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# Oxidation Reactions in Segmented and Continuous Flow Chemical Processing Using an *N*-(*tert*-Butyl)phenylsulfonimidoyl Chloride Monolith

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**Abstract:** A supported version of *N*-(*tert*-butyl)phenylsulfonimidoyl chloride on a monolithic material is described, which can be incorporated into a flow chemical processing arrangement to oxidise a variety of substrates in both stoichiometric and catalytic processes to yield products in high yields and in high purity after in-line workup.

**Key words:** oxidation, monolith, flow chemistry, polymer-supported reagents, catalysis

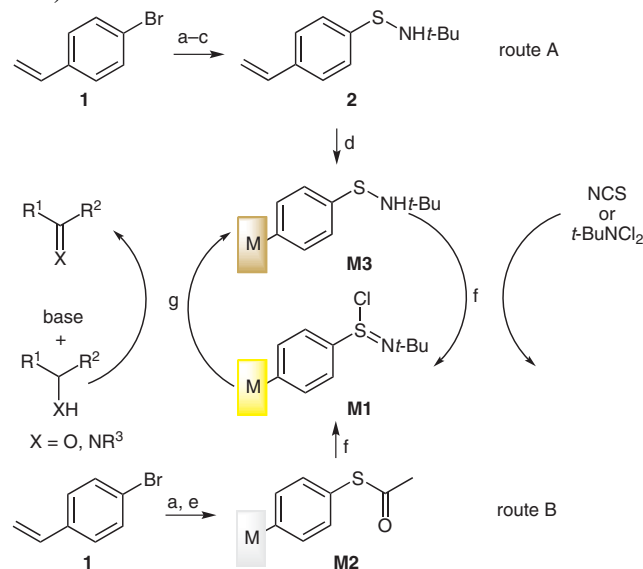
Immobilised reagents, whether on organic or inorganic supports, are ideally suited for use in continuous or segmented flow chemical processing.<sup>1</sup> Among these polymer-supported reagents, monoliths,<sup>2</sup> defined as single pieces of uniformly porous material made from organic or inorganic monomers upon precipitation polymerisation, can offer superior chemical efficiency over commonly used bead-based materials.<sup>2k-p</sup> This is due to mass transfer being governed by convective flow rather than diffusion, and by low void volume.<sup>1,2</sup> The well-defined porous structure of monolithic materials exhibits a greater surface functionality and generally allows for higher loadings. Their rigid structure is maintained across a wide range of solvents and conditions due to the high degree of cross linking, thereby facilitating multistep chemical transformations in continuous or under segmented flow conditions.<sup>2</sup>

Several types of polymer-supported reagents or otherwise solid-supported oxidants are known for performing heterogeneous oxidation reactions.<sup>2j,3-9</sup> However, a versatile and robust oxidant on a monolithic support could have numerous applications for continuous flow processes. An oxidant on monolithic support has been reported by Kirschning and co-workers.<sup>2j</sup> Ideally, the monolithic oxidant should be able to perform a wide range of oxidation reactions and preferably should adhere to current environmental standards, being regenerable, atom-efficient, and not engaging heavy metals in the process.

*N*-(*tert*-Butyl)phenylsulfonimidoyl chloride, initially reported by Mukaiyama and co-workers in 2000,<sup>10</sup> and since then applied in various oxidative transformations,<sup>10-12</sup> was

therefore chosen for this study using a monolithic support.<sup>13</sup>

Two different routes to this monolithic *N*-(*tert*-butyl)phenylsulfonimidoyl chloride (**M1**) have been investigated (Scheme 1). Route A employs the monomeric version of sulfenamide **2** in which the crucial sulfur–nitrogen bond is already established. After the polymerisation event, the monolithic sulfenamide **M3** requires oxidation with *N*-*tert*-butyl-*N,N*-dichloroamine<sup>14</sup> or *N*-chlorosuccinimide (NCS). Route B was designed by close analogy to the published procedure for the original reagent.<sup>10</sup> Here, the sulfur–nitrogen bond has to be established once the monolith has been formed in order to yield the sulfonimidoyl chloride functionality. Although route A delivers the monolithic species **M3**, we found that route B gave easier access in terms of synthetic effort necessary to yield the monomeric starting materials (see Supporting Information).



**Scheme 1** Formations and reactions of monolithic *N*-(*tert*-butyl)phenylsulfonimidoyl chloride (**M1**). *Reagents and conditions:* (a) i) *n*-BuLi, THF–hexanes (1:1), –78 °C, 2 h; ii) S<sub>8</sub>, THF–hexanes (1:1), –10 °C, 20 min; iii) Ac<sub>2</sub>O, THF–hexanes (1:1), –78 °C to r.t., 12 h, 72%; (b) i) (MeO)<sub>2</sub>Sn(*n*-Bu)<sub>2</sub>, THF, r.t.; ii) FeCl<sub>3</sub>, THF, r.t., 18 h, 37%; (c) CuI (10 mol%), TMEDA (10 mol%), *t*-BuNH<sub>2</sub>, O<sub>2</sub> (air stream), DMSO, 65 °C, 12–24 h, 20–60%; (d) DVB, AIBN (cat.), hexane–dodecanol (1:2), 80 °C, Vapourtec R4 convection heater, 24 h; (e) DVB, AIBN (cat.), dodecanol, 80 °C, Vapourtec R4 convection heater, 24 h; (f) *t*-BuNCl<sub>2</sub> or NCS (2.1 M in CH<sub>2</sub>Cl<sub>2</sub> in sample loop), PhMe, 0.05 mL/min, 90 °C, multiple runs (see schemes in Tables 1 and 2 for setup); (g) see scheme in Table 1 for both setup and reagents and conditions.

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Monomeric *S*-4-vinylphenyl ethanethioate was obtained from *p*-bromostyrene (**1**) according to the literature protocol<sup>15</sup> and was readily polymerised (typically on a 3.9 mmol scale) using 1,4-divinyl-benzene as cross-linker, 1-dodecanol as porogen and 2,2'-azobis(isobutyronitrile) (AIBN) as radical initiator to yield thioacetate monolith **M2** (Scheme 1). The resulting monolith was then routinely washed with toluene at 65 °C to remove any porogen and any residual monomeric species. Both <sup>1</sup>H NMR spectroscopic analysis of the toluene washings and elemental analysis of a monolith **M2** confirmed complete incorporation of both the monomeric *S*-4-vinylphenyl ethanethioate and the cross-linker. The monolith exhibited very good linear correlations<sup>16</sup> between flow rates and back pressures when incorporated in a continuous flow configuration using commercially available equipment.<sup>17,18</sup> Thioacetate monoliths were prepared in different sizes with an average reproducibility rate of better than 80%.

Functionalisation of the thioacetate monoliths **M2** was achieved in flow using *N*-*tert*-butyl-*N,N*-dichloroamine.<sup>14</sup> Portions (2 mL) of a ca. 2 M solution of the amine in dichloromethane were injected into a 2 mL sample loop and pumped through the heated (90 °C) monolith using toluene as the system solvent (Scheme 1, step f). Upon successful functionalisation, the initially off-white monolith **M2** turns bright yellow, namely, the colour of the original reagent<sup>10</sup> (Figure 1, left and centre). Multiple oxidation reactions using one newly synthesised monolith **M1** (see Supporting Information) as well as regeneration experiments suggest a minimum functional loading of **M1** around 30% with respect to the acetate functionalities theoretically present in **M2**. The results suggest that some of the thioacetate groups are inaccessible to the dichloroamine groups and therefore remain unchanged. Some of the functionalised sites, however, might also be inaccessible for oxidation reactions, thereby making interpretation additionally difficult. An exact determination of the loading of **M1** via elemental analysis was not feasible, as the

**Table 1** Results Obtained Using *N*-(*tert*-Butyl)phenylsulfinimidoyl Chloride Monolith **M1** in Segmented Flow Oxidation Reactions<sup>a</sup>

Entry	Substrate	Temp (°C)	Product	Conv. (%) <sup>b</sup>
1		-78		34
2		0		93 <sup>c</sup>
3		30		~80 <sup>d</sup>
4		0		89 <sup>e</sup>
5		0		>95
6		0		85
7		0		30
8		25		95
9 <sup>f</sup>		0		90–95

<sup>a</sup> Reaction conditions: as outlined in the scheme; typically, 0.25–0.5 mmol experiments were run.

<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy.

<sup>c</sup> Yield after chromatography.

<sup>d</sup> Indications of overoxidation to the acid are present.

<sup>e</sup> Yield after in-line purification using an A15/A21 mixture; purity >90%.

<sup>f</sup> 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used as a base.

sulfonimidoyl species itself is air- and moisture-sensitive. It is noteworthy, however, that the monolithic species **M1** can be stored in a sealed Omnifit® glass column for weeks without a significant loss of activity.

The use of polymeric oxidant **M1** was then examined with respect to its scope and limitations (Table 1), using dry solvent and starting from conditions reported earlier for a bead version of the reagent.<sup>13</sup> To obtain optimum temperatures for the reactions, warming of the monolith was achieved using the built-in heating device,<sup>17,18</sup> whereas the Omnifit® column containing the monolith was simply submerged into a cooling bath to achieve low temperatures. Control experiments were performed to ensure that the oxidations were accomplished by the sulfonimidoyl species and were not a result of the flow conditions chosen (see Supporting Information).

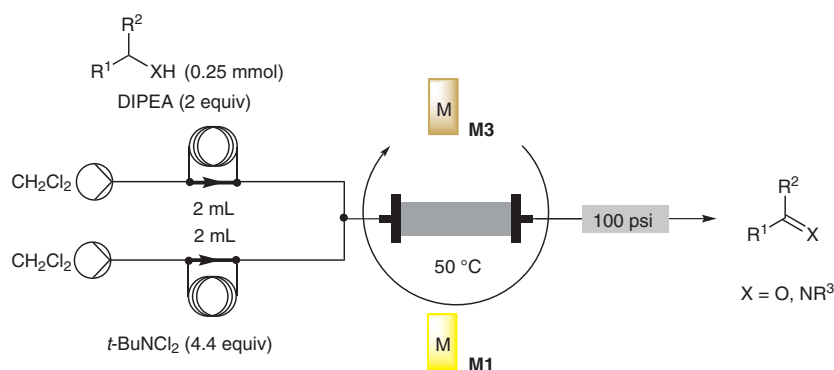
Following optimisation (Table 1, entries 1–3, 7, 8), it is apparent that benzylic and allylic alcohols can be readily oxidized in good conversions at 0 °C (Table 1, entries 1–6). The fact that only low conversion was observed when the monolith was cooled to –78 °C proves the expected lower reactivity of the monolithic reagent when compared

to the original monomeric species. Increased temperatures are needed to successfully oxidise aliphatic alcohols. Additionally, amines were also oxidised successfully to their corresponding imines (Table 1, entry 9). Upon continued use, the monolith changes colour from yellow to light brown (Figure 1, on the right), visually indicating its reduction to the *N-tert*-butylphenylsulfenamide monolith **M3**.

Given that conversions are high, an in-line purification using an Omnifit® column packed with a mixture of A15/A21 resins maintained at ambient temperature was used to scavenge the byproducts (ammonium chloride and residual alcohol) to give the carbonyl compounds in good yields and purities >90% (Table 1, entry 4).

Regeneration and reactivation of the spent monolith **M1** back to the active form **M3** can be achieved by passage of solutions of either *N-tert*-butyl-*N,N*-dichloroamine<sup>14</sup> or NCS through the column. Due to solubility issues, regeneration was typically achieved by pumping 2 mL portions of a 2 M solution of *N-tert*-butyl-*N,N*-dichloroamine through the monolith at elevated temperatures (50 °C) at low flow rates (0.05 mL/min).

**Table 2** Results Obtained Using *N-tert*-Butylphenylsulfenamide Monolith **M3** together with *N-tert*-Butyl-*N,N*-dichloroamine as Co-oxidant in Segmented Flow Oxidation Reactions<sup>a</sup>



Entry	Substrate	Flow rate (mL/min)	Product	Conv. (%) <sup>b</sup>
1		0.025		86 <sup>c</sup>
2 <sup>d</sup>		0.025		trace
3		0.025		56
4		0.025		49
5		0.025		31
6 <sup>e</sup>		0.04		82

<sup>a</sup> Reaction conditions: as outlined in the scheme; typically, 0.25–0.5 mmol experiments were run.

<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy.

<sup>c</sup> Yield after chromatography.

<sup>d</sup> NCS was used as co-oxidant.

<sup>e</sup> 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was used as a base.



**Figure 1** Thioacetate monolith **M2** (left), *N*-(*tert*-butyl)phenylsulfonimidoyl chloride monolith **M1** (centre), *N*-(*tert*-butyl)phenylsulfenamide monolith **M3** (right)

When considering larger-scale applications in flow, it would be convenient to employ monolith **M3** and a suitable co-oxidant simultaneously rather than to regenerate different batches of the monolith. A screening of potential co-oxidants revealed once more that problems arose mainly due to poor solubility and/or limited reactivity on the solid phase. NCS and *N*-*tert*-butyl-*N,N*-dichloroamine were identified as the most efficient reagents, and the combination of **M3** (fully depleted **M1**) and dichloroamine was used for the flow oxidation of a range of activated and nonactivated alcohols (Table 2, see Supporting Information for details).

The experiments discussed above were repeated multiple times by reusing a single monolith fabricated as described earlier (3.9 mmol functional groups). Those experiments show that the monoliths can be used for transformations that exceed the amounts of functionalised groups available on the initial monolith.

In summary, a polystyrene-based monolithic version of *N*-(*tert*-butyl)phenylsulfonimidoyl chloride (**M1**) has been established, that oxidises a broad range of substrates both when applied in stoichiometric and catalytic amounts. Adding an in-line purification step, oxidation products can be obtained in high yields and high purity.

#### General Procedure for Segmented Flow Oxidation Reactions Using **M1**

Solutions (2 mL each) of alcohol (0.25 mmol, 1.00 equiv) and *i*-Pr<sub>2</sub>NEt (0.5 mmol, 2.00 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> were prepared under argon and were either loaded into 2 mL injection loops of a pre-dried<sup>19</sup> Vapourtec R2+ unit<sup>17</sup> or loaded into 2 mL injection loops of a pre-dried<sup>19</sup> Uniqsis FlowSyn.<sup>18</sup> The solutions were mixed in a T-piece, and the resulting reaction stream was pumped through the

monolith **M1**, which was cooled to 0 °C using an ice-water bath (flow rate per pump 0.025 mL min<sup>-1</sup>) using dry CH<sub>2</sub>Cl<sub>2</sub> as the system solvent. The exiting stream is collected for 3–4 h, and the resulting organic phase is concentrated in vacuo to yield the crude products. Some of the crude products have been additionally purified via column chromatography on silica gel, using Et<sub>2</sub>O–light PE.

#### In-Line Workup

To achieve an in-line workup, a scavenger system is used that catches the ammonium salts formed during the reaction. Additionally, small amounts of residual alcohol species can be retained. An Omnifit<sup>®</sup> column of appropriate size (typically the same size as the column for the monolith itself) is filled with a mixture of a polymer-supported base, here A21 (polymer-supported trimethylamine), and a polymer-supported acid, here A15 (polymer-supported sulfonic acid). The scavenger column is placed in-line behind the monolith. The column can be placed in a heating jacket and maintained at 25 °C (using the Vapourtec R4 unit<sup>17</sup> or the Uniqsis FlowSyn<sup>18</sup> column heater).

**Supporting Information** for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

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#### References and Notes

- Recent reviews on flow chemistry and the use of supported reagents in flow chemistry: (a) Baumann, M.; Baxendale, I. R.; Ley, S. V. *Mol. Diversity* **2011**, in press; DOI: 10.1007/s11030-010-9282-1. (b) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675. (c) Mak, X. Y.; Laurino, P.; Seeberger, P. H. *Beilstein J. Org. Chem.* **2009**, *5*, No. 19. (d) Kirschning, A. *Beilstein J. Org. Chem.* **2009**, *5*, No. 15. (e) Baxendale, I. R.; Hayward, J. J.; Lanners, S.; Ley, S. V.; Smith, C. D. *Heterogeneous Reactions*, In *Microreactors in Organic Synthesis and Catalysis*; Wirth, T., Ed.; Wiley-VCH: Weinheim, **2008**, Chap. 4.2, 84. (f) Ley, S. V.; Baxendale, I. R. *Chimia* **2008**, *62*, 162. (g) Baxendale, I. R.; Hayward, J. J.; Ley, S. V. *Comb. Chem. High Throughput Screen.* **2007**, *10*, 802. (h) Ley, S. V.; Baxendale, I. A.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815.
- Monolithic materials have been employed in other work: (a) Smith, C. J.; Smith, C. D.; Nikbin, N.; Ley, S. V.; Baxendale, I. R. *Org. Biomol. Chem.* **2011**, *9*, 1927. (b) Baumann, M.; Baxendale, I. R.; Kirschning, A.; Ley, S. V.; Wegner, J. *Heterocycles* **2011**, *82*, 1297. (c) Baumann, M.; Baxendale, I. R.; Ley, S. V. *Synlett* **2010**, 749. (d) Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N.; Smith, C. D. *Org. Biomol. Chem.* **2008**, *6*, 1587. (e) Nikbin, N.; Ladlow, M.; Ley, S. V. *Org. Process Res. Dev.* **2007**, *11*, 458. (f) Svec, F.; Huber, C. G. *Anal. Chem.* **2006**, *78*, 2100. (g) Altava, B.; Burguete, M. I.; García-Verdugo, E.; Luis, S. V.; Vicent, M. J. *Green Chem.* **2006**, *8*, 717. (h) Kunz, U.; Schönfeld, H.; Kirschning, A.; Solodenko, W. *J. Chromatogr., A* **2003**, *1006*, 241. (i) Solodenko, W.; Kunz, U.; Jas, G.; Kirschning, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1833. (j) Kirschning, A.; Altwicker, C.; Dräger, G.; Harders, J.; Hoffmann, N.; Hoffmann, U.; Schönfeld, H.;

- Solodenko, W.; Kunz, U. *Angew. Chem. Int. Ed.* **2001**, *40*, 3995; *Angew. Chem.* **2001**, *113*, 4118; (k) Tripp, J. A.; Stein, J. A.; Svec, F.; Fréchet, J. M. J. *Org. Lett.* **2000**, *2*, 195. (l) Peters, E. C.; Svec, F.; Fréchet, J. M. J. *Adv. Mater.* **1999**, *11*, 1169. (m) Viklund, C.; Svec, F.; Fréchet, J. M. J.; Irgum, K. *Chem. Mater.* **1996**, *8*, 744. (n) Svec, F.; Fréchet, J. M. J. *Chem. Mater.* **1995**, *7*, 707. (o) Wang, Q. C.; Svec, F.; Fréchet, J. M. J. *Anal. Chem.* **1995**, *67*, 670. (p) Svec, F.; Fréchet, J. M. J. *Anal. Chem.* **1992**, *64*, 820.
- (3) Early heavy-metal-based applications: (a) Gardillo, G.; Orena, M.; Sandri, S. *Tetrahedron Lett.* **1976**, *17*, 3985. (b) Griffith, W. P.; Ley, S. V.; Whitcomb, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1981**, 1625.
- (4) Polymer-supported TPAP: (a) Hinzen, B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1907. (b) Ley, S. V.; Bolli, M. H.; Hinzen, B.; Gervois, A. G.; Hall, B. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2239. (c) Hinzen, B.; Lenz, R.; Ley, S. V. *Synthesis* **1998**, 977.
- (5) Iron oxides mixed with solid oxidants like CrO<sub>2</sub> and NiO<sub>2</sub>: Wegner, J.; Ceylan, S.; Friese, C.; Kirschning, A. *Eur. J. Org. Chem.* **2010**, *23*, 4372.
- (6) KMnO<sub>4</sub>-based: Sedelmeier, J.; Ley, S. V.; Baxendale, I. R.; Baumann, M. *Org. Lett.* **2010**, *12*, 2618.
- (7) Polymer-supported IBX: Sorg, G.; Mengel, A.; Jung, G.; Rademann, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4395; *Angew. Chem.* **2001**, *113*, 4532.
- (8) Polymer-supported TEMPO: (a) Bolm, C.; Fey, T. *Chem. Commun.* **1999**, 1795. (b) Weik, S.; Nicholson, G.; Jung, G.; Rademann, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 1436; *Angew. Chem.* **2001**, *113*, 1489.
- (9) Polymer-supported Swern-type oxidation: (a) Liu, Y.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 7856. (b) Harris, J. M.; Liu, Y.; Chai, S.; Andrews, M. D.; Vederas, J. C. *J. Org. Chem.* **1998**, *63*, 2407.
- (10) Mukaiyama, T.; Matsuo, J.; Yanagisawa, M. *Bull. Chem. Soc. Jpn.* **2000**, 1072.
- (11) (a) Mukaiyama, T.; Kawana, A.; Fukuda, Y.; Matsuo, J. *Bull. Chem. Soc. Jpn.* **2001**, 390. (b) Matsuo, J.; Mukaiyama, T.; Kitagawa, H. *ARKIVOC* **2001**, *x*, 58. (c) Kerr, W. J.; Pearson, C. M.; Thurston, G. J. *Org. Biomol. Chem.* **2006**, *4*, 47.
- (12) (a) Matsuo, J.; Iida, D.; Yamanaka, H.; Mukaiyama, T. *Chem. Lett.* **2002**, 182. (b) Matsuo, J.; Iida, D.; Yamanaka, H.; Mukaiyama, T. *Tetrahedron* **2003**, *59*, 6739.
- (13) For a supported version of *N*-(*tert*-butyl)phenylsulfonimidoyl chloride in bead form: (a) Matsuo, J.; Kawana, A.; Pudhom, K.; Mukaiyama, T. *Chem. Lett.* **2002**, 250. (b) Matsuo, J.; Kawana, A.; Yanamaka, H.; Kamiyama, H. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1433.
- (14) Prepared according to: Roberts, T. J.; Rittberg, B. R.; Kovacic, P. *J. Org. Chem.* **1981**, *46*, 4111.
- (15) Al-Hourani, B. J.; Bravo-Vasquez, J. P.; High, L. R. H.; Fenniri, H. *Tetrahedron* **2007**, *48*, 9144.
- (16) In cases where the correlation is not strictly linear, the monolith is likely to be of poor quality and should be discarded (see Supporting Information for details).
- (17) The Vapourtec R2+ and R4 units are available from Vapourtec Ltd, Park Farm Business Centre, Fornham St Genevieve, Bury St Edmunds, Suffolk, IP28 6TS, UK. Website: [www.vapourtec.co.uk](http://www.vapourtec.co.uk). See: Baumann, M.; Baxendale, I. R.; Ley, S. V.; Smith, S. D.; Tranmer, G. K. *Org. Lett.* **2006**, *8*, 5231.
- (18) The FlowSyn unit is available from Uniqsis Ltd., 29 Station Road, Shepreth, Cambridgeshire, SG8 6GB, UK. Website: [www.uniqsis.com](http://www.uniqsis.com). See the following publication for the use of this platform as a scale-up facility: Palmieri, A.; Ley, S. V.; Hammond, K.; Polyzos, A.; Baxendale, I. R. *Tetrahedron Lett.* **2009**, *50*, 3287.
- (19) For a reliable procedure to 'dry' flow chemistry reactor arrangements, see: Carter, C. F.; Lange, H.; Sakai, D.; Baxendale, I. R.; Ley, S. V. *Chem. Eur. J.* **2011**, *17*, 3398.