



Cite this: *Chem. Commun.*, 2015, 51, 334

Received 10th October 2014,  
Accepted 7th November 2014

DOI: 10.1039/c4cc07913b

www.rsc.org/chemcomm

## The direct $\alpha$ -C(sp<sup>3</sup>)-H functionalisation of *N*-aryl tetrahydroisoquinolines *via* an iron-catalysed aerobic nitro-Mannich reaction and continuous flow processing†‡

Martin Brzozowski, Jose A. Forni, G. Paul Savage and Anastasios Polyzos\*

**An efficient nitro-Mannich type direct  $\alpha$ -C(sp<sup>3</sup>)-H functionalisation of *N*-aryl-1,2,3,4-tetrahydroisoquinolines catalysed by simple iron salts in combination with O<sub>2</sub> as the terminal oxidant is described. The use of a Teflon AF-2400 membrane Tube-in-Tube reactor under continuous flow conditions allowed for considerable process intensification to be achieved relative to previous batch methods.**

Transition metal-catalysed functionalisation of C-H bonds has emerged as a powerful strategy for the development of molecular complexity.<sup>1,2</sup> Compared to traditional cross-coupling methods, this strategy removes the need for pre-functionalisation of the coupling partners and thus provides an atom economical and an environmentally benign synthetic alternative.<sup>3</sup> Due to the ubiquitous nature of C-H bonds, site selective functionalisation of one C-H bond in the presence of many others remains a considerable challenge.<sup>4</sup>

Heteroatom  $\alpha$ -C(sp<sup>3</sup>)-H bonds exhibit innate reactivity as they can be selectively oxidised and subsequently reacted with nucleophiles to give  $\alpha$ -functionalised products.<sup>5</sup> Oxidative functionalisation of amine  $\alpha$ -C(sp<sup>3</sup>)-H bonds has proven to be effective for a range of C-C and C-X bond forming transformations.<sup>6</sup> Oxidation is typically achieved with a combination of transition metal catalyst<sup>7</sup> and terminal oxidant. Although organic peroxides have by far been the most common oxidants employed, molecular O<sub>2</sub> has also been shown to be a mild oxidant and provides an attractive choice for the development of scalable, greener synthetic routes.<sup>8</sup>

Copper-catalysed amine  $\alpha$ -C(sp<sup>3</sup>)-H functionalisation with O<sub>2</sub> has been demonstrated to be a general approach, with a broad scope of nucleophilic partners exhibiting reactivity at room temperature.<sup>8b</sup> In contrast, iron catalysts for amine  $\alpha$ -C(sp<sup>3</sup>)-H functionalisation suffer from reduced reactivity, necessitating the use of peroxide oxidants,

increased catalyst loading, and elevated reaction temperatures.<sup>9</sup> Efficient iron-catalysed methodologies using O<sub>2</sub> as the oxidant are thus relatively scarce.<sup>10</sup>

The relative abundance and low-toxicity of iron has led to our interest in exploring simple iron salts<sup>11</sup> and O<sub>2</sub> as a sustainable catalyst/oxidant combination for the nucleophilic addition of nitroalkanes to imines (nitro-Mannich reaction).<sup>12</sup> The  $\beta$ -nitroamine products are valuable building blocks as they contain a vicinal nitrogen motif that can be selectively manipulated to gain access to 1,2-diamines (by nitro reduction) and  $\alpha$ -amino-carbonyls (*via* the Nef reaction).

Shirakawa *et al.* have reported the nitro-Mannich reaction of amines with FeCl<sub>3</sub> and (*t*-BuO)<sub>2</sub> and Li *et al.* have employed magnetic Fe nanoparticles with O<sub>2</sub> however a robust methodology exploiting inexpensive iron salts with O<sub>2</sub> is currently lacking.<sup>13</sup> Recently Doyle and co-workers described the use of FeCl<sub>3</sub> and O<sub>2</sub> for the vinylogous Mannich reaction of *N,N*-dialkylanilines with siloxyfurans.<sup>10b</sup> These reaction conditions were extended to the nitro-Mannich reaction by performing the reaction in neat nitroalkane for 5–7 days.

The advantages of continuous flow processing in enhancing chemical synthesis are well documented.<sup>14</sup> We envisaged that a continuous flow method would allow us to overcome the poor efficiency observed in Fe/O<sub>2</sub>-mediated nitro-Mannich reactions under batch conditions.

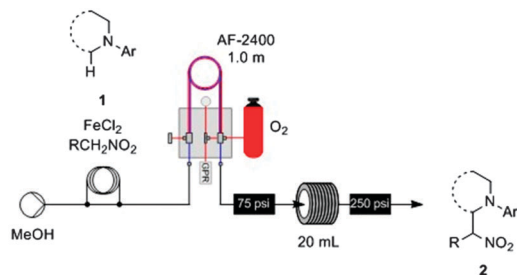
Recently, the Ley group reported the development and use of a Teflon AF-2400 membrane-based Tube-in-Tube gas-liquid reactor that allowed for efficient gas delivery to a flow stream.<sup>15,16</sup> This reactor has been successfully applied to a range of transformations employing gaseous reagents.<sup>17</sup>

Herein we report the Fe/O<sub>2</sub>-mediated nitro-Mannich reaction of *N*-aryl tetrahydroisoquinolines facilitated by continuous flow processing. The flow configuration consisted of a Vapourtec R2+/R4 module fitted with a Teflon AF-2400 Tube-in-Tube membrane reactor (Scheme 1). A 75 psi back pressure regulator was placed immediately after the gas-liquid reactor to preclude in-line degassing. The reaction stream was then directed through two 10 mL stainless steel heated reactor coils<sup>18</sup> followed by a

CSIRO Manufacturing Flagship, Bayview Avenue, Clayton 3168, Victoria, Australia.  
E-mail: tash.polyzos@csiro.au

† Part of this research was undertaken on the MX1 beamline at the Australian Synchrotron, Victoria, Australia.

‡ Electronic supplementary information (ESI) available: Experimental procedures and product characterisation. CCDC 1027557. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc07913b



**Scheme 1** Flow configuration for the aerobic nitro-Mannich reaction of *N*-aryl tetrahydroisoquinolines.

**Table 1** Selected optimisation screening of the aerobic nitro-Mannich reaction of *N*-phenyl tetrahydroisoquinoline **1a** in flow<sup>a</sup>

Entry	Cat. loading (mol%)	Temp. (°C)	O <sub>2</sub> pressure (bar)	Conv. <sup>b</sup> (%)
1	10	50	7	37
2	10	70	7	87
3	10	90	7	100
4	1	90	7	11
5	2	90	7	26
6	5	90	7	40
7	10	90	1	18
8	10	90	3	36
9	10	90	5	72

<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), FeCl<sub>2</sub>, MeNO<sub>2</sub> (5 equiv.), MeOH (2 mL), O<sub>2</sub>, T<sub>R</sub> = 1 h. <sup>b</sup> Determined by <sup>1</sup>H NMR.

250 psi back pressure regulator. We began our investigation by optimising the processing parameters for the aerobic nitro-Mannich reaction of *N*-phenyl tetrahydroisoquinoline **1a** with nitromethane catalysed by iron(II) chloride (Table 1).

Methanol was chosen as the solvent as it has been previously shown to assist the reaction by forming a hemiaminal intermediate that provides a reservoir for the reactive iminium species<sup>8a</sup> and also due to its effective solvation of the reaction components, which improved the compatibility with flow synthesis through the furnishing of a homogeneous reaction mixture. The optimisation data showed that the reaction exhibited an approximately linear dependence on temperature, with full conversion observed at 90 °C (entry 3, Table 1). Comparable results were obtained with Fe(III) and Cu(II) salts (see ESI†). Decreases in the catalyst loading, or O<sub>2</sub> pressure were not tolerated and led to a reduction in conversion (entries 4–9, Table 1). In addition, reducing the equivalents of nitromethane led to a corresponding reduction in conversion. Although 5 equivalents of the pronucleophile was necessary to furnish acceptable conversion to the nitro-Mannich adduct, this represents a considerably low concentration and the safety implications are instructive. It should be noted that the reaction was found to be very clean in all cases, with no side products observed by TLC or <sup>1</sup>H NMR.

The conditions from entry 3 were selected as optimal for further investigation and under these conditions the nitro-Mannich adduct **2a** was isolated in 72% yield after column chromatography. This result established a considerable reduction in reaction time in comparison to the previously reported Fe/O<sub>2</sub>-mediated nitro-Mannich batch reaction of **1ab**, which required a reaction time of 5 days for full conversion.<sup>10b</sup>

In order to demonstrate the scope and utility of the iron-catalysed aerobic nitro-Mannich flow reaction, a series of substituted tetrahydroisoquinolines were coupled with nitroalkanes using the developed reaction conditions (Table 2).

Initial attempts to access nitro-Mannich adducts other than **2a** gave disappointingly poor isolated yields (<30%) despite full consumption of the starting amine. Slow turnover of the nitroalkane to the nitronate anion was hypothesised to be a limiting factor and consistent with the work of Todd<sup>19</sup> and Doyle,<sup>10b</sup>

**Table 2** Scope of continuous flow iron-catalysed aerobic nitro-Mannich reaction<sup>a,b</sup>

1. FeCl <sub>2</sub> (10 mol%) RCH <sub>2</sub> NO <sub>2</sub> (5 equiv.)	2. Et <sub>3</sub> N (2 equiv.)	3. O <sub>2</sub> (7 bar), MeOH 90 °C, T <sub>R</sub> = 2 h	4. Product
<b>1a-o</b>			<b>2a-o</b>
<b>2a<sup>c</sup></b>			72% (68%) <sup>d</sup>
<b>2b</b>			65%
<b>2c</b>			77%
<b>2d</b>			39%
<b>2e</b>			67%
<b>2f</b>			58%
<b>2g</b>			56%
<b>2h</b>			64%
<b>2i<sup>e</sup></b>			48%
<b>2j</b>			73%
<b>2k</b>			71%
<b>2l</b>			54%
<b>2m</b>			31% brsm <sup>f</sup>
<b>2n</b>			60% brsm <sup>f</sup>
<b>2o</b>			70% brsm <sup>f</sup>

<sup>a</sup> Reaction conditions: **1** (0.5–1.0 mmol), FeCl<sub>2</sub> (10 mol%), RCH<sub>2</sub>NO<sub>2</sub> (5 equiv.), MeOH (0.05 M), O<sub>2</sub> (7 bar), 90 °C, T<sub>R</sub> = 2 h unless otherwise stated. All reactions quenched with 2 equiv. Et<sub>3</sub>N. <sup>b</sup> Isolated yields after column chromatography. <sup>c</sup> Residence time of 1.5 h. <sup>d</sup> 11.7 mmol scale. <sup>e</sup> Loaded onto sample loop in 9 : 1 MeOH/THF. <sup>f</sup> Based on recovered starting material.

we found that by quenching the reaction with base (2 equivalents of Et<sub>3</sub>N), the desired nitro-Mannich adducts were obtained in consistently good yields.


Reactions employing nitroethane (**2b**, **2d**) were discernibly slower than those with nitromethane, with <85% conversion typically obtained after 1 h. Thus, the residence time for all couplings was increased to 2 h to allow for full conversion.

Electron-rich tetrahydroisoquinolines with alkyl or ether substituted *N*-aryl groups reacted smoothly, giving the nitro-Mannich products in good yields (**2c–i**). *N*-Naphthyl substrate **1n** reacted cleanly, albeit slowly due to steric hinderance at the C1 oxidation site. Substrates bearing mildly electron-withdrawing substituents were well tolerated (**2j–l**), although *ortho*-fluorine substitution of the *N*-aryl ring (**2m**) significantly slowed the reaction and also gave an unidentified side product. More strongly electron-withdrawing substitution caused the reaction to fail completely,<sup>20</sup> consistent with our mechanistic hypothesis of a single electron transfer (SET) oxidation. Notably, the 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline scaffold, which is a common structural motif in bioactive compounds, was amenable to the reaction conditions (**2o**).

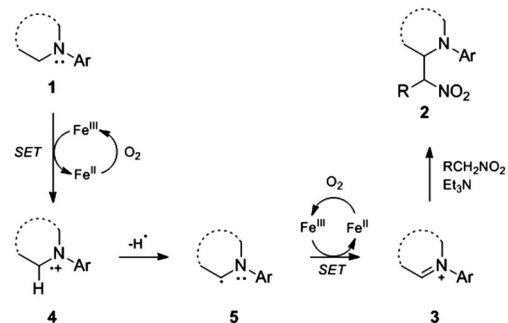
To demonstrate the scalability of the flow protocol to preparative quantities,<sup>21</sup> a gram scale run was performed. Pleasingly, 11.7 mmol of substrate **1ab** was processed continuously to provide **2a** in 68% isolated yield (2.13 g) after purification, consistent with yields achieved on smaller scale.

Doyle and Klusmann both have postulated the initiation step in transition metal-catalysed aerobic  $\alpha$ -functionalisation of amines to be a single electron oxidation to yield an amine radical cation that is then further oxidised to an iminium species.<sup>8b,10b</sup> To probe the reaction mechanism several control experiments were performed. Purging the reaction with nitrogen afforded trace amounts of the nitro-Mannich product (entry 1, Table 3). Furthermore, when the reaction was conducted under nitrogen with 10 mol% Fe(III), a 9% yield of product was observed (entry 2, Table 3), indicating that Fe(III) may be the catalytically relevant oxidation state of iron. Addition of BHT as a radical trapping agent resulted in a reduction of product yield to 33% (entry 3, Table 3), suggesting that the reaction plausibly proceeds through a radical pathway.

Table 3 Control experiments to probe reaction mechanism<sup>a</sup>

		
Entry	Changes from standard conditions	Yield <b>2a</b> <sup>b</sup> (%)
1	Under N <sub>2</sub>	—
2	Under N <sub>2</sub> , FeCl <sub>3</sub> (10 mol%)	9
3	BHT (1 equiv.)	33
4	No MeNO <sub>2</sub> , FeCl <sub>2</sub> (2 equiv.)	Quant. (3)

<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), MeNO<sub>2</sub> (5 equiv.), MeOH (1 mL), 2 h, flow rate = 0.167 mL min<sup>-1</sup>. <sup>b</sup> Determined by <sup>1</sup>H NMR.



Scheme 2 Proposed mechanism for Fe-catalysed aerobic nitro-Mannich reaction.

We next attempted to obtain evidence of an iminium intermediate (**3**). In the absence of nitroalkane, stoichiometric Fe(II) gave quantitative conversion to the iminium trichloroferrate(II) salt [3]<sup>+</sup>[FeCl<sub>3</sub>]<sup>-</sup>, which was observed by ESI MS (entry 4, Table 3). Upon standing, crystals grew from the reaction mixture that were characterised by X-ray crystallography (XRD) as the ( $\mu$ -oxo)bis[trichloroferrate(II)] salt 2[3]<sup>+</sup>[Fe<sub>2</sub>OCl<sub>6</sub>]<sup>2-</sup>.

On the basis of these considerations we tentatively propose a potential mechanism (Scheme 2). The process is initiated by a single electron transfer (SET) from the amine substrate to Fe(III) to give the amine radical cation **4**, which can undergo hydrogen atom abstraction and a second SET step in an analogous fashion to the non-classical Polonovski reaction. Nucleophilic attack on the resulting iminium intermediate **3** by a nitronate anion yields the  $\alpha$ -alkylated product **2**, with regeneration of the Fe(III) catalyst by molecular oxygen.

In summary, we have reported the efficient aerobic nitro-Mannich reaction of *N*-aryl tetrahydroisoquinolines using simple Fe salts and molecular O<sub>2</sub>. The use of continuous flow processing allowed for significant process intensification to be achieved relative to batch methodology. Preliminary studies have shown some success with other nucleophilic partners and further investigations to expand the reaction scope are currently underway.

The authors would like to acknowledge Dr David Turner, School of Chemistry, Monash University, Clayton 3168, Victoria, Australia for providing XRD crystallography data.

## Notes and references

- For general reviews on transition metal-catalysed C–H functionalisation see: (a) K. Godula and D. Sames, *Science*, 2006, **312**, 67; (b) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242; (c) O. Baudoin, *Chem. Soc. Rev.*, 2011, **40**, 4902; (d) A. A. Kulkarni and O. Daugulis, *Synthesis*, 2009, 4087; (e) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (f) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74; (g) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer and O. Baudoin, *Chem. – Eur. J.*, 2010, **16**, 2654.
- For reviews on C–H functionalisation in total synthesis see: (a) L. McMurry, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885; (b) W. R. Gutekunst and P. S. Baran, *Chem. Soc. Rev.*, 2011, **40**, 1976.
- P. Anastas and N. Eghbali, *Chem. Soc. Rev.*, 2010, **39**, 301.
- For selected approaches to achieving site selectivity in C–H functionalisation see: (a) J. A. Labinger and J. E. Bercaw, *Nature*, 2002, **417**, 507; (b) T. Brückl, R. D. Baxter, Y. Ishihara and P. S. Baran, *Acc. Chem. Res.*, 2012, **45**, 826; (c) K. M. Engle, T.-S. Mei, M. Wasa and

- J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788; (d) S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936; (e) D. Lapointe, T. Markiewicz, C. J. Whipp, A. Toderian and K. Fagnou, *J. Org. Chem.*, 2011, **76**, 749; (f) H. M. L. Davies and D. Morton, *Chem. Soc. Rev.*, 2011, **40**, 1857.
- 5 For reviews on oxidative  $\alpha$ -C(sp<sup>3</sup>)-H functionalisation see: (a) K. R. Campos, *Chem. Soc. Rev.*, 2007, **36**, 1069; (b) C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335; (c) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel and B. U. W. Maes, *Chem. – Eur. J.*, 2012, **18**, 10092; (d) S.-Y. Zhang, F.-M. Zhang and Y.-Q. Tu, *Chem. Soc. Rev.*, 2011, **40**, 1937.
- 6 For selected examples of sp<sup>3</sup>-sp coupling see: (a) S. I. Murahashi, N. Komiya, H. Terai and T. Nakae, *J. Am. Chem. Soc.*, 2003, **125**, 15312; (b) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2004, **126**, 11810; (c) W. Han and A. R. Ofial, *Chem. Commun.*, 2009, 5024; (d) Z. Li, P. D. MacLeod and C.-J. Li, *Tetrahedron: Asymmetry*, 2006, **17**, 590. For sp<sup>3</sup>-sp<sup>2</sup> coupling see: (e) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2005, **127**, 6968; (f) O. Baslé and C.-J. Li, *Org. Lett.*, 2008, **10**, 3661; (g) M. Ghobrial, M. Schnürch and M. D. Mihovilovic, *J. Org. Chem.*, 2011, **76**, 8781; (h) M. Ghobrial, K. Harhammer, M. D. Mihovilovic and M. Schnürch, *Chem. Commun.*, 2010, **46**, 8836. For sp<sup>3</sup>-sp<sup>3</sup> coupling see: (i) Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2005, **127**, 3672; (j) O. Baslé and C.-J. Li, *Green Chem.*, 2007, **9**, 1047; (k) Z. Li and C.-J. Li, *Eur. J. Org. Chem.*, 2005, 3173; (l) A. Yu, Z. Gu, D. Chen, W. He, P. Tan and J. Xiang, *Catal. Commun.*, 2009, **11**, 162. For C-X coupling see: (m) W. Han and A. R. Ofial, *Chem. Commun.*, 2009, 6023; (n) O. Baslé and C.-J. Li, *Chem. Commun.*, 2009, 4124; (o) K. Alagiri, P. Devadig and K. R. Prabhu, *Tetrahedron Lett.*, 2012, **53**, 1456; (p) A. Modak, U. Dutta, R. Kancherla, S. Maity, M. Bhadra, S. M. Mobin and D. Maity, *Org. Lett.*, 2014, **16**, 2602.
- 7 For ruthenium see: (a) S.-I. Murahashi, T. Nakae, H. Terai and N. Komiya, *J. Am. Chem. Soc.*, 2008, **130**, 11005. For copper see: (b) Z. Li and C.-J. Li, *Org. Lett.*, 2004, **6**, 4997; (c) Z. Li, D. S. Bohle and C.-J. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 8928; (d) L. Zhao and C.-J. Li, *Angew. Chem., Int. Ed.*, 2008, **47**, 7075; (e) L. Zhao, O. Baslé and C.-J. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **106**, 4106. For iron see: (f) P. Liu, Z. Wang, J. Lin and X. Hu, *Eur. J. Org. Chem.*, 2012, 1583; (g) K. Li, G. Tan, J. Huang, F. Song and J. You, *Angew. Chem., Int. Ed.*, 2013, **52**, 12942; (h) C. M. R. Volla and P. Vogel, *Org. Lett.*, 2009, **11**, 1701. For vanadium see: (i) S. Singhal, S. L. Jain and B. Sain, *Chem. Commun.*, 2009, 2371; (j) K. Alagiri, G. S. R. Kumara and K. R. Prabhu, *Chem. Commun.*, 2011, **47**, 11787; (k) K. M. Jones, P. Karier and M. Klusmann, *ChemCatChem*, 2012, **4**, 51. For molybdenum see: (l) K. Alagiri and K. R. Prabhu, *Org. Biomol. Chem.*, 2012, **10**, 835. For gold see: (m) J. Xie, H. Li, Q. Xue, Y. Cheng and C. Zhu, *Adv. Synth. Catal.*, 2012, **354**, 1646; (n) Y. Zhang, S. Luo, B. Feng and C. Zhu, *Chin. J. Chem.*, 2012, **30**, 2741. For platinum see: (o) X.-Z. Shu, Y.-F. Yang, X.-F. Xia, F.-G. Ji, X.-Y. Liu and Y.-M. Liang, *Org. Biomol. Chem.*, 2010, **8**, 4077. For cobalt see: (p) N. Sakai, A. Mutsuro, R. Ikeda and T. Konakahara, *Synlett*, 2013, 1283; (q) C. Feng, J.-H. Su, Y. Yan, F. Guo and Z. Wang, *Org. Biomol. Chem.*, 2013, **11**, 6691. For zinc see: (r) T. Sugiishi and H. Nakamura, *J. Am. Chem. Soc.*, 2012, **134**, 2504.
- 8 See ref. 6j-l and (a) E. Boess, D. Sureshkumar, A. Sud, C. Wirtz, C. Farès and M. Klusmann, *J. Am. Chem. Soc.*, 2011, **133**, 8106; (b) E. Boess, C. Schmitz and M. Klusmann, *J. Am. Chem. Soc.*, 2012, **134**, 5317.
- 9 See: ref. 6c, 6m, 7f, 7g and h and (a) W. Han, P. Mayer and A. R. Ofial, *Adv. Synth. Catal.*, 2010, **352**, 1667; (b) A. Wagner, W. Han, P. Mayer and A. R. Ofial, *Adv. Synth. Catal.*, 2013, **355**, 3058; (c) W. Shirakawa, N. Uchiyama and T. Hayashi, *J. Org. Chem.*, 2011, **76**, 25; (d) H. Richter and O. G. Mancheño, *Org. Lett.*, 2011, **13**, 6066.
- 10 (a) S. Murata, K. Teramoto, M. Miura and M. Nomura, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 1297; (b) M. O. Ratnikov, X. Xu and M. P. Doyle, *J. Am. Chem. Soc.*, 2013, **135**, 9475.
- 11 Y. Nakano, G. P. Savage, S. Saubern, P. J. Scammells and A. Polyzos, *Aust. J. Chem.*, 2013, **66**, 179.
- 12 A. Noble and J. C. Anderson, *Chem. Rev.*, 2013, **113**, 2887.
- 13 (a) E. Shirakawa, T. Yoneda, K. Moriyam, K. Ota, N. Uchiyama, R. Nishikawa and T. Hayashi, *Chem. Lett.*, 2011, **40**, 1041; (b) T. Zeng, G. Song, A. Moores and C.-J. Li, *Synlett*, 2010, 2002; (c) R. Hudson, S. Ishikawa, C.-J. Li and A. Moores, *Synlett*, 2013, 1637.
- 14 S. G. Newman and K. F. Jensen, *Green Chem.*, 2013, **15**, 1456.
- 15 (a) M. O'Brien, I. R. Baxendale and S. V. Ley, *Org. Lett.*, 2010, **12**, 1596; (b) A. Polyzos, M. O'Brien, T. P. Petersen, I. R. Baxendale and S. V. Ley, *Angew. Chem., Int. Ed.*, 2011, **50**, 1190.
- 16 For an account of the development of the Tube-in-Tube reactor see: M. Brzozowski, M. O'Brien, S. V. Ley and A. Polyzos, *Acc. Chem. Res.*, 2014, submitted.
- 17 For CO see: (a) P. Koos, U. Gross, A. Polyzos, M. O'Brien, I. R. Baxendale and S. V. Ley, *Org. Biomol. Chem.*, 2011, **9**, 6903; (b) U. Gross, P. Koos, M. O'Brien, A. Polyzos and S. V. Ley, *Eur. J. Org. Chem.*, 2014, 6418. For H<sub>2</sub> see: (c) M. O'Brien, N. Taylor, A. Polyzos, I. R. Baxendale and S. V. Ley, *Chem. Sci.*, 2011, **2**, 1250; (d) S. Newton, S. V. Ley, E. Casas Arcé and D. M. Grainger, *Adv. Synth. Catal.*, 2012, **354**, 1805; (e) S. Newton, C. F. Carter, C. M. Pearson, L. de C. Alves, H. Lange, P. Thansandote and S. V. Ley, *Angew. Chem., Int. Ed.*, 2014, **53**, 4915. For C<sub>2</sub>H<sub>4</sub> see: (f) S. L. Bourne, P. Koos, M. O'Brien, B. Martin, B. Schenkel, I. R. Baxendale and S. V. Ley, *Synlett*, 2011, 2643; (g) S. L. Bourne, M. O'Brien, S. Kasinathan, P. Koos, P. Tolstoy, D. X. Hu, R. W. Bates, B. Martin, B. Schenkel and S. V. Ley, *ChemCatChem*, 2013, **5**, 159. For NH<sub>3</sub> see: (h) P. B. Cranwell, M. O'Brien, D. L. Browne, P. Koos, A. Polyzos, M. Peña-López and S. V. Ley, *Org. Biomol. Chem.*, 2012, **10**, 5774; (i) D. L. Browne, M. O'Brien, P. Koos, P. B. Cranwell, A. Polyzos and S. V. Ley, *Synlett*, 2012, 1402; (j) J. C. Pastre, D. L. Browne, M. O'Brien and S. V. Ley, *Org. Process Res. Dev.*, 2013, **17**, 1183. For O<sub>2</sub> see: (k) T. P. Petersen, A. Polyzos, M. O'Brien, T. Ulven, I. R. Baxendale and S. V. Ley, *ChemSusChem*, 2012, **5**, 274; (l) S. L. Bourne and S. V. Ley, *Adv. Synth. Catal.*, 2013, **355**, 1905.
- 18 The use of stainless steel reactor coils is critical as significantly decreased yields were observed using standard PFA coils.
- 19 (a) A. S.-K. Tsang and M. H. Todd, *Tetrahedron*, 2009, **50**, 1199; (b) A. S.-K. Tsang, P. Jensen, J. M. Hook, A. S. K. Hashmi and M. H. Todd, *Pure Appl. Chem.*, 2011, **83**, 655.
- 20 No reaction was observed with 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub><sup>-</sup>, 4-COMeC<sub>6</sub>H<sub>4</sub><sup>-</sup> and 2-pyridyl N-aryl tetrahydroisoquinoline substrates.
- 21 For an investigation of mass transport performance and scalability of the Tube-in-Tube reactor see L. Yang and K. F. Jensen, *Org. Process Res. Dev.*, 2013, **17**, 927.