Supplementary Data

for

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[*b]

---

[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*

[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*

General Considerations

Oxygen and 8% O_2/N_2 cylinders were purchased from Airgas. Anhydrous toluene was obtained from Aldrich and used without further purification. Palladium acetate, anhydrous pyridine, triethylamine, 1-phenylethanol, α-methyl-2-naphthalenemethanol, 4-methoxy-α-methylbenzyl alcohol, 2-decanol, 1-indanol, *cis*-2-methylcyclohexanol, α-norborneol, 3,5-bis(trifluoromethyl)benzyl alcohol, benzylalcohol, and 3-methyl-2-cyclohexen-1-ol were purchased from Aldrich and used as received. Unless otherwise specified, solid oxidation products were purified via recrystalizations, and liquid oxidation products were purified via distillations. ^{1}H NMR spectroscopic data of oxidation products were obtained at 24.0 °C using a Varian 500 MHz spectrometer, and were found to be consistent with data reported in the literature.[1-3]

Table S1. Comparison of tube dimensions for 5 mL, 400 mL and 7 L flow tube reactors.

Tubing o.d. (in)	Tubing i.d. (in)	Tube length (ft)	Tube volume (mL)	Length/diameter ratio	Area/volume (m^{-1})
0.25	0.18	1	5	67	875
0.5	0.37	20	422	649	426
0.375	0.305	498	7154	19593	516

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

The 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 to 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 minutes (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.

Determination of O_2 flow rate in mmol/min.

Gas flow rates were monitored in the following manner (this method proved to be more reliable than use of an in-line flow meter). A stainless-steel chamber with a known volume was installed between the dilute-oxygen cylinders and the tube reactor (see Figure S1). Upon closing a manual valve between this chamber and the tube reactor, the pressure inside the chamber started to build up due to accumulation of the feed gas. The pressure-change profile inside the chamber was monitored by a computer-interfaced pressure transducer. The pressure-change profile typically starts with linear increase in pressure with respect to time, and eventually reaches an equilibrium pressure value. The slope of the initial linear pressure increase in units of psi/min (ΔP)

was converted into units of mmol O_2/min.

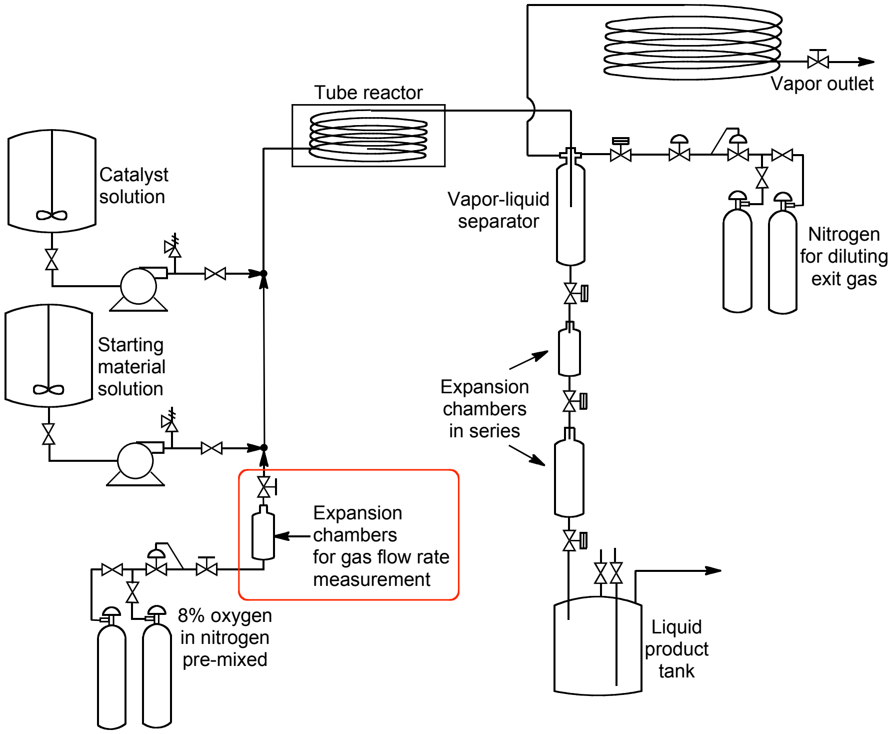
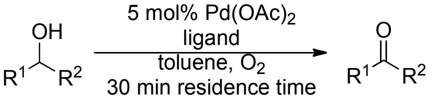
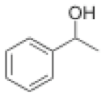
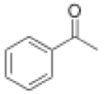
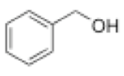
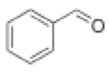
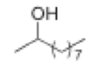
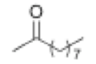


Figure S1. Schematic drawing of the flow tube reactor used with homogeneous Pd-catalyzed aerobic oxidations, illustrating the expansion chamber used for gas-flow-rate determinations.

Evaluation of different catalyst systems for aerobic alcohol oxidation in the 5 mL tube reactor.

Table S2. Batch-mode screening data with the 5 mL flow tube reactor, using pure O_2 as the oxidant on research scale.[a]



Alcohol	Oxidation product	Ligand	Optimized reaction condition	GC Yield of oxidation product
		10% NEt_3	60 °C, 15psig O_2	85%
		5% NEt_3	60 °C, 15psig O_2	74%
		20% pyridine	80 °C, 15psig O_2	92%
		20% pyridine	80 °C, 15psig O_2	74%
		10% $(CH_3)_2N(CH_2)_{13}CH_3$	80 °C, 30psig O_2	89%
		20% pyridine	80 °C, 70psig O_2	76%

[a] *Conditions*: alcohol (2.4 mmol), $Pd(OAc)_2$ (0.12 mmol), toluene (4 mL), 30 min.

Experimental results associated with the kg-scale aerobic oxidation of 1-phenylethanol in the flow reactor.

Table S3. Optimization of reaction conditions for catalytic oxidation of 1-phenylethanol (performed in 400 ml tube reactor).

Entry	[alcohol] (M)	$[Pd(OAc)_2]$ (M)	Pd loading	Pd / py	Temp (°C)	O_2 flowrate (psi/min)	Pump rate (ml/min)	Alcohol feed rate (mmol/min)	O_2 feed rate (mmol/min)	Residence time (min)	Steady-State GC conversion
1	0.6	0.03	5.0%	1 to 4	100	347	1.5	0.9	1.89	145	97%
2	1.0	0.03	3.0%	1 to 4	100	141	1.2	1.2	0.77	180	98%
3	**1.0**	**0.01**	**1.0%**	**1 to 4**	**100**	**156**	**1.0**	**1.0**	**0.85**	**210**	**97%**
4	1.0	0.01	1.0%	1 to 4	120	231	1.8	1.8	1.26	120	48%
5	1.0	0.005	0.5%	1 to 2	100	129	1.5	1.5	0.70	145	68%
6	2.0	0.02	1.0%	1 to 4	100	157	1.0	2.0	0.86	203	92%
7	2.0	0.01	0.5%	1 to 2	120	140	1.2	2.4	0.76	180	47%
8	2.0	0.01	0.5%	1 to 4	110	140	1.5	3.0	0.76	145	30%

Flow reaction parameters:

Reactor size: Total volume = 7.1 L; inner diameter = 0.305 in; total length = 494 ft.
Liquid feed rate: Feed 1 (pump A) = Feed 2 (pump B) = 7.25 ml/min.
Dilute O_2 (8% in N_2) flow rate: 7.9 mmol O_2/min
5 ft^3/h out of vent (0 psig).
N_2 back-pressure flow rate: 10 ft^3/h out of vent (0 psig) (back-pressure tank set to 500 psig).
Total gas flow out of vent: 15 ft^3/h out of vent (0 psig).
Steady-state liquid residence time: Time = 270 min = 4.5 h.
Steady-state liquid volume: 3.9 L (55% of total reactor volume).
Steady-state vapor volume: 3.2 L (45% of total reactor volume).
Steady-state vapor residence time: 47 min.

Steady-state liquid velocity: 1.8 ft/min.

Steady-state vapor velocity: 5.7 ft/min.

Reaction time-course for the kg-scale aerobic alcohol oxidation of 1-phenylethanol:

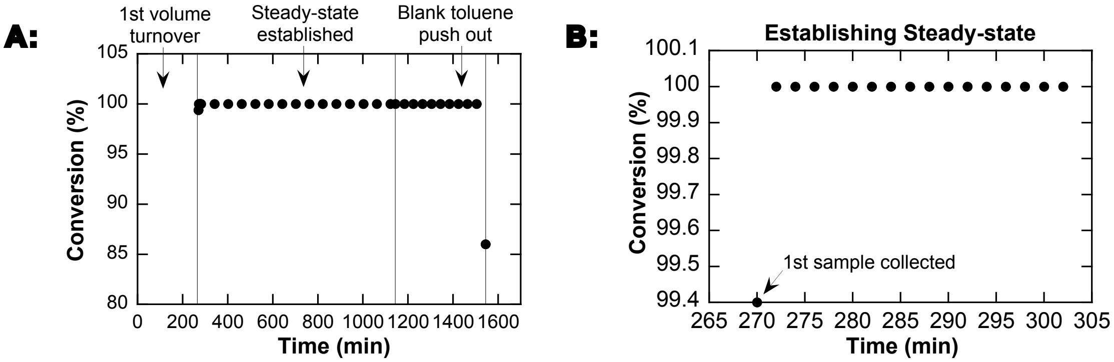


Figure S2. (A) Complete reaction time-course for the kg-scale aerobic oxidation of 1-phenylethanol. Feed solution 1: [$Pd(OAc)_2$] = 0.01 M; 7.25 ml/min, 8.3 L; Feed solution 2: [alcohol] = 1.0 M, [pyridine] = 0.04 M, [tetradecane] = 0.01 M, 7.25 ml/min, 8.3 L; 7.9 mmol O_2/min; 27 psig O_2 partial pressure; 100 °C, 4.5 h residence time. (B) Expansion of the plot in Figure S2A, in the region of early time points.

Determination of overall yield of acetophenone from the kg-scale oxidation in flow:

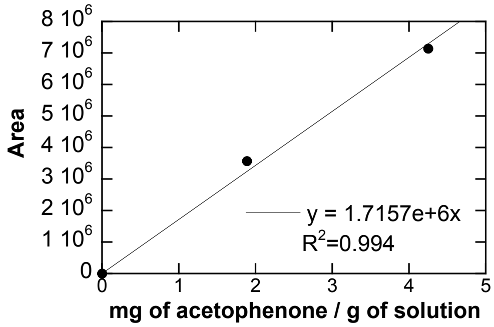


Figure S3. HPLC standard curve for acetophenone in the crude product mixture (mg acetophenone / g solution).

Mass collected = 13.86 kg; mass of acetophenone = (70.76 g/kg crude product * 13.86 kg) = 0.980 kg; Yield of acetophenone = 0.980 kg / 0.984 kg = 99.5%.

Experimental setup for the kg-scale aerobic oxidation of 1-phenylethanol:

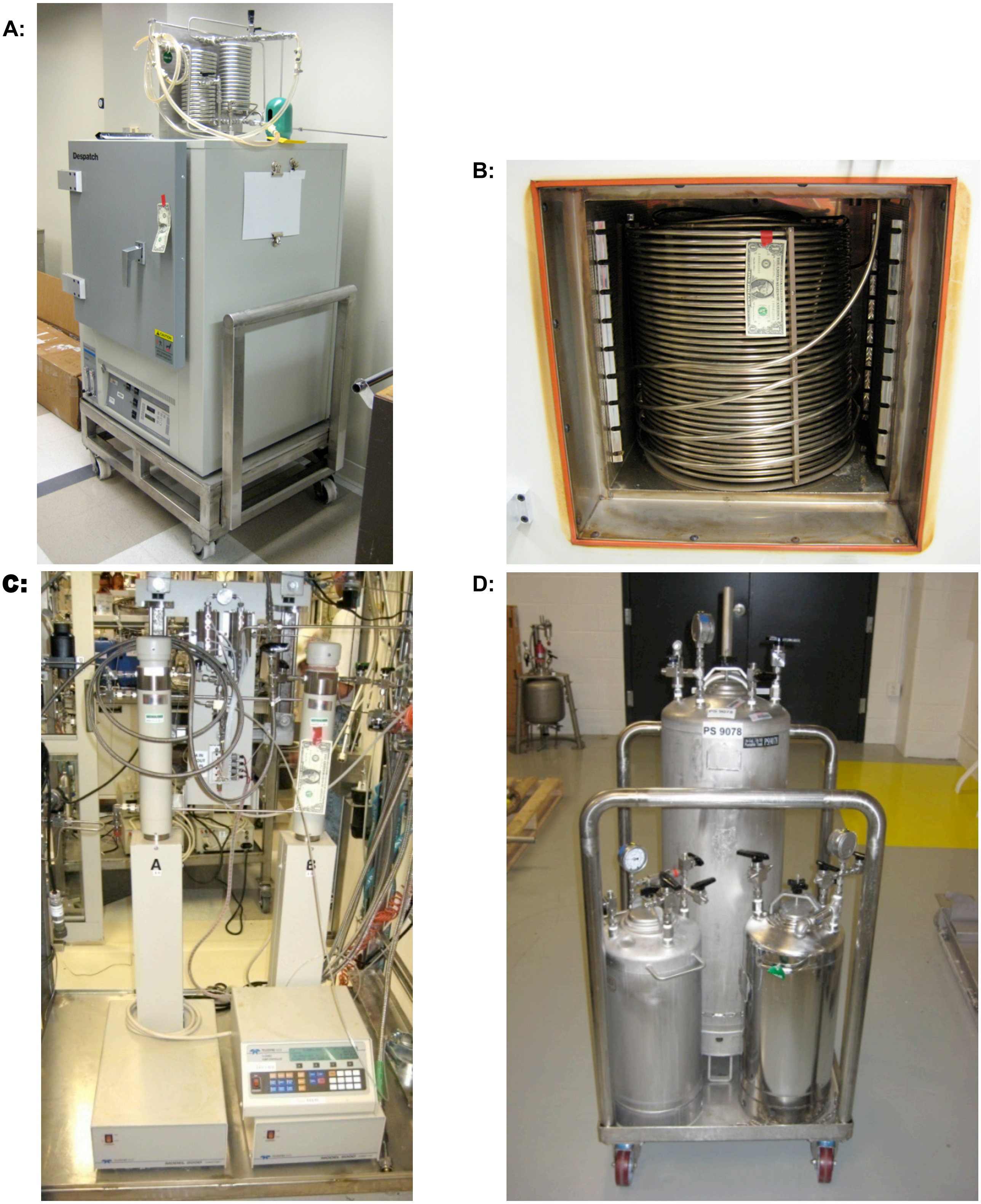


Figure S4. (A) Forced convection oven for heating tube; cooling heat exchangers at outlet. (B) 7.1 Liter, 494 feet of 3/8” 316 stainless steel tubing. (C) High-pressure ISCO pumps. (D) Product collection tanks.

Procedure for tandem aerobic alcohol oxidation / hydrogenative reductive amination

Pd(OAc)$_2$/pyridine-catalyzed aerobic oxidation of (3,5-Bis-trifluoromethyl-phenyl)-methanol.

Stock solution 1: [Pd(OAc)$_2$] = 0.03 M, 68 ml, feed rate = 1.5 ml/min.

Stock solution 2: [(3,5-Bis-trifluoromethylphenyl)-methanol] = 0.6 M, 68 ml (10 g scale), feed rate=1.5 ml/min.

O$_2$ flow rate = 1.0 mmol/min.

Residence time = 150 min.

The general procedure outlined above was followed. About 124 ml crude reaction mixture was collected from the flow reactor, and a ^{1}H NMR spectrum of the product mixture indicated a 96% in situ yield.

Condensation with 5-amino-2-methyltetrazole to form imine. The crude product solution obtained from the aerobic alcohol oxidation reaction was transferred to a 3-neck round-bottom flask. 5-Amino-2-methyltetrazole (4.0 g, 41 mmol) was added to the flask and azeotropic distillation was carried out with a Dean-Stark apparatus. After 6 hours, a ^{1}H NMR spectrum of the crude reaction mixture showed complete conversion to the imine.

Imine hydrogenation. The reaction mixture from the condensation reaction was immediately transferred to a pressure reactor, and 2 mol % of Pd/C (10 wt %) was added to the mixture. The reaction was conducted at 90 psig H$_2$ at 60 °C for 3 h. The reaction mixture was filtered through celite to remove Pd black and carbon, and the final product was purified by column chromatography (EtOAc:Hexane = 1:4). The ^{1}H NMR spectroscopic data of the product was consistent with published data.[2,3]

References:

---

1. M. J. Schultz, S. S. Hamilton, D. R. Jensen and M. S. Sigman, *J. Org. Chem.*, 2005, **70**, 3343-3352.
2. H. Imase, M. Kishida, *WO 2008/058961 A1,* 2008.
3. 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.