



Future Opportunities - The Industry Perspective

Dial-a-Molecule Annual Meeting
21st June 2017

Classification: PUBLIC

ChemSInC (Chemical Synthesis Industries Consortium)

- Chemical synthesis delivers high value molecules, which are crucial to the UK economy
- To strengthen the UK-based R&D industries' leading position, the wider scientific community need to collaborate to advance synthesis and manufacturing science
- In response to significant structural changes in industrial and academic research delivery models, ChemSInC provides a network for industries engaged in discovery, process development and manufacture of small organic molecules
 - Driving new science and new ways of working
 - Ensuring the availability of key skills within companies and in future recruits
 - Articulating industry's priorities and strategic research requirements to the academic community, funding agencies and other influential bodies with a single unified voice



Precompetitive Collaboration on Enabling Technologies for the Pharmaceutical Industry

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Potential Areas for Precompetitive Collaboration	Details
Laboratory instruments	<ul style="list-style-type: none"> • Analytical, Measurement Tools • General Labware
Process Analytical Tools (PAT)	<ul style="list-style-type: none"> • In-situ monitoring and characterization • Data management
Chemicals, Reactions, Reagents	<ul style="list-style-type: none"> • New, improved, reagents and standards • New synthetic reactions
Green Chemistry	<ul style="list-style-type: none"> • Recycling • Alternative chemistries
Modeling, Computation, Informatics	<ul style="list-style-type: none"> • Engineering and Chemistry Tools <ul style="list-style-type: none"> ○ Process Modeling ○ Predictive tools for chemical properties • Best practices/methodology for validation of models used in regulatory filings
Automation	<ul style="list-style-type: none"> • High throughput experimentation • Lab Reactors
Unit operation equipment – primary and secondary	<ul style="list-style-type: none"> • Continuous processing • Granulating equipment • Drying equipment
Toxicology data	<ul style="list-style-type: none"> • Genotoxicity • Broad Toxicity

Synthesis Needs

Discovery



1000s compounds

1 – 100s mg

Need to deliver multiple compounds as quickly as possible

Substrate scope more important than yield

Cost not a concern

Advanced Testing



1 – 10 compounds

1 – 100s g

Typically working to tight deadlines (little time to redesign synthesis)

Yield and reliability more important

Cost a minor issue
(reagent availability on scale may be limiting)

Manufacture



Single compound

1 – 1,000 tons

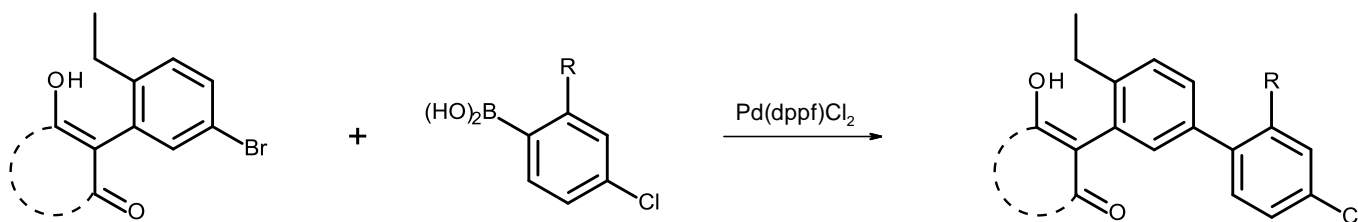
More thorough route investigation possible (but time still important)

Yield and reliability (> 99.9%) critical

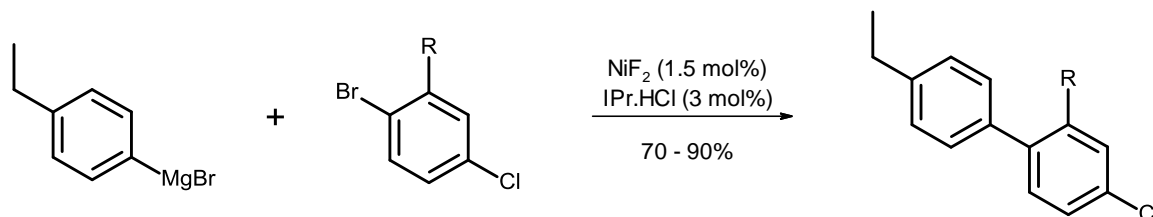
Cost critical

Scalability/Robustness

- Cost effective methods that will transfer from discovery to manufacture
 - Cheap metal catalysis that is as easy and versatile as palladium catalysis
 - Discovery start with Pd catalysts due to ease of purchase and handling, plus wide substrate scope



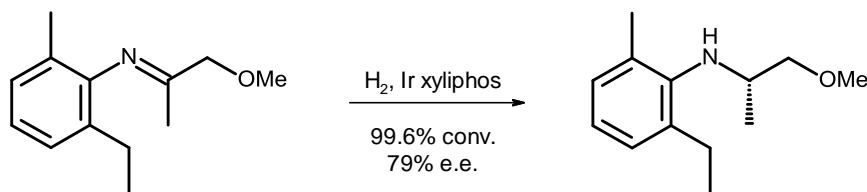
- Manufacturing prefer:
 - Use of non-precious metals, for cost reasons
 - Robust catalyst systems that will survive process chemistry conditions
- Requires development of new methods (and often new routes)



- Several months work

Catalyst Sustainability

- Replacement of precious metals
 - Not just Pd
- Alternative approaches
 - Recycling/reuse
 - Increased catalyst efficiency resulting in lower loadings
 - E.g. synthesis of *S*-metolachlor



- Process run on > 10,000 tonnes per year
- ton 1,000,000; tof > 200,000 h⁻¹;
- Development of enantioselective process took 12 years!

(Syngenta: *Topics in Catalysis* **1997**, 4, 275 – 282; *Adv. Synth. Catal.* **2002**, 344, 17 – 31)

Scalability/Robustness

- Other areas where versatile “research-friendly” methods would be valuable
 - Fluorination using fluoride
 - Recent introduction of anhydrous TMAF has increased scope, but reagent has limited availability
 - Large scale options?

Sustainable Chemistry

- Replacement of:
 - Polar aprotic solvents (DMF, DMA, NMP)
 - Less toxic/reactive and water immiscible
 - Alkylolithiums
- Clean oxidations and reductions
- Avoiding need for pre-activation
 - C-H activation
 - Regioselectivity issue
 - Terminal oxidation options
 - Amide formation

Selectivity

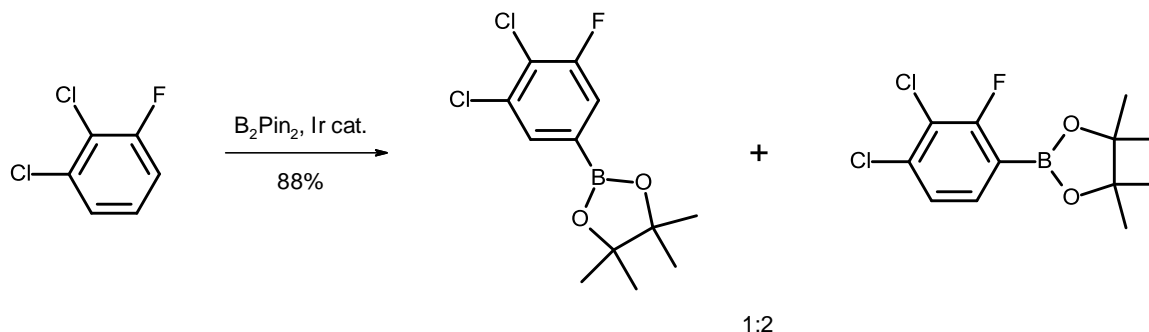
- Not just enantioselectivity

- Chemoselectivity

- Methods that provide selectivity in complex systems (late stage functionalisation)

- Regiocontrol

- Even some of the most selective methods give isomer mixtures for some substrates, which can be challenging, especially when scaling up



(Dow/U.Michigan: WO2015/035217)

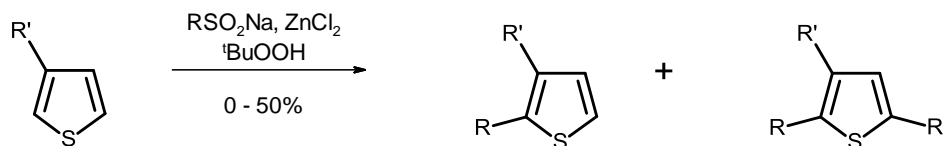
Late Stage Functionalisation

- Selective reaction of complex compounds

- Final drug molecules

(Merck: *Chem. Soc. Rev.*, **2016**, 45, 546 – 576)

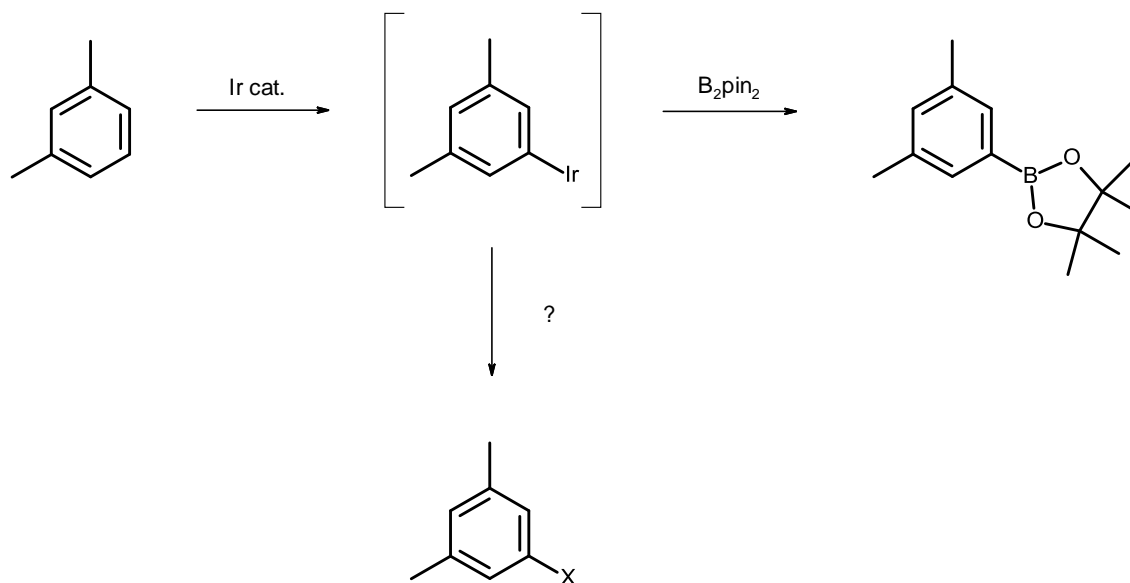
- Natural products
- Including remote/unactivated positions
 - Ability to overcome inherent reactivity of substrate is valuable
- Not all current methods are efficient or scalable



- Selective oxidation (including synthesis of metabolites)

Others

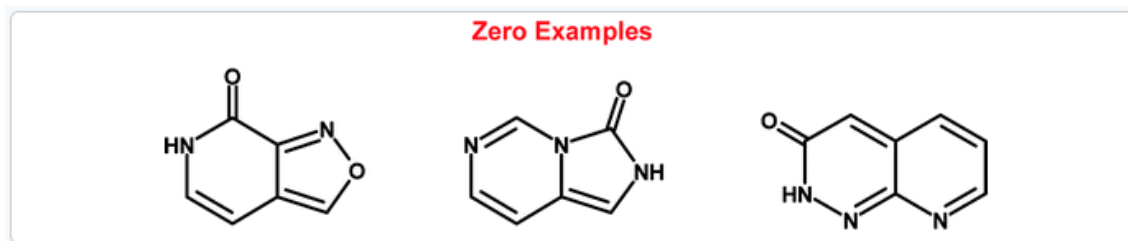
- New synthetic technologies that provide access to chemistry that is currently difficult/inefficient
 - Meta-functionalization of meta xylene, etc.
 - Ir chemistry expansion beyond borylation



- Improved approaches to dynamic kinetic resolution

Effective Routes to Key Classes of Molecule

- Versatile, scalable, ideally short, routes to structures of interest, with scope for further elaboration
 - 3D structures
 - Escape from flatland (Wyeth: *J. Med. Chem.*, **2009**, 52, 6752–6756)
 - Fluorine at sp^3 centres (alternatives to DAST, etc.)
 - Poly-substituted aromatics and heteroaromatics
 - Novel ring systems (UCB: *J. Med. Chem.*, **2009**, 52, 2952–2963)

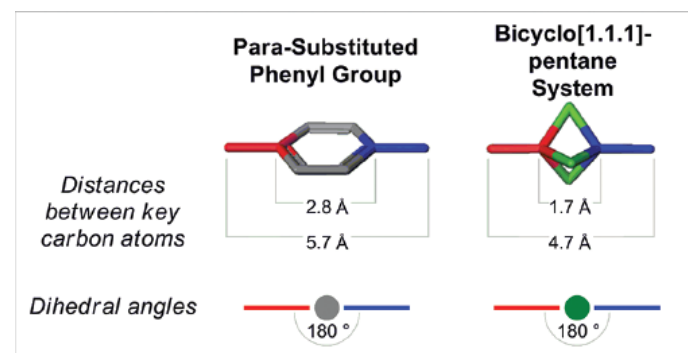


- Including partially saturated heterocycles

Design and Synthesis Combined

- Bioisosteres (Bristol-Myers Squibb: *J. Med. Chem.*, **2011**, *54*, 2529–2591)

- Mimic properties as well as shape and vectors
 - E.g. propellane mimics bond vectors for para-phenyl and improves physical properties (Pfizer: *J. Med. Chem.*, **2012**, *55*, 3414–3424)
 - Propellane acid pKa closer to benzoic acid than other alkanolic acids



- Molecules with predictable properties

- Physical and biological
 - Metabolism
 - Bioavailability
 - Toxicity

- Catalyst/biocatalyst design

Other Areas of Interest

- Process Technologies
 - E.g. reactor design
 - Including for new types of chemistry (photocatalysis)
- Data Capture and Use
 - Including predictive tools
 - For example, advanced retrosynthesis tools, including the prediction of reaction products (by-products) and kinetics
 - Prediction of solvent effects

Novel Concepts and Unforeseen Opportunities

- As well as the things we already know about, we also want the unexpected ideas which may prove to be much more innovative and disruptive to the current ways of doing things
- “It’s really hard to design products by focus groups. A lot of times, people don’t know what they want until you show it to them.”
 - (Steve Jobs)
- “If you ask people what they want they tell you a faster horse.”
 - (Henry Ford, allegedly)



Date for Your Diary

- ChemSInC- Academic exchange meeting
 - Supported by Dial-a-Molecule
 - 25th and 26th September
 - At Imperial College
 - More details to follow