Bifunctional copper catalysts for an atom efficient ether synthesis

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ABSTRACT

A direct etherification of aromatic ketones and aliphatic alcohols into the corresponding asymmetrical ethers by the use of a bifunctional heterogeneous copper catalyst is described. The reaction protocol reveals to be versatile and convenient respect to the traditional ether synthesis for both environmental and practical concerns.

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1. Introduction

The search for low-waste technologies and multifunctional processes in organic synthesis is becoming more and more pressing for both economical and environmental concerns. In fact the use of traditional stoichiometric reagents for the preparation of organic molecules is still widely common, especially due to their high activity and specificity.

Ether formation is an important reaction in organic synthesis, for both bulk and fine chemicals preparation, and it is traditionally performed with the Williamson reaction starting from an alcohol and a halide by using a strong base for the alkoxide formation.[1] Actually, the reaction is particularly useful for the preparation of mixed ethers, as it involves the direct nucleophilic displacement of halogen in the alkyl halide by the alkoxide ion. On the other hand, it is synthetically effective only when a primary alkyl halide is used, due to the competitive elimination reaction observed with the secondary or tertiary ones.[2] Moreover, the use of the conditions requested strongly limits the industrial applications, but above all imposes serious environmental and economical concerns due to waste disposal processes.

Thus, to avoid the use of bases and halide reagents could be a successful strategy in order to set up a cleaner and simple protocol.

Brønsted acid catalysts are known to promote ether formation starting from the corresponding alcohols by means of a dehydration process.[3] This strategy is especially employed in the vapour phase synthesis of dialkyl ethers as ETBE or diethylether with zeolites[4] or heteropolyacids.[5,6] However this method is particularly proper for symmetrical ethers.

In a recent communication, Sn-Beta has been reported as active heterogeneous Lewis acid for the asymmetric etherification of benzylic alcohols and aliphatic ones.[7] This system proved to be water resistant and highly selective with different benzylic substrates and mainly primary aliphatic alcohols. Actually, as already pointed out by the authors, the weak point of traditional Lewis acids resides in their sensitivity to water produced during the reaction.

Another efficient and direct access to asymmetrical ethers could be the hydroalkoxylation reaction, based on the nucleophilic attack of an alcohol to a C–C double bond. This strategy, even if attractive, revealed to be practicable only in the case of highly activated alkenes, otherwise requiring the use of strong Lewis acids[8,9] or noble metal complexes.[10,11]

In the particular case of aromatic compounds it is quite evident that the optimal route should start from the carbonyl derivatives. Actually they are the first intermediates in the functionalisation of aromatics by means of the Friedel–Crafts acylation and their use conveniently fits with the purpose of minimising the number of synthetic steps.

In this Letter, we would like to report on the use of a heterogeneous copper catalyst supported over commercial mixed oxides in the one-pot transformation of an aromatic ketone and an aliphatic alcohol into the corresponding asymmetrical ether under very mild experimental conditions and without the need of any additive for water removal. Actually, the use of a bifunctional system, able to promote both hydrogenation and acid-catalysed reactions, would allow to plan a cascade process directly starting from carbonyl compounds. Moreover, a reliable and robust heterogeneous catalyst avoids the formation of undesirable inorganic wastes.[12]

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2. Results and Discussion

The reaction between 4-methoxyacetophenone and a series of alcohols with a copper catalyst supported over an amorphous silica alumina allows one to easily obtain the corresponding asymmetrical ether in a one-pot one-step reaction with a very high conversion and selectivity (Scheme 1 and Table 1).

No symmetrical ether formation was observed, the only by-products formed in very low amount being those resulting from ketone deoxygenation. The minimisation of these by-products is not trivial, as the reductive deoxygenation of ketones is particularly favoured in the presence of acidic systems.[13] In the present case, the use of the alcohol, besides the synthetic role, is crucial in order to tune the catalyst acidity. In fact, the use of an alcohol as solvent has already been exploited in other synthetic applications in order to suppress the formation of by-products deriving from the catalyst acidity.[14]

In order to widen the application field and the pool of aliphatic alcohols we carried out some experiments by reducing the alcohol content and by using a hydrocarbon as solvent.
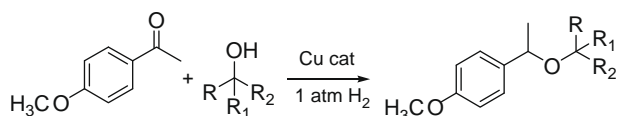
The reaction temperature, the solvent nature and the ketone/alcohol molar ratio are all relevant parameters in order to selectively obtain the asymmetrical ether. In particular, by lowering the alcohol/ketone ratio the symmetrical ether formation becomes significant. On the other hand the temperature has a significant effect on the deoxygenation product formation. A good compromise among the conditions tested was represented by the use of n-heptane at 60 °C, with a ketone/alcohol ratio of 1/10.

In Table 2 results obtained by varying the aliphatic alcohol are summed up. From these data it is evident that it is possible to use a wide series of alcohols, observing in all cases very high conversion and selectivity values, as a general trend more nucleophilic alcohols reacting faster. The excellent conversions obtained, show that the water formed during etherification does not affect the catalyst activity, therefore not requiring any additive or mechanical device for its removal.

The protocol can be easily applied to different aromatic substrates, as shown in Table 3. Moreover results and intermediates obtained with the different ketones can help to elucidate some aspects of the reaction pathway.

The first important information derives from the very low activity observed with 3-methoxyacetophenone and the longer reaction times necessary for 4-isobutylacetophenone and 4-methoxybenzaldehyde.

Moreover, the reaction profile obtained for the etherification starting from 4-isobutylacetophenone and 2-propanol (Fig. 1), clearly shows the formation of 4-isobutylphenylethanol as the

Table 2
Etherification reaction starting from 4-methoxyacetophenone and different alcohols (T = 60 °C, P = 1 atm H_2) in n-heptane[a]

Alcohol	Product	t (h)	Conv (%)	Sel (%)
2-PrOH		5	100	97
Ethanol		5	100	94
Cyclopentanol		3	100	96
2-Ph-Ethanol[b]		7	70	89
2-Butanol		3	90	99
Methanol		24	90	97

[a] 60 °C, ketone/alcohol = 1/10 mol/mol.
[b] Ketone/alcohol = 1/2 mol/mol.

intermediate, not detected with the other substrates under the present conditions.

These evidences strongly suggest that the etherification reaction proceeds through the carbonyl reduction and the nucleophilic attack of the aliphatic alcohol to the benzylic carbon of the aromatic one, activated by the Lewis sites present on the catalyst surface, namely Al^{3+} ions. The more stabilised the incipient carbocation, the faster the reaction. Nevertheless, in the case of highly activated substrates, a direct addition to the carbonyl compound cannot be excluded.

On the other hand, some interesting insights on the active site responsible for the reaction can be obtained by the use of different
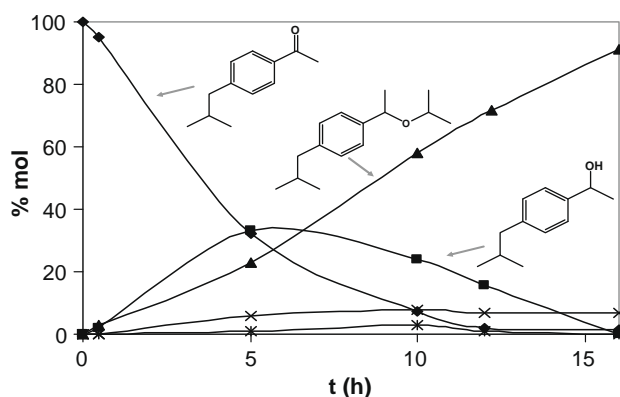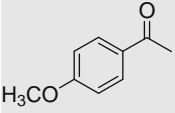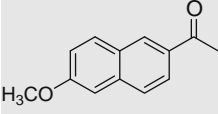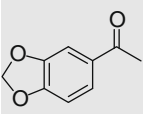
Scheme 1. Direct ether synthesis from 4-methoxyacetophenone and alcohols.

Table 1
Etherification reaction starting from 4-methoxy acetophenone and different alcohols as solvent (T = 80 °C, P = 1 atm H_2) by using Cu/SiO_2–Al_2O_3 as catalyst

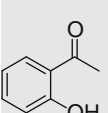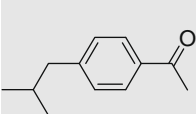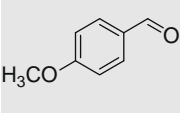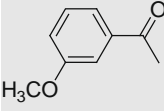| Alcohol	R	R₁	R₂	t (h)	Conv (%)	Sel (%)
2-PrOH	Me	Me	H	1.5	100	98
2-BuOH	Me	Et	H	1.5	100	98
Iso-BuOH	H	H	iPr	2.5	100	95
Di-iPr-carbinol	iPr	iPr	H	4	100	90

Figure 1. Etherification reaction starting from 4-isobutylacetophenone and 2-propanol (T = 80 °C, P = 1 atm H_2) in n-heptane.

Table 3
Etherification reaction starting from different aromatic ketones and 2-propanol ($T = 60$ °C, $P = 1$ atm H_2) in n-heptane or toluene.

Ketone	t (h)	Conv (%)	Sel (%)
	5	100	97
	7	100	98
	16	100	95
	20	90	96
	28 16[a]	100 98	86 91
	24	92	100
	24	100	13[b]

[a] Reaction carried out at 80 °C.
[b] Main by-product being the substituted phenylethanol.

Table 4
Etherification reaction starting from 4-methoxyacetophenone (under H_2) or 1-(4-methoxy)-phenylethanol (under N_2) and 2-propanol as a solvent ($T = 80$ °C)

	Catalyst	Substrate	t (h)	Conv (%)	Sel (%)
1	SiO_2	p-OMe-Acetophenone	24	0	—
2	SiO_2–Al_2O_3	p-OMe-Acetophenone	24	0	—
3	SiO_2	p-OMe-Phenylethanol	24	0	—
4	SiO_2–Al_2O_3	p-OMe-Phenylethanol	1	95	97
5	Cu/SiO_2–Al_2O_3	p-OMe-Acetophenone	1.5	100	98
6	Cu/SiO_2	p-OMe-Phenylethanol	1.5	96	98
7	Cu/SiO_2	p-OMe-Acetophenone	8	100	99

tems is peculiar for the features of metal accounting for high dispersion of the copper phase.[18,19]

The chance to prepare an active copper catalyst by using an easily available silica makes these catalytic systems highly appealing from the practical point of view.

Moreover, Cu/SiO_2, although for longer reaction times, allows one to set up the one-pot one-step reaction between 4-methoxy-acetophenone and 2-propanol (entry 7), thus giving the ether and showing that copper plays a major role in the reaction, promoting both reduction and activation of the substrate.

It is worth underlining that the preparation of the same ether, compound with a pleasant aniseed-like smell, is not trivial. Its synthesis, scarcely described in the literature, has been recently reported to be performed with a quite complex protocol based on a multistep hydrohalogenation/hydroalkoxylation of styrene promoted by a homogeneous Pd catalyst combined with a copper one in the presence of oxygen, DCE and 2-propanol.[20]

3. Conclusions

Further studies towards a deeper insight into the reaction mechanism, substrate scope and the synthetic application are currently ongoing, besides the opportunity to extend the catalytic activity also to the hydroalkoxylation of C–C double bonds.

In spite of some homogeneous methods based on preformed silane or alkoxysilane of the alcohol,[21–23] few heterogeneous metal catalysts effective for the direct etherification starting from ketones and alcohols are reported so far. In particular, noble metal-based systems, namely Pd and Pt, are described to be active in the etherification of aliphatic ketones or aldehydes only with alcohols but request high pressure of H_2,[24] or water removal solutions.[25]

It should be stressed that our reaction protocol is particularly attractive if analysed from both the environmental and economical point of view. Actually, considering that water is the only by-product and that the catalyst can be recovered after filtration, the overall atom efficiency calculated in the case of 2-propanol and 4-OMe-acetophenone reaches 90. This is even more important if we consider that Cu/support allows one to perform a one-pot one-step synthesis starting directly from the carbonyl compound.

The bifunctional process allows to substitute the use of metallic hydrides for the hydrogenation step and to circumvent the typical drawbacks of the traditional etherification reactions, avoiding the use of halides and strong bases, and in consequence, the formation of wastes demanding to be disposed off.

4. Experimental

SiO_2–Al_2O_3 (0,6% wt of Al_2O_3, PV = 1.45 mL/g, SA = 500 m²/g) was kindly supplied by Grace Davison (Worms, D) and SiO_2 (PV = 0.75 mL/g, SA = 500 m²/g) from Aldrich. Copper catalysts were prepared by a chemisorption-hydrolysis technique as already reported[15] starting from a $[Cu(NH_3)_4]^{2+}$ complex solution. The bare

oxides for the catalyst preparation (Table 4). Actually, the bare acidic support (SiO_2–Al_2O_3), even if predictably inactive with the ketone (entry 2), reveals a very high activity in the etherification reaction starting from 1-(4-methoxy)-phenylethanol (entry 4), thus showing enough acidity itself for this specific reaction. These data are in agreement with results obtained by Corma on the formation of asymmetric ethers from two alcohols over Sn-Beta showing Lewis acid character. Actually, the here described mixed oxides, with a very low content in alumina (0.6–1.5%) already showed a remarkable acidic character in α-pinene oxide isomerisation, often used as a test reaction for a qualitative evaluation of acidic sites,[16] and in the *ene* reaction of citronellal into isopulegol.[17]

The bifunctional property of the silica alumina copper supported catalyst used in the present work arises from the presence of a redox site (copper) and an acidic one in the same system. These two sites could in principle work one independently from the other.

On the contrary the use of a non-doped pure silica does not lead to any reaction (entries 1 and 3) starting from both the ketone and the alcohol, whereas the copper catalyst prepared over the same support (entry 6) shows an activity comparable to the one of the bare silica alumina when starting from the two alcohols (entry 6 vs entry 4). This is a clear evidence that the well-dispersed metallic phase can express an outstanding Lewis acidic character. Actually the technique employed for the preparation of these catalytic sys-

supports were dehydrated at 270 °C in air for 30 min, then 30 min in vacuo. The metal catalysts were treated in the same way and reduced before reaction at 270 °C and 1 atm H_2.

All the substrates used were purchased from Sigma Aldrich, except 4-methoxyphenylethanol which was prepared as already reported by using the same class of copper catalysts described herein.[26] A typical etherification reaction with the aliphatic alcohol as the solvent was carried out by filling the reactor containing the pre-reduced catalyst with a solution of 4-methoxyacetophenone (0.65 mmol) in 8 mL of alcohol and 1 atm H_2. Etherification reactions with higher ketone/alcohol ratio were carried out by filling the reactor with a solution of the aromatic ketone (0.65 mmol) and the aliphatic alcohol (6.5 mmol) in 8 mL of anhydrous *n*-heptane or toluene (depending on the solubility of the substrate) and 1 atm H_2. The reaction mixtures were analysed by GC–MS (Agilent 5975C) by using a HP-5 column and the products were characterised by NMR.

Acknowledgement

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