# An efficient and transition metal free protocol for the transfer hydrogenation of ketones as a continuous flow process†

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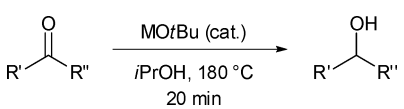
*Received 4th December 2008, Accepted 4th March 2009*
*First published as an Advance Article on the web 12th March 2009*
**DOI: 10.1039/b821752a**

**We report the efficient reduction of a selection of ketones to the corresponding secondary alcohols using only catalytic amounts of LiO*t*Bu in *i*PrOH facilitated by using a continuous flow reactor.**

The development of new and improved chemical processing techniques that are both economically viable with greater environmentally compatibility are of paramount importance to the chemical industry. The ability to conduct both complex and routine chemical transformations in a safe, reproducible and scalable fashion without recourse to costly route modification or redevelopment is highly desirable. The introduction of continuous flow reactor technologies[1,2] offers the ability to rapidly test, optimise and create scalable syntheses using a single bench top device. Furthermore, the intrinsic design of these microreactors and their high temperature and pressure tolerances enables utilisation of enhanced reaction conditions that were previously difficult to evaluate.

The formation of secondary alcohols through the direct reduction of the precursor ketone typically requires either stoichiometric amounts of a hydride donor or a combination of a transition metal catalyst and a molecular hydrogen source. Recently, Adolfsson reported upon an alternative protocol that excluded the use of expensive and toxic metal complexes, and avoided the need for molecular hydrogen.[3] Instead, a combination of inexpensive LiO*i*Pr and *i*PrOH was used. Expanding upon this idea we have developed a simple and highly efficient continuous flow process for the alkali metal catalysed reduction of ketones which makes potential scale up, with regard to industrial application, very straightforward.

We have previously shown that there is a significant benefit attained from the rapid co-evaluation of new high temperature reactions using microwave heating techniques and their subsequent translation into flow chemistry processes.[4] Consequently, our initial screening involved heating an *i*PrOH solution of 4-methoxy acetophenone in a sealed vial under microwave irradiation to 180 °C for 20 minutes (Scheme 1).




**Scheme 1** Alkali metal *tert*-butoxide catalysed reduction of ketones.

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† Electronic supplementary information (ESI) available: $^{1}H$ and $^{13}C$ NMR spectra for the alcohols. See DOI: 10.1039/b821752a

This study revealed that the nature of the alkali metal ion had a significant influence on the rate of the resulting reduction. LiO*t*Bu was superior to the corresponding Na or K salts, producing the secondary alcohol in excellent yield. In these initial transformations a reproducible 94% isolated yield of the desired alcohol was achieved using only 10 mol% of LiO*t*Bu. Of significant developmental interest was that stock solutions of the appropriate ketone and base could be prepared in advance under aerobic conditions using standard laboratory grade *i*PrOH.

This procedure was then directly transferred to a small footprint, continuous flow through reactor. We selected an experimental prototype unit from ThalesNano (X-Cube™ Flow Reactor)[5] for our investigation (Fig. 1).[6] The X-Cube system consists of a stand-alone Knauer K120 HPLC pump providing a continuous flow stream of reactants or solvent to the reactor. The main reactor itself comprises an integrated back-pressure regulator (200 bar max.) and detector, a heating module (350 °C max.) that encompasses an exchangeable stainless steel coil (various reactor cells can be inserted to give different reactor volumes of 4, 8 and 16 mL). A heat exchanger is also positioned at the exit of the reactor to rapidly cool the exiting flow stream. Use of an in-line cartridge[7] containing an excess of tosylhydrazine resin allows the scavenging of any residual ketone. For the examples described in this article no attempt was made to recover the ketone, although in practice more valuable starting materials could be subsequently released from the resin *via* a mild hydrolysis procedure.[8]

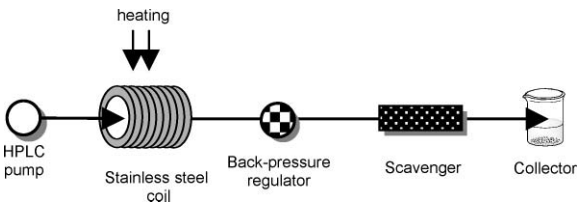



**Fig. 1** Pictorial description of the flow reactor configuration.

The control of the reaction parameters (flow rate, temperature and pressure) can be programmed, monitored and modified through a basic keypad user interface.

An initial screening of conditions was performed, which included reaction temperature, internal pressure, reagent concentration and residence time (flow rate). Optimal conversions were achieved using a 0.3–0.4 M concentration of ketone in *i*PrOH at 180 °C and a back-pressure of 160 bar. Increasing the temperature to 200 °C gave no additional benefits in conversion or reaction rates. The relatively high back-pressure employed

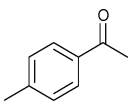
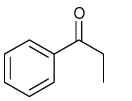
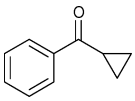
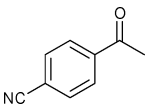
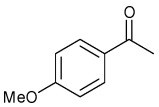
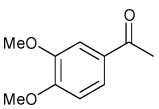
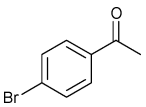
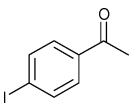
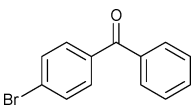
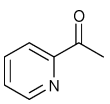
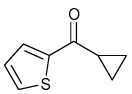
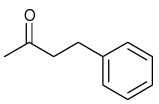
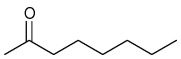
was required in order to maintain the *i*PrOH in the liquid phase at the elevated reaction temperatures, thus avoiding deposition and decomposition of the starting material, which eventually leads to the blockage of the system. The necessary residence time (flow rate) was substrate dependent and ranged between 20–30 minutes. Using these conditions a variety of ketones were readily reduced to the corresponding alcohols in high yield and excellent purity following tosyl-hydrazine resin scavenging (Table 1). The products required no additional purification following evaporation of solvent, which was pure enough to be recovered and reused.

In general the reductions proceed smoothly for substrates bearing electron-donating as well as electron-withdrawing substituents. Simple ketones (entries 1–3) reacted to the corresponding alcohols without difficulties. The presence of electron-withdrawing groups that increase the electrophilicity of the carbonyl (entries 4, 7 and 8) enabled shortening of the residence times from 30 to 20 minutes. The cyano functionalised acetophenone (entry 4) was smoothly reduced to the corresponding alcohol without affecting the nitrile functionality. In addition, the electron donating methoxy substituted acetophenones (entries 5 and 6) afforded the respective alcohols in good yield although longer residence times were required. Substrates possessing a halogen (entries 7–9) were also readily transformed; however, in the case of 4-iodo acetophenone and 4-bromo benzophenone, partial dehalogenation (6% and 5%) was also observed. The flow conditions proved to be suitable for the reduction of aliphatic (entries 12 and 13) and heteroaromatic ketones (entries 10 and 11), giving the expected products in excellent yields. Not all substrates tested reacted as efficiently. Substrates with hydroxy or amino moieties as well as easily enolisable carbonyls such as 3-chloro-4-nitro acetophenone and $\beta$-keto esters gave no conversion. The attempted reduction of ethyl 2-benzoylacetate gave the transesterified product exclusively.

The flow process easily allows for both the rapid optimisation of the reaction employing small injection aliquots of substrates as well as for scale up. Larger quantities of material can be easily prepared by running the system under steady state operation as a continuous flow process generating multi-gram batches. For example, processing a 0.3 M solution of 4-methoxy acetophenone (14.3 g, 95.2 mmol) at a flow rate of 0.53 mL $min^{-1}$ using a reactor volume of 16 mL generates 12.6 g (82.9 mmol) of material over a 10 h period. In the case of the large batch experiment the in-line scavenging procedure was slightly modified. First the *i*PrOH and the by-product acetone were evaporated, then the residue re-dissolved in *i*PrOH followed by addition of the tosyl-hydrazine scavenger (7.0 g, 2.84 mmol $g^{-1}$). The suspension was then vortexed on an orbital shaker for 1 h, and the resin removed by filtration. Following evaporation of the solvent the product was isolated in excellent purity.

In summary, we have devised a simple, efficient and transition metal free transfer hydrogenation protocol for use under flow conditions. The reaction is performed using a cheap and safe reaction medium, delivering secondary alcohol products in high yields and excellent purities following only evaporation and recovery of the solvent. The combination of the simple experimental conditions and the flow processing capabilities of

**Table 1** Lithium *tert*-butoxide catalysed transfer hydrogenation[a]

| Entry | Substrate | Residence time/min | Conversion[b] [%] |
|---|---|---|---|
| 1 |  | 30 | 96 (94) |
| 2 |  | 30 | 96 (91) |
| 3 |  | 30 | 93 (92) |
| 4 |  | 20 | 98 |
| 5 |  | 30 | 93 (87) |
| 6 |  | 30 | 85 |
| 7 |  | 20 | 98 |
| 8 |  | 20 | 96[c] |
| 9 |  | 30 | (92)[d] |
| 10 |  | 30 | 99 (97) |
| 11 |  | 30 | 89 (88) |
| 12 |  | 30 | 84 |
| 13 |  | 30 | 95 (90) |

[a] Reaction conditions: the reaction solution (0.3–0.4 M) containing LiO*t*Bu (10 mol%) and the appropriate ketone in *i*PrOH was continuously pumped through the X-Cube™ at 180 °C for the indicated residence time. After complete injection of the reaction mixture, the system was purged with pure *i*PrOH. [b] Conversions determined by $^1$H-NMR. Yields are given in parentheses. [c] 6% dehalogenated alcohol was observed. [d] An additional 5% dehalogenated alcohol was also isolated.

the reactor permits easy scale up, rendering this approach of high relevance for industrial application. The total volumes of solvent and reagents used in the flow reactions are significantly less than the batch mode process. Moreover, this reduction procedure does not involve the hazards associated with other batch mode reduction processes, such as with hydride reagents or high pressure hydrogenations and the use of toxic metal catalysts.

## Experimental

### Typical procedure

LiO*t*Bu (0.05 mmol) and ketone (0.50 mmol) were dissolved in *i*PrOH (1.5 mL) at room temperature under atmospheric conditions. The resulting solution was pumped continuously into the X-Cube™ and heated to 180 °C for the appropriate residence time. After the reaction mixture exited the system, the solvent was removed under reduced pressure.

## Acknowledgements

The authors would like to thank the DAAD for a postdoctoral fellowship (JS), the EPSRC for funding (IRB) and the BP 1702 Professorship (SVL).

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