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Very Efficient, Reusable Copper Catalyst for Carbene Transfer Reactions under Biphasic Conditions Using Ionic Liquids

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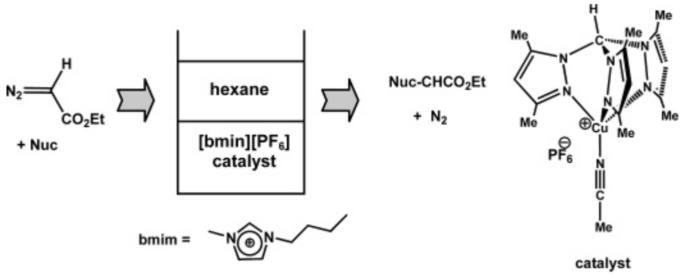
ABSTRACT



The complex {[HC(3,5-Me$_2$pz)$_3$]Cu(NCMe)}BF$_4$ catalyzes the transfer of the :CHCO$_2$Et unit from ethyl diazoacetate to several saturated and unsaturated substrates with very high yields and under biphasic conditions using the ionic liquid [bmim][PF$_6$] and hexane as the reaction medium. The catalyst has been tested for several cycles of recovery and reuse without any loss of activity.

Diazo compounds have been extensively employed as a carbene source in organic synthesis.[1] This methodology has gainered increasing interest in the past decade because of the use of transition-metal-based catalysts to promote and control the transfer of the CR^{1}R^2 unit to a plethora of organic substrates (Scheme 1). However, most of these catalytic systems operate under homogeneous conditions. The recovery and subsequent reuse of the catalysts are of interest to minimize cost in scale-up processes.[2] Despite the potential wide range of reactions involving metal-catalyzed diazo compound decomposition, only a few systems allow for the separation of the catalyst. For example, anchoring of the catalytic species to a solid support, such as silica,[3] clays, zeolites,[4] and polymeric materials,[5] has the potential for multiple catalytic sites instead of the characteristic single-site catalysis observed in the homogeneous phase. Only recently, Davies et al. have described an effective strategy for the immobilization of dirhodium dimer catalysts for carbene transfer from diazo compounds.[6] In the past decade, biphasic catalysis has emerged as a useful technique for

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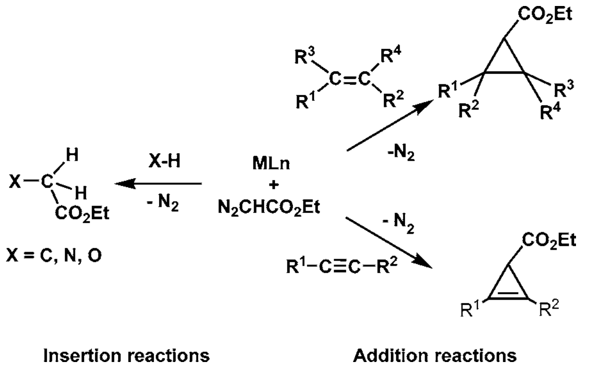
Scheme 1. Common Transition-Metal-Catalyzed Carbene Transfer Reactions from Diazo Compounds



effecting heterogeneous and homogeneous catalysis. Biphasic catalysis is currently based mainly in the use of fluorous chemistry[7] and ionic liquids (IL),[8] and its use for the catalytic decomposition of diazocompounds has still been limited to the olefin cyclopropanation reaction.[9]

In recent years, we have developed a family of copper-based catalysts of the general formula Tp^xCuL (Tp^x = homoscorpionate ligand)[10] for the transfer of the $:CHCO_2Et$ fragment from ethyl diazoacetate (EDA) to a variety of saturated (N−H,[11] O−H,[12] and C−H[13] bonds) and unsaturated (alkenes[14] and alkynes[15]) substrates under homogeneous conditions. We have now designed a catalytic system for easy separation and recycling of catalysts with behaviors similar to that observed under homogeneous conditions. An earlier report from this laboratory[16] showed that fixation of those catalysts on silica gel was feasible. However, their use in the olefin cyclopropanation reaction demonstrated that the selectivity was different from that of the homogeneous system. These results prompted us to move into biphasic catalysis and specifically into the use of ILs as the reaction medium for the copper-induced decomposition of EDA and the subsequent carbene transfer to several substrates. We chose the readily available $[bmim][PF_6]$[17] ionic liquid as the reaction medium. As expected, the neutral Tp^xCuL complexes did not dissolve in this IL. On the other hand, the related cationic complex $\{[HC(3,5\text{-}Me_2pz)_3]Cu(NCMe)\}BF_4$ (**1**) (Figure 1), reported by Reger and co-workers,[18] was soluble in $[bmim][PF_6]$. To establish the catalytic properties of **1** under homogeneous conditions, for EDA decomposition, a first set of experiments was carried out on the following substrates: styrene, 1-phenyl-1-propyne, aniline, ethanol, and cyclohexane. In a typical experiment, 1 mmol of EDA was slowly added (6 h) to a solution containing **1** (5% with respect to EDA) and the corresponding substrate in excess. After the addition, no EDA was observed by GC. As shown in Table 1, the additions to double and triple bonds were achieved with high yields (entries 1 and 2), a feature also observed for insertion into N−H and O−H bonds (entries 3 and 4). These results are similar to those obtained with the Tp^x-containing catalysts.[11,12,14,15] Insertion into the C−H bonds of cyclohexane was also observed, albeit in low yield (30%). The catalytic activity of complex **1** was noteworthy with respect to copper-based catalysts that promote the olefin cyclopropanation reaction with EDA because few catalytic copper systems perform alkyne cyclopropenation[15] and X−H functionalization (X = N, H, C).[11−13]

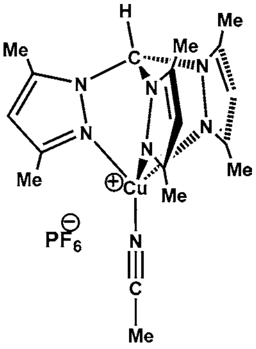


Figure 1. $\{[HC(3,5\text{-}Me_2pz)_3]Cu(NCMe)\}BF_4$ (**1**).

Once the catalytic properties of complex **1** were demonstrated, we tested it under biphasic conditions using [bmim]-

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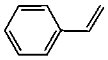
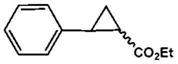
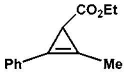
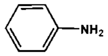
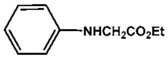
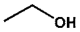
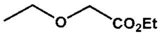
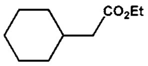
Table 1. Carbene Transfer from Ethyl Diazoacetate (EDA) Using $\{[HC(3,5\text{-}Me_2pz)_3]Cu(NCMe)\}PF_6$ (**1**) as the Catalyst in Homogeneous (Methylene Chloride) and Biphasic ([bmim][PF_6]-hexane) Media[a]

entry	substrate	product	homog.[b]	biphasic [b]
1			96	95
2	Ph-C≡C-Me		80	77
3			99	96
4			99	98
5			30	35

[a] Reactions performed at room temperature with 0.05 mmol of the catalyst, 5% with respect to EDA. [b] Based on EDA. Diethyl fumarate and maleate and ethyl glycolate accounted for the remaining diazo compound. Determined by NMR of the reaction mixture with an internal standard.

PF_6. The catalyst was dissolved in the ionic liquid (1.5 g), and 4 mL of hexane was added along with the substrate. From a syringe pump, EDA (1 mmol dissolved in hexane) was added for 6 h. After that time, the organic phase was transferred, and the ionic liquid was washed twice with hexane. Then, the products were detected and conversions were quantified by NMR. The mass balance (based on EDA) demonstrated that no products remained in the IL. To check if any significant catalyst leaching into the organic phase took place, a second 1 mmol portion of EDA was added to the organic solution in one portion, and the mixture was stirred for 6 h. No EDA consumption was observed, evidence that the amount of active catalyst in the organic solution was negligible. To our best knowledge, the examples reported herein concerning alkyne cyclopropenation as well as the functionalization of N−H, O−H, and C−H bonds by carbene insertion are unprecedented *in this reaction medium*. As mentioned above, only the cyclopropanation of olefins, with diazo compounds, has been reported in IL, either with copper-,[9a−c,h] ruthenium-,[9f] palladium-,[9g] or rhodium-based[9d] catalysts, although the conversions obtained with this **1**−[bmim]PF_6 system are higher than those obtained with those catalysts.

We concluded that this biphasic catalytic system operated similarly to the homogeneous systems, without significant catalyst leaching. Reuse of the catalyst was demonstrated next in five consecutive experiments using the recovered IL solution containing **1** and one of three different substrates: styrene, aniline, and ethanol. In each case, after the addition of EDA, the organic phase was separated and the IL was washed with more hexane prior to the next loading with more substrate and EDA. The results are shown in Table 2. Conversions were maintained for five cycles within the range 93−98% without any deactivation of the catalyst. For the styrene cyclopropanation, the diastereoselectivity was consistent throughout the cycles. The recovered IL catalyst phase was stored under nitrogen at 0 °C for several weeks and then employed for a series of experiments with the substrates in Table 1 without any significant loss of activity. In contrast, reported systems for styrene cyclopropanation in an IL have exhibited a decrease of the catalytic activity after 2−3 cycles. Bisoxazoline copper catalysts have been employed under biphasic conditions. Work by Davies et al.[9a] with these catalysts has shown that the cyclopropanation of styrene with EDA was achieved in five cycles with bmim and different counterions. The yields dropped from the initial 88 to 69% in the fifth cycle and to 51% in the eighth run. Mayoral and co-workers[9b,c,h] have also developed the use of such catalysts in ILs. However, the maximum yields, at the first run, were around 50−60% for the same reaction (EDA + styrene) and the conversions decreased in the following runs. Better yields were reported by Yadav et al.[9d] with rhodium-based catalysts, with 88% conversion in the first run dropping to 69% in the fifth run. As in the case of Ru-containing catalysts,[9f] yields varied from 62 to 13% during the five cycles. The degree of conversion observed in our system was better than that previously described in styrene cyclopropanation systems. Conversion and selectivity were nearly identical in both media: in the case of the styrene cyclopropanation, the cis/trans ratio in the homogeneous case (52:48) was similar to that found using the IL system (59:41).

Table 2. Recycling of 1-[bmim]PF_6 for the Reaction of Ethyl Diazoacetate with Styrene, Aniline, and Ethanol[a]

	styrene		aniline	ethanol
run	conversion	cis:trans	conversion	conversion
1	95	59:41	96	98
2	96	57:43	93	98
3	95	60:40	94	97
4	98	55:45	95	95
5	98	61:39	95	95

[a] Experiments carried out as those shown in Table 1.

Complex **1** was a good catalyst for the decomposition of ethyl diazoacetate and subsequent carbene transfer to saturated and unsaturated substrates in both homogeneous and biphasic conditions. The study of the effect of different groups attached to the pyrazolyl rings on the catalytic behavior of **1** is merited because diazo decomposition seems to be related to the electrophilic nature of the metal center.[1] Electrophile−nucleophile couples may be considered for the interactions between the catalyst ML_n and EDA in the transient metallocarbene intermediate and during reaction with the substrate. An increase in the electrophilic character at the metal center usually leads to a more active catalyst. Such attributes can be measured, to a certain extent, using the ν(CO) frequencies of the carbonyl adducts. A comparison[18] between the complexes Tp*Cu(CO) and $\{[HC(3,5\text{-}Me_2\text{-}pz)_3]Cu(CO)\}BF_4$ shows a difference of ca. 50 wavenumbers, the latter appearing at a higher frequency (2066 vs 2113 cm^{-1}). Back-donation from the metal center resulted in lower electron density and may explain **1** to functionalize cyclohexane with EDA. Although the corresponding Tp* catalyst does not induce such transformations,[13c] the functionalization of cyclohexane with the complexes $Tp^{Ms}Cu$ and $Tp^{Br3}Cu(NCMe)$ has been reported[13a,b] in higher yields than that now found with **1** (despite lower ν(CO) values observed for $Tp^{Ms}Cu(CO)$ and $Tp^{Br3}Cu(CO)$: 2079 and 2105 cm^{-1}, respectively). Future development of active catalysts based on the use of trispyrazolylmethane ligands for C−H bond functionalization may require other attributes to enhance conversion. The cationic nature of this new family of catalysts does provide efficiency under biphasic conditions.

In conclusion, we have demonstrated the catalytic capabilities of the complex $\{[HC(3,5\text{-}Me_2pz)_3]Cu(NCMe)\}BF_4$ for the transfer of the $:CHCO_2Et$ in homogeneous and biphasic media. The use of this methodology in ionic liquids for alkyne cyclopropenation as well as for N−H, O−H, and C−H insertion is unprecedented and makes this complex a promising catalyst for the carbene transfer reaction.

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Supporting Information Available: Experimental details of the catalytic experiments (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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