

Paths of analysis*

(re)Analysis 1381 - No Filter - Rerun

Synthia

November 28, 2023

1 Analysis parameters

Analysis type: Automatic Retrosynthesis

Saved Configuration: General

Rules: Expert-Coded Rules

Published Reactions: SPRESI by DeepMatter, USPTO, Enzyme-Catalyzed Reactions

Filters: none selected

Max. paths returned: 50

Max. iterations: 2000

Commercial:

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

Published:

1. Max. molecular weight - 1000 g/mol
2. Popularity - 15

My Stockroom:

1. Max. molecular weight - 1000 g/mol

Shorter paths: no

Pathway linearity: COMBO

Protecting groups: BALANCED

*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.

Reaction scoring formula: $\text{TUNNEL_COEF} * \text{FGI_COEF} * \text{STEP} * 20 + 100000 * (\text{FILTERS} + \text{CONFLICT} + \text{NON_SELECTIVITY}) + 40 * \text{PROTECT}$

Chemical scoring formula: $\text{SMALLER}^3, \text{SMALLER}^{1.5}$

Min. search width: 400

Max. reactions per product: 60

2 Paths

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

2.1 Path 1

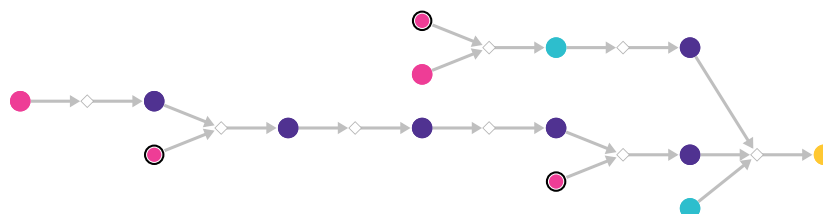
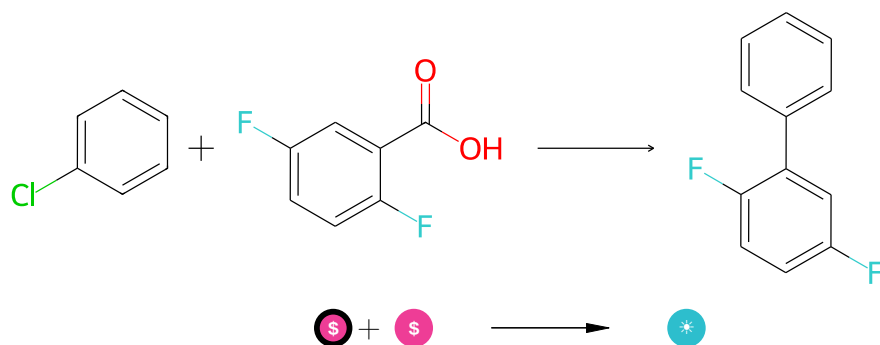


Figure 1: Outline of path 1

2.1.1 Decarboxylative cross-coupling



Substrates:

1. Chlorobenzene - *available at Sigma-Aldrich*
2. 2,5-Difluorobenzoic acid - *available at Sigma-Aldrich*

Products:

1. 2,5-Difluorobiphenyl

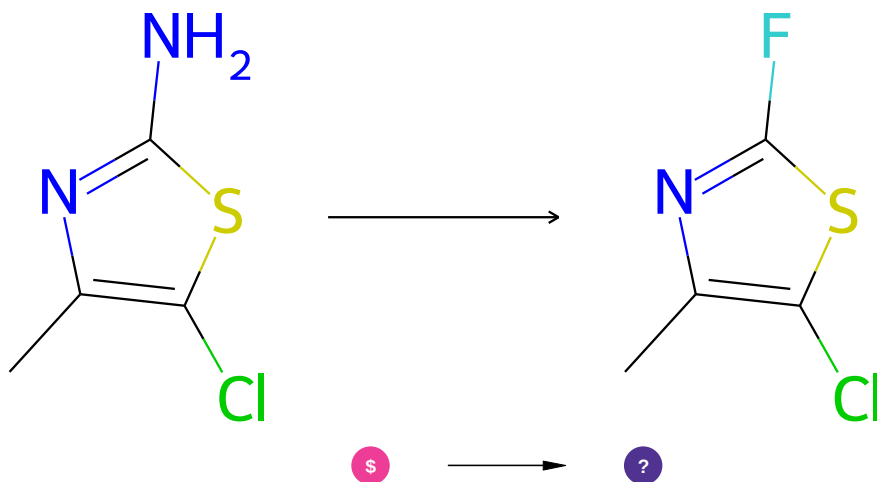
Typical conditions: eg. CuI.PdI2.ligand.K2CO3.NMP.MS.170 deg C

Protections: none

Reference: [10.1039/C1CS15093F](#) and [10.1002/anie.200800728](#) and [10.1021/ja068993+](#)

Retrosynthesis ID: 31019492

2.1.2 Balz-Schiemann Reaction



Substrates:

1. 2-Amino-5-chloro-4-methylthiazole - [available at Sigma-Aldrich](#)

Products:

1. Cc1nc(F)sc1Cl

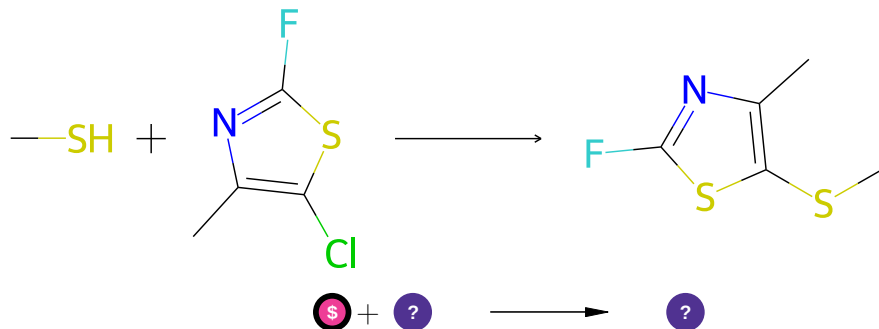
Typical conditions: NaNO2.HF-pyridine.-25 to 0C

Protections: none

Reference: [10.1021/jm100432w](#) and [10.1021/jm5008177](#) and [10.1021/ol401540k](#) and [10.1021/jm401551n](#) (main text and SI, page S8) and [10.1515/chempap-2016-0033](#) and [10.1021/jm0311442](#) and [10.1016/j.jfluchem.2007.03.012](#) and [10.1021/jo00185a023](#)

Retrosynthesis ID: 29906

2.1.3 Pd-catalyzed synthesis of aryl sulfides



Substrates:

1. Methanethiol - *available at Sigma-Aldrich*
2. Cc1nc(F)sc1Cl

Products:

1. CSc1sc(F)nc1C

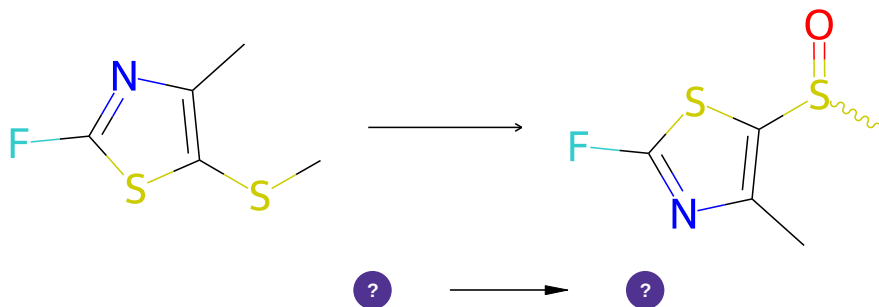
Typical conditions: Pd(OAc)2.tBuONa.DME.110C

Protections: none

Reference: [10.1021/ja0580340](#)

Retrosynthesis ID: 1299

2.1.4 Oxidation of sulfides to sulfoxides



Substrates:

1. CSc1sc(F)nc1C

Products:

1. Cc1nc(F)sc1S(C)=O

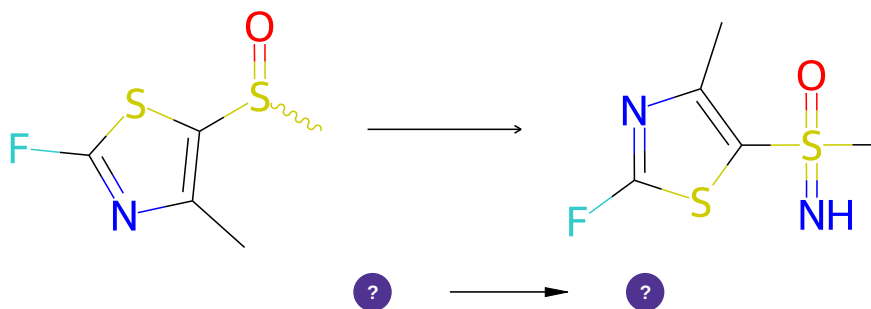
Typical conditions: TaC.H₂O₂.MeOH.45C

Protections: none

Reference: DOI: [10.1055/s-0029-1219947](https://doi.org/10.1055/s-0029-1219947) or DOI: [10.1055/s-2008-1067019](https://doi.org/10.1055/s-2008-1067019)

Retrosynthesis ID: 10584

2.1.5 Synthesis of NH-sulfoximines



Substrates:

1. Cc1nc(F)sc1S(C)=O

Products:

1. Cc1nc(F)sc1S(C)(=N)=O

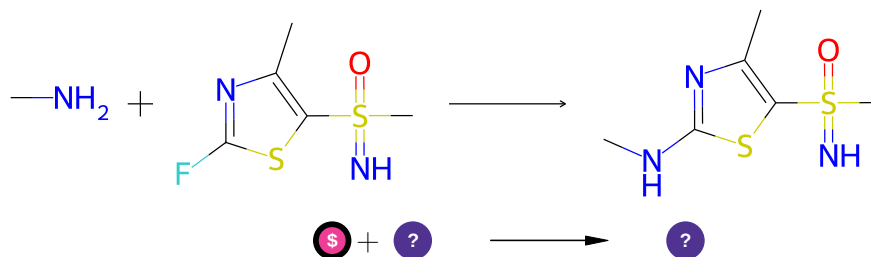
Typical conditions: NaN₃.Eaton's reagent.50C or FeSO₄.1,10-phen.NbzONH₂*TfOH.MeCN or H₂NCO₂NH₄.PhI(OAc)₂.MeOH

Protections: none

Reference: [10.1016/j.tetlet.2016.12.031](https://doi.org/10.1016/j.tetlet.2016.12.031) and [10.1002/anie.201710498](https://doi.org/10.1002/anie.201710498) and [10.1002/anie.201602320](https://doi.org/10.1002/anie.201602320) and [10.1055/s-0036-1590874](https://doi.org/10.1055/s-0036-1590874) and [10.1039/C7CC03386A](https://doi.org/10.1039/C7CC03386A)

Retrosynthesis ID: 31016630

2.1.6 Nucleophilic aromatic substitution



Substrates:

1. Methanamine - *available at Sigma-Aldrich*

2. Cc1nc(F)sc1S(C)(=N)=O

Products:

1. CNc1nc(C)c(S(C)(=N)=O)s1

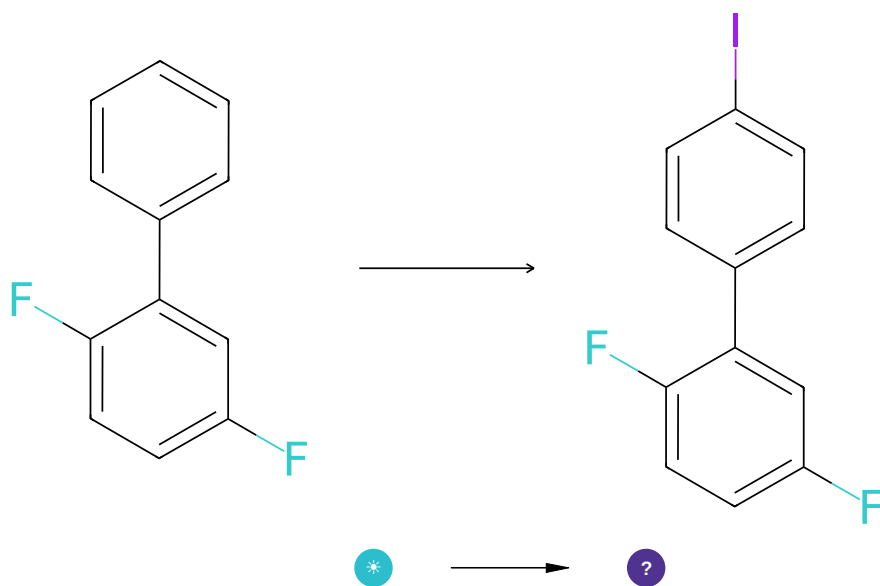
Typical conditions: Solvent

Protections: none

Reference: *10.1002/9781118093559.ch4*

Retrosynthesis ID: 49476

2.1.7 Iodination of aromatic compounds



Substrates:

1. 2,5-Difluorobiphenyl

Products:

1. Fc1ccc(F)c(-c2ccc(I)cc2)c1

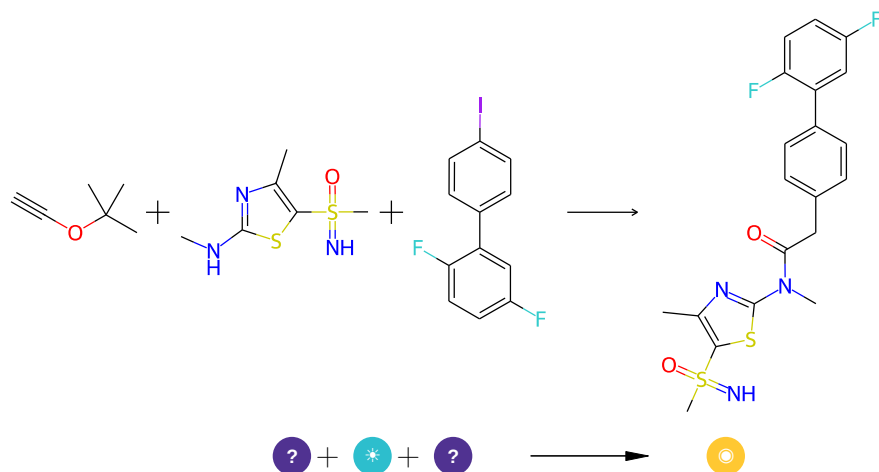
Typical conditions: I₂ or other iodinating agent e.g. NIS

Protections: none

Reference: DOI: [10.1039/C5SC00964B](https://doi.org/10.1039/C5SC00964B) and [10.1016/j.tetlet.2005.05.117](https://doi.org/10.1016/j.tetlet.2005.05.117) and [10.1007/s11178-005-0256-1](https://doi.org/10.1007/s11178-005-0256-1)

Retrosynthesis ID: 10697

2.1.8 Synthesis of amides from aryl iodides through ynoyl ethers



Substrates:

1. CNc1nc(C)c(S(C)(=N)=O)s1
2. Tert-butoxy-ethyne
3. Fc1ccc(F)c(-c2ccc(I)cc2)c1

Products:

1. Cc1nc(N(C)C(=O)Cc2ccc(-c3cc(F)ccc3F)cc2)sc1S(C)(=N)=O

Typical conditions: [Pd2(dba)3].PPh3.CuI.DIPEA.4A MS 2. amine.75C.toluene

Protections: none

Reference: DOI: [10.1002/anie.201405036](https://doi.org/10.1002/anie.201405036)

Retrosynthesis ID: 1678