The H-Cube- Continuous-flow Hydrogenation

Kathleen Battista, Regional Product Representative
Thales Nanotechnology Inc.

H-Cube is a winner of the 2005 R&D 100 Award for the top 100 most technically significant products introduced to the market in 2005.

Thales Nanotechnology

- Based in Budapest, Hungary.
- Formed in 2002 and started specialising in microfluidics, „Lab on a Chip" chemistry.
- Moved up in scale and onto designing reactors to suit specific hazardous reactions

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Why improve hydrogenation?

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- Accounts for 10-15% of reactions in the chemical industry

- Current batch reactor technology has many disadvantages:
  - Time consuming and difficult to set up
  - Expensive – separate laboratory needed!
  - Catalyst addition and filtration is hazardous
  - Analytical sample obtained through invasive means.
  - Mixing of 3 phases inefficient - poor reaction rates

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R&D 100

H-Cube Continuous-flow System

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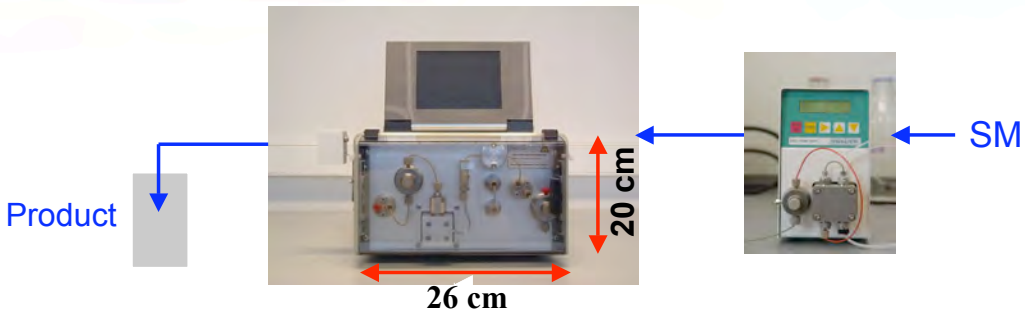

- **HPLC pump flows a continuous stream of solvent into reactor.**
- **Hydrogen generated from electrolysis of water**
- **Hydrogen is mixed with sample, heated and passed through a catalyst cartridge. Up to 100°C and 100 bar. (1 bar=14.5 psi)**
- **Hydrogenated product emerges continuously into reaction vial.**

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R&D 100

H-Cube Reaction Line

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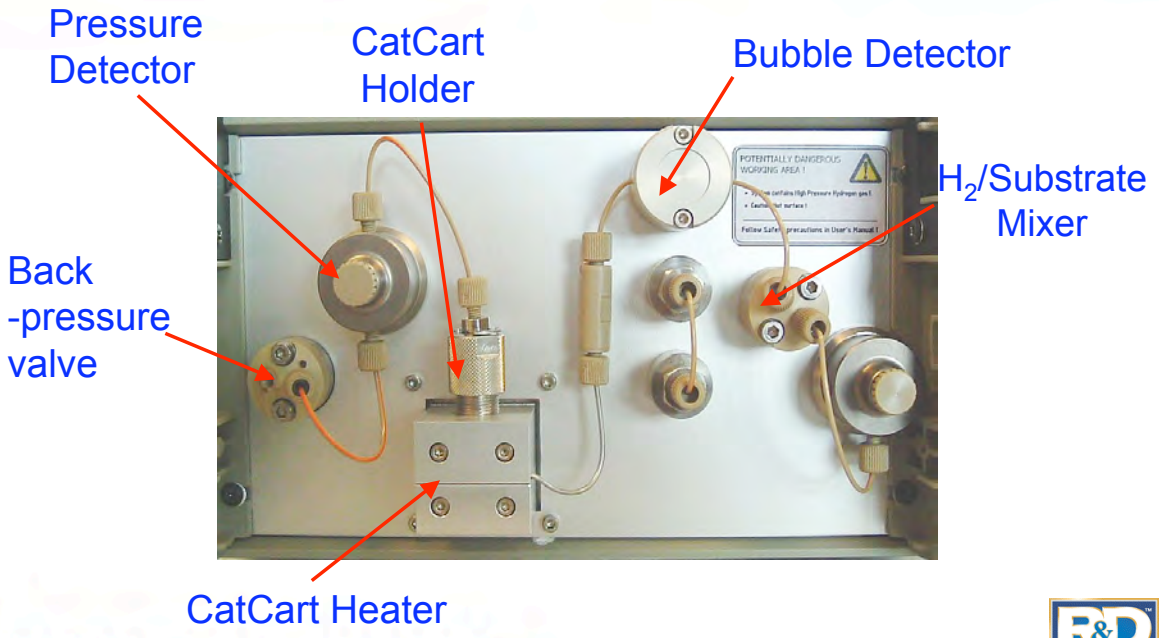

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Catalyst System-CatCart

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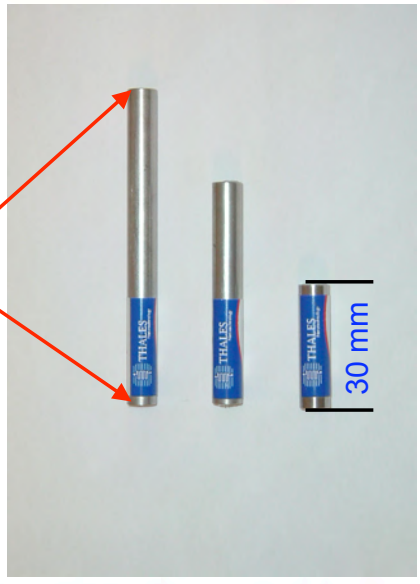

- Catalyst contained in sealed disposable cartridges
  - No filtration necessary
- Catalysts used:
  - 10% Pd/C
  - Raney Ni
  - Pearlman's Catalyst
  - 5% Rh/C
  - 5% rhenium/C
  - PtO_2
  - Lindlars catalyst
- Smallest catalysts can reduce 10mg-5g of substrate
- Largest CatCarts up to 100g

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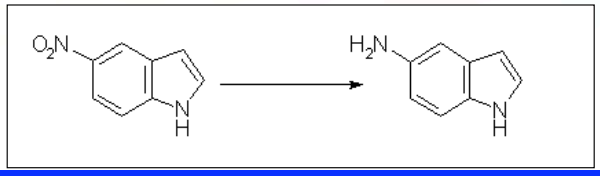
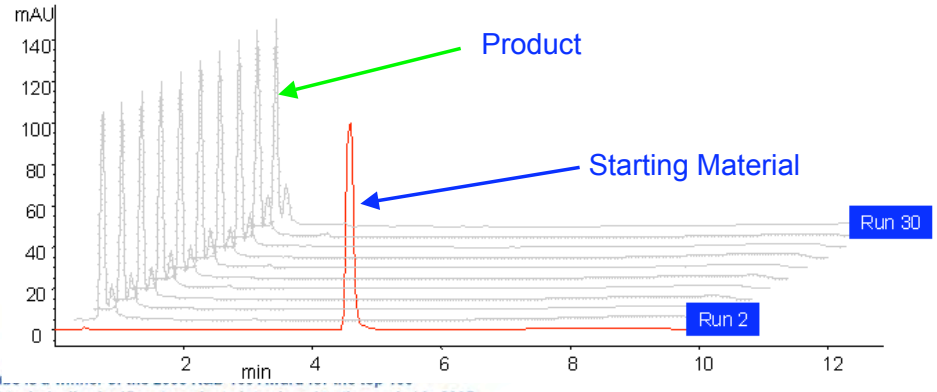
How long can a CatCart™ be reused?



H-Cube conditions: 0.1M, [50:50] EtOAc:EtOH, ~1 bar, 30 ºC, 1 mL/min;
Total material processed = 30x 1mmole fractions = 30 mmoles = 4.85 g with 140mg Pd/C



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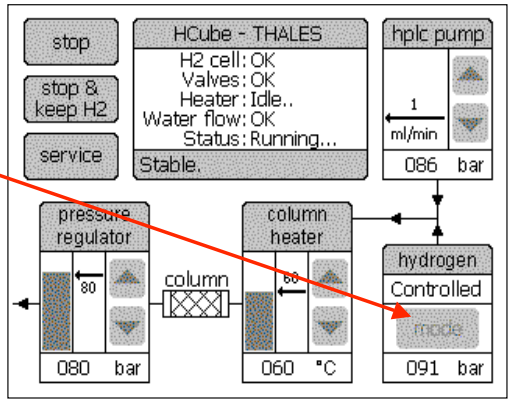
H-Cube System-Monitoring Screen

- New monitoring screen with 3 new modes
  - Full H_2
  - Controlled H_2
  - No H_2
- Allows greater reaction control and non-hydrogenations to be performed



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Faster Optimization

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- Monitor reaction progress after 4 minutes!
- Quickly change pressure and temperature and monitor the effect.
- 50 reaction conditions can be validated in a day.

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R&D 100

Chemistry Reaction Examples

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- Reductions
  - Nitro group
  - Nitrile group
  - Imine
  - Heterocycle
  - C=C bond
  - Alkyne
  - Dehalogenation
  - Desulphurization
  - Oxime
- Deprotection
  - N-benzyl
  - O-benzyl
  - cBz
- Deuteration

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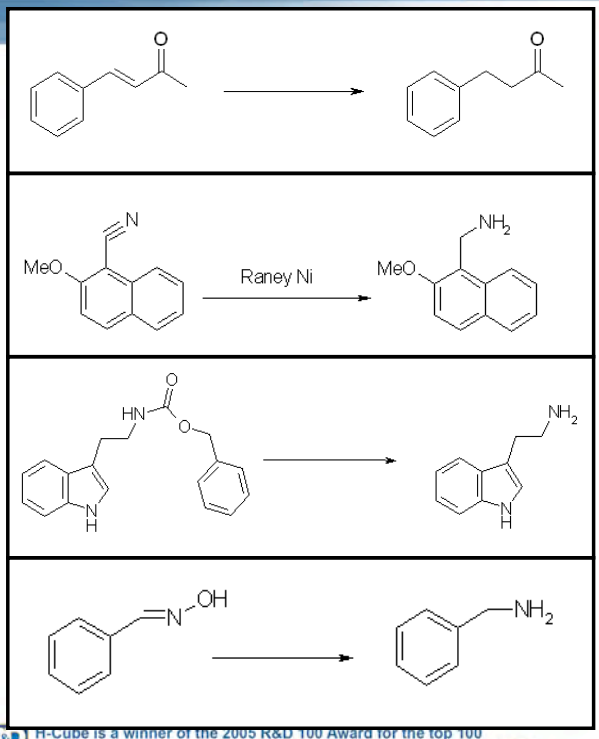
R&D 100

Validation Reactions



10% Pd/C, RT, 1 bar
Yield: 86-89%

Raney Ni, 70°C, 50 bar
Yield:>85%
2M NH_3 in MeOH

10% Pd/C, 60˚C, 1 bar
Yield:>90%

Raney Ni, 80˚C, 80 bar
Yield: 90%

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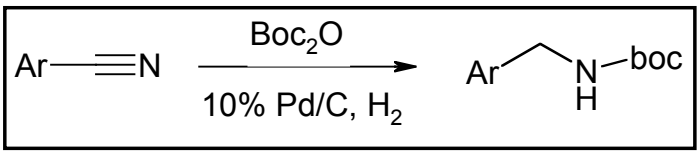
Validation reactions (Complex): 2-step-1 flow reaction



- Batch reaction took 3 days
- H-Cube performed reaction in 3 minutes!
- 70 bar, 70°C
- Quantitative yield and conversion.

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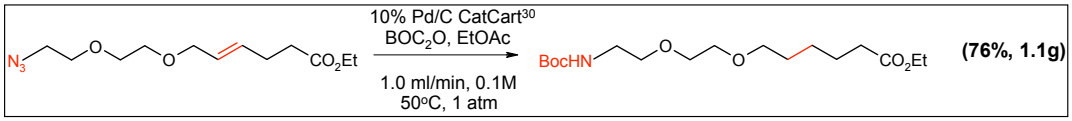
Validation reactions (Complex): Hazardous functional groups



- Highly exothermic reaction
- Low quantities react at any one time-higher safety
- H-Cube monitors and regulates temperature.
- High yield
- 3 group conversions in 1 flow through

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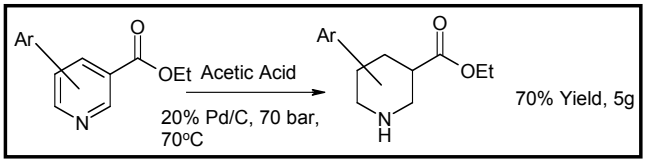
Validation reactions (Complex): High difficulty

Difficult to reduce stable aromatic heterocycles.



Ethanol, 10% Pd/C, 80-90˚C, 60-70bar
Scale 3-5 g, 1-2 hours
60-70% Yield, 95% NMR

Batch reaction took 3 days with incomplete conversion!

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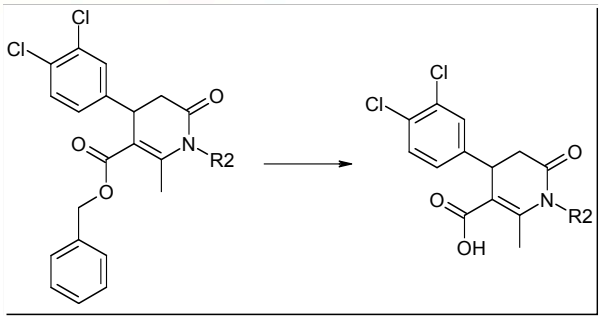
Hydrogenation without dehalogenation



T [°C]	p [bar]	Cat.	f.r. [ml/min]	sol.	LCMS [%]	Cycles
25	30	10% Pd/C	1	EtOH	65	1
25	30	10% Pd/C	1	EtOH	90	2

Mild conditions to avoid dechlorination!

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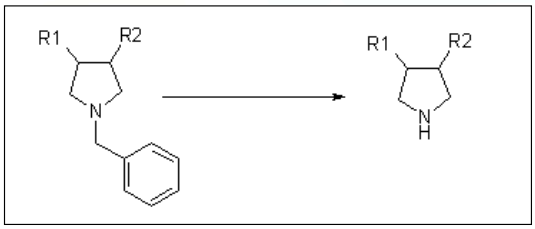
Longer CatCarts=Faster Production

Difficult debenzylation-small CatCarts-incomplete conversion

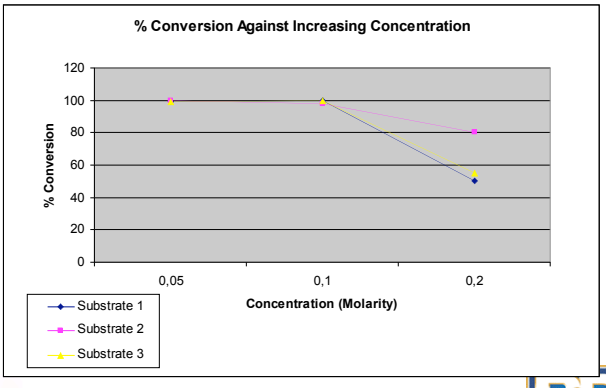
100% conversion with longer CatCarts at 2ml/min



Further tests carried out on concentration

Increase from 0.05M-0.1M

Production increased fourfold



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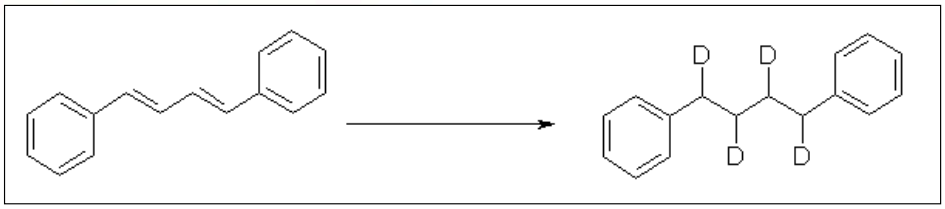
Deuteration of double bond



- Using D_2O instead of H_2O produces D_2 gas
- Above experiment successful by NMR
  - Conditions: toluene solvent, RT, and 1 bar
- On-going experiments with LCMS sensitive reactants
- Looking for collaborative partners for future developments

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Automated High-throughput Hydrogenation

- Useful for conducting small-scale reductions as part of a final library step.
  - Nitro reductions can now be performed as a final step to avoid protection and de-protection steps.
  - Benzyl protecting groups can now be used instead of BOC groups, avoiding TFA and possible decomposition

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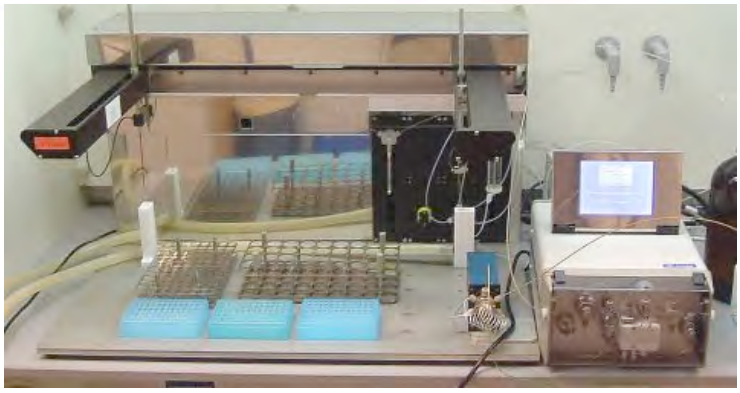
Cavro - H-Cube Integration



- H-Cube integrated into CAVRO work station
- Automated injection and collection
- Timed injections

Richard Jones, Ferenc Darvas *et al*, QSC, 2005, 24 (6), 722-727;
Journal of Combinatorial Chemistry, **2006**, *8(1)*, 110-116

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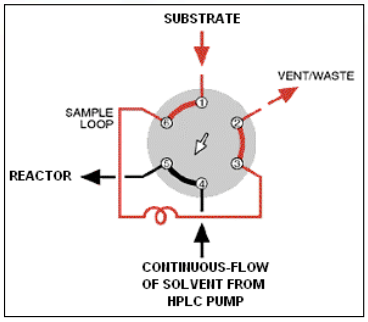
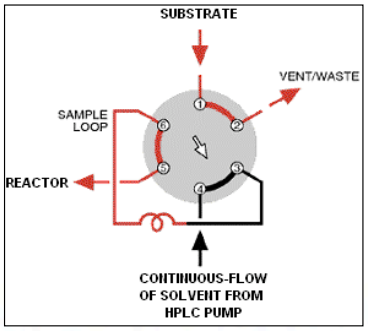
How does it work?





- Sample is injected into the loop
- Solvent is pumped through the valve into the H-Cube

The valve changes.....

- The substrate is pushed out of the loop into the H-Cube.
- It reacts on the H-Cube and the fraction is collected

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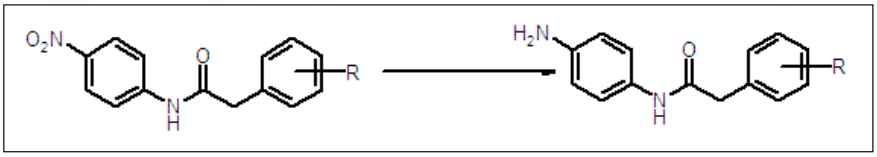
Nitro-library reduction



•Solvent: MeOH, Catalyst: 10% Pd/C, 1 bar, 30ºC
•Injection time: 25 mg every 6 minutes

•50 compounds reduced in one run~5 hours

•Yield >75%
•No cross contamination and no catalyst deactivation

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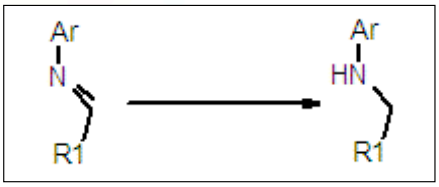
Imine library reduction at high pressure



•Reduction failed using cyanoborohydride or triacetoxyborohydride

•Reductions tested from 1-90 bar and RT- 90ºC on H-Cube
•Best results: 70mm Raney Ni cartridge, MeOH, 80 bar, 55 ºC
•Flow-rate: 2ml/min
•50 compounds tested, 10 minutes per reaction, no contamination
•100% conversion

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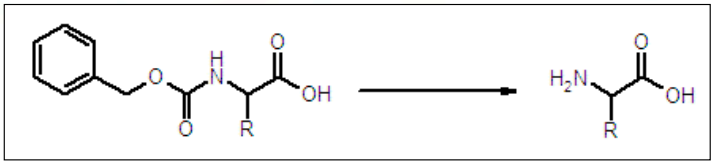
Cbz-deprotection Library



•Useful for peptide synthesis or as an alternative to using BOC protecting grps-avoiding harsh acidic deprotection

•Preliminary results show 100% conversion at 70ºC,1 bar, Using 10% Pd/C

•50-100 member library synthesis has been synthesized

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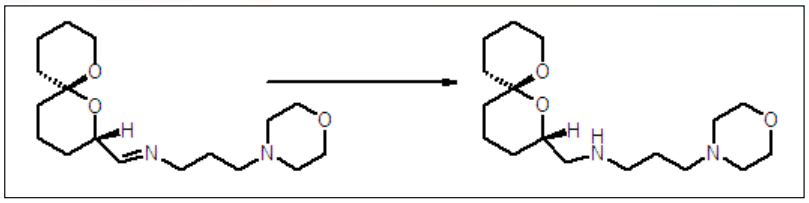
Chemoselective reduction of imines



•Use of polymer supported borohydride reagents failed

•11 different imines were reduced on the H-Cube

•Best conditions 0.025M, 1ml/min, 10% Pd/C, RT, 20 bar

•Quantitative yield-side groups not reduced

•Further studies to link flow reactors to carry out multi-step syntheses

Saaby, S., Ladlow, M., Ley, S.,*Chem. Commun.*, **2005, *23*,** 2909 – 2911

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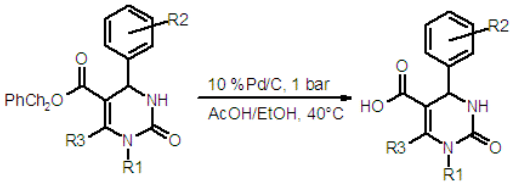
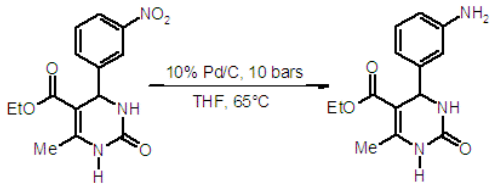
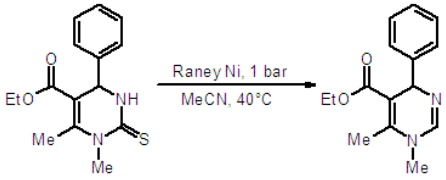
Increasing diversity to library scaffolds



4 different scaffolds underwent Hydrogenolysis to afford yields >80%



25ml, 0.025M
Afforded quant. Yield.



Quant. Yield
Batch reactor=1 hour reflux
H-Cube=25 minutes

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Future developments: X-Cube

Continuous-flow reactions at high T and high pressure without hydrogen.

- Temperature up to 200ºC
- Pressures up to 200 bar

Use of multiple cartridges for different steps

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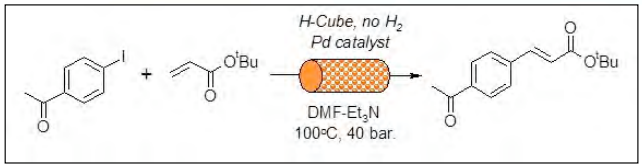
Heck reactions using Pd-EnCat

- H-Cube used in 'no H_2' mode as a generic flow reactor module for preliminary studies into Pd-mediated cross-coupling
- Reactions were conducted sequentially on a 5-10 μmol scale, residence time = 10-20 min
- CatCarts were packed with a variety of Pd catalysts
- Nb: Pd-EnCat™ are polyurea microencapsulated Pd (0) particles



Run	Catalyst	Flow Rate (ml/min)	Conversion (%)	Purity (%)
1	10% Pd/C	0.1	66	9
2	10% Pd/C	0.1	84	19
3	10% Pd/C	0.1	81	7
1	Pd-EnCat™	0.1	100	55
2	Pd-EnCat™	0.1	88	81
3	Pd-EnCat™	0.1	76	76
4	Pd-EnCat™	0.1	80	80
1	Pd-EnCat™	0.05	100	93
2	Pd-EnCat™	0.05	100	100
3	Pd-EnCat™	0.05	94	94
4	Pd-EnCat™	0.05	91	92

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Future X-Cube Chemistry

- Diels-Alder
- Diazo couplings
- Grignard reaction
- Carbanion chemistry
- Enol ethers
- Michael additions
- Pyrazole synthesis
- Suzuki
- Heck
- Evans auxiliary
- Enamines
- Ugi 4CC
- Amide synthesis
- Peptide synthesis
- Kumada
- Wittig
- Horner Wadsworth Emmons
- Hydroformylation
- Dehydration reactions
- Enzyme based reactions
- Aromatic nitration

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Ozonolysis

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- Ozonolysis with the classical glow discharge method requires pure oxygen because of the formation of nitrous oxides.

- Since ozonolysis is very exothermic, low temperatures are needed to dissipate the heat of the reaction.

- Ozonide is unstable and explosive!

Explosion of ozonolysis plant (DSM Chemie Linz in 2004)

-Continuous excess of ozone generates uncontrollable side reactions (epoxidations, peroxide formation, etc)

- Reaction parameters are difficult to control

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Ozonolysis with O-Cube

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O-Cube can eliminate almost all disadvantages of current ozonolysis:

- The ozone source is water
- Continuous-flow method
- Heat dissipation is much more efficient.

Reactions performed without cooling!

Reaction parameters (pressure, temperature, concentration, flow rate etc.) are easy to control.

Available in 2007!

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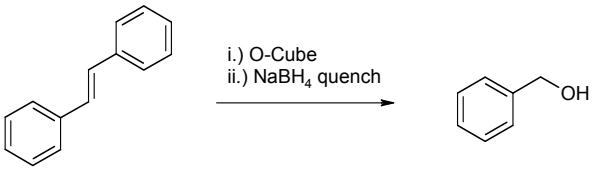
Ozonolysis at Thales



-All the reactions were made at RT.
--Selectivity up to 90%

Reactant / olefin	Conversion at RT (%)
Stilbene	90
Tetraphenylethylene	90

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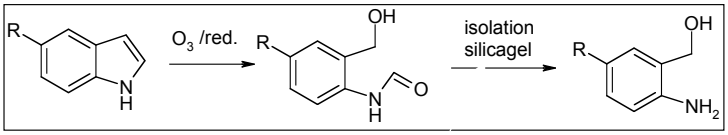
Reactivity of substituted indoles towards ozone

Substituent on the indole (-R)	Content of 1 (%)[a]	Isolated Y % of 2
-	62	
5-Me	92	70
5 MeO	83	60
5-Cl	75	67
4-Br	70	
5-Br	73	
6-Br	74	
7-Br	68	
5-I	75	
5-COOH	32	
5-COOEt	24	
$5\text{-}NO_2$	10	
$5\text{-}B(OH)_2$	26	17



*Yields are isolated yields determined after silica gel column cromatography, calculated on the converted product

Isolated products' structure are determined by the means of LCMS and NMR spectroscopies.

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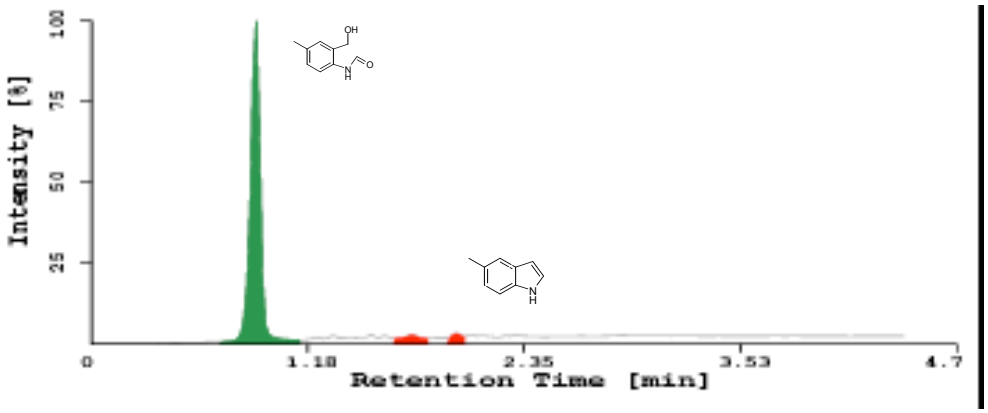
LCMS result of ozonolysis of 5-Me-Indole

(raw product: 99% conversion, 99% selectivity)



Conditions: P_{ozone}: 3 atm, flow rate: 0.25 ml/min, c_{indole} :0.03M
parameter optimization: 8 cycles in 4 hours

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Thank you for your attention!
Any questions?

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