Development of an Intermittent-Flow Enantioselective aza-Henry Reaction using an Arylnitromethane and Homogeneous Brønsted Acid-Base Catalyst with Recycle

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1. Calculation of conversion versus time in batch PFR, CSTR and CSTRs in series

This section illustrates how to derive the design equations for different reactor types and use them to calculate conversion versus time in batch, PFR, CSTR, and CSTRs in series.

To illustrate why a CSTR requires longer residence time than PFR or batch for full conversion, consider a first order irreversible reaction that requires 30 minutes for 99.9% conversion batch. In an ideal PFR, the required reaction time is also 30 minutes for 99.9% conversion, but in an ideal CSTR, the required reaction time is 72 hours for 99.9% conversion, which is impractical. The required total residence time in 3 equal-volume CSTRs in series would be 1.95 hours, which is significantly less than a single CSTR. However, this is still a significantly longer reaction time than batch or PFR, and it does not enable the type of controlled addition of imine to nitroalkane that is desired.

Case 1. Batch reactor

$$[in - out] + reaction = accumulation$$

batch reaction no flow in and out

$$reaction = accumulation$$

$$-kC_A = \frac{dC_A}{dt}$$

C_A= concentration of reagent A at one point in reactor

k = first order rate constant

t = reaction time

Integrate over time:

$$\int_0^t -kdt = \int_{C_{Ao}}^{C_{AF}} \frac{dC_A}{C_A}$$

C_{A0}= Initial concentration of reagent A

C_{AF}= Final concentration of reagent A

$$-kt = ln\left(\frac{C_{AF}}{C_{Ao}}\right)$$

$$\frac{C_{AF}}{C_{Ao}} = e^{-kt}$$

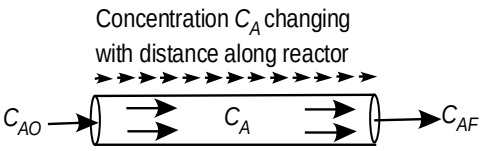
$$t = 30min$$

$$\frac{C_{AF}}{C_{Ao}} = 0.001$$

Calculate first order rate constant

$$k = 0.2303\frac{1}{min}$$

Case 2. PFR.



C_{A0}= Initial concentration of reagent A at reactor inlet

C_{AF}= Final concentration of reagent A reactor outlet

C_A= Concentration of reagent A at one point in PFR

$$\tau = \frac{L}{v_x} seconds$$

L = total reactor length

v_x = average linear velocity in reactor

$$[in - out] + reaction = accumulation$$

Steady state no accumulation

$$[in - out] + reaction = 0$$

$$\frac{D}{uL}\frac{d^2C_A}{dx^2} - v_x\frac{dC_A}{dx} - kC_A = 0$$

Assume negligible axial dispersion.

$$-v_x\frac{dC_A}{dx} - kC_A = 0$$

Integrate over distance:

$$\int_{C_{Ao}}^{C_{AF}} \frac{dC_A}{C_A} = \int_0^L \frac{-k}{v_x} dx$$

$$ln\left(\frac{C_{AF}}{C_{Ao}}\right) = -\frac{kL}{v_x} = -k\tau$$

$$\frac{C_{AF}}{C_{Ao}} = e^{-k\tau}$$

Given rate constant and time:

$$k = 0.2303\frac{1}{min}$$

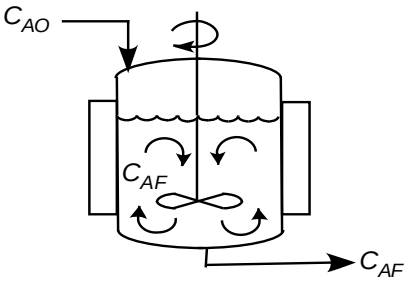
$$t = 30min$$

Calculate conversion:

$$\frac{C_{AF}}{C_{Ao}} = 0.001$$

For the same rate constant and the same time, conversion is the same in the ideal PFR and the batch reactor.

Case 3. CSTR.



$$\tau = \frac{V}{Q} seconds$$

V = volume of fluid in CSTR

Q = volumetric flow rate in CSTR

$$[in - out] + reaction = accumulation$$

Steady state no accumulation

$$[in - out] + reaction = 0$$

$$QC_{Ao} - QC_{AF} - kC_{AF}V = 0$$

$$QC_{Ao} = C_{AF}(Q + kV) = 0$$

$$\frac{C_{AF}}{C_{Ao}} = \frac{Q}{Q + kV}$$

$$\frac{C_{AF}}{C_{Ao}} = \frac{1}{1 + k\tau}$$

Given rate constant and conversion:

$$k = 0.2303 \frac{1}{min}$$

$$\frac{C_{AF}}{C_{Ao}} = 0.001$$

Calculate mean reactor residence time:

τ = 4326 minutes = 72.1 hours

Case 4. CSTRs-in-series.

See chemical engineering texts for CSTRs in series.[1]

$$\frac{C_{AF}}{C_{Ao}} = \left(\frac{1}{1 + k\tau}\right)^3$$

Given reaction rate and conversion:

$$k = 0.2303 \frac{1}{min}$$

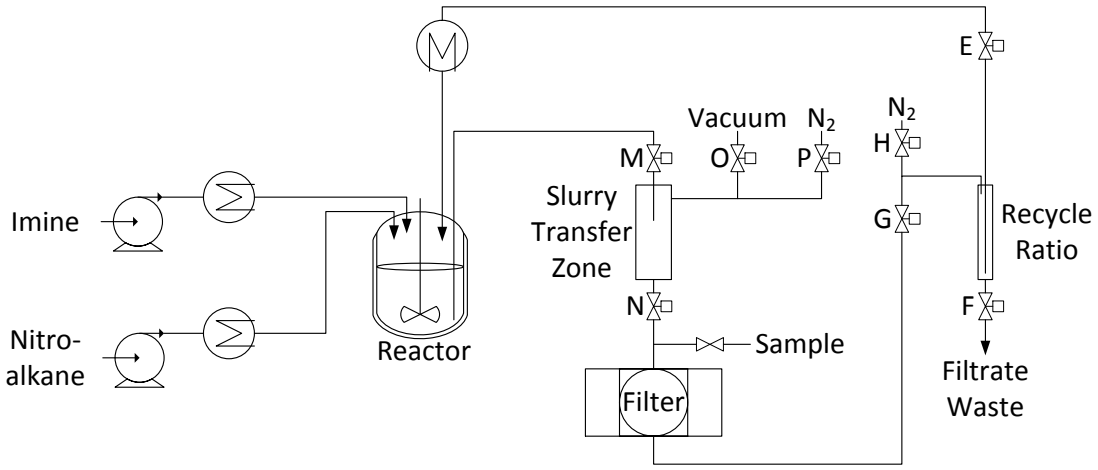
$$\frac{C_{AF}}{C_{Ao}} = 0.001$$

Calculate mean reactor residence time:

$$\tau = 39.1 \; minutes \; in \; each \; equal \; sized \; CSTR$$

$$therefore \; overall \; \tau = 117 \; minutes.$$

2. Automation

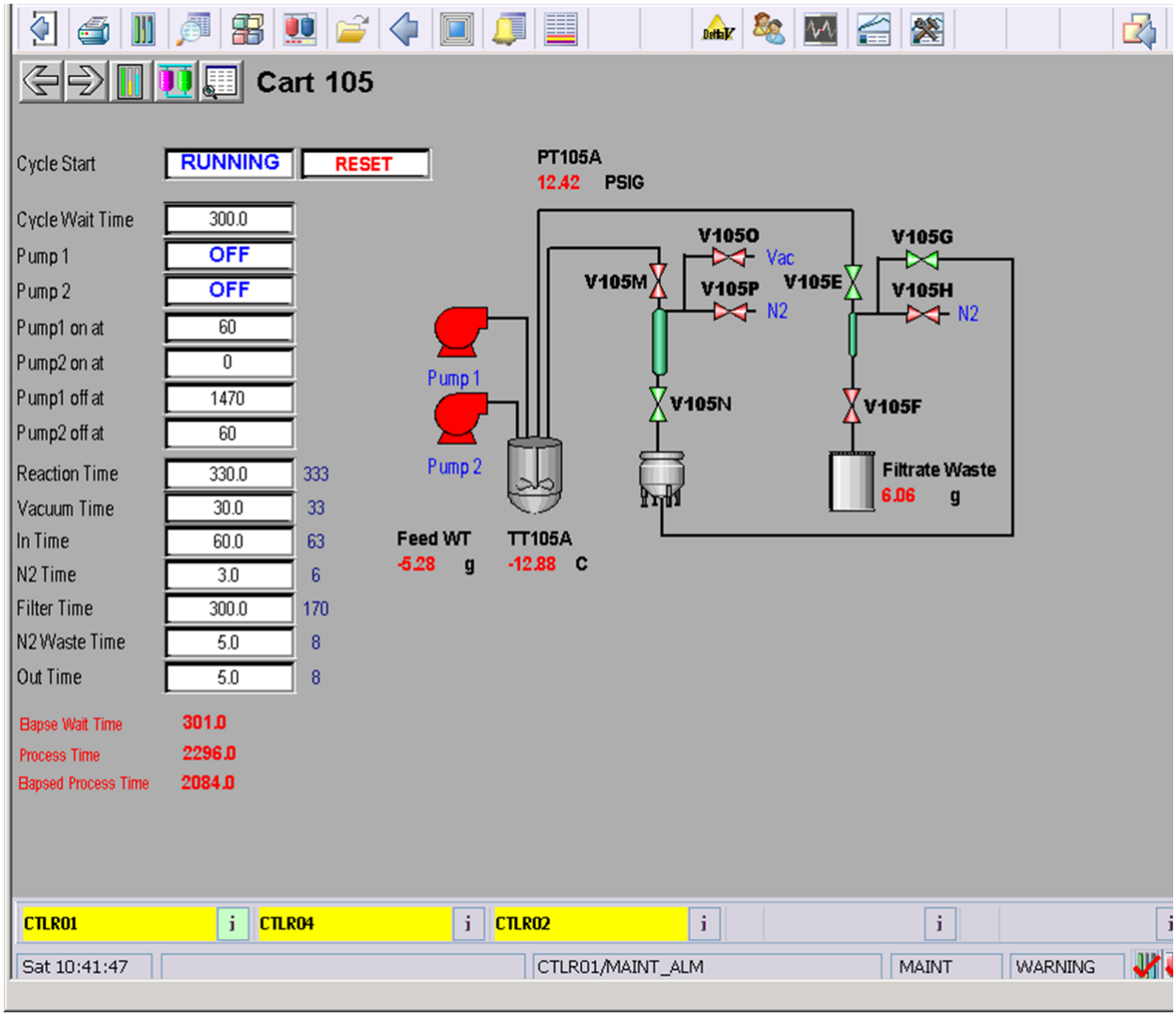


Scheme S1. Technological scheme of the process

DeltaV was used for automation of the laboratory intermittent flow CSTR system. Refer to the figure with reactor system schematic and labeled valve numbers (Scheme 1). The automation starts with the two pumps charging material into the reactor. Once the last pump turns off the reaction extra stir time begins. Total reaction time is the reagent addition time plus the extra stir time. When the reaction is finished, valves G and E are open to allow for filtrate to flow back to the reactor. Valve O opens to pull vacuum on the slurry transfer zone. A vacuum regulator is used to make sure that the MNOP transfer zone pulls down to the desired pressure, for example 400 mmHg. Valve O closes and valve M opens to allow the contents of the reactor to be pulled into the transfer zone. Valve M closes and the transfer zone is pressured up with nitrogen by opening valve P. Valve N opens to start the flow of material to the filter. Nitrogen pressure continues to push on the top of the filter, so that the filtrate flows through the filter and back to the reactor. Valve P closes, but the pressure on the top of the filter continues to push filtrate back to reactor for the filter time input by the user. When the solids have collected on the filter and the filtrate has been recycled, valves N, G and E close. The EFGH zone contains filtrate waste. The volume of filtrate waste depends on how far the dip tube is pushed down into EFGH zone. The next step is for this filtrate waste to be pushed to a waste container. Valve H opens to pressurize EFGH zone, then Valve H closes. Valve F opens to transfer the filtrate waste to the waste container. Valve F closes and the cycle wait time starts. When the cycle wait time is complete, the sequence will repeat until the user turns the sequence off.
For DeltaV automation of this cart the following variables can be adjusted by the user: time between each cycle, when pumps 1 & 2 turn on and off, the reaction time, vacuum time in transfer zone, amount of time to transfer from the reactor to the transfer zone, time to pressure up the transfer zone with nitrogen, time for slurry to pass through filter, time to pressure up transfer zone for filtrate waste, and the time to push filtrate waste out of the second transfer zone.

The automation sequence for DeltaV may be seen below:
Pump 2 on, wait 1 minute
Pump 2 off
Pump 1 on, wait 23.5 minutes
Pump 1 off, wait 5.5 minutes (reaction extra stir time)
Open G,
Open E,
Open O, 30 sec
Close O
Open M, 60 sec
Close M
Open P, 3 sec
Open N
Close P, wait 5 min
Close N

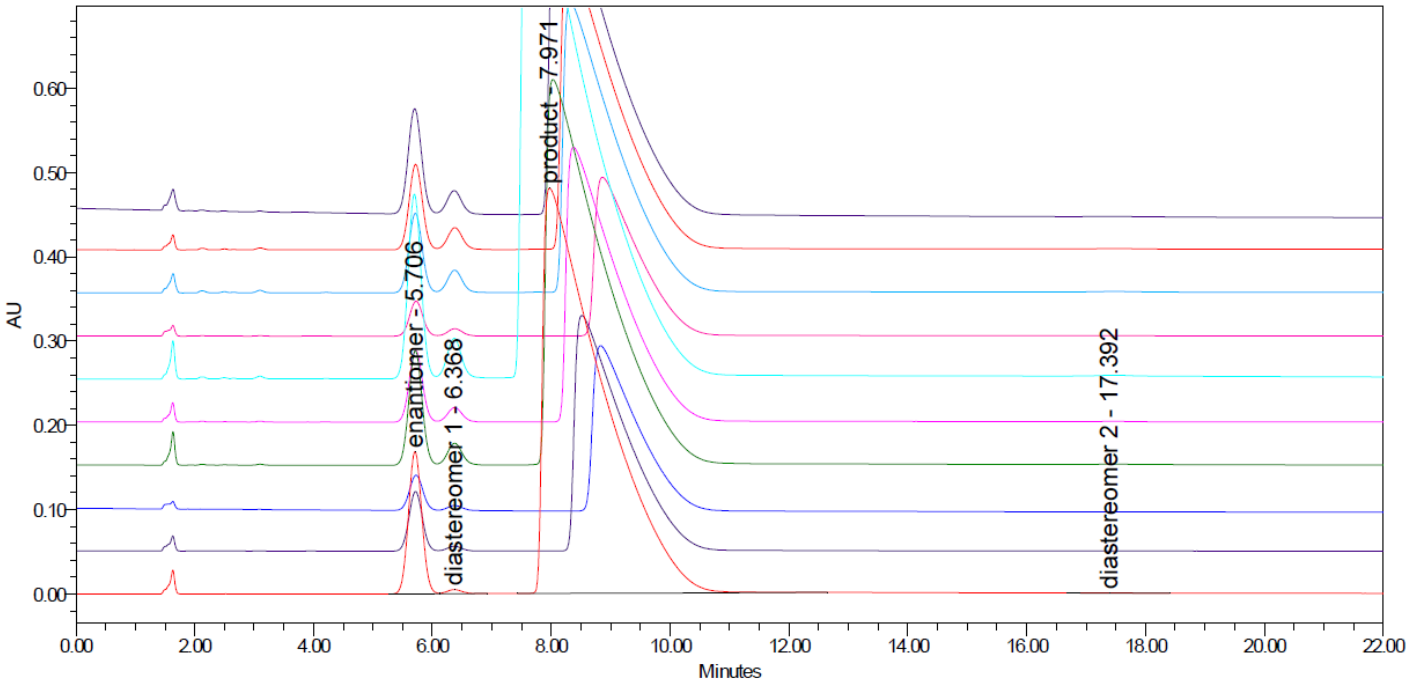
Close G
Close E
Open H, 5 sec
Close H
Open F, 5 sec
Close F, wait 5 sec



Picture S1. Screen shot of the control screen of the process

3. HPLC data

Figure S1. HPLC traces for the solid product (10 cycles, 80% recycling ratio)



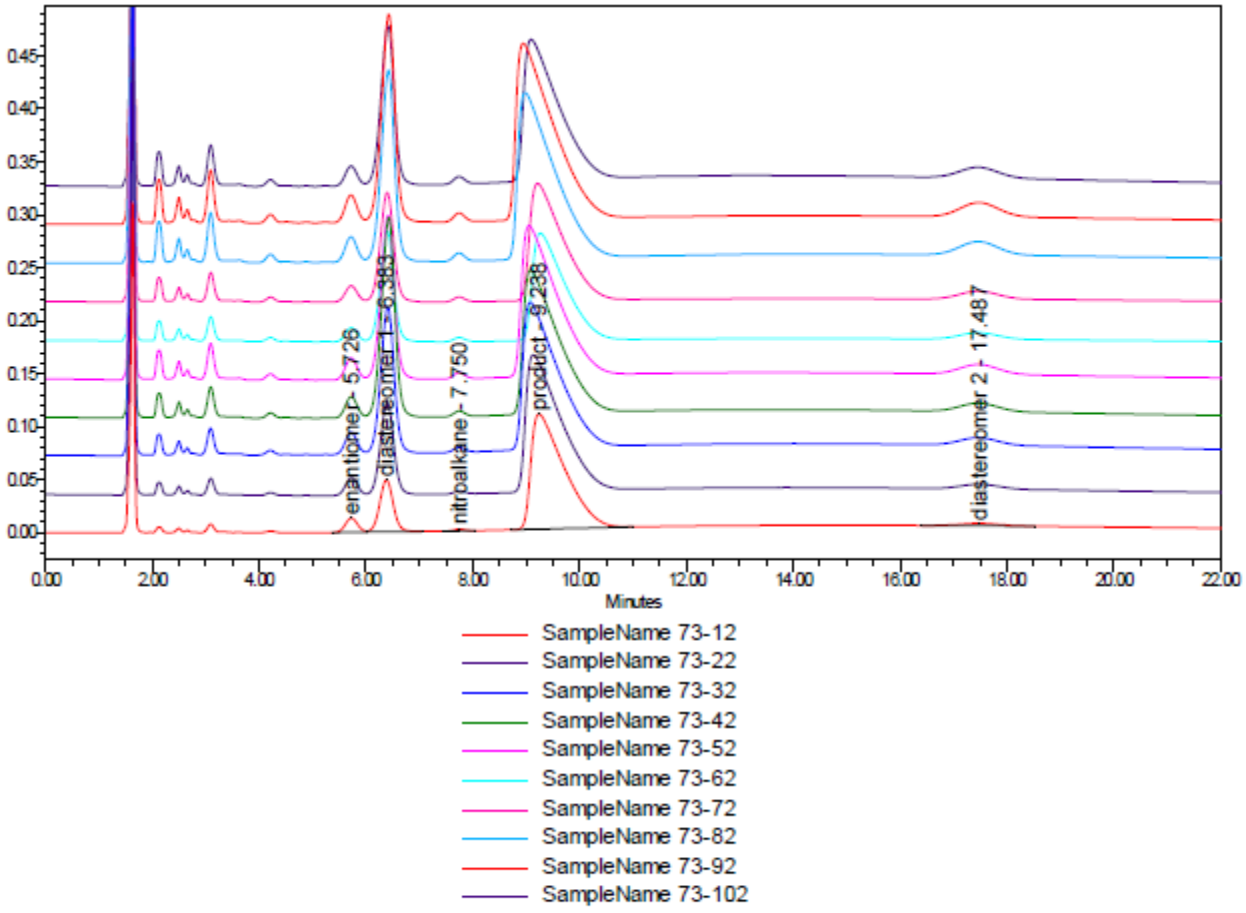
Component Summary For Percent_ee

	Sample Name	product
1	73-11	85.1
2	73-21	86.9
3	73-31	87.5
4	73-41	87.0
5	73-51	87.2
6	73-61	87.1
7	73-71	87.0
8	73-81	86.8
9	73-91	86.6
10	73-101	86.8

Component Summary For % Area

	Sample Name	enantiomer	diastereomer 1	nitroalkane	product	diastereomer 2
1	73-11	7.44	0.24		92.31	0.02
2	73-21	6.50	0.59		92.89	0.02
3	73-31	6.18	0.98		92.80	0.03
4	73-41	6.40	1.35		92.18	0.07
5	73-51	6.32	1.41		92.19	0.08
6	73-61	6.33	1.53		92.04	0.09
7	73-71	6.38	1.49		92.03	0.10
8	73-81	6.47	2.03	0.02	91.28	0.20
9	73-91	6.59	1.87	0.01	91.51	
10	73-101	6.51	1.59		91.82	0.07

Figure S2. HPLC traces for filtrates (10 cycles, 80% recycling ratio)



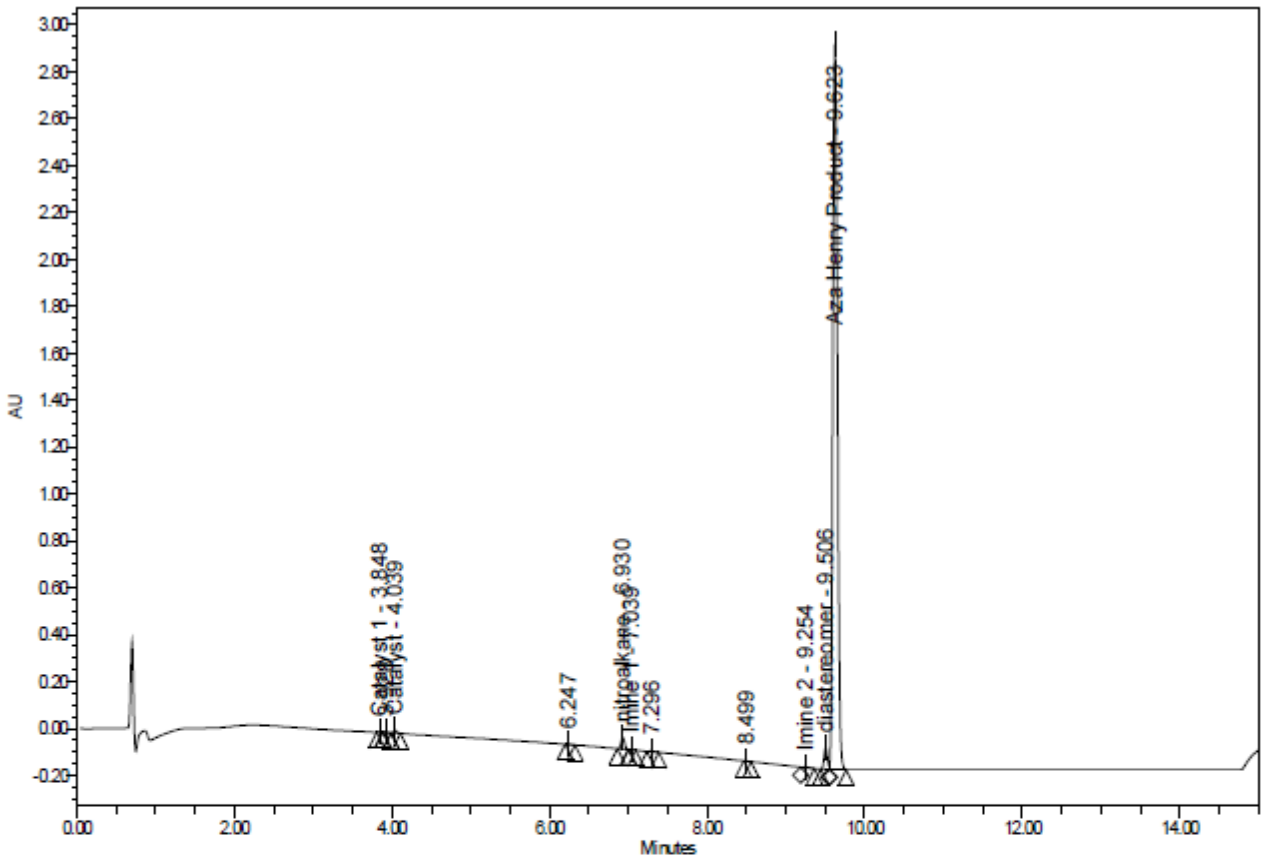
Component Summary For Percent_ee

	Sample Name	product
1	73-12	91.3
2	73-22	91.3
3	73-32	90.2
4	73-42	90.3
5	73-52	90.5
6	73-62	90.6
7	73-72	90.2
8	73-82	90.3
9	73-92	90.2
10	73-102	90.8

Component Summary For % Area

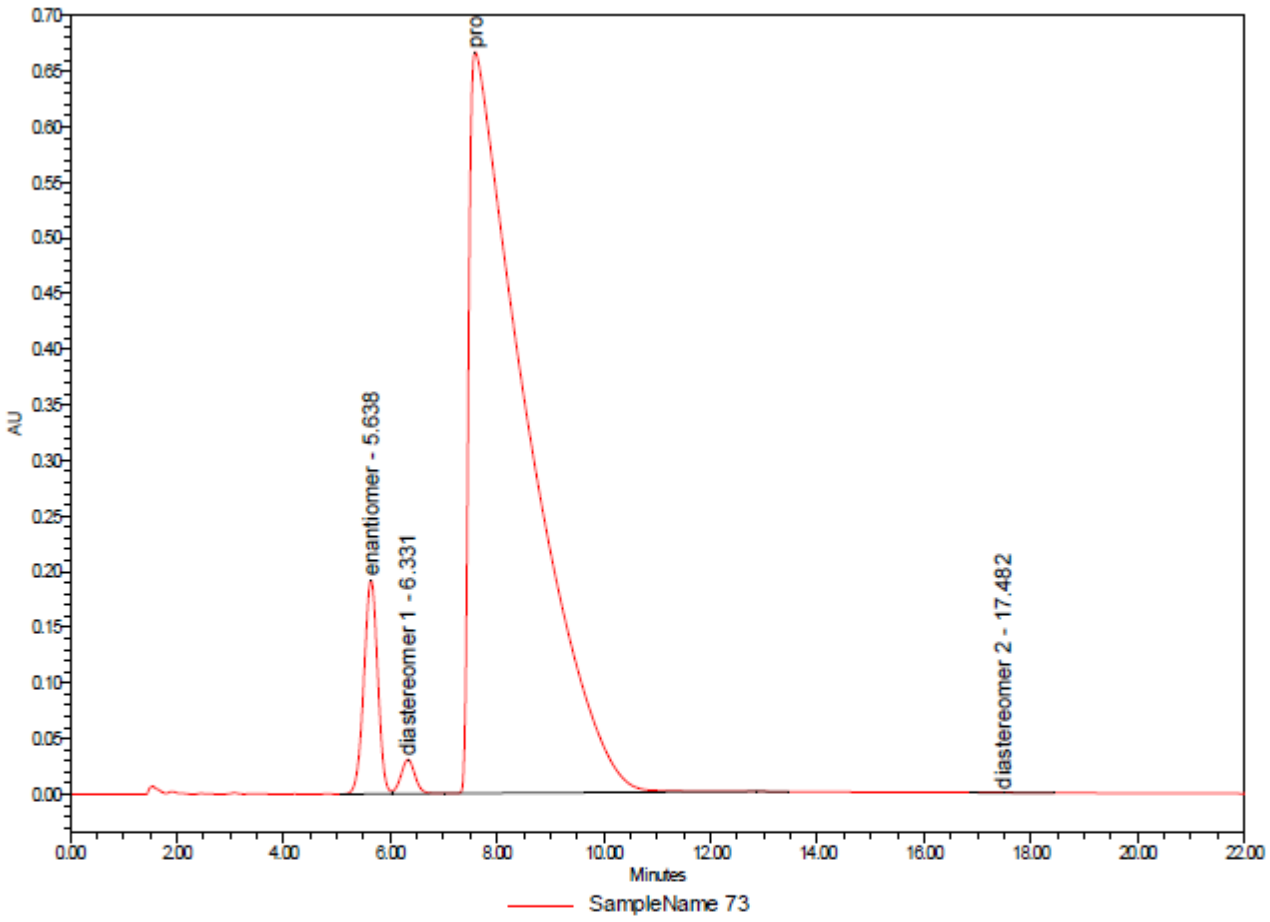
	Sample Name	enantiomer	diastereomer 1	nitroalkane	product	diastereomer 2
1	73-12	3.59	14.65	0.41	79.29	2.06
2	73-22	3.35	19.56	0.55	73.65	2.86
3	73-32	3.42	25.56	0.70	66.42	3.80
4	73-42	3.05	32.32	0.73	59.86	3.93
5	73-52	3.20	26.91	0.85	64.23	4.65
6	73-62	3.14	27.61	0.86	63.46	4.77
7	73-72	3.35	25.10	0.93	65.01	5.41
8	73-82	3.21	27.21	0.96	62.88	5.50
9	73-92	3.24	27.35	0.95	62.83	5.41
10	73-102	3.04	27.68	1.05	62.70	5.32

Figure S3. HPLC trace for the isolated dried product (10 cycles, 80% recycling ratio)



	Name	RT (min)	Area (µV*sec)	% Area
1	Catalyst 1	3.848	2615	0.02
2		3.928	4346	0.03
3	Catalyst	4.039	33623	0.26
4		6.247	4767	0.04
5	nitroalkane	6.930	148179	1.14
6	Imine 1	7.039	5534	0.04
7		7.296	12740	0.10
8		8.499	2490	0.02
9	Imine 2	9.254	14247	0.11
10	diastereomer	9.506	269298	2.06
11	Aza Henry Product	9.623	12556416	96.19

Figure S4. Chiral HPLC trace for the isolated dried product (10 cycles, 80% recycling ratio)



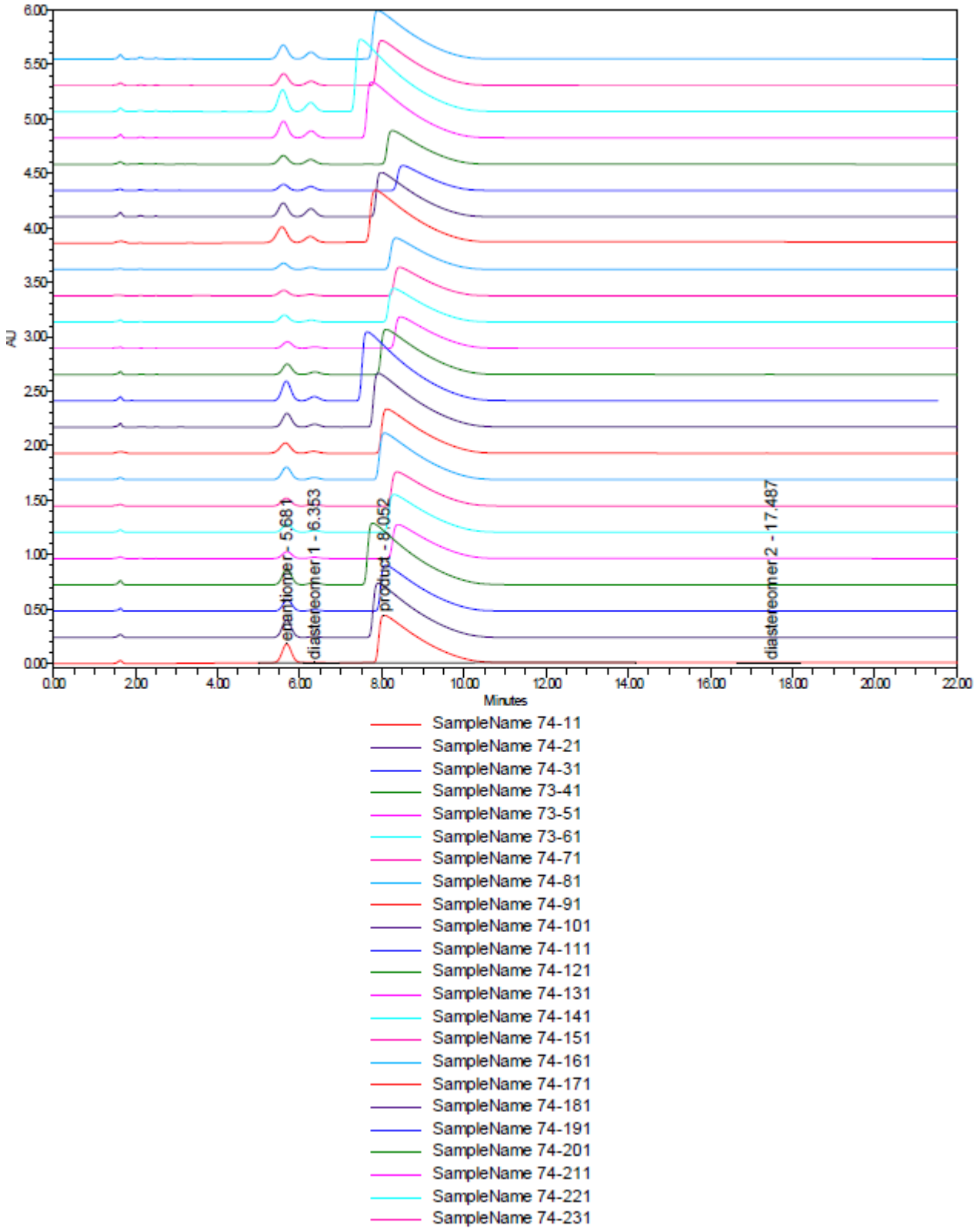
Component Summary For Percent_ee

	Sample Name	product
1	73	87.0

Component Summary For % Area

	Sample Name	enantiomer	diastereomer 1	product	diastereomer 2
1	73	6.41	1.03	92.54	0.01

Figure S5. HPLC traces for the solid product (24 cycles, 97% recycling ratio)



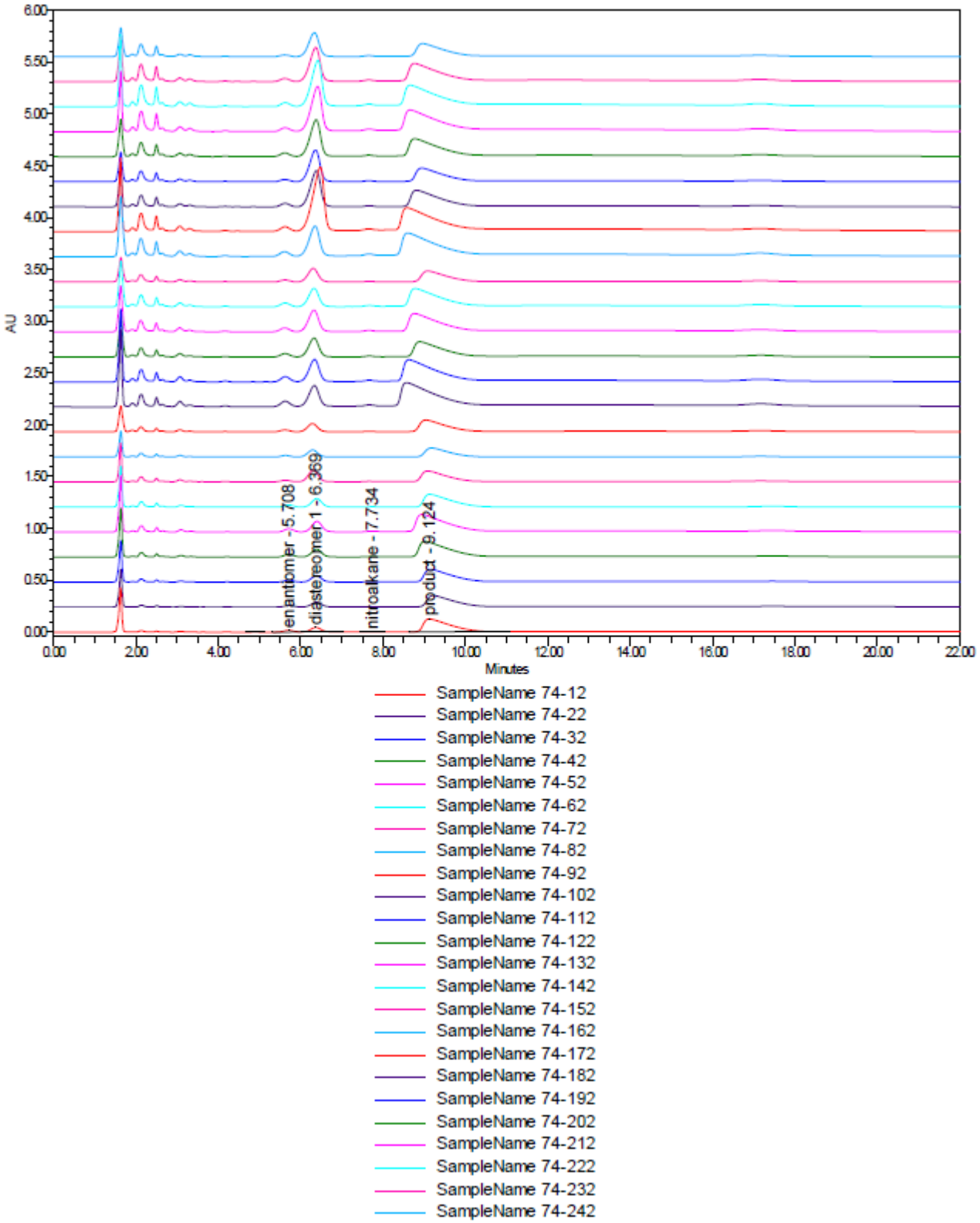
Component Summary For Percent_ee

	Sample Name	product
1	74-11	82.6
2	74-21	86.0
3	74-31	88.3
4	73-41	89.4
5	73-51	89.4
6	73-61	89.2
7	74-71	88.0
8	74-81	87.4
9	74-91	87.5
10	74-101	88.9
11	74-111	88.4
12	74-121	89.2
13	74-131	89.1
14	74-141	89.3
15	74-151	89.2
16	74-161	89.2
17	74-171	85.1
18	74-181	85.4
19	74-191	85.7
20	74-201	86.4
21	74-211	87.0
22	74-221	87.5
23	74-231	87.5
24	74-241	86.6

Component Summary For % Area

	Sample Name	enantiomer	diastereomer 1	product	diastereomer 2
1	74-11	8.69	0.29	91.00	0.02
2	74-21	6.95	0.47	92.56	0.02
3	74-31	5.79	0.80	93.38	0.02
4	73-41	5.22	0.99	92.84	0.29
5	73-51	5.26	1.06	93.62	0.04
6	73-61	5.33	1.18	93.41	0.05
7	74-71	5.91	1.32	92.73	0.04
8	74-81	6.20	1.18	92.60	0.02
9	74-91	6.15	1.24	92.58	0.03
10	74-101	5.48	1.27	93.19	0.05
11	74-111	5.71	1.35	92.89	0.05
12	74-121	5.31	1.51	93.12	0.06
13	74-131	5.39	1.36	93.17	0.04
14	74-141	5.27	1.63	92.98	0.09
15	74-151	5.34	1.50	93.09	0.05
16	74-161	5.28	1.87	92.69	0.14
17	74-171	7.24	2.72	90.03	0.01
18	74-181	6.98	4.43	88.45	0.14
19	74-191	6.80	4.81	88.13	0.21
20	74-201	6.54	3.81	89.46	0.17
21	74-211	6.32	2.87	90.72	0.09
22	74-221	6.09	2.71	91.09	0.10
23	74-231	6.09	2.37	91.47	0.07
24	74-241	6.46	3.42	89.86	0.23

Figure S6. HPLC traces for filtrates (24 cycles, 97% recycling ratio)



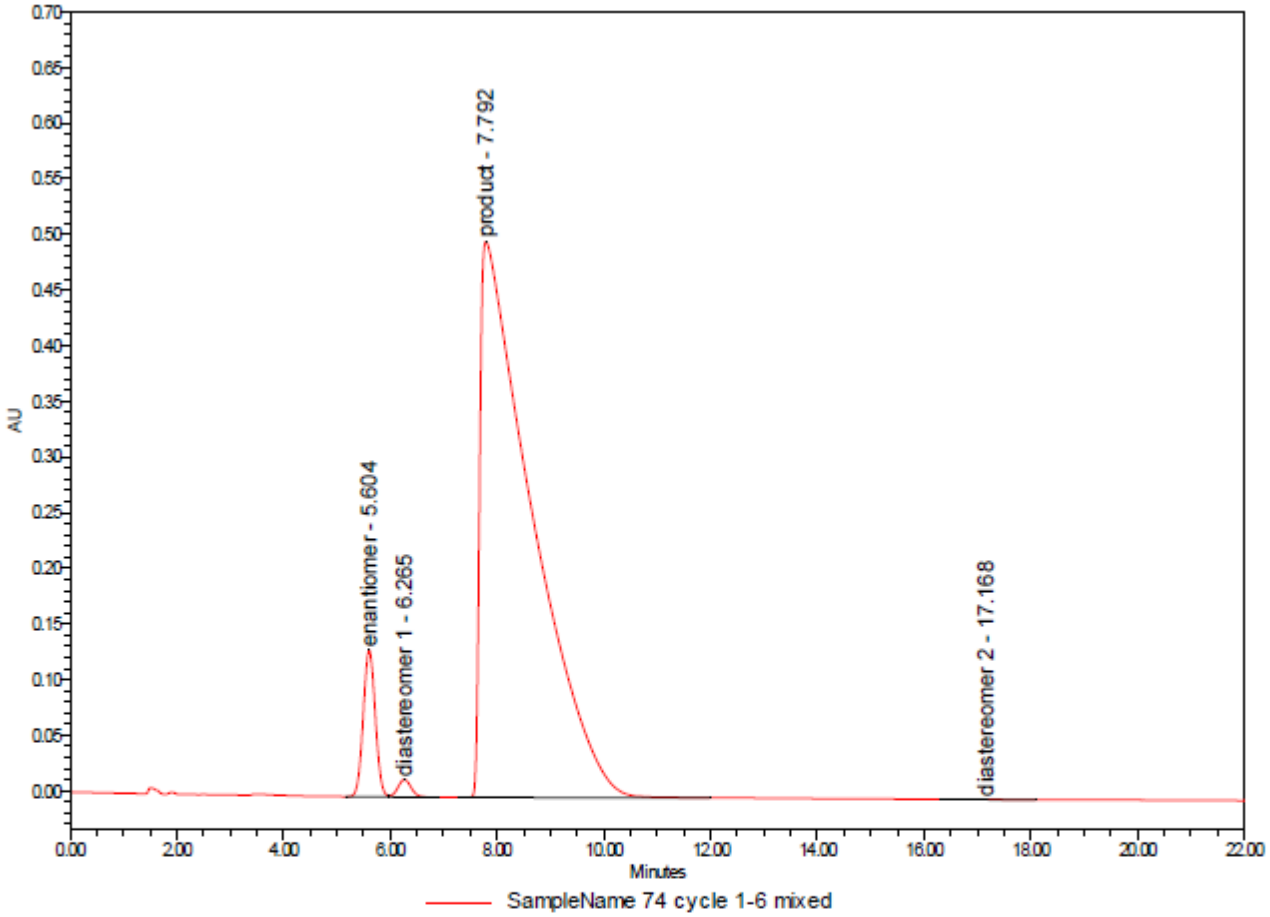
Component Summary For Percent_ee

	Sample Name	product
1	74-12	91.0
2	74-22	90.3
3	74-32	89.5
4	74-42	87.9
5	74-52	88.3
6	74-62	88.2
7	74-72	88.9
8	74-82	87.2
9	74-92	87.8
10	74-102	86.8
11	74-112	85.9
12	74-122	84.9
13	74-132	86.5
14	74-142	86.5
15	74-152	86.6
16	74-162	87.7
17	74-172	88.8
18	74-182	86.4
19	74-192	88.2
20	74-202	86.8
21	74-212	89.4
22	74-222	88.8
23	74-232	88.5
24	74-242	90.0

Component Summary For % Area

	Sample Name	enantiomer	diastereomer 1	nitroalkane	product	diastereomer 2
1	74-12	3.93	11.75	0.32	83.90	
2	74-22	4.14	14.20	0.51	81.10	
3	74-32	4.38	16.05	0.66	78.86	
4	74-42	5.09	15.12	0.73	79.02	
5	74-52	4.79	17.42	0.83	76.87	
6	74-62	4.67	19.98	0.92	74.27	
7	74-72	3.64	28.86	0.88	62.10	4.34
8	74-82	4.57	22.94	0.87	66.90	4.58
9	74-92	4.50	20.51	0.97	69.10	4.82
10	74-102	4.84	20.88	0.98	68.20	4.94
11	74-112	4.94	23.61	1.03	65.06	5.18
12	74-122	4.85	29.34	1.04	59.25	5.35
13	74-132	4.45	27.79	1.07	61.25	5.29
14	74-142	4.60	24.68	1.15	63.79	5.61
15	74-152	4.13	31.32	1.13	57.79	5.45
16	74-162	3.98	28.66	1.19	60.41	5.61
17	74-172	2.67	48.70	0.81	45.13	2.46
18	74-182	3.62	42.89	0.81	49.53	2.93
19	74-192	2.93	45.98	0.91	46.68	3.28
20	74-202	3.56	41.23	0.93	50.28	3.79
21	74-212	2.83	41.08	1.08	50.51	4.22
22	74-222	2.94	41.69	1.12	49.55	4.42
23	74-232	3.17	38.90	1.11	51.90	4.63
24	74-242	2.70	39.85	1.14	51.20	4.84

Figure S7. Chiral HPLC trace for the isolated dried product (cycles 1-6, 24 cycles, 97% recycling ratio)



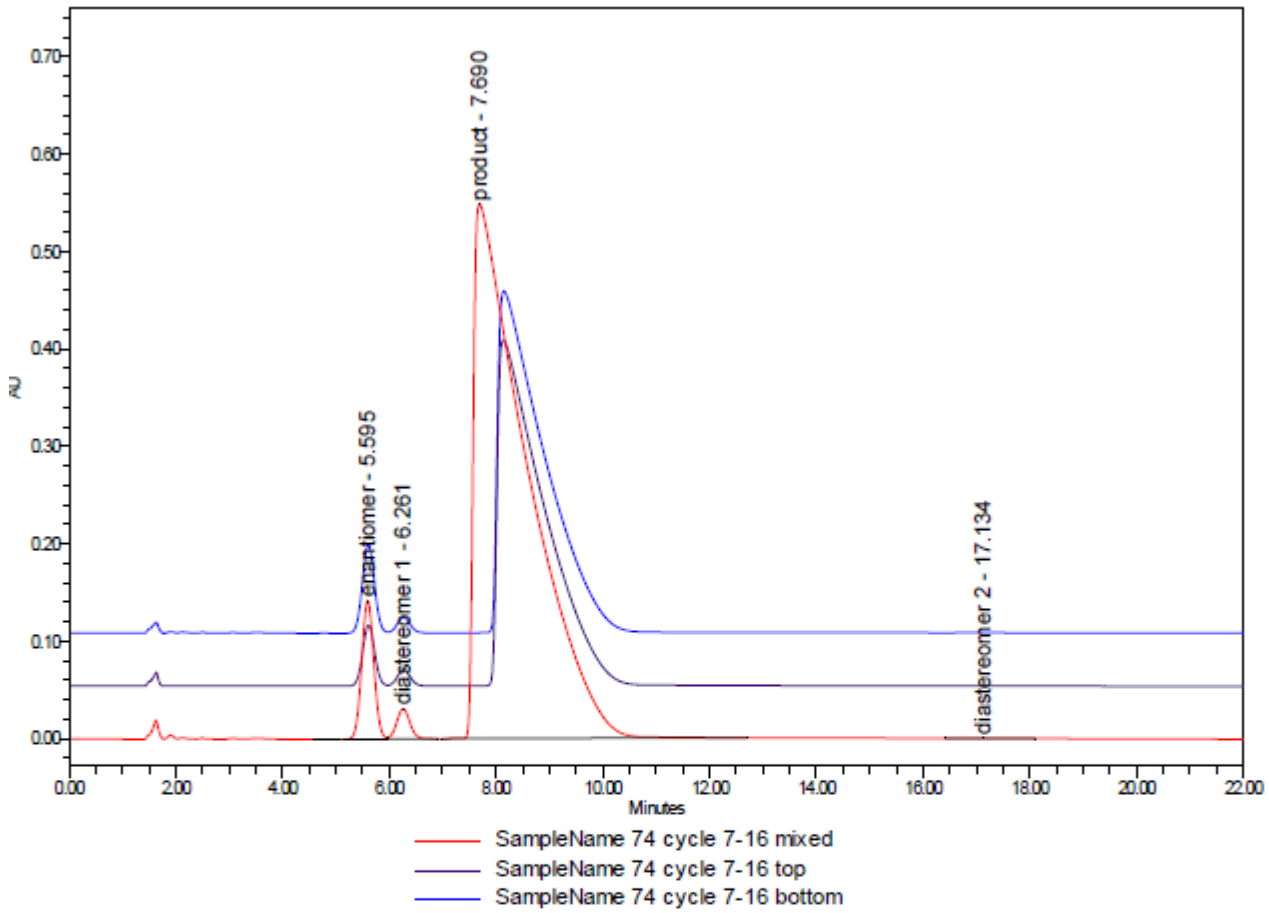
Component Summary For Percent_ee

	Sample Name	product
1	74 cycle 1-6 mixed	88.3

Component Summary For % Area

	Sample Name	enantiomer	diastereomer 1	product	diastereomer 2
1	74 cycle 1-6 mixed	5.79	0.75	93.45	0.01

Figure S8. Chiral HPLC trace for the isolated dried product (cycles 7-16, 24 cycles, 97% recycling ratio)



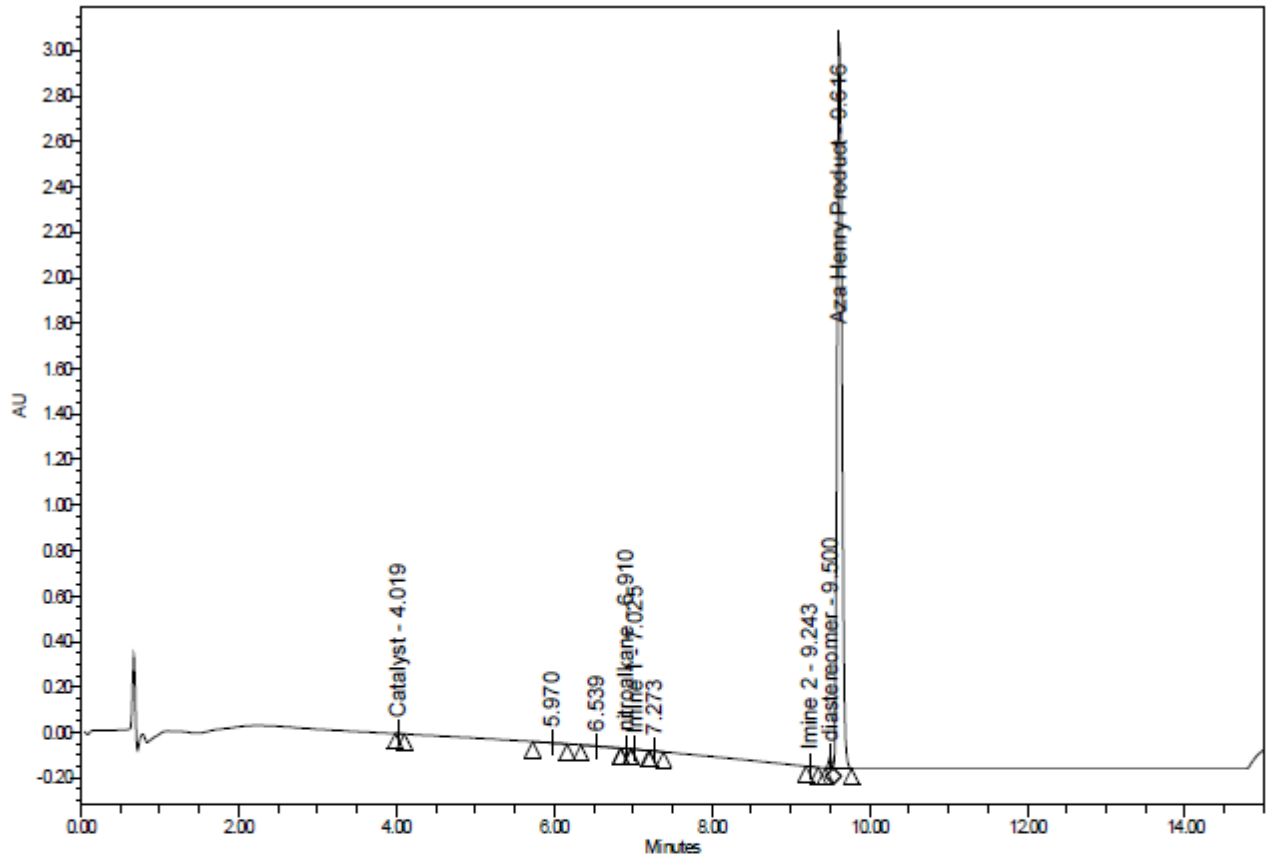
Component Summary For Percent_ee

	Sample Name	product
1	74 cycle 7-16 mixed	88.8
2	74 cycle 7-16 top	91.2
3	74 cycle 7-16 bottom	87.1

Component Summary For % Area

	Sample Name	enantiomer	diastereomer 1	product	diastereomer 2
1	74 cycle 7-16 mixed	5.53	1.30	93.13	0.02
2	74 cycle 7-16 top	4.36	1.27	94.36	0.02
3	74 cycle 7-16 bottom	6.39	1.23	92.34	0.03

Figure S9. HPLC traces for the solid product (24 cycles, 97% recycling ratio)



	Name	RT (min)	Area (µV*sec)	% Area
1	Catalyst 1	3.700		
2	Catalyst	4.019	5259	0.04
3		5.970	3279	0.02
4		6.539	4977	0.04
5	nitroalkane	6.910	8354	0.06
6	Imine 1	7.025	4839	0.04
7		7.273	13808	0.10
8	Imine 2	9.243	6473	0.05
9	diastereomer	9.500	146303	1.06
10	Aza Henry Product	9.616	13550845	98.59

4. Preliminary safety evaluation of oxime and nitro containing compounds

Compounds containing nitro and oxime groups are often suspected to possess negative characteristics from a thermal hazards perspective, and they can potentially decompose with the release of high amounts of evolved heat and pressure. Compounds **2**, **4**, and **9** were evaluated by Differential Scanning Calorimetry (DSC) to determine their thermal decomposition behavior. Their propensity for shock sensitivity or ability to propagate an explosion can be evaluated by using Yoshida's correlation.[2] While all three materials exhibit decomposition energies >350 J/g, the combination of the onset of the exotherm with the magnitude of the heat release indicate that none of these compounds are expected to be shock sensitive or able to propagate an explosion. Of the three compounds, compound **2** would merit further testing in a physical test such as the Bam-Fallhammer test as its behavior in the Yoshida correlation was borderline. While these particular samples present as non-shock sensitive and non-explosion propagating, the thermal behavior of a compound is sensitive to its thermal history (i.e. mode of preparation, purity and state decomposition) and as such these samples should be re-examined whenever synthesized or aged in order to assess their thermal decomposition characteristics.

Figure S10. DSC analysis for 1-chloro-4-(nitromethyl)benzene

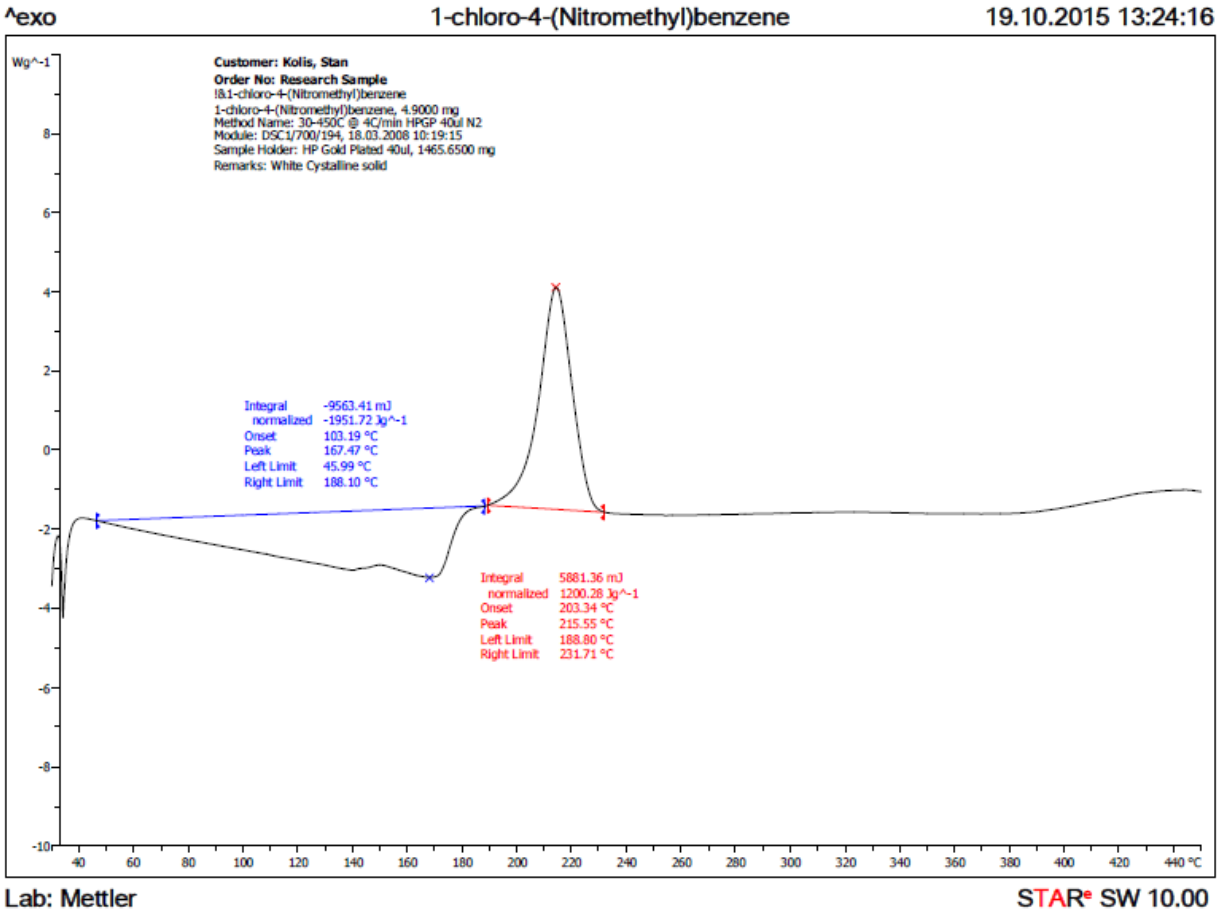


Figure S11. DSC analysis for *tert*-butyl-(1*R*,2*S*)-1,2-bis(4-chlorophenyl)-2-(nitroethyl)carbamate

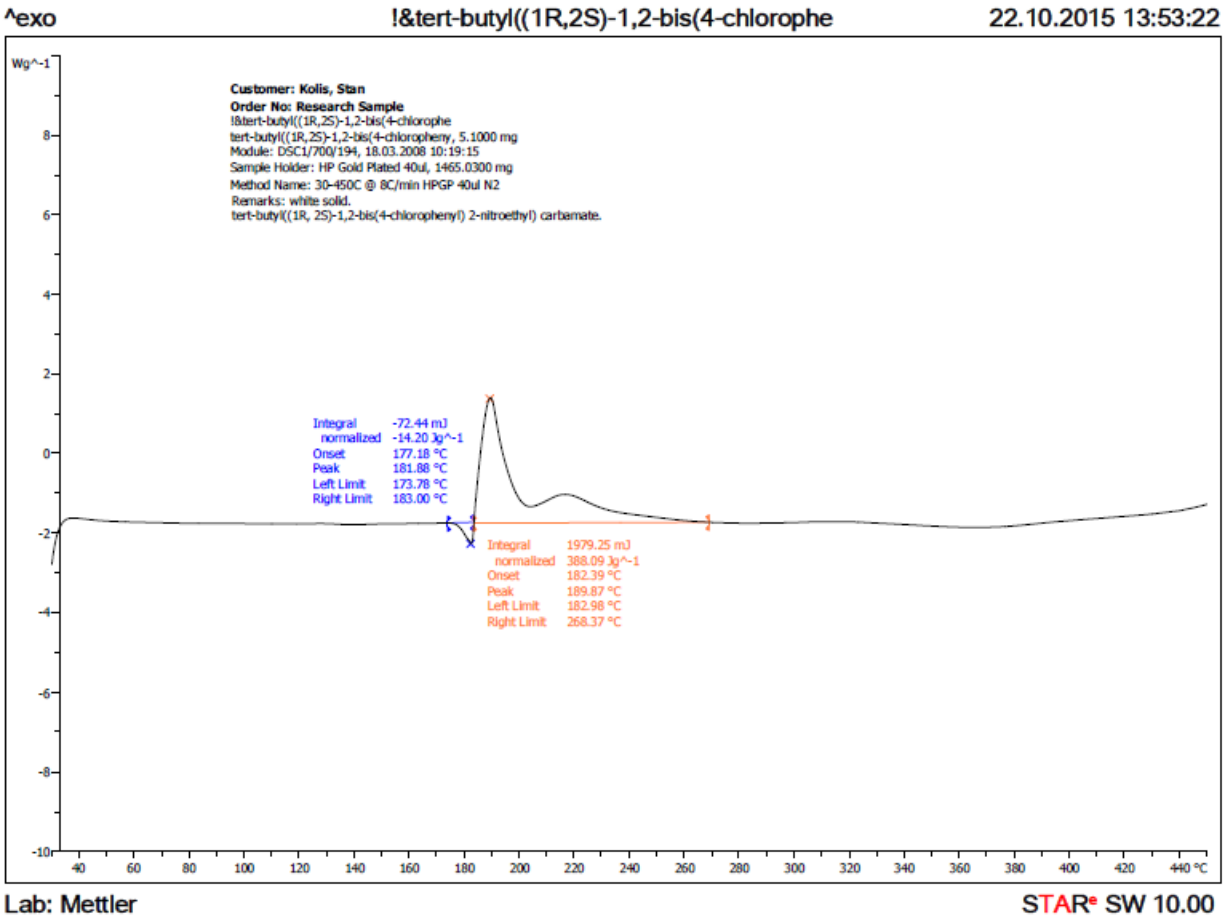
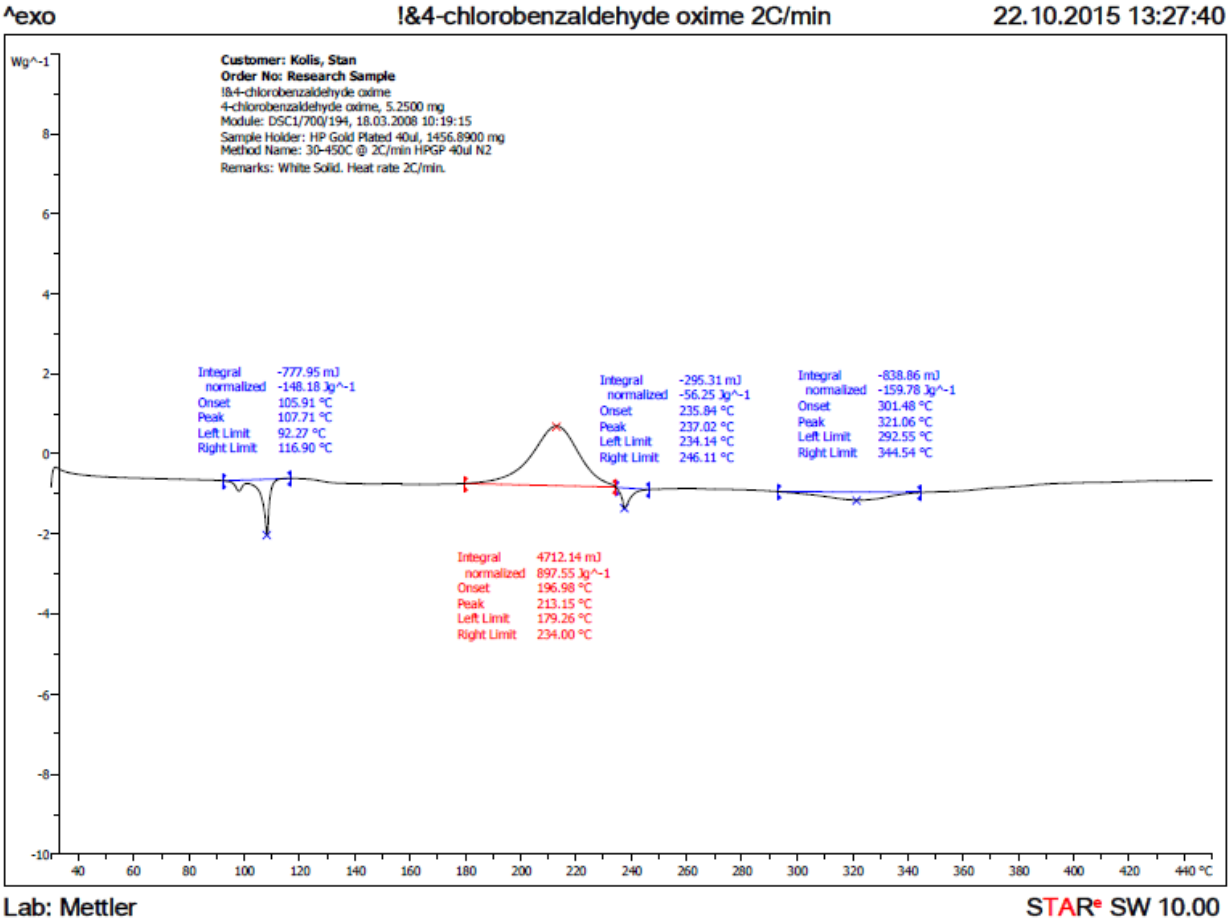


Figure S12. DSC analysis for 4-chlorobenzaldehyde oxime



5. References

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