



Experiences with H-Cubes at Novartis Horsham

Thales User Group Meeting, Cambridge, 17th Feb 2009

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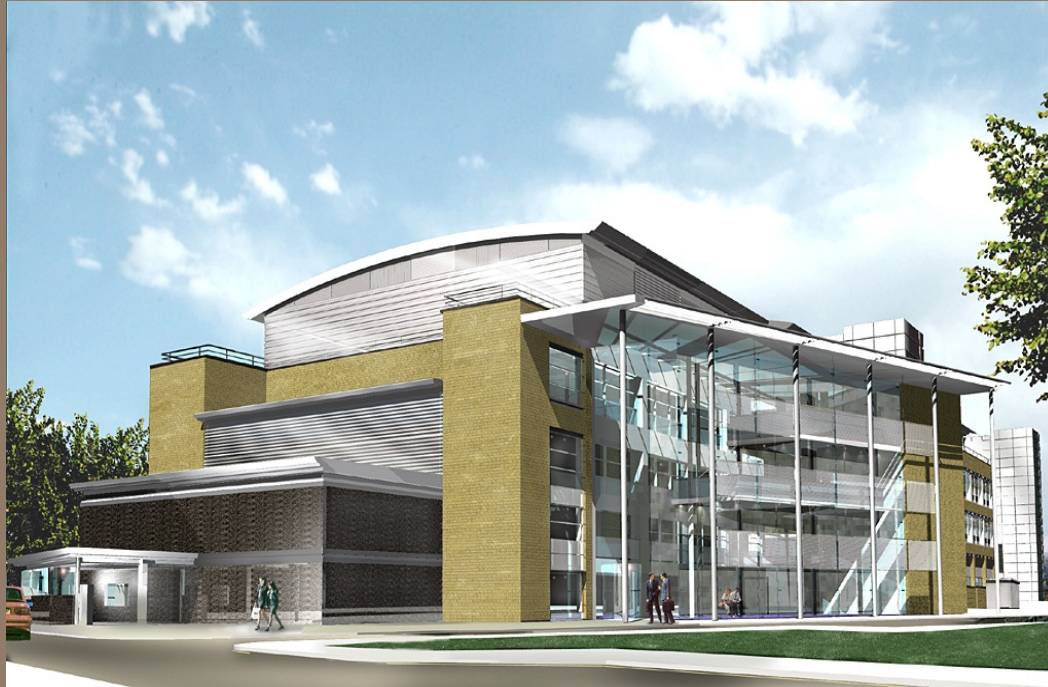
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Experiences with H-Cubes at Novartis Horsham

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- About NHRC
- The Equipment
- Routine Chemistries
- Interesting Examples
- Future plans

Novartis Horsham Research Centre



- Horsham, UK is about 100 km south of London and is the location of the main NIBR site in the UK. The 4 businesses based in Horsham are NIBR, Development, Pharmaceutical Operations, and Novartis Consumer Health.
- Approximately 300 NIBR associates – from most of the NIBR Global Line Functions – work in Horsham. This includes Translational Sciences (TS), Global Discovery Chemistry (GDC) & NIBR Information Technology and Automation Services (NITAS).

Of Chemists and H-Cubes

...and how to get the former to use the latter

- 2 H-Cubes installed in May 2006
- Initial take-up was very slow
 - A lot of the chemists are resistant to change and new technology, and for the first year or so use was sporadic and only by a handful of 'early adopters'
- However...
 - Usage has gradually increased and there are now about 20 regular users. Once people have been persuaded to use them they generally see the benefits and continue to do so.
 - Partly driven by HSE – it is strongly advised that the H-Cube should be the first port of call for hydrogenations, and required for Raney Ni and PtO₂
 - Also driven by convenience – quick and easy sampling for LCMS; no need for the “buddy” system operated in the traditional hydrogenation lab
 - And finally, an influx of younger chemists who are more accepting of new technology!

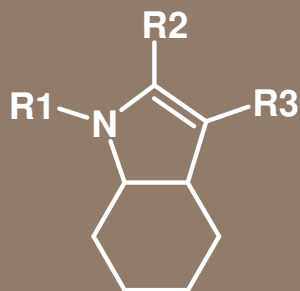
Routine chemistries

- Looking through the log book, certain types of reaction crop up again and again
- The usual suspects
 - Removing benzyl groups and CBZ protecting groups
 - Reduction of nitriles to amines
 - Reduction of nitro groups to amines – avoiding the use of SnCl_2
- Reduction of aromatic heterocycles to alicyclic systems
 - Pyridines, indoles & indazoles
 - Tried some chiral reductions but with limited success

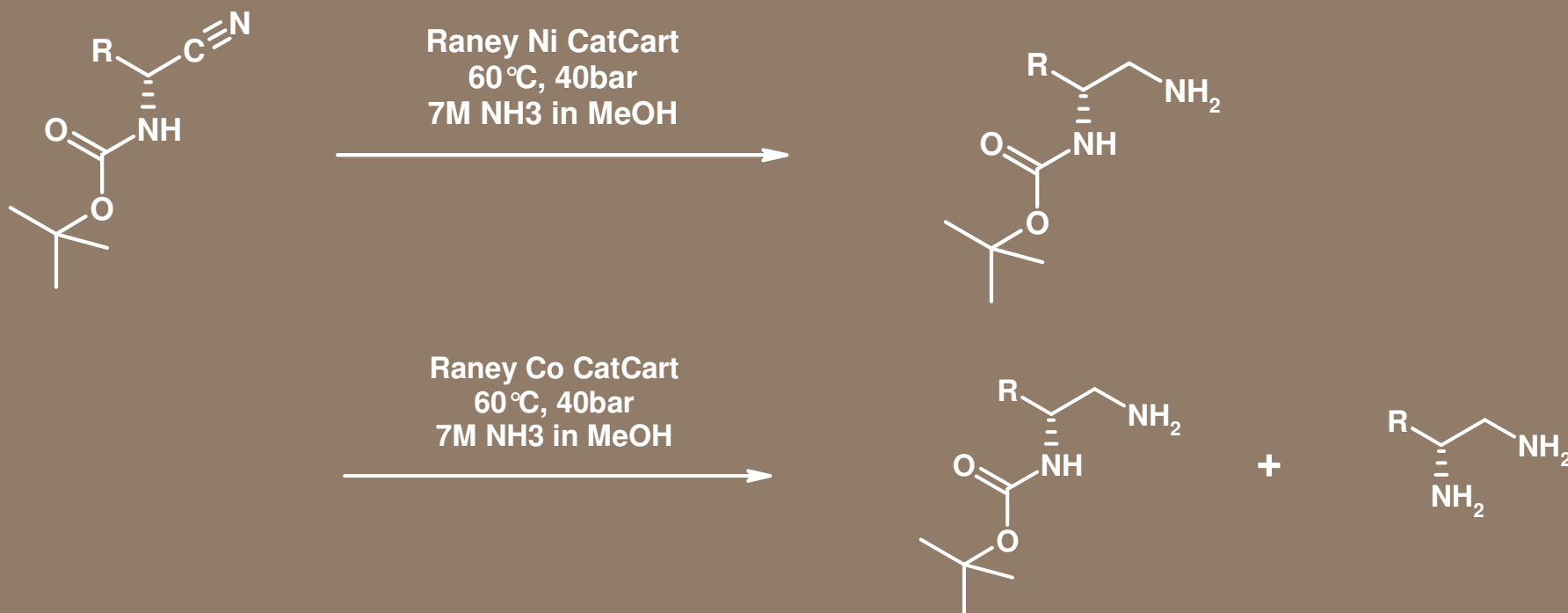
Indole Reduction



- LC-MS indicated addition of 6H
- NMR studies confirmed the structure as:



Comparison of Raney Ni with Raney Co



- Undesired loss of protecting groups is a common side-reaction
 - But it can often be avoided by careful optimisation of conditions

Future plans

- Upgrading one of our machines to the stainless steel version to allow us to perform deuterations
 - This would allow us to synthesise deuterated compounds for metabolism studies
 - Our machines do not have the necessary “Purge Water” command in the software
- No current plans to introduce an automated system
 - although usage is increasing capacity is sufficient for the time being
- Scale-up lab considering the H-Cube Midi
 - As the H-Cubes are used more frequently scale-up will eventually become an issue.
 - Novartis in Basle have recently acquired one so Horsham scale-up lab are waiting for feedback from them.

■ Questions?

■ Backups

Chiral Reductions

- Reduction of aromatic heterocycles
- Proceeds smoothly (albeit slowly) using 10% Pd-C
- Unfortunately reaction did not proceed at all with the chiral catalysts we tried
 - Pd(II)EnCat BINAP
 - Al₂O₃/HPA/[Rh(COD)(S,S)-BDPP]Cl
 - Al₂O₃/HPA/[Rh(COD)(DIPAMP)]BF₄
 - Al₂O₃/HPA/[Rh(NBD)(S,S)-BDPP]PF₆