



High-Speed Reaction Optimisation using an Automated H-Cube System

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Overview

- Background to Robotic Synthesis Team and High-Speed Synthesis at Jealott's Hill
- History of H-Cube at JH: from base unit to fully automated system
- Examples of optimisation work

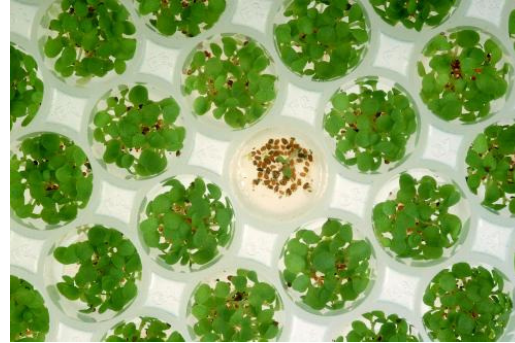
Robotic Chemistry Team

- Automated synthesis tools for medium size reaction arrays
 - Analogue syntheses
 - One x many or Many x Many
 - Reagent screening
 - Full matrices
 - DoE, e.g. Latin Squares¹
 - Reaction optimisation and reagent screening
- Technology Foresight & champion new methods/equipment
 - Microwaves, Zymark robots, H-Cube, Flow Reactors

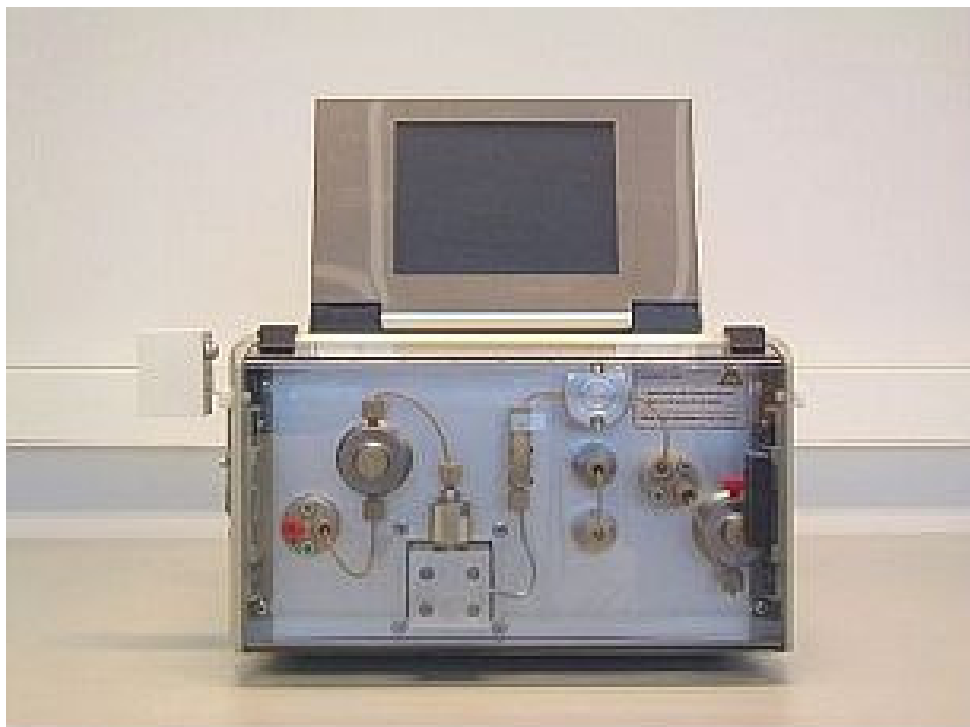
1a) Rose V. S., Stevens A., *Curr. Opinion Chem. Biol.* **2003**, 7(3), 331-339; b) Lipkin M. J., Rose V. S., Wood J., *SAR & QSAR in Env. Res.* **2002**, 13(3-4), 425-432.

Why is rapid optimisation important?

- Most compounds screened *in planta*
- Progression through screening cascade can be rapid
- Field-trials have specific application windows and seasonal
- May require 10- or 100-fold scale-up
- Hydrogenation a common reaction
 - Intermediates
 - Final products

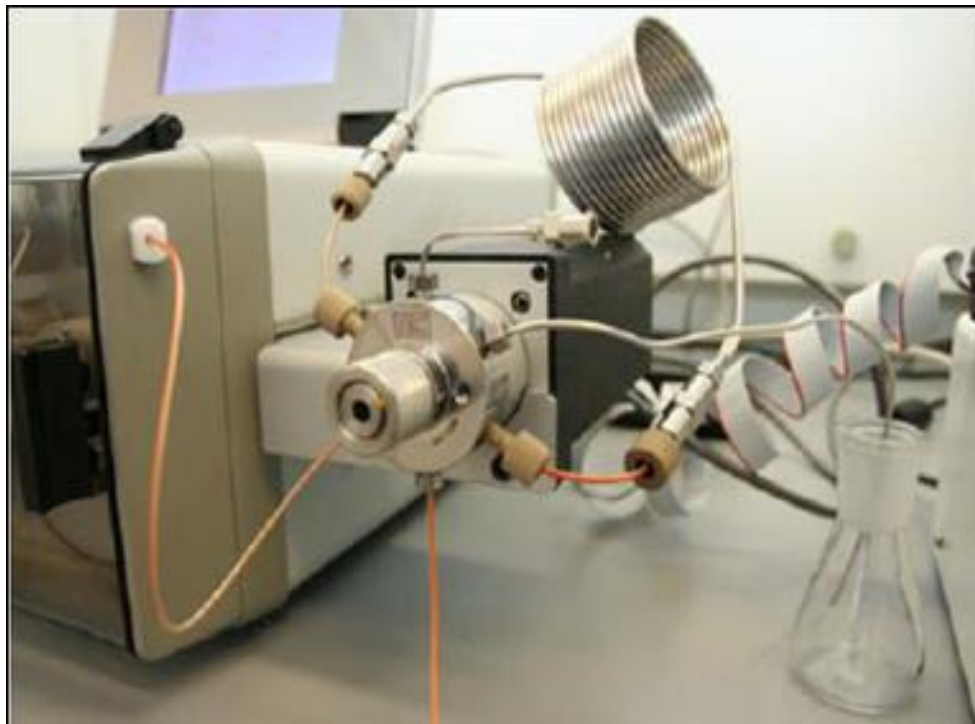


Evolution of H-Cube system



- **2005: acquired base unit**
 - Regarded as ‘specialist’ equipment
 - Not well suited for small volumes
 - Used mainly for intermediate syntheses
 - Labour intensive

Evolution of H-Cube system

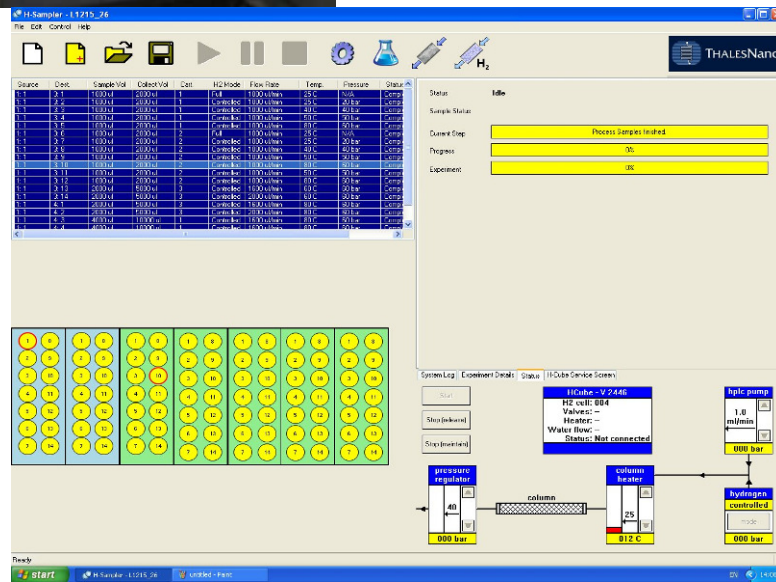


- 2005: acquired base unit
- 2006: injection module
 - Easier to run small scale (<5 ml) reactions
 - Operated as a service to CPR Chem
 - Mainly library work but some optimisation

Evolution of H-Cube system

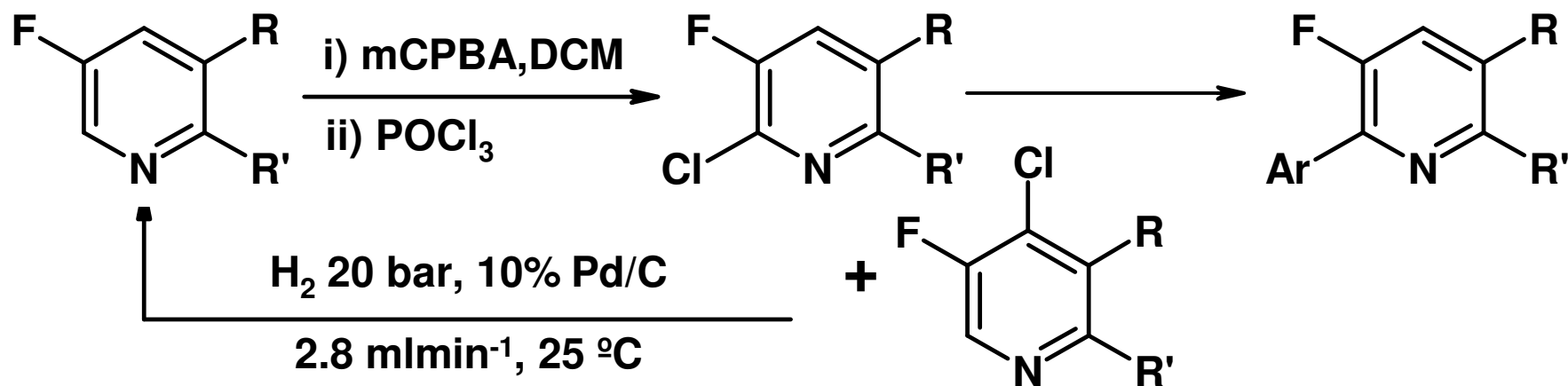


- 2005: acquired base unit
 - 2006: injection module
 - 2007: Liquid handler
- Can screen conditions more efficiently
 - User-friendly interface allows open-access operation



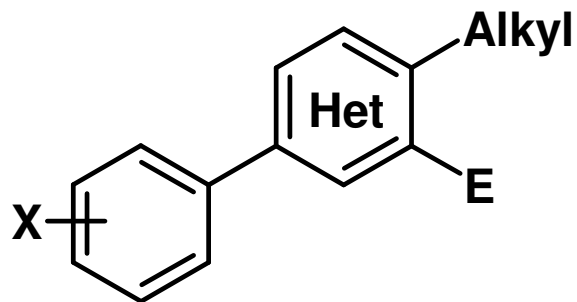
Dehalohydrogenation

- o-Substituted pyridine obtained *via* cross-coupling of heteroaryl-chloride.
- POCl₃ chlorination of N-oxide selectivity only approx. 2:1 but isomers are separable
- Found conditions that enabled recycling of unwanted isomer.
- Issue of over-reduction required mild conditions
 - Incomplete conversion but could recirculate reaction mixture
 - Ability to monitor reaction mixture in real-time crucial
- Process scaled up to 15 g with 74% conversion



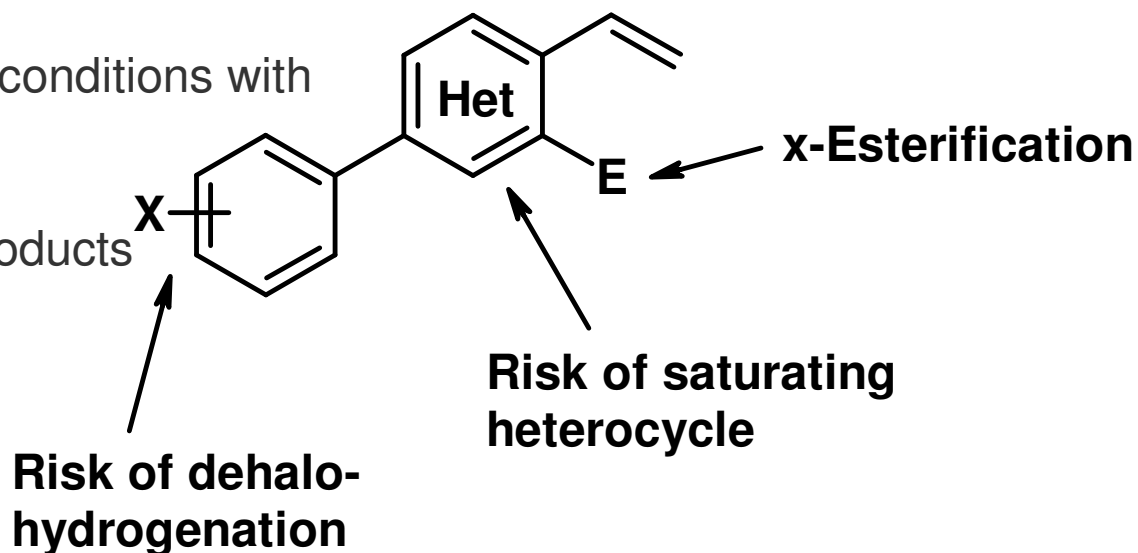
Chemoselectivity through catalyst choice

- Direct alkylation in *para*-position of heterocycle difficult
- Investigated cross-coupling followed by reduction of resultant vinyl moiety



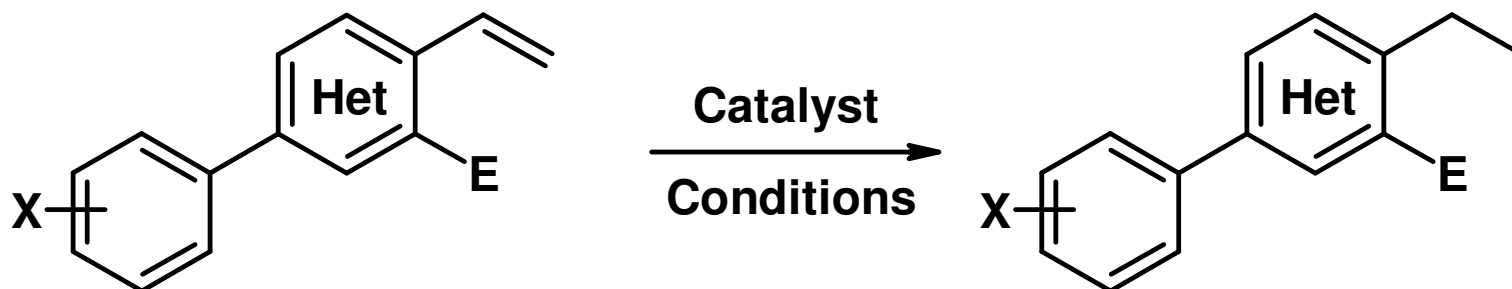
Chemoselectivity through catalyst choice

- Direct alkylation in *para*-position of heterocycle difficult
- Investigated cross-coupling followed by reduction of resultant vinyl moiety
- Molecule presents several challenges
- Investigated many conditions with 10% Pd/C
- Many undesired products



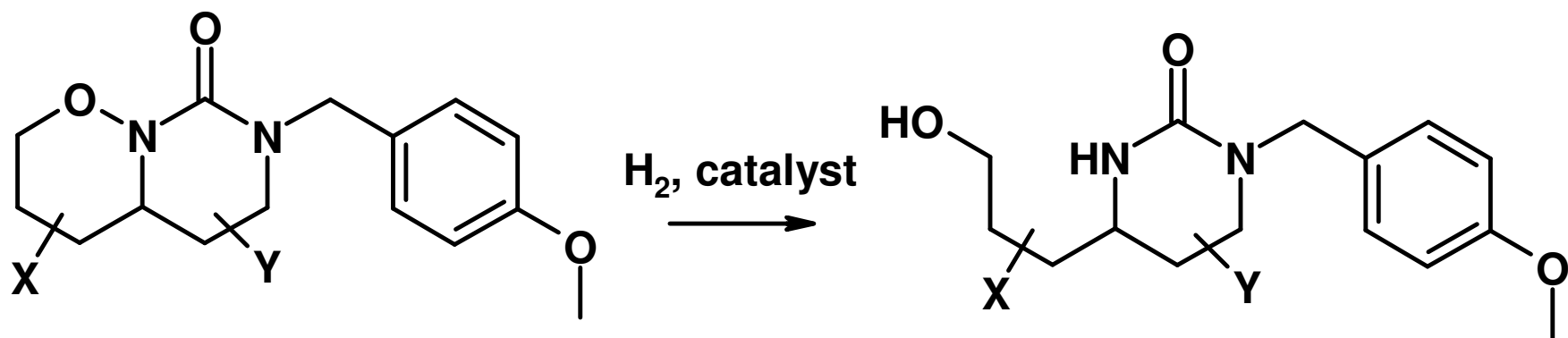
Chemoselectivity through catalyst choice

- Direct alkylation difficult in this position
- Cross-coupling followed by vinyl-reduction
- Molecule presents several challenges
- Eventually tried 5% Ir/CaCO₃
- Successful even under relatively mild conditions
 - Complete conversion at 25 °C, 20 bar, MeOH 0.05 M, 1 mlmin⁻¹



N-O Reductive cleavage

- Previous routes had relied upon $\text{Mo}(\text{CO})_6$ – not suitable for scale-up
- Literature suggests $\text{H}_2/\text{Raney Ni}$,² Pd ³
- All attempts on H-Cube failed

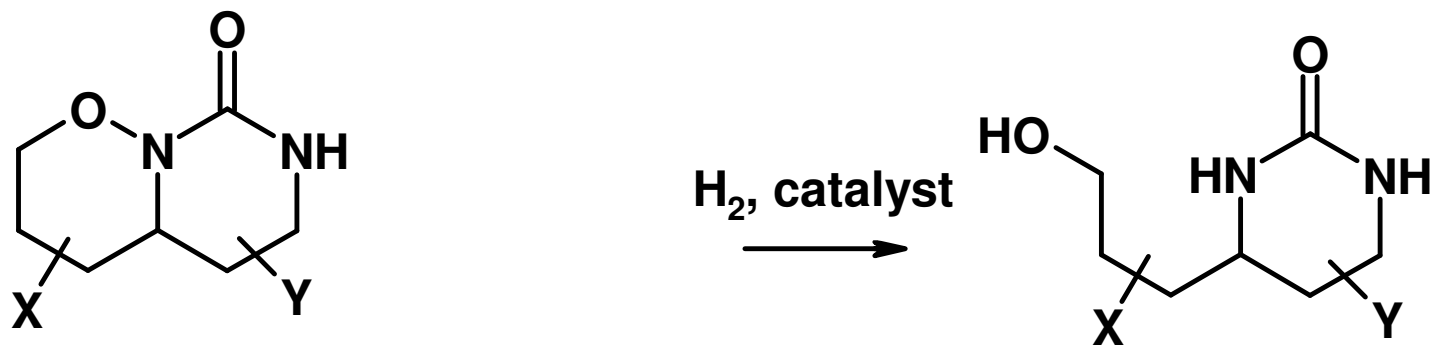


2 Huisgen R., Grashey R., Seidl H., Hauck H., *Chem. Ber.*, **1968**, 101, 2559.

3 a) Kim K.-H., Miller M. J., *Tetrahedron Lett.*, **2003**, 44, 4571 b) Quadrelli P., Fassardi V., Carderelli A., Caramella P., *Eur. J. Org. Chem.*, **2002**, 2058.

N-O Reductive cleavage

- Removal of protecting group led to some reactivity with Raney Ni and improved solubility
- <2 wks to optimise conditions and scale-up for field trials
- Using liquid handler able to set up optimisation run (full matrix)
 - Temp.: 25 – 80 °C
 - Pressure: 1 – 100 bar
 - Solvent: MeOH, EtOH, ± EtOAc
 - Additives: Et₃N, AcOH



N-O Reductive cleavage

- Using liquid handler able to set up optimisation run (full matrix)

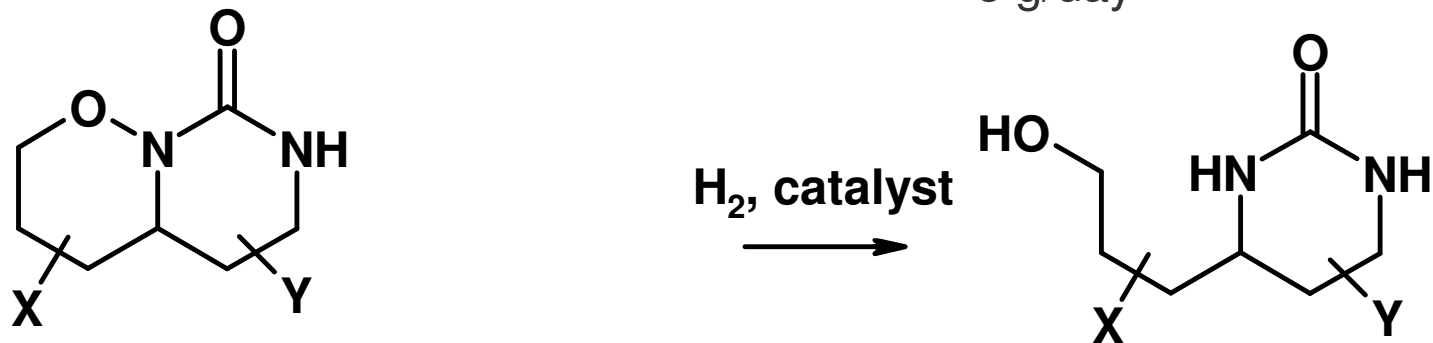
Temp.: 25 – 80 °C

Pressure: 1 – 100 bar

Solvent: MeOH, EtOH, \pm EtOAc

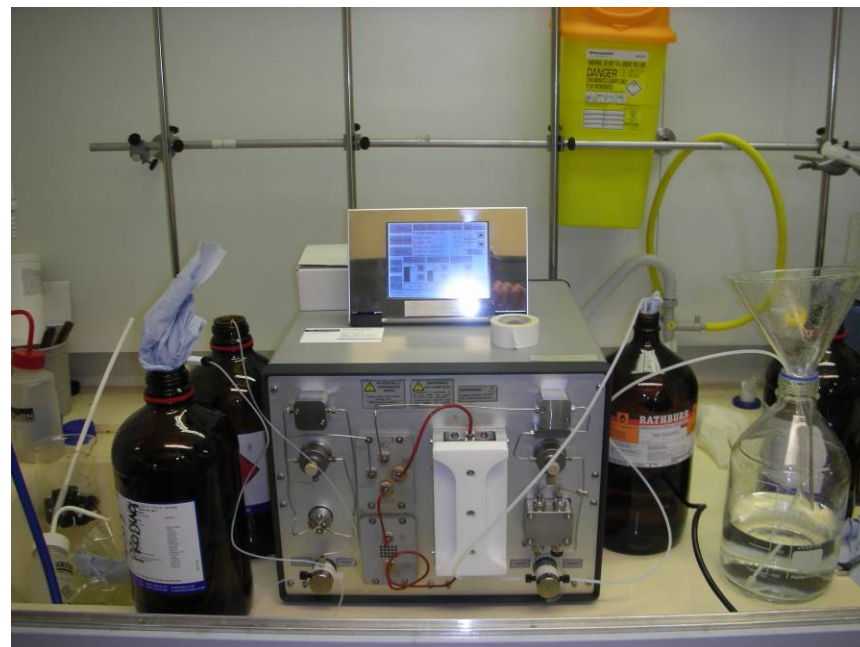
Additives: Et₃N, AcOH

- Optimum conditions on H-Cube
80 bar, 100 °C, Raney Ni (70 mm)
MeOH, no additive, 1.60 mlmin⁻¹, >95%
- Issues still with catalyst die-off (5~7 g)
(heavy metal residues) and solubility
- ~8 g/day



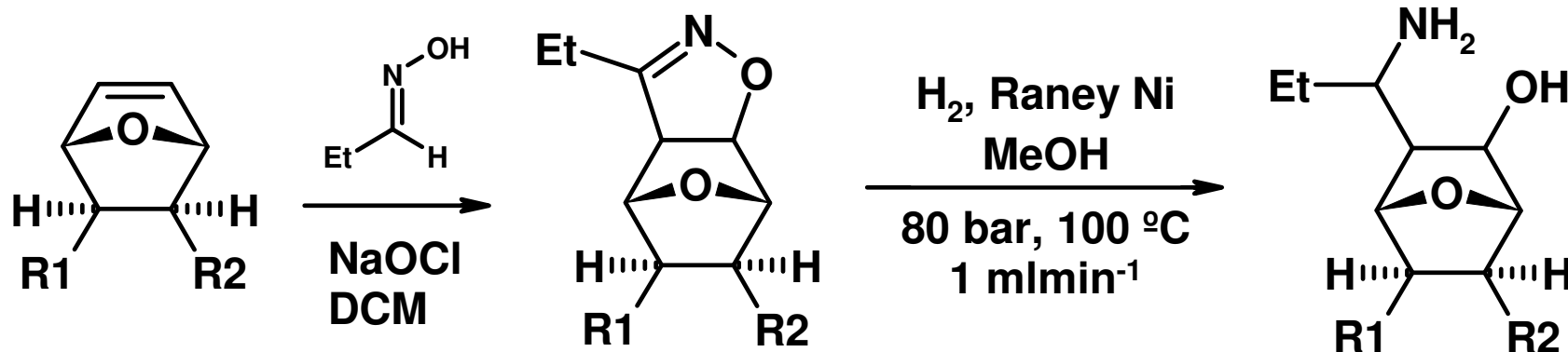
Scale-Up with H-Cube Midi

- Field-trial synthesis campaign coincided conveniently with evaluation
- Direct transfer of previously optimised conditions
- 200g of material processed in 4 days
- Ran in tandem with autoclave method using H-Cube conditions as starting point
 - High temp (100 °C) required for catalyst regeneration but can drop pressure to 4 bar (t = 5 h)
- Re-screened wider range of catalysts: Pt/C, PtO₂, Pd(OH)₂, Rh, Ru → no rxn

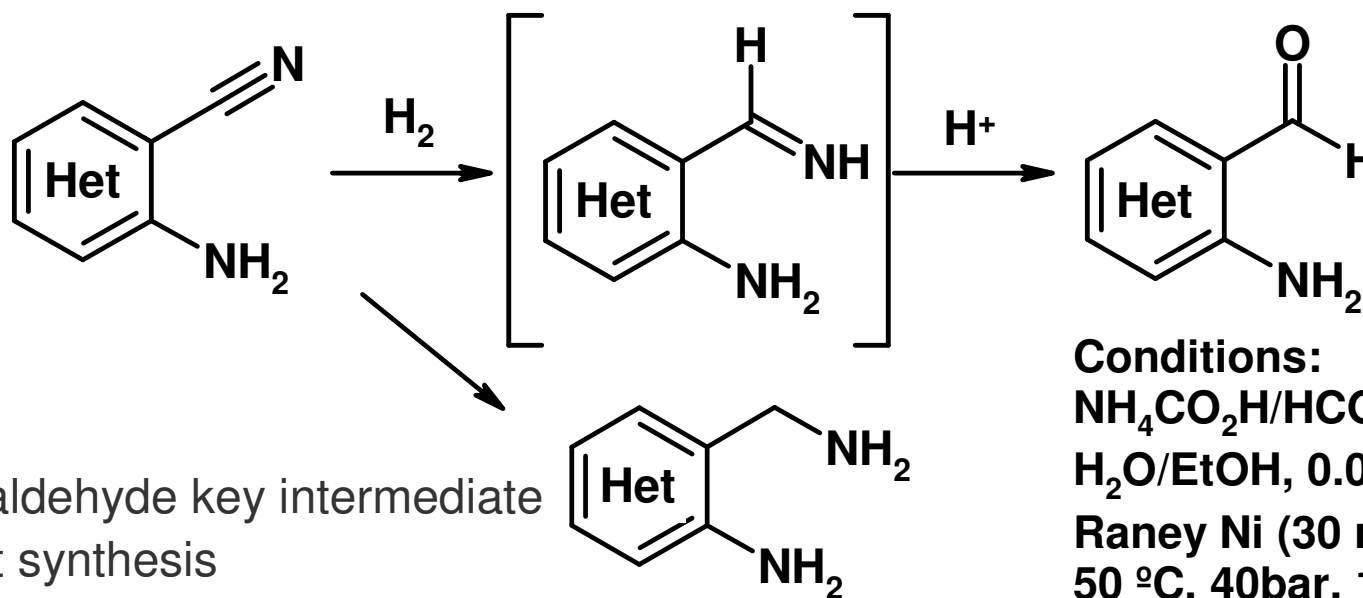


N-O Cleavage *cont.*

- Using previous N-O cleavage conditions, we were able to apply this chemistry to other projects.
- (3+2)-DPCA adduct further exemplified by ring opening



Tandem Reduction/Hydrolysis



- Amino-aldehyde key intermediate in target synthesis
- Idea to partially reduce nitrile to imine, then acid hydrolysis
- Tried several low activity catalysts (Ir, Rh, Ru) and/or mild conditions (RT, <20 bar), ± isolation
 - Gave SM/diamine mixtures
- Used H-Cube in gas free mode and generated H₂ *in situ* from HCO₂⁻ / Raney Ni
- Diamine observed (w/ leaching)
 - 'Blank' injection to tame catalyst

Summary

- We have put together a fully automated, user-friendly system that can rapidly optimise hydrogenation reactions
 - Savings in time and materials
 - System flexible enough to cope with library syntheses, larger scales, etc.
- Demonstrated system complements traditional techniques and offers access to new chemistries
- Rolled out technology across CPR Chemistry
 - Method of first rather than last resort

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