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Sustainable Flow Oppenauer Oxidation of Secondary Benzylic Alcohols with a Heterogeneous Zirconia Catalyst

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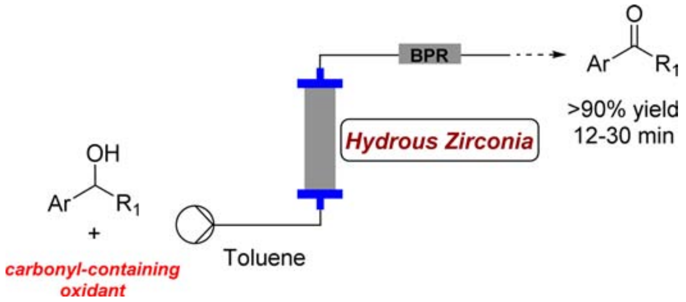
ABSTRACT



A flow chemistry process for the Oppenauer oxidation of benzylic secondary alcohols using partially hydrated zirconium oxide and a simple carbonyl containing oxidant such as acetone, cyclohexanone, and neopentanal is reported. The heterogeneous oxidative system could be applied to a wide range of functionalized alcohol substrates, allowing clean and fast delivery of ketone products within a few minutes between 40 and 100 °C.

The oxidative processing of alcohols plays a fundamental role in organic synthesis leading ultimately to many of society's functional materials.[1] Selectivity during certain oxidative reactions can be challenging to achieve, often requiring expensive metal catalysis and inevitably leading to further downstream processing problems. Although major advances have been made, there is still room for improvement. A case in point concerns the Oppenauer

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(1) (a) Hudlicky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, DC, 1990. (b) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981. (c) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; Wiley-Interscience: New York: 2001; pp 1514−1517. (d) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666. (e) Marko, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science* **1996**, *274*, 2044–2046. (f) Marko, I. E.; Giles, P. R.; Tsukazaki, M.; Chelle-Regnaut, I.; Gautier, A.; Brown, S. M.; Urch, C. J. *J. Org. Chem.* **1999**, *64*, 2433–2439. (g) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185–3189. (h) Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636–1639. (i) Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188–7189. (j) ten Brink, G.-J.; Arends, I. W. C. E.; Sheldon, R. A. *Adv. Synth. Catal.* **2002**, *344*, 355–369. (k) Guram, A. S.; Bei, X.; Turner, H. W. *Org. Lett.* **2003**, *5*, 2485–2487. (l) Minisci, F.; Recupero, F.; Pedulli, G. F.; Lucarini, M. J. *Mol. Catal. A: Chem.* **2003**, *63*, 204–205. (m) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549–7552. (n) Ohsugia, S.-I.; Nishidea, K.; Oonob, K.; Okuyamab, K.; Fudesakaa, M.; Kodamaa, S.; Node, M. *Tetrahedron* **2003**, *59*, 8393–8398. (o) Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 5323–5326.

(2) For examples of Oppenauer oxidations, see: (a) Kloetzing, R. J.; Krasovskiy, A.; Knochel, P. *Chem.—Eur. J.* **2007**, *13*, 215–227. (b) Mello, R.; Martínze-Ferrer, J.; Asensio, G.; González-Núñez, M. E. *J. Org. Chem.* **2007**, *72*, 9376–9378. (c) Graves, C. R.; Zeng, B.-S.; Nguyen, S. T. *J. Am. Chem. Soc.* **2006**, *128*, 12596–12597. (d) Ooi, T.; Otshuka, H.; Miura, T.; Ichikawa, H.; Maruoka, K. *Org. Lett.* **2002**, *4*, 2669–2672. (e) Almeida, M. L. S.; Kočovský, P.; Bäckvall, J.-E. *J. Org. Chem.* **1996**, *61* (19), 6587–6590. (f) Suzuki, T.; Morita, K.; Tsuchida, M.; Hiroi, K. *J. Org. Chem.* **2003**, *68*, 1601–1602. (g) Graves, C. R.; Campbell, E. J.; Nguyen, S. T. *Tetrahedron: Asymmetry* **2005**, *16*, 3460–3468. (h) deeGraauw, C. F.; Peters, J. A.; vanBekkum, H.; Huskens, J. *Synthesis* **1994**, 1007–1017. (i) Wang, P.; Shi, X.; Kataoka, K.; Maed, Y.; Kobiro, K. *J. Supercrit. Fluids* **2010**, *52*, 222–227. (j) Kamitanaka, T.; Ono, Y.; Morishima, H.; Hikida, T.; Matsuda, T.; Harada, T. *J. Supercrit. Fluids* **2009**, *49*, 221–226. (k) Coleman, M. G.; Brown, A. N.; Bolton, B. A.; Guan, H. *Adv. Synth. Catal.* **2010**, *352*, 967–970. (l) Borzatta, V.; Capparella, E.; Chiappino, R.; Impala, D.; Poluzzi, E.; Vaccari, A. *Catal. Today* **2009**, *140*, 112–116. (m) Du, W.; Wang, L.; Wu, P.; Yu, Z. *Chem.—Eur. J.* **2012**, *18*, 11550–11554. (n) Csuk, R.; Vasileva, G.; Barthel, A. *Synthesis* **2012**, *44*, 2840–2842. (o) Manzini, S.; Urbina-Blanco, C. A.; Nolan, S. P. *Organometallics* **2013**, *32*, 660–664. (p) Liu, S. H.; Chuah, G. K.; Jaenicke, S. *J. Mol. Catal. A: Chem.* **2004**, *220*, 267–274.

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oxidation of alcohols to carbonyl compounds by transfer dehydrogenation. Numerous reaction modifications have contributed to its re-emergence as an attractive process for oxidation;[2] however, further criteria need to be met to improve the speed and safety of the reaction to provide a more sustainable procedure.

Given that we have recently reported a flow chemistry method for the complementary Meerwein–Ponndorf–Verley (MPV) reduction of carbonyl compounds using isopropanol and hydrous zirconia[3] where we demonstrated distinct advantages over the batch reaction, it was prudent to study a similar tactic for the oxidation process.[4] The choice of hydrous zirconia makes sense in that it is heterogeneous, cheap, recyclable, and readily packed into flow tubes. These function especially well under the back pressure regulated (BPR) control common to many flow chemistry protocols and also facilitate minimal reaction workup through simple solvent removal from the product effluent stream.

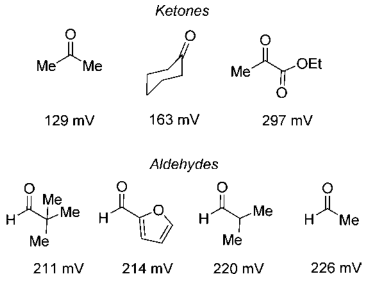


Figure 1. Oxidation potentials (E_0) of different oxidants screened in this work.[4]

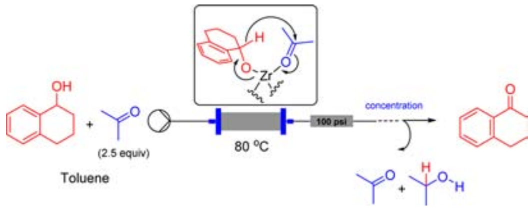
The selection of the necessary hydride acceptor for this reaction was based upon the known oxidation potentials of various ketones and aldehydes (Figure 1).[5] Being a redox process, the Oppenauer oxidation (as well as the MPV reduction) is governed by the redox potentials of the reacting species implying that the equilibrium of the reaction might be anticipated by application of the Nernst equation:

$$\log K = (2/0.0592)(E_{\text{ox}} - E_{\text{red}})$$

where E_{ox} and E_{red} correspond to the redox potentials of the oxidant and the reductant, respectively.

We found that the use of acetone and later cyclohexanone or neopentanal as hydride acceptors were particularly useful. Indeed, the use of acetone is accompanied by the formation of IPA as a volatile byproduct, making the downstream workup processing trivial. Nevertheless, the oxidation properties of acetone are quite mild, so one can envisage that its usefulness is limited to the oxidation of compounds whose redox potential is lower than 90–95 mV. In the case of substrates with higher redox potentials, a large excess of acetone is needed to drive the reaction to completion. This leads to further complications owing to the formation of aldol products from the self-condensation of acetone, which results in the difficult removal of impurities without recourse to chromatography (a common problem in other Oppenauer procedures).

Scheme 1. General Flow Protocol for the Oppenauer Oxidation of Alcohols



For our initial study we chose α-tetralol (E_0 = 80 mV) as a model substrate for the development of a sustainable flow process. Under optimized conditions, a 0.25 M solution of the alcohol and acetone (2.5 equiv) in toluene was reacted by passage through an Omnifit column containing a hydrous zirconia catalyst[6] (2.0 g, void volume 2.0 mL, 0.1 mL min^{-1} flow rate)[7] (Scheme 1). This reactor setup required only short residence times of around 20 min and a simple workup involving evaporation of the toluene solvent, mild excess of acetone, and IPA byproducts to afford nearly quantitative yields of the product.

α-Tetralols bearing electron-donating groups underwent oxidation even more rapidly (Table 1), with no evidence of any byproducts being formed. Similarly a number of other benzylic secondary alcohol substrates could be readily oxidized under these reaction conditions (Table 1). We were also pleased to find that the conditions were scalable and we were able to continuously flow process compounds on at least 15 mmol scale of product (Table 1, entry 1).

As expected, however, with certain substrates such as 1-phenylethanol, using acetone as a hydride acceptor only 35% oxidation could be realized. Neither increasing the amount of acetone nor increasing the reaction temperature improved the isolated yield.

On the other hand, if cyclohexanone, which has a significantly higher oxidation potential (163 mV),[5] was used as the oxidant in the flow process, we observed very good conversions even with these difficult substrates (Table 2).

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(3) Battilocchio, C.; Hawkins, J. M.; Ley, S. V. *Org. Lett.* **2013**, *15*, 2278–2281.

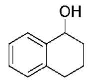
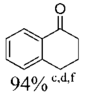
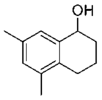
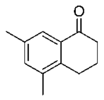
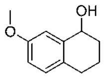
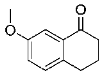
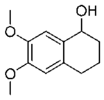
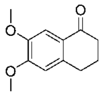
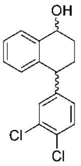
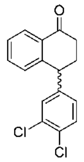
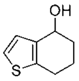
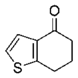
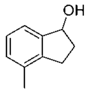
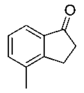
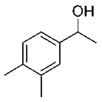
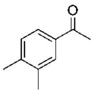
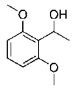
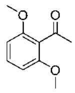
(4) (a) Kuno, H.; Takahashi, K.; Shibagaki, M.; Shimazaki, K.; Matsushita, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1943–1946. (b) Kuno, H.; Shibagaki, M.; Takahashi, K.; Matsushita, H. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 312–314. In our hands these procedures were not satisfactory and led to considerable amounts of acetone aldol by products also being formed in the process.

(5) (a) Adkins, H.; Elofson, R. M.; Rossow, A. G.; Robinson, C. C. *J. Am. Chem. Soc.* **1949**, *71*, 3622–3629. (b) Baker, R. H.; Robinson, C. C. *J. Am. Chem. Soc.* **1940**, *62*, 3305–3314.

(6) Hydrous zirconia was prepared starting from commercially available zirconium hydroxide (Sigma-Aldrich); calcination of zirconium hydroxide was carried out in a Buchi TO-51 (http://www.nist.gov/ncnr/drying-tube-buchi-to-51.cfm) at 270 °C for 24 h; we observed different catalytic properties depending upon the level of hydration of the catalyst.

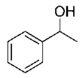
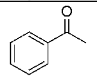
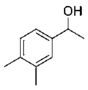
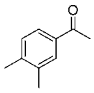
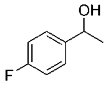
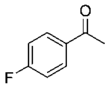
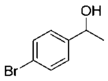
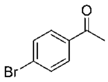
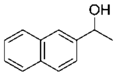
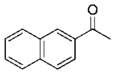
(7) Website: http://www.omnifit.com/.

Table 1. Oxidation of Secondary Benzylic Alcohols Using Acetone As the Oxidant

entry	substrate	t[a] (min)	temp (°C)	product[b] yield
1		20 min	80	 94%[c,d,f]
2		18 min	80	 96%
3		15 min	80	 96%
4		12 min	80	 96%
5		20 min	80	 95%[c]
6		20 min	80	 95%
7		20 min	80	 91%[c]
8		30 min	80	 90%[e]
9		15 min	80	 96%

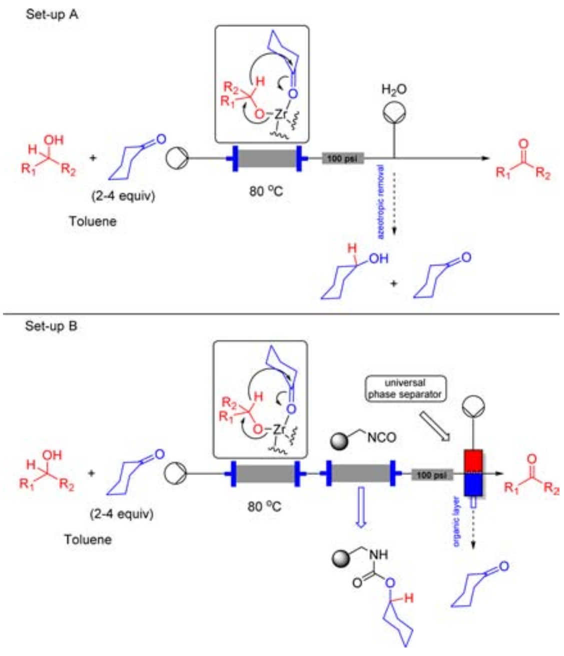
[a] Optimized residence time. [b] 1 mmol scale reaction. [c] 15 mmol scale. [d] The reaction was scaled up to 15 mmol using 6 equiv of acetone. [e] 6 equiv of acetone were used. [f] Comparative microwave reaction at 100 °C showed 86% conversion after 1 h and 99% conversion after 1.5 h.

Table 2. Oxidation of Secondary Benzylic Alcohols Using Cyclohexanone As the Oxidant

entry	substrate	t[a] (min)	temp (°C)	product[b] yield
10		20 min	80	 95%
11		20 min	80	 94%
12		20 min	80	 93%
13		25 min	100	 95%
14		25 min	100	 94%

[a] Optimized residence time. [b] 1 mmol scale reaction.

Scheme 2. General Flow Protocol for the Oppenauer Oxidation of Secondary Aromatic Alcohols Using Cyclohexanone As Oxidant

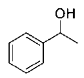
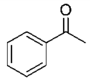
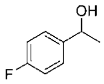
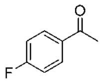
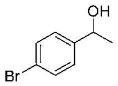
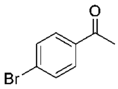
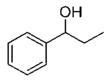
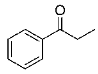
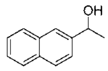
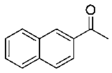
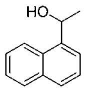
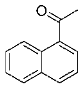
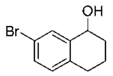
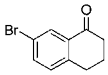
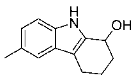
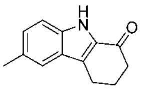


The only drawback of using cyclohexanone as the oxidant is that the product stream contains cyclohexanol which is harder to remove than the isopropanol generated when using acetone as the oxidant. Nevertheless, the cyclohexanol can be removed by using appropriate polymer supported scavengers (e.g., PS-isocyanates) or by azeotropic removal of cyclohexanol and residual cyclohexanone (Scheme 2).

In view of this workup problem, we switched to neopentanal as the oxidant since it has an even higher redox potential (E_0 = 211 mV), it lacks α-hydrogens, and the corresponding alcohol is water-soluble, making this molecule an attractive alternative to acetone or cyclohexanone.

Using this new protocol we were able to oxidize a wide range of other functionalized precursors employing neopentanal as the oxidant (Table 3). The high redox potential of neopentanal as the oxidant meant that reactions could be run at remarkably low temperature without the need to extend the residence times. Significantly, no condensation products were observed between the neopentanal and the ketone products. Under the standardized conditions, a 0.25 M solution of the alcohol and neopentanal (2.0−4.0 equiv) in toluene was passed through an Omnifit glass

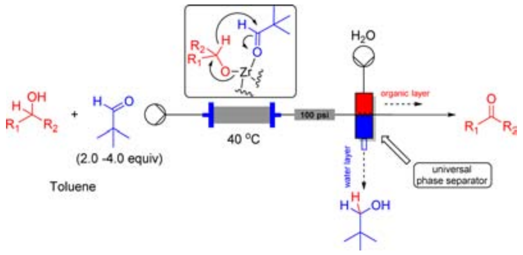
Table 3. Oxidation of Secondary Benzylic Alcohols Using Neopentanal As the Oxidant

entry	substrate	t^a (min)	temp (°C)	product^b yield
15		20 min	40	 96%
16		20 min	40	 96%
17		25 min	40	 95%
18		30 min	40	 90%
19		20 min	40	 93%
20		25 min	40	 93%
21		30 min	40	 90%
22		20 min	40	 91%

^{a} Optimized residence time . ^{b} 1 mmol scale reaction.

column packed with hydrous zirconia operating *at only 40 °C*. The output stream was combined with a stream of water and then delivered to a universal membrane separator[8] to obtain the pure product on concentration *in vacuo* of the organic fraction (Scheme 3).

Scheme 3. General Flow Protocol for the Oppenauer Oxidation of Alcohols



In conclusion, we have developed an effective flow chemistry procedure for the oxidation of secondary benzylic alcohols by passage through hydrous zirconia using various stoichiometric carbonyl compounds as the oxidants.

The procedures are mild, proceeding at as low as 40 °C, and accommodate easy reaction workup. Electron-rich and electron-deficient substrates are well tolerated. Improvement over the batch reactions are significant (typically these require extended reaction times of > 1−1.5 h and high temperatures of ≥ 100 °C) owing to the use of elevated pressure through a back pressure control device. The catalyst could be reused several times without apparent reduction of the catalytic efficiency.[9] Work is ongoing to improve the scalability still further.

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Supporting Information Available. Characterization data of compounds are available within the Supporting Information.This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (a) http://www.biotage.com/DynPage.aspx?id = 120778. (b) Battilocchio, C.; Deadman, B. J.; Nikbin, N.; Kitching, M. O.; Baxendale, I. R.; Ley, S. V. *Chem.—Eur. J.* **2013**, *19*, 7917–7930.

(9) The catalyst column was reused at least 10 times; the column was washed with a mixture 3:1 oxidant/IPA (1 mL) in toluene (4 mL) before and after every use.

The authors declare no competing financial interest.