Institution: The University of Manchester

Unit of Assessment: UoA08 Chemistry

Title of case study: The development of Selectfluor® as a commercial electrophilic fluorinating agent

1. Summary of the impact

The development of the chemistry of Selectfluor® (F-TEDA-BF_4) has resulted in this Manchester-discovered reagent becoming the world's most widely used commercial electrophilic fluorinating agent to introduce fluorine into a range of pharmaceuticals and agrochemicals. Annual worldwide production is ca. 25 tonnes and sales estimated to be US$7.5m. Selectfluor is used in the synthesis of fluticasone, a fluorinated corticosteroid which is the active ingredient in GSK's Advair ($3.6bn sales in 2010) used in the treatment of asthma and chronic obstructive pulmonary disease symptoms; top 25 selling drugs Flixonase, Flixotide, Flonase, Flovent HFA and Advair Diskus which had total sales of over $17bn between 2009-2012.

2. Underpinning research

The research was carried out in the UoA between 1993-2004. The key Manchester researchers were:

Professor R. E. Banks (professor 1993-1994, emeritus professor 1994-2004)
Dr N. J. Lawrence (lecturer 1993-1997, senior lecturer 1997-2000)
Dr M. Besheesh (PhD student 1993-1994, PDRA 1994-2001)
Dr I. Sharif (PDRA, 1993-1994)
A.L. Popplewell (PhD student, 1994-1997)

In particular work was undertaken to show the effectiveness, range of applications and utility of Selectfluor® as an electrophilic fluorinating agent, an oxidising agent and as a fluorine-transfer reagent. The key steps in demonstrating these classes of reactivity were

- Use as a fluorinating agent for 1,3-diketones and keto-amides, demonstration that fluorination with Selectfluor® occurs more rapidly for compounds which exist in their enolic form, and that Selectfluor® was as effective as DesMarteau's reagent, but more advantageous, because of its lower cost and less hazardous nature.[2]
- Demonstration of the use of Selectfluor® as an oxidising agent for alcohols via acid fluorides[3] and how this may be used to effect remote-functionalisation.[4]
- Establishing that Selectfluor® can be used under a fluorine-transfer protocol to prepare other fluorinating agents of the N-F class, which has subsequently led to asymmetric fluorinating agents and [18-F] variants for PET work.[6]
- Detailing the properties of Selectfluor® compared with other N-F reagents, how modification of counter-ions impacts on solubility and protocols for fluorination of a wide range of substrates, including how to activate otherwise unreactive substrates.[1]

Some of the limitations of the reagent, due to fluorodemethylation side-reactions, and hence how to protect against this eventuality.[5]

3. References to the research

All of the papers appear in peer-reviewed international journals, including two of the foremost Royal Society of Chemistry journals, and the specialist journal for fluorine chemists, the Journal of Fluorine Chemistry. Citations are from Google Scholar.

Key references:

[1] *N*-Halogeno compounds. Part 18. 1-Alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts: user-friendly site-selective electrophilic fluorinating agents of the N-fluoroammonium class, R. E. Banks, M. K. Besheesh, S. N. Mohialdin-Khaffaf, I. Sharif, J. Chem. Soc., Perkin 1, 1996, 2069-2076 (doi: 10.1039/P19960002069) - 96 citations

[2] Efficient electrophilic fluorination of β-dicarbonyl compounds with the selectfluor reagent F-TEDA-BF_4 {1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)}, R.E. Banks, N. J. Lawrence, A. L. Popplewell, J. Chem. Soc., Chem. Commun., 1994, 343-344.(doi: 10.1039/C39940000343) - 66 citations

[3] Oxidation of benzylic alcohols and benzaldehydes with the Selectfluor reagent F-TEDA-BF_4 {1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)}, R.E. Banks, N. J. Lawrence, A. L. Popplewell, Synlett. 1994, 831-832 (doi: 10.1055/s-1994-23021) – 26 citations

Other references

[4] Remote functionalization of (–)-menthol—synthesis of 4a,5,6,7,8,8a-hexahydro-4H-benzo[1,3]oxazine derivatives with the Selectfluor™ reagent F–TEDA–BF_4, R.E. Banks, N. J. Lawrence, M. K. Besheesh, A. L. Popplewell, R.G. Pritchard, Chem. Commun., 1996, 1629-1630.(doi: 10.1039/CC9960001629)

[5] *N*-Halogeno compounds. Part 20. Vicarious electrophilic fluorodemethylation of 1,3,5-trimethoxybenzene and 2,4,6-trimethoxytoluene with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™ reagent F-TEDA-BF_4), R. E. Banks, M. K. Besheesh, R. W. Gorski, N. J. Lawrence, A. J. Taylor, J. Fluorine Chem., 1999 , 96, 129-133. (doi: 10.1016/S0022-1139(99)00064-0)

[6] *N*-Halogeno compounds. Part 14. “Transfer fluorination” of quinuclidine using F-TEDA-BF_4 (Selectfluor™ reagent): laboratory synthesis of N-fluoroquinuclidinium salts not requiring the use of elemental fluorine, M. Abdul-Ghani, R. E. Banks, M. K. Besheesh, I. Sharif, R. G. Syvret, J. Fluorine Chem., 1995, 73, 255-257. (doi: 10.1016/0022-1139(94)03225-O)

4. Details of the impact

Context

Fluorine is one of the most reactive elements in the periodic table, yet its compounds are some of the most useful, this is exemplified in agrochemicals and pharmaceuticals where more than 1/5th of compounds on the market are fluorine containing, including 30% of the top-thirty best sellers. [O’Hagan, J. Fluorine Chem. 2010, 131, 1071]

The presence of a fluorine atom can confer advantageous potency, selectivity and/or metabolic stability attributes to prospective drug candidate molecules. This desirability is tempered by the harsh and hazardous nature of conventional fluorinating agents; many different electrophilic fluorinating agents have been investigated, but most are insufficiently reactive, too hazardous or too expensive for large-scale applications. Selectfluor® was developed at Manchester, and between 1993 and 2004 was demonstrated to fluorinate complex molecules, to the point where it has now been adopted as the method of choice in industry for the synthesis of a wide range of products, including being the preferred fluorinating reagent in medicinal chemistry drug discovery projects within Pfizer *“SelectFluor® is a milder, safer and more easily handled alternative to DAST*

(diethylaminosulfur trifluoride) and, as such, it is a preferred fluorinating reagent in medicinal chemistry drug discovery projects within Pfizer" (Senior Director, Worldwide Medicinal Chemistry – Oncology, Pfizer) [A], and used to prepare one of the most prescribed billion-dollar fluorosteroid products in the modern pharmaceutical industry. "*Prior to Selectfluor®'s discovery and development, only a very few companies would dare face the challenges of producing fluorinated steroids because of the necessity to obtain and handle perchlorylfluoride, the only reagent available at the time to provide electrophilic fluorination.*
[Previously] perchlorylfluoride used in the production of fluorosteroids had resulted in the fatalities of 2 production workers, and as a result, the industry refused to consider commercial production using the reagent. With the development of Selectfluor® chemistry, this stable, safe, and readily handled white solid made it possible for any company wishing to introduce electrophilic fluorination to do so. Selectfluor® was a game-changing innovation for commercial production of fluorinated steroids" (Research Fellow, Arkema – formerly at Air Products) [B].

Pathways to impact
Selectfluor® was developed in Manchester by Professor R. Eric Banks in collaboration with, and funded by, Air Products Inc. Following its development the research carried out in Manchester determined and exemplified the reactivity and conditions of use for Selectfluor® which has subsequently led to it becoming the world's most widely adopted electrophilic fluorinating agent to date.

Our publications of Selectfluor®'s reactivity and protocols for its use were published between 1994 and 1999, shortly afterwards patents describing the application of Selectfluor® started to appear. In total from 1993 to 2012, there have been 134 patents published which cite Selectfluor® (SciFinder search 07.01.2013), that cover a wide range of multinational companies, countries and scientific areas.

Impact
As the chemistry and applications of Selectfluor® were developed and the industrial relevance of this compound became obvious Selectfluor® production was developed over a 5 year period onto a commercial scale. It is now produced on a multi-tonne quantity in America, China and other countries, with estimated annual production and sales figures of ca. 25 tonnes and $7.5m (USD) per annum [C].

'Selectfluor®'s widespread availability at commercial volumes and its acceptance by both academic and industrial chemists changed the way researchers and process development chemists in pharmaceutical and agricultural industries think about fluorination. Selectfluor® became the first tool of choice for any process requiring electrophilic fluorination and even today it remains the most popular reagent used' (Research Fellow, Arkema – formerly at Air Products) [B].

This has impacted on some of the largest pharmaceutical companies, for example: Bayer for the application and processes for the preparation of halogen-substituted compounds, for controlling animal pests, especially arthropods, arachnids and nematodes; Pfizer for the synthesis of fluorine-containing morpholine compounds as therapeutic mineralocorticoid receptor antagonists to control hypertension, congestive heart failure and chronic kidney disease; Glaxo Group Ltd for Napththyrdin-2(1H) based compounds of use as antibacterials, for example in the treatment of tuberculosis; AstraZeneca AB for the synthesis of compounds used as selective/potent GSK3 (glycogen synthase kinase 3) inhibitors of relevance to treatment in chronic and acute neurodegenerative diseases, Alzhimer's disease, Schizophrenia and bipolar disorders, diabetes, inflammatory diseases and cancers.

The area in which the chemistry of Selectfluor® has had the most significant impact is as the electrophilic fluorinating agent of choice for the generation of fluorine-substituted corticosteroids used as anti-inflammatory drugs [D,E]. It is estimated that ca. 80 % of the currently produced fluorinated steroids, critical for the improvement in quality of many people's lives, are produced using Selectfluor® and this is backed up by the patent literature [O'Hagan, J. Fluorine Chem. 2010, 131, 1071].

Fluticasone propionate (from flumethasone or flumetasone) is the active ingredient in a very wide range of pharmaceutical products for the treatment of asthma and chronic obstructive pulmonary disease symptoms. This fluorinated ingredient was first developed and patented in the early 1960's, based on small scale routes involving the use of anhydrous HF/$Pb(OAc)_4$, SF_4 or ClO_3F (perchloryl fluoride) to introduce fluorine, all of which are hazardous and difficult to handle. Since the development of Selectfluor®'s chemistry companies, such as Hovione, Taro and Farmabios, have patented Selectfluor®-based methods as their preferred routes, including (but not limited to) EP 1207166 (2002), WO 02/100878 (2002) [F], US 7098328 (2006) [G], and US 7718793 (2010) [H]. These described (and cite) methods based on references [1], [2] and R. E. Banks et al J. Fluorine Chem. 1998, 87, 1-17, as the preferred method for the generation of this, and other corticosteroid anti-inflammatory agents.

This fluorinated steroid produced in this way is sold-on and formulated into a number of products which sell under tradenames such as Flixonase, Flixotide, Flonase, Flovent HFA and Advair Diskus. The latter two GSK products are in the top 25 selling drugs. Data from: www.drugs.com/top200.html (accessed 8.1.2013) or from the IMS Institute for Healthcare Informatics (which covers US sales alone) shows that these pharmaceuticals for the years 2009-2012 had total sales of over $17bn, corresponding to ca. 75 million units for Advair Diskus alone. The reach of this Selectfluor-prepared fluorine-containing drug is truly international and benefits many millions of users per annum.

5. Sources to corroborate the impact

A) Corroboration of Selectfluor® impact. Letter from Senior Director, Pfizer.

B) Corroboration of commercial impact of Selectfluor®. Letter from Research Fellow at Arkema.

C) An email discourse with scientist who was at Air Products when Selectfluor® was commercialised.

D) C. G. Pozzoli, F. La Loggia, F. Malanga, Farmabios SpA, Synthesis of Fluoro-corticosteroids, La Chimica, L'Industria, 2013, 124 -128.

E) Dabbling with Fluorine, C&E News, 90(9), 27th February 2012 pp. 10-17.

F) Villax, Z. Mendes, WO 02/100878, June 11, 2002, Preparation of flumethasone and its 17-carbonyl androsten analogue, assigned to Hovione Limited.

G) S. Chernyak, M. Zarbov, D. Gutman, US7098328, August 29 2006, Method for the Preparation of 6□□-fluoro corticosteroids, assigned to Taro Pharmaceutical Industries.

H) S. Chernyak, M. Zarbov, D. Gutman, US7718793, May 18, 2010, Method for the Preparation of 6□-fluoro corticosteroids, assigned to Taro Pharmaceutical Industries