Institution: University of Cambridge

Unit of Assessment: 8

Title of case study: Enabling Methods for Cleaner Chemical Synthesis

1. Summary of the impact (indicative maximum 100 words)

The pioneering work of Steven Ley on polymer-supported reagents and continuous-flow reaction technology has helped change the way we achieve cleaner chemical processes. The concepts and techniques invented in Cambridge allow more sustainable processes to be developed, with concomitant reduction in purification steps, shorter reaction times and diminished solvent usage. The work has led to a spin-out company (Reaxa), seeded the creation of a number of other companies, and resulted in the development of several devices for continuous flow synthesis that are now commercially available via Mettler-Toledo (USA) and Cambridge Reactor Design (UK). This technology is having an impact in industry, with continuous flow processing increasingly being used for full-scale commercial production.

2. Underpinning research (indicative maximum 500 words)

Steven Ley (1702 Professor of Chemistry at the University of Cambridge since 1992) and his group began work in the mid 1990s to discover improved enabling methods for cleaner and more sustainable chemical synthesis. Using recyclable polymer supported reagents in combination with flow chemistry methods, he was able to conduct multi-step synthesis sequences leading to the synthesis of complex biologically active compounds. This was achieved without recourse to techniques such as chromatography, crystallisation, distillation or reaction quenching, common to more conventional synthesis methods at the time. The first paper describing some of these methods appeared in 1997[1] and within one year he had shown that the concept could be extended to up to six linear steps (a world record at the time) without recourse to conventional and wasteful downstream processing.[2] This work attracted modest research funding from the EPSRC through a ROPA grant (GR/M50614/01) and a more substantial follow-up grant (GR/N02030/01). The concept for this work and its potential application for multi-step synthesis using polymer supported reagents with flow chemistry was the subject of a patent from his first spin-out company in 1999.[3]

The grants awarded to Ley's group facilitated very rapid development of the techniques and resulted in a highly cited review.[4] The methods were promptly adopted by the academic community (as evidenced by ISI listing 700 citations in 2011 alone) and by industry with Ley's own company leading the charge (see above). His spectacular synthesis of epothilone C, a potent anti-tumour agent, in just 15 linear steps using only polymer supported reagents, was a true demonstration of the technology and a landmark publication because it changed many people's attitudes towards organic synthesis using cleaner and more efficient methods.[5]

More significantly Ley then went on to show even further advances were possible by using these polymer supported reagents and related scavenger materials. This was achieved by constructing packed cartridges containing these species and, by appropriate machinery, passing substrates through these tubes in a flow chemistry manner; multi-step flow synthesis was made possible.[6] By 2006 he developed flow chemistry and immobilised reagents to deliver pharmaceutical agents and complex natural products such as oxomaritidine in just seven steps using this machine-assisted approach.[7] This seminal paper opened up a whole new set of opportunities for molecular assembly as a result of Ley's work. It also generated substantial interest at the EPSRC, who began to fund initiatives in the area and a large EPSRC grant in 2003 (GR/S40343/01), to support further research in Ley's group.

As these techniques were being developed and adopted worldwide, further underpinning research in Cambridge from Ley's group led to the discovery of a new range of encapsulated reagents and greatly improved polymer supported scavengers, some of which were patented.[8&9] Further research support for this area has been recently awarded to Ley's group from the EPSRC (EP/K009494/1). These immobilised systems were very effective in batch and flow conditions and this discovery led to the formation of a second spin-out company, Reaxa, based in Manchester in 2005. The products are now marketed and sold worldwide for green chemistry applications.

3. References to the research (indicative maximum of six references)

1. Polymer-Supported Perruthenate (PSP): A New Oxidant for Clean Organic Synthesis, B. Hinzen and S.V. Ley, *J. Chem. Soc., Perkin Trans. I*, 1997, 1907-1908.
2. Clean Six-Step Synthesis of a Piperidino-thiomorpholine Library using Polymer-Supported Reagents, J. Habermann, S.V. Ley and J.S. Scott, *J. Chem. Soc., Perkin Trans. I,* 1998, 3127-3130. (*****)
3. Patent No. WO 99/58475, Preparation of compounds using polymer supported reagents.
4. Multistep Organic Synthesis using Solid Supported Reagents and Scavengers: A New Paradigm in Chemical Library Generation, S.V. Ley, I.R. Baxendale, R.N. Bream, P.S. Jackson, A.G. Leach, D.A. Longbottom, M. Nesi, J.S. Scott, R.I. Storer and S.J. Taylor, *J. Chem. Soc., Perkin Trans. I,* 2000, 3815-4195.
5. A Total Synthesis of Epothilones using Solid-Supported Reagents and Scavengers, R.I. Storer, T. Takemoto, P.S. Jackson and S.V. Ley, *Angew. Chem. Int. Edn,* 2003, 42*,* 2521-2525. (*****)
6. New Tools and Concepts in Modern Organic Synthesis, S.V. Ley and I.R. Baxendale, *Nature Reviews*, 2002, 1, 573-586.
7. A Flow Process for the Multi-Step Synthesis of the Alkaloid Natural Product Oxomaritidine: A New Paradigm for Molecular Assembly, I.R. Baxendale, J. Deeley, C.M. Griffiths-Jones, S.V. Ley, S. Saaby and G. Tranmer, *J. Chem. Soc., Chem. Commun,* 2006, 2566-2568.
8. Encapsulation of Palladium in Polyurea Microcapsules, C. Ramarao, S.V. Ley, S.C. Smith, I.M. Shiley and N. DeAlmeida, *J. Chem. Soc., Chem. Commun,* 2002, 1132. (*****)
9. EnCat patent: Microencapsulated catalyst, methods of preparation and methods of use thereof. July 9 2002 WO203006151.

(*****) References that best indicate the quality of the research.

Grant Information

- Grant No: GR/M50614/01; PI: Professor Steven V Ley; Grant Title: ROPA: Orchestrated Multistep Organic Synthesis Using Polymer Bound Reagents; Period of Grant: 01 April 1999 - 31 March 2001; Grant Value: £103,821
- Grant No: GR/N02030/01; PI: Professor Steven V Ley; Grant Title: Multistep Organic Synthesis Using Solid Supported Reagents: A New Paradigm in Chemical Library Generation; Period of Grant: 01 June 2000 - 31 May 2003; Grant Value: £410,911
- Grant No: GR/S40343/01; PI: Professor Steven V Ley; Grant Title: An Organic Synthesis Programme in Cambridge; Period of Grant: 1 October 2003 – 30 September 2008); Grant Value: £3,552,215
- Grant No: EP/K009494/1; PI: Professor Steven V Ley; Grant Title: Fully-Integrated Continuous Flow Processes for Access to Forbidden Chemistries, New Reactivities and Sequential Complexity Generation; Grant Period: 1 January 2013 – 31 December 2013; Grant Value: £2,559,199

4. Details of the impact (indicative maximum 750 words)

Chemical synthesis is at the heart of modern society, being essential in the development and manufacture of everything from modern electronics to pharmaceutical agents. The research programme started by Ley in the mid 1990s sought to provide a sea change in the way molecules could be assembled in a multi-step fashion.[1] Key to the success of the approach was the use of an ensemble of immobilised reagents and scavengers to synthesise molecules without the requirement for extensive downstream processing techniques, which are wasteful in terms of materials, energy, time and labour costs. Moving from conventional batch-mode chemical production to continuous flow-based processing has had worldwide impact, with companies across the chemical space – from research operations to full-scale production – now realising the benefits and implementing continuous flow processing techniques within their facilities. Substantial benefits have been accrued in terms of safety, energy savings, scale-up and low solvent usage, all leading to more sustainable chemical practices.

Technology Seeded New Companies

This technology helped to seed the formation of a number of UK start-up companies largely focused on flow methods. Many new UK start-up companies, such as Vapourtec (2003, Suffolk, UK), Uniqsis (2007, Cambridge, UK), Cyclofluidic (2008, Welwyn Garden City, UK), Microsaic (2004, Woking, UK), and HEL (1987, Borehamwood, UK) were set up to exploit the potential of flow chemistry. These companies continue to trade and the UK is now leading the world in developing new, innovative equipment for flow chemistry. Ley has had direct input into Cyclofluidic as a member of its Scientific Advisory Board.

In 2005, Steven Ley set up the spin-out company Reaxa to exploit work on the nickel, palladium, platinum and osmium encapsulated reagents EnCat, and QuadraPure reaction clean-up scavengers. These provide a unique solution to minimise waste during chemical reactions, and allow precious spent catalysts to be easily recovered, facilitating recycling and being ideal for flow chemistry applications. The scavengers are now sold by Johnson Matthey after it acquired the patent in 2011, and Reaxa itself was acquired by Indian company S. Amit Speciality Chemicals Pvt Ltd, also in 2011, which has continued to support and promote these important reagents, now sold through Sigma-Aldrich.

Adoption and Application of Technology in the Commercial Sector

There are numerous examples of the use of these reagents in the commercial sector. Two examples published in 2012 are Pfizer’s use of palladium EnCat to effect a Suzuki cross-coupling reaction in the synthesis of potent inhibitors of LpxC that have potential as antibiotics[2], and the use of the same EnCat in the synthesis of a range of orally available CHK1 inhibitors by a team at the Institute of Cancer Research.[3]

The QuadraPure scavengers have also been employed in industrial processes. Novartis, for example, published work on the clean-up of Heck reactions in 2008, which concluded that QuadraPure TU was the most effective adsorbent.[4] Another example is Pfizer’s use of QuadraPure TU to remove traces of palladium in the process scale-up of [beta]2-adrenoceptor agonist PF-00610335.[5]

New Products Created and Commercialised

Further evidence of the impact of Ley’s work on polymer supported reagents and scavengers under flow chemistry conditions is that a local company, Cambridge Reactor Design have commercialised two products which had their genesis in his laboratories. These are the “Gastropod” for conducting mixed gas/liquid flow reactions with in-line supported catalysts and “Polar Bear” for achieving low temperatures (-89ºC) without cryogens for flow mode multi-step synthesis. Both these units have attracted wide interest as judged by ISI citations to this work (Gastropod 145, Polar Bear 30).

Similarly, in collaboration with Mettler Toledo, Ley’s flow chemistry techniques have driven the need for improved in-line analysis, which has resulted in further commercial products for flow IR monitoring being introduced to the market.[6] The impact on his work in this area has also aided the development of mini-mass spectrometers for in-line flow analysis. The details of this joint collaboration with Microsaic Systems are reported.[7&8] This equipment is now commercially available giving the UK a lead in the development of these new advances in mass spectrometer design.

5. Sources to corroborate the impact (indicative maximum of 10 references)

References in the public domain

1. Clean Six-Step Synthesis of a Piperidino-thiomorpholine Library using Polymer-Supported Reagents, J. Habermann, S.V. Ley and J.S. Scott, *J. Chem. Soc., Perkin Trans. I,* 1998, 3127-3130.
2. Potent Inhibitors of LpxC for the Treatment of Gram-Negative Infections, M.F. Brown, U. Reilly, J.A. Abramite, J.T. Arcari, R. Oliver, R.A. Barham, Y. Che, J.M. Chen, E.M. Collantes, S.W. Chung, C. Desbonnet, J. Doty, M. Doroski, J.J. Engtrakul, T.M. Harris, M. Huband, J.D. Knafels, K.L. Leach, S. Liu, A. Marfat, A. Marra, E. McElroy, M. Melnick, C.A. Menard, J.I. Montgomery, L. Mullins, M.C. Noe, J. O'Donnell, J. Penzien, M.S. Plummer, L.M. Price, V. Shanmugasundaram, C. Thoma, D.P. Uccello, J.S. Warmus, and D.G. Wishka, *J. Med. Chem*., 2012, 55(2), 914-923.
3. Discovery of 3-Alkozyamino-5-(pyridin-2-ylamino)pyrazine-2-carbonitriles as Selective, Orally Bioavailable CHK1 Inhibitors, M. Lainchbury, T.P. Matthews, T. McHardy, K.J. Boxall, M.I. Walton, P.D. Eve, A. Hayes, M.R. Valenti, A.K. de Haven Brandon, G. Box, G.W. Aherne, J.C. Reader, F.I. Reynaud, S.A. Eccles, M.D. Garrett, I. Collins, *J. Med. Chem*., 2012**,** 55(22), 10229-40.
4. Removal of Soluble Palladium Complexes from Reaction Mixtures by Fixed-Bed Adsorption, M.J. Girgis, L.E. Kuczynski, S.M. Berberena, C.A. Boyd, P.L. Kubinski, M.L. Scherholz, D.E. Drinkwater, X. Shen, S. Babiak and B.G. Lefebvre, *Org. Proc. Res. Dev.,* 2008**,** *12,* 1209-1217.
5. Development of a Potential Manufacturing Route to PF-00610355: A Novel Inhaled β_2-Adrenoreceptor Agonist, P. D. de Koning, N. Castro, I.R. Gladwell, N.A. Morrison, I.B. Moses, M.S. Panesar, A.J. Pettman, and N.M. Thomson, *Org. Proc. Res. Dev.,* 2011**,** 15*,* 1256).
6. ReactIR^{TM} Flow Cell – A New Analytical Tool for Continuous Flow Chemistry Processing, C.F. Carter, H. Lange, I.P. Baxendale, S.V. Ley, J. Goode, N. Gaunt, B. Wittkamp, *Org. Proc. Res. Dev*., 2010, *14*, 393-404.
7. Microsaic Systems (http://www.microsaic.com).
8. Continuous Flow Reaction Monitoring using an On-Line Miniature Mass Spectrometer, D.L. Browne, S. Wright, B.J. Deadman, S. Dunnage, I.R. Baxendale, R.M. Turner and S.V. Ley, *Rapid Commun. Mass Spectrom,* 2012, 26, 1999-2010.

Users/Beneficiaries who can be contacted to corroborate claims

- Director, Cambridge Reactor Design Ltd, Cottenham, UK.
- Technical Applications Consultant, Mettler Toledo Ltd, Leicester, UK.
- SVP, Head of Worldwide Medicinal Chemistry Pfizer, Cambridge MA, USA.
- Fellow, Novartis Pharma AG, Basel, Switzerland.