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Heterogeneous selective catalytic hydrogenation of aryl ketones to alcohols without additives

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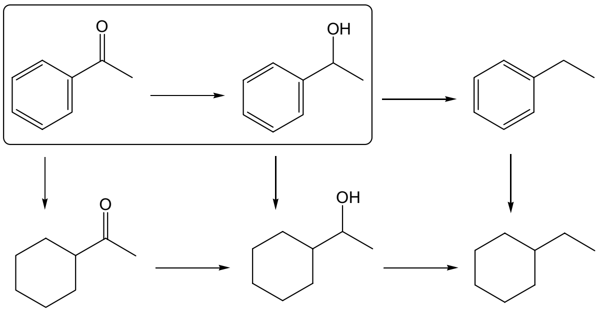
Abstract—A selective hydrogenation of different aryl ketones can be obtained by using a heterogeneous copper catalyst under very mild experimental conditions, namely 90 °C and 1 atm of hydrogen, without using any kind of additive or poisoning agent.

Selective reduction of carbonyl compounds by means of heterogeneous catalysts rather than metal hydrides and stoichiometric reagents still remains an important goal for fine chemicals synthesis, both for economical and environmental concerns. In particular, selective hydrogenation of aromatic ketones into the corresponding alcohols is complicated by different kind of side reactions as the aromatic ring hydrogenation, as well as hydrogenolysis of the produced alcohol (Scheme 1).

Nevertheless this transformation is a very attracting target, as it represents a key step in several industrial processes for pharma and fine chemicals.



Scheme 1.

This is the case, for example, of the *p*-isobutylacetophenone hydrogenation for the synthesis of the non-steroidal anti-inflammatory Ibuprofen®. Heterogeneous catalysts reported for this transformation are usually noble or toxic metal based systems that need the use of additives to reach high selectivities and that are efficient only under moderate to high pressure of hydrogen.[1]

We already reported that Cu/SiO_2 can selectively reduce differently substituted cyclohexanones under very mild experimental conditions.[2] Unfortunately, with the same protocol, copper on silica is not likewise selective towards alcohol formation from aryl ketones. Thus, the acidity of the catalytic system leads to the formation of hydrogenolysis products and ethers.

Here we wish to report that a very selective transformation can be achieved with a new, milder catalyst prepared by using alumina as support. In particular, Cu/Al_2O_3 with a 8% copper contents allows to obtain very high conversions and selectivities without the need of any kind of basic additive. Actually, with the conventional heterogeneous systems, the formation of undesired hydrogenolysis products is usually avoided by adding amines[3] or NaOH[4] or by designing bimetallic catalysts in which one of the metals acts as poisoning agent,[5,6] resulting in a more complex and sensitive system, both during preparation and use in catalysis.

Also with new and non-conventional catalytic systems, such as the use of supercritical CO_2 as solvent or of organic polymers as catalyst supports, still remains the

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Keywords: Selective hydrogenation; Acetophenone; Copper catalysts; Aromatic ketones.

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problem of selectivity[7] and the need of basic reaction conditions.[8]

The most interesting results obtained with Cu/Al_2O_3 are reported in Table 1.

Respect to the case previously reported,[2] not only the reaction conditions are very mild, but also the catalyst reduction can be carried out at 180 °C.

Hydrogenation of unsubstituted acetophenone has been widely studied, in particular, on Pd, Pt, Ni and Ru catalytic systems,[9] but even in this instance the most selective systems are those based on mixed metals.[10]

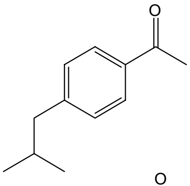
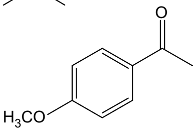
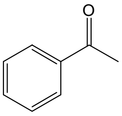
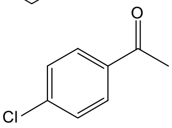
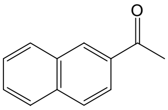
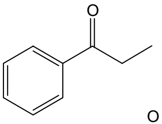
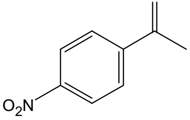
On the contrary reduction of 4-methoxyacetophenone has rarely been studied and toxic catalysts and basic additives are required in order to suppress by-products formation. Thus Kuhn and Funk report the hydrogenation of 4-methoxyacetophenone with Raney Ni modified with Cr and Fe, in NaOMe solution at 10 atm of H_2 and 90°C to obtain 90.7% of the corresponding alcohol.[11]

It is worth noting that completely selective reduction of *p*-chloro-acetophenone is also possible, although in longer reaction times, without observing any hydrodechlorination products (entry 4a), as on the contrary happens with other catalytic systems.[12,13] The reaction rate can be suitably increased by pretreating catalyst at higher temperature, without observing any significant changes in selectivity (entry 4b).

It should be underlined that selective reduction of this substrate is only reported by using reducing agents such as metal hydrides[14] or homogeneous systems.[15]

In the hydrogenation of *p*-isobutylacetophenone, intermediate in the synthesis of Ibuprofen®, excellent selectivity was obtained and Cu/Al_2O_3 appears to be

Table 1. Hydrogenation of different aryl ketones over Cu/Al_2O_3[a]

Entry	Substrate	Solvent	*t* (h)	Conv %	Sel %
1		(a) *n*-Heptane (b) *n*-Heptane[b] (c) 2-Propanol, N_2[c]	1.5 5 5	98 99 98	98 97 100
2		*n*-Heptane	0.5 1.5	96 100	97 90
3		*n*-Heptane	1.5	96	98
4		(a) *n*-Heptane (b) *n*-Heptane[d]	24 10	82 83	100 94
5		*n*-Heptane	0.5 1	86 100	94 90
6		*n*-Heptane	7	97	98
7		*n*-Heptane	24	0	—

[a] Reaction conditions: 100 mg substrate, 100 mg catalyst, 8 mL *n*-heptane, 90 °C, 1 atm H_2.

[b] Reaction conditions: 600 mg substrate, 120 mg catalyst, 60 mL *n*-heptane, 90 °C, 6 atm H_2.

[c] Reaction carried out under transfer hydrogenation conditions.

[d] The catalyst was preactivated at 270 °C instead of 180 °C.

certainly competitive with the other heterogeneous catalysts reported so far,[1] especially for the very mild working conditions.

As far as productivity is concerned, a catalytic run with catalyst/substrate ratio of 1/5 by weight under 6 atm of H_2 (entry 1b) showed that this system can be proposed as a valuable alternative to both toxic metal based Ni Raney and noble metal based Pd–C.[16]

Finally the reduction of *p*-isobutylacetophenone can be conveniently done also in absence of hydrogen, by using hydrogen transfer conditions (entry 1c). In fact this catalyst shows also excellent performances in secondary alcohol dehydrogenation, that can be exploited for their oxidation in the presence of an hydrogen acceptor[17] or for selective transfer hydrogenation from 2-propanol.

From the results obtained (entries 1, 2 and 5) is apparent that electron donating substituents accelerate the hydrogenation, whereas the nitro group (entry 7) completely suppresses reaction, anyway not leading to any kind of side products but leaving the reagent unchanged.

Control experiments showed that hydrogenation of *p*-isobutylacetophenone is completely inhibited by the presence of nitrobenzene, but not by the presence of aniline, although in this case relevant amounts of by-products were formed. This shows that the inactivity of *p*-nitro-acetophenone over Cu/Al_2O_3 may be due not only to electronic effects but also to functional group incompatibility of the starting compound. On the other hand inhibition by means of the product can be excluded.

Moreover, steric hindrance strongly influences the reaction rate, as shown by the slower reduction of propiophenone respect to acetophenone. In this molecule, the methyl group in α position has a significant effect, as well as in the case of cyclohexanones.[2]

So far, no other heterogeneous catalytic system allows such mild and simple conditions for selective and general aryl ketones hydrogenation, avoiding the use of any additive or poisoning agent.

The use of Cu/Al_2O_3 allows the set up of a simple, safe and clean protocol for reduction of aromatic ketones. The catalyst can be prepared in a simple way and it is neither pyrophoric nor pyrogenic even in the reduced state. The use of a truly heterogeneous catalyst and its high selectivity avoid the production of inorganic and organic wastes.

Catalyst preparation: the catalyst was prepared as already reported[18] starting from $(CuNH_3)_4^{2+}$ solution and using Al_2O_3 from Grace Davison as support (BET = 280 m^2/g, PV = 1.75 mL/g). Before reaction, the catalyst obtained (Cu = 8% by weight) was reduced at 180 °C with H_2 (1 atm) before use, removing water formed under reduced pressure.

Experimental conditions: a solution of the substrate (100 mg) in anhydrous *n*-heptane (8 mL) was transferred under N_2 in the reaction vessel containing the catalyst previously reduced (100 mg). Catalytic tests were carried out at 90 °C at atmospheric pressure of hydrogen under magnetic stirring. Reaction mixtures were analyzed by GC (5% phenyl–95% methylpolysiloxan capillary column, 30 m) and by ^1H NMR.

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