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Development of a Continuous-Flow Process for a Pd-Catalyzed Olefin Cleavage using Oxygen within the Explosive Regime

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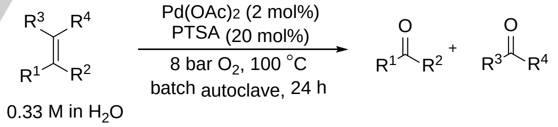
The development of a continuous-flow protocol for a Pd-catalyzed olefin cleavage using molecular oxygen as the sole oxidant to give carbonyl compounds is described. The flow protocol uses a low catalyst loading (0.1 mol%) and decomposition of the active catalyst is prevented through stabilization by poly(ethylene)glycol-400 (PEG-400), which is present as a co-solvent. Radical scavengers inhibit the reaction indicating the involvement of a free radical path in the reaction mechanism. The applicability of the continuous-flow protocol is demonstrated on several olefin substrates. The continuous-flow process enables safe and scalable olefin cleavage using pure O_2.

The utility of aldehydes and ketones as valuable intermediates in modern organic synthesis has made the oxidative cleavage of the C=C double bond a fundamentally important transformation.[1] The classical protocol for olefin cleavage is by ozonolysis using ozone (O_3) gas. Ozonolysis is generally a high yielding, highly selective and green process.[2,3] However, ozonolysis with olefins is highly exothermic and involves the formation of a hazardous ozonide intermediate. O_3 is also a highly flammable and extremely poisonous gas with a characteristic pungent odor. Therefore, ozonolysis is often avoided in synthesis due to safety concerns, particularly at industrial scales.[3,4] Alternative strategies for olefin cleavage to form aldehydes and ketones using more benign oxidants have proved successful.[5-8] Selective olefin cleavage with high-valent oxometal catalysts, such as OsO_4 or RuO_4, in the presence of a secondary stoichiometric oxidant, normally either $NaIO_4$ or NaClO, was achieved in the early 2000s.[5,6] Even more recently aryl-λ^3-iodane-based protocols have been reported, which utilize environmentally friendly iodine reagents.[7,8] In this procedure $PhIO/HBF_4$ (1.1 equiv. each) induces alkene scission into aldehydes selectively.[7] Subsequently, a procedure using catalytic iodomesitylene with *m*CPBA as stoichiometric oxidant was developed.[8] These methods generally suffer from the limitation that they are inherently atom inefficient due to the requirement of a stoichiometric oxidant, which also needs to be removed after the reaction.

Significant progress has been made in the development of olefin cleavage reactions that utilize molecular oxygen as a suitable green alternative to existing oxidizing agents.[9] O_2 has the advantage that it is a cheap, highly abundant and odorless non-toxic gas, which can easily be removed after reaction.[10] However, O_2 generally displays low reactivity and poor selectivity. Therefore, despite the advances made, many of the protocols suffer from limitations such as high catalyst loadings, specialized ligand systems, very high operating pressures or environmentally unfriendly solvents.[9] Pd-catalyzed aerobic oxidation reactions have shown great versatility and promise in organic synthesis.[11] In particular, the Tsuji−Wacker oxidation of terminal olefins to methyl ketones, which uses a Pd catalyst and Cu cocatalyst under an oxygen atmosphere, is a very important reaction to the chemical industry.[12] We were intrigued by the work of Wang and Jiang which reported a highly efficient Pd-catalyzed olefin cleavage using molecular oxygen as the sole oxidant.[13,14] This discovery opens a new route for the direct oxidation of olefins with molecular oxygen. The reactions were performed in a batch pressure autoclave, with $Pd(OAc)_2$ as catalyst, PTSA (*p*-toluenesulfonic acid monohydrate) as additive, pure O_2 as oxidant and H_2O as reaction solvent giving the best result (Scheme 1).[13]



Scheme 1. Batch conditions for a Pd-catalyzed direct oxidation of olefins to carbonyl compounds (see ref 13 for more details).

O_2 has the disadvantage that it is a highly energetic gas and oxidizer, which in the presence of an organic solvent as a fuel and an ignition source results in a potentially flammable mixture. The safety issues surrounding O_2 make it one of the least frequently used oxidants.[10] A diluted form of O_2 gas, consisting of less than 10% O_2 in N_2, is normally used to prevent the risk of combustions in the presence of flammable organic solvents.[15] Many of the safety and process challenges associated with O_2 are better addressed through the application of continuous-flow reactors.[16-18] In a recent concept article we have demonstrated that safe operation can be ensured employing properly designed continuous-flow reactors even when using pure O_2 in the presence of flammable organic solvents at elevated temperatures and pressure.[18]

Herein, we present preliminary results for a scalable Pd-catalyzed olefin cleavage protocol using molecular oxygen under process intensified conditions in continuous-flow mode. To our

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knowledge, this is the first reported continuous-flow olefin cleavage procedure using molecular oxygen as the sole oxidant.

A flow reactor system (Figure 1) was assembled consisting of a high-pressure pump (Uniqsis, P), a sample loop (SL, volume = 2 mL), a reactor coil (o.d. 1/16", i.d. 1/8", 60 mL internal volume) made from 316 stainless steel, which was heated within a GC oven (RTU), and a backpressure regulator (BPR, Vapourtec, max. 10 bar).[19] A mass flow controller (ThalesNano, MFC) was used for the introduction of oxygen in a controller manner. The mixing of the gas and liquid stream was achieved using a T-piece (T) to provide a gas-liquid segmented flow regime.

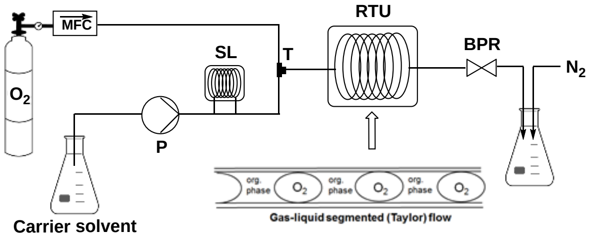


Figure 1. Continuous-flow setup for Pd-catalyzed olefin cleavage using molecular oxygen (for further details, see the Supporting Information).

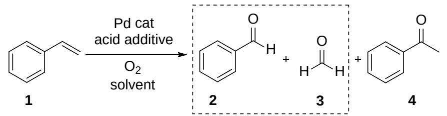
We commenced our studies using styrene **1** as a model compound to provide benzaldehyde **2** and formaldehyde **3** as the cleaved products (Table 1). Styrene and its derivatives are a notoriously difficult substrate class due to facile polymerization. Formaldehyde is also known to polymerize or can undergo further oxidation to form CO_2 as side product. We initially undertook an additive, catalyst, ligand screening and solvent campaign (see the Supporting Information for a summary). We assessed the reactions against two main criteria: (i) to provide a homogeneous liquid feed; and (ii) to achieve moderate to good conversion in residence times appropriate for a tubular flow reactor setup (<30 min). The previously reported batch conditions were unsuitable for direct transfer to continuous processing due to the insolubility of the reaction components in H_2O and long reaction time (24 h) (Scheme 1).[13]

Apart from H_2O, *tert*-butanol was the best performing solvent in the study by Wang and Jiang. A solvent mix of *t*-BuOH/PhMe (5:1) was used to prevent *t*-BuOH from freezing in the flow tubes and pumps at room temperature. This solvent mix was used for the additive, catalyst and ligand screening (Table S1). Similar benzaldehyde yields were obtained when different Pd catalysts were trialed. The presence of nitrogen ligands appeared to reduce conversion. The addition of an acid additive increased the benzaldehyde yield. The absence of water from the reaction appeared to decrease conversion. However, the addition of too much water favored the formation of acetophenone, the Tsuji−Wacker product.[12] Most experiments performed poorly with <40% benzaldehyde yield in virtually all cases (see Supporting Information). Insufficient conversion was observed at 100 °C (Table 1, entry 1). A reaction temperature of 120 °C gave the best conversion and benzaldehyde yield (Table 1, entry 2). Significant levels of catalyst and substrate decomposition were observed at 140 °C (Table 1, entry 3).

The use of DMA and DMSO, both with water as a co-solvent, gave high conversion but favored the formation of acetophenone (Table 1, entries 4 and 5). Interestingly, the use of poly(ethylene glycol)-400 (PEG-400) as solvent resulted in good substrate conversion and gave benzaldehyde in a moderate 57% yield (Table 1, entry 6). PEG is known to stabilize active Pd catalysts.[20] In addition, PEG has received significant interest as an inexpensive, non-volatile, and an environmentally benign solvent.[21] PEG-400 is endowed with a viscosity value of 90 cP at 25 °C, which drops to 7.3 cP at 100 °C. A co-solvent is typically used to reduce the viscosity of the solution for more amenable flow processing.[22] Pleasingly, PEG_{400}/PhMe (1:1) provided good solubility of the reaction components and benzaldehyde in 61% yield (Table 1, entry 7). In addition, increasing the concentration from 0.35 M to 1.0 M gave a slight increase in benzaldehyde yield (Table 1, entry 8). However, Pd black precipitation was observed in these screening experiments which indicated catalyst decomposition.

Importantly, higher benzaldehyde yields were obtained when the catalyst loading was decreased (Figure 2). With a catalyst loading of only 0.1 mol% of $Pd(OAc)_2$ a benzaldehyde yield of 72% was obtained (Table 1, entry 9). Appreciable Pd black precipitation was not observed at this catalyst loading. Pd(0) species aggregate to generate Pd clusters, which ultimately irreversibly precipitate in the form of Pd black. [23] The reduction of catalyst loading to 0.1 mol% gave significantly higher activity (TON=720) compared to 2 mol% loading (TON=45).[24] Doubling the residence time resulted in no improvement in benzaldehyde yield.

Table 1. Solvent and temperature optimization of styrene oxidation.[a]



Entry	Solvent	T [°C]	Conv. **1** [%][b]	Yield **2** [%][b]	Yield **4** [%][b]
1[c]	*t*-BuOH/PhMe (5:1)	100	30	15	7
2[c]	*t*-BuOH/PhMe (5:1)	120	48	38	8
3[c]	*t*-BuOH/PhMe (5:1)	140	40	17	7
4	DMA/H_2O (5:1)	120	75	16	52
5	DMSO/H_2O (5:1)	120	85	14	63
6[c]	PEG_{400}	120	90	57	7
7[c]	PEG_{400}/PhMe (1:1)	120	78	61	15
8[c,d]	PEG_{400}/PhMe (1:1)	120	79	63	13
9[c,e]	PEG_{400}/PhMe (1:1)	120	81	72	3

[a] Conditions: substrate (0.700 mmol), $Pd(OAc)_2$ (2 mol%), PTSA.H_2O (20 mol%), diphenylether (internal standard (IS), 25 mol%) in solvent 2 mL, organic flow rate 0.5 mL min^{-1}, O_2 gas flow rate = 11 mL_n min^{-1}, 10 bar, t_{res} = ~25 min. [b] Conversion and yields based on absolute quantities measured using an internal standard by HPLC (at 254 nm). [c] H_2O (1.1 equiv). [d] substrate (2.00 mmol). [e] substrate (2.00 mmol), $Pd(OAc)_2$ (0.1 mol%).

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The intensified continuous-flow process therefore enables a significantly shorter reaction time to be used, from 24 h in batch to 25 min in flow. In addition, the catalyst loading has been reduced from 2 mol% in batch to 0.1 mol% in flow. The PEG_{400}/PhMe solvent mix provides good solubility of all the reaction components and PEG_{400} stabilizes the active Pd catalyst. The substrate concentration was also successfully increased from 0.33 M in batch to 1.0 M in flow.

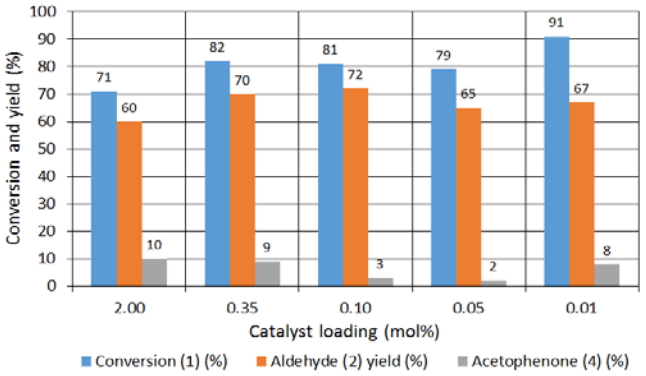
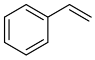
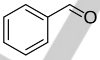
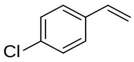
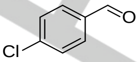
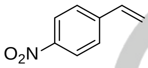
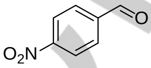
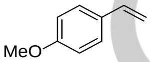
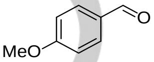
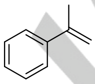
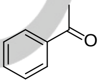
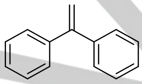
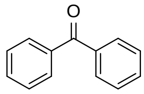
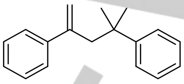
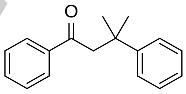
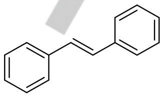
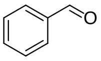
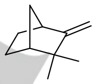
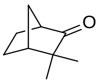
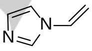
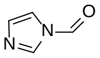
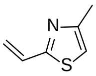
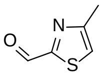


Figure 2. Influence of catalyst loading on conversion and product yields. For reaction conditions and analytics, see Table 2 entry 1.

Table 2. Scope of the Pd-catalyzed oxidative olefin cleavage under continuous-flow conditions.^{a}

Entry	Substrate	Product	Conv [%]$^{[b]}$	Yield [%]$^{[b,c]}$
1			81	72
2			100	94
3			45	42
4			95	45(40)^f
5			87	73
6^e			94^d	87^d
7^e			74	56
8^e			74	52
9			85^d	14^d
10			52	46
11			74	70

[a] Conditions: substrate (2.00 mmol), $Pd(OAc)_2$ (0.1 mol%), PTSA.H_2O (20 mol%), diphenylether (IS, 25 mol%) and H_2O (1.1 equiv) in PhMe/PEG_{400} 1:1 (2 mL), organic flow rate 0.5 mL min^{-1}, O_2 gas flow rate = 11 mL_n min^{-1}, 120 °C, 10 bar, t_{res} = 25 min. [b] Conversion and yield based on absolute quantities measured using an internal standard by HPLC (at 254 nm). [c] Molecular weights confirmed by GC-MS. [d] Conversion and yield based on absolute quantities measured using an internal standard by GC-FID. [e] substrate (1.00 mmol) due to solubility. [f] Eliminated aldol product.

To shed light on the possible mechanism of the transformation, radical scavengers were added to the reaction. Styrene conversion and benzaldehyde yield dropped dramatically by the addition of 10 mol% radical inhibitor such as 4-*tert*-butylcatechol (TBC) or 2,6-dibutyl-4-methylphenol (BHT) (Figure S2). A radical scavenger acts as a terminating agent which suppresses autoxidation by converting peroxy radicals to hydroperoxides. These results indicate that the olefin cleavage goes through a radical auto-oxidation mechanism.[25] 4-*Tert*-butylcatechol (TBC) at 10 to 15 ppm is added to commercially-available styrene and many of its derivatives as a stabilizer to prevent decomposition from radical polymerization during storage and reaction.

The applicability of this continuous-flow protocol to olefin substrates is shown in Table 2.[26] Aromatic terminal alkenes with electron-rich and electron-poor substituents in the para position were reacted to give the corresponding aldehydes (Table 2, entries 2–4). 4-Chlorostyrene showed high reactivity giving full conversion and 94% product yield (Table 2, entry 2). The presence of an electron withdrawing nitro group within the substrate resulted in the cleavage working less effectively (Table 2, entry 3). Unfortunately, 4-vinylanisole proved susceptible to forming the eliminated aldol product (Table 2, entry 4). The oxidation of α-methylstyrene occurred efficiently to give the corresponding ketone in 73% yield (Table 2, entry 5). The cleavage reaction was also highly selective for an aromatic gem-disubstituted alkene to give the desired ketone in 87% yield (Table 2, entry 6). We next turned to substrates not included in the original scope (Table 2, entries 3,7–11).[13] The olefin cleavage of (4-methylpent-1-ene-2,4-diyl)dibenzene proved more difficult with only 56% yield and multiple side product formation (Table 2, entry 7). In line with expectations, *trans*-stilbene was less reactive than 1,1-disubstituted alkenes (Table 2, entry 8). However, the oxidative cleavage of aliphatic camphene proved the most challenging with only 16% conversion (Table 2, entry 9). These results indicate that steric hindrance plays a significant role in affecting the efficiency of oxidation. Interestingly, heterocyclic terminal olefins, not tested by Wang and Jiang, could also be transformed into the corresponding aldehydes using the continuous-flow protocol (Table 2, entries 10, 11).

The continuous-flow process for the olefin cleavage of styrene could be operated consistently over a period of 20 min to give 81% conversion of styrene and 72% benzaldehyde yield (HPLC assay yields, averages of 11 samples collected throughout operation, see Figure 3).

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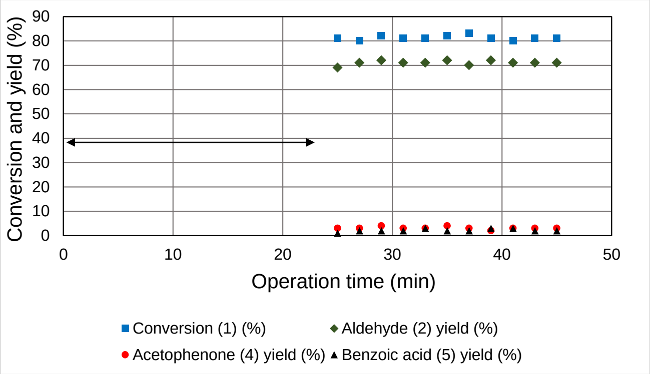

Figure 3. Long run profiles. For reaction conditions and analytics, see Table 2 entry 1. No samples were taken until the carrier solvent (colorless) had passed through (indicated by the double headed arrow) and color (reaction mixture) was observed at the BPR.

In conclusion, we have demonstrated a Pd-catalyzed direct oxidation of olefins into carbonyl compounds using a continuous-flow reactor. Low catalyst loadings (0.1 mol%) provided moderate to excellent product yields in a short 25 min residence time. The presence of a radical scavenger was shown to have a negative effect on the olefin cleavage and indicates the reaction takes place via a free radical mechanism. A major advantage of the flow protocol is the ability to handle pure O_2 under process intensified conditions in a safe and scalable manner.

Keywords: continuous flow • oxidation • olefin cleavage • molecular oxygen • Pd-catalyzed • gas-liquid transformations

[1] a) F. E. Kuhn, R. W. Fischer, W. A. Herrmann, T. Weskamp, *in* Transition Metals for Organic Synthesis, *Vol. 2* (Eds.: M. Beller, C. Bolm), Wiley-VCH: Weinheim, **2004**, p 427; b) D. G. Lee, T. Chen, *in* Comprehensive Organic Synthesis, *Vol 7* (Eds: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, p 541.

[2] R. Criegee, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 745–752.

[3] M. Nobis, D. M. Roberge, *Chim. Oggi* **2011**, *29*(1), 56−58.

[4] Serious accidents involving explosions have been reported, see: a) K. Koike, G. Inoue, T. J. Fukuda, *Chem. Eng. Jpn.* **1999**, *32*, 295–299; b) R. A. Ogle, J. L. Schumacher, *Process Saf. Prog.* **1998**, *17*, 127–133.

[5] B. R. Travis, R. S. Narayan, B. Borhan, *J. Am. Chem. Soc.* **2002**, *124*, 3824–3825

[6] D. Yang, C. Zhang, *J.Org. Chem.* **2001**, *66*, 4814–4818.

[7] K. Miyamoto, N. Tada, M. Ochiai, *J. Am. Chem. Soc.* **2007**, *129*, 2772–2773

[8] L. Miyamoto, Y. Sei, K. Yamaguchi, M. Ochiai, *J. Am. Chem. Soc.* **2009**, *131*, 1382–1383.

[9] a) Y. Hayashi, M. Takeda, Y. Miyamoto, M. Shoji, *Chem. Lett.* **2002**, *31*, 414–415; b) A. Dhakshinamoorthy, K. Pitchumani, *Tetrahedron* **2006**, *62*, 9911–9918; c) A. Dhakshinamoorthy, K. Pitchumani, *Catal. Commun.* **2009**, *10*, 872–878; d) C.-X Miao, B. Yu, L.-N. He, *Green Chem.* **2011**, *13*, 541–544 e) R. Lin, F. Chen, N. Jiao *Org. Lett.* **2012**, *14*, 4158–4161; f) C. Sun, B. Hu, Z. Liu, *Chem. Eng. J.* **2013**, *232*, 96–103; g) A. Fujiya, A. Kariya, T. Nobuta, N. Tada, T. Miura, A. Itoh, *Synlett* **2014**, *25*(6), 884–888; h) M. M. Hossain, S. G. Shyu, *Tetrahedron* **2014**, *70*, 251–255; i) A. Rubinstein, P. Jiménez-Lozanao, J. J. Carbý, J. M. Poblet, R. Neumann, *J. Am. Chem. Soc.* **2014**, *136*, 10941–10948; j) G.-Z. Wang, X.-L Li, J.-J. Dai, H.-J Xu, *J. Org. Chem.* **2014**, *79*, 7220–7225; k) A. Gonzalez-de-Castro, J. Xiao, *J. Am. Chem. Soc.* **2015**, *137*, 8206–8218; l) G. Urgoitia, R. SanMartin, M. T. Herrero, E. Domínguez, *Adv. Synth. Catal.* **2016**, *358*, 1150–1156; m) Y. Deng, X.-J Wei, H. Wang, Y. Sun, T Noël, X. Wang, *Angew. Chem. Int. Ed.* **2017**, *56*, 832–836.

[10] S. Caron, R. W. Dugger, S. G. Ruggeri, J. A. Ragan, D. H. B. Ripin, *Chem. Rev.* **2006**, *106*, 2943–2989.

[11] D. Wang, J. N. Jaworski, S. S. Stahl, *in* Liquid Phase Aerobic Oxidation Catalysis: Industrial Applications and Academic Perspectives (Eds.:S. S. Stahl, P. L. Alsters), Wiley-VCH, Weinheim, **2016**, p 115.

[12] J. Tsuji, *Synthesis*, **1984**, 369–384.

[13] A. Wang, H. Jiang, *J. Org. Chem.* **2010**, *75*, 2321–2326.

[14] Other important contributions (in batch) were: $PdCl_2$ and a biphasic supercritical CO_2 and PEG-300 solvent mix, see: a) J. Q. Wang, F. Cai, E. Wang, L. N. He, *Green Chem.* **2007**, *9*, 882–887; b) water soluble Pd(II) PEG-2000 anchored bidentate dipyridyl ligand, see: B. Feng, Z. Hou, X. Wang, Y. Hu, H. Li, Y. Qiao, *Green Chem.* **2009**, *11*, 1446–1452.

[15] a) Also known as the “limiting oxygen concentration”, see: a) P. M. Osterberg, J. K. Niemeier, C. J. Welch, J. M. Hawkins, J. R. Martinelli, T E. Johnson, T. W. Root, S. S. Stahl, *Org. Process Res. Dev.* **2015**, *19*, 1537–1543; Sanofi has defined an oxygen concentration of 5% by volume as the maximum oxygen concentration admissible for pilot-plant scale or larger, see: b) M. P. Feth, K. Rossen, A. Burgard, *Org. Process Res. Dev.* **2013**, *17*, 282–293;

[16] For reviews on flow chemistry, see: a) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688–6728; b) M. Movsisyan, E. I. P. Delbeke, J. K. E. T. Berton, C. Battilocchio, S. V Ley, *Chem. Soc. Rev.* **2016**, *45*, 83–117; for a gas-liquid flow review, see: c) C. J. Mallia, I. R. Baxendale, *Org. Process Res. Dev.* **2015**, *20*, 327–360; for reviews on aerobic oxidations in flow, see: d) H. P. L. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque, T. Noël, *Chem. Soc. Rev.* **2016**, *45* 83–117; and e) B. Pieber, C. O. Kappe, *Top. Organomet. Chem.* **2015**, *57*, 97−136.

[17] For an overview on the opportunities of aerobic oxidations using flow reactors, see: A. Gavriilidis, A. Constantinou, K. Hellgardt, K. K. Hii, G. J. Hutchings, G. L. Brett, S. Kuhn, S. P. Marsden *React. Chem. Eng.* **2016**,*1*, 595–612.

[18] C. A. Hone, D. M. Roberge, C. O. Kappe, *ChemSusChem* **2017**, *10*, 32–41.

[19] A similar flow reactor configuration has been previously reported by our group for aerobic oxidations involving Pd catalysis, see: a) B. Gutmann, U. Weigl, D. P. Cox, C. O. Kappe, *Chem. Eur. J.* **2016**, *22*, 10393–10398; b) B. Gutmann, P. Elsner, D. P. Cox, U. Weigl, D. M. Roberge, C. O. Kappe, *ACS Sust. Chem. Eng.* **2016**, *4*, 6048–6061.

[20] PEG is also known to reduce Pd(II) to Pd(0), see: C. C. Luo, Y. H. Zhang, Y. G. Wang, *J. Mol. Catal. A: Chem.* **2005**, *229*, 7–12.

[21] J. Chen, S. K. Spear, J. G. Huddleston, R. D. Rogers, *Green Chem.* **2005**, *7*, 64–82.

[22] For examples of PEG-400 in flow synthesis, see: a) A. Gioiello, E. Rosatelli, M. Teofrasti, P. Filipponi, R. Pellicciari, *ACS Comb. Sci.* **2013** *15*, 235−239; b) A.-C. Bédard, S. Régnier, S. K. Collins, *Green Chem.* **2013**, *15*, 1962–1966.

[23] A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Henderickx, J. G. de Vries, *Org. Lett.* **2003**, *5*, 3285–3288.

[24] TON was calculated as follows: TON = (moles of styrene) × (yield of benzaldehyde) / (moles of Pd).

[25] a) J. Xie, H. Jiang, Y. Cheng, C. Zhu, *Chem. Commun.* **2012**, 979–981; b) H. Jiang, Q.-D. Qiao, H. Gong, *Petrol. Sci. Technol.* **1999**, *17*, 955–965.

[26] The yields given are HPLC or GC assay yields based on absolute quantities measured against an internal standard. The compounds were fully isolated and characterized by Wang and Jiang, see ref 13.

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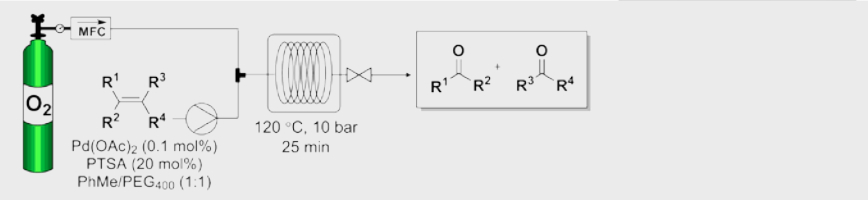

The development of a continuous-flow protocol for a Pd-catalyzed olefin cleavage using molecular oxygen as the sole oxidant to give carbonyl compounds is described. The applicability of the continuous-flow protocol is demonstrated on several olefin substrates. The continuous-flow process enables safe and scalable olefin cleavage using pure O_2.

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Page No. – Page No.

Development of a Continuous-Flow Process for a Pd-Catalyzed Olefin Cleavage using Oxygen within the Explosive Regime

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