Synthesis and Structural Features of α-Fluorocarbonyl Systems

FISHER, CRAIG,AARON

Electronic Supplementary Material (ESI) for Green Chemistry.

Sustainable synthesis of enantiopure fluorolactam derivatives by a selective direct fluorination - amidase strategy

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SUPPORTING INFORMATION 2

Green Metrics calculations

SI-2.1 General

The following formulae were used for calculating Atom Economy (AE), Reaction Mass Efficiency (RME) and Mass Intensity (MI) [D. J. C. Constable, A. D. Curzons, V. L. Cunningham *Green Chem.,* 2002, **4***,* 521-527.]

$$AE = \frac{Molecular\ Weight\ of\ Product}{Total\ Molecular\ Weight\ of\ Reactants} \times 100$$

$$RME = \frac{Mass\ of\ Isolated\ Product}{Total\ Mass\ of\ Reactants} \times 100$$

$$MI = \frac{Total\ Mass\ in\ a\ Process\ or\ Process\ Step}{Mass\ of\ Product}$$

For the calculation of cumulative metrics over several synthetic steps, the following formulae were used:

$A + B \rightarrow C \qquad C + D \rightarrow E$

MW = molecular weight of compound; *m* = weight of component.

$$AE(E) = \frac{MW(E)}{MW(A) + MW(B) + MW(D)} \times 100 = \frac{MW(E)}{\frac{MW(C)}{\frac{AE(C)}{100}} + MW(D)} \times 100$$

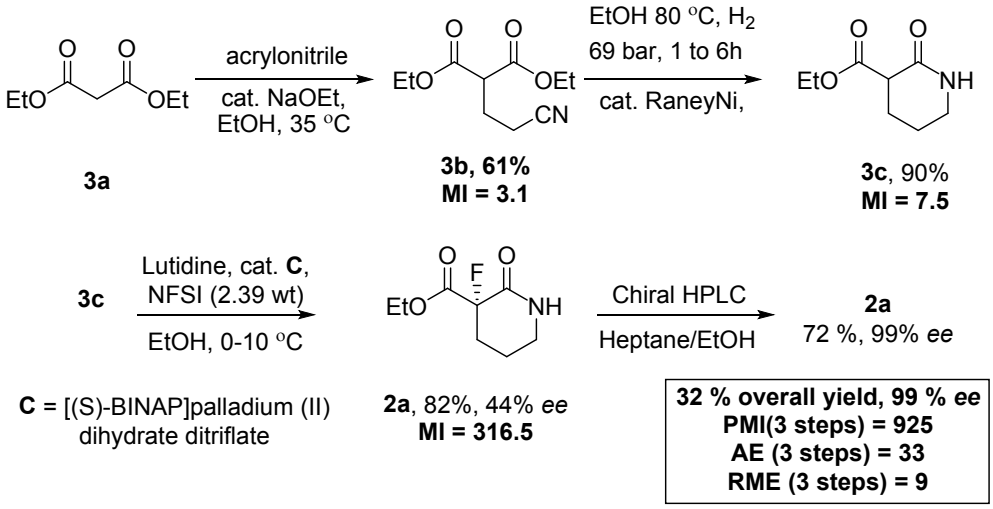
$$RME(E) = \frac{m(E)}{m(D) + m(C)} \times 100 = \frac{m(E)}{\frac{m(C)}{\frac{RME(C)}{100}} + m(D)} \times 100$$

$$MI(E) = \frac{m(C) \times MI(C) + Total\ Mass\ of\ Other\ Chemicals\ in\ the\ Step}{Mass\ of\ Product}$$

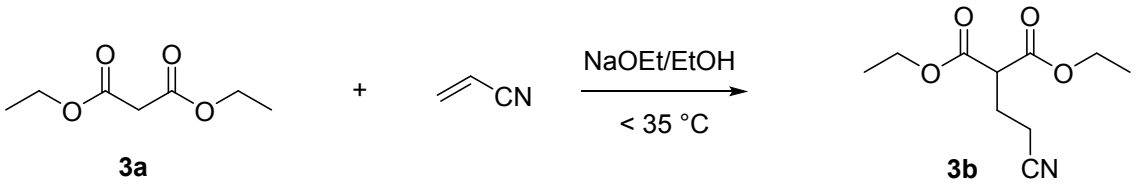
The specific MI for Reaction, Solvents and Workup were calculated using the MI formula using only the corresponding data (total mass of reaction components, solvents and work-up components).

SI-2.2 Literature synthesis methods

Reported procedures for the synthesis of diethyl fluoromalonate do not always contain all the required information, therefore, some realistic assumptions were used where appropriate and are *italicised* in the calculations given below. Drying agents, when used, were not included in the calculations.



Diethyl 2-(2-cyanoethyl)-malonate **3b** [N. F. Albertson and J. L. Fillman, *J. Am. Chem. Soc.,* 1949, **71**, 2818-2820].



Experimental procedure: To a solution of sodium (7.0 g, 0.3 mol) in ethanol (200 mL) and diethyl malonate **3a** (992 g, 6.2 mol) there was added acrylonitrile (168.5 g, 3.2 mol) at such a rate to maintain the temperature below 35 °C. The product was distilled under vacuum (104-110 °C, 0.8 mbar) to yield *diethyl 2-(2-cyanoethyl)-malonate* **3b** (421 g (average of 3 experiments), 61 %) as a colourless oil.

Materials used for metrics calculations: Sodium (7.0g, 0.3 mol), ethanol (200 mL, 158 g), diethyl malonate (945 mL, 992 g, 6.2 mol), acrylonitrile (208 mL, 168.5 g, 3.2 mol), diethyl 2-(2-cyanoethyl)-malonate (421 g, 1.97 mol).

$$AE(3b) = \frac{213.23}{160.17 + 53.06} \times 100 = 100$$

$$RME(3b) = \frac{421}{992 + 168.5} \times 100 = 36.3$$

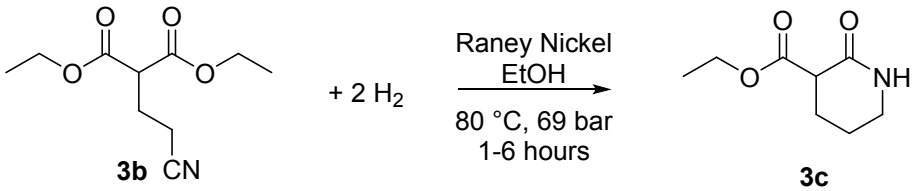
$$MI(3b) = \frac{7 + 158 + 992 + 168.5}{421} = 3.1$$

$$MI(3b\ reaction) = \frac{7 + 158 + 992 + 168.5}{421} = 3.1$$

$$MI(3b\ solvents) = \frac{158}{421} = 0.4$$

$$MI(3b\ work - up) = \frac{0}{421} = 0$$

Ethyl 2-oxopiperidine-3-carboxylate **3c** [N. F. Albertson and J. L. Fillman, *J. Am. Chem. Soc.*, 1949, **71**, 2818-2820].



MW: 213.23 MW: 2.02 MW: 171.20

Experimental procedure: A solution of diethyl 2-(2-cyanoethyl)-malonate **3b** (380 g) in ethanol (1.3 L) was reduced using Raney Nickel (7-10 g) and hydrogen (1000 psi = 69 bar) at 80 °C. The solution was evaporated (*assuming a filtration to remove catalyst*) and the residue poured into Skelly B (1 L, *assume hexanes*) with stirring. The product was filtered and air dried to give *ethyl 2-oxopiperidine-3-carboxylate* **3c** (278.5 g, average of 3 runs, 90 % yield) as a solid.

Materials used for metrics calculations: Diethyl 2-(2-cyanoethyl)-malonate (380 g, 1.8 mol), ethanol (1300 mL, 1026 g), Raney Nickel (10 g, 0.17 mol), hydrogen (*assuming use of 5 L autoclave meaning 3.5 L gas volume, treating hydrogen as an ideal gas gives 16.6 g, 8.2 mol, 2.75 equivalents*) Skelly B (*assume hexanes, 660 g*), ethyl 2-oxopiperidine-3-carboxylate (278.5 g, 1.63 mol).

$$AE(3c) = \frac{171.20}{213.23 + 2 \times 2.02} \times 100 = 78.8$$

$$RME(3c) = \frac{278.5}{380 + 20} \times 100 = 69.6$$

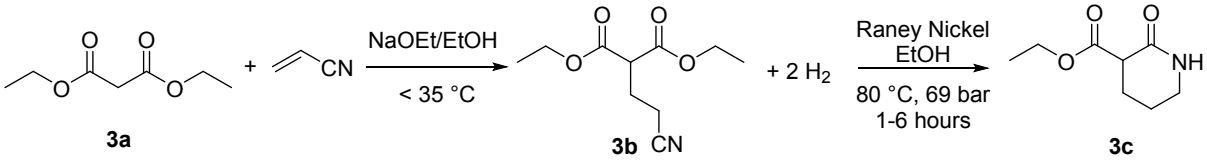
$$MI(3c) = \frac{380 + 1026 + 10 + 16.6 + 660}{278.5} = 7.5$$

$$MI(3c\ reaction) = \frac{380 + 1026 + 10 + 16.6}{278.5} = 5.1$$

$$MI(3c\ solvents) = \frac{1026 + 660}{278.5} = 6.0$$

$$MI(3c\ work - up) = \frac{660}{278.5} = 2.4$$

Cumulative metrics:



3a MW: 160.17 + MW: 53.06 → **3b** MW: 213.23 + 2 H_2 → **3c** MW: 171.20

$$AE(3c\ cumulative) = \frac{171.20}{160.17 + 53.06 + 2 \times 2.02} \times 100 = 78.8$$

$$RME(3c\ cumulative) = \frac{278.5}{\frac{380}{0.363} + 20} \times 100 = 26.1$$

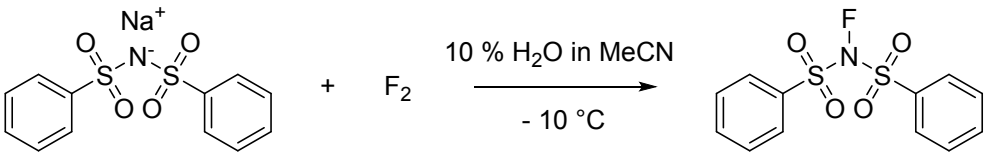
$$MI(3c\ cumulative) = \frac{380 \times 3.1 + 1026 + 10 + 16.6 + 660}{278.5} = 10.4$$

$$MI(3c\ reaction\ cumulative) = \frac{380 \times 3.1 + 1026 + 10 + 16.6}{278.5} = 8.0$$

$$MI(3c\ solvents\ cumulative) = \frac{380 \times 0.4 + 1026 + 660}{278.5} = 6.6$$

$$MI(3c\ work - up\ cumulative) = \frac{380 \times 0 + 660}{278.5} = 2.4$$

N-Fluorobenzenesulfonimide [W. J. Wagner, G. A. Shia, A. J. Poss, US5403957, 1992].



MW: 319.32 MW: 38.00 MW: 315.33

Experimental procedure: The sodium salt of the benzensulfonimide (16.0 g, 0.05 mol) was dissolved in 10% *v/v* water-acetonitrile mixture (150 mL). This was cooled to -10 °C and a gaseous mixture of 10% F_2 in nitrogen (*v/v*) was added at a rate of 100 cc/min (25 mmol/hour). Over two hours, one equivalent of fluorine was added, the reaction was evaporated to dryness, dissolved in DCM (*135 mL*), filtered to remove the insoluble material (sodium fluoride) and evaporated to dryness to give N-fluorobenzenesulfonimide (13.5 g, 85 % yield) as a white solid. [US5403957]

Materials used for metrics calculations: Benzenesulfonimide sodium salt (16 g, 50 mmol), water (15 mL, 15 g), acetonitrile (135 mL, 106 g), fluorine (1.9 g, 50 mmol), DCM (135 mL, 180 g), N-fluorobenzenesulfonimide (13.5 g, 42.5 mmol).

$$AE(NFSI) = \frac{315.33}{319.32 + 38.00} \times 100 = 88.2$$

$$RME(NFSI) = \frac{13.5}{16 + 1.9} \times 100 = 75.4$$

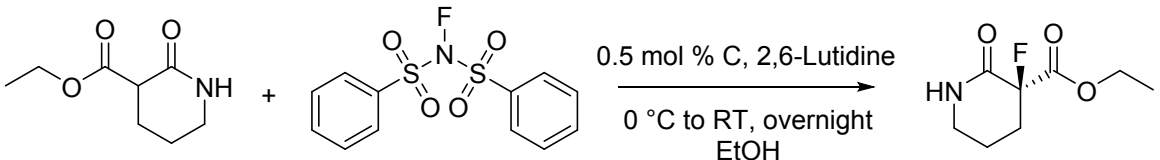
$$MI(NFSI) = \frac{16 + 15 + 106 + 1.9 + 180}{13.5} = 23.6$$

$$MI(NFSI\ reaction) = \frac{16 + 15 + 106 + 1.9}{13.5} = 10.3$$

$$MI(NFSI\ solvents) = \frac{15 + 106 + 180}{13.5} = 22.3$$

$$MI(NFSI\ work - up) = \frac{180}{13.5} = 13.3$$

Ethyl 3-fluoro-2-oxopiperidine-3-carboxylate **2a** [F. L. Atkinson, M. D. Barker, C. Douault, N. S. Garton, J. Liddle, V. K. Patel, A. G. S. Preston, D. M. Wilson, US20130040984].



3c
MW: 171.20

NFSI
MW: 315.33

2a
MW: 189.19

C: [((*S*)-BINAP)Pd(H_2O)$_2$]$^{2+}$ (TfO^-)$_2$

Experimental procedure: 2,6-Lutidine (31.7 g, 296 mmol) was added dropwise over 30 min to a suspension of ethyl 2-oxopiperidine-3-carboxylate **3c** (101.2 g, 591 mmol), ((*S*)-BINAP)Pd(H_2O)$_2$(OTf)$_2$ [A. Fuji, E. Hagiwara and M. Sodeoka, *J. Am. Chem. Soc.,* 1999, **121**, 5450-5458] (3.14 g, 2.96 mmol) and *N*-fluorobenzenesulfonimide (242 g, 768 mmol) in EtOH (500 mL) at 0 °C in an ice bath. The temperature was maintained at approximately 10 °C during addition and allowed to warm up to room temperature overnight as the ice melted. The reaction was filtered and the solid was washed with EtOH (*estimated 200 mL*) then DCM (200 mL). The liquors were evaporated and re-dissolved in DCM (3500 mL), the organics were washed with saturated NH_4Cl solution (300 mL) and the aqueous phase was extracted with DCM (2 x 200 mL). The combined organics were evaporated and re-dissolved in DCM (300 mL), filtered through celite and washed with DCM (200 mL). The organic solution was allowed to stand overnight, a fine precipitate formed and the mixture was filtered through celite and washed with DCM (*estimated 200 mL*). The organic fraction was loaded onto silica (1500 g, *estimated volume: 2.4 L*) and was purified on the companion XL eluting with 0-100% ethyl acetate in cyclohexane gradient (*estimated 10 column volumes = 12 L each*). Appropriate fractions were identified by LC-MS, combined and the solvent evaporated to give *ethyl 3-fluoro-2-oxopiperidine-3-carboxylate* **2a** (92.2 g, 82 %, 44 % *ee* after vacuum drying) as a yellow solid. High purity (99 % *ee*) product was obtained by preparative scale chiral chromatography. [F. L. Atkinson, M. D. Barker, C. Douault, N. S. Garton, J. Liddle, V. K. Patel, A. G. S. Preston, D. M. Wilson, US20130040984].

Materials used for metrics calculations: 2,6-Lutidine (31.7 g, 296 mmol), ethyl 2-oxopiperidine-3-carboxylate (101.2 g, 591 mmol), ((*S*)-BINAP)Pd(H_2O)$_2$(OTf)$_2$ (3.14 g, 2.96 mmol), N-fluorobenzenesulfonimide (242 g, 768 mmol), EtOH (700 mL, 552 g), DCM (4800 mL, 6384 g), saturated aq. NH_4Cl solution (300 mL, 318 g), silica (1500 g *assume 2.4 L volume, 1 g =1.6 mL*), ethyl acetate (*assume 5 column volumes: 12 L, 10.7 kg*),

cyclohexane (*assume 5 column volumes: 12 L, 9.35 kg*), ethyl 3-fluoro-2-oxopiperidine-3-carboxylate (92.2 g, 44 % *ee* after vacuum drying).

$$AE(2\ 44\%ee) = \frac{189.19}{171.20 + 315.33} \times 100 = 38.9$$

$$RME(2\ 44\%ee) = \frac{92.2}{101.2 + 242} \times 100 = 26.9$$

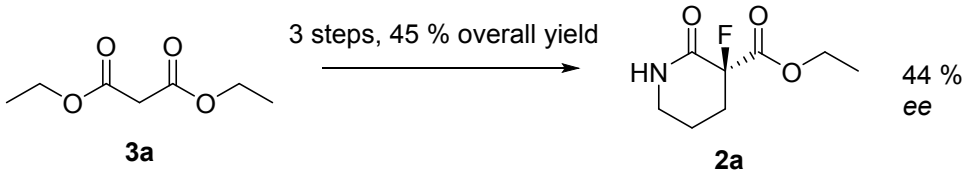
$$MI(2\ 44\%ee) = \frac{32 + 101 + 3 + 242 + 552 + 6384 + 318 + 1500 + 10700 + 9350}{92.2} = 316.5$$

$$MI(2\ reaction\ 44\%ee) = \frac{32 + 101 + 3 + 242 + 395}{92.2} = 8.4$$

$$MI(2\ solvents\ 44\%ee) = \frac{552 + 6384 + 318 + 10700 + 9350}{92.2} = 296.1$$

$$MI(2\ work-up\ 44\%ee) = \frac{158 + 6384 + 318 + 1500 + 10700 + 9350}{92.2} = 308.1$$

Ethyl 3-fluoro-2-oxopiperidine-3-carboxylate **2a** cumulative metrics:



3a **2a**

$$AE(2\ 44\%ee\ cumulative) = \frac{MW(2)}{\frac{MW(3c)}{\frac{AE(3c\ cumulative)}{100}} + \frac{MW(NFSI)}{\frac{AE(NFSI)}{100}}} \times 100$$

$$AE(2\ 44\%ee\ cumulative) = \frac{189.19}{\frac{171.20}{0.788} + \frac{315.33}{0.882}} \times 100 = 32.9$$

$$RME(2\ 44\%ee\ cumulative) = \frac{m(2)}{\frac{m(3c)}{\frac{RME(3c\ cumulative)}{100}} + \frac{m(NFSI)}{\frac{RME(NFSI)}{100}}} \times 100$$

$$RME(2\ 44\%ee\ cumulative) = \frac{92.2}{\frac{101.2}{0.261} + \frac{242}{0.754}} \times 100 = 13.0$$

$$MI(2\ 44\%ee\ cumulative)$$

$$= \frac{32 + 101 \times MI(3c) + 3 + 242 \times MI(NFSI) + 552 + 6384 + 318 + 1500 +}{92.2}$$

$$\frac{32 + 101 \times 10.4 + 3 + 242 \times 23.6 + 552 + 6384 + 318 + 1500 + 10700 + 9}{92.2}$$

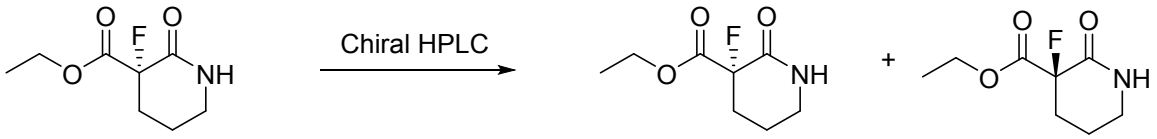
$$= 386.1$$

$$MI(2\ 44\%ee\ cumulative\ reaction) = \frac{32 + 101 \times 8 + 3 + 242 \times 10.3 + 395}{92.2} = 40.5$$

$$MI(\ 44\%ee\ cumulative\ solvents)$$
$$= \frac{552 + 6384 + 318 + 10700 + 9350 + 101 \times 6 + 242 \times 22.3}{92.2} = 361.2$$

$$MI(2\ cumulative\ 44\%ee\ work - up)$$
$$= \frac{101 \times 2.4 + 242 \times 13.3 + 158 + 6384 + 318 + 1500 + 10700 + 9350}{92.2} = 345.7$$

Chiral HPLC purification of 44 % *ee* material [F. L. Atkinson, M. D. Barker, C. Douault, N. S. Garton, J. Liddle, V. K. Patel, A. G. S. Preston, D. M. Wilson, US20130040984].



crude **2**

44 % *ee* = 72 % (*S*) + 28 % (*R*)

pure **2**

72 % yield, 99 % *ee*

28 % yield, 99 % *ee*

Experimental procedure: Ethyl-3-fluoro-2-oxo-3-piperidinecarboxylate **2** (25 g, *assume it contributes 20 mL to total volume*) was dissolved in ethanol (450 mL) with gentle heating and sonication. The solution was then filtered through a Pall Acrodisc 37 mm syringe filter with a glass fibre membrane. The filtered solution was adjusted to a total volume of 500 mL with ethanol (*assume 30 mL*) to give a solution with nominal concentration of 50 mg/mL. The preparative HPLC details were as follows:

Column:	Chiralpak AD, 330 x 50 mm, 20 pm
Mobile Phase:	A: Heptane B: Ethanol
Gradient Profile:	15% B Isocratic
Run Time:	20 min
Flow Rate:	473 mL/min
Column Temperature:	20 °C.
Wavelength:	220 nm

Materials used for metrics calculations: Ethyl 3-fluoro-2-oxopiperidine-3-carboxylate (25 g, 44 % *ee*), ethanol (*assume 480 mL, 379 g for dissolution* + 1419 mL, 1120 g for chromatography), heptane (8041 mL, 5500 g), ethyl 3-(*S*)-fluoro-2-oxopiperidine-3-carboxylate (*assume 100 % recovery*, 18 g, 99 % *ee*).

$$AE(2\ Chiral\ HPLC) = \frac{189.19}{189.19} \times 100 = 100$$

$$RME(2\ Chiral\ HPLC) = \frac{18.0}{25.0} \times 100 = 72.0$$

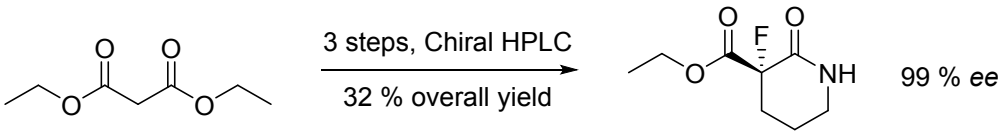
$$MI(2\ Chiral\ HPLC) = \frac{25 + 1499 + 5500}{18.0} = 390.2$$

$$MI(2\ Chiral\ HPLC\ reaction) = \frac{25.0}{18.0} = 1.4$$

$$MI(2\ Chiral\ HPLC\ solvents) = \frac{1499 + 5500}{18.0} = 388.8$$

$$MI(2\ Chiral\ HPLC\ work-up) = \frac{1499 + 5500}{18.0} = 388.8$$

Ethyl 3-fluoro-2-oxopiperidine-3-carboxylate **2** cumulative metrics:



3a **2**

$$AE(2\ cumulative) = \frac{189.19}{\frac{189.19}{0.329}} \times 100 = 32.9$$

$$RME(2\ cumulative) = \frac{18.0}{\frac{25.0}{0.130}} \times 100 = 9.4$$

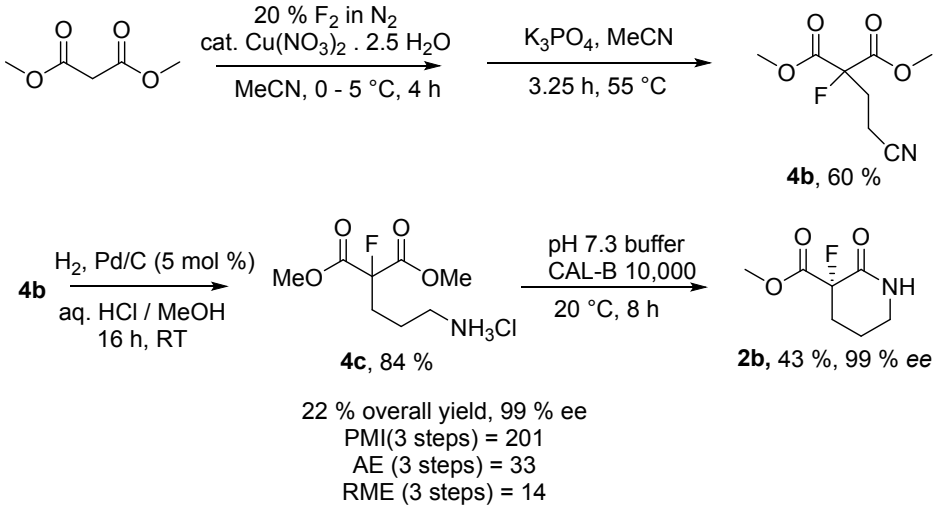
$$MI(2\ cumulative) = \frac{25 \times 386.1 + 1499 + 5500}{18.0} = 925.1$$

$$MI(2\ cumulative\ reaction) = \frac{25 \times 40.5}{18.0} = 56.3$$

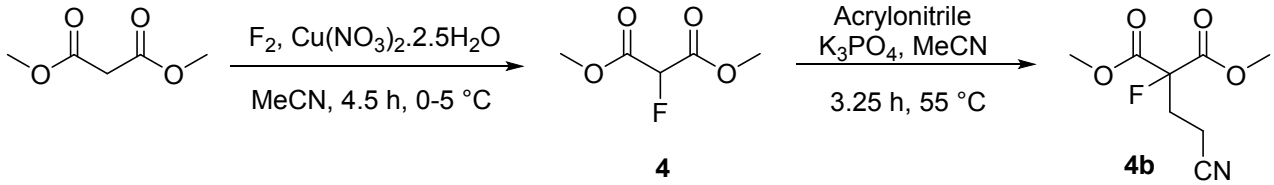
$$MI(2\ cumulative\ solvents) = \frac{25 \times 361.2 + 1499 + 5500}{18.0} = 890.5$$

$$MI(2\ work-up) = \frac{25 \times 345.7 + 1499 + 5500}{18.0} = 868.9$$

SI-2.3 Direct fluorination and enzymatic resolution approach



Dimethyl 2-(2-cyanoethyl)-2-fluoromalonate **4b**



MW: 132.12 MW(F_2): 38.00 MW: 53.06 MW: 203.17

Experimental procedure: as described in **SI-1.9**.

Materials used for metrics calculations: Dimethyl malonate (26.4 g), $Cu(NO_3)_2.2.5H_2O$ (4.65 g), acetonitrile (210 mL, 165 g), fluorine (8.36 g), K_3PO_4 (84.9 g), acrylonitrile (12.7 g), dimethyl 2-(2-cyanoethyl)-fluoromalonate (24.45 g).

$$AE(4b) = \frac{203.17}{132.12 + 38.00 + 53.06} \times 100 = 91.0$$

$$RME(4b) = \frac{24.45}{26.4 + 8.36 + 12.7} \times 100 = 51.1$$

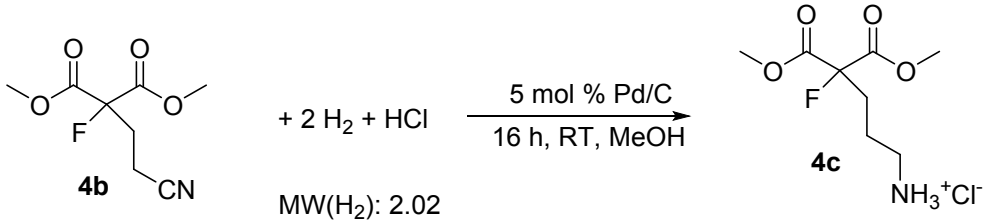
$$MI(4b) = \frac{26.4 + 4.65 + 165 + 8.36 + 84.9 + 12.7}{24.45} = 12.3$$

$$MI(4b\ reaction) = \frac{26.4 + 4.65 + 8.36 + 42.45 + 12.7 + 118}{24.45} = 8.7$$

$$MI(4b\ solvents) = \frac{165}{24.45} = 6.7$$

$$MI(4b\ work-up) = \frac{47 + 42.45}{24.45} = 3.6$$

Dimethyl 2-(3-aminopropyl)-2-fluoromalonate, hydrochloride salt **4c**



MW: 203.17

MW(H_2): 2.02
MW(HCl): 36.45

MW: 243.66

Experimental procedure: as described in **SI-1.10**.

Materials used for metrics calculations: 10 % Pd/C (2.62 g), 37 % HCl (4.85 mL, 5.82 g, 2.15 g HCl and 3.67 g water), dimethyl 2-(2-cyanoethyl)-2-fluoromalonate (10.0 g), hydrogen (*1.0 g, assuming 3 L gas volume (autoclave + storage tank) at 4 bar and 20 °C*), methanol (103.3 mL, 81.7 g), acetone (30 mL, 23.7 g), dimethyl 2-(3-aminopropyl)-2-fluoromalonate, hydrochloride salt (10.43 g).

$$AE(4c) = \frac{243.66}{203.17 + 2 \times 2.02 + 36.45} \times 100 = 100$$

$$RME(4c) = \frac{10.43}{10.0 + 2 + 2.15} \times 100 = 73.7$$

$$MI(4c) = \frac{2.62 + 5.82 + 10.0 + 1 + 81.7 + 23.7}{10.43} = 12.0$$

$$MI(4c\ reaction) = \frac{2.62 + 5.82 + 10 + 1 + 34.3}{10.43} = 5.2$$

$$MI(4c\ solvents) = \frac{81.7 + 23.7}{10.43} = 10.1$$

$$MI(4c\ work-up) = \frac{47.5 + 23.7}{10.43} = 6.8$$

Cumulative metrics for 2 steps (50 % yield):

$$AE(4c\ cumulative) = \frac{243.66}{\frac{203.17}{0.91} + 2 \times 2.02 + 36.45} \times 100 = 92.3$$

$$RME(4c\ cumulative) = \frac{10.43}{\frac{10.0}{0.511} + 2 + 2.15} \times 100 = 44.5$$

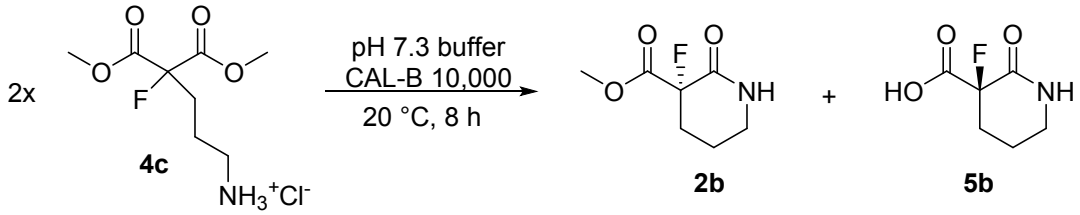
$$MI(4c\ cumulative) = \frac{2.62 + 5.82 + 10.0 \times 12.3 + 1 + 81.7 + 23.7}{10.43} = 22.8$$

$$MI(4c\ reaction\ cumulative) = \frac{2.62 + 5.82 + 10 \times 8.7 + 1 + 34.3}{10.43} = 12.5$$

$$MI(4c\ solvents\ cumulative) = \frac{81.7 + 23.7 + 10 \times 6.7}{10.43} = 16.5$$

$$MI(4c\ work-up\ cumulative) = \frac{47.5 + 23.7 + 10 \times 3.6}{10.43} = 10.3$$

(*S*)-Methyl 3-fluoro-2-oxopiperidine-3-carboxylate **2b**



MW: 243.66 MW: 175.16

Experimental procedure: as described in **SI-1.11**.

Materials used for metrics calculations: 0.06 M Na_2HPO_4 : 0.06 M KH_2PO_4 buffer (*assume overall 246 mL*, *assume d = 1.0 g/mL, 246 g*), **4c** (10.0 g), 05 M NaOH solution (*assume 1 equivalent NaOH, 82 mL, 83.6 g solution*), Fermase immobilised CAL-B 10,000 (7.2 g), water (30 mL, 30 g), 20 % formic acid (*assume d = 1.04 g/mL,* 30 mL, 31.2 g), acetone (10 mL, 7.9 g), (*S*)-*methyl 3-fluoro-2-oxopiperidine-3-carboxylate* **2b** (3.15 g).

$$AE(6a) = \frac{175.16}{2 \times 243.66} \times 100 = 35.9$$

$$RME(6a) = \frac{3.15}{10.0} \times 100 = 31.5$$

$$MI(6a) = \frac{246 + 10 + 83.6 + 7.2 + 30 + 31.2 + 7.9}{3.15} = 132.0$$

$$MI(6a\ reaction) = \frac{246 + 10 + 83.6 + 7.2}{3.15} = 110.1$$

$$MI(6a\ solvents) = \frac{246 + 83.6 + 30 + 31.2 + 7.9}{3.15} = 126.6$$

$$MI(6a\ work-up) = \frac{30 + 31.2 + 7.9}{3.15} = 21.9$$

Cumulative metrics for 3 steps (22 % overall yield):

$$AE(6a\ cumulative) = \frac{175.16}{2 \times \frac{243.66}{0.923}} \times 100 = 33.2$$

$$RME(6a\ cumulative) = \frac{3.15}{\frac{10.0}{0.445}} \times 100 = 14.0$$

$$MI(6a\ cumulative) = \frac{246 + 10 \times 22.8 + 83.6 + 7.2 + 30 + 31.2 + 7.9}{3.15} = 201.2$$

$$MI(6a\ reaction\ cumulative) = \frac{246 + 10 \times 12.5 + 83.6 + 7.2}{3.15} = 146.6$$

$$MI(6a\ solvents\ cumulative) = \frac{246 + 83.6 + 30 + 31.2 + 7.9 + 10 \times 16.5}{3.15} = 179.0$$

$$MI(6a\ work-up\ cumulative) = \frac{30 + 31.2 + 7.9 + 10 \times 10.3}{3.15} = 54.7$$

First pass Metrics Assessment (C.R. McElroy, A. Constantinou, L.C. Jones, L. Summerton and J.H. Clark, *Green Chem.,* 2015, accepted manuscript (DOI: 10.1039/C5GC00340G))**.**

Literature Method	**Michael addition (3b)**		**Reduction (3c)**		**NFSI**		**Enantioselective fluorination (2)**		**Chiral chromatography (2)**	
Yield	61 %		90 %		85 %		82 %		72 %	
RME	36.3		69.6		75.4		26.9		72.0	
AE	100		78.8		88.2		38.9		100	
Solvents	EtOH		Hexane		DCM		DCM		Heptane	
Health and Safety	H350, H411		H250, H372		H330		First pass OK		First pass OK	
MI: Total	3.1		7.5		23.6		233.9		390.2	
MI: Reaction	3.1		5.1		10.3		8.4		1.4	
MI: Workup	0		2.4		13.3		225.5		388.8	
Catalysts used	Na		Raney Nickel		Not used		Not used		Not used	
Catalysts recovered			No catalysts recovered							
Reactor	Batch		Batch		Batch		Batch			
Elements					S		S			
Energy			Above solvent BP–5 °C (80.0 °C > 74.0 °C)							
Work-up							Chromatography		Chromatography	

This work	One-pot fluorination, Michael addition		Reduction		Resolution	
Yield	60 %		84 %		44 %	
RME	51.1		73.7		31.5	
AE	91.0		100		35.9	
Solvents	MeCN				Formic acid	
Health and Safety	H330, H350, H411, H410		H370		First pass OK	
MI: Total	12.3		12.1		132.0	
MI: Reaction	8.7		5.3		110.1	
MI: Workup	3.6		6.8		21.9	
Catalysts used	$Cu(NO_3)_2.2.5H_2O$		Pd/C 10%		Fermase CAL-B 10,000	
Catalysts recovered	No catalysts recovered		No catalysts recovered		All catalysts recovered	
Reactor	Batch		Batch		Batch	
Elements	P, Cu		Pd			
Energy						
Work-up					Ion exchange	

	Enantioselective fluorination (literature procedure)	Chemo-enzymatic route (this work)
Yield	32 % (99 % *ee*)	22 % (99 % *ee*)
RME	9.4	14.0
AE	32.9	33.2
MI: Total	925.1	201.2
MI: Reaction	56.3	146.6
MI: Workup	868.9	54.7