Institution: University of Bristol

Unit of Assessment: Chemistry UoA 8

Title of case study:
CH7: Design and Application of a Tool for the Qualitative and Quantitative Analysis and Prediction of the Effect of Ligand Structure on the Catalytic Activity of Metal Complexes

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

The selection of ligand(s) for the transition metal complexes that are frequently employed as catalysts for the production of fine chemicals is a key activity ultimately governing the financial viability of the process. Traditionally, the method for discovery of ligands with the appropriate balance of cost and efficiency has been achieved empirically via screening. This Impact Case Study reports on the development of a novel methodology for the qualitative and quantitative analysis and prediction of the effect of ligand structure on the catalytic activity of late-transition metals. It has been applied in process and discovery chemistry in pharmaceutical and agrochemical industries in the UK (and beyond). The analysis allows rapid, and therefore cost efficient, identification of ligands and catalysts with the potential to bypass intellectual property issues.

2. Underpinning research (indicative maximum 500 words)

- The underpinning research was carried out in the period 2003 to 2013.
- Key Researchers were **Lloyd-Jones**, **Orpen**, **Harvey**, **Fey**, Paul Murray (AstraZeneca and CatSci Ltd) and Bob Osborne (AstraZeneca catalyst discovery).

The impact followed on from pure research in the instigation and development of a 'Ligand Knowledge Base' by **Orpen**, **Fey** and **Harvey** (**1**). The Ligand Knowledge Base aims to capture the properties of donor ligands coordinating to transition metal centres by way of a collection of up to 29 descriptors. The descriptors evaluated and used are computationally-derived from a range of coordination environments in order to maximise their transferability and hence utility for the investigation of the ligands. These descriptors are analysed using different statistical approaches, both individually to determine their chemical context, and collectively by principal component analysis thereby allowing the derivation of maps of 'ligand space' for different ligand sets.

Lloyd-Jones acted as a consultant to AstraZeneca Process Research and Development during 2003-2010. Through discussion with Process Research and Development scientists at the AstraZeneca Avlon and Charnwood sites, it became evident that catalyst discovery and optimisation for medicinal chemistry projects and scale-up, predominantly involving Pd-based systems, was heavily dependent on, or influenced by, statistical or anecdotal approaches. It was proposed that with funding from AstraZeneca, the Ligand Knowledge Base could: (i) be substantially increased in ligand class, ligand space, and ligand population density and (ii) be applied to model systems for the types of Pd-coupling process that were of interest to AstraZeneca so that the feasibility of qualitative and quantitative analysis and prediction of the effect of ligand structure on the catalytic activity could be explored. Between 2006 and 2010 AstraZeneca provided £763k to fund this research in the laboratories of **Lloyd-Jones** and **Orpen**, **Harvey** and **Fey** at Bristol (**2**). In parallel, AstraZeneca invested £1m in the provision of a semi-automated catalyst testing facility at Avlon to service catalytic reactions in projects within the company that were proving unreliable or low-yielding for drug discovery or for scale-up for clinical trials.

A successful proof of concept emerged from the Bristol-based four-year fully-funded "Phase 1" study (2006-2010) in terms of: (i) approximate prediction of relative activity for various ligands in a model allylation reaction (**3**), and (ii) successful application of the Ligand Knowledge Base-based ligand map (**4**) to a number of active projects within AstraZeneca, leading to vastly improved ligand choice for a scale-up process (see Section 5, Source 1).

A second phase ("Phase 2", 2010-2012) of underpinning research was supported by a Knowledge Transfer Partnership grant of £116k that allowed the laboratory-based postdoc (Gareth Owen-Smith) from Phase 1, to develop the application of the Ligand Knowledge Base for amination reactions at AstraZeneca, by working full-time at Avlon in their semi-automated catalyst testing facility. This led to a number of improvements in the way in which data were collected for qualitative and quantitative analysis of ligand effects in rate (**5**); it also allowed the Ligand Knowledge Base-analysis methodology to be disseminated to all of the other chemistry sites at AstraZeneca in the UK and Sweden.

During the period of the Knowledge Transfer Partnership grant, and based on the extensive experience in catalyst development generated by collaboration with the Bristol based team during Phases 1 and 2 (**6**), Murray established "CatSci" in May 2011 (see section 5, Source 2). This spin-out from AstraZeneca was established as a start-up company based in Cardiff which has led to a third phase ("Phase 3", 2012-2014) of underpinning research being supported (£175k) by a Welsh Government "Research, Development and Innovation Grant" in collaboration with CatSci to support **Fey** in a project to link calculated catalyst property descriptors with optimally designed catalyst screening data, and thus to develop novel catalysts. This project is allowing CatSci to more effectively apply its expertise in the development and optimisation of transition-metal catalysed reactions, and thus assist in the efficient evolution of this industrial spin-out activity.

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

(1) Development of a ligand knowledge base, Part 1: Computational descriptors for phosphorus donor ligands, N. Fey, A. Tsipis, J. N. Harvey, A. G. Orpen, and R. A. Mansson, *Chem. Eur. J.* 2006, **12**, 291-302, DOI: 10.1002/chem.200500891.

(2) Computational Descriptors for Chelating P,P- and P,N-Donor Ligands, N. Fey, J. N. Harvey, G. C. Lloyd-Jones, P. l. Murray, A. G. Orpen, R. Osborne and M. Purdie, *Organometallics* 2008, **27**, 1372-1383, DOI: 10.1021/om700840h.*

(3) Counterintuitive Kinetics in Tsuji-Trost Allylation: Ion-pair Partitioning and Implications for Asymmetric Catalysis**,** L. A. Evans, N. Fey, J. N Harvey, D. Hose, G. C. Lloyd-Jones, P. Murray, A G. Orpen, R. Osborn, G. J. J. Owen-Smith, and M. Purdie, *J. Am. Chem. Soc.,* 2008, **130**, 14471-14473, DOI: 10.1021/ja806278e.

(4) The Newman-Kwart Rearrangement of O-aryl thiocarbamates: Substantial Reduction in Reaction Temperatures via Pd Catalysis, J. N. Harvey, J. Jover, G. C. Lloyd-Jones, J. D. Moseley, P. Murray and J. S. Renny, *Angew. Chem., Int. Ed.,* 2009, **48**, 7612-7615, DOI: 10.1002/anie.200903908.

(5) Expansion of the Ligand Knowledge Base for Monodentate P-Donor Ligands, J. Jover, N. Fey, J. N. Harvey, G. C. Lloyd-Jones, A. G. Orpen, G. J. J. Owen-Smith, P. M. Murray, D. R. J. Hose, R. Osborne, and M. Purdie, *Organometallics,* 2010, **29**, 6245-6258, DOI: 10.1021/om100648v.*

(6) Expansion of the Ligand Knowledge Base for Chelating P,P-Donor Ligands (LKB-PP), J. Jover, N. Fey, J. N. Harvey, G. C. Lloyd-Jones, A. G. Orpen, G J. J. Owen-Smith, P. Murray, D. R. J. Hose, R. Osborne, and M. Purdie, *Organometallics,* 2012, **31**, 5302-5306, DOI: 10.1021/om300312t.*

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

There are three sites of impact:

AstraZeneca

This company can now identify ligands for transition metal catalysis (mostly with Pd, Rh, Ru and Ir) more efficiently. The Ligand Knowledge Base principal component analysis feeds into a Design of Experiment programme that defines the 'chemical space' within which ligands will be tested and how most efficiently to explore this space. This could not be done well previously because there were no 'coordinates' for the ligand space (unlike, for example, the parameterisations available for solvents). AstraZeneca estimated at the end of Phase 2, that this advance has already led to about £250k cost saving and it anticipates on-going savings will be in the region of millions of pounds, through faster development of scale-up processes with reduced development time and costs and

ultimately a reduction in manufacturing costs with the potential to reduce the environmental impact of their processes.

The impact of these developments were recognised in the form of an AstraZeneca Science & Technical Award (to Murray and Osborne) in October 2010. The award nomination read "*The design and application of high quality ligand descriptors in this way is a scientific breakthrough and leading academics refer to this innovation as 'revolutionary'. This capability is now in routine operation and supporting Discovery in gaining access to high value areas of chemical space*". Murray, quoted in an internal AstraZeneca document announcing the award, suggested that savings derived from the breakthrough are "*estimated at around $200k per project to produce 60 kilos of drug substance for a clinical trial. This saving would rise with a market launch to $2.5m for 600 kilos or $25m for six tonnes*", (**a**).

CatSci Ltd

this company, which predominantly arose from activities conducted in the labs of Murray at AZ under the auspices of the Ligand Knowledge Base programme, has a mission "*To establish new and improved chemical reactions and processes through a world-leading understanding and application of transition metal catalysis*". A major component in the portfolio of services offered by CatSci is "*Optimisation of processes through predictive catalysis: Identification and development of an optimised catalytic process and for the interrogation of reaction space in line with Quality by Design principles delivered through exploiting unique predictive catalysis techniques*". These techniques derive directly from Phases 1 and 2 of the collaboration, and solely use the Ligand Knowledge Base descriptors and principal component analysis-derived ligand maps developed at Bristol. Initial investment in facilities has been £0.52m in equipment and 5 staff, with £1.2m of business already secured. Further investment by the Welsh Government has been made in a CatSci-University of Bristol collaborative project to develop an improved ligand screening protocol for homogeneous catalysis, integrating fully the computational evaluation of catalyst properties with CatSci's high-throughput automated catalyst screening and analysis facilities. Focusing on the need to ensure 'manufacturability' in the chemical industries, this two-year project aims to deliver efficient, stable and selective catalysts that are economically viable for process scale-up and discovery (**b**).

Phosphonics Ltd

Concepts arising during the initial phases of the research led to the design of unique 'catalyst capture/release' technology. This concept is now being studied in the School of Chemistry and made ready for the market by Phosphonics via a collaboration supported by the TSB/EPSRC through the Technology Strategy Board "*Sustainable Manufacturing for the Process Industry*" programme. This £700k project ("*Recyclable Catalyst Technology for Cross-Coupling Reactions at Manufacturing Scale*") draws together Phosphonics, CatSci, Syngenta, AstraZeneca, Albany Molecular Research and the University of Bristol, to explore and design novel functionalised silica materials that allow purification of reaction products by temporary capture of the Pd catalyst in heterogeneous form, capable of triggered release back in an active form into solution. The technology will be employed in semi-continuous format, with application possible across multiple process industries. Initial applications towards the manufacture of pharmaceuticals & agrochemicals will be a demonstrable output during 2013-2015 (**c**).

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

(a) For AstraZeneca, Dr Mark Purdie, AstraZeneca Macclesfield. Project manager for the collaboration into predictive catalysis with Bristol (Phases 1 and 2) and Christina Fröjd, publication of internal (AZ) document online regarding AZ Science and Technical Award, October 25th 2010.

(b) For CatSci, Dr Jonathan Moseley, Research Director of CatSci Ltd. (Phases 1, 2 and 3).

(c) For Phosphonics, Dr Robin Wilkes, Business Director, Pharmaceuticals & Fine Chemicals, Phosphonics Limited.