

The Oxygen-Mediated Synthesis of 1,3-Butadiynes in Continuous Flow: Using Teflon AF-2400 to Effect Gas/Liquid Contact

Trine P. Petersen,^[a, b, c] Anastasios Polyzos,^[a, d] Matthew O'Brien,^[a] Trond Ulven,^[b] Ian R. Baxendale,^[a] and Steven V. Ley^{*[a]}

In recent years, as the ecological impact of technology and industrial processes has become clearer, there has been a growing demand for more environmentally benign and sustainable chemical processes.^[1] One noteworthy example of this ongoing trend has been the development of oxidative processes that use molecular oxygen as the reagent, either directly or in conjunction with catalysis.^[2] As well as for typical functional group oxidations, molecular oxygen is seeing significant and increasing use in several synthetically important carbon–carbon bond forming reactions.^[3] Of these, the Glaser–Hay oxidative acetylene coupling reaction to form 1,3-butadiynes is an important example.^[4] The intense research interest in this reaction is largely due the importance of the conjugated diyne and polyyne products, which have very interesting electronic, optical, and material properties.^[5]

Being completely ecologically compatible, the use of molecular oxygen is clearly advantageous when compared with other common metal-based oxidants (e.g., chromium(VI) reagents, permanganate). The latter have significant toxicity and their use necessitates expensive and energy-intensive clean-up procedures.^[6] Importantly, the gaseous nature of oxygen facilitates its separation from products, thereby permitting the use of excess oxidant in order to drive reactions to completion. However, this also leads to severe complications from a process standpoint, in that gas/liquid phase-transfer phenomena have to be considered.^[7] Whilst several practical methods exist to increase the dissolution rate of oxygen (and other gases) into solution (e.g., sparging, agitation, vortex mixing), the accurate control of these processes is by no means trivial. In addition, owing to changes in physical parameters such as surface-to-volume ratios, the scale-up of batch chemical processes that involve a gas/liquid interface is often much more complex than simply using a bigger reaction vessel. An obvious further consideration with gaseous reagents such as oxygen is that the high pressures often required to obtain adequate solution

concentrations (according to Henry's law) call for specialized and expensive containment vessels, and raise safety concerns.

Flow chemistry (and related continuous processing techniques) has emerged recently as an alternative paradigm of synthesis chemistry that offers solutions to some of the problems associated with batch processing.^[8] In particular, as the physical parameters of the processing zones are fixed (and small), the scale-up of reaction processes is greatly simplified and can be achieved either by increasing the running-time of a reaction, or by parallelization of the reaction through multiple identical paths ("scale-out"). This is especially advantageous for processes that involve hazardous intermediates or conditions (e.g., high pressures or temperatures), as the total hazard present at any one time is kept to a minimum. Additionally, mixing processes (including interfacial transfer) are often enhanced due to the small physical scale (and, hence, increased surface-to-volume ratio) of the reaction zones.

Notwithstanding the potential benefits of conducting gas/liquid chemistry in flow, development in this area has been relatively slow, perhaps due to the difficulty of achieving accurate and reliable control of the interfacial processes. Until recently, approaches to solve these problems have focused on "mechanical mixing" of the two phases in order to achieve greater interfacial surface areas, and this has resulted in some interesting engineering developments.^[9] However, the relationship between the morphology of the interface (hence, reaction conversion) and flow rate is often non-linear, and this can cause severe difficulty with reaction optimization.

Seeking a more generally applicable, consistent, and well-controlled method of gas/liquid contact, we conceived the use of semi-permeable membranes to generate homogeneous gas solutions. We have shown that Teflon AF-2400^[10] (a co-polymer of tetrafluoroethene and a perfluorodimethyldioxolane) is very well suited to this purpose as it is extremely permeable to a wide range of gases but practically impermeable to liquids, and exhibits much of the chemical resistance associated with polytetrafluoroethylene (PTFE). By using a simple "jar" reactor we demonstrated the use of this material for the ozonolysis of alkenes,^[11] and more recently we have developed a "tube-in-tube" reactor that has been used to effect carboxylations^[12] and hydrogenations^[13] at elevated pressures.

Herein, we present our initial findings on the use of oxygen in such a reactor to effect Glaser–Hay couplings of terminal alkynes in continuous flow. The permeability of the AF-2400 tubing to molecular oxygen can be demonstrated by using a visual indicator that changes color in the presence of the gas. Shown in Figure 1 are photographs of a coil of the AF-2400 tubing in a sealed glass vessel, the contents of which were continuously flushed with either air, oxygen, or argon (all at

[a] T. P. Petersen, Dr. A. Polyzos, Dr. M. O'Brien, Dr. I. R. Baxendale, Prof. S. V. Ley
Whiffen Laboratory, Department of Chemistry
University of Cambridge
Lensfield Road, Cambridge (UK)
E-mail: svl1000@cam.ac.uk

[b] T. P. Petersen, Dr. T. Ulven
Department of Physics and Chemistry
University of Southern Denmark, Odense (Denmark)

[c] T. P. Petersen
Discovery Chemistry and DMPK
H. Lundbeck A/S, Valby (Denmark)

[d] Dr. A. Polyzos
CSIRO, Materials Science and Engineering
Bayview Avenue, Clayton South, VIC 3169 (Australia)

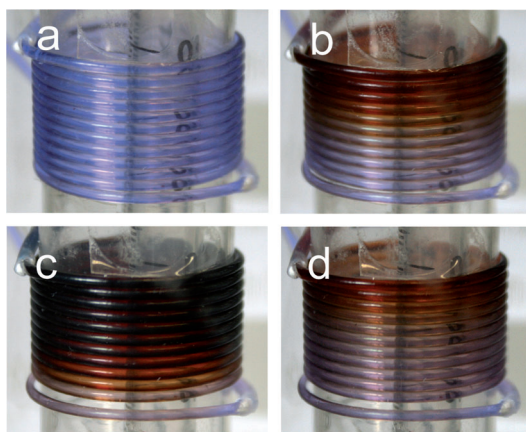


Figure 1. Visual indication of oxygen permeation through oxidation of vanadium(II). a) argon, 1 atm, $100 \mu\text{L min}^{-1}$; b) air, 1 atm, $100 \mu\text{L min}^{-1}$; c) O_2 , 1 atm, $100 \mu\text{L min}^{-1}$; d) O_2 , 1 atm, 1.0 mL min^{-1} (1 atm = 1.013×10^5 Pa).

ambient pressure). Through this tubing was flowed a lilac solution of vanadium(II) [obtained by reducing a solution of vanadium(III) chloride with zinc metal and hydrochloric acid/ammonium chloride under argon]. In a control experiment with an argon atmosphere (Figure 1a) there was no color change, but when the vessel was filled with air (Figure 1b) the lilac color faded and then eventually turned to a dark red/brown. With an atmosphere of oxygen at the same flow rate the color change was much faster (Figure 1c). There was a more gradual color change (in terms of length of tube) with oxygen when a greater indicator flow rate was used, as expected (Figure 1d).

For the Glaser–Hay couplings, we used the “tube-in-tube” reactor/injector to allow the use of oxygen at elevated pressures (Figure 2). It operates by allowing a liquid flow stream to pass through an inner tube of the gas-permeable Teflon AF-2400 membrane tubing (1.0 mm outer diameter, 0.8 mm inner diameter), contained within an outer tube of a slightly larger diame-

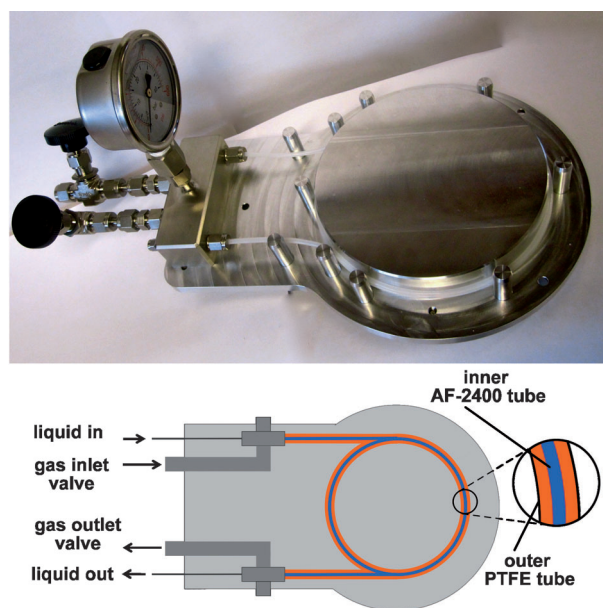
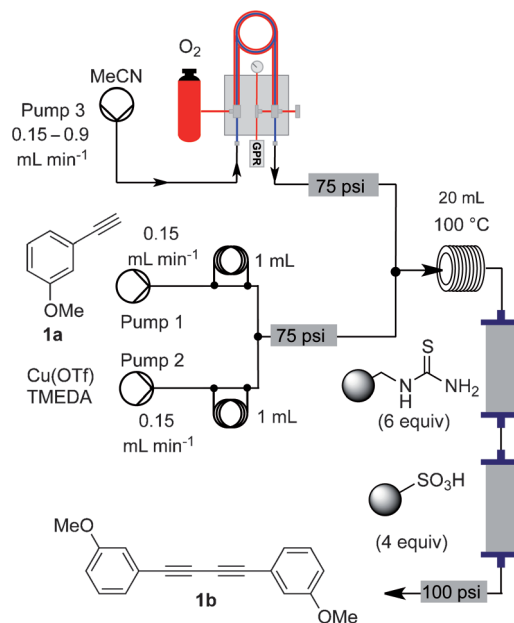


Figure 2. Photograph and schematic illustration of the tube-in-tube reactor/injector.

ter (e.g., standard thick-walled PTFE or stainless steel) pressurized with gas. This results in homogeneous solutions of gas in solvent, rather than the biphasic segmented-flow obtained by simply mixing the gas and liquid streams at a junction. An important requirement in this regard is the back-pressure regulator at the downstream terminus of the flow system, which maintains total pressure and prevents premature outgassing of dissolved oxygen (which occurs spontaneously as the solution exits the back-pressure regulator). No outgassing upstream of the back-pressure regulator was observed in any of the experiments described herein. These simple and economical apparatuses can be constructed from commercially available interconnects (e.g., Swagelok) and can be easily assembled without any special skill or equipment. In order to allow efficient control of the reaction temperature, we decided to use the tube-in-tube device to obtain oxygenated streams of solvent which would be mixed with reactants and heated downstream (because the outer pressurized jacket might act as an insulator and complicate direct heating of the device). A schematic of the full flow chemistry setup is shown in Scheme 1. A Vapourtec R2/R4 unit (along with a Knauer K100 HPLC pump for the third stream) was used to effect pumping of the system, although any suitable flow equipment could be used with the tube-in-tube device.

Three pumps are used: two to pump the substrate and catalyst/ligand streams, respectively (introduced via injection loops), whilst a third one is used to pump solvent through the tube-in-tube membrane device where it is oxygenated. After the substrate and catalyst streams are united at a T-junction, the resulting stream is combined with the oxygenated stream and the mixture is passed through a heating coil. Copper is then removed from the flow stream by passing through a cartridge of polymer-supported thiourea. Similarly, a cartridge of polymer-supported sulfonic acid is used to scavenge the TMEDA. In order to preclude the formation of precipitates



Scheme 1. Schematic of the continuous-flow synthesis setup (1 psi = 6.894×10^3 Pa).

(which could potentially cause blockages in the flow channels) we carried out preliminary solubility studies and found that $\text{CuOTf}(\text{MeCN})_4$ (with a three-fold relative quantity of TMEDA) in acetonitrile was agreeable, and this also effectively dissolved the acetylenic substrates. Other copper salts were less soluble. DMF was also a good solvent but deemed unsuitable due to its toxicity and high boiling point, which would make its removal problematic. Using this setup, the oxidative coupling of 3-ethynyl-anisole (**1a**) to afford the 1,4-bis-(3-methoxyphenyl)-buta-1,3-diyne (**1b**) was used for initial investigation and rudimentary optimization.

As can be seen from Table 1 (entries 1–3), increasing the ratio of oxygenated stream to substrate/catalyst stream clearly increases the conversion of the reaction. Temperature is also an important parameter: an increase from 25 °C to 40 °C gave much higher conversion with other conditions held constant (entries 3 and 5). Lowering the O_2 pressure from 8 bar to 4 bar was accompanied by a reduction in conversion from 87% to 76% (entries 4 and 5). Increasing the temperature further to 100 °C gave much higher conversions, now quantitative with only 0.6 mL min^{-1} of oxygenated stream (entry 7; almost quantitative with 0.15 mL min^{-1} , entry 6). Based on the results from this initial screening, conditions were chosen (8 bar O_2 , pump 1 = pump 2 = 0.15 mL min^{-1} , pump 3 = 0.9 mL min^{-1} , 100 °C) in order to give high conversions, and they were used in preparative homocoupling of a series of alkynes, the results of which are shown in Table 2. The couplings of electron-rich and electron-deficient aromatic acetylenes generally proceeded in high yields, affording products in high purity without the need for chromatography.

The aniline derivative **3b** was synthesized without the in-line sulfonic acid resin to avoid inadvertent scavenging of the basic product, which in this case was separated from the TMEDA by column chromatography. A lower isolated yield was achieved, perhaps due to polymerization/degradation of the compound on silica gel. (The conversion from starting material in this case was 91%, in all other cases no starting material was present according to $^1\text{H NMR}$ analysis.) The moderate yield observed for the phenyl ether (Table 2, entry 7) was possibly due to the poor solubility of the product in the solvent system, which led to partial blocking of the instrument tubing.

Several aliphatic and silyl acetylenes were also coupled in good to excellent yields after the conditions were modified to include the addition of 25 mol% 1,8-diazabicyclo-[5.4.0]-undec-

Table 1. Influence of reaction parameters on the Glaser–Hay coupling of 3-ethynyl anisole to afford **1**.

Entry	<i>T</i> [°C]	<i>P</i> [bar]	Flow rate pump 1 [mL min^{-1}]	Flow rate pump 2 [mL min^{-1}]	Flow rate pump 3 [mL min^{-1}]	Conv. ^[a] [%]
1	25	8	0.15	0.15	0.3	54
2	25	8	0.15	0.15	0.6	69
3	25	8	0.15	0.15	0.9	71
4	40	4	0.15	0.15	0.9	76
5	40	8	0.15	0.15	0.9	87
6	100	8	0.15	0.15	0.15	98
7	100	8	0.15	0.15	0.6	100

[a] Determined by $^1\text{H NMR}$.

Table 2. Results of preparative Glaser–Hay couplings in continuous flow.

Entry	Product	Yield ^[a] [%]
1		99 84 ^[b]
2		96
3		65 ^[c]
4		87
5		96
6		100
7		49 ^[d]
8		94 ^[d,e]
9		92 ^[d,e]
10		65 ^[e]
11		88 ^[e]

[a] Reaction carried out on 1.0 mmol scale unless stated otherwise. [b] Reaction carried out on a 17.4 mmol scale (2.30 g). [c] Purified by column chromatography, 91% conversion by $^1\text{H NMR}$. [d] Toluene used as solvent to improve solubility. [e] 25 mol% DBU added to alkyne stream.

7-ene (DBU) to the alkyne stream.^[14] These products were also isolated in high purity without any chromatographic purification. In order to determine the scalability of the process for laboratory-scale preparations, we carried out a coupling reaction with 17.4 mmol of 3-ethynyl-anisole (2.30 g). Pleasingly, a high (84%) isolated yield of pure material was obtained without any chromatography.

Having demonstrated the efficiency of the system for Glaser–Hay coupling reactions, we sought to obtain some quantitative data about the extent to which oxygen was permeating the Teflon AF-2400 membrane and the relationship of this to pressure/flow rate. We chose to assay this indirectly, by measuring the oxygen outgassing from solution downstream of the back-pressure regulator. This was achieved by using a simple gas burette apparatus. We made the assumption that residual dissolved oxygen at ambient pressure would be negligible relative to the amount dissolved at higher pressures.^[15] Shown in Figure 3 are plots at several pressures of the calculated concentration of dissolved oxygen (expressed as volume of outgassed oxygen collected per unit time divided by amount of solvent pumped through per unit time) against residence time (volume inside membrane tubing divided by flow rate).

At low residence times the concentration of oxygen increases approximately linearly with residence time, but at higher residence times the concentration seems to reach a plateau, indicating saturation. This plateau appears to vary roughly linearly with pressure, in line with Henry's law. Remarkably, at all pressures investigated, the onset of saturation was observed at approximately 16 s residence time, indi-

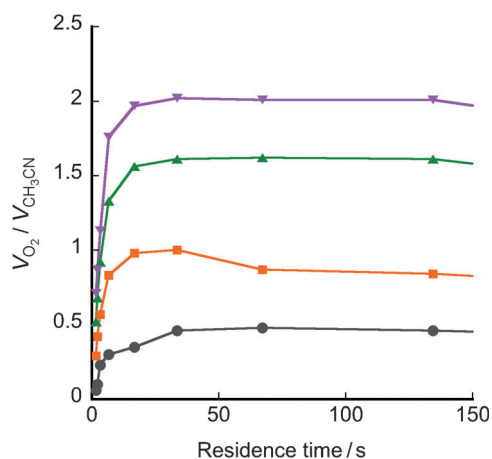


Figure 3. Gas burette data from out-gassing measurements. ●: 2.5 bar, ■: 5.0 bar, ▲: 7.5 bar, ▼: 9.5 bar (1 bar = 10^5 Pa).

cating a very efficient delivery of the gas to the solvent stream. This could be attributable to the large effective surface-area-to-volume ratio, derived from the microporous polymeric structure of Teflon AF-2400, thereby permitting rapid gas diffusion across the membrane. We have recently shown that this type of out-gassing measurement can be carried out using a computer-assisted "pixel counting" method, which lends itself to automation.^[13] Work in our laboratory is now underway using such automated systems to obtain extensive oxygen (and other gas) permeation/solubility data for a wide range of solvents, which will be useful for the further exploitation of this ecologically benign gas by the synthesis chemistry community in a wider range of continuous-flow processes.

Acknowledgements

We thank the following institutions for financial support: The Danish Agency for Science, Technology and Innovation and H. Lundbeck A/S (T.P.P.), CSIRO Material Science and Engineering (A.P.), EPSRC (M.O'B.), the BP 1702 Professorship (S.V.L.), and The Royal Society (I.R.B.).

Keywords: alkynes · C–C coupling · flow chemistry · membranes · oxygen

- [1] a) *Sustainable Industrial Chemistry* (Eds.: F. Cavani, G. Centi, S. Perathoner, F. Trifiro), Wiley-VCH, Weinheim **2009**; b) N. Winterton, *Green Chemistry For Sustainable Technologies: A Foundation*, RSC, Cambridge **2010**.
- [2] a) T. Punniyamurthy, S. Velusamy, J. Iqbal, *Chem. Rev.* **2005**, *105*, 2329; b) K. M. Gligorich, M. S. Sigman, *Chem. Commun.* **2009**, 3854; c) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981; d) J. Piera, J. E. Backvall, *Angew. Chem.* **2008**, *120*, 3558; *Angew. Chem. Int. Ed.* **2008**, *47*, 3506; e) S. S. Stahl, *Angew. Chem.* **2004**, *116*, 3480; *Angew. Chem. Int. Ed.* **2004**, *43*, 3400.
- [3] a) E. M. Beccalli, G. Broggin, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318; b) B. Karimi, H. Behzadnia, D. Elhamifar, P. F. Akhavan, F. K. Esfahani, A. Zamani, *Synthesis* **2010**, 1399; c) K. S. Yoo, C. P. Park, C. H. Yoon, S. Sakaguchi, J. O'Neill, K. W. Jung, *Org. Lett.* **2007**, *9*, 3933; d) K. S. Yoo, C. H. Yoon, K. W. Jung, *J. Am. Chem. Soc.* **2006**, *128*, 16384.
- [4] a) C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422; b) A. S. Hay, *J. Org. Chem.* **1962**, *27*, 3320; c) H. R. Liang, J. X. Li, Z. Y. Wang, K. Yang, *Chin. J. Org. Chem.* **2011**, *31*, 586; d) H. A. Stefani, A. S. Guarezemini, R. Cella, *Tetrahedron* **2010**, *66*, 7871; e) P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632.
- [5] a) *Acetylene Chemistry: Chemistry, Biology and Material Science* (Eds.: F. Diederich, P. Stang, R. R. Tykwinski), Wiley-VCH, Weinheim **2005**; b) *Carbon-Rich Compounds: From Molecules to Materials* (Eds.: M. M. Haley, R. R. Tykwinski), Wiley-VCH, Weinheim **2006**; c) F. Diederich, *Chem. Commun.* **2001**, 219; d) M. B. Nielsen, F. Diederich, *Chem. Rev.* **2005**, *105*, 1837; e) W. A. Chalifoux, R. R. Tykwinski, *Nat. Chem.* **2010**, *2*, 967; f) S. Eislser, A. D. Slepko, E. Elliott, T. Luu, R. McDonald, F. A. Hegmann, R. R. Tykwinski, *J. Am. Chem. Soc.* **2005**, *127*, 2666.
- [6] R. Saha, R. Nandi, B. Saha, *J. Coord. Chem.* **2011**, *64*, 1782.
- [7] a) L. C. Han, H. A. Luo, Y. J. Liu, K. Y. You, P. L. Liu, *AIChE J.* **2011**, *57*, 886; b) J. Markopoulos, C. Christofi, I. Katsinaris, *Chem. Eng. Technol.* **2007**, *30*, 829.
- [8] a) J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.* **2011**, *47*, 4583; b) D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675; c) I. R. Baxendale, J. J. Hayward, S. Lanners, S. V. Ley, C. D. Smith, in *Microreactors in Organic Synthesis and Catalysis* (Ed.: T. Wirth), Wiley, New York **2008**; d) C. Wiles, P. Watts, *Chem. Commun.* **2011**, *47*, 6512; e) X. Y. Mak, P. Laurino, P. H. Seeberger, *Beilstein J. Org. Chem.* **2009**, *5*; f) T. Razzaq, C. O. Kappe, *Chem. Asian J.* **2010**, *5*, 1274; g) V. Hessel, *Chem. Eng. Technol.* **2009**, *32*, 1655; h) B. D. A. Hook, W. Dohle, P. R. Hirst, M. Pickworth, M. B. Berry, K. I. Booker-Milburn, *J. Org. Chem.* **2005**, *70*, 7558; i) A. R. Bogdan, S. L. Poe, D. C. Kubis, S. J. Broadwater, D. T. McQuade, *Angew. Chem.* **2009**, *121*, 8699; *Angew. Chem. Int. Ed.* **2009**, *48*, 8547; j) A. R. Bogdan, N. W. Sach, *Adv. Synth. Catal.* **2009**, *351*, 849; k) M. Brasholz, B. A. Johnson, J. M. Macdonald, A. Polyzos, J. Tsanakisidis, S. Saubern, A. B. Holmes, J. H. Ryan, *Tetrahedron* **2010**, *66*, 6445; l) P. J. Nieuwland, K. Koch, N. van Harskamp, R. Wehrens, J. C. M. van Hest, F. Rutjes, *Chem. Asian J.* **2010**, *5*, 799; m) J. I. Yoshida, *Chem. Rev.* **2010**, *10*, 332; n) A. Nagaki, E. Takizawa, J. Yoshida, *Chem. Eur. J.* **2010**, *16*, 14149.
- [9] a) Y. Wada, M. A. Schmidt, K. F. Jensen, *Ind. Eng. Chem. Res.* **2006**, *45*, 8036; b) E. R. Murphy, J. R. Martinelli, N. Zaborenko, S. L. Buchwald, K. F. Jensen, *Angew. Chem.* **2007**, *119*, 1764; *Angew. Chem. Int. Ed.* **2007**, *46*, 1734; c) S. Hübner, U. Benstrup, U. Budde, K. Lovis, T. Dietrich, A. Freitag, L. Kupper, K. Jahnisch, *Org. Process Res. Dev.* **2009**, *13*, 952; d) J. X. Hou, G. Qian, X. G. Zhou, *Chem. Eng. J.* **2011**, *167*, 475; e) E. Dluska, S. Wronski, T. Ryszczyk, *Exp. Therm. Fluid Sci.* **2004**, *28*, 467; f) A. Heyouni, M. Roustan, Z. Do-Quang, *Chem. Eng. Sci.* **2002**, *57*, 3325; g) S. Saaby, K. R. Knudsen, M. Ladlow, S. V. Ley, *Chem. Commun.* **2005**, 2909; h) T. Fukuyama, T. Rahman, N. Kamata, I. Ryu, *Beilstein J. Org. Chem.* **2009**, *5*; i) M. T. Rahman, T. Fukuyama, N. Kamata, M. Sato, I. Ryu, *Chem. Commun.* **2006**, 2236; j) C. B. Kelly, C. Lee, M. A. Mercadante, N. E. Leadbeater, *Org. Process Res. Dev.* **2011**, *15*, 717; k) H. Oyamada, T. Naito, S. Kobayashi, *Beilstein J. Org. Chem.* **2011**, *7*, 735; l) J. Kobayashi, Y. Mori, K. Okamoto, R. Akiyama, M. Ueno, T. Kitamori, S. Kobayashi, *Science* **2004**, *304*, 1305; m) X. Han, R. A. Bourne, M. Poliakoff, M. W. George, *Chem. Sci.* **2011**, *2*, 1059; n) C. Csajági, B. Borcsek, K. Niesz, I. Kovacs, Z. Szekelehyidi, Z. Bajko, L. Urge, F. Darvas, *Org. Lett.* **2008**, *10*, 1589; o) P. W. Miller, L. E. Jennings, A. J. deMello, A. D. Gee, N. J. Long, R. Vilar, *Adv. Synth. Catal.* **2009**, *351*, 3260; p) R. D. Chambers, M. A. Fox, G. Sandford, J. Trmcic, A. Goeta, *J. Fluorine Chem.* **2007**, *128*, 29; q) R. Abdallah, V. Meille, J. Shaw, D. Wenn, C. de Bellefon, *Chem. Commun.* **2004**, 372; r) M. Irfan, T. N. Glasnov, C. O. Kappe, *Org. Lett.* **2011**, *13*, 984.
- [10] a) P. R. Resnick, W. H. Buck, in *Fluoropolymers II* (Eds.: G. Hougham, P. E. Cassidy, K. Johns, T. Davidson), Kluwer Academic, New York **1999**; b) Teflon AF-2400 was purchased from Biogeneral Inc., 9925 Mesa Rim Road, San Diego, CA (USA). See <http://www.biogeneral.com> (accessed August 2011).
- [11] M. O'Brien, I. R. Baxendale, S. V. Ley, *Org. Lett.* **2010**, *12*, 1596.
- [12] A. Polyzos, M. O'Brien, T. P. Petersen, I. R. Baxendale, S. V. Ley, *Angew. Chem.* **2011**, *123*, 1222; *Angew. Chem. Int. Ed.* **2011**, *50*, 1190.
- [13] M. O'Brien, N. Taylor, A. Polyzos, I. R. Baxendale, S. V. Ley, *Chem. Sci.* **2011**, *2*, 1250.
- [14] S. Adimurthy, C. C. Malakar, U. Beifuss, *J. Org. Chem.* **2009**, *74*, 5648.
- [15] J. M. Achord, C. L. Hussey, *Anal. Chem.* **1980**, *52*, 601.

Received: July 4, 2011

Published online on September 21, 2011