ChemComm

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| Journal: | *ChemComm* |
| Manuscript ID: | CC-COM-10-2014-007913.R1 |
| Article Type: | Communication |
| Date Submitted by the Author: | 06-Nov-2014 |
| Complete List of Authors: | Brzozowski, Martin; CSRIO, Manufacturing Flagship<br>Forni, Jose; CSRIO, Manufacturing Flagship<br>Savage, Gregory; CSIRO, Materials Science and Engineering<br>Polyzos, Anastasios; CSIRO, Materials Science and Engineering |
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Journal Name

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# The Direct α-C(sp$^3$)-H Functionalisation of *N*-Aryl Tetrahydroisoquinolines via an Iron-Catalysed Aerobic Nitro-Mannich Reaction and Continuous Flow Processing

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org

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**An efficient nitro-Mannich type direct α-C(sp$^3$)-H functionalisation of *N*-aryl-1,2,3,4-tetrahydroisoquinolines catalysed by simple iron salts in combination with $O_2$ 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.[1,2] 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.[3] 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.[4]

Heteroatom α-C(sp$^3$)-H bonds exhibit innate reactivity as they can be selectively oxidised and subsequently reacted with nucleophiles to give α-functionalised products.[5] Oxidative functionalisation of amine α-C(sp$^3$)-H bonds has proven to be effective for a range of C-C and C-X bond forming transformations.[6] Oxidation is typically achieved with a combination of transition metal catalyst[7] and terminal oxidant. Although organic peroxides have by far been the most common oxidants employed, molecular $O_2$ has also been shown to be a mild oxidant and provides an attractive choice for the development of scalable, greener synthetic routes.[8]

Copper-catalysed amine α-C(sp$^3$)-H functionalisation with $O_2$ has been demonstrated to be a general approach, with a broad scope of nucleophilic partners exhibiting reactivity at room temperature.[8b] In contrast, iron catalysts for amine α-C(sp$^3$)-H functionalisation suffer from reduced reactivity, necessitating the use of peroxide oxidants, increased catalyst loading, and elevated reaction temperatures.[9] Efficient iron-catalysed methodologies using $O_2$ as the oxidant are thus relatively scarce.[10]

The relative abundance and low-toxicity of iron has led to our interest in exploring simple iron salts[11] and $O_2$ as a sustainable catalyst/oxidant combination for the nucleophilic addition of nitroalkanes to imines (nitro-Mannich reaction).[12] The *β*-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 α-aminocarbonyls (via the Nef reaction).

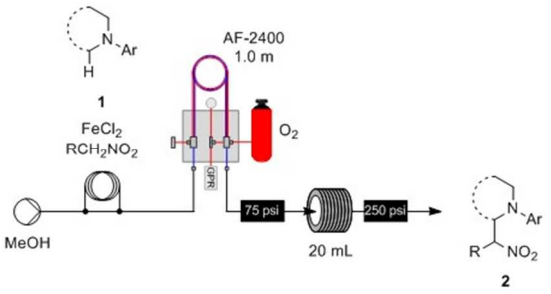
Shirakawa *et al.* have reported the nitro-Mannich reaction of amines with $FeCl_3$ and $(t\text{-BuO})_2$ and Li *et al.* have employed magnetic Fe nanoparticles with $O_2$ however a robust methodology exploiting inexpensive iron salts with $O_2$ is currently lacking.[13] Recently Doyle and co-workers described the use of $FeCl_3$ and $O_2$ for the vinylogous Mannich reaction of *N*,*N*-dialkylanilines with siloxyfurans.[10b] 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.[14] We envisaged that a continuous flow method would allow us to overcome the poor efficiency observed in Fe/$O_2$-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.[15,16] This reactor has been successfully applied to a range of transformations employing gaseous reagents.[17]

Herein we report the Fe/$O_2$-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

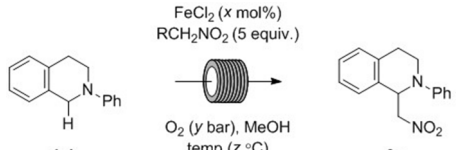
coils[18] followed by a 250 psi back pressure regulator. We began our investigation by optimising the processing parameters for the aerobic nitro-Mannich reaction of *N*-phenyl tetrahydroisoquinoline **1ab** with nitromethane catalysed by iron(II) chloride (Table 1).




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

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[8a] 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 $O_2$ pressure were not tolerated and lead 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 pronucelophile 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 $^1$H NMR.

**Table 1** Selected optimisation screening of the aerobic nitro-Mannich reaction of *N*-phenyl tetrahydroisoquinoline **1a** in flow.[a]



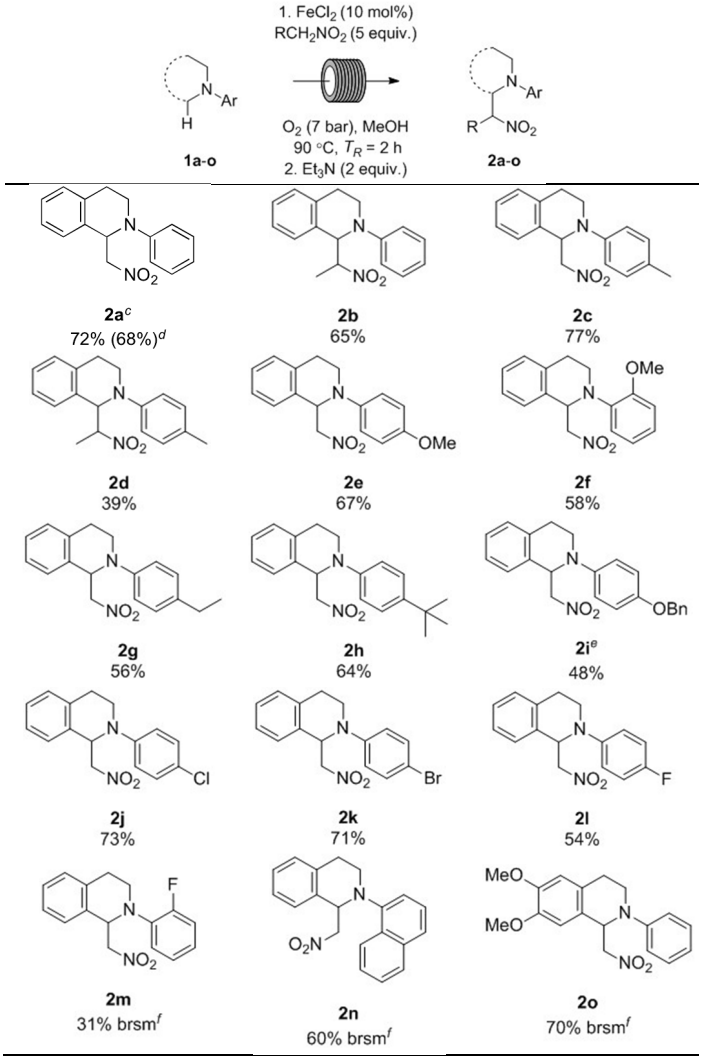

| Entry | Cat. loading (mol%) | Temp. (°C) | $O_2$ pressure (bar) | Conv. (%)[b] |
|---|---|---|---|---|
| 1 | 10 | 50 | 7 | 37 |
| 2 | 10 | 70 | 7 | 87 |
| **3** | **10** | **90** | **7** | **100** |
| 4 | 1 | 90 | 7 | 11 |
| 5 | 2 | 90 | 7 | 26 |
| 6 | 5 | 90 | 7 | 40 |
| 7 | 10 | 90 | 1 | 18 |
| 8 | 10 | 90 | 3 | 36 |
| 9 | 10 | 90 | 5 | 72 |

[a]Reaction conditions: **1a** (0.1 mmol), $FeCl_2$, $MeNO_2$ (5 equiv.), MeOH (2 mL), $O_2$, $T_R$ = 1 h. [b]Determined by $^1$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/$O_2$-mediated nitro-Mannich batch reaction of **1ab**, which required a reaction time of 5 days for full conversion.[10b]

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).

**Table 2** Scope of continuous flow iron-catalysed aerobic nitro-Mannich reaction.[a,b]




[a]Reaction conditions: **1** (0.5-1.0 mmol), $FeCl_2$ (10 mol%), $RCH_2NO_2$ (5 equiv.), MeOH (0.05 M), $O_2$ (7 bar), 90 °C, $T_R$ = 2 h unless otherwise stated. All reactions quenched with 2 equiv. $Et_3N$. [b]Isolated yields after column chromatography. [c]Residence time of 1.5 h. [d]11.7 mmol scale. [e]Loaded onto sample loop in 9:1MeOH/THF. [f]Based on recovered starting material.

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[19] and Doyle,[10b] we found that by quenching the reaction with base (2 equivalents of $Et_3N$), the desired nitro-Mannich adducts were obtained in consistently good yields.

Reactions employing nitroethane (**2b**, **2d**) were noticeable 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.

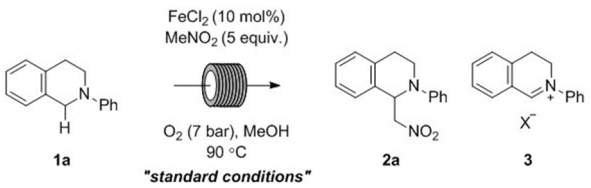
Electron-rich tetrahydroisoquinolines with alkyl or ether substituted *N*-aryl groups reacted smoothly, giving the nitro-Mannich products in good yields (**2c**-**i**). *N*-Naphthyl substrate **1n** reacted cleanly, albeit slowly due to steric hinderance at the C1 oxidation site. Substrates bearing mildly 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,[20] 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,[21] 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 Klussmann both have postulated the initiation step in transition metal-catalysed aerobic α-functionalisation of amines to be a single electron oxidation to yield an amine cation radical that is then further oxidised to an iminium species.[8b,10b] 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.

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**]$^+$[$FeCl_3$]$^-$, 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 (μ-oxo)bis[trichloroferrate(II)] salt 2[**3**]$^+$[$Fe_2OCl_6$]$^{2-}$.

**Table 3** Control experiments to probe reaction mechanism.[a]

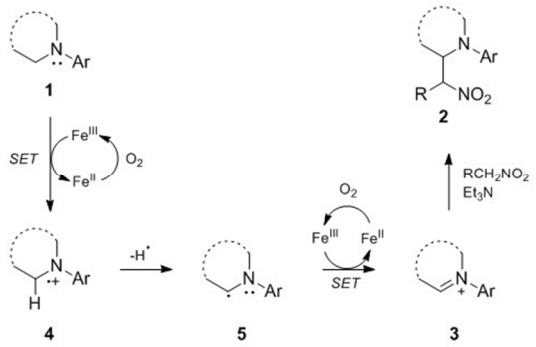



1a 2a 3

| Entry | Changes from standard conditions | Yield **2a** (%)[b] |
|---|---|---|
| 1 | Under $N_2$ | - |
| 2 | Under $N_2$, $FeCl_3$ (10 mol%) | 9 |
| 3 | BHT (1 equiv.) | 33 |
| 4 | No $MeNO_2$, $FeCl_2$ (2 equiv.) | quant. (**3**) |

[a]Reaction conditions: **1a** (0.1 mmol), $MeNO_2$ (5 equiv.), MeOH (1 mL), 2 h, flow rate = 0.167 mL min$^{-1}$. [b]Determined by $^1$H NMR.

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 α-alkylated product **2**, with regeneration of the Fe(III) catalyst by molecular oxygen.




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

In summary, we have reported the efficient aerobic nitro-Mannich reaction of *N*-aryl tetrahydroisoquinolines using simple Fe salts and molecular $O_2$. 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.

## Notes and references

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†Electronic Supplementary Information (ESI) available: Experimental procedures and product characterisation. See DOI: 10.1039/c000000x/

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

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

1 For general reviews on transition metal-catalysed C-H functionalisation see: (a) K. Godula, D. Sames, *Science*, 2006, 312, 67; (b) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev*., 2009, 38, 3242; (c) O. Baudoin, *Chem. Soc. Rev*., 2011, 40, 4902; (d) A. A. Kulkarni, O. Daugulis, *Synthesis*, 2009, 24, 4087; (e) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed*., 2009, 48, 5094; (f) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem. Int. Ed*., 2014, 53, 74; (g) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J*., 2010, 16, 2654.

2 For reviews on C-H functionalisation in total synthesis see: (*a*) L. McMurry, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.,* 2011, **40**, 1885; (*b*) W. R. Gutekunst, P. S. Baran, *Chem. Soc. Rev.,* 2011, **40**, 1976.

3 P. Anastas, N. Eghbali, *Chem. Soc. Rev.*, 2010, **39**, 301.

4 For selected approaches to achieving site selectivity in C-H functionalisation see: (*a*) J. A. Labinger, J. E. Bercaw, *Nature*, 2002,

**417**, 507; (*b*) T. Brückl, R. D. Baxter, Y. Ishihara, P. S. Baran, *Acc. Chem. Res.*, 2012, **45**, 826; (*c*) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788; (*d*) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936; (*e*) D. Lapointe, T. Markiewicw, C. J. Whipp, A. Toderian, K. Fagnou, *J. Org. Chem.*, 2011, **76**, 749; (*f*) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.*, 2011, **40**, 1857.

5 For reviews on oxidative α-C($sp^3$)-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, B. U. W. Maes, *Chem. Eur. J.*, 2012, **18**, 10092; (*d*) S.-Y. Zhang, F.-M. Zhang, Y.-Q. Tu, *Chem. Soc. Rev.*, 2011, **40**, 1937.

6 For selected examples of $sp^3$-sp coupling see: (*a*) S. I. Murahashi, N. Komiya, H. Terai, T. Nakae, *J. Am. Chem. Soc.*, 2003, **125**, 15312; (*b*) Z. Li, C.-J. Li, *J. Am. Chem. Soc.*, 2004, **126**, 11810; (*c*) H. Wei, A. R. Ofial, *Chem. Commun.*, 2009, **33**, 5024; (*d*) Li, P. D. MacLeod, C.-J. Li, *Tetrahedron: Asymmetry,* 2006, **17**, 590. For $sp^3$-$sp^2$ coupling see: (*e*) Z. Li, C.-J. Li, *J. Am. Chem. Soc.*, 2005, **127**, 6968; (*f*) O. Baslé, C.-J. Li, *Org. Lett.*, 2008, **10**, 3661; (*g*) M. Ghobrial, M. Schnürch, M. D. Mihovilovic, *J. Org. Chem.*, 2011, **76**, 8781; (*h*) M. Ghobrial, K. Harhammer, M. D. Mihovilovic, M. Schnürch, *Chem. Commun.*, 2010, **46**, 8836; For $sp^3$-$sp^3$ coupling see: (*i*) Z. Li, C.-J. Li, *J. Am. Chem. Soc.*, 2005, **127**, 3672; (*j*) O. Baslé, C.-J. Li, *Green Chem.*, 2007, **9**, 1047; (*k*) Z. Li, C.-J. Li, *Eur. J. Org. Chem.*, 2005, 3173; (*l*) A. Yu, Z. Gu, D. Chen, W. He, P. Tan, J. Xiang, *Catal. Commun.*, 2009, **11**, 162; For C-X coupling see: (*m*) W. Han, A. R. Ofial, *Chem. Commun.*, 2009, 6023; (*n*) O. Baslé, C.-J. Li, *Chem. Commun.*, 2009, **27**, 4124; (*o*) K. Alagiri, P. Devadig, K. R. Prabhu, *Tetrahedron Lett.*, 2012, **53**, 1456; (*p*) A. Modak, U. Dutta, R. Kancherla, S. Maity, M. Bhadra, S. M. Mobin, D. Maiti, *Org. Lett.*, 2014, **16**, 2602.

7 For ruthenium see: (*a*) S.-I. Murahashi, T. Nakae, H. Terai, N. Komiya, *J. Am. Chem. Soc.*, 2008, **130**, 11005. For copper see: (*b*) Z. Li, C.-J. Li, *Org. Lett.*, 2004, **6**, 4997; (*c*) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2006, **103**, 8928; (*d*) L. Zhao, C.-J. Li, *Angew. Chem. Int. Ed.*, 2008, **47**, 7075; (*e*) L. Zhao, O. Baslé, C.-J. Li, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **106**, 4106. For iron see: (*f*) P. Liu, Z. Wang, J. Lin, X. Hu, *Eur. J. Org. Chem.*, 2012, 1583; (*g*) K. Li, G. Tan, J. Huang, F. Song, J. You, *Angew. Chem. Int. Ed.*, 2013, **52**, 12942; (*h*) C. M. R. Volla, P. Vogel, *Org. Lett.*, 2009, **11**, 1701. For vanadium see: (*i*) S. Singhal, S. L. Jain, B. Sain, *Chem. Commun.*, 2009, 2371; (*j*) K. Alagiri, G. S. R. Kumara, K. R. Prabhu, *Chem. Commun.*, 2011, **47**, 11787; (*k*) K. M. Jones, P. Karier, M. Klussmann, *ChemCatChem*, 2012, **4**, 51. For molybdenum see: (*l*) K. Alagiri, K. R. Prabhu, *Org. Biomol. Chem.*, 2012, **10**, 835. For gold see: (*m*) J. Xie, H. Li, Q. Xue, Y. Cheng, C. Zhu, *Adv. Synth. Catal.*, 2012, **354**, 1646; (*n*) Y. Zhang, S. Luo, B. Feng, 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, Y.-M. Liang, *Org. Biomol. Chem.*, 2010, **8**, 4077. For cobalt see: (*p*) N. Sakai, A. Mutsuro, R. Ikeda, T. Konakahara, *Synlett*, 2013, **24** 1283; (*q*) C. Feng, J.-H. Su, Y. Yan, F. Guo, Z. Wang, *Org. Biomol. Chem.*, 2013, **11**, 6691. For zinc see: (*r*) T. Sugiishi, H. Nakamura, *J. Am. Chem. Soc.*, 2012, **134**, 2504.

8 See refs 6j-l and (*a*) E. Boess, D. Sureshkumar, A. Sud, C. Wirtz, C. Farès, M. Klussmann, *J. Am. Chem. Soc.*, 2011, **133**, 8106; (*b*) E. Boess, C. Schmitz, M. Klussmann, *J. Am. Chem. Soc.*, 2012, **134**, 5317.

9 See: refs 6c, 6m, 7f, 7g-h and (*a*) W. Han, P. Mayer, A. R. Ofial, *Adv. Synth. Catal.*, 2010, **352**, 1667; (*b*) A. Wagner, W. Han, P. Mayer, A. R. Ofial, *Adv. Synth. Catal.*, 2013, **355**, 3058; (*c*) W. Shirakawa, N. Uchiyama, T. Hayashi, *J. Org. Chem.*, 2011, **76**, 25; (*d*) H. Richter, O. G. Mancheño, *Org. Lett.*, 2011, **13**, 6066.

10 (*a*) S. Murata, K. Teramoto, M. Miura, M. Nomura, *Bull Chem. Soc. Jpn.*, 1993, **66**, 1297; (*b*) M. O. Ratnikov, X. Xu, M. P. Doyle, *J. Am. Chem. Soc.*, 2013, **135**, 9475.

11 Y. Nakano, G. P. Savage, S. Saubern, P. J. Scammells, A. Polyzos, *Aust. J. Chem.*, 2013, **66**, 179.

12 A. Noble, J. C. Anderson, *Chem. Rev.*, 2013, **113**, 2887.

12 (*a*) E. Shirakawa, T. Yoneda, K. Moriyam K. Ota, N. Uchiyama, R. Nishikawa, T. Hayashi, *Chem. Lett.*, 2011, **40**, 1041. (*b*) T. Zeng, G. Song, A. Moores, C.-J. Li, *Synlett,* 2010, **13**, 2002; (*c*) R. Hudson, S. Ishikawa, C.-J. Li, A. Moores, *Synlett*, 2013, **24**, 1637.

14 S. G. Newman, K. F. Jensen, *Green Chem.*, 2013, **15**, 1456.

15 (*a*) M. O'Brien, I. R. Baxendale, S. V. Ley, *Org. Lett.*, 2010, **12**, 1596; (*b*) A. Polyzos, M. O'Brien, T. P. Petersen, I. R. Baxendale, 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, A. Polyzos, *Acc. Chem. Res.*, 2014, *submitted 30-09-2014.*

17 For CO see: (*a*) P. Koos, U. Gross, A. Polyzos, M. O'Brien, I. R. Baxendale, S. V. Ley, *Org. Biomol. Chem.*, 2011, **9**, 6903; (*b*) U. Gross, P. Koos, M. O'Brien, A. Polyzos, S. V. Ley, *Euro. J. Org. Chem.*, 2014, DOI: 10.1002/ejoc.201402804. For $H_2$ see: (*c*) M. O'Brien, N. Taylor, A. Polyzos, I. R. Baxendale, S. V. Ley, *Chem. Sci.*, 2011, **2**, 1250; (*d*) S. Newton, S. V. Ley, E. Casas Arcé, 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, S. V. Ley, *Angew. Chem. Int. Ed.*, 2014, **53**, 4915. For $C_2H_4$ see: (*f*) S. L. Bourne, P. Koos, M. O'Brien, B. Martin, B. Schenkel, I. R. Baxendale, S. V. Ley, *Synlett*, 2011, **18**, 2643; (*g*) S. L. Bourne, M. O'Brien, S. Kasinathan, P. Koos, P. Tolstoy, D. X. Hu, R. W. Bates, B. Martin, B. Schenkel, S. V. Ley, *ChemCatChem.*, 2013, **5**, 159. For $NH_3$ see: (*h*) P. B. Cranwell, M. O'Brien, D. L. Browne, P. Koos, A. Polyzos, M. Peña-López, S. V. Ley, *Org. Biomol. Chem.*, 2012, **10**, 5774; (*i*) D. L. Browne, M. O'Brien, P. Koos, P. B. Cranwell, A. Polyzos, S. V. Ley, *Synlett*, 2012, **23**, 1402; (*j*) J. C. Pastre, D. L. Browne, M. O'Brien, S. V. Ley, *Org. Process Res. Dev.*, 2013, **17**, 1183. For $O_2$ see: (*k*) T. P. Petersen, A. Polyzos, M. O'Brien, T. Ulven, I. R. Baxendale, S. V. Ley, *ChemSusChem.*, 2012, **5**, 274; (*l*) S. L. Bourne, 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, M. H. Todd, *Tetrahedron*, 2009, **50**, 1199; (*b*) A. S.-K. Tsang, P. Jensen, J. M. Hook, A. S. K. Hashmi, M. H. Todd, *Pure Appl. Chem.*, 2011, **83**, 655.

20 No reaction was observed with 4-$NO_2C_6H_4$-, 4-$COMeC_6H_4$- 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, K. F. Jensen, *Org. Process Res. Dev.*, 2013, **17**, 927.

 