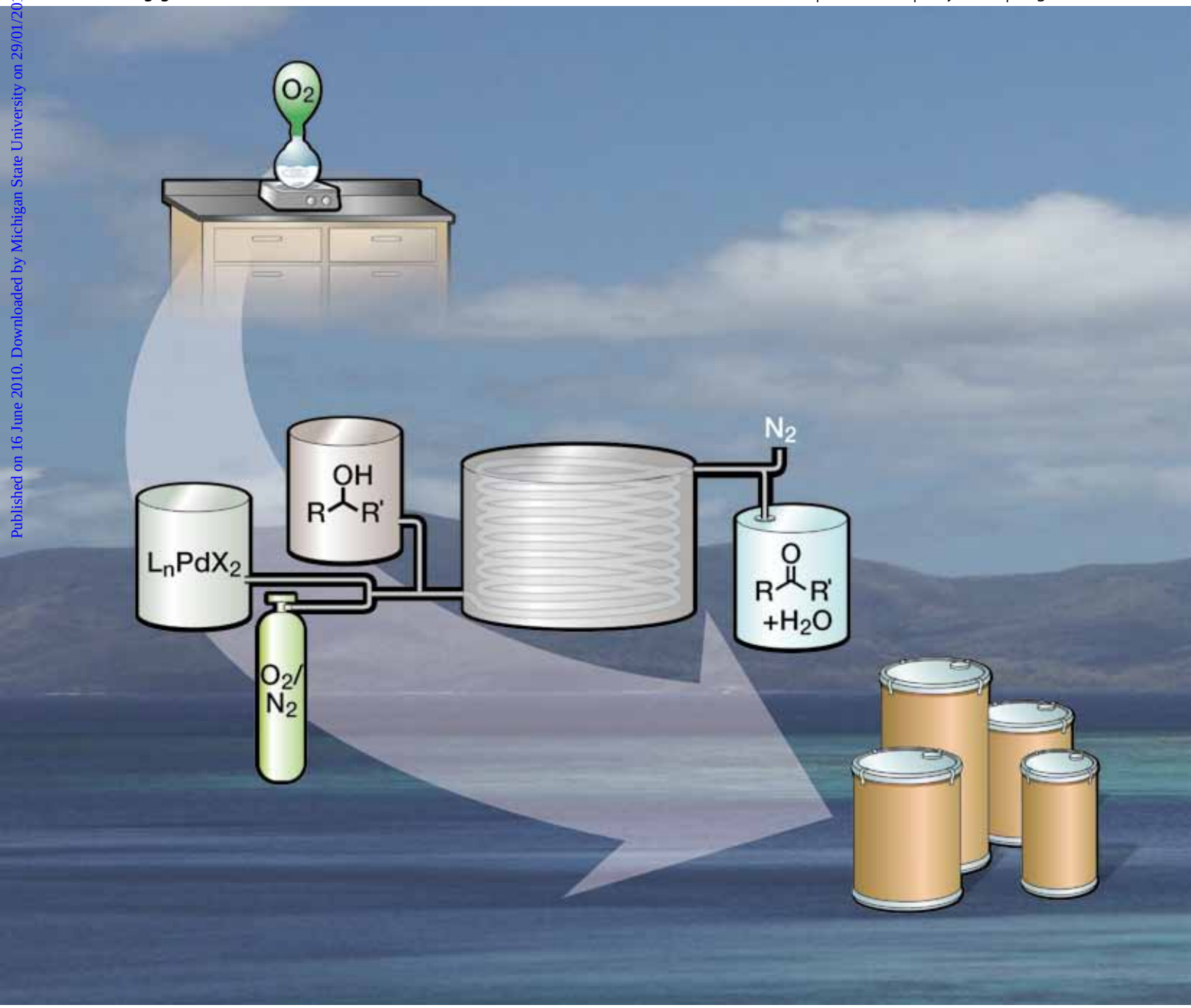
Green Chemistry

Cutting-edge research for a greener sustainable future

www.rsc.org/greenchem

Volume 12 | Number 7 | July 2010 | Pages 1113–1316



ISSN 1463-9262

RSC Publishing

1463-9262(2010)12:7;1-W

Development of safe and scalable continuous-flow methods for palladium-catalyzed aerobic oxidation reactions†

Xuan Ye,[a] Martin D. Johnson,*[b] Tianning Diao,[a] Matthew H. Yates*[b] and Shannon S. Stahl*[a]

Received 14th May 2010, Accepted 28th May 2010
First published as an Advance Article on the web 16th June 2010
DOI: 10.1039/c0gc00106f

The synthetic scope and utility of Pd-catalyzed aerobic oxidation reactions has advanced significantly over the past decade, and these reactions have the potential to address important green-chemistry challenges in the pharmaceutical industry. This potential has not been realized, however, because safety concerns and process constraints hinder large-scale applications of this chemistry. These limitations are addressed by the development of a continuous-flow tube reactor, which has been demonstrated on several scales in the aerobic oxidation of alcohols. Use of a dilute oxygen gas source (8% O_2 in N_2) ensures that the oxygen/organic mixture never enters the explosive regime, and efficient gas-liquid mixing in the reactor minimizes decomposition of the homogeneous catalyst into inactive Pd metal. These results provide the basis for large-scale implementation of palladium-catalyzed (and other) aerobic oxidation reactions for pharmaceutical synthesis.

Introduction

The pharmaceutical industry is under increasing pressure to integrate green-chemistry and green-engineering practices into the development and production of pharmaceuticals.[1–3] This emphasis arises, in part, from widely publicized data showing a disproportionate fraction of waste generated by the pharmaceutical industry relative to other sectors of the chemical industry.[4] Whereas commodity chemicals represent a much larger volume of products, the relative proportion of waste generated in their syntheses is 1–2 orders of magnitude smaller than for pharmaceuticals. This disparity partly reflects intrinsic differences between the two industries (for example, complex pharmaceutical compounds typically require 5–10 steps in their preparation and purification), but it also suggests that certain practices used within the commodity chemicals industry could be adopted by the pharmaceutical industry to reduce waste generation. The practice of oxidation chemistry represents a prominent example of this principle. Massive-scale commodity chemicals are often produced *via* selective oxidation of simple feedstocks,[5] and molecular oxygen is highly preferred as the stoichiometric oxidant in these reactions because of its low cost and negligible environmental impact. In contrast, aerobic oxidation reactions are virtually never used in pharmaceutical synthesis, owing to two main limitations.[1,6,7] Pharmaceutical precursors and advanced intermediates often contain diverse functional groups, and until recently very few synthetic methods have been available for selective aerobic oxidation of complex organic molecules. Secondly, process-scale syntheses of pharmaceuticals are typically performed in multi-use stirred-tank reactors that are poorly equipped to address safety hazards associated with aerobic oxidation reactions, and stirred-tank autoclaves equipped to handle high pressures fail to address important process constraints associated with these methods. Here, we describe a high-pressure continuous-flow tube reactor that enables safe and reliable performance of aerobic oxidation reactions on several scales. Application of this reactor to a series of Pd-catalyzed aerobic alcohol oxidation reactions provides the basis for broad implementation of aerobic oxidation reactions in pharmaceutical synthesis and establishes important benchmarks for the development of improved aerobic oxidation reactions.

The past decade has witnessed the emergence of a broad range of synthetically versatile catalytic aerobic oxidation methods that use homogeneous palladium catalysts.[8–15] Applications of these reactions include the oxidation of alcohols to aldehydes and ketones, α,β-dehydrogenation of aldehydes and ketones to prepare enals and enones, allylic and vinylic functionalization of alkenes, and oxidative coupling reactions with aromatic substrates, including C–H functionalization methods, to form carbon-carbon and carbon-heteroatom bonds (Fig. 1B). These methods proceed *via* a Pd^{II}/Pd^{0} catalytic cycle (Fig. 1A) analogous to Pd-catalyzed cross-coupling reactions, which are used throughout the pharmaceutical industry. The latter reactions demonstrate the large-scale viability of homogeneous palladium catalysis. In order for the synthetic opportunities and environmental benefits of Pd-catalyzed aerobic oxidation reactions to be fully realized, reliable methods must be developed to translate the results of small-scale laboratory reactions into large-scale pharmaceutical processes.

[a]*Department of Chemistry, University of Wisconsin-Madison, 1101 University Avenue, Madison, Wisconsin, 53706, USA. E-mail: stahl@chem.wisc.edu; Fax: (+1) 608-262-6143; Tel: (+1) 608-265-6288*
[b]*Chemical Product Research and Development Division, Eli Lilly and Company, Indianapolis, IN, 46285, USA. E-mail: johnsonmd@lilly.com, yatesmh@lilly.com; Fax: (+1) 317-277-0175; Tel: (+1) 317-651-7729*

† Electronic supplementary information (ESI) available: Experimental procedures, photographs of 7 L flow reactor and catalyst evaluation data. See DOI: 10.1039/c0gc00106f

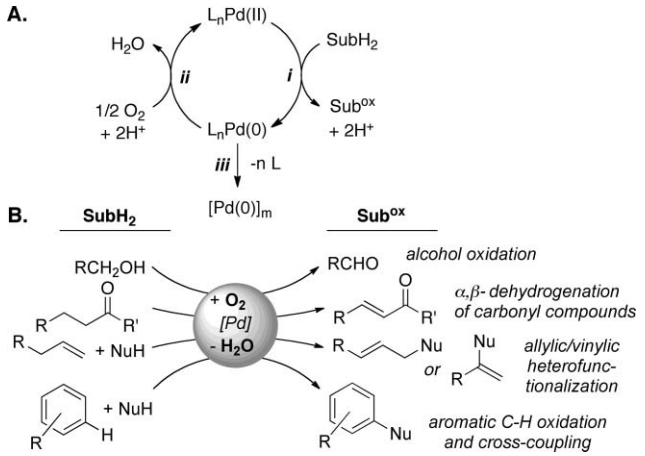


Fig. 1 (A) Simplified catalytic mechanism for Pd-catalyzed aerobic oxidation reactions. (B) Representative Pd-catalyzed aerobic oxidation reactions.

Continuous flow methods provide a means to address both safety issues and process challenges associated with Pd-catalyzed aerobic oxidation reactions.[16–22] Stirred-tank autoclaves that exist within the pharmaceutical industry have a sufficient pressure rating to perform aerobic oxidations safely by using dilute air (*e.g.* 5–8% O_2 in N_2), but they are expensive and less common than traditional stirred-tank reactors, and are typically dedicated to hydrogenation bunkers. In addition, the use of dilute air as the oxidant requires constant gas flow into and out of the reactor to remove the inert gas and ensure adequate levels of O_2 throughout the process. Vapor mass-flow controllers needed for this operation are non-standard on commercial autoclaves; most reagent gases used in pharmaceutical synthesis (*e.g.*, H_2, CO) are delivered in pure form and, therefore, controlled gas removal is not needed. Perhaps most significantly, Pd-catalyzed aerobic oxidation reactions face acute challenges associated with gas-liquid mass transfer. The catalyst stability is highly sensitive to the dissolved oxygen concentration. Low steady-state levels of dissolved O_2, or even temporary periods of poor gas-liquid mixing, can lead to irreversible catalyst decomposition *via* agglomeration of the homogeneous Pd^0 species into metallic Pd (*cf.* steps *ii* and *iii* of the catalytic mechanism in Fig. 1A).[23,24] This feature makes Pd-catalyzed aerobic oxidation reactions rather unforgiving with respect to operational variation and represents a distinct challenge in scaling up a traditional batch process. Flow-based methods provide a reliable means to achieve efficient gas-liquid mixing throughout the reaction and to ensure reproducibility across different reaction scales.

The present study focuses on alcohol oxidation as a prototypical Pd-catalyzed aerobic oxidation reaction. The mechanistic and operational similarities that have been established among the different reactions in Fig. 1A suggest that insights gained from this work will apply to the full breadth of examples in this reaction class. Numerous Pd catalyst systems have been reported for aerobic alcohol oxidation (Fig. 2).[25] The reactions typically proceed under mild reaction conditions, use relatively low catalyst loading (0.1–5 mol%) and are compatible with a broad scope of substrates. Molecular oxygen serves as the sole oxidant for catalyst regeneration in these reactions (Fig. 1B), without requiring additional redox-active co-catalysts

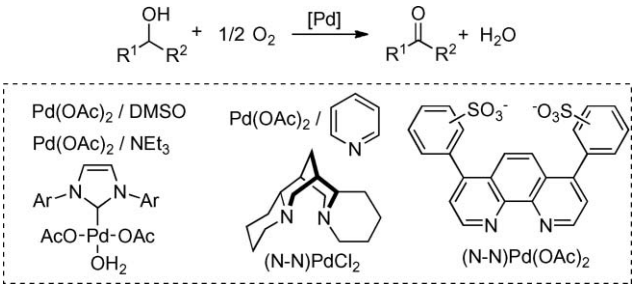


Fig. 2 Pd catalyst systems for aerobic oxidation of alcohols.

or other stoichiometric reagents. The simplicity of the catalyst systems and reaction conditions greatly minimizes reaction by-products and facilitates product isolation, and the absence of heterogeneous bases or other solid additives greatly simplifies the reactor design.

Results and discussion

The palladium catalyst systems in Fig. 2 were discovered and investigated under batch reaction conditions, typically in a round-bottom flask with oxygen gas supplied from a balloon above the flask. Our development of a continuous flow process for these reactions was carried out according to the following sequence: (1) design and construction of a suitable flow reactor, (2) evaluation of a small-scale test reaction, comparing batch *vs.* flow conditions, (3) demonstration of multiple alcohol oxidation reactions under flow conditions and utilization of one of these reactions in a pharmaceutically relevant tandem synthetic sequence, and (4) performance of a kg-scale alcohol oxidation reaction to establish the scalability of the present flow-based method. Each of these steps is elaborated below.

Reactor design and operation

The flow reactor developed for these applications has a straightforward design with three principal components (Fig. 3): (i) a reagent addition module consisting of reagent and catalyst reservoirs, high-pressure stainless-steel liquid-feed syringe pumps, and a gas-inlet junction; (ii) a reaction zone consisting of stainless-steel tubing with suitable temperature control (*e.g.*, heat-transfer fluid on the jacket side of the tube or placement of the tubing in a forced convection oven); and (iii) a product collection unit with a vapor-liquid separation device.

The flow of catalyst solution is premixed with the oxygen gas and then is combined with a flow of the reagent solution (Fig. 3). This mixing sequence ensures that O_2 is present when the organic substrate encounters the catalyst, thereby preventing reduction of Pd^{II} to Pd^0 and decomposition of the catalyst in the absence of oxygen (see discussion above and Fig. 1A, steps *i* and *iii*). As indicated in the reactor diagram, the reagent and catalyst solutions and the oxygen gas proceed through the reactor co-currently, and the respective flow rates are set to achieve the appropriate substrate : O_2 : catalyst stoichiometry and the desired residence time of the combined solution in the temperature-controlled reaction zone. The volume of the reaction zone can be readily varied by using the appropriate diameter and length of tubing. Reaction volumes of 5 mL, 400 mL and 7 L were employed in the present study (see

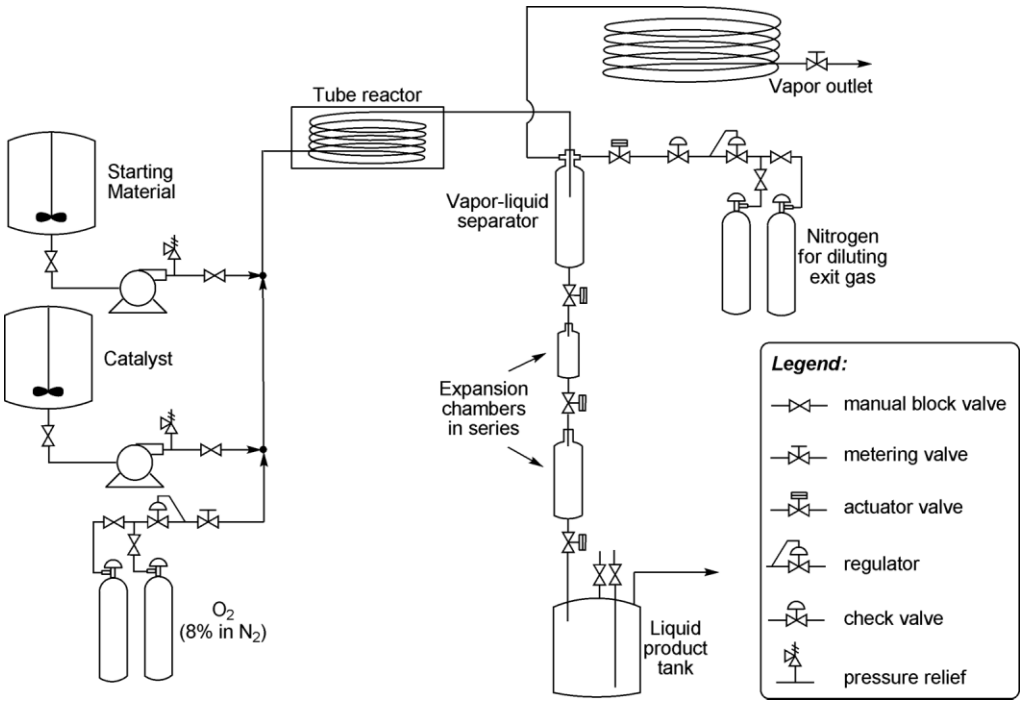


Fig. 3 Schematic drawing of a continuous-flow tube reactor designed for use with homogeneous Pd-catalyzed aerobic oxidation reactions.

below). Under typical operating conditions, a diluted oxygen gas mixture (8% O_2 in N_2) is used to ensure that the O_2 content always remains below the lower explosive limit of the O_2 : organic mixtures.[26,27] The reactor contents flow continuously out the end of the reaction tube into a vapor-liquid separator. The overall pressure of the system is established by supplying a back pressure of inert gas to the vapor-liquid separator. The design allows product solution to exit the bottom of the separator, while excess gas exits the top through a restricting orifice, ultimately venting at atmospheric pressure. The computer-controlled interface allows the liquid product solution to exit the system and steps down the pressure through a series of expansion chambers in series by operating sequenced automated block valves on a programmed timer. The latter method is preferred over continuous flow through a small-orifice process-control valve because it is less prone to fouling and plugging, especially at research scale. No flow restrictions with a smaller cross-sectional area than the reactor itself are present between the reactor and the gas-release zone to ensure that gas can expand freely in the event of an exotherm or another source of pressure increase. The flow reactor is designed to accommodate a variety of reaction conditions, including temperatures up to 300 °C and pressures up to 1500 psig, although temperatures and pressures typically will not exceed 120 °C and 1000 psig for most oxidations.

Comparison of batch *vs.* flow-based aerobic alcohol oxidation

Recent studies directed toward the discovery of new catalytic aerobic oxidation reactions have relied almost exclusively on batch reaction methods. Reactions carried out at ambient pressure are often carried out in a reaction flask equipped with an O_2-filled balloon, and high-pressure reactions typically use stainless steel pressure vessels. While these reaction configurations work well for small-scale reactions, they become problematic at larger scales because they are poorly equipped to ensure efficient gas-liquid mixing and high concentrations of dissolved O_2, which are essential for the Pd-catalyzed aerobic oxidations described here.

In our initial studies, we sought to establish whether aerobic alcohol oxidation reactions developed under batch conditions could translate effectively into a flow-based process. The oxidation of 1-phenylethanol with $Pd(OAc)_2/NEt_3$ as the catalyst proceeded in 93% yield at room temperature in 12 h, as originally described by Sigman and coworkers (Fig. 4A).[28] The use of 3 Å molecular sieves reported for this reaction was viewed as suboptimal for large-scale applications, and subsequent bench-top tests determined that a 90% product yield could be obtained in the absence of molecular sieves by extending the reaction time (18 h) (Fig. 4B, I).[29] The same reaction was then performed in the flow reactor, equipped with a 5 mL vertical tube as the reaction zone (0.25 in O.D., 316 stainless steel). Initial testing of the reaction was carried out by filling the reaction zone with a single volume of solution (*i.e.*, without a continuous liquid feed, Fig. 4B, II) and supplying a continuous flow of oxygen through the mixture. This operation formally represents a batch reaction, but it mimics the vapor-liquid contact that exists in the flow-tube reactor and provides an efficient approach to optimize various flow-reaction parameters (O_2 pressure and flow rate, reaction residence time and temperature). These studies revealed that an 88% yield of product could be obtained in 45 min by performing the reaction at somewhat higher temperature and pressure (60 °C, 30 psia O_2). Use of these conditions in a *continuous-flow* process led to a nearly identical outcome (Fig. 4B, III). After passage of approximately two reactor-volumes of solution (90 min), the reaction achieved a steady-state yield of 87% (1.4 g product; Fig. 4C).

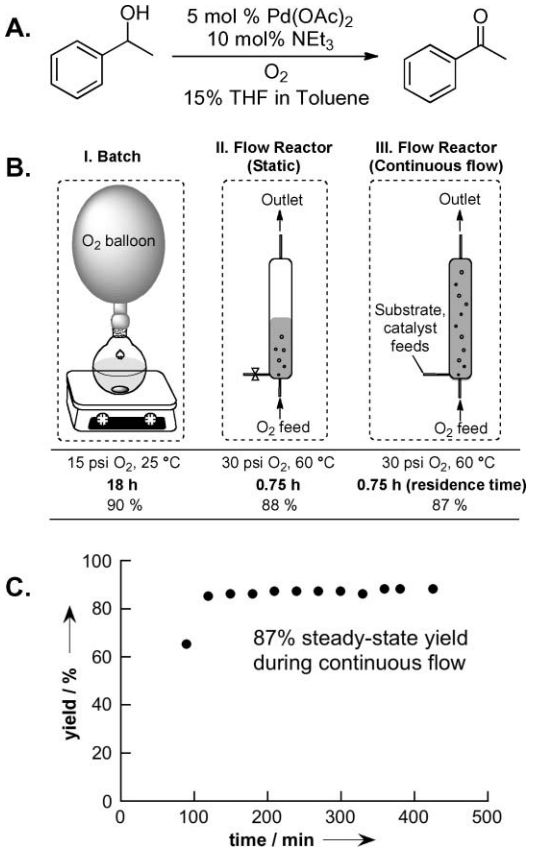


Fig. 4 (A) Aerobic oxidation of 1-phenylethanol catalyzed by $Pd(OAc)_2/NEt_3$. (B) Comparison of the bench-reaction results with those obtained in a flow reactor. (C) Reaction time-course of $Pd(OAc)_2/NEt_3$-catalyzed oxidation of 1-phenylethanol under continuous flow conditions.

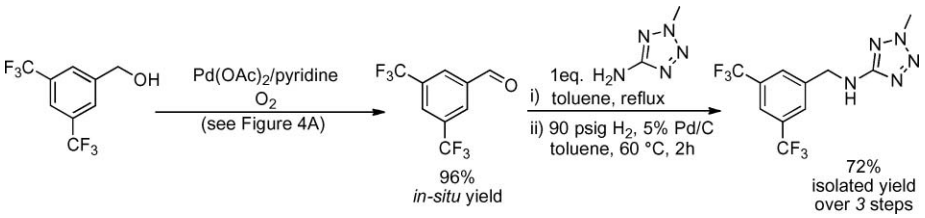
These results provide clear indication that a Pd-catalyzed aerobic oxidation reaction developed in a small-scale batch process can be translated effectively to a continuous flow process. Moreover, a substantial reduction in the reaction time was achieved in the flow reactor, from 18 h to 45 min. This improvement was made possible by the ability to use a higher temperature in the flow process (60 °C) relative to the batch reaction in a flask (25 °C). Catalyst decomposition becomes more problematic at higher temperatures and improved gas-liquid mixing, such as that available in the flow reactor, is essential to operate under these conditions. For example, when the batch reaction shown in Fig. 3B was repeated at 60 °C, rapid formation of Pd black was evident in the flask, and the reaction reached a maximum conversion of 55% to the desired ketone.

Flow-based aerobic oxidation of diverse alcohols

The initial demonstration of the flow-reactor described above provided the basis for modification of the reactor and operating conditions in order to mimic more closely the anticipated performance of large-scale applications. The 5 mL vertical-tube reactor was replaced with a 400 mL coiled-tube reactor (0.5 in O.D., 316 stainless steel). Pure O_2, which represents a significant safety hazard, was replaced with a diluted oxygen source (8% O_2 in N_2: 375 psia total pressure to maintain 30 psia partial pressure of O_2). The higher linear velocities of the liquid (due to the longer tube length), the higher linear velocity of the gas phase (due to dilution of the O_2), and the ten-fold higher length-to-diameter ratio of the 400 mL tube reactor relative to the 5 mL reactor, all contribute to better gas-liquid mixing in the larger-scale reactor.[30]

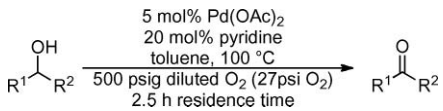
Evaluation of different Pd catalysts for alcohol oxidation revealed that a $Pd(OAc)_2$/pyridine catalyst system, similar to that originally reported by Uemura and co-workers,[31] is more robust than the $Pd(OAc)_2/NEt_3$ system at higher temperatures and enabled us to achieve higher turnover rates by performing the reactions at 100 °C.[30] Once again, reaction conditions were identified that avoided the use of molecular sieves, which were included in most of the originally reported reactions. Oxidation of 1-phenylethanol on 25 g scale in the modified reactor resulted in a 98% steady-state conversion of the alcohol to the ketone product, based on GC analysis (Table 1, Entry 1). Evaluation of other alcohol oxidation reactions revealed similarly successful performance. In the larger scale reactions (>20 g), the continuous product yield monitored by GC exhibited nearly quantitative conversion to the desired products (93–99%). Isolated yields were obtained for all of the alcohols; isolated yields were lower than those indicated by GC and largely reflect losses from unoptimized isolation procedures for individual products. These results provide further evidence that this flow process is effective for aerobic oxidation methods initially discovered and developed under batch conditions. As a corollary, the substrate scope of the catalytic methods in this flow process should reflect that of the methods originally developed in batch.[32]

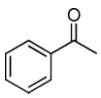
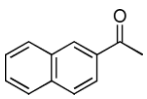
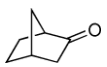
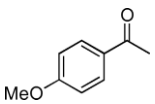
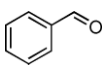
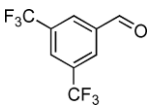
With these results in hand, we sought to demonstrate one important application of these reactions relevant to green-chemistry priorities within the pharmaceutical industry.[3] Aldehydes and ketones are seldom an end goal of pharmaceutical synthesis. Rather, these functional groups represent highly useful intermediates for subsequent carbon–carbon and carbon–heteroatom bond-forming reactions. Aerobic alcohol oxidation reactions of the type described here generate virtually no by-products and should enable direct progression to subsequent synthetic steps, without isolation or purification of the intermediate aldehyde or ketone. This feature has important green-chemistry implications because solvents and water used in product isolation represent major contributions to the overall waste generated in pharmaceutical syntheses.[3] We elected to illustrate this concept in the sequential conversion of a simple alcohol into an amine *via* aerobic oxidation of an alcohol followed by reductive amination of the aldehyde with H_2 as the reducing agent (Scheme 1).[33,34] 5-Amino-2-methyltetrazole was added to the crude product solution obtained from aerobic oxidation of 3,5-bis-trifluoromethylbenzyl alcohol, and the mixture was refluxed for 6 h. The *in situ*-generated imine underwent hydrogenation to afford the desired amine in 72% isolated yield over the three-step oxidation-condensation-hydrogenation sequence. This amine is an important pharmacophore featured in several drug candidates designed to alter human cholesterol levels.[35,36] Sequential transformations of this type consume only O_2 and H_2 as stoichiometric reagents, generate water as the sole stoichiometric by-product, and are well suited for incorporation into process intensification platforms receiving significant attention in the pharmaceutical industry. This O_2/H_2-coupled



Scheme 1 Tandem flow-based aerobic alcohol oxidation/hydrogenative reductive amination.

Table 1 Aerobic alcohol oxidation results for reactions performed in a 400 mL flow reactor[a]



Entry	Product	Scale	Isolated yield (GC yield)
1		25 g	85% (98%)
2		15 g	73%
3		35 g	93% (99%)
4		37 g	92% (96%)
5		32 g	78% (99%)
6		7 g	81%
7		12 g	77%
8		8 g	87%
9		26 g	76% (93%)
10		10 g	91% (96%)

[a] Conditions: Feed solution 1: [alcohol] = 0.6 M, [pyridine] = 0.12 M; Feed solution 2: [$Pd(OAc)_2$] = 0.03 M; Solution feed rates = 0.9 mmol alcohol/min; O_2 feed rate = 0.9 mmol min^{-1}.

strategy to achieve net displacement of a hydroxyl group with an amine represents an appealing, atom-economical alternative to stoichiometric activation of an alcohol by converting it into a halide or sulfonate leaving group followed by S_N2 displacement with the appropriate nucleophile.

Kilogram-scale aerobic alcohol oxidation

Straightforward modification of the flow reactor enabled us to test a $Pd(OAc)_2$/pyridine-catalyzed aerobic oxidation reaction on a 1 kg scale. The 400 mL coiled-tube reactor was exchanged for a 7 L coil of stainless-steel tubing (0.375 in O.D.) constructed for this purpose.[30] After a series of optimizations of the catalytic reaction conditions,[30] we elected to perform the reaction with 1 mol% $Pd(OAc)_2$/4 mol% pyridine at 100 °C with flow rates of alcohol and O_2 at 7.2 and 7.9 mmol min^{-1}, respectively ([alcohol] = 1 M in toluene, 500 psia of 8% O_2 in N_2). The solution residence time in the reactor was 4.5 h, and the steady-state liquid volume under the reaction conditions was 3.9 L (*i.e.*, 55% of the total reactor volume), with the balance occupied by the diluted oxygen gas mixture. The similar volumes occupied by the gas and liquid in the reactor, together with a 3.2 : 1 ratio of volumetric flow rates for the gas and liquid at steady-state, contributes to very efficient gas-liquid mixing. Under these reaction conditions, the aerobic oxidation of 1 kg of 1-phenylethanol to acetophenone proceeded in near quantitative yield (99.5%), thereby demonstrating the viability of larger-scale applications of this method and showing that the reaction performance in flow can be even better than that observed in a batch process. A more extensive compilation of the experimental parameters for this reaction is documented in the Supporting Information.†

This kilogram-scale application highlights the reliability of continuous-flow tube reactors as a platform for development of large-scale aerobic oxidation processes. Ongoing work at Eli Lilly suggests that the 7 L tube reactor can be scaled up by a minimum of two orders of magnitude, while retaining the high-pressure rating, low cost and a length/diameter ratio for the tube of ≥20000/1. Homogeneous catalyst systems that do not require heterogeneous additives or reagents, such as those described here, are especially well suited for this format. Preliminary tests demonstrate that continuous-reaction methods compatible with slurries or heterogeneous reaction mixtures are also possible (*i.e.*, by using continuous stirred-tank reactors); however, methods that employ homogeneous reactions in flow tubes require less capital investment, are more readily scaled and are more suitable for continuous processing. These considerations

provide an important framework for research efforts directed towards the discovery of new catalysts and aerobic oxidation reactions.

Conclusions

This study demonstrates that Pd-catalyzed aerobic alcohol oxidations developed on a small scale can be translated effectively into a scalable flow-based process. The safety hazards typically associated with aerobic oxidations are overcome by using dilute air as the oxidant. As a consequence, Pd-catalyzed aerobic oxidation reactions (and other aerobic oxidations) represent viable steps in large-scale preparation of pharmaceutical target molecules. The synthetic versatility and environmental benefits of such reactions can now be fully realized, eliminating by-products associated with undesirable oxidants or alternative synthetic routes and enabling streamlined syntheses that avoid wasteful product isolation and purification procedures.

Experimental

Representative experimental procedure for aerobic alcohol oxidation in the 7 L flow reactor.

An oven used to regulate the reaction-zone temperature of the flow reactor was set to 100 °C. The flow reactor was rinsed with dry toluene and dried by passing nitrogen gas through the tubing at 100 °C. The reactor was pressurized by applying a 500 psig nitrogen back-pressure from a high-pressure nitrogen cylinder connected to the vapor-liquid separator. The regulator for the diluted O_2 gas cylinder (8% O_2 in N_2) was set to 100 psi higher than the N_2 background pressure (600 psig). Two sequential metering valves connected to the O_2 outlet were adjusted to obtain the desired gas flow rate. The total gas flow out of the vapor-outlet valve was maintained around 5 scf per hour. The reactor was then purged with the dilute oxygen gas for 10–15 min (8% O_2 in N_2; 500 psig). The first syringe pump was charged with $Pd(OAc)_2$ stock solution in toluene (10 mM), and the second syringe pump was charged with alcohol/pyridine stock solution in toluene (1.0 M/40 mM, respectively). The feed rates of both pumps were adjusted to achieve the desired liquid residence time in the reaction zone. The flow tube between the reaction zone and the vapor-liquid separator consisted of a jacketed stainless-steel tube, and prior to the start of the reaction, a flow of ethylene glycol cooling fluid (–10 to –20 °C) was initiated through the outer jacket. Both syringe pumps were started to initiate the flow of liquid solution with the dilute-oxygen gas through the reactor. After starting the pumps ($t = 0$), the time when liquid started to accumulate in the liquid product tank was recorded as the actual liquid residence time.

Acknowledgements

We are grateful to the NIH (RC1-GM091161) and Eli Lilly for generous financial support of this work, and we thank Bret Huff, Wei-Ming Sun, Tim Braden, Ed Deweese and Paul Millenbaugh for valuable support on this project.

Notes and references

1 P. T. Anastas, J. C. Warner, In *Green Chemistry: Theory and Practice*, Oxford Univ. Press., New York, 1998.
2 M. Poliakoff and P. Licence, *Nature*, 2007, **450**, 810–812.
3 D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411–420.
4 R. A. Sheldon, *Chem. Ind.*, 1992, 903–906.
5 F. Cavani and J. H. Teles, *ChemSusChem*, 2009, **2**, 508–534.
6 J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337–2347.
7 S. Caron, R. W. Dugger, S. G. Ruggeri, J. A. Ragan and D. H. B. Ripin, *Chem. Rev.*, 2006, **106**, 2943–2989.
8 R. A. Sheldon, I. W. C. E. Arends, G.-J. ten Brink and A. Dijksman, *Acc. Chem. Res.*, 2002, **35**, 774–781.
9 In some cases, homogeneous Pd catalyst precursors have been shown to undergo *in situ* formation of Pd nanoparticles. Reactions employing such catalysts may be carried out similar to those employing homogeneous, mononuclear Pd catalysts. For a leading reference, see: M. Mifsud, K. V. Parkhomenko, I. W. C. E. Arends and R. A. Sheldon, *Tetrahedron*, 2010, **66**, 1040–1044.
10 T. Nishimura and S. Uemura, *Synlett*, 2004, 201–216.
11 S. S. Stahl, *Angew. Chem., Int. Ed.*, 2004, **43**, 3400–3420.
12 B. M. Stoltz, *Chem. Lett.*, 2004, **33**, 362–367.
13 S. S. Stahl, *Science*, 2005, **309**, 1824–1826.
14 K. M. Gligorich and M. S. Sigman, *Chem. Commun.*, 2009, 3854–3867.
15 X. Chen, K. M. Engle, D. H. Wang and J. Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115.
16 N. G. Anderson, *Org. Process Res. Dev.*, 2001, **5**, 613–621.
17 N. W. Wang, T. Matsumoto, M. Ueno, H. Miyamura and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2009, **48**, 4744–4746.
18 T. L. LaPorte, M. Hamedi, J. S. DePue, L. F. Shen, D. Watson and D. Hsieh, *Org. Process Res. Dev.*, 2008, **12**, 956–966.
19 K. Jähnisch, V. Hessel, H. Löwe and M. Baerns, *Angew. Chem., Int. Ed.*, 2004, **43**, 406–446.
20 D. M. Roberge, B. Zimmermann, F. Rainone, M. Gottsponer, M. Eyholzer and N. Kockmann, *Org. Process Res. Dev.*, 2008, **12**, 905–910.
21 F. E. Valera, M. Quaranta, A. Moran, J. Blacker, A. Armstrong, J. T. Cabral and D. G. Blackmond, *Angew. Chem., Int. Ed.*, 2010, **49**, 2478–2485.
22 A. O. Chapman, G. R. Akien, N. J. Arrowsmith, P. Licence and M. Poliakoff, *Green Chem.*, 2010, **12**, 310–315.
23 B. A. Steinhoff, I. A. Guzei and S. S. Stahl, *J. Am. Chem. Soc.*, 2004, **126**, 11268–11278.
24 B. A. Steinhoff and S. S. Stahl, *J. Am. Chem. Soc.*, 2006, **128**, 4348–4355.
25 M. J. Schultz and M. S. Sigman, *Tetrahedron*, 2006, **62**, 8227–8241.
26 R. H. Perry, D. W. Green, ed. In *Perry's Chemical Engineers' Handbook*, (McGraw-Hill, 1997), chap. 26, pp. 51–57. [7th edition].
27 P. B. Laut and D. Johnstone, *Chem. Eng. (New York)*, 1994, **101**, 96.
28 M. J. Schultz, C. C. Park and M. S. Sigman, *Chem. Commun.*, 2002, 3034–3035.
29 B. A. Steinhoff, A. E. King and S. S. Stahl, *J. Org. Chem.*, 2006, **71**, 1861–1868.
30 See Supporting Information.
31 T. Nishimura, T. Onoue, K. Ohe and S. Uemura, *J. Org. Chem.*, 1999, **64**, 6750–6755.
32 A broader discussion of the scope and limitations of the $Pd(OAc)_2$/pyridine catalyst system is presented in ref. 31. For example, successful substrates not included in our study include primary aliphatic alcohols, diols, steroidal alcohols and substrates containing other functional groups, including alkenes, ethers, silyl ethers and esters. Certain substrate limitations are also considered in this original report.
33 From a safety perspective, it is important to note that the aerobic oxidation and hydrogenation steps were carried out in different labs, and the condensation step ensured that O_2 was completely removed from the reaction prior to performing the hydrogenation step. Moreover, the O_2 and H_2 gas cylinders were not housed in the same lab, and the oxidation and reduction reactions should be carried out in separate modules in a production facility.

34 Recently, a number of catalytic methods have been developed for the conversion of alcohols into amines *via in situ* dehydrogenation/hydrogenation ("hydrogen borrowing"). For leading references, see: (*a*) T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, *Dalton Trans.*, 2009, 753–762; (*b*) C. Gunanathan and D. Milstein, *Angew. Chem., Int. Ed.*, 2008, **47**, 8661–8664; (*c*) F. Shi, M. K. Tse, X. Cui, D. Gördes, D. Michalik, K. Thurow, Y. Deng and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 5912–5915.
35 G. Chang, M. T. Didiuk, P. H. Dorff, R. S. Garigipati, W. Jiao, B. A. Lefker, D. A. Perry, R. B. Ruggeri and T. J. Underwood, *WO 2006/056854 A1*, 2006.
36 H. Imase and M. Kishida, 2008, *WO 2008/058961 A1*.

