Paths of analysis*

C123

Synthia

March 3, 2022

1 Analysis parameters

Analysis type: Automatic Retrosynthesis

Rules: none selected

Filters: FGI, FGI with protections

Max. paths returned: 5

Max. iterations: 300

Commercial:

1. Max. molecular weight - 1000 g/mol
2. Max. price - 1000 $/g

Published:

1. Max. molecular weight - 1000 g/mol
2. Popularity - 10

My Stockroom:

1. Max. molecular weight - 1000 g/mol

Reaction scoring formula: TUNNEL_COEF*FGI_COEF*STEP*20+1000000*(CONFLICT+NON_SELECTIVITY+FILTERS+PROTECT)

Chemical scoring formula: SMALLER^ 3,SMALLER^ 1.5

Min. search width: 400

Max. reactions per product: 60

Strategies: none selected

*The results stated herein were generated using the proprietary platform owned and maintained by Grzybowski Scientific Inventions, Inc., a subsidiary of Merck KGaA, Darmstadt Germany. The results are provided on an as is basis, and shall be used solely in connection with the rights afforded in the license agreement and for no other purpose.

FGI Coeff: 0

JSON Parameters: {}

2 Paths

3 paths found. *Paths are sorted by score. Reactions are sorted in appearance order for each path.*

2.1 Path 1

Score: 138.68

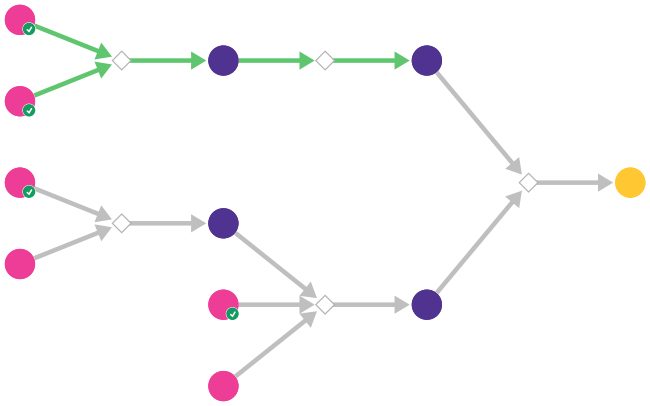
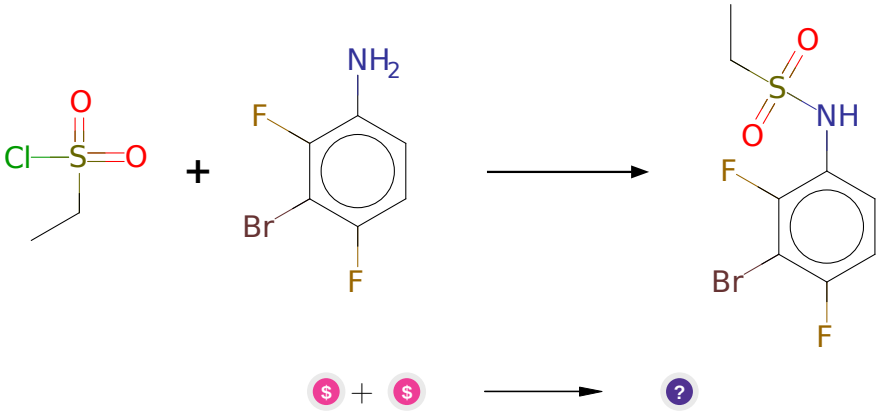


Figure 1: Outline of path 1

2.1.1 N-Sulfonylation



Substrates:

1. Ethanesulfonyl chloride - *available at Sigma-Aldrich*
2. 3-Bromo-2,4-difluoroaniline - *AstaTech*

Products:

1. CCS(=O)(=O)Nc1ccc(F)c(Br)c1F

Typical conditions: THF.rt

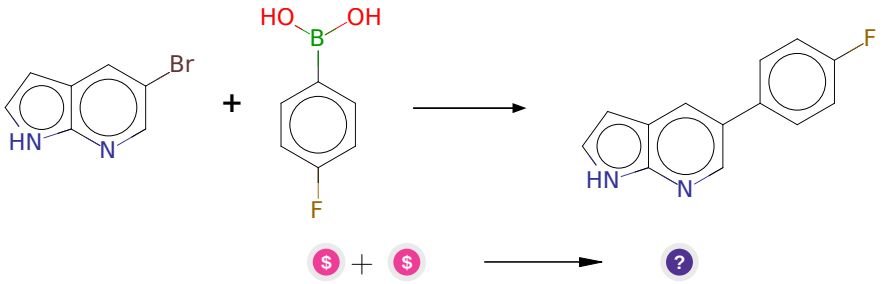
Protections: none

Yield: good

Reference: *10.1055/s-0029-1217565* and *10.1002/(SICI)1099-0690(199806)1998:6<945::AID-EJOC945>3.0.CO;2-3* and *10.1055/s-2001-14567* and *10.1016/j.bmc.2014.07.022*

Retrosynthesis ID: 14718

2.1.2 Suzuki coupling of arylboronic acids with aryl bromides



Substrates:

1. 5-Bromo-7-azaindole - *available at Sigma-Aldrich*
2. (p-Fluorophenyl)boric acid - *available at Sigma-Aldrich*

Products:

1. Fc1ccc(-c2cnc3[nH]ccc3c2)cc1

Typical conditions: Pd catalyst.base.solvent

Protections: none

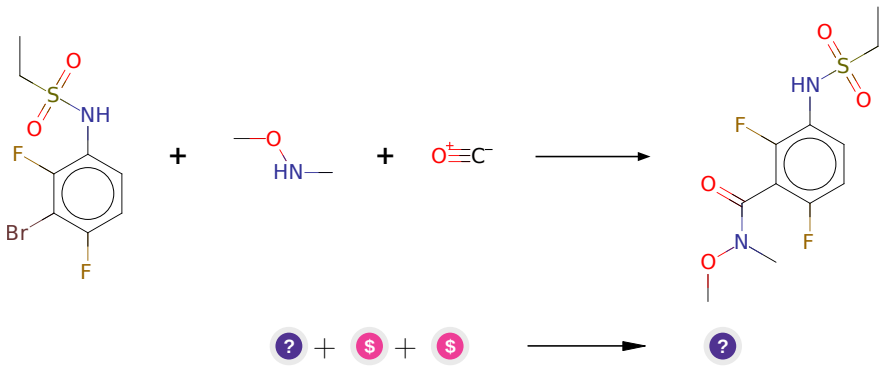
Yield: good

Reference: *10.1021/cr00039a007* and *10.1007/3418_2012_32* and *10.1021/cr0505268* and *10.1016/j.jfluchem.2016.01.018* and *10.1039/C3CS60197H*

and *10.1016/j.ejmech.2018.08.092* and *10.1038/s41929-020-00564-z* (metal-free coupling)

Retrosynthesis ID: 25150

2.1.3 Pd-catalyzed conversion of aryl bromides to Weinreb amides



Substrates:

1. CCS(=O)(=O)Nc1ccc(F)c(Br)c1F
2. Carbon monoxide - *available at Sigma-Aldrich*
3. n-methoxymethylamine - *ChemImpexInternational*

Products:

1. CCS(=O)(=O)Nc1ccc(F)c(C(=O)N(C)OC)c1F

Typical conditions: Pd(OAc)2.Xantphos.CO(1 atm).Na2CO3.toluene.80C

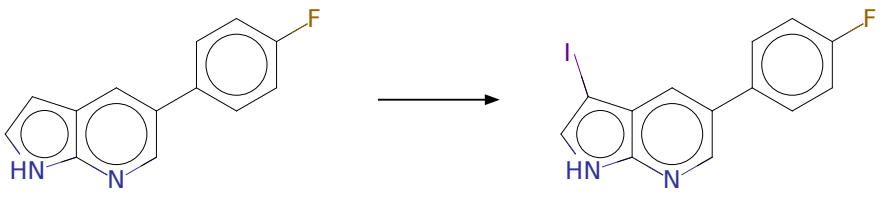
Protections: none

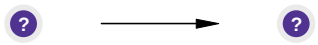
Yield: moderate

Reference: DOI: *10.1021/ol061902t*

Retrosynthesis ID: 1688

2.1.4 Iodination of aromatic compounds





Substrates:

1. Fc1ccc(-c2cnc3[nH]ccc3c2)cc1

Products:

1. Fc1ccc(-c2cnc3[nH]cc(I)c3c2)cc1

Typical conditions: I2 or other iodinating agent e.g. NIS

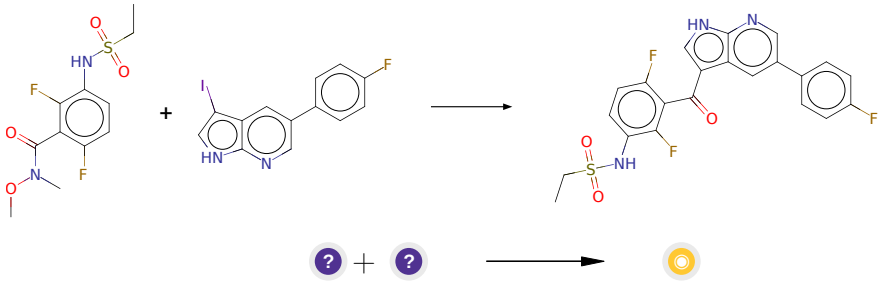
Protections: none

Yield: good

Reference: DOI: *10.1039/C5SC00964B* and *10.1016/j.tetlet.2005.05.117* and *10.1007/s11178-005-0256-1*

Retrosynthesis ID: 10697

2.1.5 Synthesis of ketones from Weinreb amides



Substrates:

1. CCS(=O)(=O)Nc1ccc(F)c(C(=O)N(C)OC)c1F
2. Fc1ccc(-c2cnc3[nH]cc(I)c3c2)cc1

Products:

1. CCS(=O)(=O)Nc1ccc(F)c(C(=O)c2c[nH]c3ncc(-c4ccc(F)cc4)cc23)c1F

Typical conditions: 1.RmgBr.THF 2.TFA.DCM

Protections: none

Yield: good

Reference: *10.1021/jm051185t* and *10.1021/ol101021v* (supporting info)

Retrosynthesis ID: 5060

2.2 Path 2

Score: 165.66

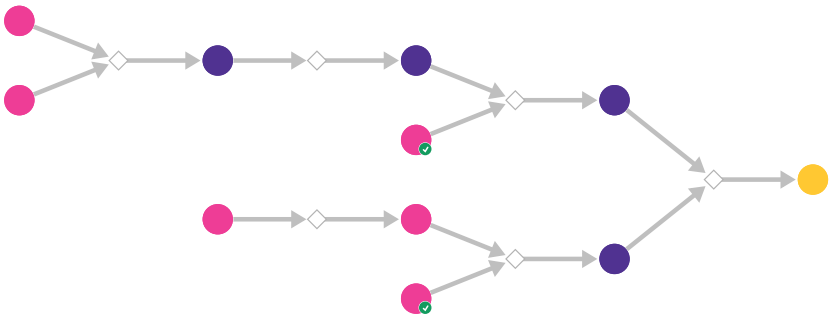
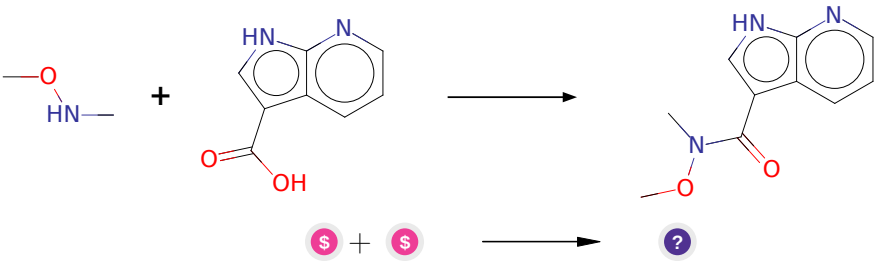


Figure 2: Outline of path 2

2.2.1 Synthesis of O-substituted N-substituted hydroxamic acids



Substrates:

1. n-methoxymethylamine - *ChemImpexInternational*
2. 7-Azaindole-3-carboxylic acid - *Combi-Blocks*

Products:

1. CON(C)C(=O)c1c[nH]c2ncccc12

Typical conditions: DCC.DMAP or CDI.TEA.DCM

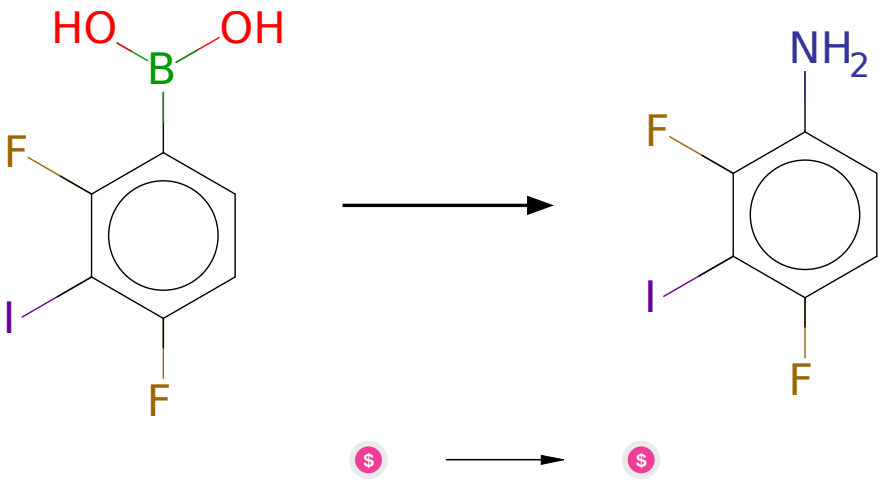
Protections: none

Yield: good

Reference: Patent: WO2007/67333A2, 2007 & *10.1016/j.bmcl.2008.09.100*

Retrosynthesis ID: 1152

2.2.2 Synthesis of anilines from aryl boronic acids



Substrates:

1. 2,4-Difluoro-3-iodophenylboronic acid - *AOBChem*

Products:

1. 2,4-Difluoro-3-iodoaniline - *Enamine*

Typical conditions: Cu2O.NH3.H2O.air.rt

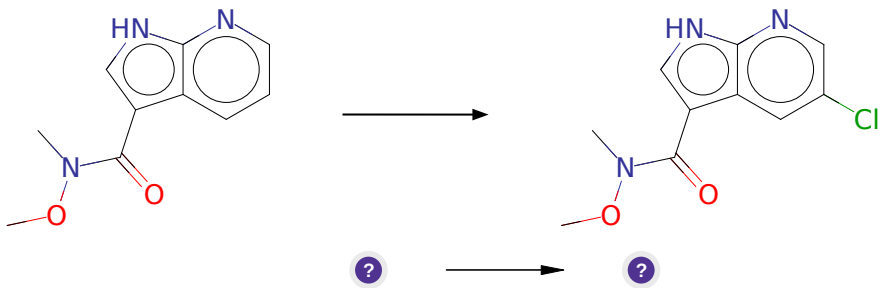
Protections: none

Yield: moderate

Reference: DOI: *10.1002/chem.201003711*

Retrosynthesis ID: 2265

2.2.3 Chlorination of aromatic compounds



Substrates:

1. CON(C)C(=O)c1c[nH]c2ncccc12

Products:

1. CON(C)C(=O)c1c[nH]c2ncc(Cl)cc12

Typical conditions: Cl2 or other chlorinating agent like NCS

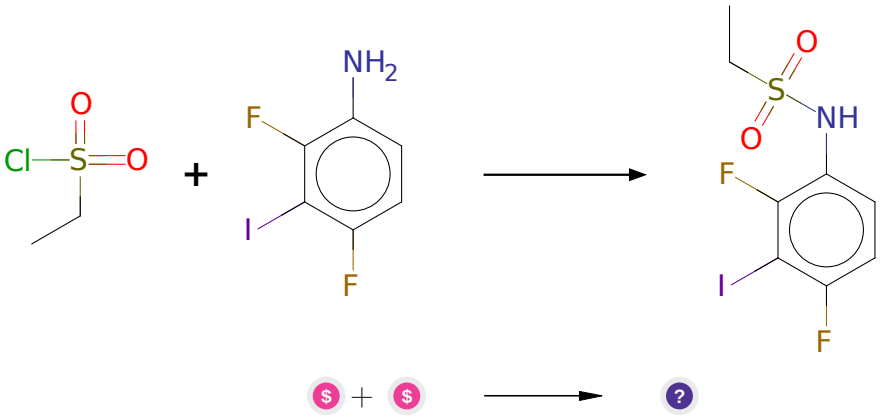
Protections: none

Yield: moderate

Reference: DOI: *10.1007/s11178-005-0256-1*

Retrosynthesis ID: 11125

2.2.4 N-Sulfonylation



Substrates:

1. 2,4-Difluoro-3-iodoaniline - *Enamine*
2. Ethanesulfonyl chloride - *available at Sigma-Aldrich*

Products:

1. CCS(=O)(=O)Nc1ccc(F)c(I)c1F

Typical conditions: THF.rt

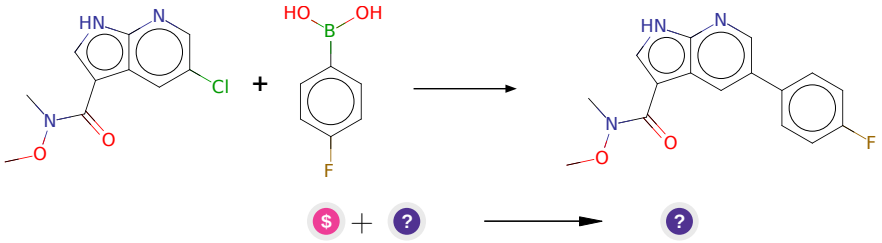
Protections: none

Yield: good

Reference: *10.1055/s-0029-1217565* and *10.1002/(SICI)1099-0690(199806)1998:6<945::AID-EJOC945>3.0.CO;2-3* and *10.1055/s-2001-14567* and *10.1016/j.bmc.2014.07.022*

Retrosynthesis ID: 14718

2.2.5 Suzuki coupling with aryl chlorides



Substrates:

1. (p-Fluorophenyl)boric acid - *available at Sigma-Aldrich*
2. CON(C)C(=O)c1c[nH]c2ncc(Cl)cc12

Products:

1. CON(C)C(=O)c1c[nH]c2ncc(-c3ccc(F)cc3)cc12

Typical conditions: [Pd].catalyst.base.

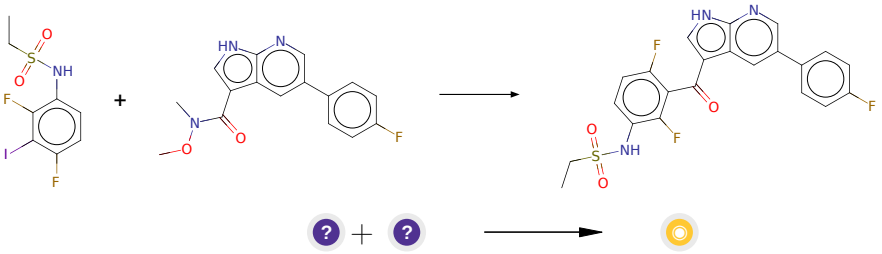
Protections: none

Yield: good

Reference: *10.1002/anie.201108608* and *10.1002/anie.200801465* and *10.1055/s-0033-1338293* and *10.1039/c1cc10708a* and *10.1055/s-0030-1260169* and *10.1016/j.tet.2005.05.071* and *10.1038/s41929-020-00564-z* (metal-free coupling)

Retrosynthesis ID: 26284

2.2.6 Synthesis of ketones from Weinreb amides



Substrates:

1. CCS(=O)(=O)Nc1ccc(F)c(I)c1F
2. CON(C)C(=O)c1c[nH]c2ncc(-c3ccc(F)cc3)cc12

Products:

1. CCS(=O)(=O)Nc1ccc(F)c(C(=O)c2c[nH]c3ncc(-c4ccc(F)cc4)cc23)c1F

Typical conditions: 1.RmgBr.THF 2.TFA.DCM

Protections: none

Yield: good

Reference: *10.1021/jm051185t* and *10.1021/ol101021v* (supporting info)

Retrosynthesis ID: 5060

2.3 Path 3

Score: 187.60

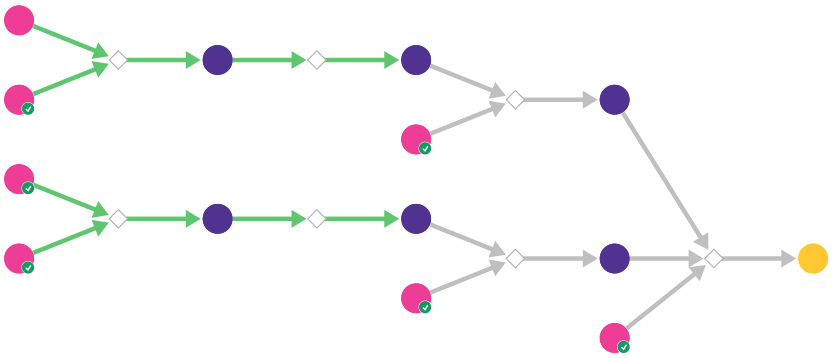
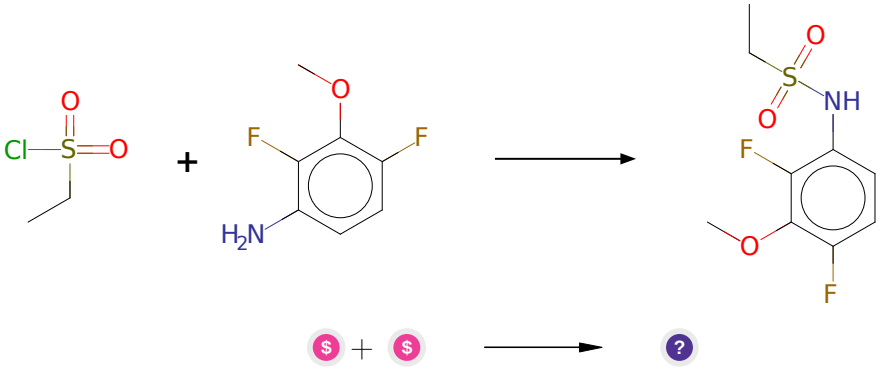


Figure 3: Outline of path 3

2.3.1 N-Sulfonylation



Substrates:

1. Ethanesulfonyl chloride - *available at Sigma-Aldrich*
2. 2,4-Difluoro-3-methoxyaniline 1g pack - *available at Sigma-Aldrich*

Products:

1. CCS(=O)(=O)Nc1ccc(F)c(OC)c1F

Typical conditions: THF.rt

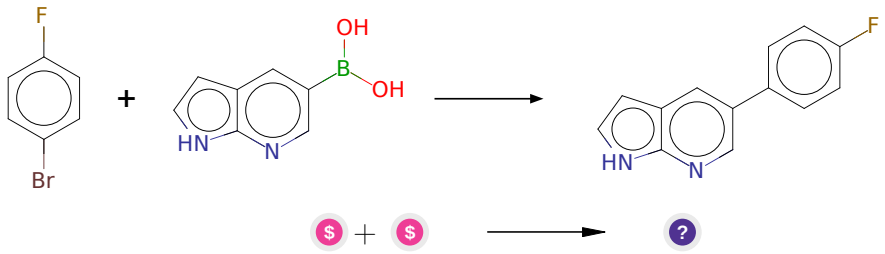
Protections: none

Yield: good

Reference: *10.1055/s-0029-1217565* and *10.1002/(SICI)1099-0690(199806)1998:6<945::AID-EJOC945>3.0.CO;2-3* and *10.1055/s-2001-14567* and *10.1016/j.bmc.2014.07.022*

Retrosynthesis ID: 14718

2.3.2 Suzuki coupling of arylboronic acids with aryl bromides



Substrates:

1. (1H-Pyrrolo[2,3-b]pyridin-5-yl)boronic acid - *Combi-Blocks*
2. 4-Bromofluorobenzene - *available at Sigma-Aldrich*

Products:

1. Fc1ccc(-c2cnc3[nH]ccc3c2)cc1

Typical conditions: Pd catalyst.base.solvent

Protections: none

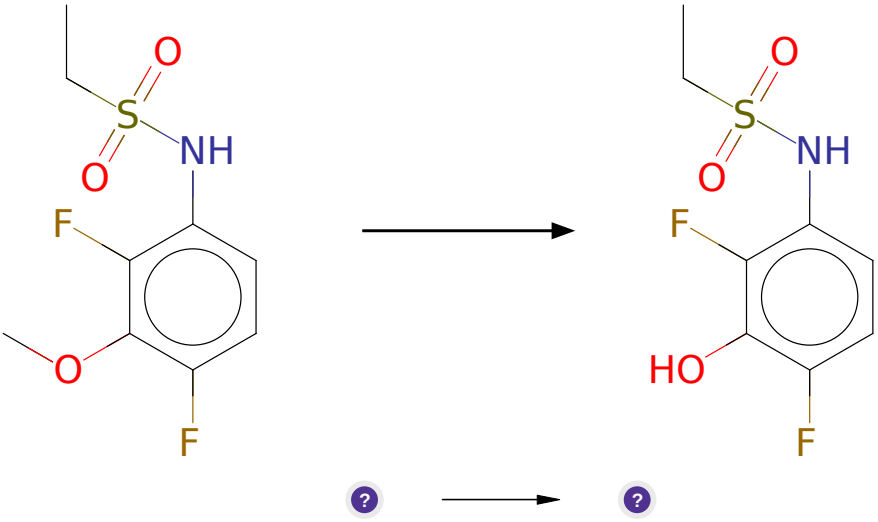
Yield: good

Reference: *10.1021/cr00039a007* and *10.1007/3418_2012_32* and *10.1021/cr0505268* and *10.1016/j.jfluchem.2016.01.018* and *10.1039/C3CS60197H*

and *10.1016/j.ejmech.2018.08.092* and *10.1038/s41929-020-00564-z* (metal-free coupling)

Retrosynthesis ID: 25150

2.3.3 Demethylation of Phenols



Substrates:

1. CCS(=O)(=O)Nc1ccc(F)c(OC)c1F

Products:

1. CCS(=O)(=O)Nc1ccc(F)c(O)c1F

Typical conditions: BBr3.CH2Cl2

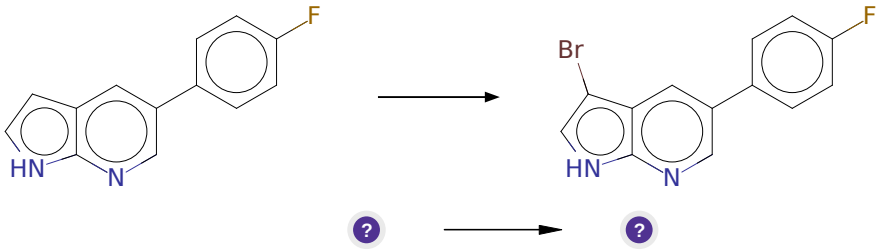
Protections: none

Yield: moderate

Reference: DOI: *10.1021/ja00105a021* and *10.1021/jm00176a011* and *10.1021/jm970277i* and *10.1021/ja0106164* and Patent: US2010/16298, 2010, A1, page 185

Retrosynthesis ID: 10011837

2.3.4 Bromination of aromatic compounds



Substrates:

1. Fc1ccc(-c2cnc3[nH]ccc3c2)cc1

Products:

1. Fc1ccc(-c2cnc3[nH]cc(Br)c3c2)cc1

Typical conditions: Br2.Fe

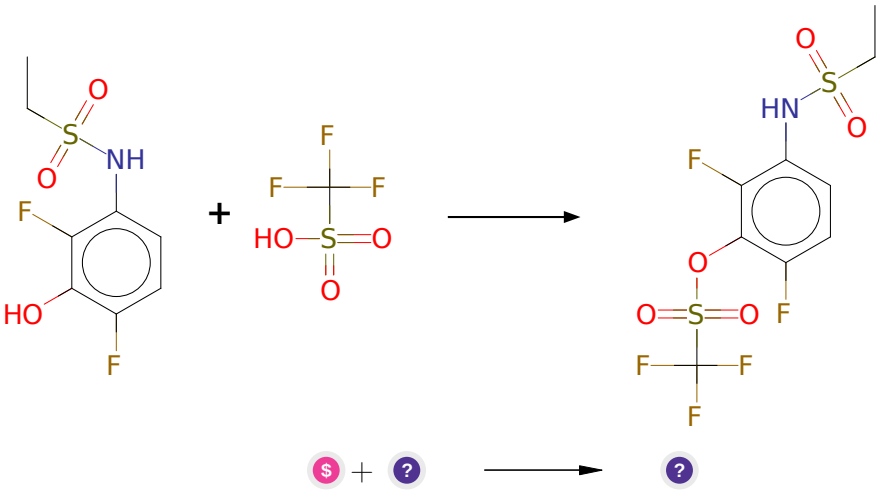
Protections: none

Yield: good

Reference: *10.1021/acs.accounts.6b00120*

Retrosynthesis ID: 7777000

2.3.5 Synthesis of aryl triflates



Substrates:

1. TFMSA - *available at Sigma-Aldrich*

2. CCS(=O)(=O)Nc1ccc(F)c(O)c1F

Products:

1. CCS(=O)(=O)Nc1ccc(F)c(OS(=O)(=O)C(F)(F)F)c1F

Typical conditions: Tf2O. pyridine, dmap or other base

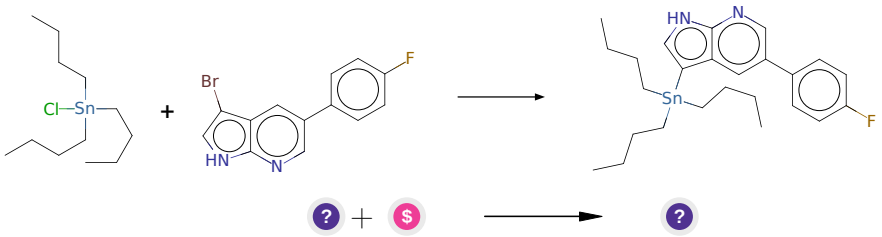
Protections: none

Yield: moderate

Reference: *10.1021/jacs.9b05224* (Supplementary, page S39) and *10.1021/jo971377z* and *10.1021/jo035309q* (suppelementary, page S6)

Retrosynthesis ID: 11335

2.3.6 Synthesis of arylstannanes



Substrates:

1. Fc1ccc(-c2cnc3[nH]cc(Br)c3c2)cc1
2. Tributylchlorotin - *available at Sigma-Aldrich*

Products:

1. CCCC[Sn](CCCC)(CCCC)c1c[nH]c2ncc(-c3ccc(F)cc3)cc12

Typical conditions: 1.nBuLi.2.ClSiR3

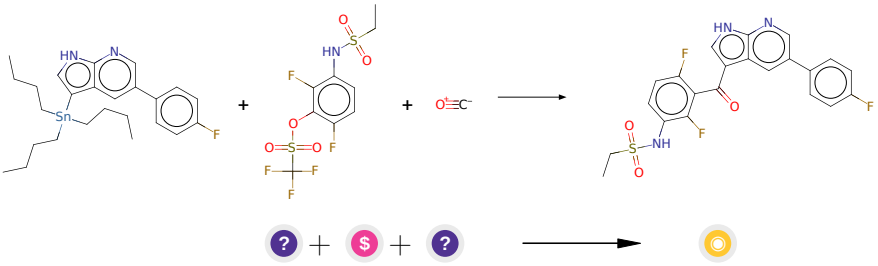
Protections: none

Yield: good

Reference: *10.1016/j.dyepig.2012.11.014*

Retrosynthesis ID: 5368

2.3.7 Stille Carbonylative Cross-Coupling



Substrates:

1. CCS(=O)(=O)Nc1ccc(F)c(OS(=O)(=O)C(F)(F)F)c1F
2. Carbon monoxide - *available at Sigma-Aldrich*
3. CCCC[Sn](CCCC)(CCCC)c1c[nH]c2ncc(-c3ccc(F)cc3)cc12

Products:

1. CCS(=O)(=O)Nc1ccc(F)c(C(=O)c2c[nH]c3ncc(-c4ccc(F)cc4)cc23)c1F

Typical conditions: Pd(0) complex

Protections: none

Yield: moderate

Reference: DOI: *10.1002/anie.198605081*

Retrosynthesis ID: 245570