catalysts

SUPPORTING INFORMATION

Usefulness of the Global *E* Factor as a Tool to Compare Different Catalytic Strategies: Four Case Studies

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E factor diastereo- and enantioselective Diels Alder reaction by List

1.83 g methyl cynnamate (8.0 mmol), of which 0.08 mmol waste, 0.013 g

6.6 mL cyclopentadiene (78.48 mmol, d= 0.786 g/mL, 5.188 g), of which (78.48-7.92)= 70.56 mmol waste, 4.664 g

0.2 mol% **5a** (1.6 mmol, 0.250 g, all waste)

0.0143 g catalyst (all waste)

COLUMN CHROMATOGRAPHY

m_{SiO2} = 59.8 x 1.826 = 109.195 g (all waste)

Euent: Hexane/DCM 2.33:1 (average value of the gradient), d= 0.858 g/mL

m_{eluent} = 6.2 x 0.858 x 109.195 = 580.873 g (all waste)

Mass of useful product = 1.83 g (99% yield)

Total waste amount = 695.009 g

***E* factor =** 380

E_G factor diastereo- and enantioselective Diels Alder reaction by List

1.83 g methyl cynnamate (8.0 mmol), of which 0.08 mmol waste, 0.013 g

6.6 mL cyclopentadiene (78.48 mmol, d= 0.786 g/mL, 5.188 g), of which (78.48-7.92)= 70.56 mmol waste, 4.664 g

0.2 mol% **5a** (1.6 mmol, 0.250 g, all waste)

0.0143 g catalyst (*E* factor= 4841, all waste)

69.226 g waste produced for the synthesis of 0.0143 mg of catalyst (all waste)

COLUMN CHROMATOGRAPHY

m_{SiO2} = 59.8 x 1.826 = 109.195 g (all waste)

Euent: Hexane/DCM 2.33:1 (average value of the gradient), d= 0.858 g/mL

m_{eluent} = 6.2 x 0.858 x 109.195 = 580.873 g (all waste)

Mass of useful product = 1.83 g (99% yield)

Total waste amount = 764.235 g (10% additional waste)

E_G **factor =** 418

E factor copper-bipyridine complex by Feringa

STEP 1

0.93 g 4-methylpyridine (1 mmol, of which 0.0328 g waste)

20 mL AcOH (d= 1.05 g/mL), 21 g (all waste)

15 mL 30% H_2O_2 (d= 1.11 g/mL), 16.65 g (all waste)

0.0118 g Pd/C (all waste)

165 g PCl_3 (all waste)

20 mL EtOAc (d= 0.902 g/mL), 18.04 g (all waste)

Non-Normalized Waste Amount (NNWA) = 220.7346 g

Normalization factor (NF) = 0.042354

Normalized Waste Amount (NWA) = 9.349 g

Mass of useful product = 0.8972 g (97.4% yield)

STEP 2

0.038 g bipyridine (0.24 mmol), of which 0.10 mmol, 0.018 g waste

0.100 g $Cu(NO_3)_2$*$3H_2O$ (0.41 mmol), of which 0.065 g (0.27 mmol) waste

10 mL flat-rate EtOH (d= 0.789 g/mL), 7.89 g (all waste)

NNWA = NWA = 7.973 g

Mass of useful product = 0.049 g (0.14 mmol, 59% yield)

Total waste amount = 9.349 + 7.973 = 17.322 g

***E* factor =** 354

E factor diastereo- and enantioselective Diels Alder reaction by Feringa

STEP 1

0.212 g 2-(1-methylimidazolyl)cynnamate (1 mmol, of which 0.3 mmol, 0.064 g waste)

0.019 g copper complex, 0.05 mmol (all waste)

166 g H_2O (all waste)

333 mL st-DNA aqueous solution (d= 1.0 g/mL, approx), 333 g (all waste)

2 mL DMSO (d= 1.1 g/mL), 2.2 g (all waste)

0.67 mL cyclopentadiene (8.0 mmol, d= 0.786 g/mL, 0.527 g), of which 7.3 mmol, 0.483 g waste

500 mL EtOAc (flat-rate for extractions, d= 0.902 g/mL), 451 g (all waste)

53.2 g Na_2SO_4 (20 flat-rate 1 cm^3-spoons, d= 2.66 g/cm^3)

COLUMN CHROMATOGRAPHY

m_{SiO2} = 59.8 x 0.278 = 16.624 g (all waste)

Eluent: Pentane/EtOAc 25:1 (d= 0.637 g/mL)

m_{eluent} = 6.2 x 16.624 x 0.637 = 65.655 g (all waste)

NNWA = 1088.245 g

NF = 0.12857

NWA = NNWA x NF = 1088.245 x 0.12857 = 139.916 g

Mass of useful product = 0.194 g (0.7 mmol, 70% yield)

STEP 2

0.024 g, 0.09 mmol (of which 59%, 0.0531 mmol, 0.015 g waste)

0.010 g molecular sieves (all waste)

0.6 mL CH_3CN (d= 0.786 g/mL), 0.472 g (all waste)

0.15 mL DBU (d= 1.02 g/mL), 0.153 g (all waste)

30 mL EtOAc (d= 0.902 g/mL), 27.06 g (all waste)

30 mL sat. $NaHCO_3$ (d= 1.1 g/mL), 33 g (all waste)

15 mL brine (d= 1.15 g/mL), 17.25 g (all waste)

2.66 g Na_2SO_4 (1 flat-rate 1 cm_3-spoon, d= 2.66 g/cm^3) (all waste)

COLUMN CHROMATOGRAPHY

m_{SiO2} = 59.8 x 0.0205 = 1.226 g (all waste)

Eluent: Pentane/EtOAc 25:1 (d= 0.637 g/mL)

m_{eluent} = 6.2 x 1.226 x 0.637 = 4.842 g (all waste)

NWA = NNWA= 86.688 g

Mass of useful product = 0.008 g (0.037 mmol, 41% yield)

Total waste amount = 89.688 + 139.916 = 229.604 g

***E* factor =** 28700

E_G factor diastereo- and enantioselective Diels Alder reaction by Feringa

STEP 1

0.212 g 2-(1-methylimidazolyl)cynnamate (1 mmol, of which 0.3 mmol, 0.064 g waste)

0.019 g copper complex (E factor= 354, 0.05 mmol, all waste)

6.726 g waste produced for the synthesis of 0.019 g of copper complex (all waste)

166 g H_2O (all waste)

333 mL st-DNA aqueous solution (d= 1.0 g/mL, approx), 333 g (all waste)

2 mL DMSO (d= 1.1 g/mL), 2.2 g (all waste)

0.67 mL cyclopentadiene (8.0 mmol, d= 0.786 g/mL, 0.527 g), of which 7.3 mmol, 0.483 g waste

500 mL EtOAc (flat-rate for extractions, d= 0.902 g/mL), 451 g (all waste)

53.2 g Na_2SO_4 (20 flat-rate 1 cm^3-spoons, d= 2.66 g/cm^3)

COLUMN CHROMATOGRAPHY

m_{SiO2} = 59.8 x 0.278 = 16.624 g (all waste)

Eluent: Pentane/EtOAc 25:1 (d= 0.637 g/mL)

m_{eluent} = 6.2 x 16.624 x 0.637 = 65.655 g (all waste)

NNWA = 1094.971 g

NF = 0.12857

NWA = NNWA x NF = 1094.971 x 0.12857 = 140.780 g

Mass of useful product = 0.194 g (0.7 mmol, 70% yield)

STEP 2

0.024 g, 0.09 mmol (of which 59%, 0.0531 mmol, 0.015 g waste)

0.010 g molecular sieves (all waste)

0.6 mL CH_3CN (d= 0.786 g/mL), 0.472 g (all waste)

0.15 mL DBU (d= 1.02 g/mL), 0.153 g (all waste)

30 mL EtOAc (d= 0.902 g/mL), 27.06 g (all waste)

30 mL sat. NaHCO3 (d= 1.1 g/mL), 33 g (all waste)

15 mL brine (d= 1.15 g/mL), 17.25 g (all waste)

2.66 g Na_2SO_4 (1 flat-rate 1 cm^3-spoon, d= 2.66 g/cm^3) (all waste)

COLUMN CHROMATOGRAPHY

m_{SiO2} = 59.8 x 0.0205 = 1.226 g (all waste)

Eluent: Pentane:EtOAc 25:1 (d= 0.637 g/mL)

m_{eluent} = 6.2 x 1.226 x 0.637 = 4.842 g (all waste)

NWA = NNWA = 86.688 g

Mass of useful product = 0.008 g (0.037 mmol, 41% yield)

Total waste amount = 89.688 + 140.780 = 230.468 g

***E*G factor =** 28808.5 (0.38% additional waste)

E_G factor regioselective internal arylalkyne hydration by Bassetti

1.0 mmol 1-phenylpropyne (MW=116.16, of which 0.22 mmol, 0.025 g waste)

0.1 mmol Fe catalyst (MW= 561.97, 0.056 g, all waste)

2 mL AcOH (d= 1.05 g/mL), 2.10 g, all waste except for 0.78 mmol H_2O, 0.014 g,

total waste amount 2.086 g)

20 mL Et_2O (d= 0.713 g/mL), 14.26 g (all waste)

20 mL sat. $NaHCO_3$ (d= 1.1 g/mL), 22 g (all waste)

2.66 g Na_2SO_4 (1 flat-rate 1 cm^3 spoon, all waste)

COLUMN CHROMATOGRAPHY

m_{SiO2} = 59.8 x 0.134 = 8.013 g (all waste)

Euent: petroleum ether (d= 0.640 g/mL)

m_{eluent} = 6.2 x 0.640 x 8.013 = 31.796 g (all waste)

Mass of useful product = 0.105 g (MW= 134.18, 78% yield)

Total waste amount = 80.896 g

***E* factor = E_G factor =** 770

E factor Wang and Li catalyst

1 g P123

3 g KCl

31 g diluted HCl (all waste)

1.8 mL BTEE (bis-(triethoxysilyl)ethane, d= 0.958 g/mL), 1.724 g

0.13 mL MPTMS (trimethoxysilane, d= 0.96 g/mL), 0.125 g

100 g H_2O (all waste)

500 mL EtOH (d= 0.789 g/mL), 394.5 g (all waste)

7 mL 0.017 M (5.776 g/L) $HAuCl_4$, 0.040 g $HAuCl_4$ in 7 mL EtOH (d= 0.789 g/mL), 5.523 g

50 g H_2O (all waste)

50 mL EtOH (d= 0.789 g/mL), 39.45 g (all waste)

Mass of useful product = 1.0 g (0.10 mmol Au/g, 19.7 mg Au/g)

Total waste amount = 625.322 g (waste calculated by difference)

***E* factor =** 625

E factor regioselective internal arylalkyne hydration by Wang and Li

0.25 mmol 1-phenylpropyne (MW=116.16, of which 0.0025 mmol, 1.5 mg waste)

0.1 g (0.1 mmol, 1.0 mmol Au/g) Au catalyst (recovered, no waste)

4 g H_2O (of which 3.9991 g waste)

6 mL (3 x 2 mL) EtOAc (d= 0.902 g/mL), 5.412 g (all waste)

Mass of useful product = 31.9 mg

Total waste amount = 9412.6 mg

***E* factor =** 295

E_G factor regioselective internal arylalkyne hydration by Wang and Li

0.25 mmol 1-phenylpropyne (MW=116.16, of which 0.0025 mmol, 1.5 mg waste)

0.1 g (0.1 mmol, 1.0 mmol Au/g) Au catalyst (recovered, no waste)

62.5 g due to the synthesis of 0.1 g Au catalyst (E factor = 625, all waste)

4 g H_2O (of which 3.9991 g waste)

6 mL (3 x 2 mL) EtOAc (d= 0.902 g/mL), 5.412 g (all waste)

Mass of useful product = 31.9 mg

Total waste amount = 71912.6 mg

***E* factor =** 2254

E factor Rhodium chiral Pincer complex by Arai

STEP 1

1.111 g 5-(t-butyl)isophtalic acid (5.0 mmol, of which 5.0 mmol, 0.032 g O_2 waste)

45 mL THF (d= 0.888 g/mL), 39.96 g (all waste)

1,518 g $LiAlH_4$ (40 mmol, all waste)

45 mL (flat-rate amount for quenching) sat. aqueous potassium sodium tartrate (d= 1.1 g/mL), 49.5 g (all waste)

135 mL EtOAc (flat-rate amount for extractions, d= 0.902 g/mL), 121.77 g (all waste)

14.364 g Na_2SO_4 (5,4 flat-rate1 cm^3-spoons, all waste)

17.4 g MnO_2 (200 mmol, all waste except for 5.0 mmol of O_2, 0.160 g; resulting waste mass of 17.24 g)

15 mL DCM (d= 1.33 g/mL), 19.95 g (all waste)

FILTRATION ON CELITE (d= 0.47 g/mL)

m_{celite} = 62.83 g (4 cm-diameter and 5 cm high cylindrical column, all waste)

50 mL DCM (flat-rate amount for washing, d= 1.33 g/mL), 66.5 g (all waste)

Non-Normalized Waste Amount (NNWA) = 393.664 g

Normalization factor (NF) = 0.2

Normalized Waste Amount (NWA) = 393.664 x 0.2 x 1.1828 x 1.1086 = 103.239 g

Mass of useful product = 5.0 mmol (100% yield)

STEP 2

0.1902 mg 5-(t-butyl)isophtalaldehyde S2.1 (MW= 190.24, 1.0 mmol, of which 7%, 0.07 mmol, 0.013 g waste)

25 mL DCM (d= 1.33 g/mL), 33.25 g (all waste)

126 μL AcOH (d= 1.05 g/mL), 0.132 g (all waste)

0.6653 g (*1R,2R*)-N-benzyl-1,2-diphenylethane-1,2-diamine (MW= 312.41, 2.2 mmol, of which 0.214 mmol, 0,067 g waste)

25 g H_2O (flat-rate amount for quenching, all waste)

75 mL DCM (flat-rate amount for extraction d= 1.33 g/mL), 99,75 g (all waste)

7.98 g Na_2SO_4 (3 flat-rate 1 cm^3-spoons, all waste)

COLUMN CHROMATOGRAPHY

m_{SiO2} = 59.8 x 0.759 = 45.388 g

Euent: Hex/EtOAc 5:1 (d= 0.696 g/mL)

m_{eluent} = 6.2 x 0.696 x 45.388 = 195.858 g waste

NNWA = 407.438 g

NF = 1.1828

NWA = 407.438 x 1.1828 x 1.1086 = 534.254 g

Mass of useful product = 0.93 mmol **S2.2** (93% yield)

STEP 3

1.1 mmol **S2.2** (MW= 759.05, 0.835 g, all waste except for 0.451 mmol, 0.203 g, total waste amount 0.632 g)

20 mL MeOH (d= 0.792 g/mL), 15.84 g (all waste)

0.084 $NaHCO_3$ (all waste)

1.0 mmol $RhCl_3$ trihydrate (0.2633 g, all waste, except for 0.451 mmol "RhCl2", 0.0783 g, total waste amount 0.185 g)

10 mL MeOH (d= 0.792 g/mL), 7.92 g (all waste)

10 mL CH_3CN (MW= 41.05 d= 0.786 g/mL), 7.86 g (all waste, except for 0.451 mmol, 0.019 g,

total waste amount 7.841 g)

NNWA = 32.502 g

NF = 1.1086

NWA = 32.502 x 1.1086 = 36.032 g

Mass of useful product = 0.451 mmol (41% yield)

STEP 4

0.5 mmol Rh-chloride Pincer complex (no waste, 100% yield assumed)

0.334 g AgOAc (all waste, except for 1.0 mmol AcO-, 0.059 g, total waste amount 0.275 g)

15 mL DCM (d= 1.33 g/mL), 19.95 g (all waste)

COLUMN CHROMATOGRAPHY

m_{SiO2} = 59.8 x 0.510 = 30.498 g (all waste)

Euent: EtOAc/MeOH 1:1 (d= 0.847 g/mL)

m_{eluent} = 6.2 x 0.847 x 30.498 = 160.157 g (all waste)

NNWA = NWA = 210.88 g

Mass of useful product = 0.5 mmol, 0.510 g

Total waste amount = 103.239 + 534.254 + 36.032 + 210.88 = 884.405 g

***E* factor =** 1734

E factor Rh-catalyzed enantioselective Mannich reaction by Arai

6.3 mg Rh catalyst (all waste)

19.8 mg malononitrile (MW= 66.06, 0.3 mmol, of which 0.1 mmol waste, 6.6 mg)

0.2 mmol benzaldehyde N-Boc aldimine (MW= 205.26, 41.1 mg, no waste)

4 mL toluene (d= 0.867 g/mL), 3468 mg (all waste)

COLUMN CHROMATOGRAPHY

m_{SiO2} = 59.8 x 54.264 = 3245 mg (all waste)

Euent: Hex/EtOAc 4:1 (d= 0.704 g/mL)

m_{eluent} = 6.2 x 0.704 x 3245 = 14163.8 mg (all waste)

Mass of useful product = 53.7 mg (MW= 271.32, 99% yield)

Total waste amount = 20889.7 mg

***E* factor =** 389

E_G factor Rh-catalyzed enantioselective Mannich reaction by Arai

6.3 mg Rh catalyst (E factor = 1734, all waste)

10924.2 mg waste to produce the necessary amount of catalyst

19.8 mg malononitrile (MW= 66.06, 0.3 mmol, of which 0.1 mmol waste, 6.6 mg)

0.2 mmol benzaldehyde N-Boc aldimine (MW= 205.26, 41.1 mg, no waste)

4 mL toluene (d= 0.867 g/mL), 3468 mg (all waste)

COLUMN CHROMATOGRAPHY

m_{SiO2} = 59.8 x 54.264 = 3245 mg

Euent: Hex/EtOAc 4:1 (d= 0.704 g/mL)

m_{eluent} = 6.2 x 0.704 x 3245 = 14163.8 mg

Mass of useful product = 53.7 mg (MW= 271.32, 99% yield)

Total waste amount = 31813.9 mg (52.3% additional waste)

E factor = 592

E factor *Cinchona* alkaloid-based chiral halogen bond donor organocatalyst by Arai

0.5 mmol iodoperfluorobenzoic acid (MW= 319.9, of which 25%, 0.125 mmol, 0.040 g waste)

0.5 mmol aminoquinidine (*E* factor= 150, MW= 323.44, 0.162 g, of which 25%, 0.125 mmol, 0.040 g waste)

24.3 g waste produced to synthesize 0.5 mmol aminoquinidine (all waste)

0.5 mmol EDCI*HCl (MW= 191.70, of which 25%, 0.125 mmol, 0.024 g waste)

0.015 mmol HOBt (MW= 135.12, 0.002 g, all waste)

10 mL DCM (d= 1.33 g/mL), 13.3 g (all waste)

0.375 mmol H_2O produced (MW = 18.01, 0.007 g, all waste)

1.064 g Na_2SO_4 (d= 2.66 g/mL, flat-rate, all waste)

COLUMN CHROMATOGRAPHY

m_{SiO2} = 59.8 x 0.313 = 18.717 g

Euent: Hex/EtOAc/Et_3N 1:1:0.3 (d= 0.772 g/mL)

m_{eluent} = 6.2 x 0.772 x 18.717 = 89.587 g

Mass of useful product = 0.235 g (MW= 625.41, 0.375 mmol, 75% yield)

Total waste amount = 147.081 g

E factor = 626

E factor organocatalyzed enantioselective Mannich reaction by Arai

0.6 mg organocatalyst (all waste)

26.4 mg malononitrile (MW= 66.06, 0.4 mmol, of which 0.214 mmol waste, 14.1 mg)

0.2 mmol benzaldehyde N-Boc aldimine (MW= 205.26, 41.1 mg, of which 7%, 0.014 mmol, 2.9 mg waste)

2 mL $CHCl_3$ (d= 1.49 g/mL), 2980 mg (all waste)

COLUMN CHROMATOGRAPHY

m_{SiO2} = 59.8 x 54.264 = 3245 mg

Euent: Hex/EtOAc 4:1 (d= 0.704 g/mL)

m_{eluent} = 6.2 x 0.704 x 3245 = 14163.8 mg

Mass of useful product = 50.5 mg (0.186 mmol, 93% yield)

Total waste amount = 20406.4 mg

***E* factor =** 404

E_G factor organocatalyzed enantioselective Mannich reaction by Arai

0.6 mg organocatalyst (E factor= 626, all waste)

375.6 mg waste produced to synthesize 0.6 mg of organocatalyst (all waste)

26.4 mg malononitrile (MW= 66.06, 0.4 mmol, of which 0.214 mmol waste, 14.1 mg)

0.2 mmol benzaldehyde N-Boc aldimine (MW= 205.26, 41.1 mg, of which 7%, 0.014 mmol, 2.9 mg waste)

2 mL $CHCl_3$ (d= 1.49 g/mL), 2980 mg (all waste)

COLUMN CHROMATOGRAPHY

m_{SiO2} = 59.8 x 54.264 = 3245 mg

Euent: Hex/EtOAc 4:1 (d= 0.704 g/mL)

m_{eluent} = 6.2 x 0.704 x 3245 = 14163.8 mg

Mass of useful product = 50.5 mg (0.186 mmol, 93% yield)

Total waste amount = 20782 mg (1.8% additional waste)

E_G **factor =** 412