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A Simple and Efficient Catalytic Method for the Reduction of Ketones

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Abstract: A range of ketones was efficiently reduced in the presence of catalytic amounts of lithium isopropoxide in 2-propanol under microwave heating, with alcohol products being formed in yields up to 99%.

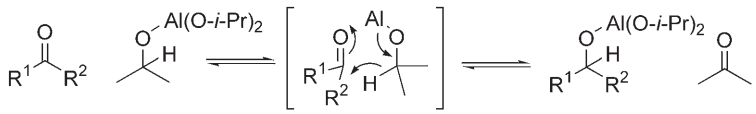
Keywords: alkali metals; hydrogen transfer; ketones; microwave heating; reduction

The formation of secondary alcohols through ketone reduction is typically performed using hydride reagents in stoichiometric amounts, or with molecular hydrogen in combination with a catalytic amount of an active transition metal. Hydrogen-transfer processes where covalently bonded hydrogen changes its point of attachment represent a mild and safe alternative for the reduction of ketones.[1] The latter type of reaction typically uses alcohols or formic acid as hydrogen source, often in combination with a main group metal or a transition metal complex. The pioneering work on ketone reductions *via* transfer hydrogenation was performed by Meerwein[2] and Verley[3] who discovered that aluminium ethoxide and ethanol facilitated the formation of secondary alcohols. Ponndorf further refined the procedure and developed an effective method by using stoichiometric aluminium isopropoxide and 2-propanol.[4] The reduction is believed to proceed *via* a six-membered cyclic transition state, Scheme 1, which involves the ketone and the aluminium-bound alkoxide.[5]

The reverse reaction, oxidation of alcohols to their corresponding carbonyl compounds, was reported a few years later by Oppenauer.[6] Consequently, by varying the reaction conditions, the equilibrium between the alcohol and the ketone can be changed which allows for the MPVO reaction to be executed in any direction.[7] A practical feature with the oxidation step is that due to the nature of the reaction, overoxidation to the carboxylic acid is not possible.

The aluminium alkoxides, initially employed in MPVO reactions, can be replaced by other metal salts including samarium,[8] and other lanthanide alkoxides.[9] More recently, transition metal complexes were introduced as catalysts for the transfer hydrogenation reaction of ketones to alcohols under basic conditions in 2-propanol.[10,11]

We have previously reported on the use of ruthenium- and rhodium-based catalysts for the asymmetric reduction of prochiral ketones under transfer hydrogenation conditions.[12] However, a general disadvantage with the majority of all metal-based catalytic protocols is the inherent toxicity associated with the transition metals. In an attempt to find more biocompatible catalysts for this particular transformation we focussed on investigating the catalytic power of some first row transition metals. Interestingly, we found that transfer hydrogenation of ketones using environmentally more indulgent Fe-based catalysts was recently reported.[13] In these reports, catalytic amounts of various iron complexes together with stoichiometric or substoichiometric amounts of base were employed for the reduction reaction. We were intrigued by the excellent results obtained by Beller and coworkers, who reported that a number of differently substituted aryl and alkyl ketones were efficiently reduced at elevated temperatures using 2-propanol as hydrogen source.



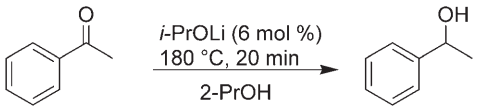
Scheme 1. Aluminium isopropoxide-mediated MPV reactions.

In our previously developed protocols for the reduction of ketones under transfer hydrogenation conditions using chiral ruthenium or rhodium catalysts containing amino acid-based ligands, we found that these reactions do require a catalytic amount of base, typically sodium isopropoxide, in order to generate the desired product. In addition we found that the nature of the alkali ion introduced with the base was crucially important and had a strongly beneficial effect on the reactivity and selectivity of the reduction reaction.[12f] In particular, the addition of lithium alkoxides or lithium salts influenced the outcome of the reaction, and the secondary alcohols were formed in high yields and with good to excellent enantioselectivity. The reactions using Ru or Rh catalysts are normally performed at room temperature and in an investigation to increase the rate of the reduction process using higher temperatures we found that high conversion was indeed achieved albeit at the cost of lower selectivity.[12c]

In an attempt to investigate whether the ruthenium or rhodium catalyst could be replaced by iron in these transfer hydrogenation reactions, we set up a series of experiments trying to 1) reproduce the results reported by Beller and co-workers,[13b] and 2) investigate if the simple ligand systems previously developed by us could be employed for this reaction. We did indeed obtain the secondary alcohol using the Beller catalytic system, however, to our surprise we found that performing a blank experiment, excluding the transition metal, we observed good conversion to the secondary alcohol when the reaction mixture was heated according to the published procedure. Obviously, the formation of product in the absence of a transition metal catalyst indicates that the alkali base itself catalysed the reduction. Alkali metal alkoxides have previously been used to mediate transfer hydrogenations. However, due to the low activity associated with alkali alkoxides these reactions required a stoichiometric amount of base to accomplish product formation.[14,15]

The interesting results presented above which indicate that ketone reductions can be efficiently performed in the absence of other catalysts than an alkali alkoxide prompted us to further investigate this protocol. Herein we report on a simple, efficient and most practical protocol for ketone reductions using catalytic amounts of inexpensive lithium or sodium isopropoxide and 2-propanol as hydrogen donor.

The above described observation that a catalytic amount of sodium isopropoxide in 2-propanol was capable of reducing acetophenone when the reaction mixture was heated led us to further investigate the potential of this reducing system. In an initial set of experiments, using microwave irradiation for fast and efficient heating, we screened different alkali alkoxides by heating a 2-propanol solution of acetophenone in a sealed pyrex tube to 120 °C for 90 min. In the initial reaction containing 6 mol % of sodium isopropoxide we observed a 71 % conversion to the alcohol. Replacing the base with potassium *tert*-butoxide resulted in lower conversion (20 %), however, when lithium isopropoxide was employed the conversion was again restored (71 %). Increasing the reaction temperature further improved the conversion, and when a 2-propanol solution of acetophenone containing a catalytic amount of *i*-PrOLi (6 %) was heated at 180 °C in a sealed pyrex tube we obtained 96 % conversion after only 20 min (Scheme 2 and entry 1, Table 1).



Scheme 2. Lithium isopropoxide-catalysed reduction of acetophenone.

Table 1. Lithium isopropoxide-catalysed reduction of ketones under microwave irradiation.[a]

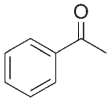
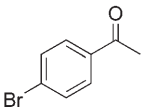
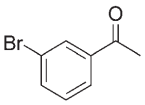
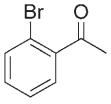
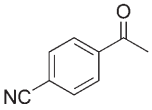
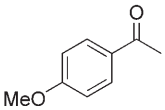
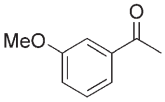
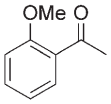
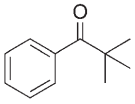
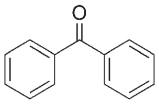
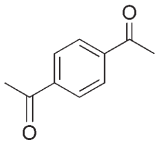
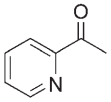
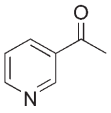
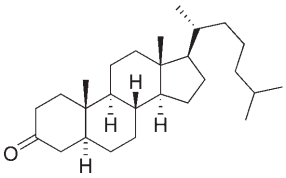
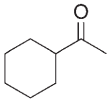
Entry	Substrate	Time [min]	Conversion[b] [%]
1		20	96 (94)
2		20	88 (83)
3		20	96
4		20	93
5		20	96 (87)
6[c]		30	86 (80)
7		20	92
8		20	93
9		30	96 (87)

Table 1. (Continued)

Entry	Substrate	Time [min]	Conversion[b] [%]
10		30	(93)
11[d]		40	89 (83)
12		20	99 (99)
13		20	99 (96)
14[e]		20	(93)
15		20	54

[a] Reactions conditions: a mixture of ketone (0.5 mmol, 0.2 M) and lithium isopropoxide (0.03 mmol) in 2.6 mL 2-PrOH was heated to 180 °C in sealed pyrex tube under argon atmosphere for the times stated.

[b] Conversions determined by GLC or ^{1}H NMR. Isolated yields are presented in parentheses.

[c] 82 % conversion after 20 min.

[d] Conversion and isolated yield reported for the diol.

[e] Dihydrocholesterol was obtained in 88:12 diastereomeric mixture with 5-α-cholestan-3-β-ol as the major diastereomer.

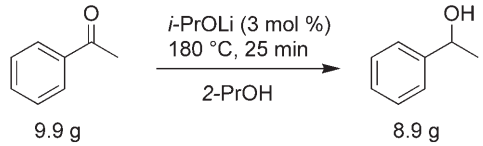
The reduction protocol turned out to be reasonably general and we were able to efficiently convert a number of simple aryl alkyl ketones to their corresponding alcohols (Table 1). The conversions differed somewhat between substrates depending on their electronic nature.[16] Hence, when a deactivating group such as Br is positioned in the *para* position, the coordination to Li becomes weaker and a drop in conversion (88 %) was detected (entry 2, Table 1). This effect is less pronounced when the deactivating group is placed in the *ortho* or *meta* position (entries 3 and 4). Thus it seems as if the electronic effect of having the substituent in the *para* position is larger than the steric one from the *ortho* or *meta* substitution. Halobenzenes are known to undergo nucleophilic aromatic substitutions when heated with strong nucleophilic bases, however, in the case of the bromo-substituted acetophenones we did not observe any substitution products, since only starting material and the desired product were found when the reaction mixture was analysed by NMR. In the reduction of fluoro-substituted acetophenones though, this side reaction occurred and such substrates are not suitable for this protocol. The highly deactivated 4-cyanoacetophenone was efficiently reduced and the alcohol was isolated in good yield (entry 5). The reduction of this particular substrate using transition metal-based catalysts is normally problematic due to coordination between the nitrile and the catalyst. The electronically opposite methoxy-substituted acetophenones behaved in a similar fashion to the bromo derivatives. With the methoxy-group in the *ortho* or the *para* position, the carbonyl moiety experiences higher electron density and thereby the hydride attack should be less favourable. In the reductions we obtained lower conversion for the *p*-methoxy compound as compared to the corresponding *ortho* or *meta* substituted acetophenones (entries 6–8). Extending the reaction time to 30 min in the former case resulted in better conversion. The sterically hindered *tert*-butyl phenyl ketone as well as benzophenone were efficiently reduced (entries 9 and 10). Acetylpyridines have previously been problematic substrates in the aluminium-mediated MPV reduction due to coordination between the aromatic nitrogen and the metal centre. These problems are efficiently overcome using catalytic amounts of *i*-PrOLi, and excellent results for the reduction of 2- and 3-acetylpyridine were reached (entries 11 and 12).

Additionally, the method proved to be efficient for the reduction of aliphatic ketones such as dihydrocholesterol and cyclohexyl methyl ketone (entries 14 and 15). Easily enolisable aliphatic ketones did not undergo reduction and starting material along with condensation products were detected in the reaction mixtures. Other substrates which turned out to be problematic using this methodology include ester or silyl ether functionalised ketones. The reduction of ethyl 4′-acetylbenzoate resulted in transesterification rather than formation of the secondary alcohol, an expected outcome due to the base lability of the ester functionality. However, the attempted reduction of (4′-*tert*-butyldimethylsilyloxy)acetophenone gave most surprisingly no conversion to the product, and the starting material was recovered unaffected.

It was previously reported that MPVO-type reactions could be performed without any catalyst or mediator when performed at high temperatures or under supercritical conditions at 300 °C.[17] However, we observed undesired side reactions like condensations and eliminations for certain substrates when the reaction mixtures were heated for longer times than what is presented in Table 1. In addition, we would like to stress that no special microwave effect can be ob-

served in this system since the reduction using conventional heating gave results similar to those presented above.

In addition to the small-scale reductions which were possible to perform using the Emrys™ Creator (maximum volume of 5 mL) we have demonstrated that the reduction protocol using catalytic lithium isopropoxide is applicable to larger reaction set-ups. Employing the Advancer instrument from Biotage AB, we heated a reaction mixture containing 41 mmol of acetophenone and 6 mol% of *i*-PrOLi, and this resulted in 97% conversion to the alcohol. Encouraged by the promising result we doubled the amount of acetophenone to 82 mmol, otherwise keeping the system constant, and this gave 95% conversion and 89% isolated yield after work-up and purification (Scheme 3).



Scheme 3. Gram-scale reduction of acetophenone using microwave heating.

In conclusion, we have demonstrated that simple alkali alkoxides work as efficient transfer hydrogenation catalysts for the conversion of ketones to their corresponding alcohols. The use of microwave irradiation allows for rapid heating which in turn leads to short reaction times. The method is simple to execute, does not require any hazardous or highly reactive hydride reagents and is performed in an environmentally friendly media. The current findings should provide a competitive alternative to other reduction methods for substrates which are able to withstand heating to temperatures up to 180 °C.

Experimental Section

Microwave heating experiments was performed in a Emrys™ Creator except the large scale setup which was performed in an Advancer both from Biotage AB (formerly Personal Chemistry AB) Uppsala, Sweden. All microwave irradiation experiments were performed in sealed reaction vessels and with fixed hold time.

General Procedure for the Reduction of Ketones

To 2-PrOH (1.9 mL) in a sealed pyrex tube was added *i*-PrOLi (0.625 mL, 0.03 mmol in 2-PrOH) and ketone (0.5 mmol). The solution was heated at 180 °C (for reaction times, see Table 1). After cooling to room temperature, the solution was filtered through a plug of silica, the solvent evaporated and the products were analysed. The conversions were determined by GLC or ^{1}H NMR analysis.

1-Phenylethanol

A solution of *i*-PrOLi (50 mL, 2.4 mmol in 2-PrOH) was added to 2-PrOH (150 mL) in a Teflon beaker. After addition of acetophenone (9.9 g, 81 mmol), the solution was heated at 180 °C for 25 min. The reaction mixture was ejected out of the reactor and cooled to room temperature, whereafter the solvent was evaporated under reduced pressure. The product was purified using column chromatography (pentane:Et_2O, 6:1) affording 1-phenylethanol; yield: 8.9 g (89%).

Supporting Information

Further experimental details and characterisation data for the compounds in Table 1. This material is available free of charge *via* the Internet.

Acknowledgements

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