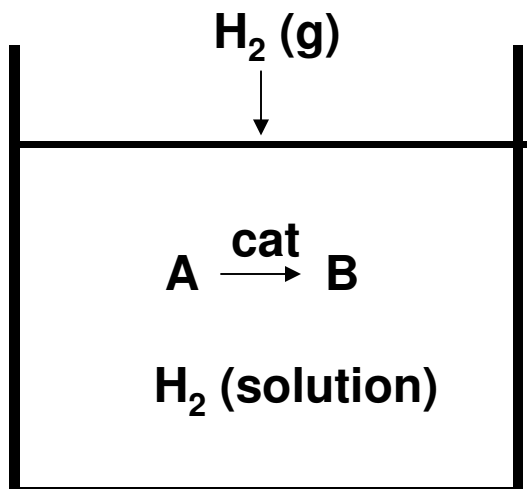


Flow Hydrogenation of 3-Aminobenzoic Acid: A Case Study Demonstrating the Utility of Flow Hydrogenations

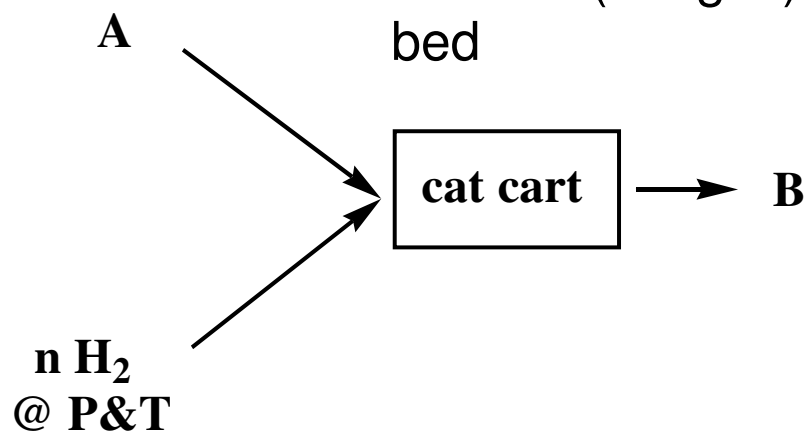
John C. Lucas
Pfizer Global Research Development
Industry First Seminar Series on Flow Chemistry
Boston University
Boston, Massachusetts
November 6, 2008

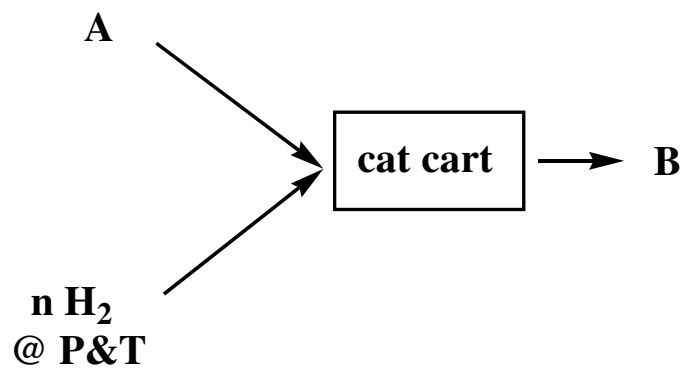
Typical Batch Hydrogenation



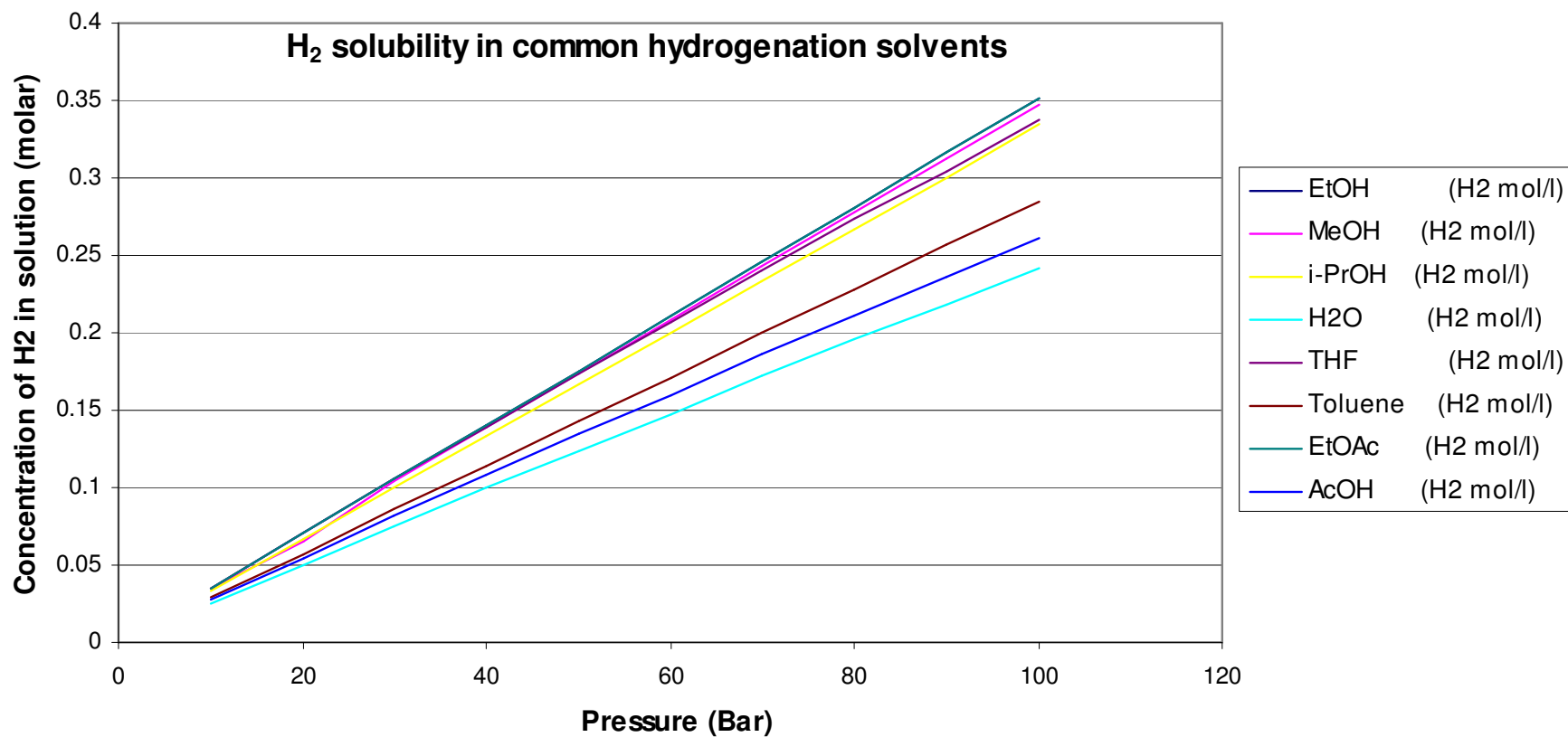
Typical H-Cube Reduction

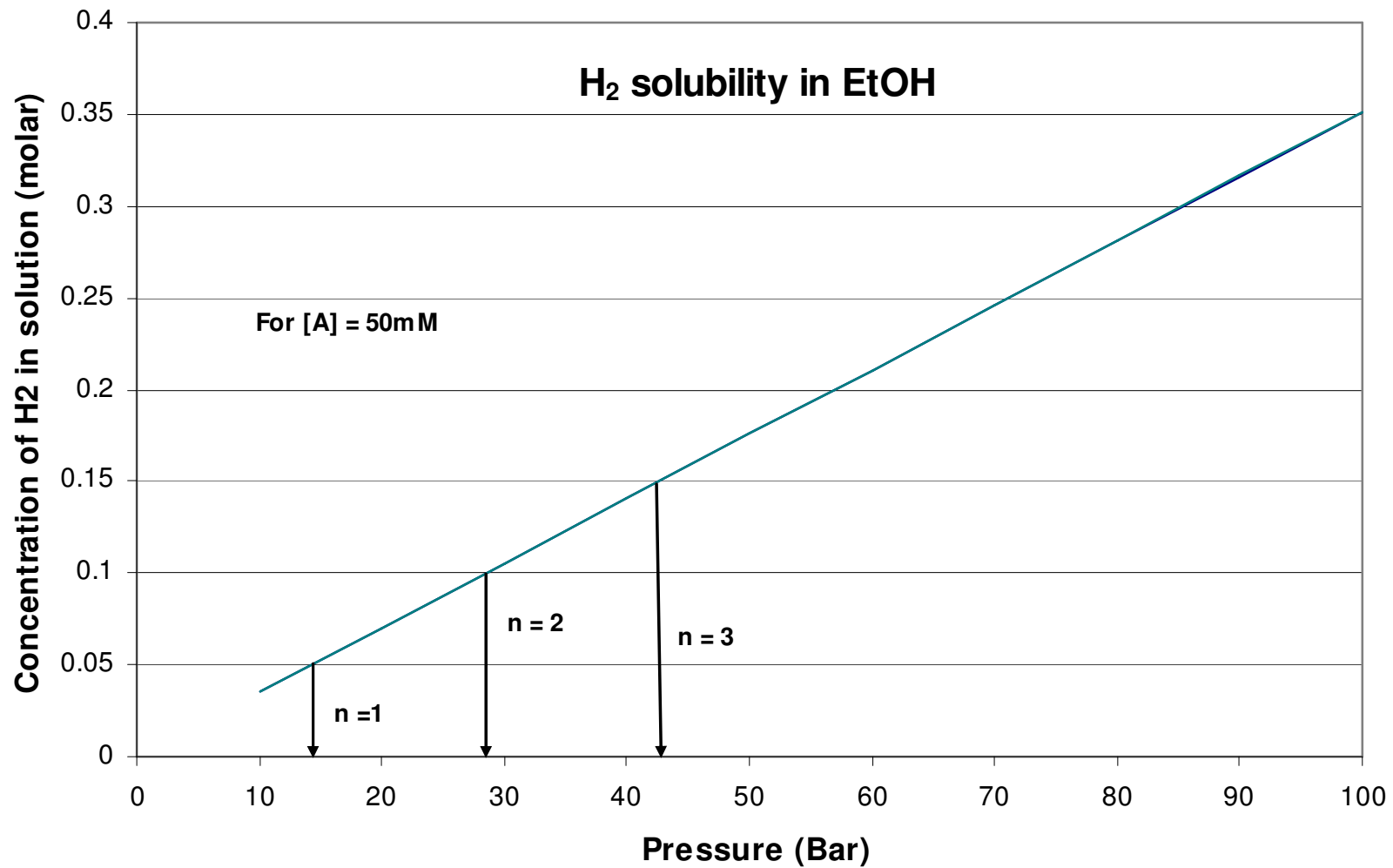
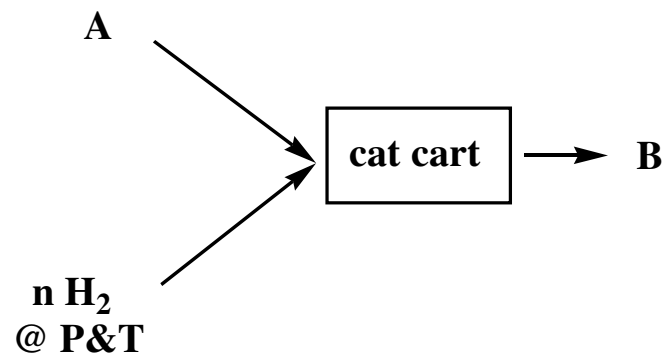
[A] is limited by the solubility of H_2 (in the reaction solvent) if only solution (not gas) enters catalyst bed



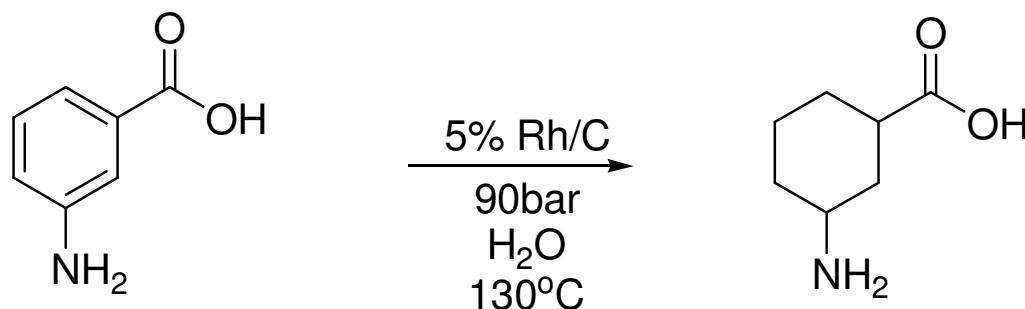


The solubility of H_2 was predicted @ room temperature





Request from Early Development to evaluate reduction in house



5 days, 33 % yield of desired diastereomer

40 g prepared at an outside vendor

High pressure and temperature batch reaction

Long reaction time (5 days)

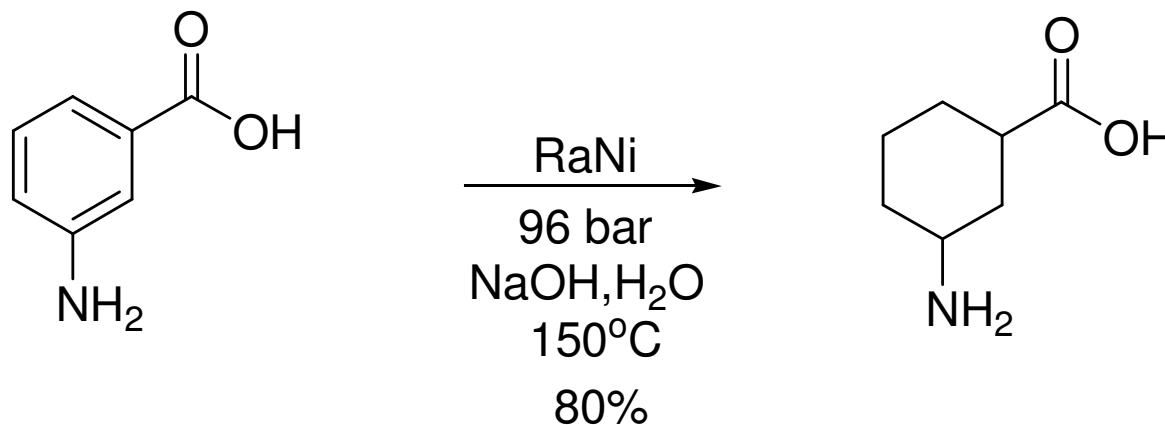
Modest yield (33% desired diastereomer)

How does Flow hydrogenation compare?

Challenges:

- 1. starting material not soluble in H₂O at room temperature**
- 2. cannot get to 130°C on H-cube**

Literature conditions

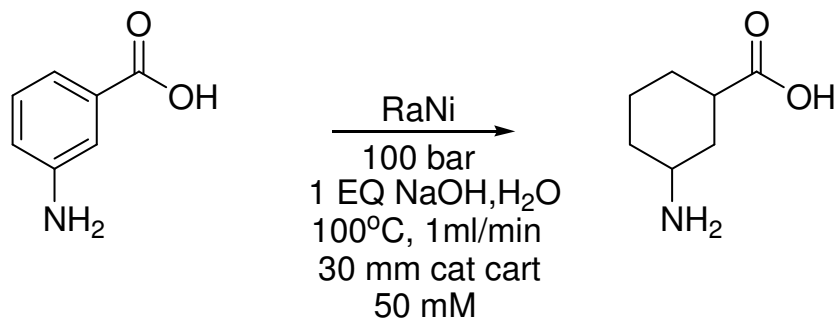


J.R. Granja *Chem. Eur. J.* **2005**, *11*,6543-6551

Pressure accessible on H-Cube

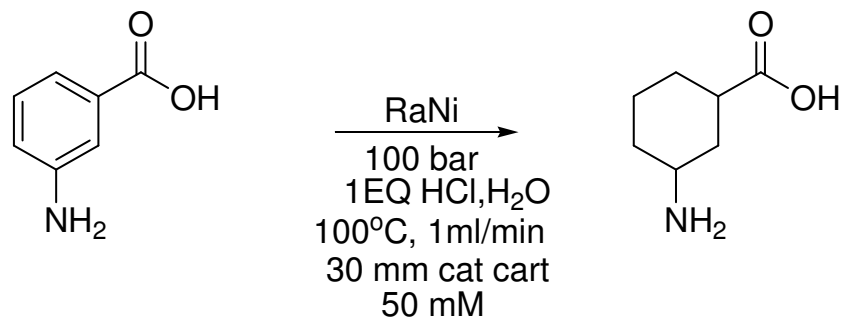
Temperature above upper limit for H-Cube (but not for H-Cube Midi)

Repeat Literature conditions



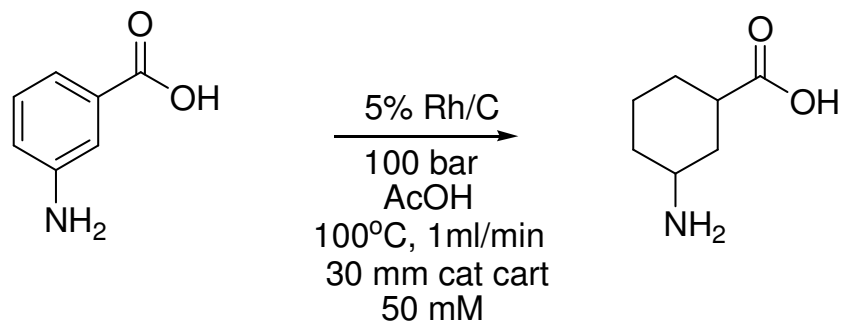
Total volume flowed = 120 mL = 822 mg. No conversion

Modify Literature Conditions



Total volume flowed = 120 mL = 822 mg. No conversion

Our Modifications



mL flowed	Mass/ fraction	conversion (¹ HNMR)	Cis/Trans (¹ HNMR)	Con. (mM)	Flow rate	yield
50	462 mg	>95%	2/1	50	1mL/mn	84%

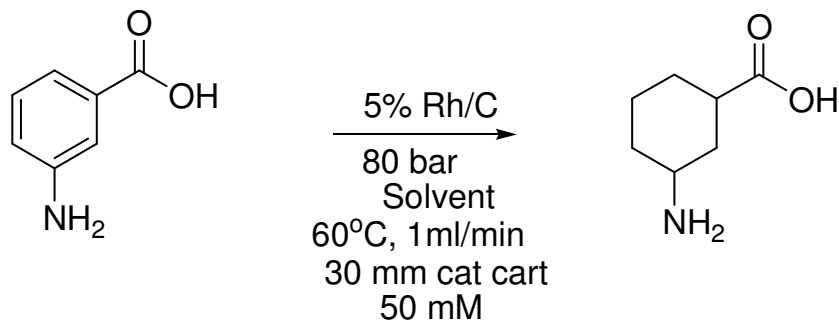
Recirculation at lower Temperature, Pressure, and solvent change



mL flowed	Mass	conversion (¹ HNMR)	Cis/Trans (¹ HNMR)	Conc.	Flow rate
150	1.2 g	88%	2/1	48mM	1mL/min

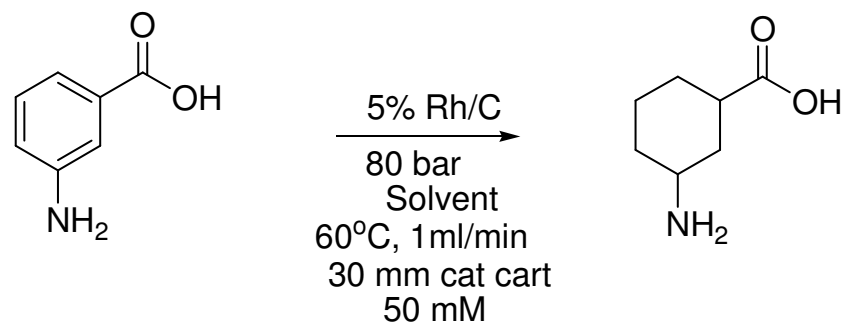
Reaction time = 5 hr

Broader screen, Solvent, Additive, Pressure, and Temperature

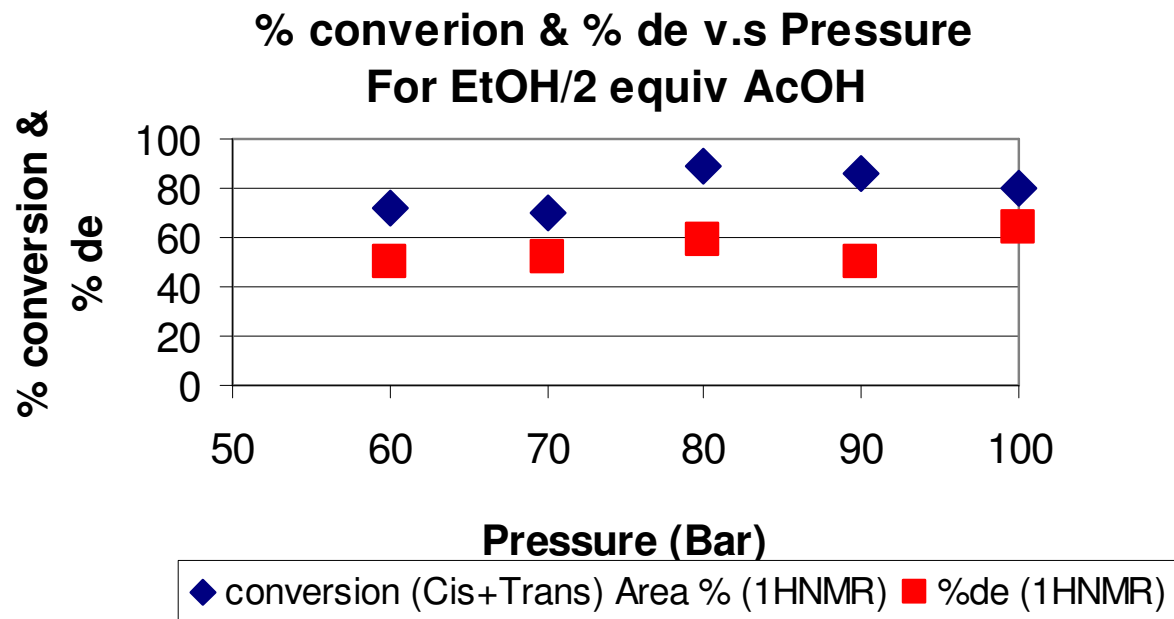


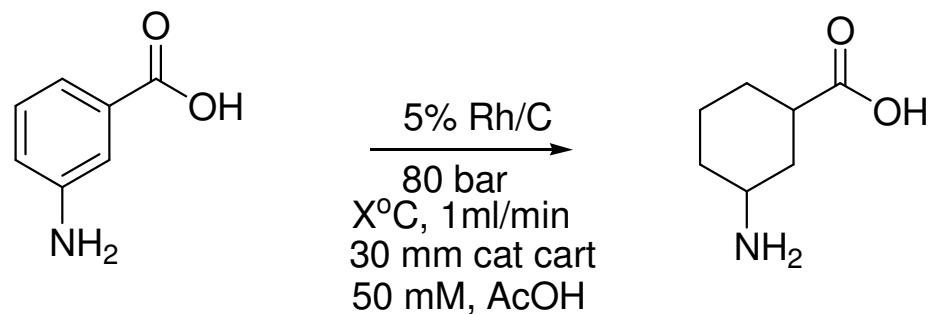
Screen 1
looking at solvent
additive @ 80 bar, 60°C

	solvent	additive	conversion (Cis+Trasn) Area % (¹ HNMR)	%de (¹ HNMR)	Excess H ₂ in solution (eq)	notes
run1	EtOH	none	70	61	1.8	Product not soluble in EtOH
run2	EtOH	1eq 12NHCl	96	33	1.8	
run3	H ₂ O	1eq 12NHCl	86	34	1.3	SM not soluble with AcOH as additive
run4	AcOH	none	>98	38	1.4	
run5	EtOH	1eq AcOH	86	61	1.8	solution hazy
run6	EtOH	2eq AcOH	89	59	1.8	
run7	MeOH	2eq AcOH	90	40	1.8	

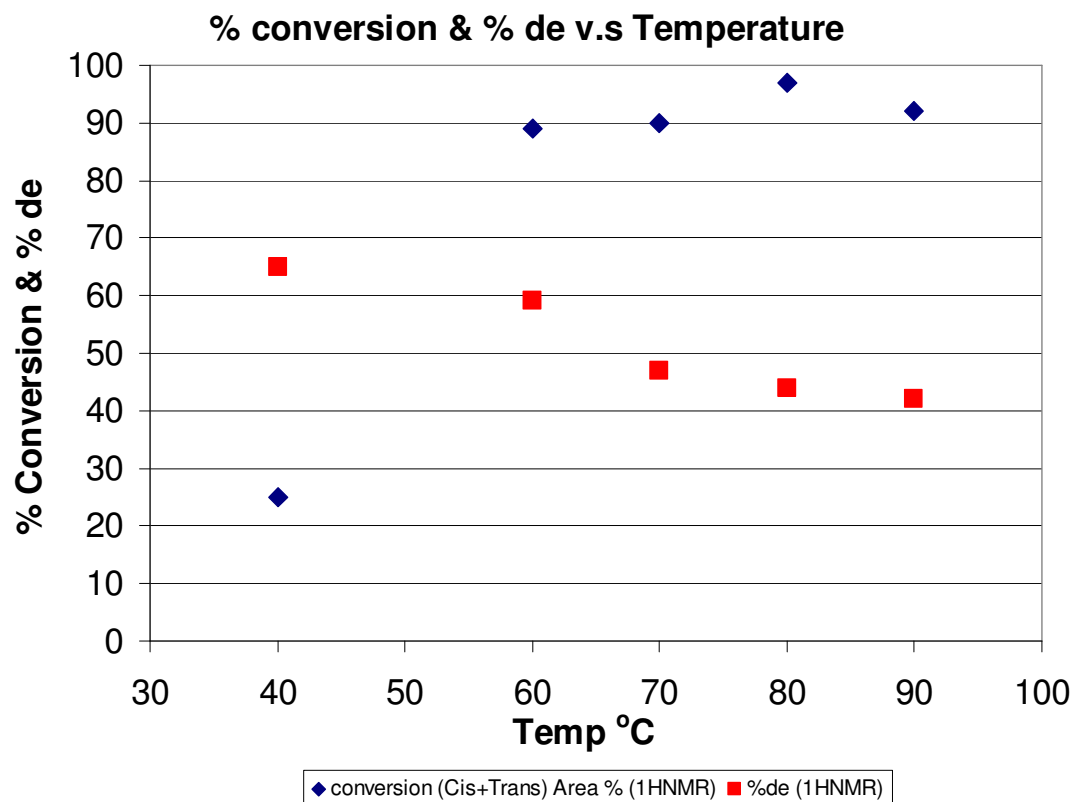


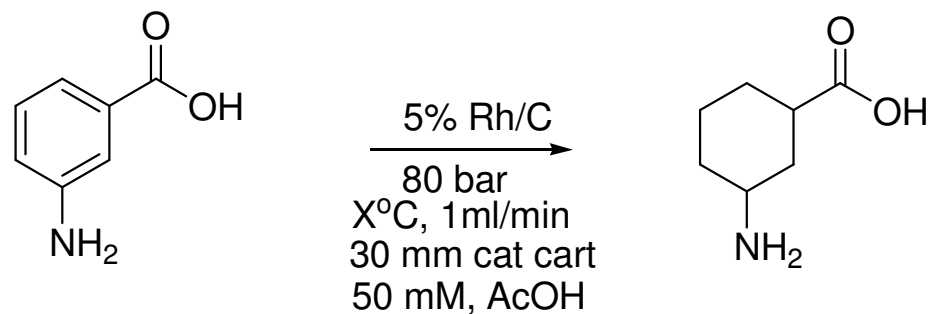
Screen 2 looking at pressure @ 60°C EtOH / 2 equiv AcOH



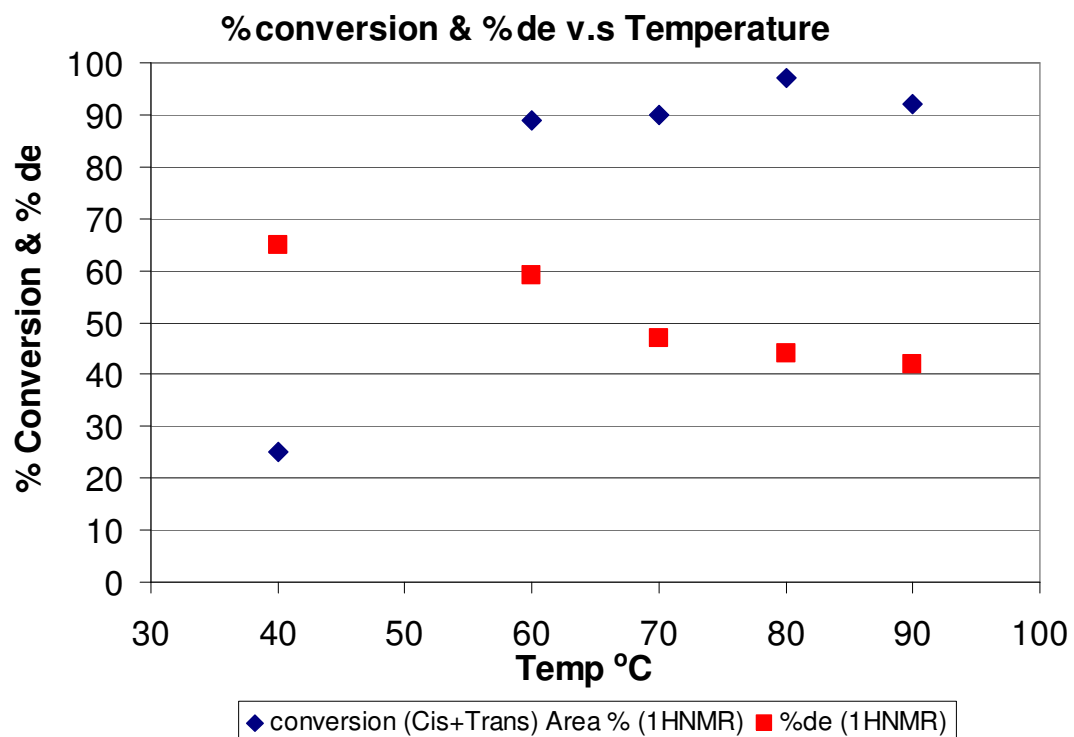


Screen 3 looking at Temp
 @ 80 bar, EtOH / 2 equiv
 AcOH

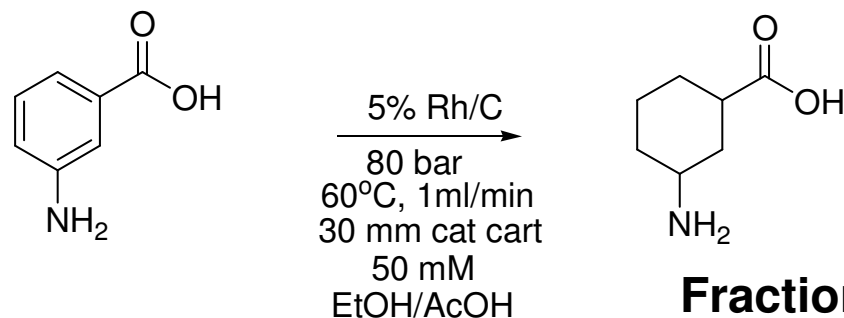




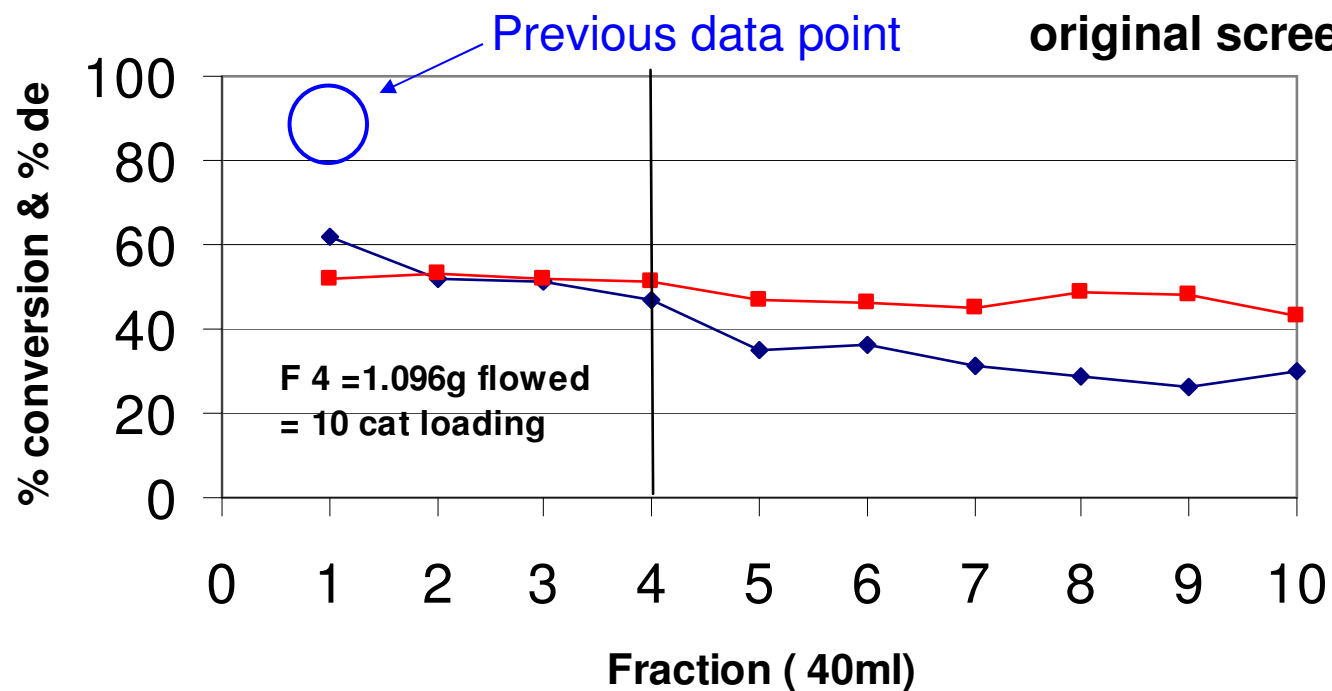
Screen 3 looking at Temp
 @ 80 bar, EtOH / 2 equiv
 AcOH



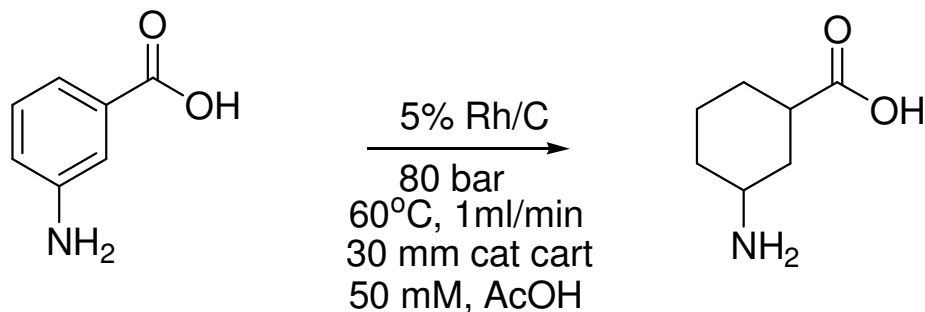
Testing Best conditions and Cat Cart Life on Larger Scale and Testing Flask to Flask reaction



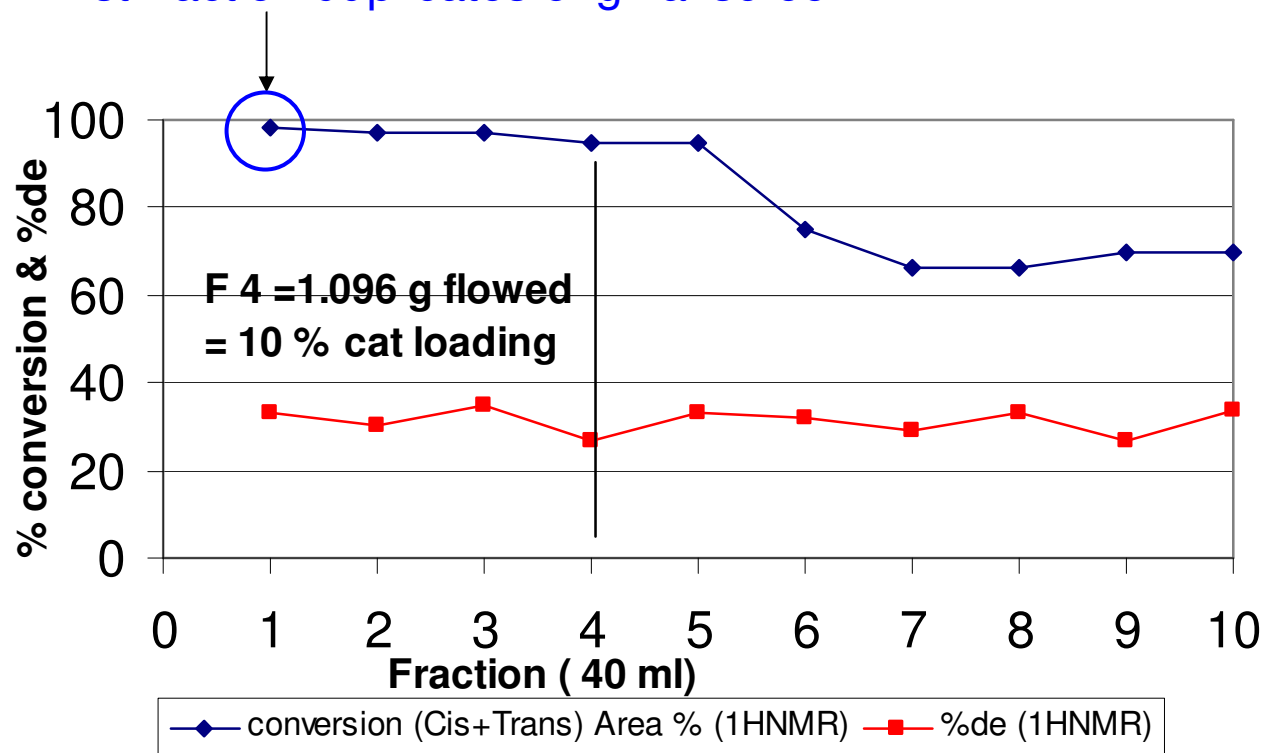
Fraction 1 does not duplicate original screen



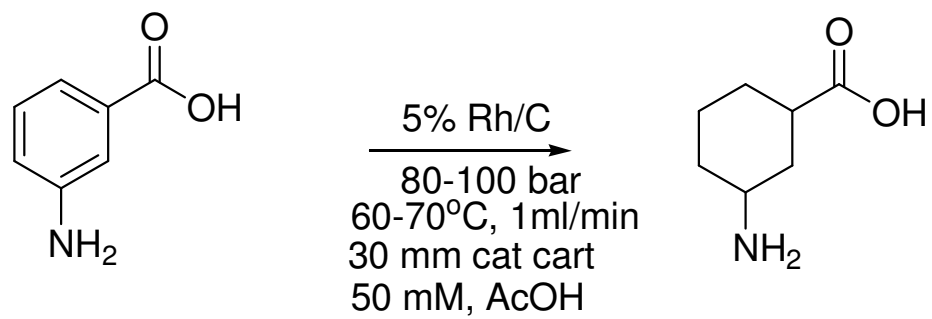
◆ conversion (Cis+Trans) Area % (1HNMR) ■ %de (1HNMR)



First fraction duplicates original screen ...



25 hr recirculation on 5g of substrate

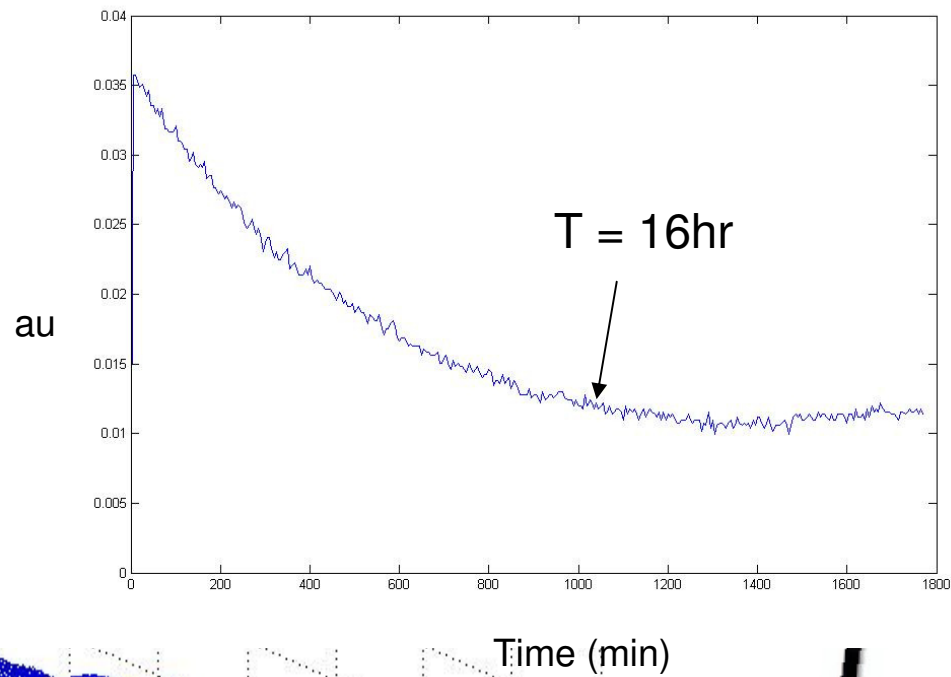
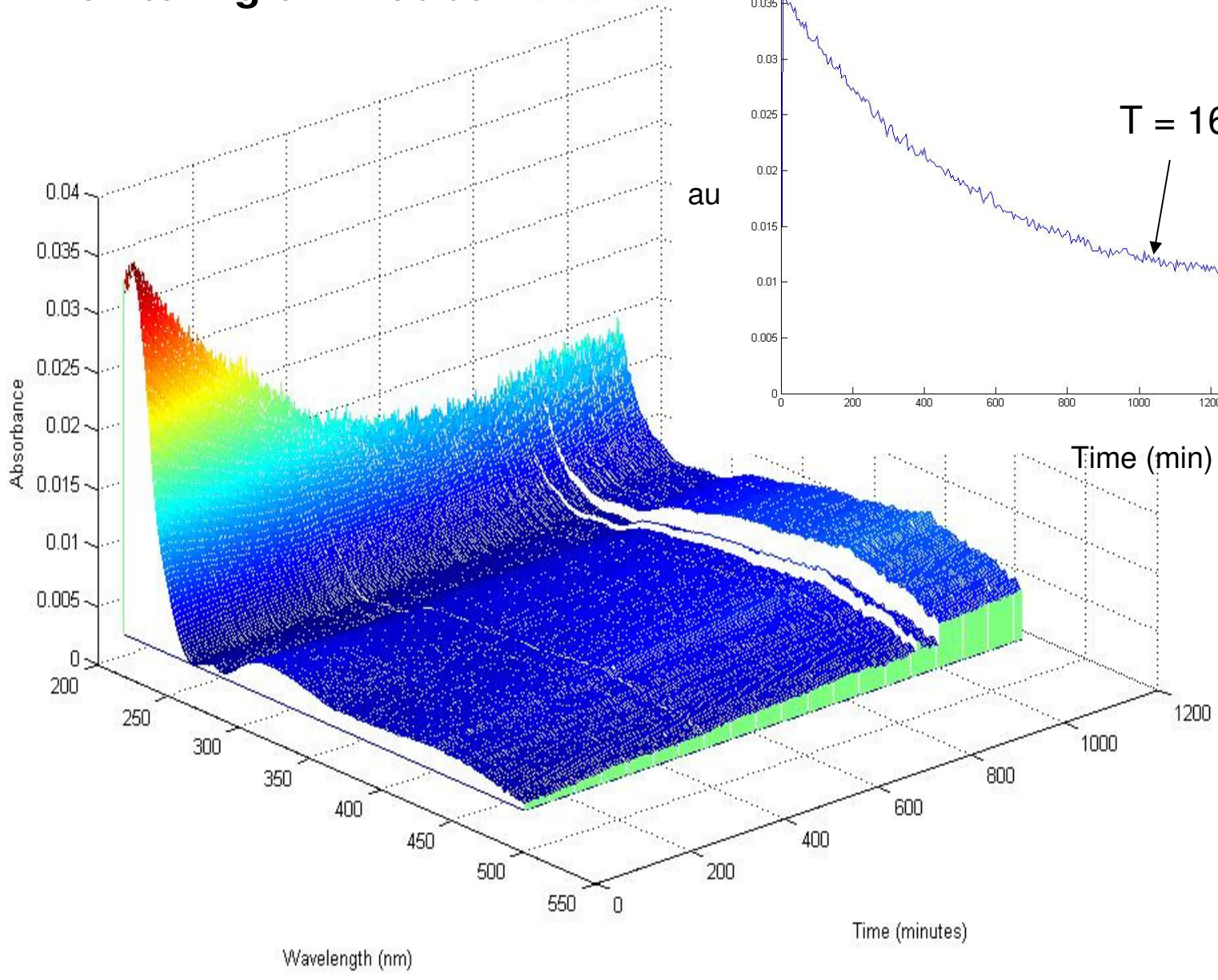


Pressure (bar)	Temp °C	% Conversion	% de
80	60	70	35
80	70	74	33
80 (75 mm cat cart)	60	88	33
90	70	82	38
100	70	85	31

ATR UV as PAT for Reaction monitoring on H-Cube

100 bar 5 g recircu

229 nm, 100 bar



Acknowledgments

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Dave Damon

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