Institution: Durham University

Unit of Assessment: 8

Title of case study: Elemental fluorine for fine chemical manufacture

1. Summary of the impact

Durham selective direct fluorination methodology using fluorine gas has been scaled up by F2 Chemicals Ltd to supply the Pfizer company with multi-tonne quantities of a key pharmaceutical intermediate used in the synthesis of V-Fend (voriconazole). This antifungal agent has achieved global sales of $4.65bn from 2008-present and is used extensively for the treatment of invasive pulmonary aspergillosis. Multi-channel continuous flow gas/liquid microreactor technology for direct fluorination was licensed to the Asahi Glass Co (Japan) and other transformations enabled by fluorine gas are being exploited by a DU spin-out company, Brock Fine Chemicals Ltd.

2. Underpinning research

Research in elemental fluorine for organic synthesis at DU was led by Prof R.D. Chambers FRS (Durham staff 1960-2000) and continued by Prof G Sandford (Durham staff 1993-present).

Elemental fluorine gas (F_2) has long been considered to be too reactive and uncontrollable for use as a reagent in organic synthesis and this perception still predominates. General comments in standard organic chemistry textbooks such as "Direct fluorination of aromatic rings with F_2 is not feasible at room temperature because of the extreme reactivity of F_2….is not yet of preparative significance (J. March, *Advanced Organic Chemistry*)" are typical.

Despite this background, research into the use of F_2 for controlled organic synthesis began a new phase in 1993 after encouragement from Durham led British Nuclear Fuels (BNFL) to exploit its expertise in handling F_2 for non-nuclear purposes and to create a subsidiary company, BNFL Fluorochemicals Ltd (Preston, UK), later F2 Chemicals Ltd. Considerable research funding from the company to Durham allowed the development of a wide ranging blue-skies research programme into the use of F_2 for organic synthesis and this continues at Durham to the present. Expertise was developed to overcome the many problems of using F_2 for the safe synthesis of fine chemicals. In particular, techniques involving the use of dilute F_2 in nitrogen, appropriate solvent choice (high dielectric constant media such as formic acid, sulfuric acid or acetonitrile) [1], reactor vessel design, gas flow regulator systems and stainless steel/monel fluorine gas handling lines have been developed over the years in Durham. This has allowed selective direct fluorination of a range of aliphatic, dicarbonyl [2], aromatic, heteroaromatic, heterocyclic, steroid and carbohydrate derivatives to be established and the mechanism (regiochemistry, stereochemistry, selectivity) of these processes to be explored. Indeed, we have shown that controlled direct fluorination of aromatic rings *is* now feasible at room temperature [1].

The control of F_2 reactivity by promoting selective electrophilic reactions using high dielectric constant media [1] was particularly important, and F_2 can now be considered to act as a typical electrophilic reagent for a range of electrophilic aliphatic and aromatic substitution processes. In particular, efficient direct selective fluorination processes of β-dicarbonyl and β-ketoester substrates were established for the first time using acetonitrile or formic acid as reaction media [2] to give various fluoro-dicarbonyl and fluoro-ketoester systems in high yield.

Further control of selective fluorination reactions was achieved by the design, fabrication and commissioning of single and multi-channel continuous flow reactor systems, establishing the use of convenient and inexpensive flow reactors for gas/liquid processes in the laboratory [3]. Key new techniques for the supply of individual gas (F_2) and liquid reagents from single sources to a parallel array of many flow channels at the same flow rate and pressure whilst maintaining laminar flow within the reactor channels were incorporated into the reactor designs.

Fluorine gas can also be used an enabler of other chemical transformations. For example, reaction of fluorine *in situ* with iodine leads to iodine monofluoride which has been used in highly efficient electrophilic iodination processes [4] within acidic reaction media for the synthesis of iodoaromatic systems directly from corresponding aromatic substrates.

3. References to the research

[1] R. D. Chambers, C. J. Skinner, J. Hutchinson and J. Thomson, Synthesis of fluoroaromatic

compounds. *J. Chem. Soc., Perkin Trans. I*, 1996, 605-609. **DOI:** 10.1039/P19960000605. **[27 citations]**

[2] R. D. Chambers, M.P. Greenhall and J. Hutchinson. Direct fluorination of 1,3-dicarbonyl compounds. *Tetrahedron*, 1996, 1-8. **DOI**: 10.1016/0040-4020(95)00883-A **[57]**

[3] R.D. Chambers, M.A. Fox, D. Holling, T. Nakano, T. Okazoe and G. Sandford. Versatile thin-film gas–liquid multi-channel microreactors for effective scale-out. *Lab. Chip,* 2005, **5**, 191-198. **DOI**: 10.1039/B416400 **[53]**

[4] R.D. Chambers, C.J. Skinner, M.J. Atherton and J.S. Moilliet. Use of elemental fluorine for the halogenation of aromatics. *J. Chem. Soc., Perkin Trans 1*, 1996, 1659-1664. **DOI**: 10.1039/P19960001659. **[17]**

The research quality of the elemental fluorine research programme (1993-present) led by Prof RD Chambers (RDC) and Prof G Sandford (GS) is supported by: RDC's election to FRS in 1997; and the 2003 award of the Prix Moissan to RDC in 2003 (the premier international award in Fluorine Chemistry). GS and RDC have given many plenary and keynote lectures at major international conferences (European Symposium on Fluorine Chemistry, ACS Winter Fluorine Symposium, ACS National Meetings and International Symposium on Fluorine Chemistry). R.D. Chambers, *Fluorine in Organic Chemistry* (1st edition: 1973; 2nd edition: 2004) remains the standard textbook in the field.

Research funding allowing the fluorination programme to be established included: industrial support from BNFL Fluorochemicals (three employees seconded to Durham for 3 years; 3 year PDRA; 2 PhD studentships); the Asahi Glass Co. Japan (2 PhD studentships including one employee from Japan seconded to Durham); and the Royal Society (URF to GS, 1996–2001). The development of single and multi-channel microreactors was funded by: EPSRC ROPA (1 PDRA, 3 years) and EPSRC Crystal Faraday (1 PDRA, 3 years) schemes, both in collaboration with F2 Chemicals.

4. Details of the impact

In 1992 BNFL established a spin-out company, BNFL Fluorochemicals Ltd, later F2 Chemicals Ltd, to develop new markets in the fine chemicals sector using their expertise in the production and handling of F_2 developed from nuclear power generation applications. A research team (3 PDRA employees, 3 years) from the company was seconded to the Chemistry Department at Durham (1992–1995) in order to establish a skill base, expertise and IPR in the field. The company also provided funds for building and equipping a new, purpose-built research laboratory for handling F_2 within the Chemistry Department and RDC subsequently became a non-executive Director of the company. The following period (1993-1996) resulted in a suite of over 20 patent applications which were filed, granted and maintained by F2 Chemicals arising from the Durham research collaboration. Most importantly, development of new selective fluorination methodology of β-ketoesters in high dielectric constant media was investigated and exemplified at Durham on a 1 g scale and published by the DU research team in collaboration with F2 Chemicals in 1996 [2] following IPR protection [Im1]. Subsequently, Durham direct fluorination reaction methodology using F_2 [2] was adopted and scaled up to a manufacturing process by F2 Chemicals Ltd [Im2] with the design, investment and construction of a 1000 litre Selective Direct Fluorination (SDF) plant (Fig. 1a) at their headquarters in Preston to synthesise products for customers in the life science industries.

V-FEND (Voriconazole, Pfizer, Fig. 1b) is the world-wide best-selling systemic, antifungal agent and has a 5-fluoropyrimidine sub-unit **1** as part of its structure. Manufacture of fluoropyrimidine intermediate **1** had been carried out previously by multi-step, resource intensive strategies described by Pfizer scientists [Im3] but new Durham methods for selective direct fluorination of β-ketoesters using F_2 [2] provided the opportunity for a more efficient 2-step process, that is far less expensive and generates less waste than other procedures. Given this new business opportunity, Durham direct fluorination methodology [2] for the synthesis of β-fluoroketoester **2** (Fig. 1b), as the key starting material for the manufacture of 5-fluoropyrimiide system **1**, was developed and scaled-up by F2 Chemicals and used through all the clinical trial, launch and commercialization periods of V-FEND by Pfizer [Im3]. In the period from January 2008 to July 2013, multi-tonne quantities of F-ketoester **1** were manufactured by F2 Chemicals Ltd [Im2] as the exclusive supplier for Pfizer using

Durham direct fluorination chemistry [2]. World-wide sales of V-FEND in the 2008-2012 REF period total $4.65 billion [Im4] making this product one of the global top 100 best-selling pharmaceuticals.

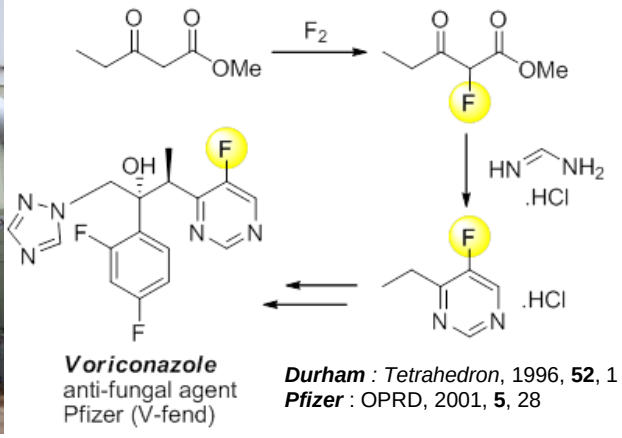

Figure: impact of Durham selective direct fluorination methodology. Left: Selective Direct Fluorination plant at F2 Chemicals (Preston). Right: new strategy for the synthesis of a fluoro-ketoester, a key intermediate of Pfizer's V-Fend antifungal agent.

V-FEND's economic and societal impact arises from its use as a triazole antifungal medication [Im5] active against serious, invasive fungal infections such as candidiasis, aspergillosis, and certain emerging fungal infections [Im6]. Aspergillosis is primarily an infection of the lungs caused by the inhalation of airborne spores of the fungus *Aspergillus* which is commonly found growing on dead leaves, stored grain, compost piles, or in other decaying vegetation. There are several forms of aspergillosis: pulmonary aspergillosis is an allergic reaction to the fungus that usually develops in people who already have lung problems (such as asthma or cystic fibrosis); aspergilloma is a growth (fungus ball) that develops in an area of past lung disease or lung scarring (such as tuberculosis or lung abscess) and pulmonary aspergillosis (invasive type) is a serious infection associated with pneumonia that can spread to other parts of the body. This infection almost always occurs in people with a weakened immune system due to cancer, AIDS, leukaemia, an organ transplant, chemotherapy, or other conditions or medications that lower the number of normal white blood cells or weaken the immune system. For example, invasive pulmonary aspergillosis (IPA) is estimated to occur in 5–13% of people who have a bone marrow transplant, 5–25% of people with a heart or lung transplant and 10–20% of people who undergo high-dose radiotherapy for leukaemia.

Durham selective fluorination chemistry [2, Im1] has therefore played a significant role in impacting many patients treated by V-FEND, giving world-wide health benefits in the treatment of fungal infections for a wide range of disease control.

In order to further develop the use of Durham F_2 chemistry for fine chemical manufacture, a Durham University spin-out company, Brock Fine Chemicals Ltd [Im7], was established in April 2011 by Graham Sandford with assistance and legal expertise from Durham Business Innovation Services (DBIS). Brock (UK registered company 7610103) attracted proof of concept funding (£100K) from the NorthStar regional investment group [Im8] to further exploit the use of fluorine for fine chemical manufacturing, particularly for the synthesis of a range of iodo-aromatic derivatives using Durham fluorine-mediated iodination chemistry [4]. The company now employs 2 FTE chemists and associated marketing and finance expertise. It has made sales of over 100 fine chemical products to chemical distributors such as Fluorochem, Acros, Alfa Aesar, Apollo Scientific and Shigematsu since trading began. Sales in Year 1 were £8K growing to £40K in Year 2 and within the proof-of-concept business plan.

Multi-channel continuous flow microreactor techniques developed at Durham [3] were patented by Durham University [Im9] and a world-wide exclusive license negotiated by the University (DBIS) and granted to the Asahi Glass Co., Japan for a significant fee and a subsequent royalty stream. This acquisition formed a core part of the IP knowledge base in flow reactor technology at Asahi Glass.

5. Sources to corroborate the impact

[Im1] Fluorination of β-ketoesters patent: R.D. Chambers, M.P. Greenhall, J. Hutchinson, J.S. Moilliet, J. Thomson, PCT Intl Appl WO 95/14646 (June 1st 1995); *Chem. Abstr.* **1995**, *123*, 339705.

[Im2] F2 Chemicals: Managing Director, F2 Chemicals Ltd, www.f2chemicals.com.

[Im3] V-FEND application: the use of Durham/F2 Chemicals direct fluorination methods for the synthesis of V-FEND is described by Pfizer scientists in M. Butters and co-workers, *Org. Proc. Res. Dev.*, 2001, **5**, 28–36.

[Im4] V-FEND sales: annual global sales of V-FEND are given in successive Pfizer Annual reports:
2008: http://www.pfizer.com/files/annualreport/2008/financial/financial2008.pdf (p 2)
2009: http://www.pfizer.com/files/annualreport/2009/financial/financial2009.pdf (p 21)
2010: http://www.pfizer.com/files/annualreport/2010/financial/financial2010.pdf (p 25)
2011: http://www.pfizer.com/files/annualreport/2011/financial/financial2011.pdf (p 21)
2012: http://www.pfizer.com/files/annualreport/2012/financial/financial2012.pdf (p115)

[Im5] V-FEND (Pfizer): trade name of Voriconazole: http://en.wikipedia.org/wiki/Voriconazole; http://www.pfizer.com/products/rx/rx_product_vfend.jsp .

[Im6] V-FEND applications: for details on the various types of aspergillosis and treatment regimes, see: http://www.nhs.uk/conditions/Aspergillosis/Pages/Introduction.aspx.

[Im7] Brock Fine Chemicals Ltd: UK registered company 7610103, April 19th 2011, www.brockfinechemicals.com; sales figures contained in Annual Reports registered with Companies House.

[Im8] Brock investment: investment analyst, NorthStar http://www.northstarei.com.

[Im9] Flow systems: multi-channel microreactors patented by DU: R.D. Chambers, G. Sandford and D. Holling, U.K. Pat Appl. 0210809.0, 11th May 2002.