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A Mild and Efficient Flow Procedure for the Transfer Hydrogenation of Ketones and Aldehydes using Hydrous Zirconia

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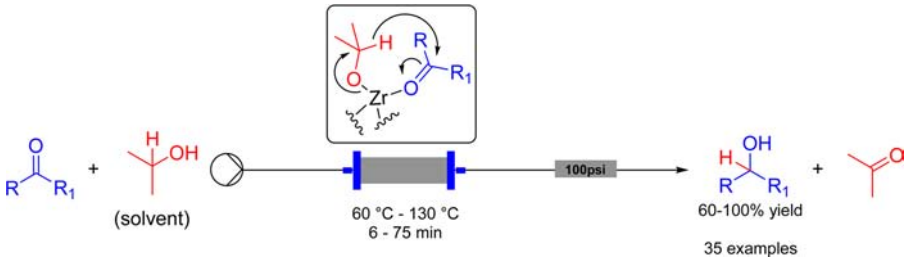
ABSTRACT



A flow chemistry Meerwein–Ponndorf–Verley (MPV) reduction procedure using partially hydrated zirconium oxide *via* a machine-assisted approach is reported. The heterogeneous reductive system could be applied to a wide range of functionalized substrates, allowing clean and fast delivery of the alcohol products within a few minutes (6–75 min). In three examples the system was scaled to deliver 50 mmol of product.

The increasing demand for clean and environmentally benign processes is driving the way we develop and deliver our chemistry.[1] Reductions and oxidations represent a significant part of the synthesis repertoire and consequently are under intense scrutiny.[2] The Meerwein–Ponndorf–Verley (MPV) reduction is recognized as an attractive process due to many favorable features such as high selectivity, mild conditions, and use of relatively cheap reagents.[3] In recent years modifications to the MPV reaction have been introduced to address some of the remaining problems with its application, including long reaction times, solvent selection, side reactions, workup issues, and catalyst effectiveness.[3d−v] However to date a completely reliable, fast, safe, and sustainable procedure has not been fully developed.

We have previously reported a flow chemistry protocol for the transfer hydrogenation of carbonyl compounds using a catalytic amount of lithium *tert*-butoxide.[3v] Nevertheless, there are still a number of limitations to our protocol, such as the high temperature required, the use of a lithiated reagent, and its inability to process aldehydes.

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(1) Ley, S. V. *Chem. Rec.* **2012**, *12*, 378–390.
(2) Sheldon, R. A.; Arens, I.; Hanefeld, U. *Green Chemistry and Catalysis*; Wiley-VCH Verlag GmbH & Co. kGaA: 2007.
(3) (a) Meerwein, N. H.; Schmidt, R. *Liebigs Ann. Chem.* **1925**, *444*, 221–238. (b) Ponndorf, W. Z. *Angew. Chem.* **1926**, *39*, 138–143. (c) Verley, M. *Bull. Soc. Chim. Fr.* **1925**, *37*, 871. (d) Ooi, T.; Ichikawa, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3610–3612. (e) Node, M.; Nishide, K.; Shigeta, Y.; Shiraki, H.; Obata, K. *J. Am. Chem. Soc.* **2000**, *122*, 1927–1936. (f) Corma, A.; Domine, M. E.; Nemeth, L.; Valencia, S. *J. Am. Chem. Soc.* **2002**, *124*, 3194–3195. (g) Mojtahedi, M. M.; Akbarzadeh, E.; Sharifi, R.; Abaee, M. S. *Org. Lett.* **2007**, *9*, 2791–2793. (h) Yin, J.; Huffman, M. A.; Conrad, K. M.; Armstrong, J. D. *J. Org. Chem.* **2006**, *71*, 840–843. (i) Seifert, A.; Scheffler, U.; Markert, M.; Mahrwald, R. *Org. Lett.* **2010**, *12*, 1660–1663. (j) Akamanchi, K. G.; Varalakshmy, N. R.; Chaudari, B. A. *Synlett* **1997**, 371. (k) Akamanchi, K. G.; Varalakshmy, N. R. *Tetrahedron Lett.* **1995**, *36*, 3571–3572. (l) Akamanchi, K. G.; Noorani, V. R. *Tetrahedron Lett.* **1995**, *36*, 5085–5088. (m) Barbry, D.; Torchy, S. *Tetrahedron Lett.* **1997**, *38*, 2959–2960. (n) Akamanchi, K. G.; Chaudhari, B. A. *Tetrahedron Lett.* **1997**, *38*, 6925–6928. (o) Anwander, R.; Palm, C.; Gerstberger, G.; Groeger, O.; Engelhardt, G. *Chem. Commun.* **1998**, 1811–1812. (p) Mebane, R. C.; Mansfield, A. M. *Synth. Commun.* **2005**, *35*, 3083–3086. (q) Baratta, W.; Siega, K.; Rigo, P. *Adv. Synth. Catal.* **2007**, *349*, 1633–1636. (r) Su, F.-Z.; He, L.; Ni, J.; Cao, Y.; He, H.-Y.; Fan, K.-N. *Chem. Commun.* **2008**, 3531–3533. (s) Polshettiwar, V.; Varma, R. S. *Green Chem.* **2009**, *11*, 1313–1316. (t) Lee, J.; Ryu, T.; Park, S.; Lee, P. H. *J. Org. Chem.* **2012**, *77*, 4821–4825. (u) Mollica, S.; Genovese, S.; Pinnen, S.; Stefanucci, A.; Curini, M.; Epifano, F. *Tetrahedron Lett.* **2012**, *53*, 890–892. (v) Sedelmeier, J.; Ley, S. V.; Baxendale, I. R. *Green Chem.* **2009**, *11*, 683–685.

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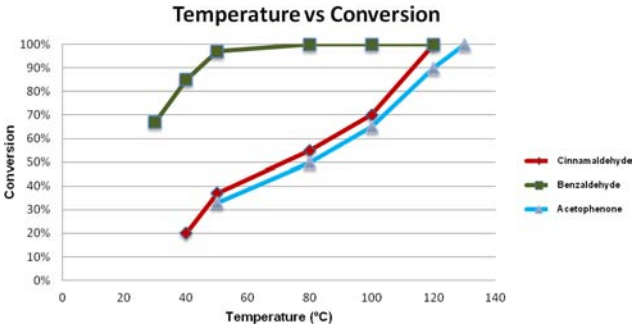


Figure 1. Conversion of benzaldehyde (**1**, τ = 12 min) to benzyl alcohol, acetophenone (**11**, τ = 30 min) to 1-phenylethanol, and cinnamaldehyde (**35**, τ = 22 min) to cinnamic alcohol at different temperatures, measured at the indicated fixed residence times.

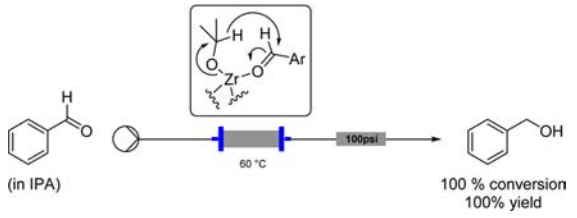
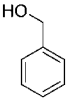
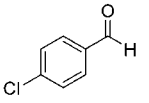
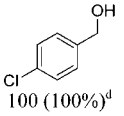
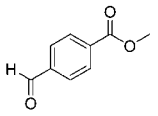
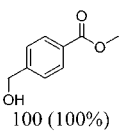
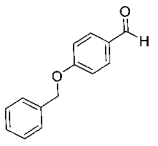
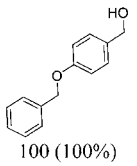
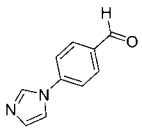
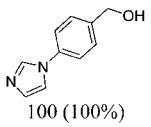
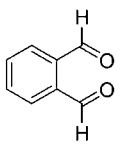
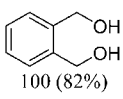
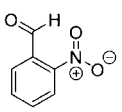
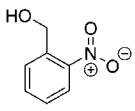
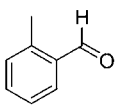
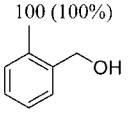
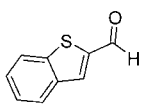
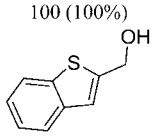
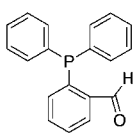
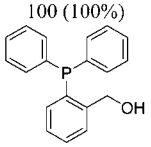


Figure 2. Flow setup for the reduction of benzaldehyde (**1**).

With a view to performing MPV reactions on scale, we envisaged a process which had to satisfy more stringent criteria by using a cheap and reusable catalyst, which would be safe to employ in quantity, and requiring minimal downstrem processing.

From our experience with flow chemistry utilizing solid-supported reagents,[4] we have found that a heterogeneous catalyst within a flow stream can enable these additional criteria. Indeed, zirconium-based heterogeneous catalysts are reported to be effective for MPV reduction of both aldehydes and ketones.[5a–e]

Table 1. Reduction of Aromatic Aldehydes

entry	substrate	τ^a (min)	temp (°C)	product[b] (conversion/yield)[c]
1		12 min	60	 100 (100%)
2		8 min	60	 100 (100%)[d]
3		8 min	60	 100 (100%)
4		15 min	60	 100 (100%)
5		12 min	60	 100 (100%)
6		12 min	60	 100 (82%)
7		6 min	60	 100 (100%)
8		15 min	60	 100 (100%)
9		12 min	60	 100 (100%)
10		15 min	60	 100 (98%)

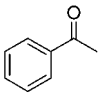
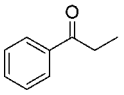
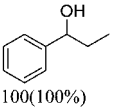
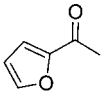
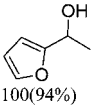
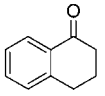
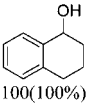
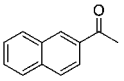
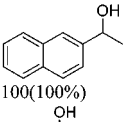
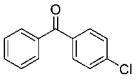
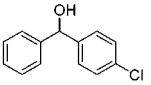
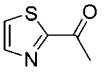
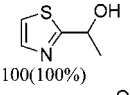
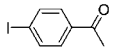
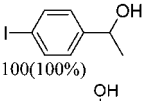
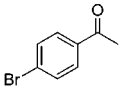
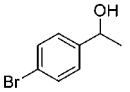
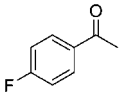
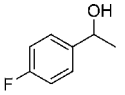
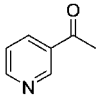
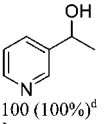
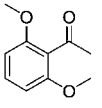
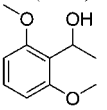
[a] Residence time. [b] 2 mmol scale reaction. [c] Conversions were determined by ^{1}H NMR. [d] 50 mmol scale.

We chose therefore to investigate zirconium hydroxide as a heterogeneous catalyst and isopropanol (IPA) as

(4) (a) Ingham, R.; Riva, E.; Nikbin, N.; Baxendale, I. R.; Ley, S. V. *Org. Lett.* **2012**, *14*, 3920–3923. (b) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N.; Smith, C. D. *Org. Biomol. Chem.* **2008**, *6*, 1587–1593. (c) Smith, C. J.; Smith, C. D.; Nikbin, N.; Ley, S. V.; Baxendale, I. R. *Org. Biomol. Chem.* **2011**, *9*, 1927–1937. (d) Lange, H.; Capener, M.; Jones, A.; Smith, C. J.; Nikbin, N.; Baxendale, I. R.; Ley, S. V. *Synlett* **2011**, 869–873. (e) Nikbin, N.; Ladlow, M.; Ley, S. V. *Org. Process Res. Dev.* **2007**, *11*, 458–462. (f) Roper, K.; Lange, H.; Polyzos, A.; Berry, M. B.; Baxendale, I. R.; Ley, S. V. *Beilstein J. Org. Chem.* **2011**, *7*, 1648–1655. (g) Guetzoyan, L.; Nikbin, N.; Baxendale, I. R.; Ley, S. V. *Chem. Sci.* **2013**, *4*, 764–769. (h) Battilocchio, C.; Deadman, B. J.; Nikbin, N.; Baxendale, I. R.; Ley, S. V. *Chem.—Eur. J.*, DOI: 10.1002/chem.201300696. (j) Baxendale, I. R.; Lee, A. L.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, *16*, 1850–1857. (k) Heberman, J.; Ley, S. V.; Smits, R. *J. Chem. Soc., Perkin Trans. 1* **1999**, *17*, 2121–2423. (l) Baxendale, I. R.; Ley, S. V.; Nessi, M.; Piutti, C. *Tetrahedron* **2002**, *58*, 6285–6304. (m) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N.; Smith, C. D.; Tieney, J. P. *Org. Biomol.Chem.* **2008**, *6*, 1577–1586. (n) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N.; Smith, C. D. *Org. Biomol. Chem.* **2008**, *6*, 1587–1593.

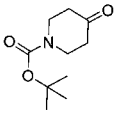
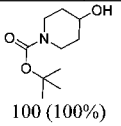
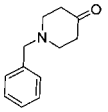
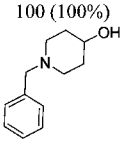
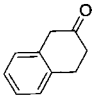
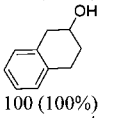
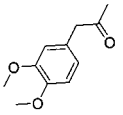
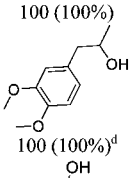
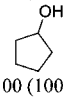
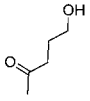
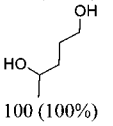
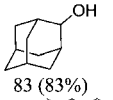
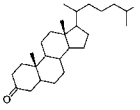
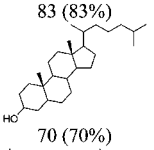
(5) (a) Zhu, Y.; Liu, S.; Jaenicke, S.; Chuah, G. *Catal. Today* **2004**, *97*, 249–255. (b) Minimbres, J. F.; Aramendia, M. A.; Marinas, A.; Marinas, J. M.; Urbano, F. J. *J. Mol. Catal.* **2011**, *338*, 121–129. (c) Axpuac, S.; Aramendia, M. A.; Hidalgo-Carrillo, J.; Marinas, A.; Marinas, J. M.; Montes-Jimenez, V.; Urbano, F. J.; Borau, V. *Catal. Today* **2012**, *187*, 183–190. (d) Heveling, J.; Laffan, D.; Wellig, A. U.S. Patent 6,075,145, 2000. (e) Zhu, Y.; Jaenicke, S.; Chuah, G. K. *J. Catal.* **2003**, *218*, 396–404.

Table 2. Reduction of Aromatic Ketones

entry	structure	τ [a](min)	temp (°C)	product[b] (conversion/yield)[c]
11		30 min	130	 100(100%)
12		30 min	130	 100(100%)
13		30 min	130	 100(94%)
14		60 min	130	 100(100%)
15		30 min	130	 100(100%)
16		25 min	130	 100(98%)
17		35 min	130	 100(100%)
18		22 min	130	 100(100%)
19		22 min	130	 100 (100%)
20		25 min	130	 100(100%)
21		25 min	130	 100 (100%)[d]
22		45 min	130	 60 (60%)[e]

[a] Residence time. [b] 2 mmol scale reaction. [c] Conversions were determined by ^{1}H NMR. [d] Reaction run on 50 mmol. [e] Comparative microwave reaction showed 16% conversion after 4 h and 55% conversion after 11 h.

Table 3. Reduction of Aliphatic Aldehydes and Ketones

entry	structure	τ [a](min)	temp (°C)	product[b] (conversion/yield)[c]
23		40 min	130	 100 (100%)
24		40 min	130	 100 (100%)
25		40 min	130	 100 (100%)
26		40 min	130	 100 (100%)[d]
27		40 min	130	 100 (100%)
28		40 min	130	 100 (100%)
29		45 min	130	 83 (83%)
30		75 min	130	 70 (70%)
31		75 min	130	1.0 / 0.6
32		45 min	130	73%(73%)
33		18 min	120	70 (70%) 100 (100%)
34		18 min	120	100 (96%)
35		22 min	120	100 (100%)

[a] Residence time. [b] 2 mmol scale reaction. [c] Conversions were determined by ^{1}H NMR. [d] Reaction run on 50 mmol.

a hydrogen donor and solvent. We anticipated that this system would be amenable to easy reuse of the catalyst using a flow chemistry platform. Also, the process should be readily scalable and safe to operate, therefore meeting our further demands of the reaction.

Pleasingly, we discovered that passing the substrate in isopropanol through a glass column packed with the catalyst constituted a simple and easily accessible setup for the MPV reduction.

The best catalytic efficiency was obtained when the zirconium hydroxide was partially dehydrated at atmospheric pressure for 10 h at 270 °C before use (surface area calculated by the BET method of 178.24 m^2/g; total pore area calculated by mercury porosimetry of 21.51 m^2/g). These conditions provided a catalyst which was readily recyclable with consistent results over several weeks, providing dry (reagent grade) solvents are used to conduct any flow chemistry. The catalyst can be handled in air without any special precautions. The reduction of benzaldehyde to benzyl alcohol was then investigated as a model reaction. Remarkably, the reaction was complete after only 12 min operating at a temperature of 60 °C (Figure 1).

As the equivalent batch mode reduction takes in excess of 1 h to go to completion,[5e] we postulate that the increase in rate observed is a result of the high local catalyst loading within the column reactor.

Under the optimized flow conditions, a 0.25 M solution of benzaldehyde in IPA (reagent grade solvent) was pumped (flow rate 120 μL min^{-1}) through a glass column (Omnifit glass column, 6.6 mm i.d. × 100.0 mm length) packed with hydrous zirconia (void volume 1.5 mL) (Figure 2).

The use of the heterogeneous catalyst under flow conditions necessitated only a minimal workup procedure whereby the exiting flow outstream from the reaction could be concentrated directly to give the product in essentially quantitative yield. This constitutes a considerable advantage over the batch reaction.

As anticipated, benzaldehydes bearing electron-withdrawing groups underwent reduction even more rapidly (Table 1). The reaction tolerated a wide range of functionalities including esters (entry 3), where no transesterification was observed. Heterocycles, nitro groups, and halides also remained intact.

These conditions were also easily scalable, since we were able to continuously process a 50 mmol reaction (entry 2) which procedeed with the same catalytic efficiency, as detected by mass spectrometry.

It is interesting to note that virtually no byproducts (for instance isopropyl ethers) were detected in any of the examples.

We next turned our attention to the reduction of aromatic ketones. Using acetophenone (**11**) as a model substrate, we discovered that the conditions optimized for the aldehydes were unsatisfactory when applied to ketone substrates. Indeed, conducting the reaction at 120 °C for 15 min gave only a 36% yield, with the remaining material (64%) being the starting acetophenone (**11**). However, with an increased temperature of 130 °C and a longer residence time of 30 min, we were able to obtain a complete transformation to the corresponding alcohol. Again, collection of the solution and direct concentration provided a quantitative yield of the product in most cases.

Given the significant difference in reactivity between aldehydes and ketones, we expected that aromatic aldehydes could therefore be selectively reduced over ketones. To test this, a mixture of benzaldehyde (**1**) and acetophenone (**11**) was processed at 60 °C for 12 min and proceeded with complete selectivity for the reduction of benzaldehyde.

In order to determine the scope of the ketone reductive process a wide range of substrates were studied. We were encouraged to see that the presence of nitrogen atoms, as well as sulfur, were all well tolerated (Table 2).

Aliphatic ketones on the other hand under the normal conditions required a longer reaction time to go to completion (Table 3).

As anticipated aliphatic aldehydes reacted more rapidly than aliphatic ketones (Table 3, entries 33−35).

In conclusion we believe we have developed a rapid, recyclable, and sustainable system for the MPV reduction of carbonyl compounds. The system is robust and reliable and tolerates the presence of a large variety of functional groups. The system also accommodates a significant amount of steric hindrance. Flowing through a heterogeneous catalyst[6] where the only byproduct (acetone) is volatile greatly streamlined the overall process.

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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.

(6) The catalyst can be reused continuously for at least 31 days with no appreciable change in the catalytic activity being observed.

The authors declare no competing financial interest.