C_2H_5OCH_2CO_2Et$	>95
$n\text{-}C_3H_7OH$	$n\text{-}C_3H_7OCH_2CO_2Et$	>95
$i\text{-}C_3H_7OH$	$i\text{-}C_3H_7OCH_2CO_2Et$	>95
$n\text{-}C_4H_9OH$	$n\text{-}C_3H_7OCH_2CO_2Et$	>95
$sec\text{-}C_4H_9OH$	$sec\text{-}C_4H_9OCH_2CO_2Et$	>95
$n\text{-}C_5H_{11}OH$	$n\text{-}C_5H_{11}OCH_2CO_2Et$	>95
$n\text{-}C_6H_{13}OH$	$n\text{-}C_6H_{13}OCH_2CO_2Et$	>95

[a] See Experimental Section. EDA addition time 6 h. [b] Determined by ^1H NMR after reaction completion.

We have also carried out competition experiments between different alcohols in order to gain information about the relative reactivity. The group of alcohols employed ranged from lineal to branched, from C2 to C8 chains. Some with electron-withdrawing atoms such fluorine were also employed. Ten competition experiments were performed (see Experimental Section), using ethanol as the reference in all cases. This methodology has allowed the construction of a reactivity scale, which is shown in Figure 1. The following trends can be inferred from these data: (i) linear alcohols of higher chains are more reactive than ethanol; (ii) for a series of identical general formula alcohols, e.g., $C_4H_{10}O$, the higher the branching, the lower the reactivity (*n*-butanol > *sec*-butanol > *tert*-butyl alcohol); (iii) the existence of electron-withdrawing atoms diminishes the reactivity (ethanol > 2-fluoroethanol >>> 2,2,2-trifluoroethanol). The inductive effect of the R alkyl chain in *n*-ROH increases with the number of carbons, and this supposes that the enhancement of the electronic density at the oxygen atom favors the reaction. In good accord with this, when fluorine-containing alcohols were used, the reactivity was considerably reduced: from a competition experiment with ethanol, 2-fluoroethanol, and 2,2,2-trifluoroethanol this ratio was determined to be 1:0.5:0.01. The increase in reactivity when enlarging the chain contrasts with the results reported for the systems

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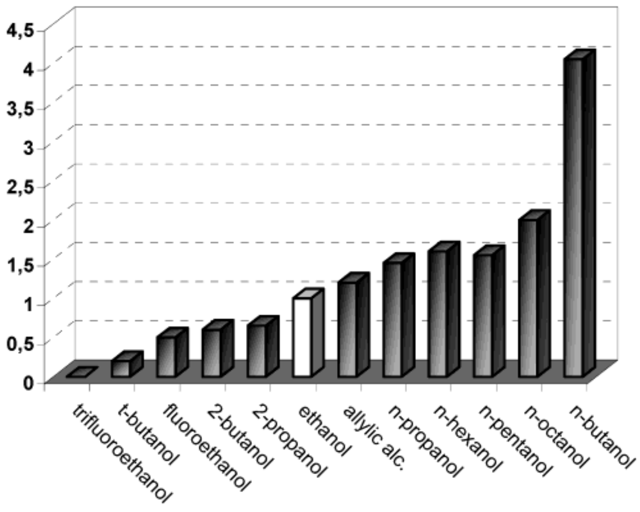
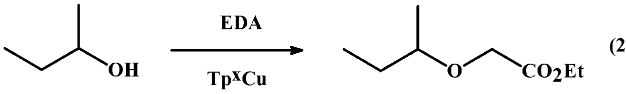


Figure 1. Relative reactivity of alcohols toward carbene insertion catalyzed by **1**.

based on Ru[8a] and Pt,[11] which showed the opposite effect. With branched alcohols, an increase in the size of R (in R−OH) produced a decrease in reactivity, as inferred from the series *n*-butanol, *sec*-butanol, and *tert*-butyl alcohol. It is obvious that in some cases a delicate balance between both steric and electronic effects takes place. This is the case of the linear alcohols with longer chains, which may undergo different conformations that enhance the steric effect. This could explain the decrease in reactivity of pentanol, hexanol, and octanol when comparing with *n*-butanol.

The existence of a number of homoscorpionate ligands[12] with different electronic and steric properties has allowed the study of the effect of the catalyst in this reaction. We have carried out four reactions with 2-butanol as the substrate, under identical conditions, and using Tp*Cu, $Tp^{Cy}Cu$ (**2**), $Tp^{Br3}Cu$ (**3**), and $Tp^{Ms}Cu$ (**4**) as the catalysts. The yields in the corresponding ether (eq 2) were 80, 85, 88, and 92%, respectively. The



(2)

evaluation of the electronic effect can be qualitatively made in terms of the ν(CO) frequency for the series $Tp^{X}Cu(CO)$ complexes: 2056 cm^{-1} for Tp*Cu(CO), 2061 cm^{-1} for $Tp^{Cy}Cu(CO)$, 2105 cm^{-1} for $Tp^{Br3}Cu(CO)$, and 2079 cm^{-1} for $Tp^{Ms}Cu(CO)$. It is clear that the highest frequency of the perbromo derivative does not correspond with the best yield of the mesityl case. A possible evaluation of the steric effect can be done in terms of the diethyl fumarate/diethyl maleate ratio obtained in the reaction as byproducts. The fumarate (*trans*) geometry requires a higher catalytic pocket than the maleate (*cis*) isomer. Figure 2 shows a plot of the ether yields versus the fumarate/maleate ratio, where a good linear correlation is observed. Since the fumarate/maleate ratio must be mainly influenced by the steric hindrance at the catalytic site, we believe that these results, in conjuction with the IR values, support the proposition that this transformation is mainly affected by the size of the catalysts.

The mechanism of the transformation of alcohols into ethers via carbene insertion has been described in a general way for several metals,[1] although to our knowledge, no proposal for a copper-based system has yet been reported. Scheme 1 shows the mechanistic proposal that is in accord with the pieces of information that we have collected. Previous studies with copper-homoscorpionate catalysts for carbene transfer reactions showed that the $Tp^{X}Cu$ complex adopts a dihapto geometry in advance of its interaction with EDA.[13d] The next step is the formation of a copper-carbene intermediate, with a trigonal geometry, similar to that detected very recently by Hofmann.[18] This metallocarbene transient species displays an electrophilic behavior, as inferred from the data already mentioned: electron-withdrawing groups diminished the reactivity, whereas an increase in the nucleophilicity in the substrate (e.g., by means of an increase in the inductive effect of the carbon chain) originated the opposite effect. Depending on the relative concentrations of EDA and the alcohols, the carbene can react with one or another to give the nondesired fumarate/maleate or the corresponding ether. Because of this, the use of slow addition devices allowed quantitative yields in ether (Table 1), just by enlarging the reaction time. The reactivity of the carbene seems to be affected by sterics at the catalytic pocket: the smaller this is, the higher the selectivity toward the alcohol. A similar trend was observed for the olefin cyclopropanation reaction, for which a kinetic control was proposed.[13d]

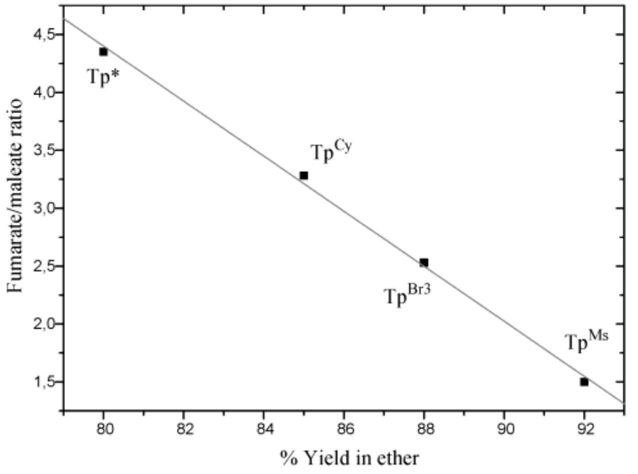
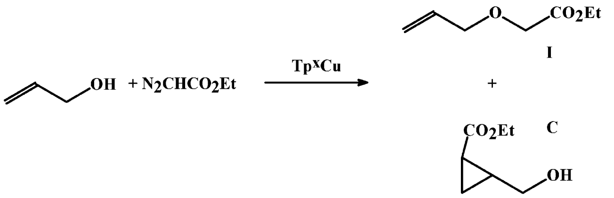


Figure 2. Plot of the yield in ether in the reaction of 2-butanol with EDA vs the fumarate/maleate ratio obtained with several $Tp^{X}Cu$ catalysts.

Unsaturated Alcohols. Alcohols with multiple C−C bonds have also been studied using complex **1** as the catalyst. When allyl alcohol was reacted with EDA in the presence of Tp*Cu, the insertion product **I** (eq 3) was obtained in 80% yield. Interestingly, the addition



(3)

product, i.e., the cyclopropane derivative **C** (or the

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Scheme 1

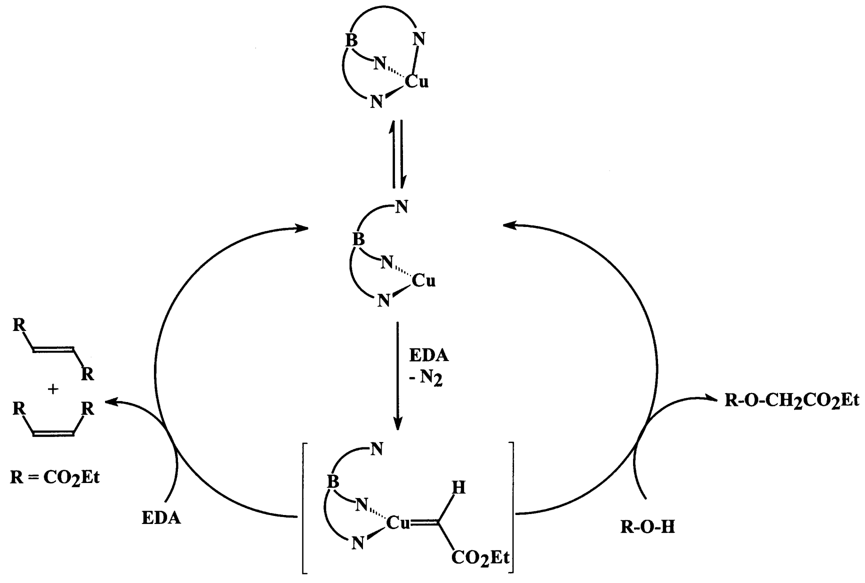
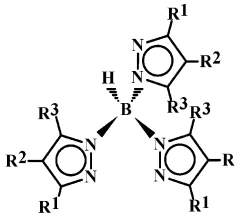


Table 2. Catalytic Conversion of Allyl Alcohol and Ethyldiazoacetate (EDA) in the Presence of Complexes $\mathrm{Tp^XCu}^a$



$\mathrm{Tp^X}$	R^1	R^2	R^3	% $\mathbf{C}^b$	% $\mathbf{I}^b$	
Tp*	Me	H	Me	nd	80^c	$>95^d$
$\mathrm{Tp^{Ms}}$	Ms	H	H	nd	27^c	40^d
$\mathrm{Tp^{Cy}}$	Cy	H	H	nd	80^c	$>95^d$
$\mathrm{Tp^{Br3}}$	Br	Br	Br	nd	$>95^c$	$>95^d$

[a] See Experimental Section. [b] **C** and **I** products in eq 3, yields determined by ^{1}H NMR after reaction completion; nd = not detected. [c] EDA added in 1 h. [d] EDA added in 6 h.

lactone spontaneously formed from the *cis* isomer) has not been detected, whereas diethyl fumarate or maleate and ethyl glycidate accounted for 100% of initial EDA. We have tested several complexes of general formulas $\mathrm{Tp^XCu}$ for this reaction, using a 1:20:40 [catalyst]:[EDA]:[allyl alcohol] ratio, with the results shown in Table 2. Using a 1 h addition time for EDA; the $\mathrm{Tp^{Br3}Cu}$ catalyst induced a nearly quantitative conversion into the insertion product, again with no addition product being detected. The $\mathrm{Tp^{Cy}}$-containing catalyst gave yields similar to complex **1**. The $\mathrm{Tp^{Ms}Cu}$ complex also gave no cyclopropane at all, although the yield in the insertion product was low. When increasing the EDA addition time from 1 to 6 h, yields were optimized, and both Tp* and $\mathrm{Tp^{Br3}}$ gave similar conversions.

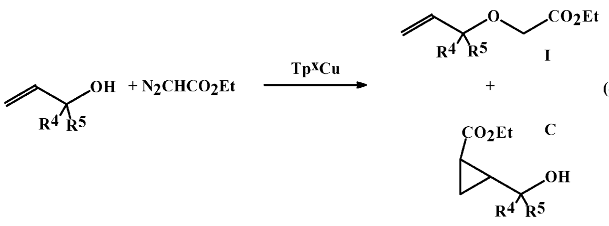
The values reported for the reaction depicted in eq 3 when using $\mathrm{Rh_2(OAc)_4}$ as the catalyst were 66% for **I** and 15% for **C**, and other related catalysts gave in all cases a mixture of both.[5] The **C**/**I** ratio was much higher when using copper-based catalysts such as triflate salts.[5] Only the aforementioned platinum-based system reported by Demonceau et al. has provided similar yields (90–97%), although the reaction conditions were quite different from our $\mathrm{Tp^XCu}$ system: in the Pt case,[11] a 20-fold excess of alcohol was required and the reaction was performed at 45 °C (2:1 alcohol:EDA ratio, room temperature, for **1** as the catalyst).

Table 3. Catalytic Conversion of the Unsaturated Alcohols in Eq 4 in the Presence of Complexes Tp*Cu (1) and $\mathrm{Tp^{Br3}Cu}^a$

		Tp*Cu		$\mathrm{Tp^{Br3}Cu}$	
R^4	R^5	% $\mathbf{I}^b$	%$\mathbf{C}^b$	% $\mathbf{I}^b$	%$\mathbf{C}^b$
H	H	>95	nd	>95	nd
H	Me	92	nd	>95	nd
Me	Me	75	nd	75	nd

[a] See Experimental Section. [b] **C** and **I** products in eq 4, yields determined by ^{1}H NMR after reaction completion; nd = not detected.

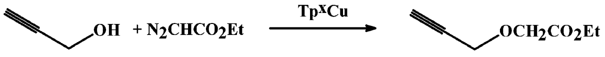
An important feature pointed out by Noels and coworkers in their seminal work with $\mathrm{Rh_2(OAc)_4}$ was the relationship between the selectivity and the steric hindrance near the OH group. They found that the **C**/**I** ratio increased when increasing the steric hindrance in the carbon supporting the hydroxyl group.[5] We have also studied this effect, by means of the reactions summarized in eq 4. Three unsaturated alcohols have been studied: allyl alcohol, 3-buten-2-ol, and 2-methyl-3-buten-2-ol, with none, one, and two methyl groups in the carbon atom attached to the OH group. The results are shown in Table 3, and again in no case was the addition product observed. With Tp* and $\mathrm{Tp^{Br3}}$ as the ligands, the enhancement of the steric bulk around the OH group induced a slight decrease in the yields of **I**, but this was not accompanied of the appearance of **C**; instead an increase in the yields of the EDA-coupling products and/or ethyl glycidate was observed. These



(4)

results assess that the steric hindrance affects the selectivity of the carbene intermediate toward more EDA or the unsaturated alcohol. However, at variance with the known rhodium-based catalysts, it has no effect on the regioselectivity of the reactions in terms of the relative amounts of the insertion and the addition products.

Propargyl alcohol has also been studied with these catalysts. In a similar manner, under the conditions of the experiments shown in Table 3, the use of Tp*Cu induced a 65% conversion into the insertion product (eq 5). No addition product, i.e., cyclopropene, has been observed. When employing $Tp^{Cy}Cu$ as the catalyst (which has been reported to efficiently catalyze the alkyne cyclopropenation reaction),[14] the yield increased to 70%, but again, cyclopropenes were not detected in the reaction mixture.



(5)

In conclusion, the complexes Tp^XCu catalyze the insertion of the $CHCO_2Et$ fragment (from EDA) into the OH bond of saturated and unsaturated alcohols with very high degrees of chemoselectivity (high yields in ethers) and regioselectivity (for unsaturated alcohols, only the insertion products were obtained). We believe that the catalytic properties of this system, particularly with the readily available complex Tp*Cu (**1**), make this methodology a synthetic tool for alcohol functionalization.

Experimental Section.

General Methods. All preparations and manipulations were carried out under oxygen-free nitrogen atmosphere using conventional Schlenck techniques. The solvents were dried and degassed before use. The Tp^X ligands were prepared as reported in the literature.[12] Alcohols and ethyl diazoacetate were purchased from Aldrich and employed without any further purification. GC data were collected with a Varian GC-3350 instrument. NMR were run in a Varian Mercury 400 MHz spectrometer.

Synthesis of the Catalysts. A 1 mmol sample of CuI and an equimolar amount of Tp^XTl (potasium salt in the case of hydrotris(3,5-dimethylpyrazolyl)borate) were dissolved in 50 mL of the appropriate solvent (THF for $Tp^{Ms}Cu$, MeCN for $Tp^{Br3}Cu$, $Tp^{Ph}Cu$, and $Tp^{Cy}Cu$, and CH_2Cl_2 for Tp*Cu), and the mixture was stirred for 6−8 h. The resulting suspension was filtered to remove the KI or TlI salts, and the filtrate was evaporated under reduced pressure. The residue was extracted with a 5:1 petroleum ether/CH_2Cl_2 mixture (20 mL), and the colorless solution was concentrated and cooled at −20 °C to give complexes Tp^XCu as white microcrystalline material. Yields: 70%−90%.

General Catalytic Reaction. To a solution of the Tp^XCu catalyst (0.05 mmol) in CH_2Cl_2 (20 mL) was added 2 mmol of the corresponding alcohol. A solution of EDA (1 mmol) in CH_2Cl_2 (10 mL) was added with the aid of a syringe pump for the corresponding time (1−6 h). 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.

Competition Experiments with Alcohols. Following the above procedure, equimolar mixtures of several alcohols were evaluated. At the end of the reactions, the mixture of products was studied by GC, and the relative peaks were compared with previous calibration curves.

The complexes Tp^XCu (Tp^X = homoscorpionate ligands) efficiently catalyze the insertion of the carbene fragment $:CHCO_2Et$, generated from ethyl diazoacetate, into the OH bond of saturated and unsaturated alcohols, under mild conditions. In the case of unsaturated alcohols, the reaction proceeds selectively toward the insertion product, and in no case has the addition product been observed.

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Supporting Information Available: Tables with NMR data of the ethers prepared and ^1H NMR spectra of representative products. This material is available free of charge via the Internet at http://pubs.acs.org.

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