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Short Communication

C-H bonds

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Heterogeneous copper-based catalysts for the amidation of activated

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1. Introduction

The application of copper-based catalysts to fine chemical synthesis is currently experiencing a renaissance, powered by the low cost and toxicity of copper compared to the more commonly employed noble metals, as well as by the rational development of reaction protocols enabling efficient catalysis under mild conditions [1-10]. Nevertheless, a high amount of copper catalyst (5–10 mol%) is often still needed for these applications, which raises the issue of its separation and recycling. In response to this problem, the use of heterogeneous copper catalysts has been pursued [11]: for example, we have previously reported on the successful use of copper species highly dispersed on inert oxides as catalysts for the Sonogashira reaction [12], though in that case the copper-containing solid was found to release most of the copper into solution in the course of the reaction. More recently, some of us have reported on the use of copper species on similar supports as catalysts for carbene insertions into C-H bonds, and evidence was provided that the reaction was heterogeneous in nature [13]. In the present work, we extend this study by investigating on the performance of similar catalysts in nitrene transfer reactions, most notably in the insertion of nitrenes into C-H bonds (C-H amination) [9,14]. To the best of our knowledge, there is at present no report in the literature on the successful application of heterogeneous copper-based catalysts for this reaction.

ABSTRACT

Copper species highly dispersed on suitable inert oxide supports catalyze the amidation of the α -C – H bond of cyclic ethers using a commercial, environmentally benign nitrene source such as chloramine T. The catalytic efficiency depends on the nature of the support and of the dispersed copper species. The heterogeneous catalysts apparently operate by liberating low amounts of highly catalytically active copper species into solution, the exact nature of which is yet to be determined. The heterogeneous catalysts are easily separable and recyclable, although the catalytic activity decreases upon recycling.

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2. Results and discussion

A series of previously synthesized catalysts on different inert oxide supports was considered. All catalysts contained the same amount of copper (8% w/w) and were prepared by the chemisorption–hydrolysis method. This technique, based on electrostatic interactions taking place between the support surface and a $[Cu(NH_3)_4]^{2+}$ solution used at a fixed pH, represents a valuable method to obtain high metal dispersions, even at high metal loading when the point of zero charge of the support is below the solution pH [15]. Table 1 reports the surface areas and the pore volume of the supports and of the related catalysts.

TEM analysis of the supported copper oxide phase in the various materials showed an average particle size between 4 and 6 nm [17], except over SiO₂ and SiO₂–TiO₂ where the average particle size was found to be 3-4 nm [19].

Catalytic tests were performed on the α -amidation of cyclic ethers (Scheme 1), a reaction previously employed to probe the reactivity of copper species in nitrene insertions [20–24]. Chloramine T was chosen as nitrene source, since in respect to other reagents is commercial and more sustainable (NaCl is the only reaction coproduct). Gratifyingly, initial tests performed with 10 mol% CuO_x/SiO₂ or CuO_x/SiAl with neat reagents (excess 1,4-dioxane) at 70 °C pointed out that the catalysts were indeed able to promote the reaction: dioxane was converted into the desired product with about 50% yield after 22 h. In contrast, use of less reactive substrates such as toluene or cyclohexane proved ineffective, with negligible yields in nitrene insertion products (2 and <1%, respectively) obtained under comparable conditions. Negligible yields were also obtained in the absence of the copper catalyst.



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Table 1						
Supports	and	catalysts	employed	in the	present	work.

Catalyst	Surface area (m ² /g)	Pore volume (mL/g)	Ref.
SiO ₂	480	0.75	[16]
CuO _x /SiO ₂	363	0.68	
Al_2O_3	280	1.15	[17]
CuO_x/Al_2O_3	238	1.24	
SiO ₂ -Al ₂ O ₃	400	0.77	[18]
CuO _x /SiAl	412	0.75	
SiO ₂ -Al ₂ O ₃ 0.6	483	1.43	[16]
CuO _x /SiAl 0.6	430	0.86	
TiO ₂	50	n.a.	[17]
CuO _x /TiO ₂	45	n.a.	
SiO ₂ -TiO ₂ 2.3	340	1.20	[19]
CuO _x /SiTi 2.3	349	1.01	

We next set out to optimize the reaction conditions using catalyst CuO_x/SiAl (Fig. 1). Analysis of the conversion vs. time curves made it clear that the maximum yield at 70 °C (58%) was reached already after 8 h of reaction, hence this reaction time was taken as standard for the subsequent tests. The yield was found to slightly decrease at prolonged reaction times, possibly due to some product decomposition under the reaction conditions. Indeed, the reaction product is an N-tosylated cyclic hemiaminal (Scheme 1), which has been reported to undergo decomposition with relative ease (e.g. isomerisation to an open chain N-tosylated imine) [24]. Variations of the reaction temperature in the range 50-90 °C affected the reaction rate but not the maximum yield of the reaction, apart from the highest temperature, at which perhaps the reaction product again underwent partial decomposition, thereby resulting in lower reaction yields at all times. An increase of the amount of catalyst to 20 mol% Cu using CuO_x/SiAl resulted in no appreciable increase in yield, whereas with a lower catalyst amount (5 mol% CuO_x/SiAl) a lower yield (35%) was obtained after 8 h. Identical observations concerning the dependence of the catalytic efficiency on temperature and amount of catalyst have been previously reported with homogeneous copper(I) catalysts in a closely related reaction (styrene aziridination) and attributed to a competing copper-catalyzed decomposition process of the nitrene source [25]. Remarkably, and in contrast to most homogeneous catalytic systems described before, the reaction could be conveniently performed also with commercial chloramine T trihydrate, without the need for previous dehydration of the same, which according to some reports involves explosion hazards [26]. This results into a safer and more economical reaction procedure, with yields equal to those obtained with anhydrous chloramine T.

Using the optimized reaction conditions, a screening of the various catalysts was performed with dioxane or THF as substrates (Table 2). As outlined above, the catalysts differ primarily for the chemical nature of the oxide support and for the surface area and pore volume. The results obtained with the various catalysts were rather comparable when dioxane was employed as substrate, whereas the differences



Scheme 1. Amidation reactions via nitrene insertion investigated in the present work.

were greater in the case of THF. The least active catalyst appeared to be CuO_x/TiO₂, which could be explained with the low surface area of this nonporous support (Degussa P25) and with the consequent lower degree of dispersion of the copper(II) oxide phase. The most active catalysts, namely CuOx/SiAl, CuOx/Al2O3 and CuOx/SiTi2.3, were instead obtained when deposition of Cu did not clog the pores of the support (Table 1). The presence of copper(I) species may however also play a significant role, particularly with THF as the substrate. Thus, the employed catalyst preparation method allows formation of well dispersed CuO on all the supports but one, namely silica-alumina. In this case, the presence of strong acidic sites similar to those determined for a H-Beta zeolite [27] makes a pure exchange mechanism of these sites with the $[Cu(NH_3)_4]^{2+}$ solution possible (competitive with the chemisorption hydrolysis one). This exchange generates isolated copper species, hardly reducible to an oxidation state lower than monovalent copper, as evidenced by several techniques [18]. Copper^{δ +} species resistant to reduction have been also detected in solvated CuO_x/Al₂O₃ by ATR-IR and XAS [17], and to a minor extent in CuO_v/SiTi 2.3 in the gas phase [19]. Consequently, the increased catalytic efficiency of these materials seems to correlate also with the presence of copper(I) sites. This may be due to the fact that, according to the current understanding of the mechanism of this reaction, copper(I) species are the actual catalyst [28], hence when they are present from the beginning they are directly available for reaction, whereas copper(II) species have to be prereduced to copper(I) by the nitrene source before entering the catalytic cycle [25]. Furthermore, such copper(I) species are present as isolated species on the support, rather than as copper(I) oxide nanoparticles, hence they are more available for reaction with the substrate due to their higher degree of dispersion.

To shed some light into the relevance of the oxidation state, we also tested some of the catalyst in reduced form [16–19] (Table 2). In the case of the best catalyst, namely CuO_x/SiAl a significant drop in yield was obtained with both dioxane and THF on moving to reduced Cu/SiAl. On the contrary, the activity of both Cu/SiO₂ and Cu/TiO₂ showed only a minor decrease. As already mentioned, on the surface of CuO_x/SiAl a minor part of the metal is present as CuO, while most of the Cu is present as copper(I). Since reduction of the CuO fraction on the surface results in a lower yield, it seems that the presence of both oxidation states on the surface is advantageous for the reaction (it should be remarked that pore volume measurements show that there is almost no Cu in the pores). A similar positive effect of the simultaneous presence of copper in different oxidation states was already observed in the polymerization of 2,6-dimethyl-phenol with the same kind of catalysts [29]. On the other hand, Cu/SiO₂ and Cu/TiO₂, are promptly reoxidized (the catalysts turn greenish under reaction conditions), which restores their catalytic activity.

Finally, an evaluation of the true nature of catalysis was performed. Leaching of copper into solution in the course of the reaction, as well as after reaction, was invariably found to be very low (<5% of added copper, most commonly 2-3%). However, upon removal of the solid catalyst at the reaction temperature after only 1 h of reaction ("hot filtration test") the reaction was found to continue in the solution phase, reaching after 8 h a final yield fully analogous to that recorded with the solid catalyst. Thus, it can be concluded that the catalytically competent species are highly active copper species released into solution by the solid catalyst. The exact nature of this species is presently unknown; it needs to be remarked that control reactions performed with dioxane under identical reaction conditions using as catalyst simple copper salts such as copper(II) triflate (the most efficient copper salt as catalyst for this reaction) [22] invariably showed much lower yields of C-H insertion product, reaching after 8 h 30% yield at the best with 10 mol% copper (average TOF 0.37 h^{-1}) to be compared with the average TOF of 27 h^{-1} estimated with the best heterogeneous catalyst upon taking into account the low amount of catalytically competent, leached copper species. Importantly, the solid catalysts maintain some activity upon recycling. For example, as it can be appreciated in Table 2 (last two



Fig. 1. Amidation of dioxane with CuO_x/SiAl: effect of reaction time and temperature.

entries) catalyst CuO_x /SiAl has been recycled two times, allowing to reach 47% yield in the second cycle and 30% in the third cycle, compared to 58% in the first cycle. Thus, although the capacity of the solid catalyst to release catalytically competent species into solution decreases with every reaction cycle, it is not completely exhausted in the first run.

3. Conclusions

In conclusion, we have shown in the present paper that copper species dispersed onto suitable oxide supports are viable precatalysts for the amidation of the α -C–H bond of cyclic ethers using a commercial, sustainable nitrene source such as chloramine T. The heterogeneous precatalysts likely act as a reservoir of low amounts of highly catalytically active species which are released into solution. The precatalysts are easily separable and recyclable, although their catalytic efficiency decreases upon recycling. Studies are currently underway in order to fully understand the nature of the catalytically competent species and to extend their application to other classes of nitrene C–H insertion reactions.

4. Experimental section

All manipulations were carried out using standard Schlenk techniques under an atmosphere of dry argon or dinitrogen. The reagents were purchased by Aldrich or Merck as high-purity products and generally used as received. All solvents were dried by standard procedures and distilled under dinitrogen immediately prior to use. The catalysts were prepared according to literature procedures [16–19]. NMR spectra were recorded on a Bruker Avance 300 MHz (300.1 MHz for ¹H and 75.5 MHz for ¹³C); chemical shifts (δ) are reported in units of ppm relative to the residual solvent signals.

Table 2

Nitrene insertion reaction with dioxane or THF and heterogeneous Cu catalysts on various supports.

Catalyst	Yield with dioxane (%)	Yield with THF (%)
CuO _x /SiO ₂	45	31
Cu/SiO ₂	40	30
CuO _x /SiAl	58	64
Cu/SiAl	34	15
CuO _x /SiAl 0.6	41	15
CuO _x /Al ₂ O ₃	36	49
CuO _x /TiO ₂	29	10
Cu/TiO ₂	23	n.d.
CuO _x /SiTi 2.3	42	48
CuO _x /SiAl ^a	47	n.d.
CuO _x /SiAl ^b	30	n.d.

Reaction conditions: 4 ml substrate, 0.5 mmol anhydrous chloramine T, 10 mol% Cu, 70 °C, 8 h.

^a first catalyst recycle.

^b second catalyst recycle.

4.1. Catalytic tests

In a 50 mL two-necked round-bottomed flask were placed chloramine T (0.263 mmol) and the solid catalyst (26.3 µmol [Cu], 10 mol%) under an inert atmosphere. The flask was thermostated to the desired temperature, and the cyclic ether substrate (4 mL) was then added. The mixture was maintained at the desired temperature under stirring. After the given reaction time, the reaction mixture was filtered, the filtrate was evaporated to dryness and analyzed by ¹H NMR spectroscopy in CDCl₃ using 1,4-bis(trimethylsilyl)benzene as an internal standard.

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