

Advanced
**Synthesis &
Catalysis**

Supporting Information

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Supporting Information

Integration of Solventless Reaction in Multi-Step Process.

Application to Efficient Synthesis of PA-824

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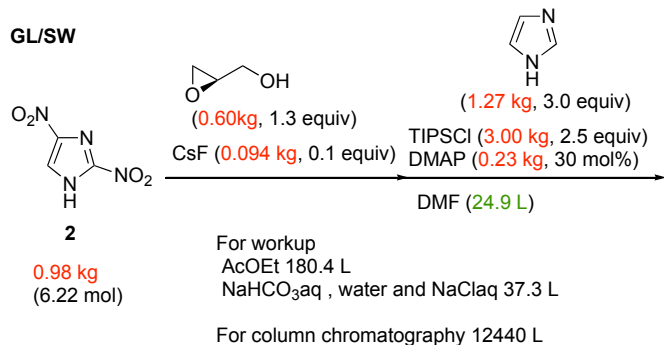
Okayama 700-0005, Japan

Fax: (+81)-86-256-4292; e-mail: otera@high.ous.ac.jp

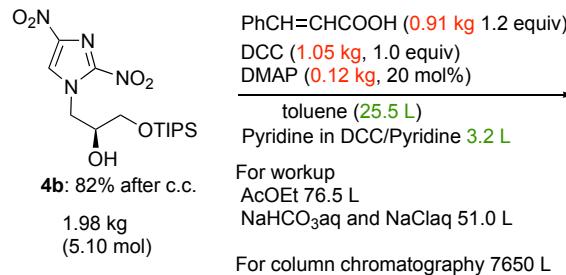
Summary of reaction mass efficiencies (RMEs) and necessary solvents for PG, THP,

CIN and PG processes.

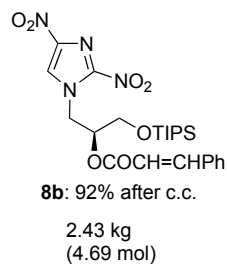
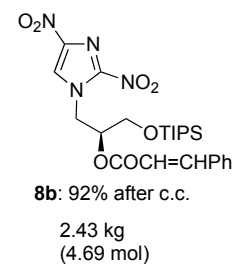
GL/SW



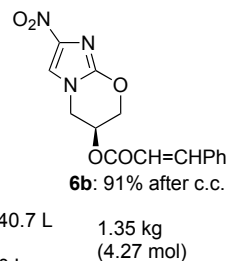
Total amount of solvents
(12682.6 L)



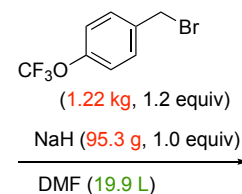
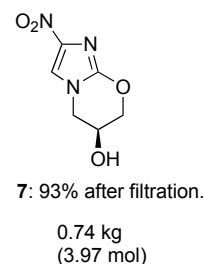
Total amount of solvents
(7806.2 L)



Total amount of solvents
(23758.6 L)



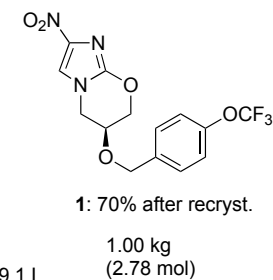
Total amount of solvents
(725.9 L)



For workup
CH₂Cl₂ 119.1 L
NaHCO₃aq, water and NaCl_{aq} 119.1 L

For column chromatography 7940 L
For recrystallization 11.9 L

Total amount of solvents
(8210.0 L)

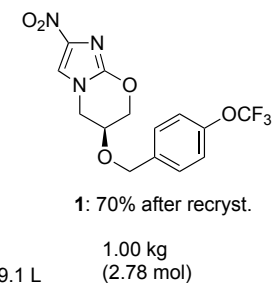
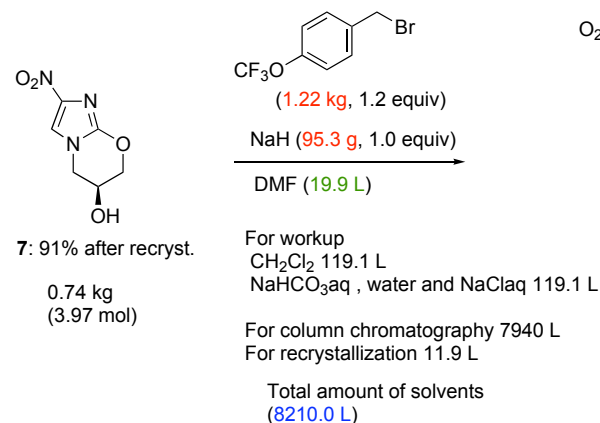
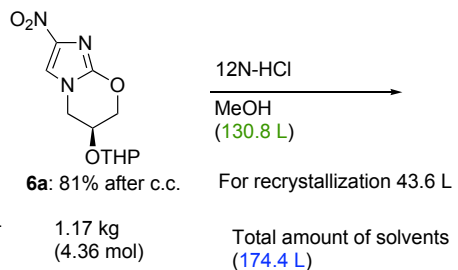
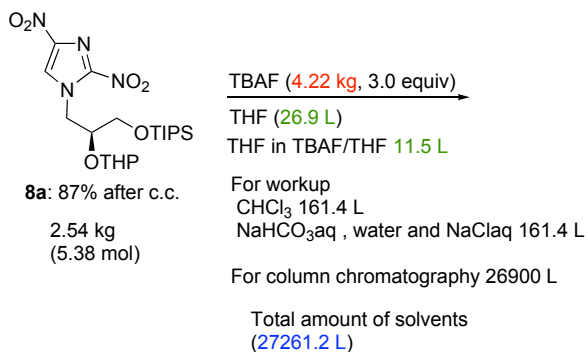
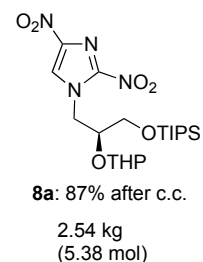
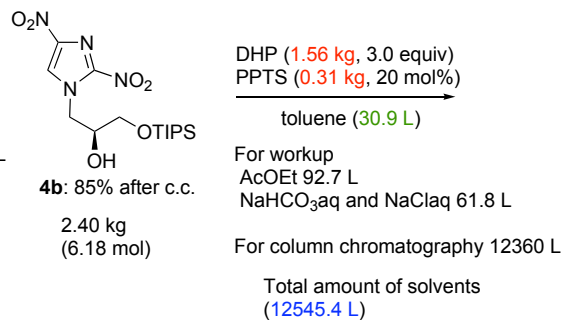
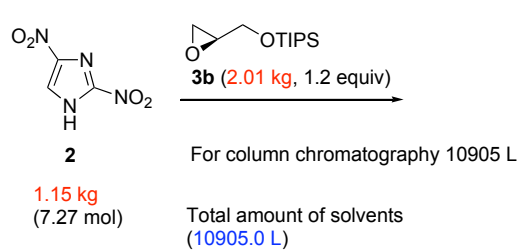


$$\text{RME} = \frac{1.00}{0.98 + 0.60 + 0.094 + 1.27 + 3.00 + 0.23 + 0.91 + 1.05 + 0.12 + 1.35 + 0.012 + 1.22 + 0.0953} = \frac{1.00}{10.93} = 0.091$$

Solvent employed = 12682.6 + 7806.2 + 23758.6 + 725.9 + 8210.0 = 53183 L

Solvents for reaction = 24.9 + 25.5 + 3.2 + 23.5 + 3.7 + 170.8 + 19.9 = 272 L

THP/SW

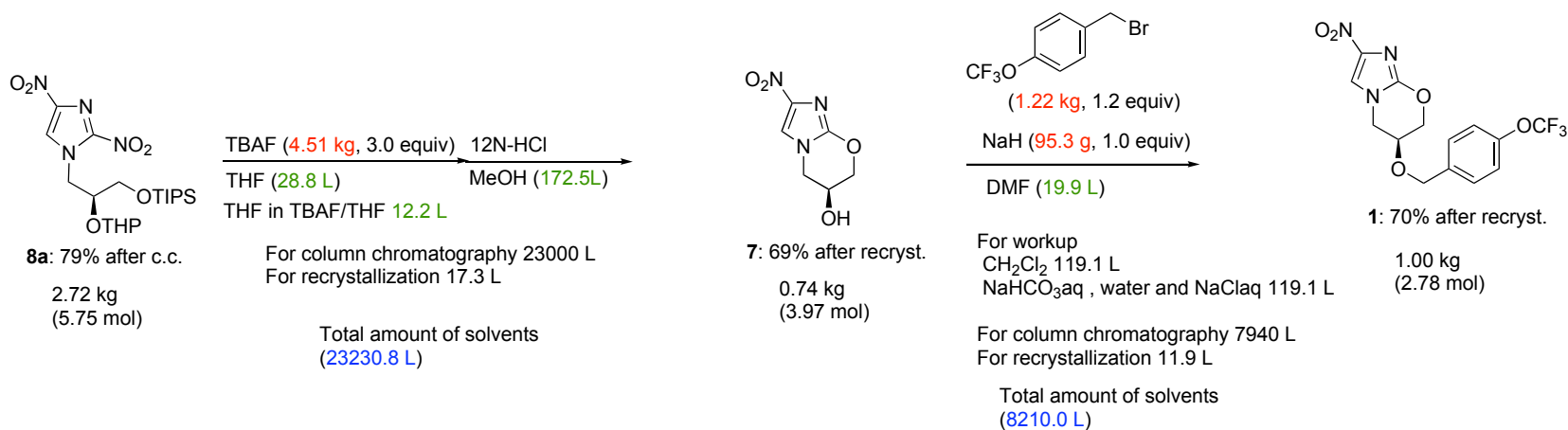
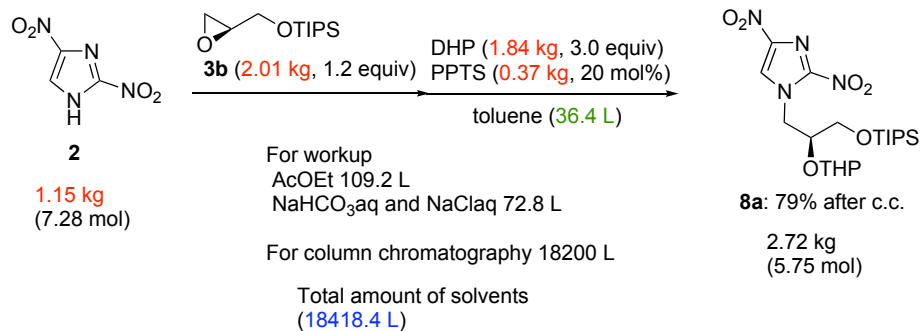


$$\text{RME} = \frac{1.00}{1.15 + 2.01 + 1.56 + 0.31 + 4.22 + 1.22 + 0.0953} = \frac{1.00}{10.6} = 0.094$$

$$\text{Solvent employed} = 10905.0 + 12545.4 + 27261.2 + 174.4 + 8210.0 = 59096 \text{ L}$$

$$\text{Solvents for reaction} = 30.9 + 26.9 + 11.5 + 130.8 + 19.9 = 220 \text{ L}$$

THP/IP-1

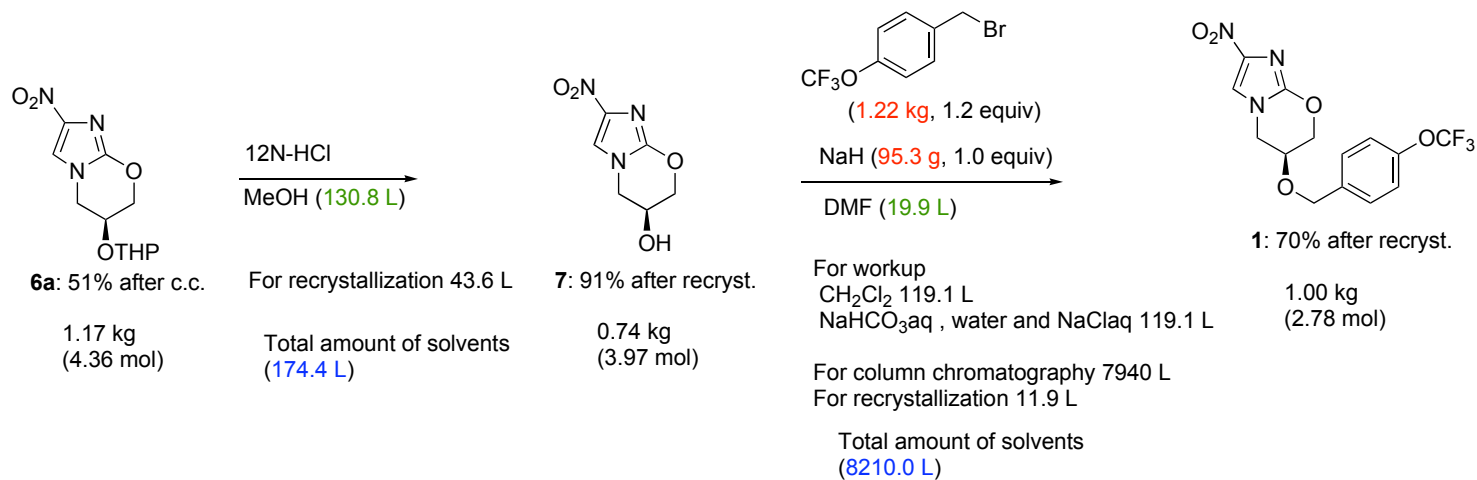
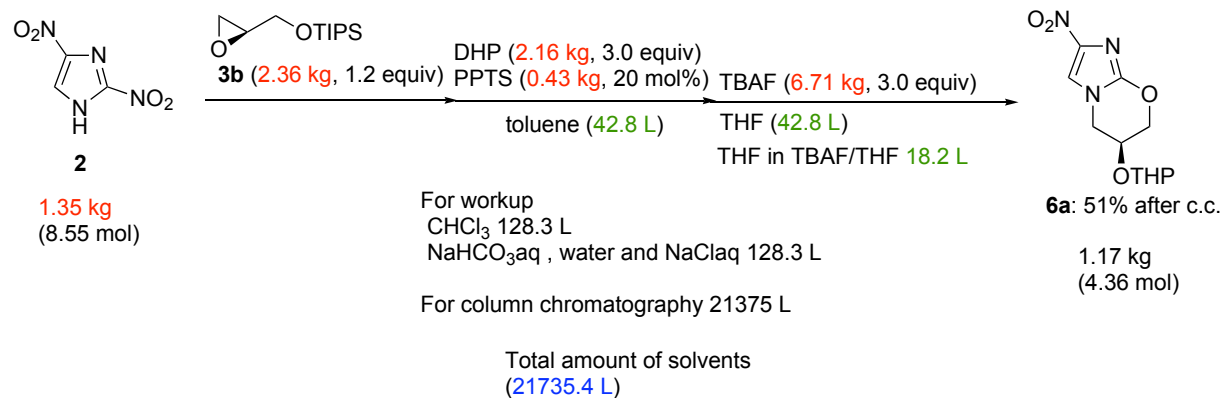


$$\text{RME} = \frac{1.00}{1.15+2.01+1.84+0.37+4.51+1.22+0.0953} = \frac{1.00}{11.2} = 0.089$$

$$\text{Solvent employed} = 18418.4 + 23230.8 + 8210.0 = 49859 \text{ L}$$

$$\text{Solvents for reaction} = 36.4 + 28.8 + 12.2 + 172.5 + 19.9 = 270 \text{ L}$$

THP/IP-2

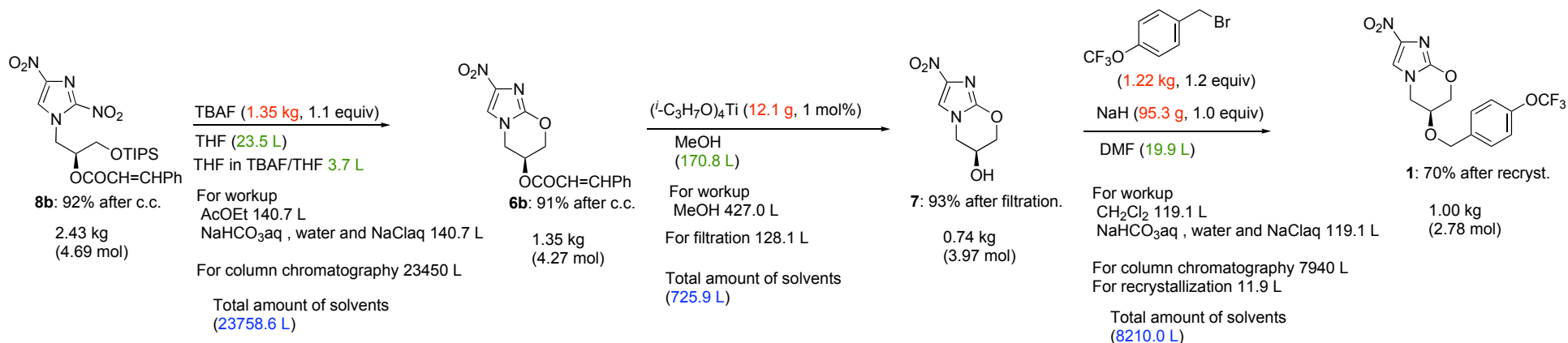
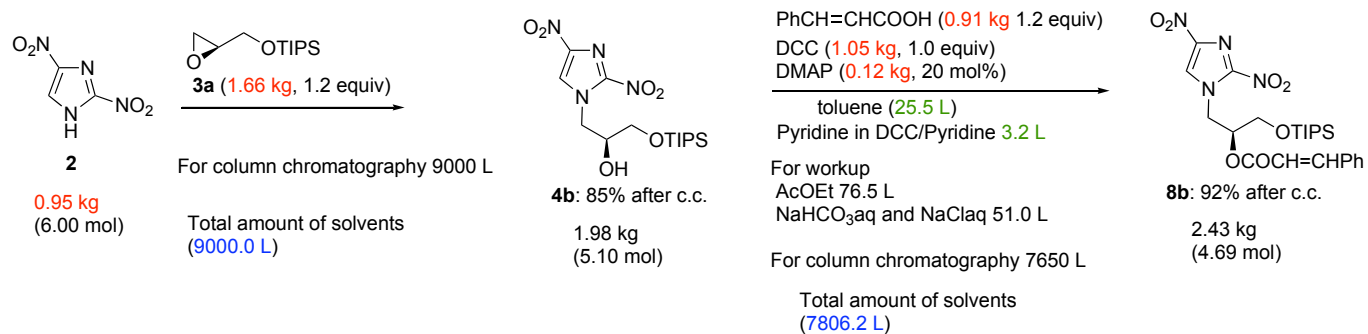


$$RME = \frac{1.00}{1.35+2.36+2.16 + 0.43 +6.71+1.22+0.0953} = \frac{1.00}{14.3} = 0.070$$

$$\text{Solvent employed} = 21735.4 + 174.4 + 8210.0 = 30120 \text{ L}$$

$$\text{Solvents for reaction} = 42.8 + 42.8 + 18.2 + 130.8 + 19.9 = 255 \text{ L}$$

CIN/SW

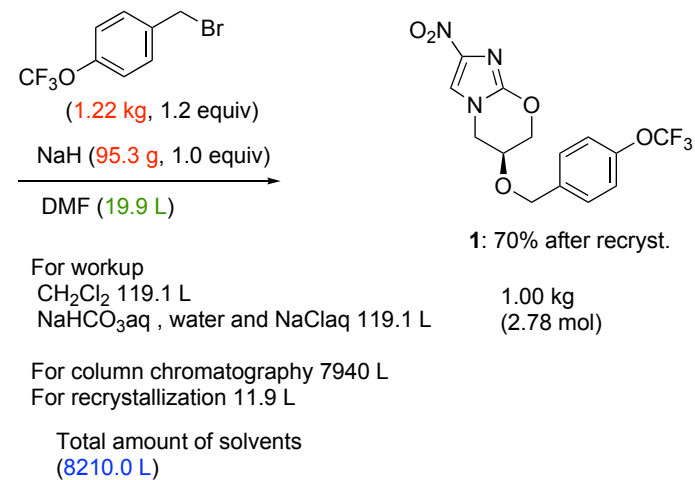
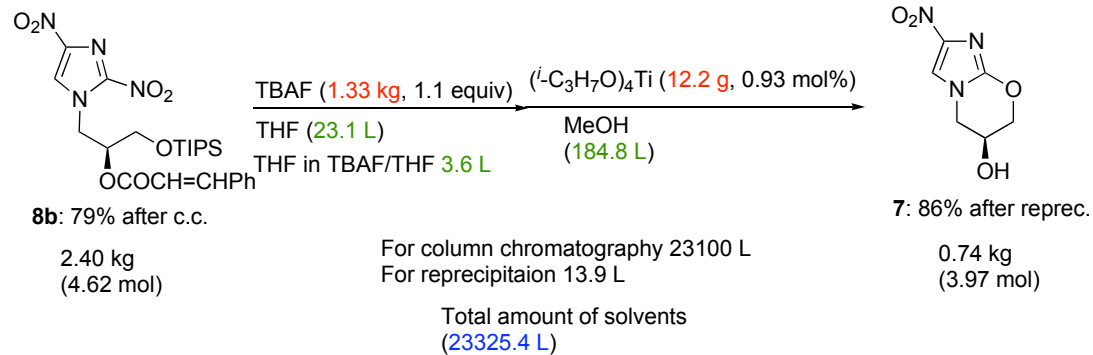
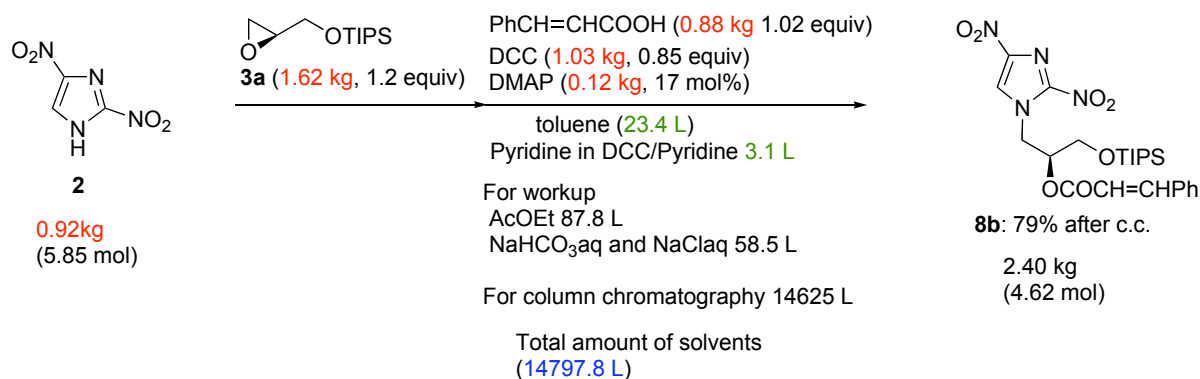


$$RME = \frac{1.00}{0.95 + 1.66 + 0.91 + 1.05 + 0.12 + 1.35 + 0.012 + 1.22 + 0.0953} = \frac{1.00}{7.37} = 0.136$$

Solvent employed = 9000.0 + 7806.2 + 23758.6 + 725.9 + 8210.0 = 49501 L

Solvents for reaction = 25.5 + 3.2 + 23.5 + 3.7 + 170.8 + 19.9 = 247 L

CIN/IP-1

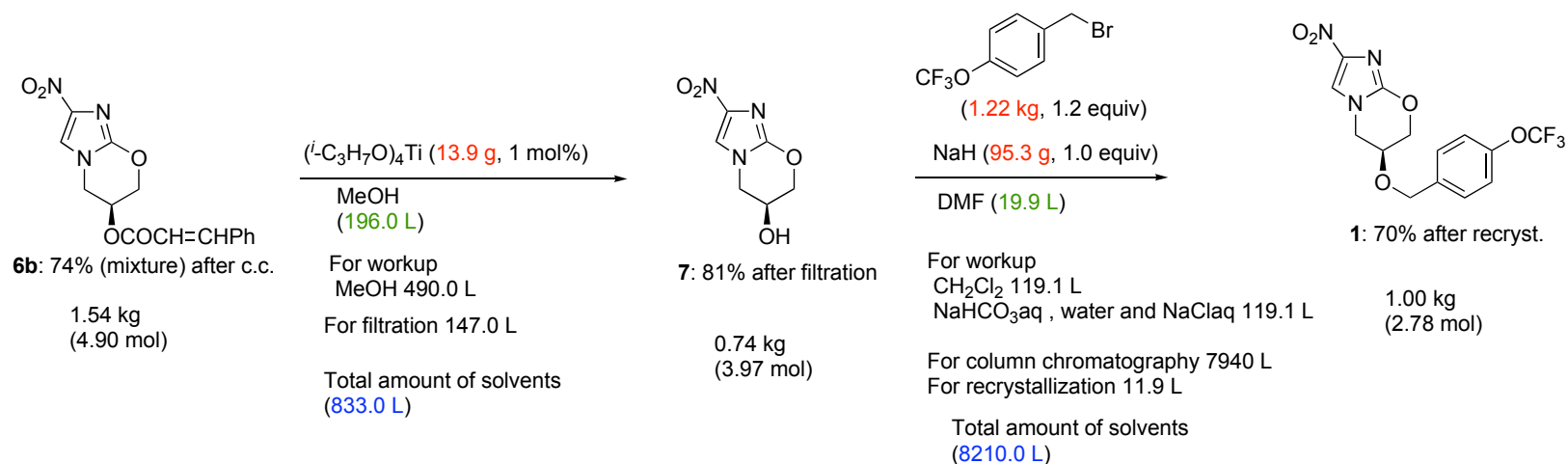
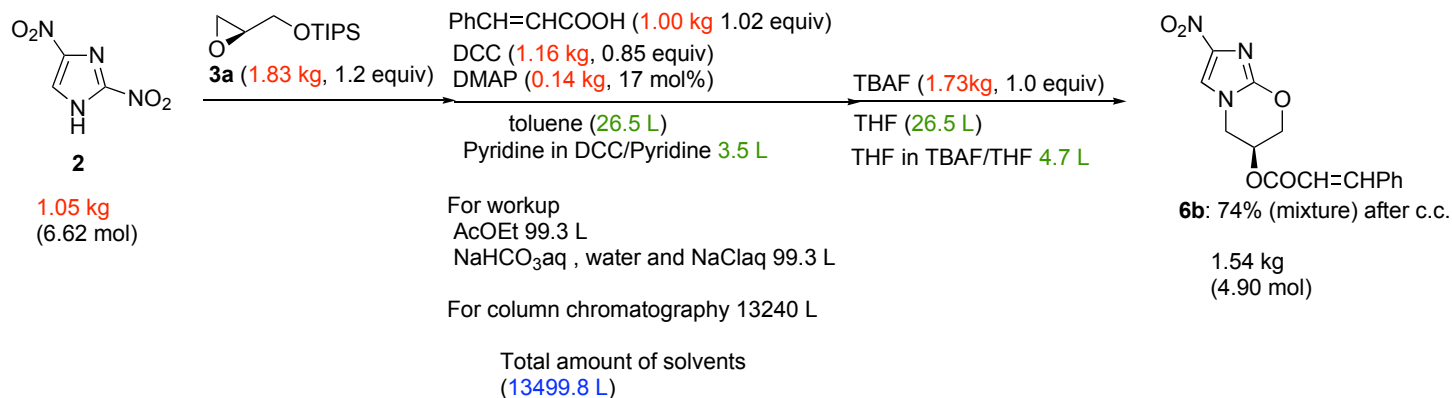


$$\text{RME} = \frac{1.00}{0.92 + 1.62 + 0.88 + 1.03 + 0.12 + 1.33 + 0.0122 + 1.22 + 0.0953} = \frac{1.00}{7.23} = 0.138$$

$$\text{Solvent employed} = 14797.8 + 23325.4 + 8210.0 = 46333 \text{ L}$$

$$\text{Solvents for reaction} = 23.4 + 3.1 + 23.1 + 3.6 + 184.8 + 19.9 = 258 \text{ L}$$

CIN/IP-2

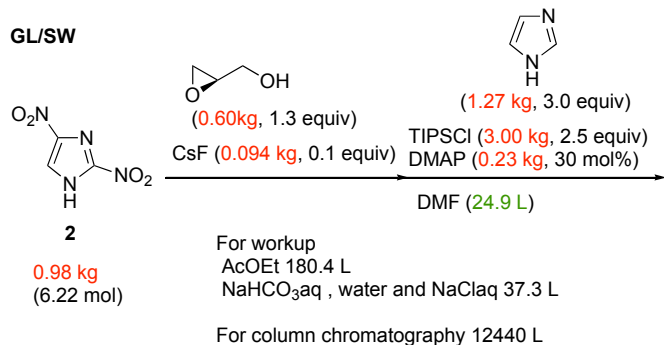


$$\text{RME} = \frac{1.00}{1.05 + 1.83 + 1.00 + 1.16 + 0.14 + 1.73 + 0.0139 + 1.22 + 0.0953} = \frac{1.00}{8.24} = 0.121$$

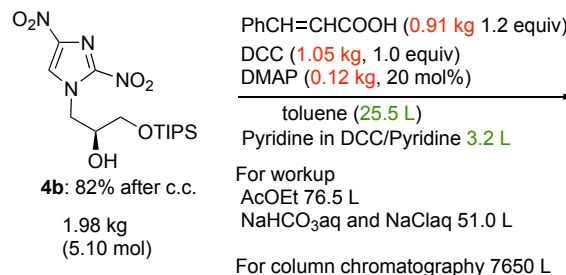
$$\text{Solvent employed} = 13499.8 + 833.0 + 8210.0 = 22543 \text{ L}$$

$$\text{Solvents for reaction} = 26.5 + 3.5 + 26.5 + 4.7 + 196.0 + 19.9 = 277 \text{ L}$$

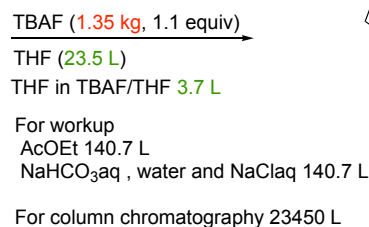
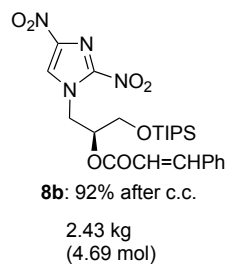
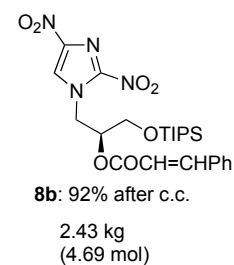
GL/SW



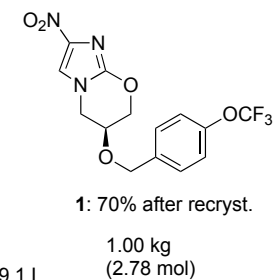
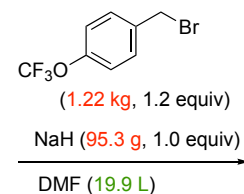
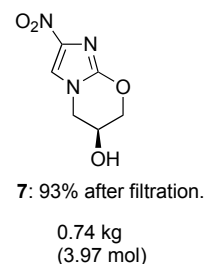
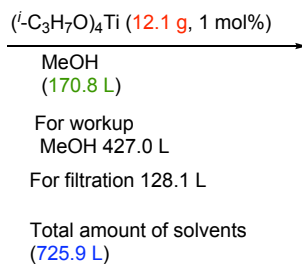
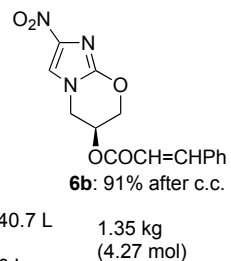
Total amount of solvents
(12682.6 L)



Total amount of solvents
(7806.2 L)



Total amount of solvents
(23758.6 L)

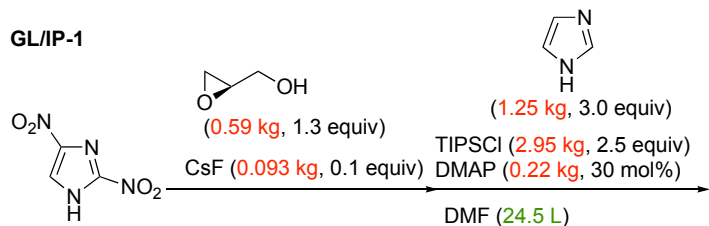


$$\text{RME} = \frac{1.00}{0.98 + 0.60 + 0.094 + 1.27 + 3.00 + 0.23 + 0.91 + 1.05 + 0.12 + 1.35 + 0.012 + 1.22 + 0.0953} = \frac{1.00}{10.93} = 0.091$$

Solvent employed = 12682.6 + 7806.2 + 23758.6 + 725.9 + 8210.0 = 53183 L

Solvents for reaction = 24.9 + 25.5 + 3.2 + 23.5 + 3.7 + 170.8 + 19.9 = 272 L

GL/IP-1

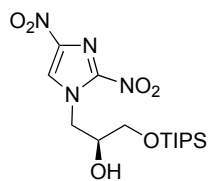


2
0.97 kg
(6.12 mol)

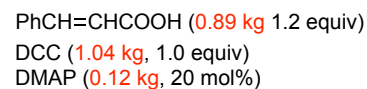
For workup
AcOEt 177.5 L
NaHCO₃aq, water and NaCl_{aq} 36.7 L

For column chromatography 12240 L

Total amount of solvents
(12478.7 L)



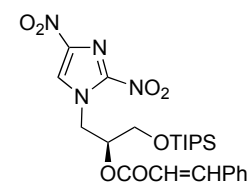
4b: 82% after c.c.
1.95 kg
(5.02 mol)



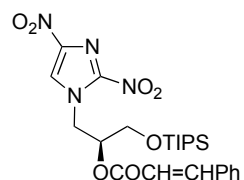
For workup
AcOEt 75.3 L
NaHCO₃aq and NaCl_{aq} 50.2 L

For column chromatography 7530 L

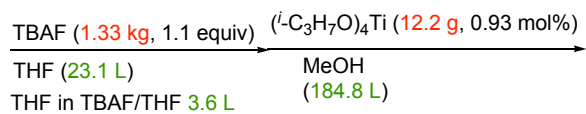
Total amount of solvents
(7683.8 L)



8b: 92% after c.c.
2.40 kg
(4.62 mol)

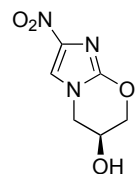


8b: 92% after c.c.
2.40 kg
(4.62 mol)

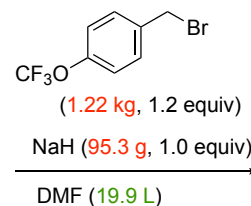


For column chromatography 23100 L
For reprecipitation 13.9 L

Total amount of solvents
(23325.4 L)



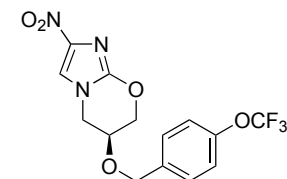
7: 86% after reprec.
0.74 kg
(3.97 mol)



For workup
CH₂Cl₂ 119.1 L
NaHCO₃aq, water and NaCl_{aq} 119.1 L

For column chromatography 7940 L
For recrystallization 11.9 L

Total amount of solvents
(8210.0 L)

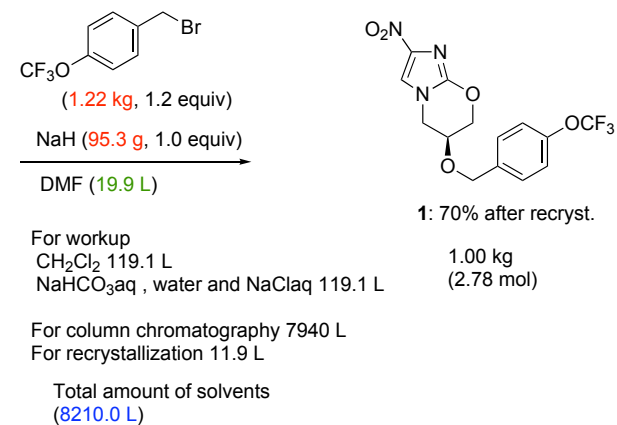
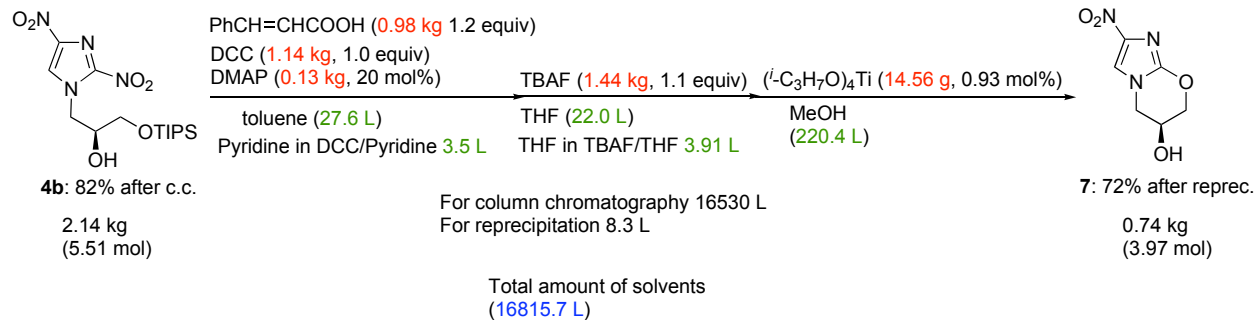
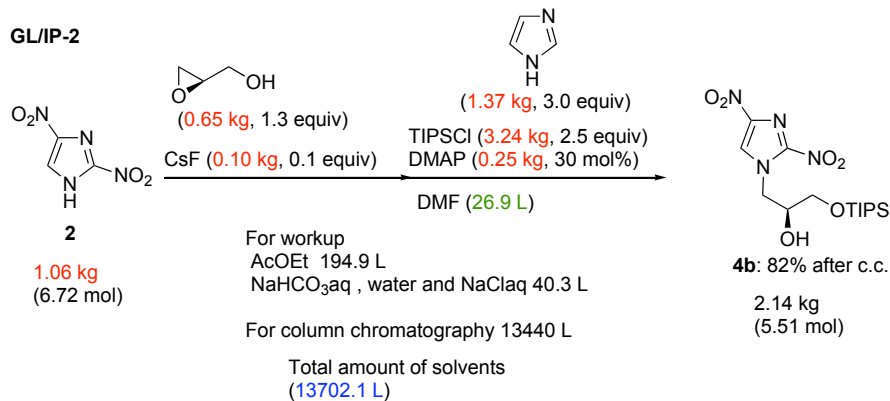


1: 70% after recryst.
1.00 kg
(2.78 mol)

$$\text{RME} = \frac{1.00}{0.97 + 0.59 + 0.093 + 1.25 + 2.95 + 0.22 + 0.89 + 1.04 + 0.12 + 1.33 + 0.0122 + 1.22 + 0.0953} = \frac{1.00}{10.78} = 0.093$$

$$\text{Solvent employed} = 12478.7 + 7683.8 + 23325.4 + 8210.0 = 51698 \text{ L}$$

$$\text{Solvents for reaction} = 24.5 + 25.1 + 3.2 + 23.1 + 3.6 + 184.8 + 19.9 = 284 \text{ L}$$

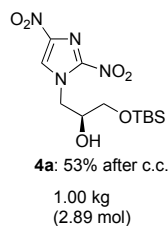
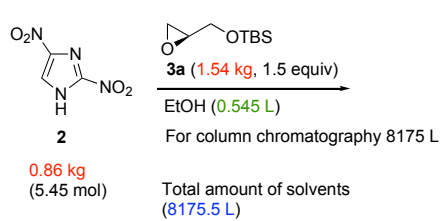


$$\text{RME} = \frac{1.00}{1.06 + 0.65 + 0.10 + 1.37 + 3.24 + 0.25 + 0.98 + 1.14 + 0.13 + 1.44 + 0.01456 + 1.22 + 0.0953} = \frac{1.00}{11.69} = 0.086$$

$$\text{Solvent employed} = 13702.1 + 16815.7 + 8210.0 = 38728 \text{ L}$$

$$\text{Solvents for reaction} = 26.9 + 27.6 + 3.5 + 22.0 + 3.91 + 220.4 + 19.9 = 324 \text{ L}$$

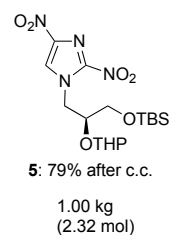
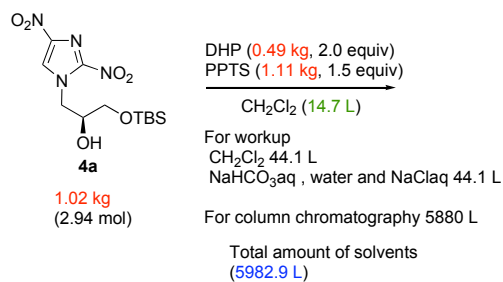
PG process/SW (stepwise)



$$\text{RME} = \frac{1}{0.86 + 1.54} = \frac{1}{2.4} = 0.417$$

Solvent employed = 8176 L

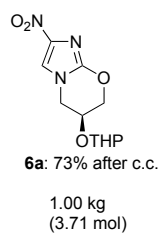
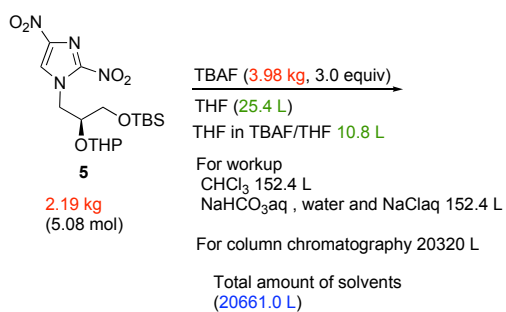
Solvents for reaction = 0.545 L



$$\text{RME} = \frac{1}{1.02 + 0.49 + 1.11} = \frac{1}{2.62} = 0.382$$

Solvent employed = 5983 L

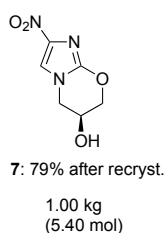
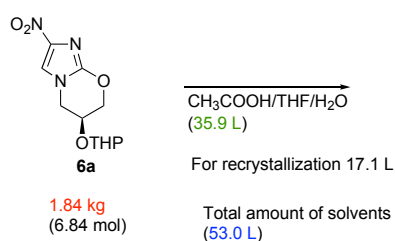
Solvents for reaction = 14.7 L



$$\text{RME} = \frac{1}{2.19 + 3.98} = \frac{1}{6.17} = 0.162$$

Solvent employed = 20661 L

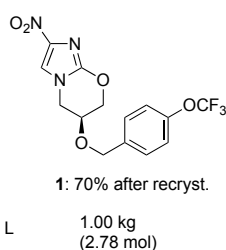
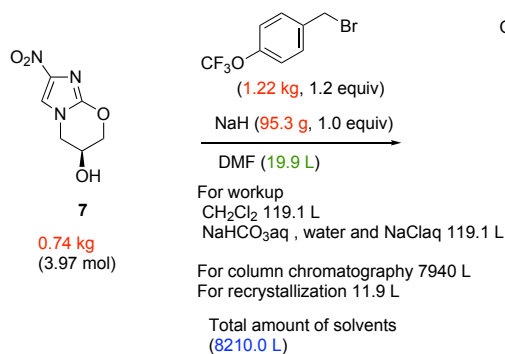
Solvents for reaction = 25.4 + 10.8 = 36.2 L



$$\text{RME} = \frac{1}{1.84} = 0.543$$

Solvent employed = 53 L

Solvents for reaction = 35.9 L

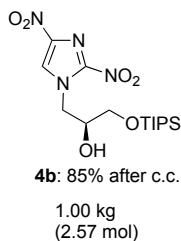
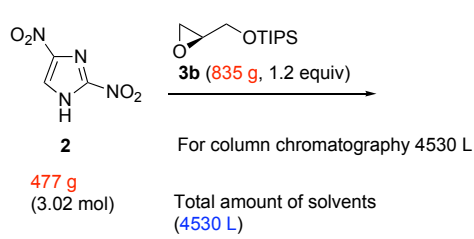


$$\text{RME} = \frac{1}{0.74 + 1.22 + 0.0953} = \frac{1}{2.06} = 0.485$$

Solvent employed = 8210 L

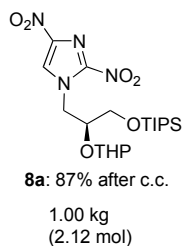
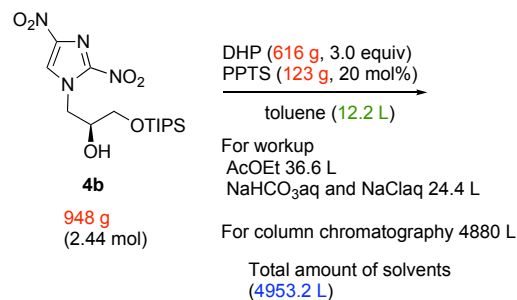
Solvents for reaction = 19.9 L

THP/SW (stepwise)



$$\text{RME} = \frac{1000}{477+835} = \frac{1000}{1312} = 0.762$$

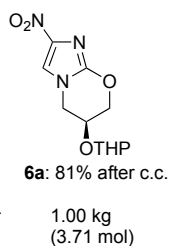
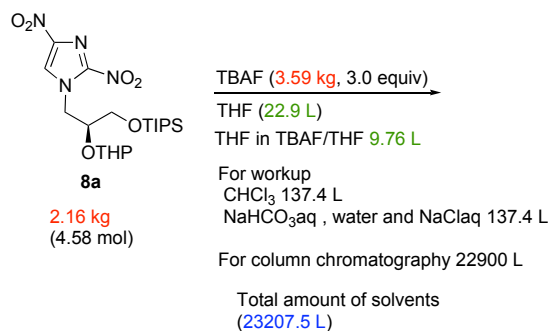
Solvent employed = 4530 L



$$\text{RME} = \frac{1000}{948+616+123} = \frac{1000}{1687} = 0.593$$

Solvent employed = 4953 L

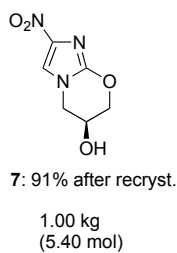
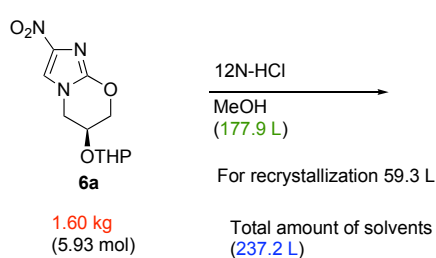
Solvents for reaction = 12.2 L



$$\text{RME} = \frac{1}{2.16+3.59} = \frac{1}{5.75} = 0.174$$

Solvent employed = 23208 L

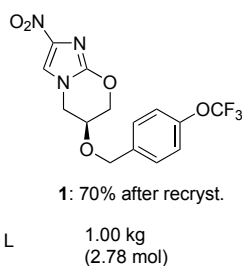
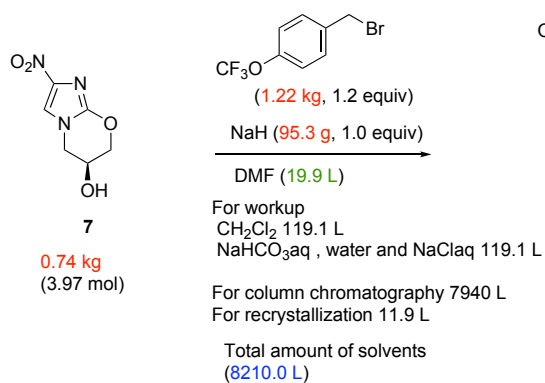
Solvents for reaction = 22.9 + 9.76 = 32.7 L



$$\text{RME} = \frac{1}{1.60} = 0.625$$

Solvent employed = 237 L

Solvents for reaction = 177.9 L

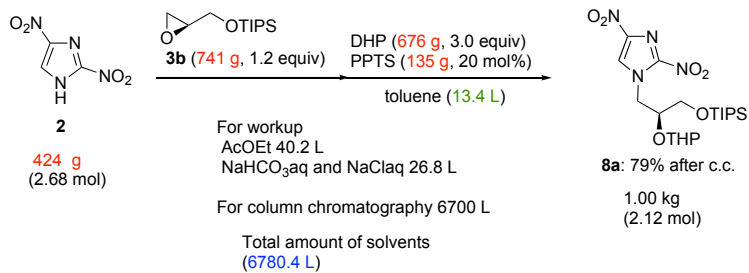


$$\text{RME} = \frac{1}{0.74+1.22+0.0953} = \frac{1}{2.06} = 0.485$$

Solvent employed = 8210 L

Solvents for reaction = 19.9 L

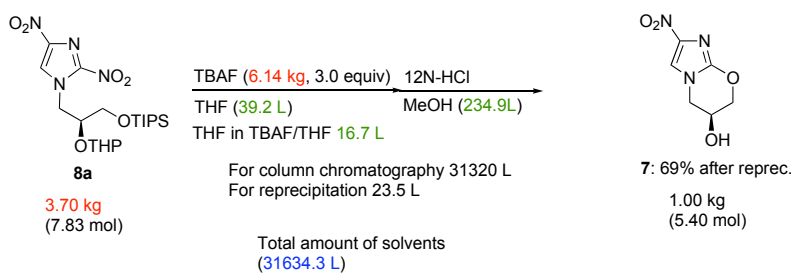
THP/IP-1 (stepwise)



$$\text{RME} = \frac{1000}{424 + 741 + 676 + 135} = \frac{1000}{1976} = 0.506$$

Solvent employed = 6780 L

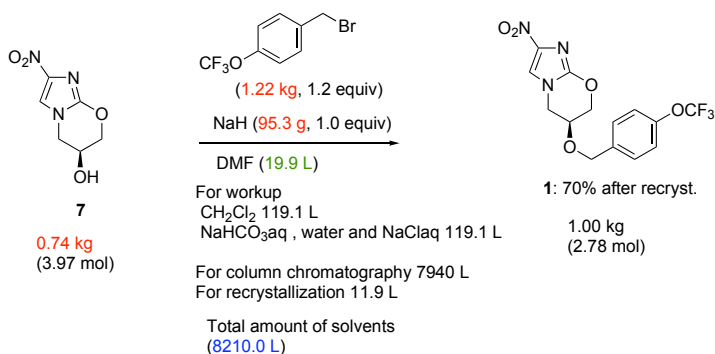
Solvents for reaction = 13.4 L



$$\text{RME} = \frac{1}{3.70 + 6.14} = \frac{1}{9.84} = 0.102$$

Solvent employed = 31634 L

Solvents for reaction = 39.2 + 16.7 + 234.9 = 290.8 L

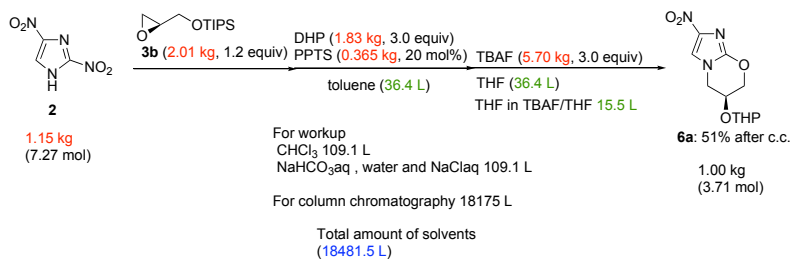


$$\text{RME} = \frac{1}{0.74 + 1.22 + 0.0953} = \frac{1}{2.06} = 0.485$$

Solvent employed = 8210 L

Solvents for reaction = 19.9 L

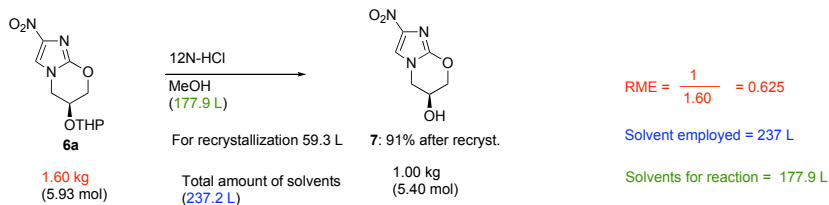
THP/IP-2 (stepwise)



$$RME = \frac{1}{1.15 + 2.01 + 1.83 + 0.365 + 5.70} = \frac{1}{11.06} = 0.090$$

Solvent employed = 18482 L

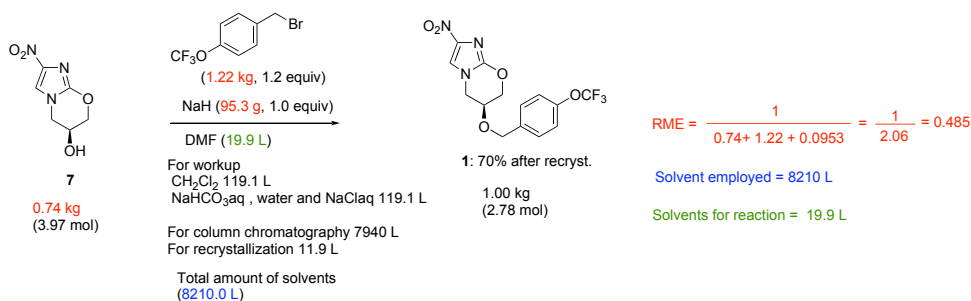
Solvents for reaction = 36.4 + 36.4 + 15.5 = 88.3 L



$$RME = \frac{1}{1.60} = 0.625$$

Solvent employed = 237 L

Solvents for reaction = 177.9 L

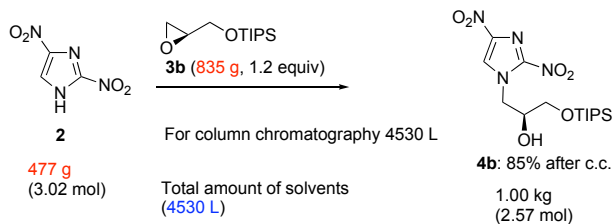


$$RME = \frac{1}{0.74 + 1.22 + 0.0953} = \frac{1}{2.06} = 0.485$$

Solvent employed = 8210 L

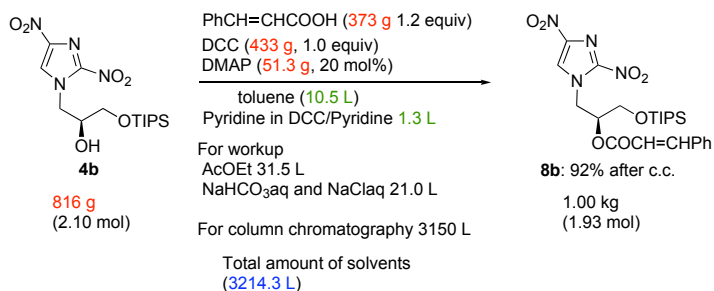
Solvents for reaction = 19.9 L

CIN/SW (stepwise)



$$\text{RME} = \frac{1000}{477+835} = \frac{1000}{1312} = 0.762$$

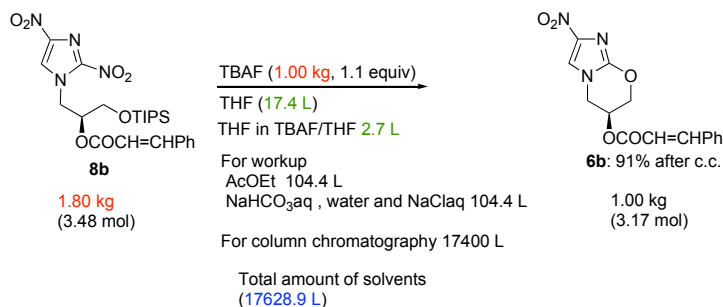
Solvent employed = 4530 L



$$\text{RME} = \frac{1000}{816 + 373 + 433 + 51.3} = \frac{1000}{1673} = 0.598$$

Solvent employed = 3214 L

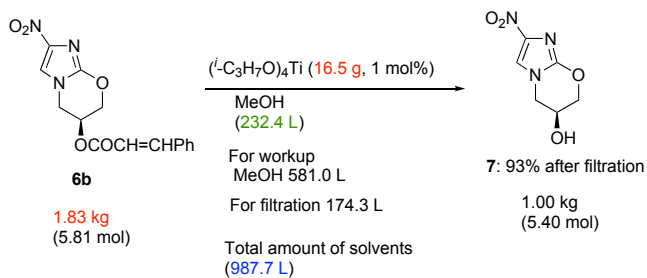
Solvents for reaction = 10.5 + 1.3 = 11.8 L



$$\text{RME} = \frac{1}{1.80 + 1.00} = \frac{1}{2.8} = 0.357$$

Solvent employed = 17629 L

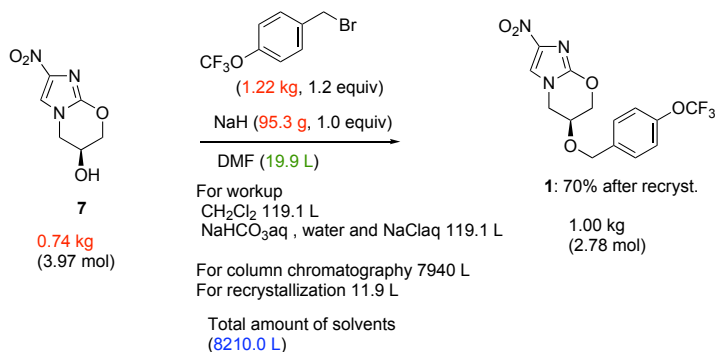
Solvents for reaction = 17.4 + 2.7 = 20.1 L



$$\text{RME} = \frac{1}{1.83 + 0.0165} = \frac{1}{1.85} = 0.541$$

Solvent employed = 988 L

Solvents for reaction = 232.4 L

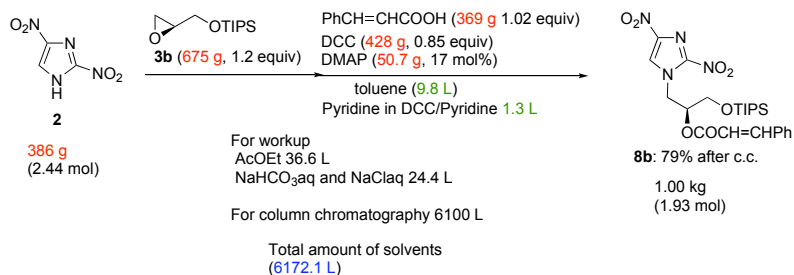


$$\text{RME} = \frac{1}{0.74 + 1.22 + 0.0953} = \frac{1}{2.06} = 0.485$$

Solvent employed = 8210 L

Solvents for reaction = 19.9 L

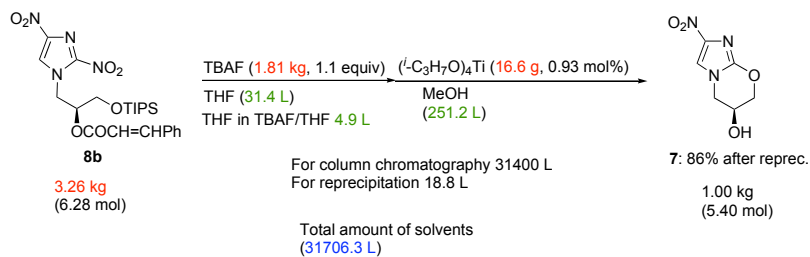
CIN/IP-1 (stepwise)



$$RME = \frac{1000}{386 + 675 + 369 + 428 + 50.7} = \frac{1000}{1909} = 0.524$$

Solvent employed = 6172 L

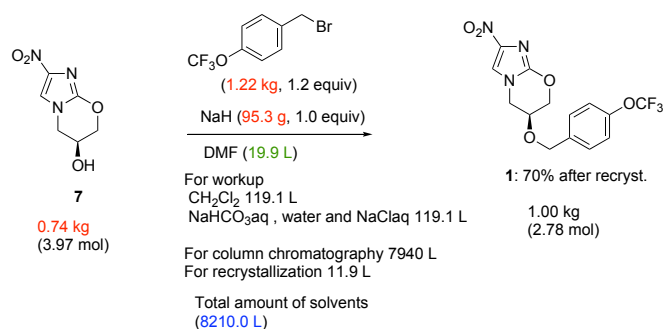
Solvents for reaction = 9.8 + 1.3 = 11.1 L



$$RME = \frac{1}{3.26 + 1.81 + 0.0166} = \frac{1}{5.09} = 0.196$$

Solvent employed = 31706 L

Solvents for reaction = 31.4 + 4.9 + 251.2 = 287.5 L

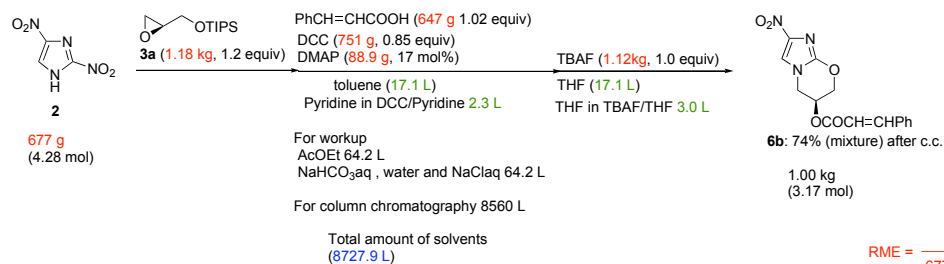


$$RME = \frac{1}{0.74 + 1.22 + 0.0953} = \frac{1}{2.06} = 0.485$$

Solvent employed = 8210 L

Solvents for reaction = 19.9 L

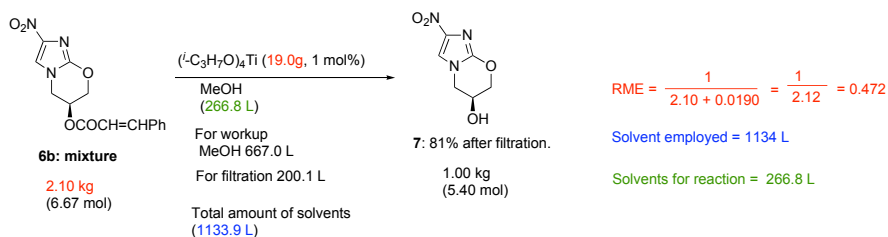
CIN/IP-2 (stepwise)



$$RME = \frac{1000}{677 + 1180 + 647 + 751 + 88.9 + 1120} = \frac{1000}{4464} = 0.224$$

Solvent employed = 8728 L

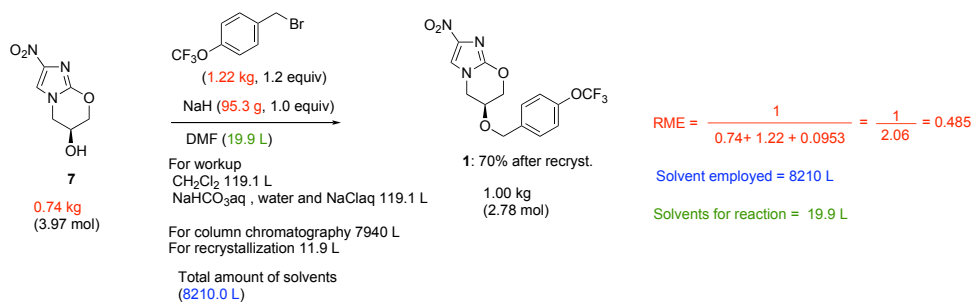
Solvents for reaction = 17.1 + 2.3 + 17.1 + 3.0 = 39.5L



$$RME = \frac{1}{2.10 + 0.0190} = \frac{1}{2.12} = 0.472$$

Solvent employed = 1134 L

Solvents for reaction = 266.8 L

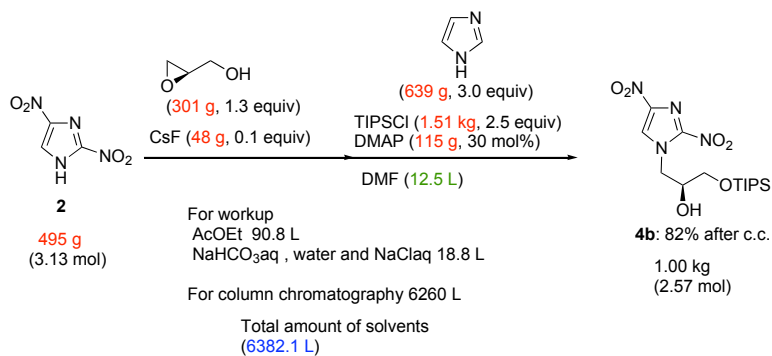


$$RME = \frac{1}{0.74 + 1.22 + 0.0953} = \frac{1}{2.06} = 0.485$$

Solvent employed = 8210 L

Solvents for reaction = 19.9 L

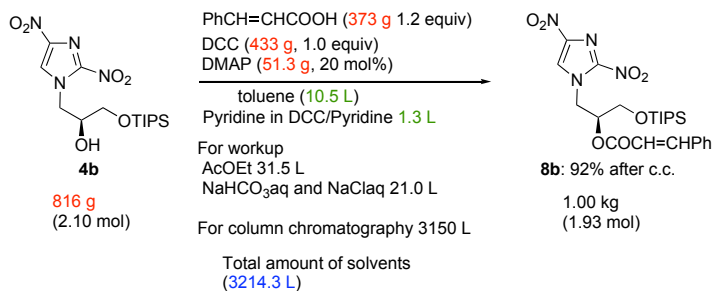
GL/SW (stepwise)



$$\text{RME} = \frac{1000}{495 + 301 + 48 + 639 + 1510 + 115} = \frac{1000}{3108} = 0.322$$

Solvent employed = 6382 L

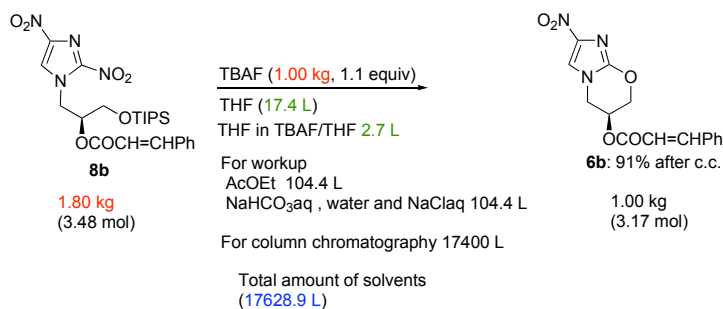
Solvents for reaction = 12.5 L



$$\text{RME} = \frac{1000}{816 + 373 + 433 + 51.3} = \frac{1000}{1673} = 0.598$$

Solvent employed = 3214 L

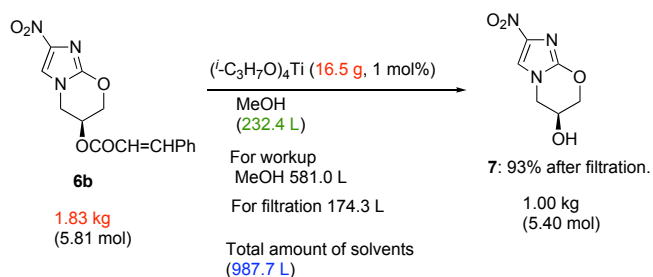
Solvents for reaction = 10.5 + 1.3 = 11.8 L



$$\text{RME} = \frac{1}{1.80 + 1.00} = \frac{1}{2.8} = 0.357$$

Solvent employed = 17629 L

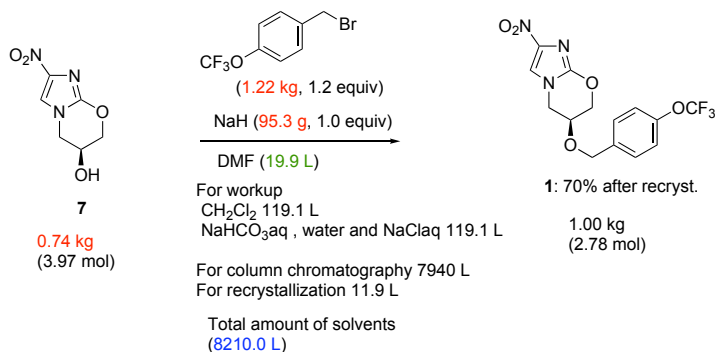
Solvents for reaction = 17.4 + 2.7 = 20.1 L



$$\text{RME} = \frac{1}{1.83 + 0.0165} = \frac{1}{1.85} = 0.541$$

Solvent employed = 988 L

Solvents for reaction = 232.4 L

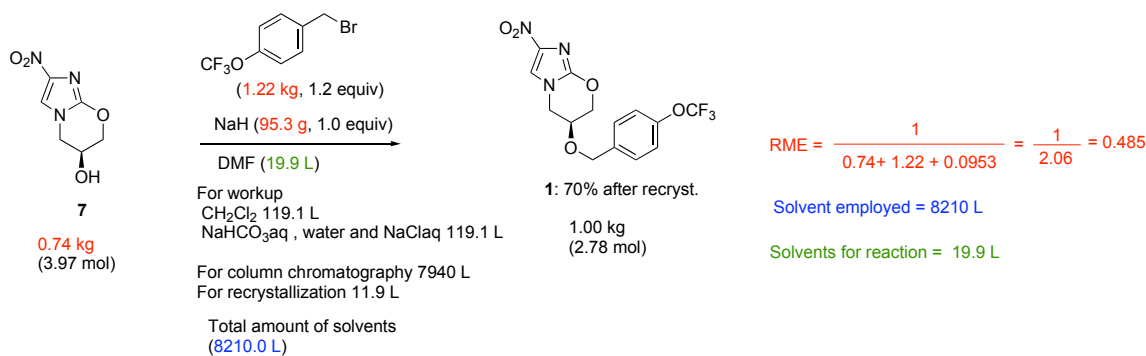
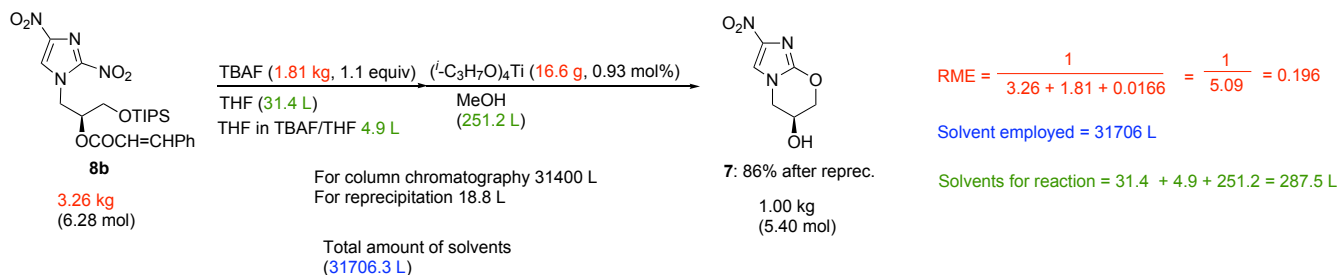
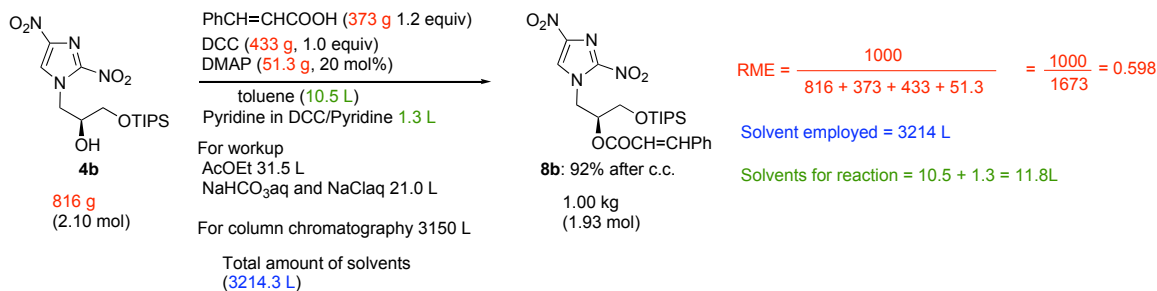
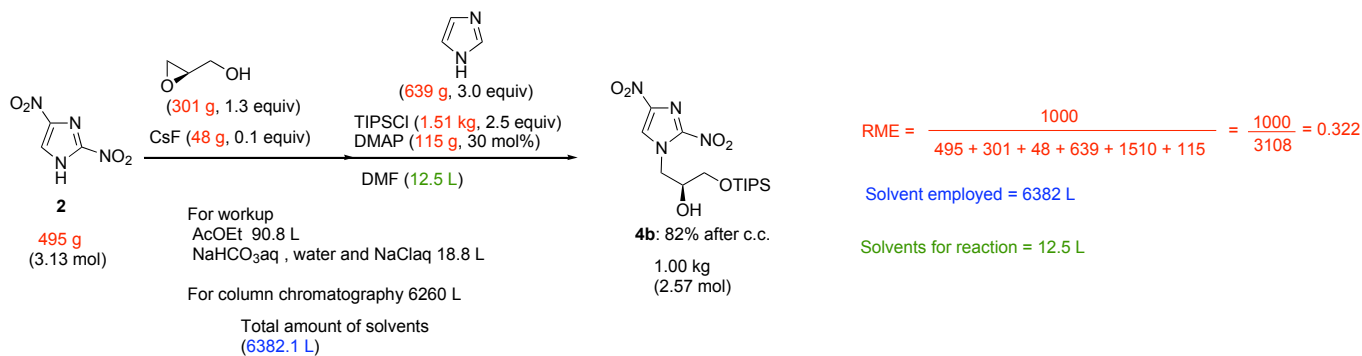


$$\text{RME} = \frac{1}{0.74 + 1.22 + 0.0953} = \frac{1}{2.06} = 0.485$$

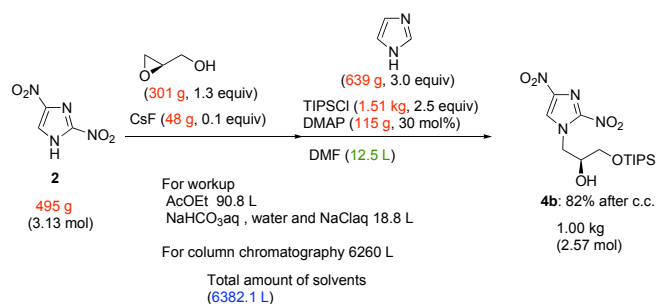
Solvent employed = 8210 L

Solvents for reaction = 19.9 L

GL/IP-1 (stepwise)



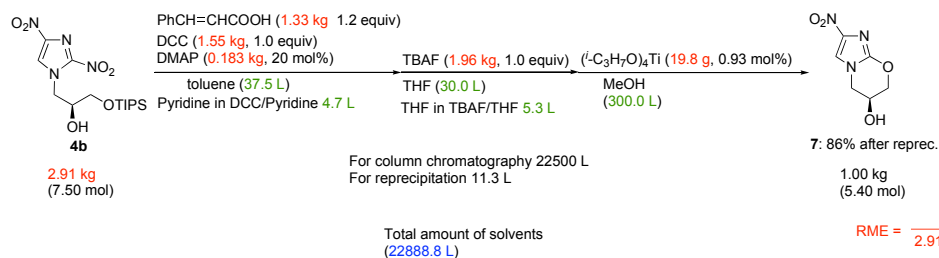
GL/IP-2 (stepwise)



$$RME = \frac{1000}{495 + 301 + 48 + 639 + 1510 + 115} = \frac{1000}{3108} = 0.322$$

Solvent employed = 6382 L

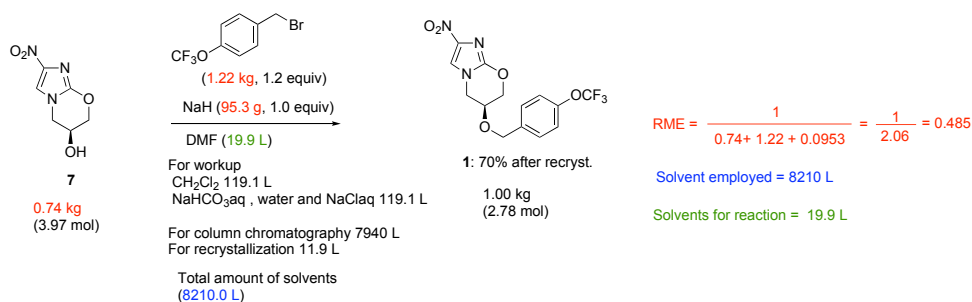
Solvents for reaction = 12.5 L



$$RME = \frac{1}{2.91 + 1.33 + 1.55 + 0.183 + 1.96 + 0.0198} = \frac{1}{7.95} = 0.126$$

Solvent employed = 22889 L

Solvents for reaction = 37.5 + 4.7 + 30.0 + 5.3 + 300.0 = 377.5 L



$$RME = \frac{1}{0.74 + 1.22 + 0.0953} = \frac{1}{2.06} = 0.485$$

Solvent employed = 8210 L

Solvents for reaction = 19.9 L