Continuous Flow Ruthenium-catalysed Hydrogen-transfer Methods

Ricardo Labes[1], Claudio Battilocchio[1], Carlos Mateos [2]*,Davir G. Calderón,[1] Graham R. Cumming[2], Juan A. Rincón[2], Oscar de Frutos[2], Carlos Jaramillo[2], Talbi Kaoudi[2], Maria José Nieves-Remacha[2], Steven V. Ley[1]*.

[1]ITC for ACS, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, U.K.

[2]Centro de Investigación Lilly S.A., Avda. de la Industria 30, Alcobendas-Madrid 28108, Spain.

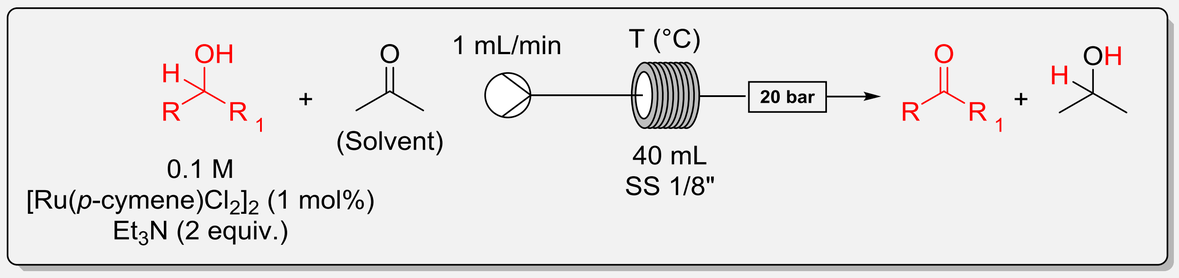
*c.mateos@lilly.com *svl1000@cam.ac.uk

Introduction

Oxidations and reduction processes are pivotal reactions in chemical synthesis and industrial processes. The development of selective, safe and practical methods continues to drive major interest in the scientific community. Catalytic methods have special importance in large-scale industrial processes, in that perspective hydrogen-transfer systems represent an attractive approach towards selective catalytic transformations.

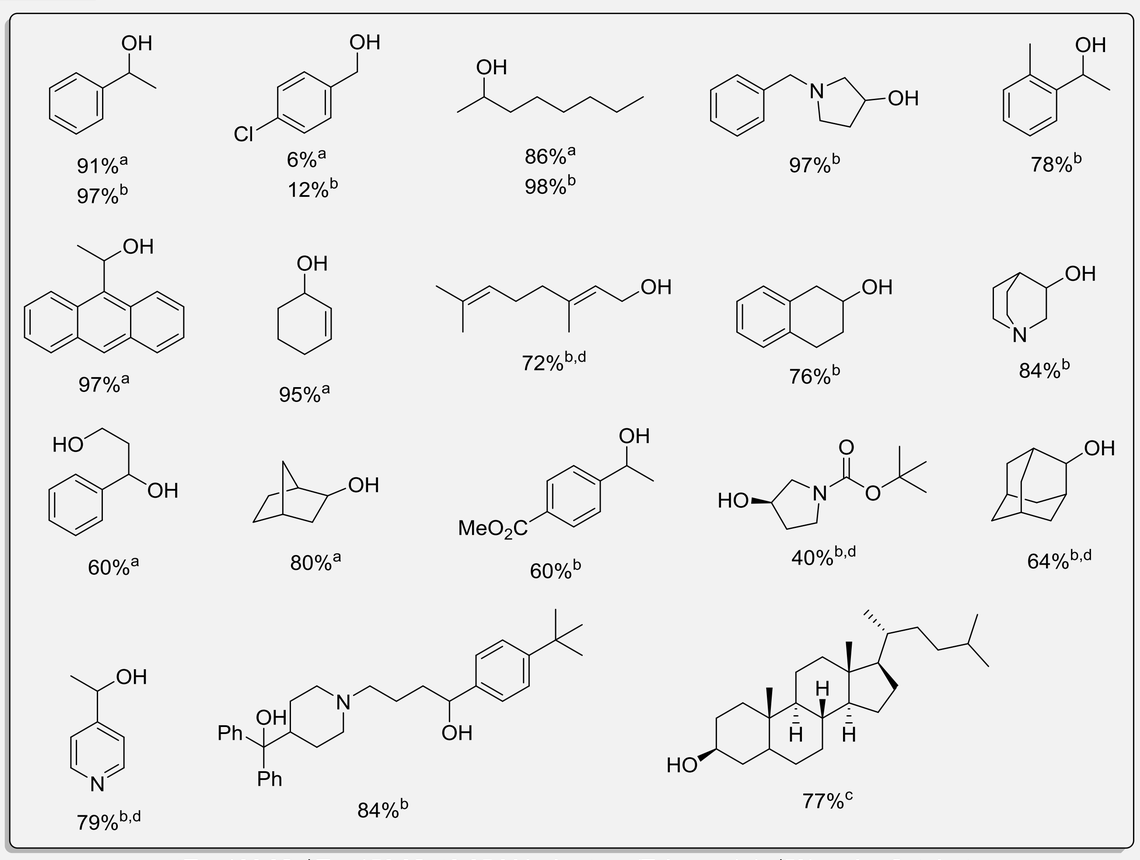
Oxidation of Secondary Alcohols

General procedure:



The studied system used acetone as solvent and hydrogen acceptor, dichloro(*p*-cymene)ruthenium(II) dimer as a cheap, readily available catalyst and triethylamine (**Figure 1**).[1] The ability to work with higher pressures in continuous flow allowed acetone to be used in higher temperatures.

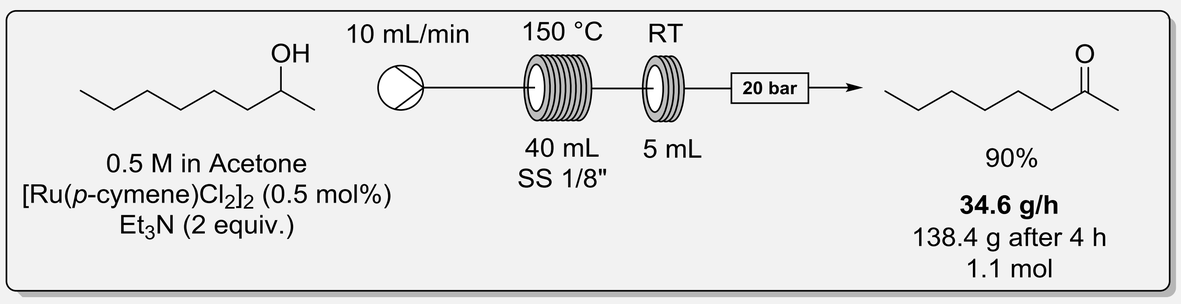
Scope:

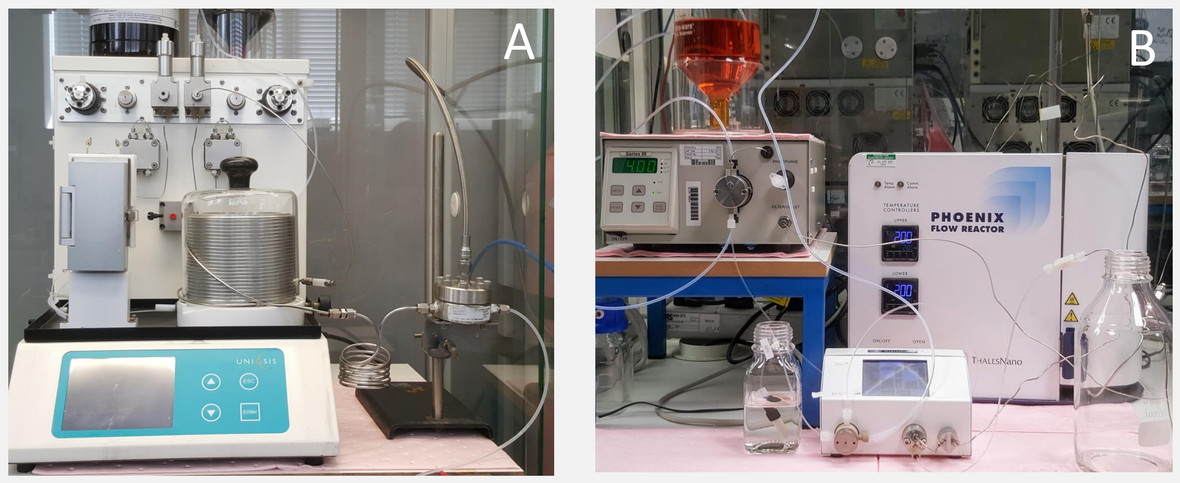


[a]T = 100 ºC. [b]T = 150 ºC. [c]0.05 M in Acetone/Toluene 1:1. [d]5% molar Catalyst.

The methodology demonstrated good chemoselectivity for secondary alcohols. When a mixture of octan-2-ol and nonan-1-ol were reacted, more than 98% of the secondary alcohol was oxidized while less than 2% of the aldehyde could be identified.

Scale-up:

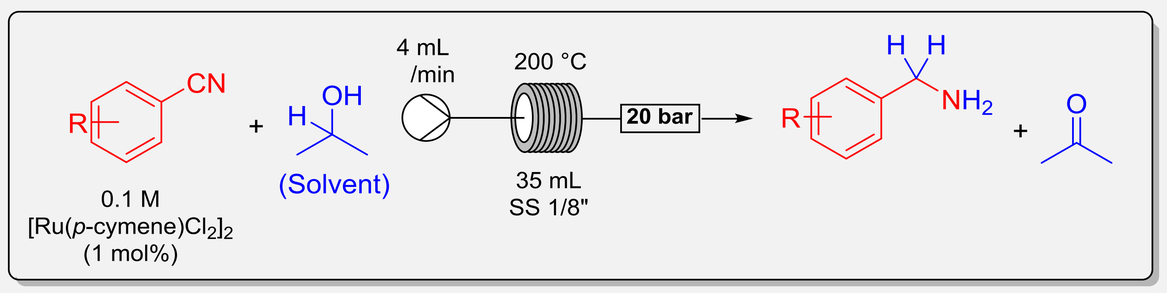




(**A**) System used for the oxidation of secondary alcohols. (**B**) System used for the reduction of nitriles.

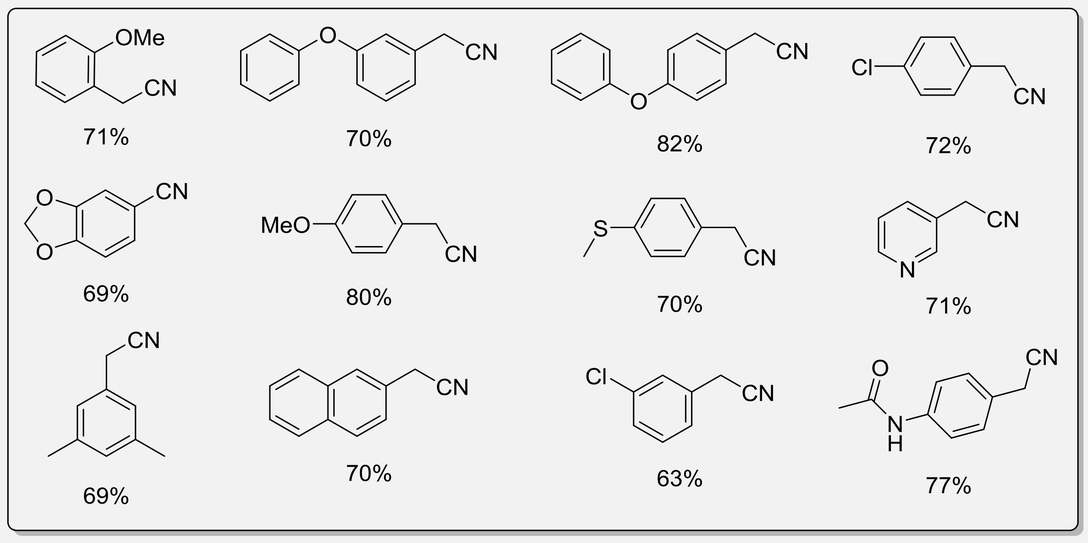
Reduction of Aromatic Nitriles

General procedure:



The method developed for the reduction of nitriles to primary amines requires no additives, and uses isopropanol as both solvent and reducing agent. It utilizes 1 mol% of the commercially available [Ru(*p*-cymene)Cl_2]$_2$, and has a residence time of ca. 9 min with throughput of 50 mmol/h.

Scope:



Conclusions

In summary we have developed a continuous flow system for the ruthenium-catalysed Oppenauer-type oxidation of mainly secondary alcohols, and for the reduction of aromatic nitriles to primary amines. The platform utilizes 1 mol% of a cheap and commercially available ruthenium catalyst, and acetone/2-propanol as hydrogen acceptor/donor. The system was successfully applied to a range of different substrates.

Acknowledgements

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References

1. Labes, R.; Battilocchio, C.; Mateos, C.; Cumming, G.R.; Frutos, O.; Rincón, J.A.; Binder, K.; Ley, S.V.; **Org. Process Res. Dev.** 21, 1419, 2017.
2. Labes, R.; González-Calderón, D.; Battilocchio, C.; Mateos, C.; Cumming, G.R.; Frutos, O.; Rincón, J.A.; Ley, S.V.;; **Synlett** (eFirst) DOI: 10.1055/s-0036-1590900

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@itc_cambridge