Communication

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Org. Process Res. Dev., Just Accepted Manuscript • DOI: 10.1021/acs.oprd.7b00190 • Publication Date (Web): 04 Aug 2017 Downloaded from http://pubs.acs.org on August 5, 2017

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Chemoselective Continuous Ru-Catalyzed Hydrogen-transfer Oppenauer-type Oxidation of Secondary Alcohols

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KEYWORDS: Continuous processing, Hydrogen transfer, Homogeneous catalysis, Oxidation, Ruthenium catalysis.

ABSTRACT: A continuous flow method for the selective oxidation of secondary alcohols is reported. The method is based on an Oppenauer-type ruthenium-catalyzed hydrogen-transfer process that uses acetone as both solvent and oxidant. The process utilizes a low loading (1 mol%) of the commercially available ruthenium catalyst [Ru(*p*-cymene)Cl₂]₂, triethylamine as base, and can be successfully applied to a range of different substrates, with a reasonable level of functional group tolerance.

The oxidation of alcohols is a fundamental transformation in chemical synthesis and many protocols have been developed over the years to afford different product outcomes and functional group tolerances. However, the development of chemoselective, safe and practical oxidation methods continue to be of major interest in the community.^{1–4}

Catalytic oxidation is particularly relevant for large scale industrial processes and, despite the outstanding progress, further development is needed if we are to respond to contemporary environmental challenges and with limited resources.^{1,5}

Hydrogen transfer methods constitute an attractive approach for many synthetic transformations.^{6–8} Among these, reduction processes are more well established.^{9–17} Hydrogen transfer oxidation methods have also evolved, with the development of new catalysts, employing aqueous media, supported catalysts and in the absence of hydrogen acceptors.^{18–25} Most notably, Bäckvall's group has implemented procedures for hydrogen transfer oxidation employing commercial catalysts, and a base, to achieve high yields, and with good functional group compatibility.^{26,27}

Furthermore the advantages of continuous flow methods applied to research and development programs are now well recognized in academia and industry.^{28–38}

Following our interest in redox reactions using continuous flow methods,^{39–42} we report here efforts to develop a continuous ruthenium-catalyzed hydrogen-transfer oxidation process.

We reasoned that we needed to combine the safety and selectivity of hydrogen transfer oxidation and continuous flow systems to deliver a method with broad application. For the work, a

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minimal system was assembled comprising a pump, heated coil and backpressure regulator (BPR), with acetone as the chosen proton acceptor to facilitate downstream processing. Steady state of the system was followed using an in-line UV-Vis detector.⁴³ The continuous system that was developed facilitates work beyond normal solvent reflux temperatures employed in other studies, and avoids any formation of aldol by-products.

Dichloro(p-cymene)ruthenium(II) dimer was selected as the catalyst to facilitate the oxidation of alcohols. [Ru(p-cymene)Cl₂]₂ was favored as it is commercially available, air-stable, and relatively inexpensive when compared to other precious metal catalysts.

Previous reports demonstrate that the addition of a base improves the oxidative catalytic cycle.^{27,44,45} To avoid the use of inorganic bases, which have poor solubility in acetone, and might compromise downstream processes, we opted to use triethylamine. Triethylamine is liquid, soluble and can be easily removed by evaporation, and gave us better yields, especially when compared to *N*,*N*-diisopropylethylamine (see ESI). The initial optimization (see ESI) provided a method whereby a 0.1 M solution of the alcohol in acetone, 1 mol% of the ruthenium catalyst and 2 equivalents of triethylamine were passed through a 40 mL heated coil (1/8″ o.d. stainless-steel) reactor (ESI Figure S1) at 1 mL/min. This same protocol was then applied to a variety of other alcohols including aromatic, aliphatic and allylic examples (**Table 1**).

Table 1. Substrate scope for the ruthenium catalyzed hydrogen transfer oxidation of alcohols



16	Br OH ↓ ↓	150	0
17	OH	150	78
18	ОН	100	50 ^d
19		150	64(60) ^d
20	HO S	150	58
21	OH MeO ₂ C	150	60
22		150	77(75) ^d
23		100	75 ^e
24		150	84(79) ^e
25	0	150	22
26	HO	150	40 ^f
27	OH	150	14
28		150	79 ^f
29	OH CI	150	99(96) ^g
30	ОН	100	6
31	CI	150	12
32	усторовно он	100	50
22		150	70f



^aYield determined by ¹H NMR integration against internal standard (1,3,5-trimethoxybenzene). ^bIsolated yields. ^cSolution prepared in a mixture 9:1 acetone/toluene. ^dSolution prepared in a mixture 8:2 acetone/toluene. ^eA 0.05M solution in a mixture 1:1 acetone/toluene was used. ^f5 mol% of catalyst used. ^gIn a small scale experiment we have directly compared the flow procedure to batch, as expected we obtained a comparable isolated yield.^{46 h}Yield of ketone, no aldehyde observed by ¹H NMR.

The reaction proved to be compatible with double bonds, heterocycles and esters. Pleasingly, very hindered alcohols could be successfully oxidized, such as *exo*-norborneol (entries 3 & 4) and adamanthanol (entries 18 & 19). 5α-Cholestan-3β-ol and terfenadine further exemplified the application of the method to natural product and active pharmaceutical ingredient substrates (entries 22 & 23 respectively). While nitrogen-containing substrates were successfully oxidized (e.g. entries 5 & 13), N-Boc-L-prolinol and a pyridine derivative (entries 25-28) required a higher catalyst loading to provide good yields of products. Reaction outputs were generally very clean, being composed of unreacted starting material and product. The system demonstrated high selectivity towards secondary alcohols over primary alcohols. For instance, *p*-chlorobenzyl alcohol provided only 12% of product at 150 °C (entry 31), while its secondary analogue was readily oxidized (entry 29). So when (R)-1-phenyl-1,3-propanediol was submitted to the reactor system, only the secondary position was oxidized, showing excellent chemoselectivity (entry 34). Despite the lower reactivity of geraniol (entries 32 & 33), it could be oxidized by increasing the catalyst loading at 150 °C. Not surprisingly, strongly chelating substrates such as 1,2octanediol (entry 35) failed to oxidize under a range of different reaction conditions. When (R)-

1-(2-bromophenyl)ethan-1-ol (entry 16) was submitted to the system, starting material was recovered, while the *para* substituted analogue (entry 15) was readily converted to the corresponding ketone. This can be rationalized as the *alpha* substituted can hinder the hydroxyl group, differently from the *para* substituted analogue.

To further evaluate the chemoselectivity of the method a mixture of octan-2-ol and nonan-1-ol was reacted under standard conditions. In this experiment, more than 98% of the secondary alcohol was oxidized while less than 3% of the aldehyde was detected (Scheme 1).

Scheme 1. Oxidation of a mixture of primary and secondary alcohols



The scalability of the system was rapidly evaluated using 2-octanol as a model substrate (Table S2, ESI). By increasing concentration of the substrate and flow rate it was possible to achieve a productivity of 34.6 g/h of 2-octanone (Scheme 2). At 10 mL/min a second coil was used to cool the reaction mixture and prevent it from boiling after the BPR. The reaction was operated continuously for 4 hours with no issues, such as clogging, being observed. When we attempted to use the system using even higher concentration and catalyst load, blockage occurred after 40 minutes (Table S2, ESI).

Scheme 2. Scale-up experiment for the oxidation of 2-octanol



Downstream processing was incorporated with the reaction output (28 mL) delivered to a flask containing QuadraSilTM-MP (1.94 g, 1.2 mmol/g) to remove the soluble residual Ru content from the reaction stream. After filtration and solvent removal, effective removal of Ru was shown by ICP-MS data (1.19 ppm) delivering the product with high level of purity.

We were also interested in understanding the role of the Ru catalyst, as previous reports had shown that Ru-catalyzed hydrogen transfer reactions can proceed through different routes.⁴⁷ Ruthenium dichloride catalysts are understood to follow a mono or di-hydric pathway in both dehydrogenation and hydrogenation reaction. Sasson argued that Ru⁰ nanoparticles are the real catalyst for the hydrogen transfer reductions using $[(C_6H_5)_3P]_3RuCl_2$.⁴⁸ Similarly to Sasson's report, our process was characterized by a color change during the reaction progression (from red to black), with the eventual deposition of particles after time (see ESI). We also noticed that the formation of Ru particles was directly related to the temperature of the system. To help understand the nature of the catalyst, mercury poisoning experiments were performed^{48,49} and no difference in catalytic activity was observed. These results support the proposal of a soluble catalyst, and that the particles observed are formed as a by-product from the redox process. Elemental analysis of the black particles showed 3-6% of carbon and 1%< for both hydrogen and nitrogen. TEM analysis (see ESI) showed the particles are highly aggregated with an average

diameter of diameter of 2.35697 nm (+0.13) and particle distribution of 5.36%. Measurement of lattice fringes are in accordance with the values expected for ruthenium.

In summary, we have developed a continuous flow system for the ruthenium-catalyzed hydrogen-transfer oxidation of mainly secondary alcohols. The method utilizes 1 mol% of the commercially available catalyst [Ru(*p*-cymene)Cl₂]₂ and triethylamine as base. The process was successfully applied to a range of different substrates, and represents a notable improvement on our previous related oxidation studies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Detailed experimental data and characterization of compounds.

Additional data is available from the University of Cambridge Data Repository website: https://doi.org/10.17863/CAM.10216

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

The authors are grateful to Eli Lilly & Co. (RL) and the EPSRC (SVL, grants EP/K009494/1, EP/M004120/1 and EP/K039520/1) for financial support. This work was supported by Eli Lilly & Co. through the Lilly Research Award Program (LRAP).

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