Institution: University of Liverpool		
Unit of Assessment: Chemistry		
Title of case study: Laboratory study of asymmetric catalysis leads to a spin out		
Period when the underpinning research was undertaken: 2005-2014		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): Jianliang Xiao	**Role(s) (e.g. job title):** Professor	**Period(s) employed by submitting HEI:** 1996-now
Period when the claimed impact occurred: 18/02/2014 – 31/12/2020		
Is this case study continued from a case study submitted in 2014? No		

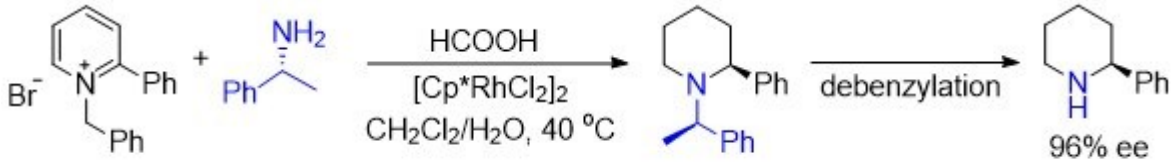
1.Summary of the impact

Created in 2014, Liverpool ChiroChem (LCC) provides previously unavailable building blocks for new drug molecule discovery programmes in pharmaceutical and biotech industries. LCC exploits asymmetric hydrogenation, in particular asymmetric reductive transamination, patented by Xiao. Impacts on commerce and the economy are claimed, including:

- Generation of a new company now worth >£9M with gross sales *ca.* £2M.
- Creation of 61 new jobs at its Liverpool R&D base and Chinese production site.
- Raising >£6M of investment and funding for R&D and commercialisation.
- Creation of new products including a differentiated proprietary catalogue of >1,000 high-value chiral amine compounds.
- The supply of unique LCC products to >300 pharma/biotechnology companies enabling their drug discovery programmes.

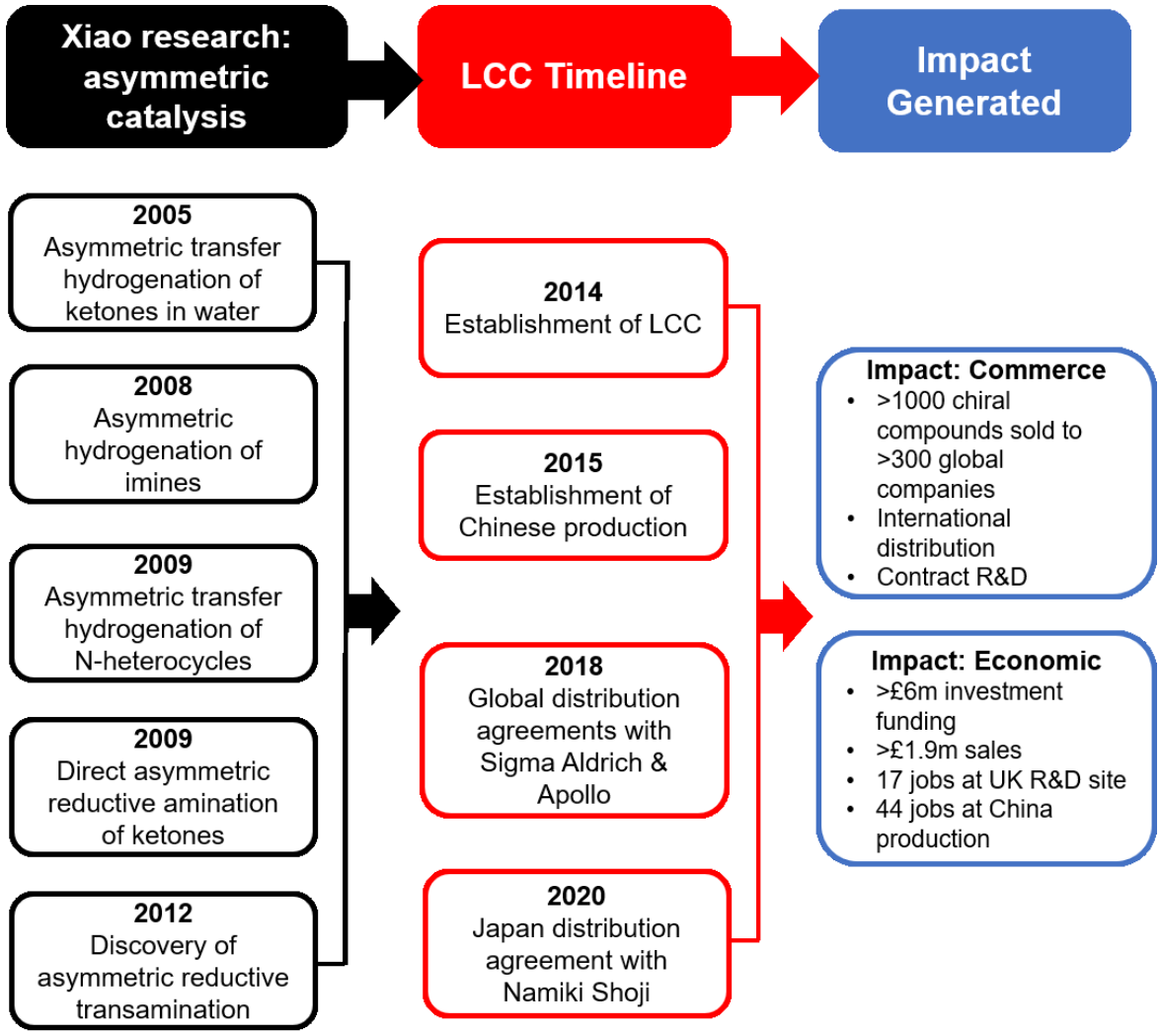
2. Underpinning research

Asymmetric catalysis is used to generate enantiomerically pure compounds, which are key active ingredients for pharmaceutical, biotech and agrochemical industries. In 2012, a new catalytic method for a safe and economically viable asymmetric chiral amine synthesis was discovered by the Xiao group. Asymmetric reductive transamination yields chiral piperidines with a very high enantioselectivity (Scheme 1). In pharmaceutical synthesis, piperidines are the most used N-heterocycles which are the most privileged building blocks, being present in 60% marketed small-molecule drugs. However, as described by [text removed for publication] "*Chiral N-heterocyclic compounds, as exemplified by piperidines.... [are] extremely difficult to produce by traditional chemical methods, and are very expensive or simply unavailable*" [Evidence 5.1]. This is echoed by [text removed for publication] *"[piperidines] are notoriously difficult to synthesize asymmetrically… and hence have been very difficult to access*" [5.2].



Scheme 1. Discovery of asymmetric reductive transamination by the Xiao group.

Realising the commercial potential, the University of Liverpool (UoL) protected the invention in 2013 (WO2015145143 published in 2015; US20170107208A1, granted in the US 2018) [3.1]. Along with the expertise and know-how of the Xiao group in asymmetric catalysis, this patent became the foundation for the establishment of LCC by former Xiao students: Dr Jianjun Wu, Dr Paul Colbon and Dr Jiwu Ruan along with Xiao in 2014. The patent was licenced to LCC exclusively in 2014 by UoL. Scheme 2 illustrates the history of LCC and its interaction with the Xiao group. LCC is now an internationally recognised company, specialising in the production of chiral molecules for the pharmaceutical and biotech industries [5.1-5.3].



Scheme 2. Timeline and role of Xiao's research which led to LCC forming and impact generation.

The key intellectual property [3.1] arose following funding from Pfizer (2009) to develop new chiral catalysts for asymmetrical synthesis of chiral amines. Chiral amines are conventionally accessed via the difficult asymmetric reduction of imines. These existing asymmetric reduction methods generally require high H_2 pressures, special equipment and expensive chiral ligands. Xiao's discovery of asymmetric reductive transamination (Scheme 1) is notable, as not only does it produce chiral piperidines with a high enantioselectivity, it uses a low cost chiral amine reagent, 1 phenylethylamine (<$1.00/g), to induce chirality and neither chiral ligands nor high pressure H_2. Therefore the intellectual property [3.1] gives LCC a critical competitive advantage, providing a facile, highly selective new pathway for accessing chiral N-heterocycles [5.1-5.3].

More widely, the Xiao group has been actively researching asymmetric catalysis (ca. 40 peer-reviewed papers since 2000; exemplars include [3.2-3.6]) through industry (Pfizer, AstraZeneca, GSK), DTI (DTI MMI) and EPSRC (EP/G031444; EP/K504166) funded programmes. In addition to the founding patent, other major discoveries from the Xiao group that LCC makes use of include:

- The first development of highly enantioselective protocols for the asymmetric transfer hydrogenation of ketones in water [3.2].
- Demonstration of highly enantioselective counter anion-controlled catalysis for asymmetric hydrogenation of imines with H_2 [3.3,3.4].

- Creation of a highly enantioselective protocol for pH-regulated aqueous-phase asymmetric transfer hydrogenation of N-heterocycles [3.5].
- Discovery of a highly enantioselective catalytic system for direct asymmetric reductive amination, making the synthesis of chiral amines more cost effective [3.6].
- C-X (X = C, N) coupling chemistry in which the Xiao group have published ca. 50 peer-reviewed papers since 2000.

The key role that Xiao's wider research plays in LCC's activities is evidenced by the supporting letter from the CEO that states that "[LCC] was built upon the founding technology and has also benefited extensively from the expertise and know-how in asymmetric catalysis generated in your research group since 2000." [5.4].

3. References to the research Citation data as of 05/10/2020

3.1 J. Xiao, J. Wu, Synthetic Process, WO2015145143; US20170107208A1.

3.2 X. F. Wu, X. G. Li, F. King, J. Xiao, "Insight into and practical application of pH-controlled asymmetric transfer hydrogenation", *Angew. Chem. Int. Ed.* **2005,** *44*, 3407. DOI: 10.1002/anie.200500023 [225 citations]

3.3 C. Li, J. Xiao, "Asymmetric hydrogenation of cyclic imines with an ionic Cp*Rh(III) catalyst", *J. Am. Chem. Soc*. **2008***, 130,* 13208. DOI: 10.1021/ja8050958 [178 citations]

3.4 C. Li, C. Wang, B. Villa-Marcos, J. Xiao, "Chiral Counteranion-Aided Asymmetric Hydrogenation of Acyclic Imines", *J. Am. Chem. Soc*. **2008***,130,* 14450. DOI: 10.1021/ja807188s [230 citations]

3.5 C. Wang, C. Li, X. Wu, A. Pettman, J. Xiao, "pH Regulated Asymmetric Transfer Hydrogenation of Quinolines in Water", *Angew. Chem. Int. Ed*. **2009**, *48*, 6524. DOI: 10.1002/anie.200902570 [236 citations]

3.6 C. Li, B. Villa-Marcos, J. Xiao, "Metal-Brønsted Acid Cooperative Catalysis for Asymmetric Reductive Amination", *J. Am. Chem. Soc*. **2009***,131,* 6967. DOI: 10.1021/ja9021683 [275 citations]

4. Details of the impact

Since its launch in 2014, LCC has achieved rapid, continued growth in investment, employee numbers and sales (Figure 1) and **LCC is now valued at >£9M** based on the most recent investment round [5.5]. A viable, expanding company that is enabling drug discovery programmes of >300 companies [5.1-5.4] has been generated as a result of Xiao's research. The success of LCC has led to several awards including: Bionow Startup Company of the Year (2015), Grand prize Merseyside Innovation Awards (2015), LCR Tech Climber (2019) and it was shortlisted for the UKBAA Angel Investment Awards (2018) [5.6].

LCC's headquarters are in the North West of England, where it also has its research and development centre. Initially all syntheses were carried out in Liverpool, but in 2015 LCC built its own production and analytical facility in China (Taizhou), which was expanded in 2019 (from 500 to 1800m^2), to meet the increased demand for its products [5.7, 5.8]. LCC's rapid growth and unique product portfolio has generated impacts primarily on commerce and the economy both in the UK and world-wide.

Sales of new products and services: LCC is now an established supplier of chiral molecules to multinational pharma/biotechnology companies [5.1-5.4]**. LCC has gross sales of £1.97M (2014-2020) with year-on-year sales growth,** except for 2019 (see Figure 1 and [5.4]). The one-off decrease in sales during 2019 was due to works on the production site in Taizhou to expand capacity (the facility more than tripled in size). The products sold by LCC include novel fragments, scaffolds, API (active pharmaceutical ingredient) and building blocks at the grams to kg scale, with chiral heterocycles enabled by Xiao research [3.1] accounting for the largest proportion of sales to date [5.4, 5.7]. A strategic decision was taken by LCC to enter into global

distribution agreements with Sigma-Aldrich (now Merck KGaA) and Apollo Scientific in 2018 to enhance global sales reach [5.9]. These partnerships are with the largest fine chemical distributors worldwide. A more recent distribution agreement was signed with Namiki Shoji Co, one of the largest distributors in Japan (2020) [5.9]. LCC has also recently expanded its business model to include direct R&D programmes, leading to contracts with two top-5 global pharmaceutical companies to provide new processes for catalytic production of pharmaceutical intermediates through asymmetric hydrogenation.

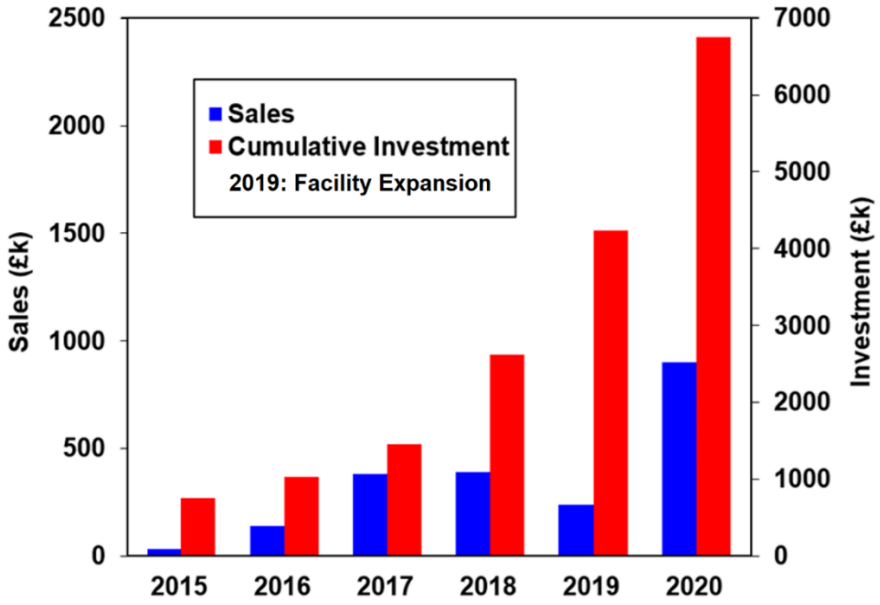


Figure 1. Sales and Investment of LCC have grown over the REF period.

Jobs created and support of regional development: During the REF period **LCC has created 61 new jobs** (employment figures as of December 2020) and the letter from the LCC CEO states that they plan to increase the workforce further in the next 24 months to 70-90 full time staff, despite the poor short-term global economic outlook [5.4]. Currently LCC has 17 employees in the UK split between the head office and R&D laboratories with 10 of the R&D scientist roles being for PhD level workers. Therefore LCC is providing high quality employment opportunities in the Liverpool City Region and the gross value added through LCC as an employer in the region is *ca.* £2.8M [5.10]. A further 44 employees are based in China at the production site, LCC Taizhou. This site, in Jiangsu province, is an important partner for the local economic development strategy with the importance of the production facility being recognised through the provision of grants and facilities, as confirmed in the letter from the Taizhou local authority [5.8] which states "*LCC in Taizhou has become a high-quality partner in the pharmaceutical industry in and outside of China".*

Investment: LCC has raised >£6M in investment funding (Figure 1, and [5.4]). The initial investment from Deepbridge Capital of £60k (2014) targeted the exploitation of the intellectual property [3.1] developed in the Xiao group. A second round of investment of £1.1M from Deepbridge, NWF and angel investors in 2015/16 allowed LCC to expand the resources within the company to 6 full time employees. Additionally, expansion into China (Taizhou) was made possible by grants of more than ¥6M RMB from Chinese local authority in 2015-2020, creating the scope to own a production facility that complies to the EHS regulations. Further investment of £2.4M by Deepbridge and £2M by Praetura has allowed LCC to accelerate the expansion of the production and increase its customer base further.

Increased access to key pharmaceutical building blocks and unique new molecules: Greater than 300 LCC customers (>100 direct, >200 indirect) including multinational

pharma/biotechnology companies regularly purchase LCC's specialist building blocks for their new drug molecule discovery programmes around the world (UK, Europe, USA, Japan, South Korea, China and India) [5.1-5.4]. LCC is offering unique products that are enabling customers to do this. As described by the [text removed for publication], "*the LCC products … have made a significant impact by enriching and expanding the market of small homochiral compounds,* ***filling a gap in the availability and diversity of enantiomerically pure N-heterocycles*** *… [and]* ***the LCC homochiral piperidines are unprecedented, unique, and simply not as readily available elsewhere***" [5.1]. [Text removed for publication] further highlighted "*The recent generation of a virtual library [at [text removed for publication]] based on LCCs chemical equity is state of the art*" [5.1]. Further testament comes from the [text removed for publication], "***LCC offers products that are differentiated from other suppliers***" with "*The novelty and quality … undeniable*" [5.3]. This has allowed [text removed for publication], a world leader in DEL screening (DNA-encoded libraries), to use "*LCC's unique technology [that] can effectively supply numerous 3-dimensional and stereo defined products that has allowed [text removed for publication] to increase the breadth and depth of chemical space*" [5.3]. These are just two examples of how customers have benefited from LCC technology to access compounds that are not easily available elsewhere, enabling innovative research activities, and subsequent IP generation [5.1-5.4].

LCC market an online catalogue of >1000 products derived from catalysis approaches [5.7]. The LCC catalogue has been built strategically with the focus placed on chiral N-heterocycle compounds. **In the FDA-approved drugs, ca 60% are based on N-heterocycles, among which chiral piperidines are the most widely used in the synthesis of chiral drugs**. Commercially, chiral piperidines were limited in variety and generally very expensive [5.1, 5.2]. LCC is able to produce critical pharmaceutical building blocks at scale, at a low price. For example, (S)-2-phenylpiperidine has a commercial cost of $431USD/g (Asta Tech, 95% purity, as of Sept 2020); LCC offer this compound at £200/g (97% purity) and LCC offer unique fluorinated analogues which are not available elsewhere. A further example is (3R,4R)-3-hydrox-4-carboxylate-pipridine, a key intermediate to a Phase I drug candidate ICEC0942, for which LCC is one of the few suppliers worldwide. The wider impact of LCC's enabling role in drug discovery is summarised by the Head of Emerging Chemical Synthesis at [text removed for publication] who states ***"[thanks to LCC], scaffolds containing asymmetric piperidines are now available to every chemist in the world"*** [5.2].

5. Sources to corroborate the impact

[5.1] Letter from Head of Augmented Molecular Design, [text removed for publication], confirming novelty & utility of LCC products.
[5.2] Letter from Head of Emerging Chemical Synthesis, [text removed for publication], confirming the importance & commercialisation of LCC chiral piperidines.
[5.3] Letter from Associate Director, Discovery Chemistry, [text removed for publication], confirming the novelty & utility of LCC products.
[5.4] Letter from LCC CEO confirming underpinning role of Xiao research, sales and product range details, and the generation of IP by customers using LCC products.
[5.5] Letter from LCC CFO showing the valuation of LCC based on latest round of investment.
[5.6] Document confirming awards a) links to awards received and b) email of shortlisting.
[5.7] LCC website, confirming two sites, employee numbers and products including catalogue: https://www.liverpoolchirochem.com/
[5.8] Letter from Taizhou authority confirming the importance of LCC.
[5.9] Evidence for a) Sigma-Aldrich (Merck KGaA) and b) Namiki Shoji (Japan) partnership.
[5.10] Document showing how the Gross Value Added is estimated.