CatSci

EXCELLENCE IN MEDICINES DEVELOPMENT

WHITEPAPER

Supporting Early Clinical Supply Through Process Development Excellence

Introduction

When a molecule is selected to be advanced into development, it triggers the need for the manufacture of the API on a greater scale than has previously been undertaken. This highlights important new factors which need to be considered, and will also incur an increase in costs to deliver required materials.

In the following whitepaper, you will discover more about the strategies we use and how we implemented them to rapidly develop a robust and inherently safe process which enabled our customer to support their early clinical supply without surprises or delays.

Our Development Philosophy

Every process is different, meaning each one has its own unique challenges. This is why it is essential that there is a clear plan, which fully takes into account the customers' requirements so that risks can be mitigated, and the requisite timeline, budget, and quality can be met. At CatSci, our team of experts have played an integral role in taking hundreds of compounds through clinical development. We always begin with the end-in-mind and by having detailed discussions with the customer to ensure that we are perfectly meeting their project objectives, ensuring we are aligned every step of the way.

To direct the critical elements required to deliver a high-quality process, we adopt the SELECT model as our guide, which is routinely used in process chemistry.

Although all phases of the SELECT thinking are valuable to enable early deliveries, not all elements are necessarily equal at this stage. We see three as the most important: Safety, Legal, and Control.

SELECT Model
Safety: Thermal and Chemical Hazards
Environmental: Minimise Impact, reagent choices and reaction volumes
Legal: Freedom to operate
Economy: Cost minimisation where possible
Control: Ensure all processes are controlled and deliver a quality product
Throughput: Maximise throughput where possible

Safety: It is vital that any chemistry we run is safe. We never compromise on the safety of our colleagues, or colleagues from any organisation we partner with.

Legal: We must ensure that we are legally able to operate any chemistry that comes our way. We can collaborate with customers to complete appropriate searches and ensure we have freedom to operate. We also operate with 100% confidentiality; there is no risk of any of our customer's work being shared or seen outside of our organisation, and any IP we generate will be owned by the customer.

Control: Clearly, delivering a compound of the required quality is crucial. We will collaborate with customers to set required specifications to ensure we deliver a product that is suitable for its intended purpose and meets the requisite timeline and budget needs of our client.

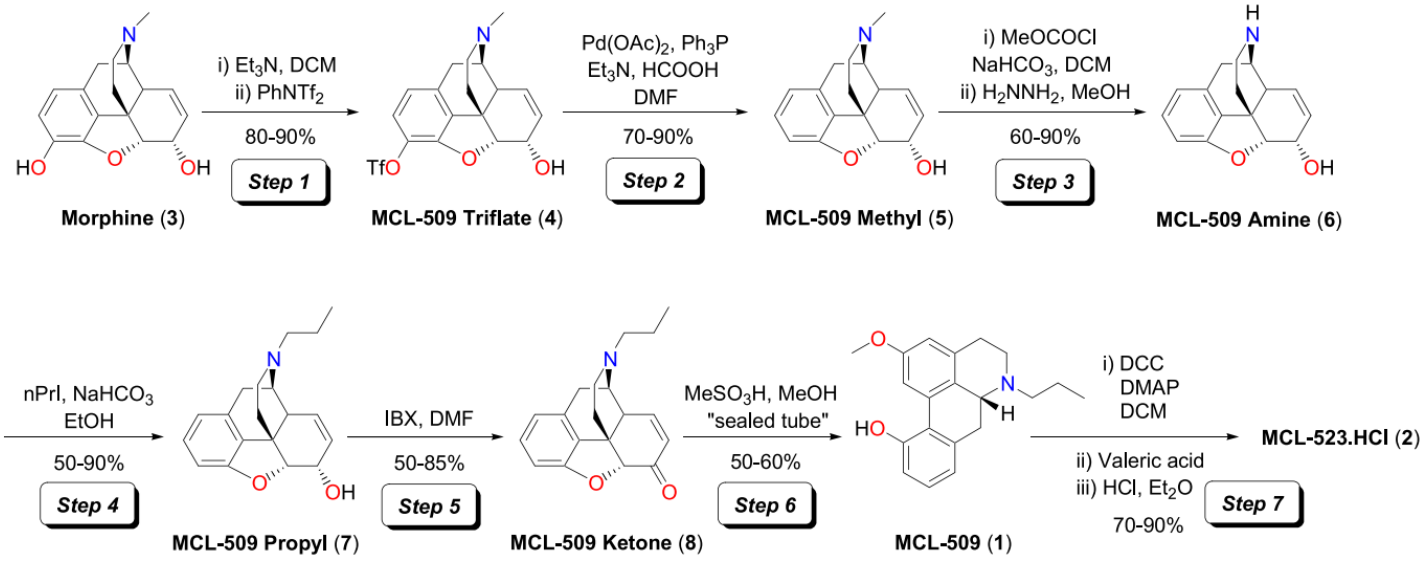
As well as focussing on the three points above, we take a phase appropriate approach to cost, throughput, and environmental impact. We target the best process whilst ensuring we hit the delivery date and balancing the time and costs spent developing a process.

Case Study

The CatSci team was tasked with taking the synthesis of a novel apomorphine Parkinson's drug candidate and designing a safe and robust way to scale-up the synthesis of the molecule. Our customer was looking to expedite the advancement of their API into the clinic. They came to CatSci and required our expertise to help them develop a robust synthesis capable of delivering low kilogramme quantities of API.

In the following case study, you can see how CatSci demonstrated significant improvements across all aspects of safety, robustness and cost which enabled facile transfer of the process to pilot scale with minimal accommodation work required. Our customer met all their project timeline and objectives in an efficient, timely, and cost-effective manner.

The synthesis provided by the customer can be seen below in Scheme 1:



Scheme 1: Discovery route to MCL-509 (1) and MCL-509 (2)

Route Assessment

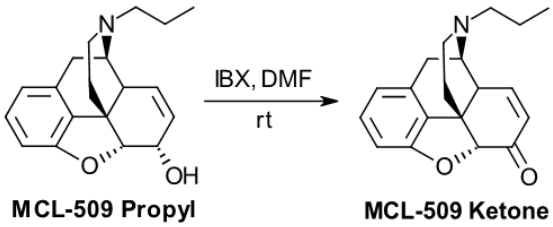
We first conducted a rapid route assessment to assess whether it would be advantageous to go with a different route. We quickly concluded that other syntheses were unlikely to provide any significant advantage; the starting material, Morphine, is cost-effective (approx. $1000/kg) and brings most of the structure, including chirality, we require in our final API. We reached an agreement with the client to focus on the development of a safe, scalable process using the current synthetic route.

In parallel to considering an alternative route, we had assessed issues with the current process which would need addressing ahead of manufacture at Kg scale.[1]

Some of the critical issues we identified were:

1. Use of potentially explosive IBX in step 5.
2. Use of a large excess of the carcinogen hydrazine hydrate in step 3.
3. Use of chromatography to purify material at two separate stages.

A detailed example with the development of step 5 (Scheme 2) is detailed below:



MCL-509 Propyl **MCL-509 Ketone**

Scheme 2. Discovery step to MCL-509 Ketone

We screened a wide range of conditions to assess alternative reaction conditions. More challenges were identified as, during the investigation, we quickly came to understand the MCL-509 ketone was unstable (Table 1).

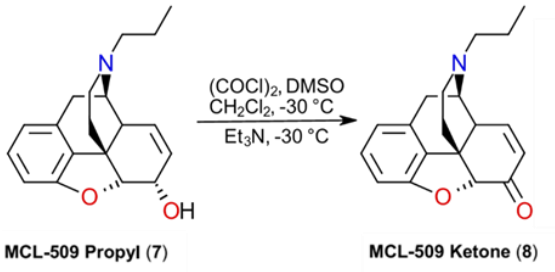
[1] You can find further details on other issues which were solved on our OPR&D paper (https://doi.org/10.1021/acs.oprd.2c00297). It is also available in the format of a presentation, delivered by our Director of Chemical Sciences, Rob Crook, at Scientific Update OPR&D Conference on 13 – 15 March 2023 in Florida. To access the presentation, please contact us.

Oxidation method	Reaction profile	Key issues
TEMPO/NaClO	Complex mixture of products	n/a
Swern $(COCl)_2$/DMSO	High conversion and low level of impurities	Cryogenic conditions and release of toxic CO and DMS (also malodorous) **acceptable for delivery**
Moffatt DCC/DMSO	Complex mixture of products	n/a
TFAA/DMSO	Complex mixture of products	n/a
Parikh-Doering SO_3·Py/DMSO	Complex mixture of products	n/a
Corey-Kim NCS/DMS	Complex mixture of products	n/a
MnO_2	Complex mixture of products	n/a
Dess-Martin	Complex mixture of products	n/a
PCC	Complex mixture of products	n/a
Ley-Griffith TPAP/NMO, inc. polymer bound	High conversion and low level of impurities	High loading of scavenger to remove Ru and product instability upon scavenging
Fetizon's reagent Ag_2CO_3/Celite	Complex mixture of products	n/a

Table 1. Screening conditions

The Achievement

After assessing the results of the screening, we made the decision to proceed with the Swern conditions.



Scheme 3. Final conditions developed for the oxidation of MCL-509 Propyl (7) to MCL-509 Ketone (8)

Following a rapid assessment of many factors, including, but not limited to temperature, solvents, and time, we were able to deliver a process which furnished the product in a yield of 95% with a purity of 97% (Scheme 3).

This was sufficient to advance the development and would allow us to manufacture an API of a necessary quality.

There were improvements across many other steps in the synthesis. We focused on ensuring the process was safe to operate, that hazardous and toxic reagents were minimised, and that an API of high quality was delivered in a way which could be run at the requisite scale.

The most important factor is that our work enabled the process, which successfully delivered material at >1kg scale. This enabled the customer to complete both their toxicology studies and their first regulatory batch to support their first patient studies at a cost and in a timeframe which worked for their development plans.

Some key improvements made include:

- Yield of the synthesis was improved from 8% to 30%
- All highly hazardous reagents were removed
- Chromatography-free synthesis was designed
- Throughput was increased by approximately 3x
- Waste generated from the synthesis was reduced by about 85%

About CatSci

CatSci
EXCELLENCE IN MEDICINES DEVELOPMENT

CatSci Ltd is an award-winning innovation partner, dedicated to breaking down the silos in drug development to accelerate the delivery of life-changing medicines to patients in need. We proudly serve customers across the globe with projects, meeting their needs from candidate selection to product launch and beyond.

Our tailored services include route scouting and selection, initial scale-up and risk management for early development. For later development, we provide process design, assessment and optimisation, scale-up for clinical and commercial manufacture, tech transfer and post-approval improvements. We possess specialist facilities in Process R&D, catalysis, high pressure reactions, crystallisation, preformulation, analytical development, HPAPI development and non-GMP material supply, and recently launched our oligonucleotides capability. Through our partnership with AGC Pharma Chemicals, we offer scalable small molecule API manufacturing, from grams to tonnes, with complete accountability of tech transfer.

Recent recognition includes the highly esteemed Queen's Award for Enterprise: International Trade 2022, the 2022 Bionow Awards (Export of the Year), the 2022 Inspire Business Awards (Business of the Year (25+ employees)), and the 2022 Wales Business Awards (Workplace Wellbeing).

Contact us to learn more about how CatSci can support your project: enquiries@catsci.com