Electronic Supporting Information

An automated repeating batch with catalyst recycle approach to nitro group hydrogenolysis

Kevin P. Cole,*[a] Martin D. Johnson,[a] Michael E. Laurila[a] and James R. Stout[b]

[a]Small Molecule Design and Development, Eli Lilly and Company, Indianapolis, IN, 46285, USA
[b]D&M Continuous Solutions, LLC, Greenwood, IN, 46143, USA

Contents

Experimental Section

This is the procedure used for the first of 3 fresh catalyst charges to the reactor. There were a total of 51 reactor volume turnovers on this catalyst charge. The procedure was similar for the next 2 catalyst charges. The feed solutions were prepared in 20 L polypropylene vessels. In a 20 L vessel, 494.86 g nitrobenzene was dissolved in 14.8 L THF. The solution was gravity filtered through fluted filter paper into a clean 20 L polypropylene vessel. The density of the solution was measured using a 10 mL volumetric flask and was found to be 0.893 g/mL. A catalyst slurry was prepared by charging 68.8 g of 5% Pd/C (58.3% water Johnson-Matthey Lot LW0434, 4.93% Pd, 2.06% Pd (w/w, corrected for water content) Type 39, Product Code 113068) to a 3 L Morton flask and 718 mL of THF was added. Therefore, a 590 mL charge of catalyst slurry would charge about 54 g of catalyst to the reactor. At 2.06% (w/w) Pd this was 1.13 g or 0.011 mol Pd. A 590 mL feed solution charge at 3.2% (w/w) and 0.89 g/mL density would be 0.0395 mol. This gave an initial catalyst loading of 26.8 mol%, but much lower catalyst loading overall because of the large number of reactor volume turnovers on the same catalyst.

The automated 1 L autoclave system was operated as described in a later section (see "Description of Automated Sequence for Fill-Empty Reactor"). The initial 4 reactor turnovers on the fresh catalyst used feed with 0.1 mole equivalents triethylamine (TEA) in order to curb the catalyst activity to minimize the defluorinated (DesF) impurity. The catalyst was run for a total of 51 cycles. This gave an overall catalyst use of ~26.8/51 = 0.525 mol%. Baseline reactor conditions were 60 °C, 60 psig H_2, 590 rpm agitator speed, and 590 mL fresh nitrobenzene reagent solution added each reactor turnover.

HPLC Conditions

High performance liquid chromatography was performed using an Agilent 1260 HPLC equipped with a diode array detector.

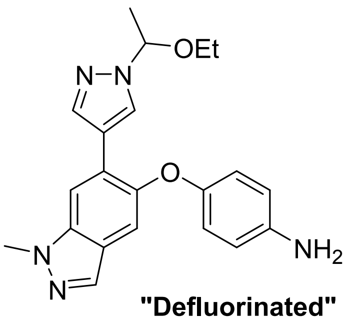
Column: XBridge BEH C18, 2.5 µm × 100 mm
Mobile Phase A = 0.1% (v/v) trifluoroacetic acid in water
Mobile Phase B = 0.1% (v/v) trifluoroacetic acid in acetonitrile
Temperature = 25 °C, detection at 234 nm, flowrate = 1.2 mL/min
Gradient

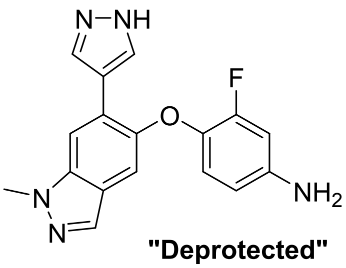
Minutes	% A	% B
0.00	95	5
10.00	5	95
12.00	5	95
12.10	95	5
14.00	95	5

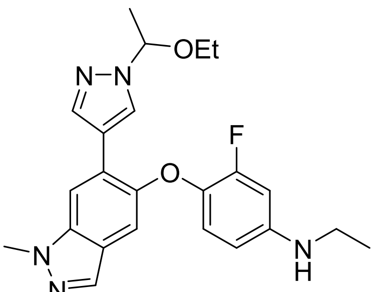
HPLC Retention times:
Deprotected Aniline = 4.0 min
Defluorinated = 4.4 min
Aniline (**3**) = 5.0 min
N-Ethylaniline = 5.4 min
Hydroxylamine = 5.60 min
Nitro (**2**) = 8.0 min
Azo Dimer = 9.7 min

Example Impurity Profile from 2nd Catalyst Charge (ND = Not Detected):

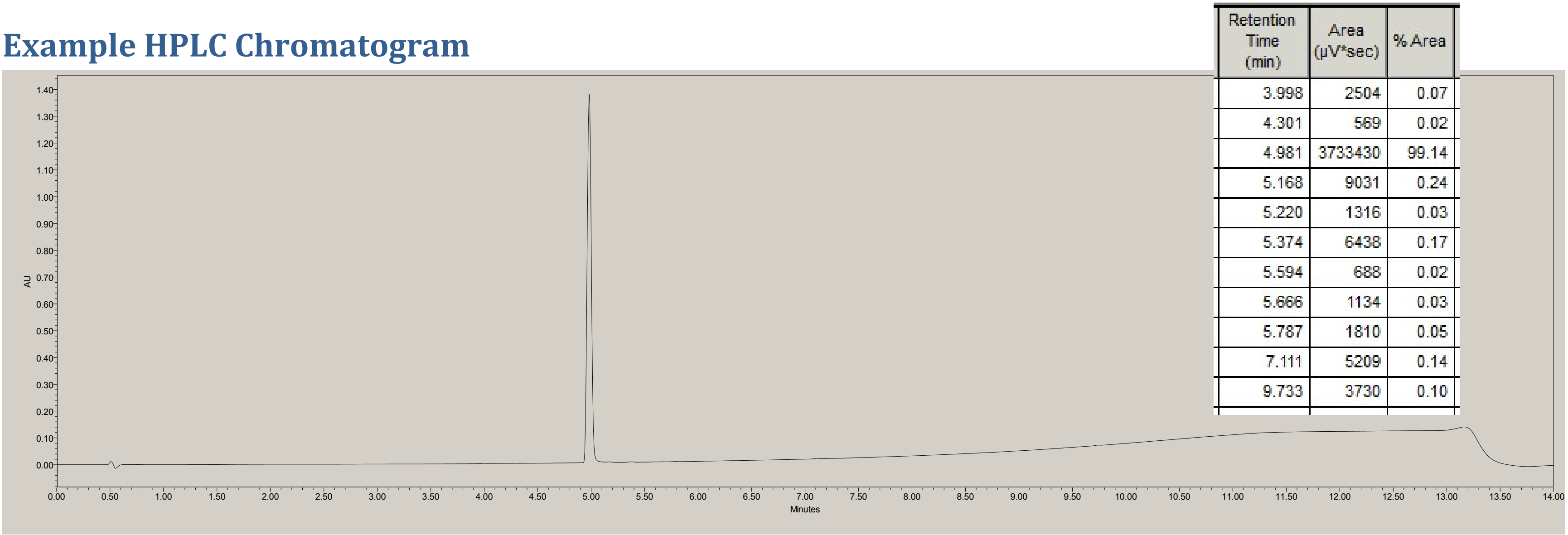
Composite	Nitro (**2**)	Aniline (**3**)	Defluorinated	Hydroxylamine	Deprotected	*N*-Ethylaniline
Reactor turnovers 1–4	ND	98.84	ND	ND	0.3	0.44
Reactor turnovers 5–25	ND	99.46	ND	ND	0.12	0.13


"Defluorinated"

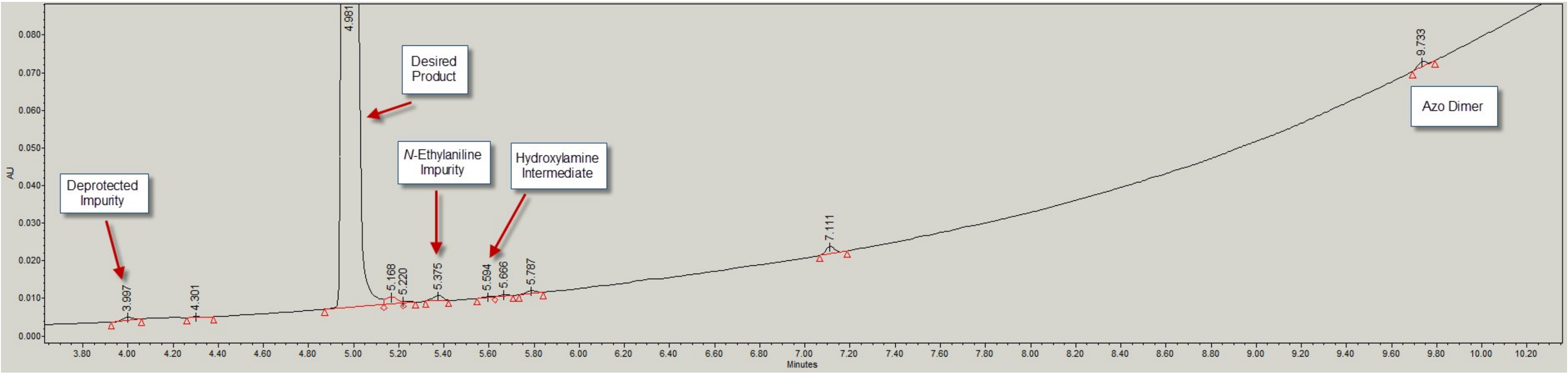

"Deprotected"


"*N*-Ethylaniline"

Example HPLC Chromatogram



Retention Time (min)	Area (µV*sec)	% Area
3.998	2504	0.07
4.301	569	0.02
4.981	3733430	99.14
5.168	9031	0.24
5.220	1316	0.03
5.374	6438	0.17
5.594	688	0.02
5.666	1134	0.03
5.787	1810	0.05
7.111	5209	0.14
9.733	3730	0.10



K. P. Cole *et al*. An automated repeating batch with catalyst recycle approach to nitro group hydrogenolysis

Mass Balance Data for Third Catalyst Charge

	Mass (g)	Substrate (w/w)	Substrate (moles)
Feed solution charged with TEA	2012	3.93	0.186
Feed solution charged with no TEA	10581	3.97	0.987
Total	12593		1.173
Product solution turnovers 1–4	1934	3.26	0.159
Product solution turnovers 5–19	7452	3.69	0.696
Product solution turnovers 20–25	2427	3.76	0.231
Samples/Waste	237	3.70	0.022
Total	12050		1.109
Total material balance	95.7%		
Total solution yield			94.5%

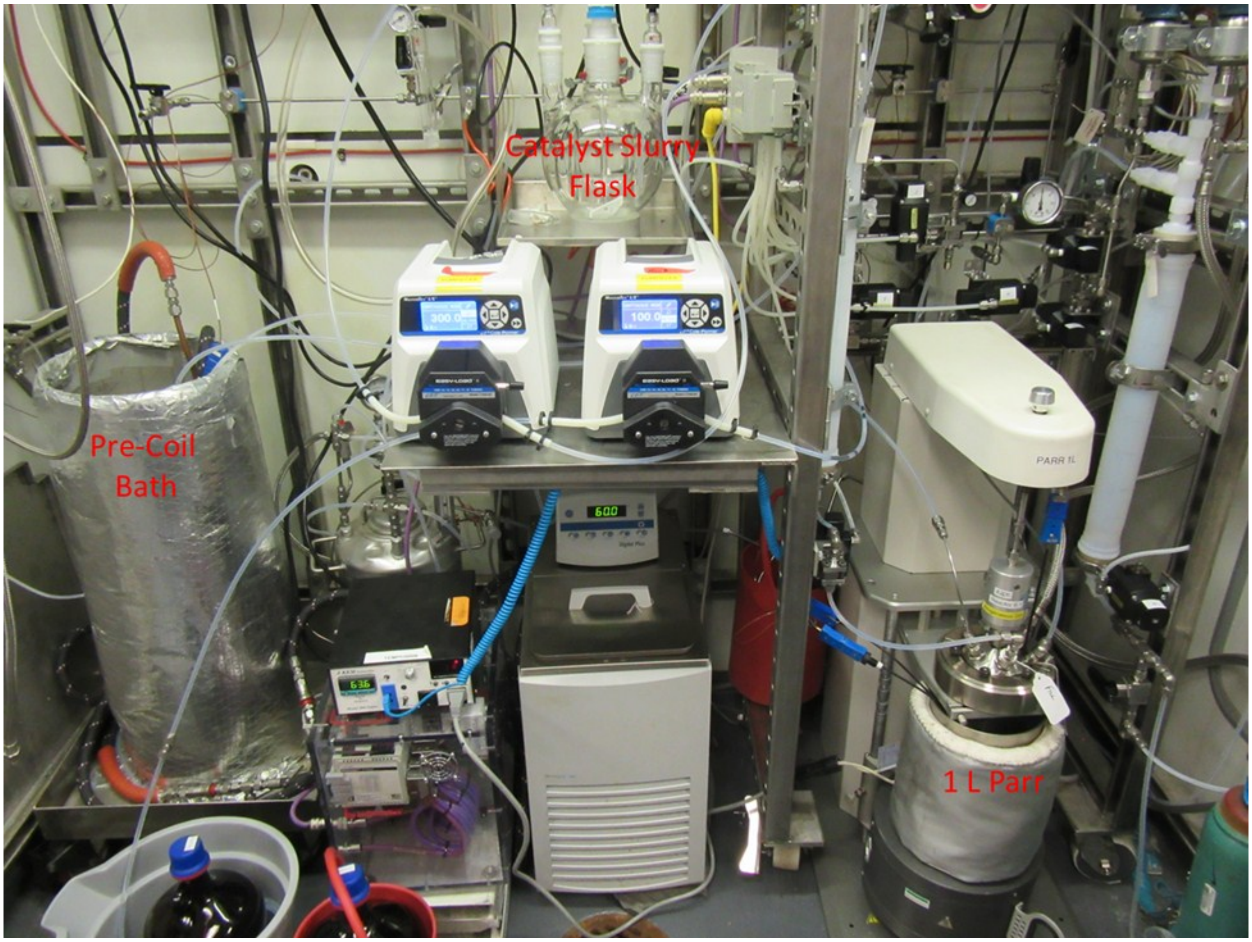
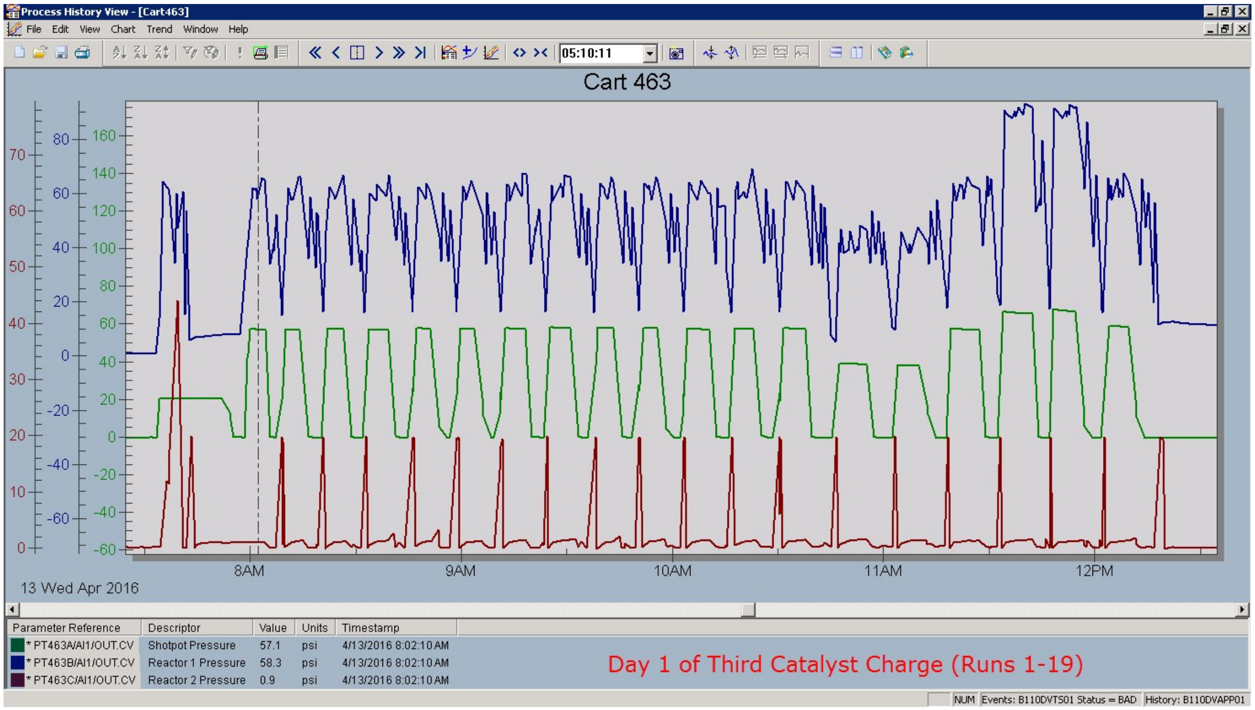


Figure 1. Picture of the 1 L Parr reactor setup in laboratory fume hood.

Figure 1 shows a picture of the 1 L Parr reactor and auxiliary equipment in laboratory fume hood. The constant temperature bath for submerging the 600 mL reagent feed preheat tubing coils is shown on the left. The pre-heat bath was set at a temperature below the desired reaction operating temperature to allow for the heat of reaction. The peristaltic pumps used for transferring catalyst slurry or reagent feed solution into the reactor are shown in the middle. The stirred flask for catalyst slurry feed is shown in the top of the picture. The 20 L vessel for reagent feed solution is not shown in the picture. The 1 L Parr reactor is shown in the lower right. It is submerged in a constant temperature water bath heated by electrical heating mantle. The 20 L vessel for product solution is not shown in the picture.



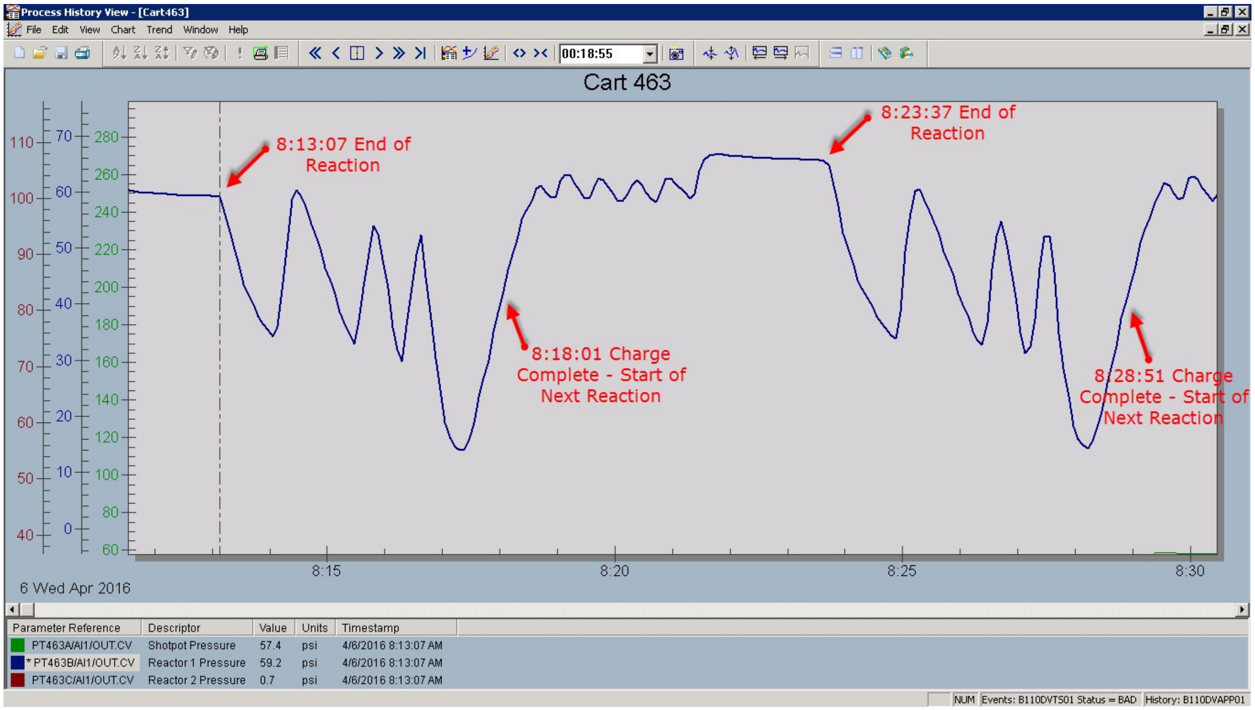
Parameter Reference	Descriptor	Value	Units	Timestamp
🟩 * PT463A/AI1/OUT.CV	Shotpot Pressure	57.1	psi	4/13/2016 8:02:10 AM
🟦 * PT463B/AI1/OUT.CV	Reactor 1 Pressure	58.3	psi	4/13/2016 8:02:10 AM
■ * PT463C/AI1/OUT.CV	Reactor 2 Pressure	0.9	psi	4/13/2016 8:02:10 AM

Day 1 of Third Catalyst Charge (Runs 1-19)

Figure 2. Pressure versus time for the first 19 reactor volume turnovers after the third fresh catalyst charge.

Figure 2 illustrates reactor productively. After the third fresh catalyst charge, there were 19 reactor volume turnovers in about four hours. The data in blue shows pressure in the reactor versus time, the data in green shows pressure in the inlet transfer zone, and the data in red shows pressure in the outlet transfer zone. Pressure setpoint for two of the reactor turnovers was 40 psig and pressure setpoint for two of the reactor volume turnovers was 80 psig. For all the rest of the reactor volume turnovers, pressure setpoint was 60 psig.

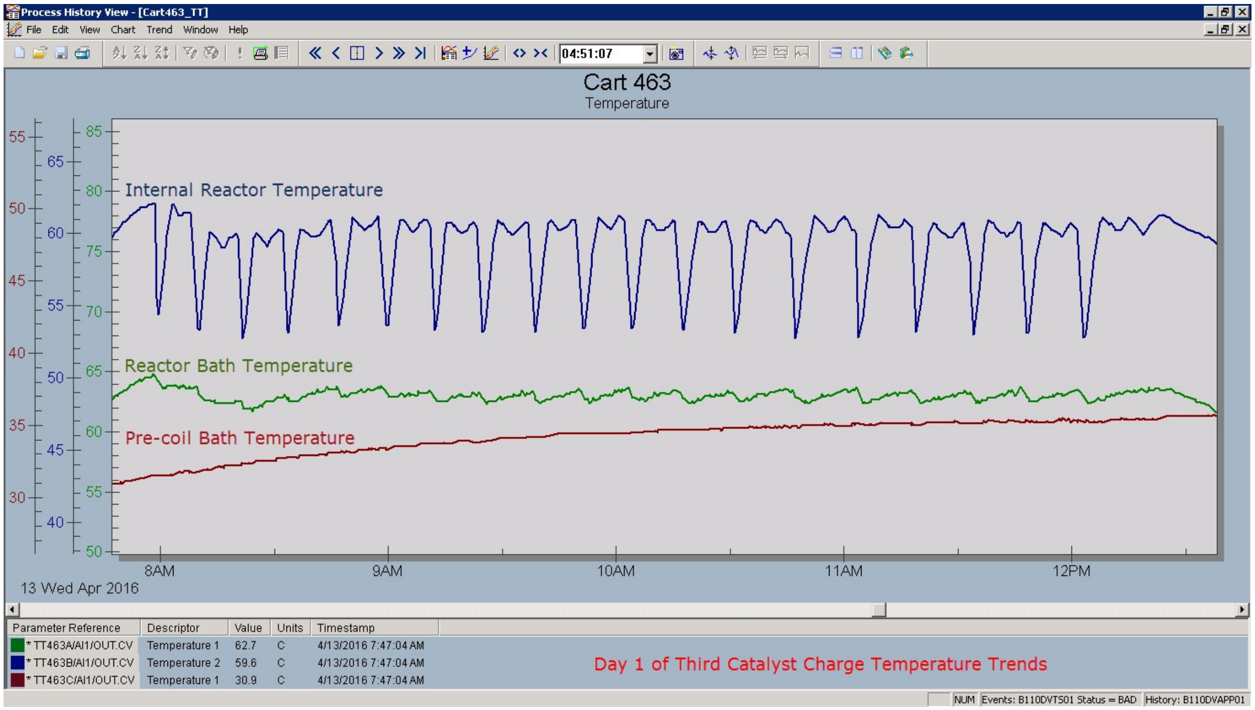
Figure 3 shows reactor pressure versus time for a typical reaction cycle in the 1 L stirred tank. “Unproductive” time for pushing out and refilling between reactions was about five minutes. A reaction ended at 8:13, and the reactor started to push liquid out through the internal filter. By 8:18, all of the liquid was pushed out from the reactor through the filter, sequestering the catalyst, and the nitrobenzene reagent solution for the next reaction cycle was completely transferred into the reactor. Once reaction pressure reached 60 psig, an oscillating pattern in reaction pressure began and remained between about 58–63 psig as controlled by the automation program. This represents the time that hydrogen was periodically added to the reactor. The decrease in pressure was observed due to uptake of hydrogen by the reaction, while the increase in pressure resulted from periodic pressurization of the reactor with hydrogen gas. At 8:23 the automation system calculated the pressure change as < 0.1 psig per minute, and the reaction was considered complete. The liquid product solution was emptied from the reactor through the internal filter. Pressure oscillations between 8:23 to 8:28 indicate the system’s automated hydrogen blow backs to keep the internal filter free of solid particle build up during transfer from the reactor. The blow backs have been shown to reduce overall transfer time out of the reactor.



Parameter Reference	Descriptor	Value	Units	Timestamp
🟩 PT463A/AI1/OUT.CV	Shotpot Pressure	57.4	psi	4/6/2016 8:13:07 AM
🟦 * PT463B/AI1/OUT.CV	Reactor 1 Pressure	59.2	psi	4/6/2016 8:13:07 AM
🟥 PT463C/AI1/OUT.CV	Reactor 2 Pressure	0.7	psi	4/6/2016 8:13:07 AM

Figure 3. Reactor pressure versus time for one and a half fill-empty cycles, keeping catalyst sequestered in the reactor.

Figure 4 shows the consistent and repeatable temperature trend for the first 19 reactor volume turnovers after the third fresh catalyst charge. This is the same four-hour time period represented in Figure 2. The blue data trend shows the internal reactor temperature and the spikes down and then back up indicate when the reactor refilled with fresh reagent feed solution. Reactor temperature was about 60–61 °C during most of the active reaction time. The green temperature trend represents the constant temperature bath in which the 1 L reactor was submerged. The constant temperature bath was used instead of the electrical heating mantle because it provided a more constant temperature versus time as the reactor filled and emptied, analogous to reactor jacket temperature control. Temperature of the bath was held between 62 °C and 63 °C. The red data trend in the figure represents the temperature for preheating the reactor feed tubing. Feed solution was pre-heated to about 35°C on the way into the reactor. Heat of reaction took the reactor temperature quickly up from 35°C to 60°C for each of the reaction cycles. The heat of reaction was determined by calorimetry as 514.0 kJ/mol of nitrobenzene derivative. One of the main reasons why reaction temperature reached 60 °C quickly was because of the feed preheater. It consisted of a 1 L PFA tube coil submerged in the 35 °C bath. The feed sat in the preheat coil and gradually warmed for the >10 minutes time between cycles.

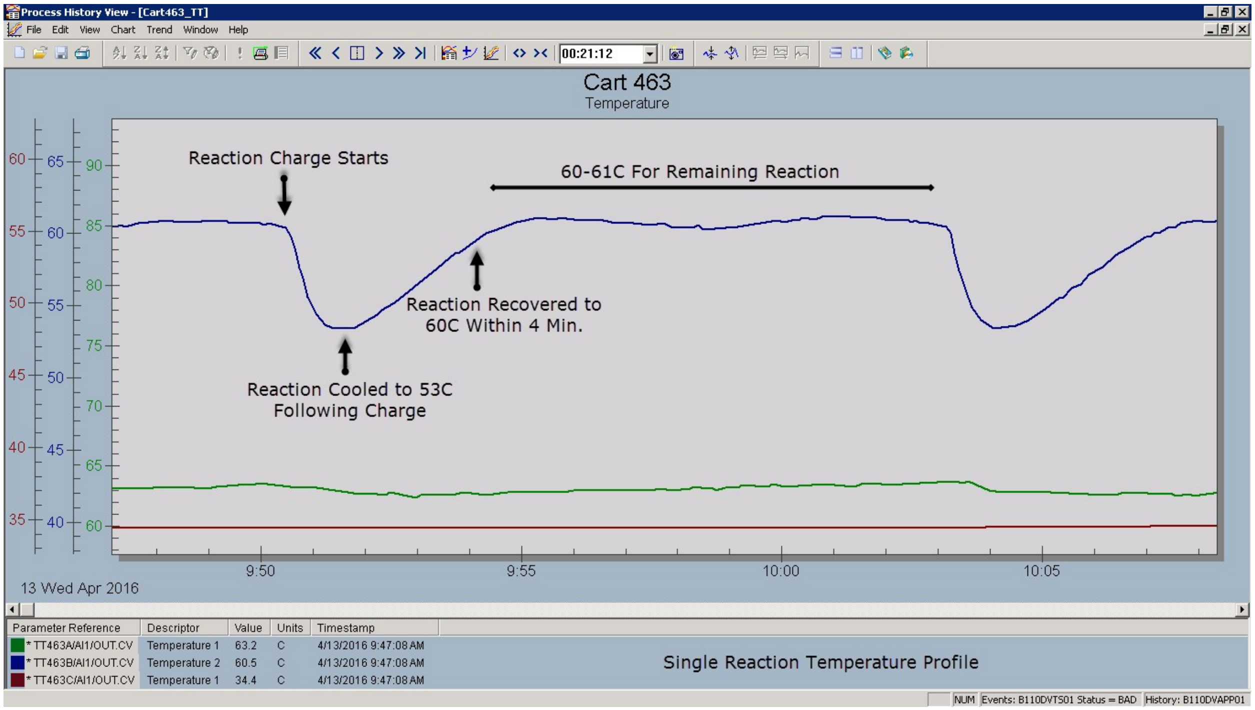


Parameter Reference	Descriptor	Value	Units	Timestamp
🟩 * TT463A/AI1/OUT.CV	Temperature 1	62.7	C	4/13/2016 7:47:04 AM
🟦 * TT463B/AI1/OUT.CV	Temperature 2	59.6	C	4/13/2016 7:47:04 AM
🟥 * TT463C/AI1/OUT.CV	Temperature 1	30.9	C	4/13/2016 7:47:04 AM

Day 1 of Third Catalyst Charge Temperature Trends

Figure 4. Temperature versus time for reactor, reactor heating jacket, and feed preheater for 19 reactor volume turnovers.

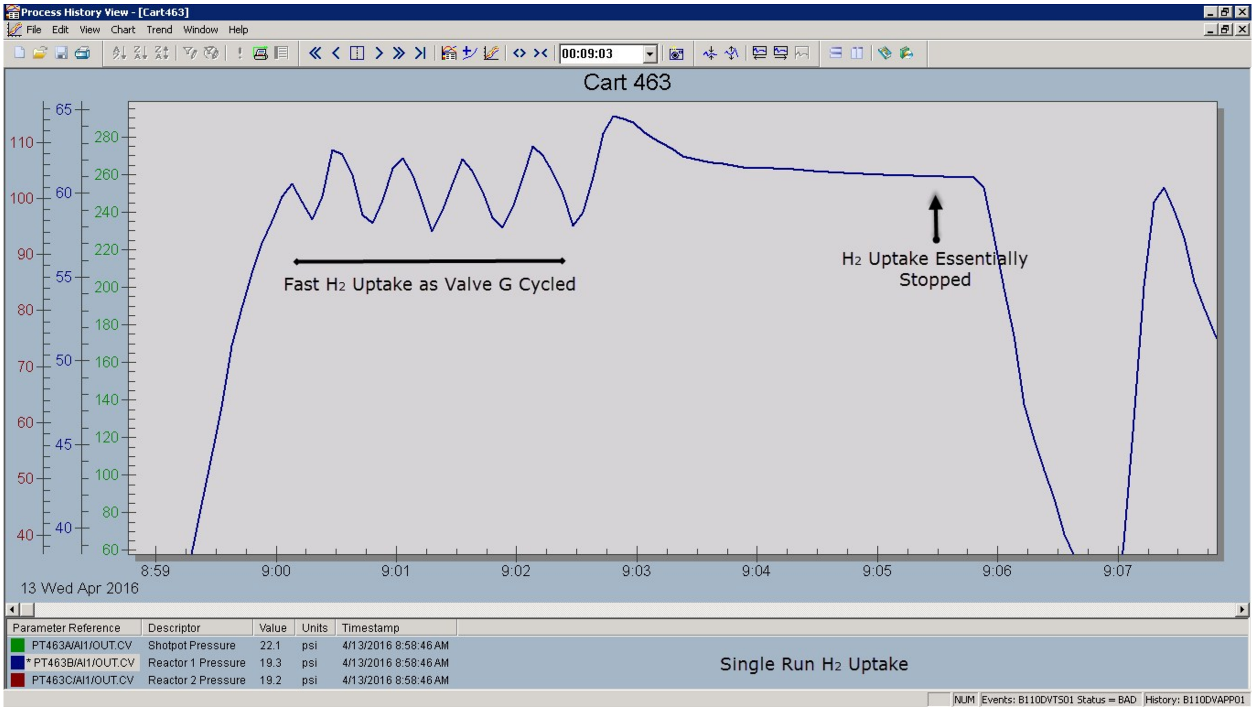
Internal reaction temperature for one and a half reactor volume turnovers is shown by the blue data in Figure 5. At this time in the catalyst life cycle, one turnover was about 13 minutes of total operating time, including feeding, reaction time, and emptying. Reaction started when the fresh reagent feed was pushed into the stirred tank autoclave under hydrogen pressure. Temperature dropped to about 53 °C following the feed charge. The feed was deliberately only preheated to 35 °C, to allow the reactor to heat up the rest of the way to 60 °C via the reactor wall temperature and also the heat of reaction. Reactor temperature recovered to 60 °C within four minutes. The reaction temperature remained constant at about 60–61 °C for the remaining time of reaction plus push out. The green data shows that the constant temperature bath used to submerge the reactor remained at about 62–63 °C. The red data shows that the constant temperature bath for submerging the feed preheat coils remained at 35 °C.



Parameter Reference	Descriptor	Value	Units	Timestamp
🟩 * TT463A/AI1/OUT.CV	Temperature 1	63.2	C	4/13/2016 9:47:08 AM
🟦 * TT463B/AI1/OUT.CV	Temperature 2	60.5	C	4/13/2016 9:47:08 AM
🟥 * TT463C/AI1/OUT.CV	Temperature 1	34.4	C	4/13/2016 9:47:08 AM

Figure 5. Temperature versus time data for one and a half reactor turnovers.

The DeltaV control system automatically decided when reaction was complete. Figure 6 shows a typical pressure versus time data trend in the fill-empty stirred tank reactor. At this time in the catalyst life cycle, the reaction time was about seven minutes. Near the beginning of the reaction time, when hydrogen uptake was fast, pressure versus time oscillated quickly as the hydrogen supply valve opened and closed. After about seven minutes, the pressure versus time trend had flattened out. At this time, the rate of pressure change was less than 0.1 psig per minute. Therefore, the distributed control system decided that the reaction was complete, and automatically began the reactor push out through the internal filter. In this manner, the reactor system automatically compensated for decreased catalyst activity by increasing reaction time for later runs on the same catalyst charge.



Parameter Reference	Descriptor	Value	Units	Timestamp
🟩 PT463A/AI1/OUT.CV	Shotpot Pressure	22.1	psi	4/13/2016 8:58:46 AM
🟦 * PT463B/AI1/OUT.CV	Reactor 1 Pressure	19.3	psi	4/13/2016 8:58:46 AM
🟥 PT463C/AI1/OUT.CV	Reactor 2 Pressure	19.2	psi	4/13/2016 8:58:46 AM

Figure 6. Pressure versus time for one reaction cycle in the stirred tank.

Details on Catalyst Discharge and Recharge

Spent catalyst was discharged and fresh catalyst was charged by the automation system at a user defined frequency. For production in a GMP manufacturing environment, this has a significant advantage compared to a packed bed reactor. If using a packed bed reactor, the activity of a catalyst gradually decreases over time, and therefore the reactor must eventually be exchanged for a fresh bed reactor. This may require a complete stoppage of the process so that operators can depressurize and remove the hydrogen hazard, go into the processing area and swap out the reactor safely. This is in contrast with the stirred tank method in which the reactor automatically changes out its own powdered catalyst, there is no process stoppage, and there is no need for a person to switch reactors. Furthermore, if the product solution is worked up and isolated in larger batches, the same number of fresh catalyst charges can be used for each batch. Thus all batches can have the same yield and purity. In contrast, consider a packed catalyst bed continuous reactor that runs for more than a week before it is exchanged for a new fresh catalyst bed. If the product solution is isolated as batches once every day or two days, then not all batches will be the same because of decreasing catalyst activity in the packed bed reactor near the end of its life.

Figure 7 shows HPLC results for desired product and desF impurity for the first of three fresh catalyst charges. For the first 10 reactor volume turnovers on the fresh catalyst, desF impurity was higher, reaching a maximum of about 0.32 HPLC area% (green triangles in the Figure). This is because catalyst activity was higher at the start. The first 4 turnovers used 0.1 molar equivalents TEA in attempts to minimize the desF impurity by reducing the activity of the fresh catalyst. This approach also served to limit the levels of deprotected product and protected N-ethyl impurities. All subsequent turnovers used feed with no TEA added to prevent over deactivation of the catalyst. The red squares in the figure show that area % desired product exiting the reactor gradually increased for the first 10 volume turnovers and then remained higher than about 98% for most of the 51 reactor volume turnovers. After this, the spent catalyst was emptied and fresh catalyst charged via the automated system.

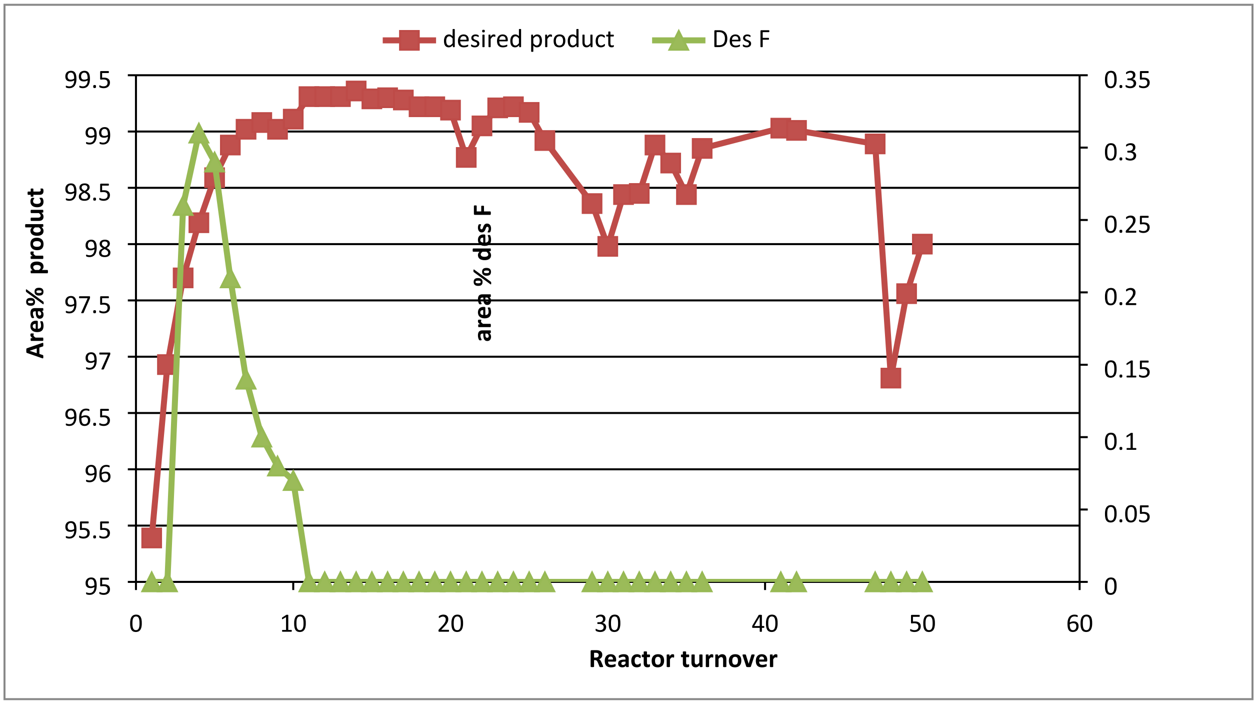


Figure 7. HPLC results for product and desF impurity for the first of three fresh catalyst charges.

By reactor turnover 51, the reaction was taking about 30 minutes to complete. Additional runs could have been completed on the catalyst depending on the desired purity and desired turnaround time needed. The decision was made to increase productivity by using a fresh catalyst charge before subsequent reactor volume turnovers.

Figure 8 shows HPLC results for product and desF impurity for the second of three fresh catalyst charges. As previously, area % product gradually increased during the first 10 reactor volume turnovers and then remained high, at about 99.5%. In contrast to the first catalyst charge, the desF impurity was below detection limit for the entire 25 reactor volume turnovers. The first 4 turnovers used 0.1 molar equivalents TEA in attempts to minimize the desF impurity by reducing the activity of the fresh catalyst. Figure 9 shows analogous data from the third catalyst charge.

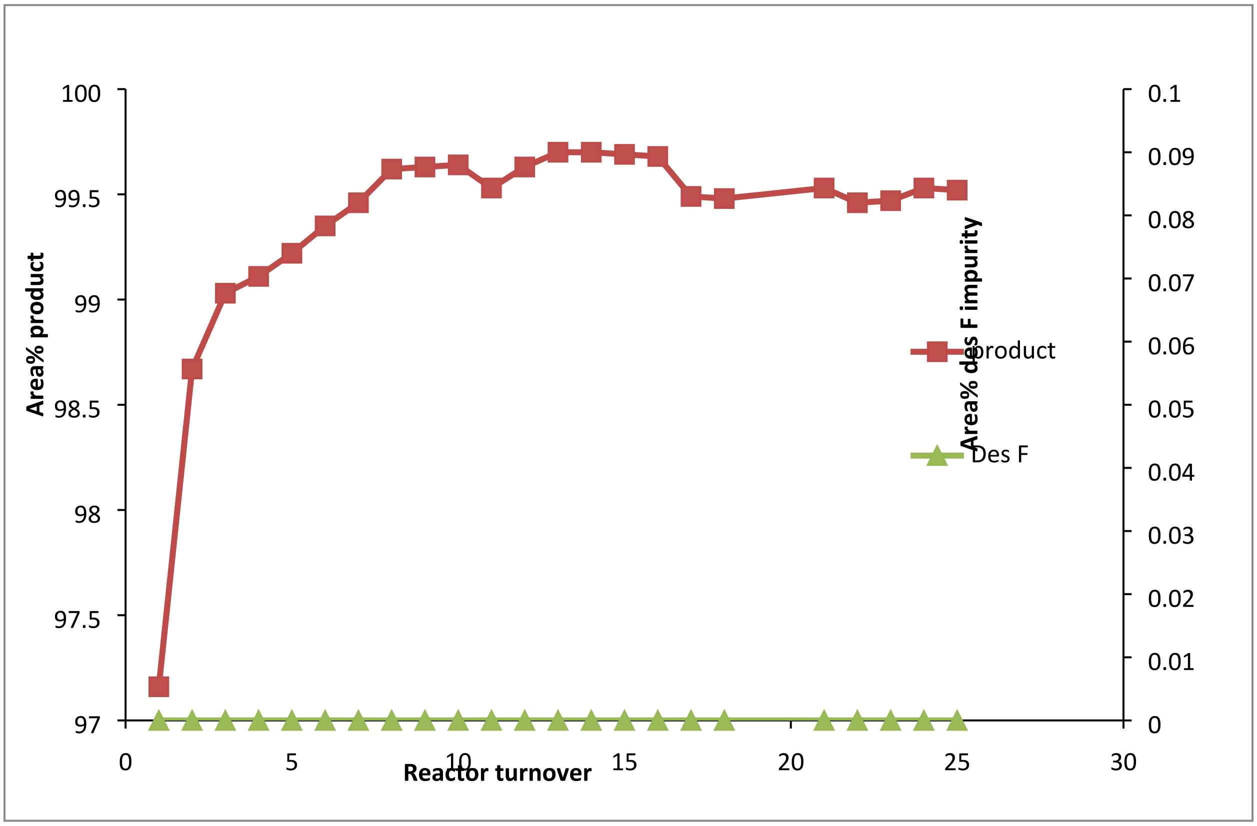


Figure 8. HPLC results for product and desF impurity for the second of three fresh catalyst charges.

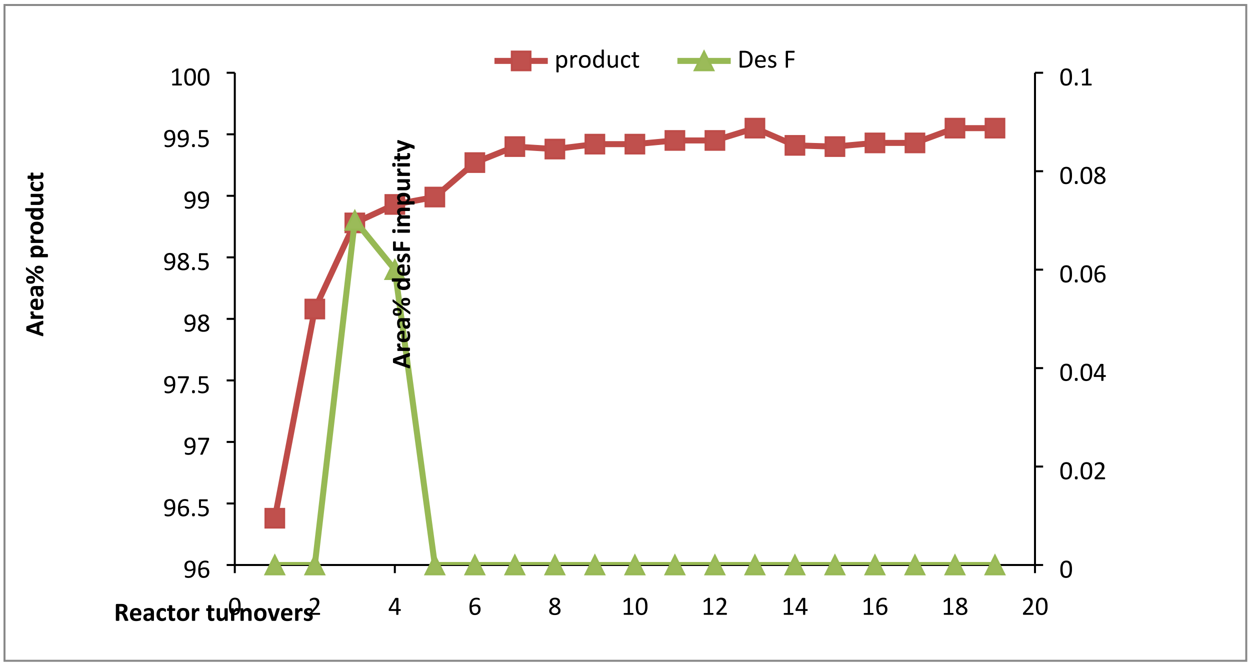


Figure 9. HPLC results for product and desF impurity for the third of three fresh catalyst charges.

Slurry Feed Details

The nitrobenzene reagent was fed as a slurry for the last six reactor volume turnovers of the second catalyst charge. The feed was swapped between turnovers 25 and 26. The baseline feed used 30 mL of THF per every gram nitrobenzene. The more concentrated feed used only 10 mL THF per gram nitrobenzene. As a consequence, the substrate was not soluble in the feed vessel at room temperature. Therefore, the reagent feed slurry was continuously stirred in a baffled vessel, and the slurry was intermittently pumped out of the vessel into the inlet transfer zone with a peristaltic pump. The process tubing was 3.2 mm inside diameter, which was sufficient to avoid fouling or clogging with solids for these six reactor volume turnovers. The process would need to be run for much longer duration to test ability to prevent clogging, but in this short run there were no signs that clogging would be an issue yet. The aniline product was more soluble in THF, therefore the product solution coming out of the reactor was homogeneous at room temperature. It is important to note that this is not possible with a packed catalyst bed reactor. The reagent feed to the packet catalyst bed reactor must be homogeneous solution. For situations like this nitrobenzene example, where the reagent is less soluble than the product, it is possible to use less solvent volumes by the stirred tank method compared to the packed catalyst bed. This also makes the process more productive for a given reactor volume.

In Figure 10, Picture A shows the nitrobenzene slurry stirring in a 3 L flask. Picture B shows the slurry after it has pumped into the inlet transfer zone and before it has pushed into the reactor. There was some settling of the solids in the transfer zone during the pause, but it was inconsequential, as the slurry cleanly pushed completely into the reactor out of the bottom of the transfer zone when the bottom valve was automatically opened. Picture C shows the small amount of residual slurry in the transfer tubing between the pump and the inlet transfer zone. The same automated pumping procedure was used here as was used for the catalyst slurry feed. The pump transferred slurry in the forward direction to the transfer zone, and then emptied the tubing in reverse direction back to the feed tank every reaction cycle.

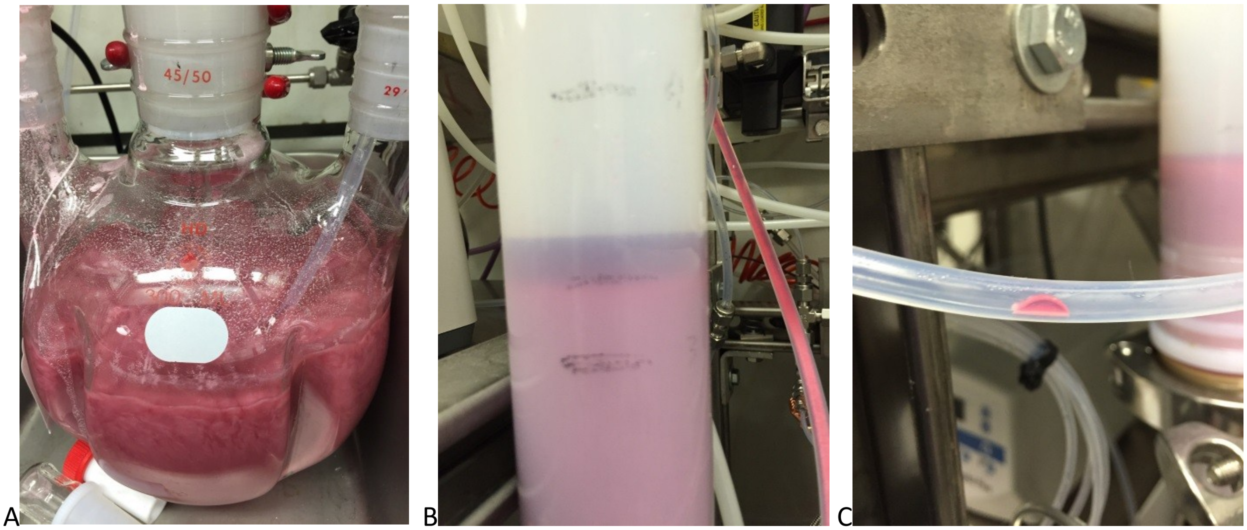


Figure 10. Pictures of (A) nitrobenzene slurry stirring in a 3 L flask. (B) slurry after it has pumped into the inlet transfer zone, (C) residual slurry in the transfer tubing between the pump and the inlet transfer zone.

Figure 11 shows HPLC results for product and desF impurity for the last 6 reactor turnovers of the second catalyst charge, using the slurry feed. Conversion to desired product was greater than 98.6 area % by HPLC, and the desF impurity was non-detect for all six turnovers. After this, the spent catalyst was emptied and fresh catalyst charged via the automated system.

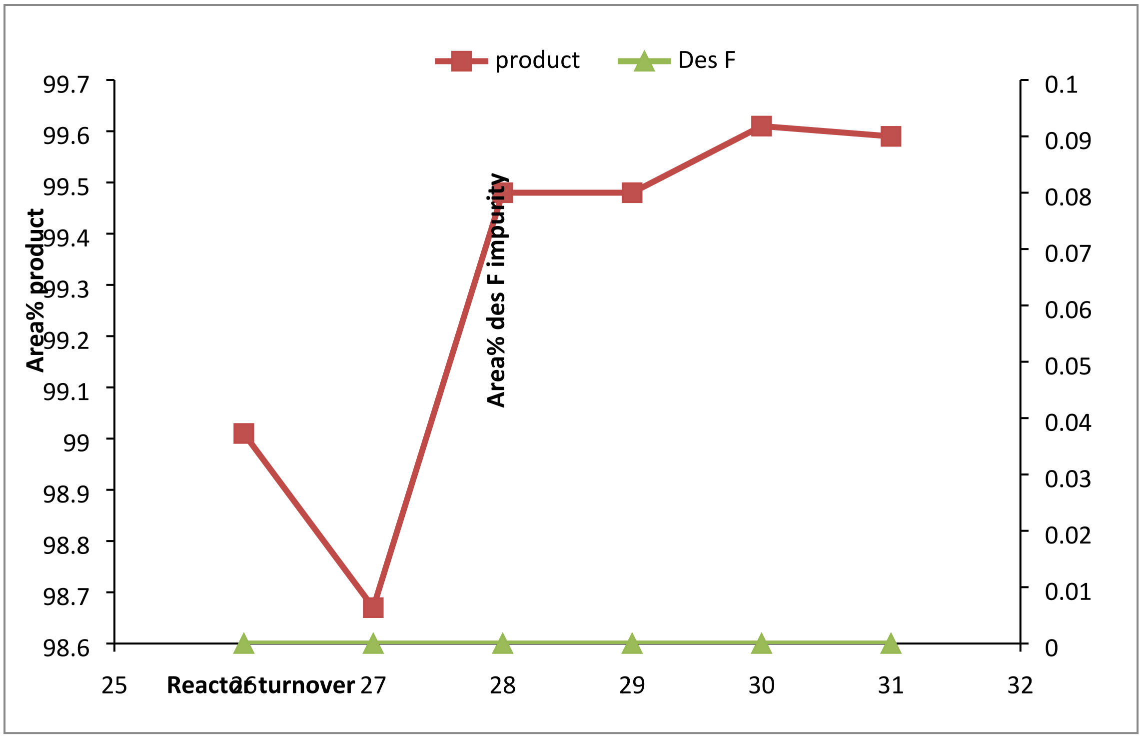


Figure 11. HPLC results for product and desF impurity for the last 6 reactor turnovers of the second catalyst charge, using slurry feed.

Figure 12 shows that time to full conversion was a strong function of the amount of slurry charged to the reactor. The green triangles show normalized hydrogen uptake rate when only 180 mL of slurry was pushed into the reactor. The purple X symbols show the rate when 350 mL of the slurry was pushed into the reactor. The blue diamonds show the hydrogen uptake rate when 590 mL of the nitrobenzene slurry was pushed into the reactor. Time to full conversion was 10 minutes, 18 minutes, and 20 minutes, respectively. The greater the amount of nitrobenzene solids in the reactor, the longer the reaction time, because the nitrobenzene solids must dissolve before it can react and because of higher substrate to catalyst ratio. Furthermore, nitrobenzene could only dissolve as fast as it was reacting. For reference, reaction time for the 25th reactor volume turnover, which used homogeneous solution feed with baseline 30 volumes solvent, was 10 minutes.

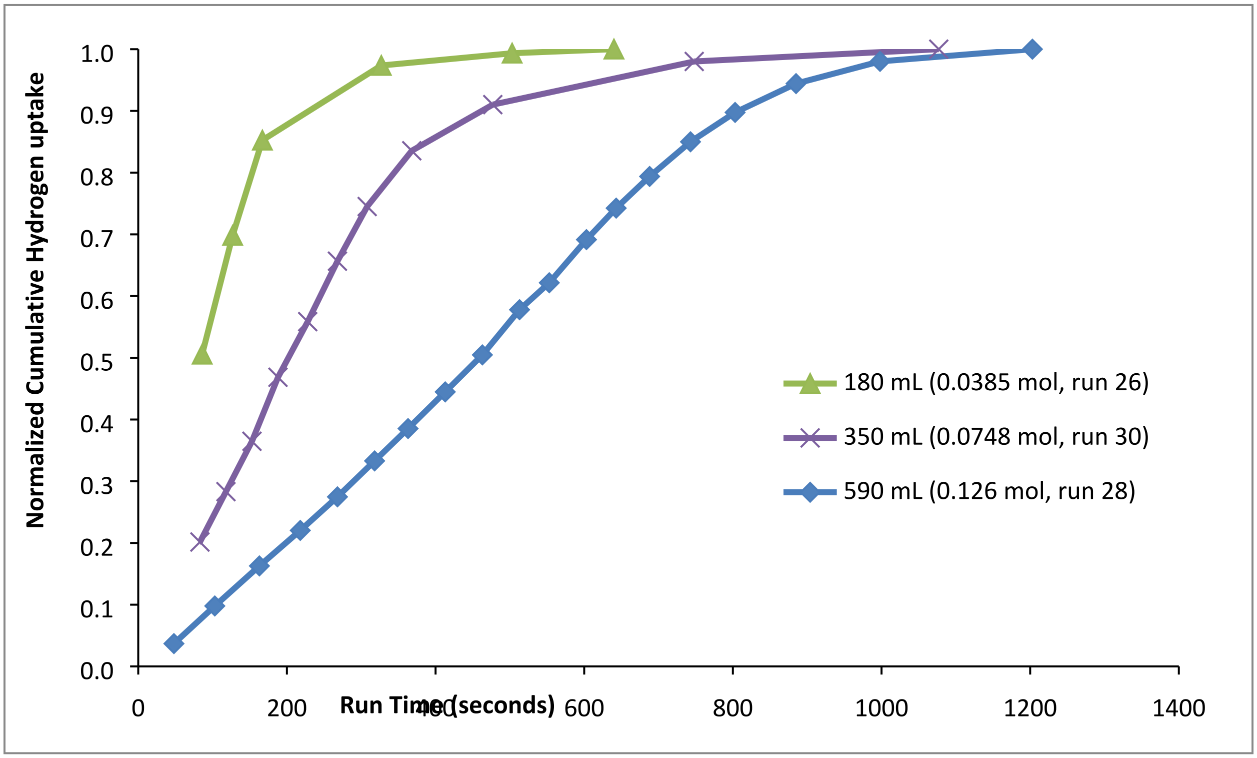


Figure 12. Reaction rate as a function of moles nitrobenzene charged for the slurry feed reactions.

In the main text, Figure 4 (bottom) showed that, near the end of the catalyst life for the first catalyst charge, the impact of pressure in the range 40–90 psig on reaction rate was small. That pressure testing began after 38 reactor volume turnovers. Time to full conversion was about 16 minutes. During the third catalyst charge, the impact of pressure on reaction rate was tested again. However, this was done after only 15 reactor volume turnovers, while catalyst was still near the beginning of its life and time to full reaction conversion was only about 8 minutes. Results are shown in Figure 13. Time to full conversion was about 8 minutes for reaction pressures 40, 60, and 90 psig. During the first five minutes, normalized hydrogen uptake was slightly faster for the higher pressure, but overall time to full conversion was the same, as shown in the Figure.

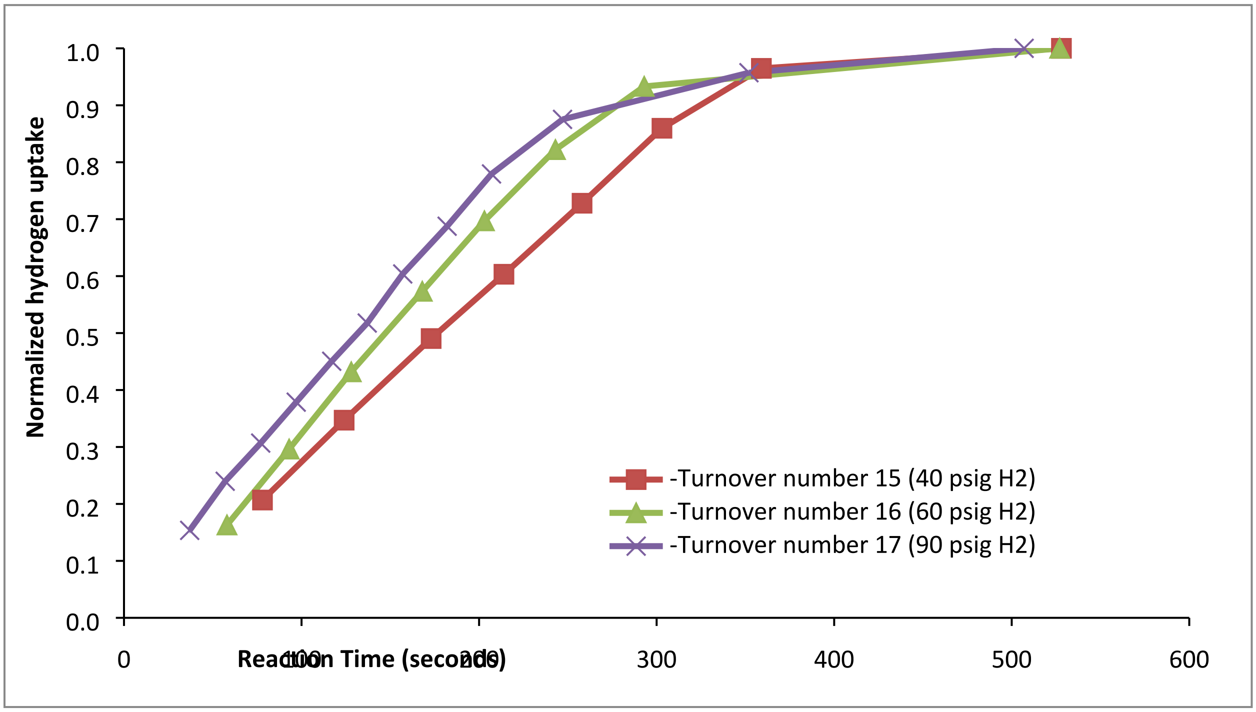


Figure 13. Reaction rate as a function of pressure near the beginning of catalyst life.

Description of Automated Sequence for Fill-Empty Reactor

Interlock:

Valve G cannot open if PT_B > HI Limit, PT_B < LO Limit, or TT_B > HI Limit

Sequence:

Do either 'Feed option 1' or 'Feed option 2'.

Feed option 1.

Pump catalyst slurry into inlet transfer zone. This is either reagent feed with catalyst or catalyst in solvent with no reagent. Feed option 1 only happens once every ~ 50 cycles (user input) because the catalyst particles are sequestered in the stirred tank and are used over and over again for each subsequent reactor turnover, until the catalyst activity becomes too low. The amount of catalyst charged is usually more than would be used in a batch process. The goal is to speed up the reaction with larger catalyst loading to get a larger number of reactor turnovers per day.

The distributed control system did the following:

- Open C
- Wait until PT_A < setpoint (e.g. 2 psig)
- Open A
- Set Pump 1 to Clockwise. Start Pump 1
- Wait x time (User input: e.g. 2 minutes) The volume pumped depends on the automated pumping time and the pump rate setpoint.
- Stop Pump 1
- Set Pump 1 to Counter-Clockwise. Start Pump 1
- Wait x time (User input: e.g. 15 seconds) Pump backwards long enough to clear slurry from process tubing back to slurry feed tank.
- Stop Pump 1. Set Pump 1 to Clockwise
- Close A
- Close C

Feed option 2.

Pump reagent feed solution with no catalyst. Feed option 2 is done for a large number of turnovers in a row, so that the same catalyst is used until activity decreases too much.

- Open C
- Wait until PT_A < setpoint (e.g. 2 psig)
- Open B
- Set Pump 2 to Clockwise. Start Pump 2

- Wait x time (User input: e.g. 2 minutes) The volume pumped depends on the automated pumping time and the pump rate setpoint.
- Stop Pump 2
- Close B
- Close C

Reaction.

- Open E
- Wait until PT_A > PT_B
- Open D
- Wait until PT_B > Setpoint 1 (User input, e.g. 40 psig. This is high enough so that all the material from the inlet transfer zone is pushed into the reactor)
- Close D
- Close E
- Open G
- Wait until PT_B > Setpoint 2 (User input, e.g. 50 psig. This is high enough so that all the liquid will push back from the outlet tube back into the reactor)
- Close G
- Open J
- Wait until PT_B > Setpoint 3 (User input, e.g. 60 psig. This is high enough so that all the liquid will push back from the outlet tube into the reactor)
- Close J
- Wait Minimum Reaction Time (Starts out as a user input, e.g. 5 minutes. Then it is automatically increased depending on the previous cycle actual reaction time. It is assumed that reactions only get slow, not faster, until the next fresh catalyst charge.)
- During reaction time, if PT_B < PT_B_LO setpoint (User input, e.g. 58 psig), then open G. If PT_B > PT_B_HI setpoint (User input, e.g. 62 psig), then close G. Reactor pressure measured by PT_B will oscillate up and down between the setpoints in a sawtooth pattern (see for example Figure 6). Pressure rises quickly from 58 psig to 62 psig when valve G is open, then is gradually drops down to 58 psig because of H_2 uptake because of reaction.
- Wait until minimum reaction time is reached, and until H_2 uptake rate is lower than setpoint (User input, e.g. <0.1 psig/minute with G valve closed.)

Do either ‘reactor empty option 1’, or ‘reactor empty option 2’.

Reactor empty option 1. Transfer from Reactor to outlet transfer zone using F valve. (keeps catalyst sequestered in reactor but pushes liquid product solution out) .

- Open F
- Open K
- Wait until PT_B < User Setpoint (e.g. 40 psig)
- Close F

- Open G
- Wait PT_B > User Setpoint (e.g. 60 psig). This blow back clears solid catalyst particles from the filter frit.
- Close G
- Open F
- Repeat the last 3 steps X number of times (user input, e.g. 3 times)
- Wait until PT_B < Setpoint 4 (e.g. 15 psig)
- Close F

Reactor empty option 2. Transfer from Reactor to outlet transfer zone using H valve. (Empties all reactor contents including catalyst particles).

- Open H
- Wait Vent Delay
- Open K
- Wait until PT_B < Setpoint 5 (User input, e.g. 10 psig)
- Close H

Purge outlet transfer zone with N2 and push out to filter and/or product collection tank.

- Close K
- Open L
- Wait until PT_C > Setpoint (user input, e.g. 15 psig)
- Close L
- Open K
- Wait until PT_C < Setpoint (user input, e.g. 2 psig)
- Close K
- Open L
- Wait until PT_C > Setpoint (user input, e.g. 15 psig)
- Close L
- Repeat the last 6 steps for user specified number of purge cycles (e.g. 2)
- Open M
- Wait until PT_C < Setpoint (user input, e.g. 2 psig)
- Close M

There is overlap so that filling and emptying happen simultaneously. Feed option 1 or feed option 2 begins while the reactor is emptying, so that the next reaction can start immediately after the previous reaction product is out. This saves cycle time and makes the reactor system more productive.

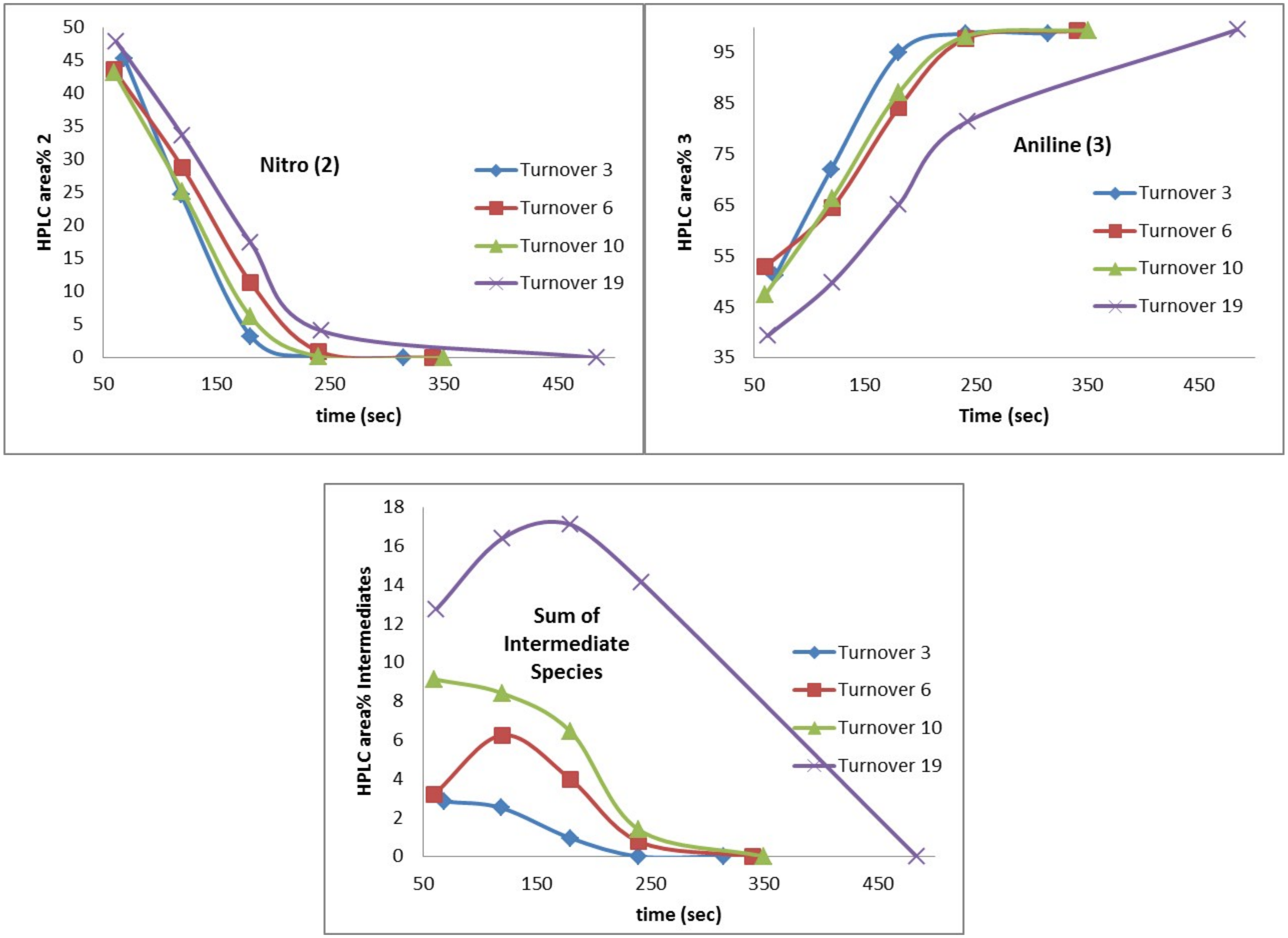


Figure 14. Effect of catalyst age on (A) Consumption of starting material, (B) Formation of product, (C) Formation and consumption of intermediate species.