

Paths of analysis*

(re)(re)(re)Analysis 1381 - Heterocycle

Synthia

November 28, 2023

1 Analysis parameters

Analysis type: Automatic Retrosynthesis

Rules: Expert-Coded Rules

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

Filters: Cut All Heterocycles

Max. paths returned: 50

Max. iterations: 2000

Commercial:

1. Max. molecular weight - 1000 g/mol
2. Max. price - 10 \$/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

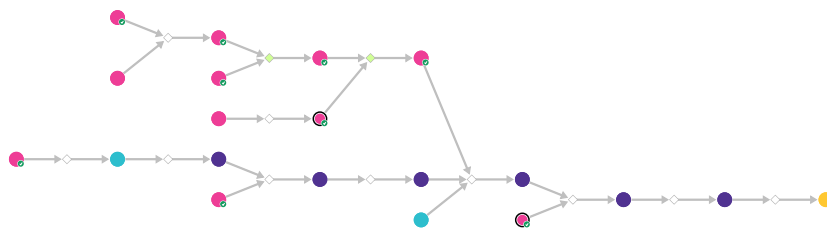
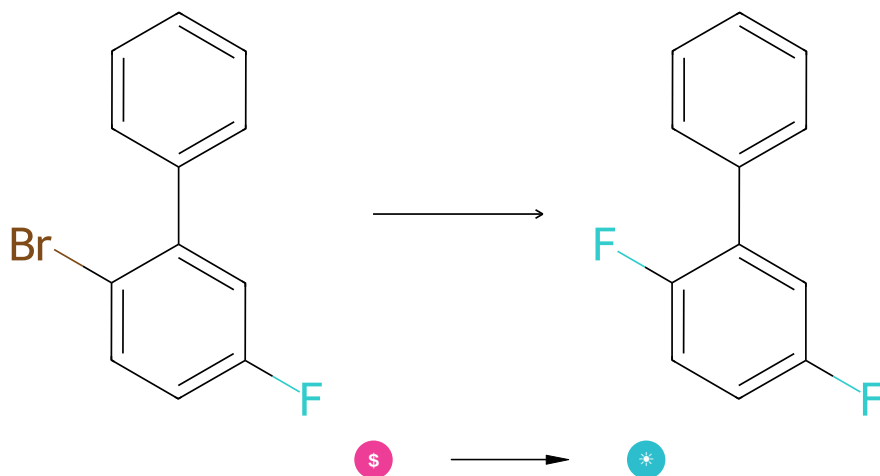


Figure 1: Outline of path 1

2.1.1 Synthesis of fluoroarenes



Substrates:

1. 2-Bromo-5-fluoro-1,1'-biphenyl - *available at Sigma-Aldrich*

Products:

1. 2,5-Difluorobiphenyl

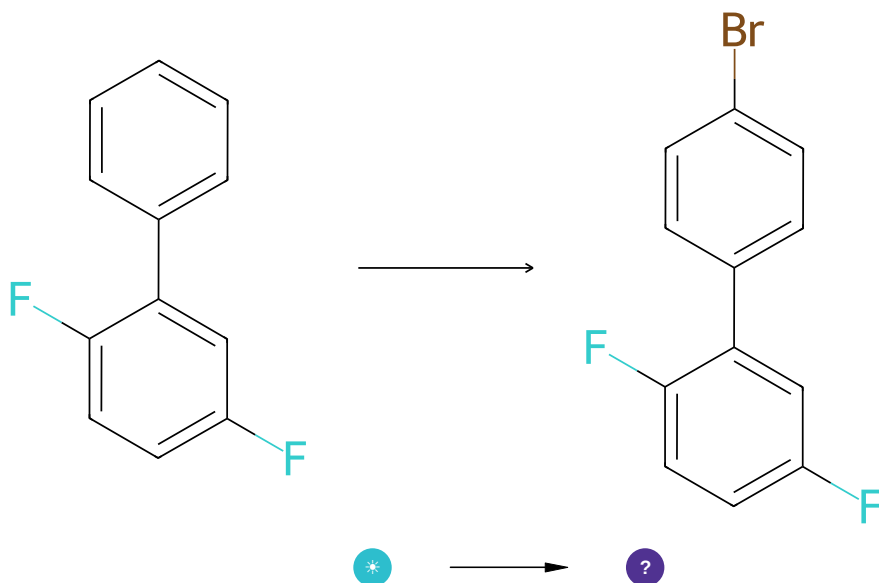
Typical conditions: 1.Mg(iPr)Cl 2.N-fluoro-N-(phenylsulfonyl)benzenesulfonamide.fluorinated naphthalene.DCM.25C or 1.Mg.LiCl.THF.DCM.0 to 50C 2.NFSI.fluorinated naphthalene.DCM.25C

Protections: none

Reference: *10.1055/s-0029-1218816* and *10.1002/anie.200905855*

Retrosynthesis ID: 10545

2.1.2 Bromination of aromatic compounds



Substrates:

1. 2,5-Difluorobiphenyl

Products:

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

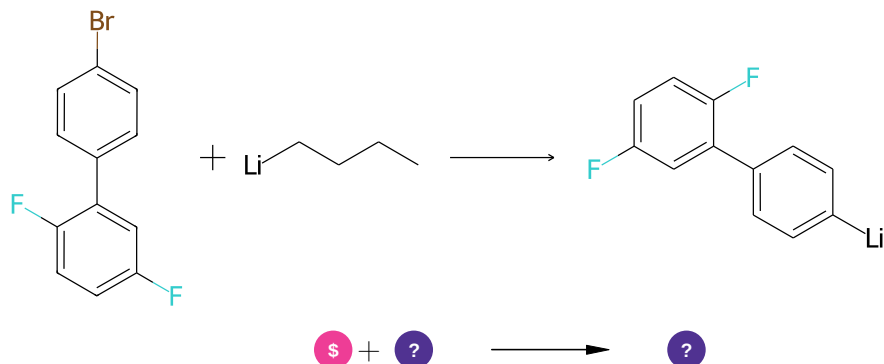
Typical conditions: Br₂.Fe

Protections: none

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

Retrosynthesis ID: 7777000

2.1.3 Br/Li exchange



Substrates:

1. n-BuLi - *available at Sigma-Aldrich*
2. Fc1ccc(F)c(-c2ccc(Br)cc2)c1

Products:

1. [Li]c1ccc(-c2cc(F)ccc2F)cc1

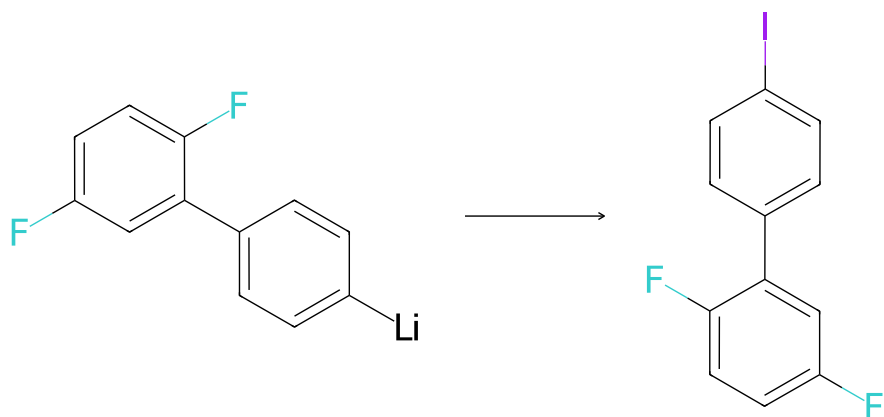
Typical conditions: nBuLi.or.tBuLi.THF.-78C

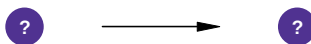
Protections: none

Reference: [10.1002/ejoc.201101490](#) and [10.1016/j.tet.2012.03.058](#)
and [10.1016/j.tetlet.2015.01.032](#) and [10.1021/ja0541175](#) and
[10.1016/j.tetlet.2016.06.123](#)

Retrosynthesis ID: 30672

2.1.4 Addition of electrophiles to lithiated arenes/heteroarenes





Substrates:

1. [Li]c1ccc(-c2cc(F)ccc2F)cc1

Products:

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

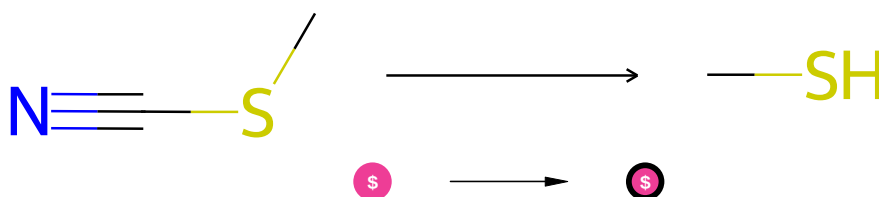
Typical conditions: Br or BrCH₂CH₂Br or I₂

Protections: none

Reference: [10.1039/C7CC09818A](#) and [10.1021/acs.joc.7b03210](#)
and [10.1002/anie.201711990](#) (SI) and [10.1002/ejoc.201701142](#) and
[10.1002/ejoc.201701142](#)

Retrosynthesis ID: 10019523

2.1.5 Reduction of thiocyanates to thiols



Substrates:

1. Methyl thiocyanate

Products:

1. Methanethiol - *available at Sigma-Aldrich*

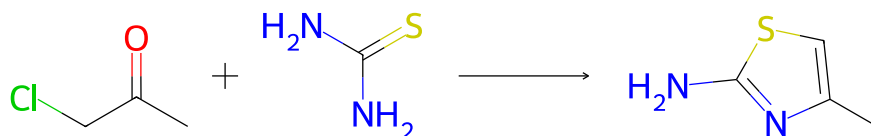
Typical conditions: NaBH₄.EtOH

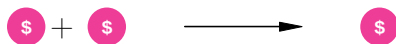
Protections: none

Reference: [10.1021/jm100213c](#) p. 4864, 4873 and [10.1016/j.ejmech.2014.09.071](#)
p. 308, 310

Retrosynthesis ID: 50811

2.1.6 Synthesis of thiazoles from thioureas





Substrates:

1. Chloroacetone - *available at Sigma-Aldrich*
2. Thiourea

Products:

1. 2-Amino-4-methylthiazole - *available at Sigma-Aldrich*

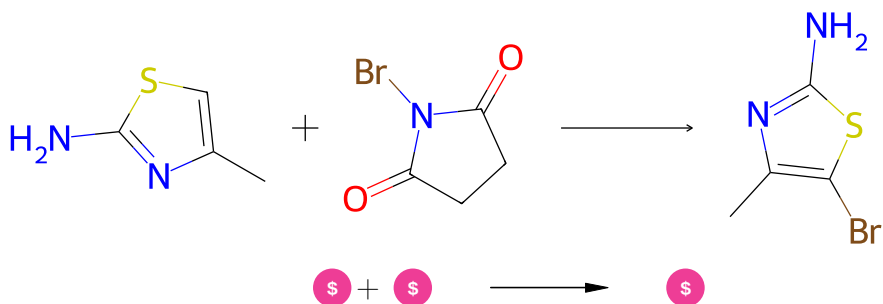
Typical conditions: ethanol.80C

Protections: none

Reference: DOI:[10.1021/jo00103a021](https://doi.org/10.1021/jo00103a021)

Retrosynthesis ID: 4

2.1.7 Published reaction



Substrates:

1. 2-Amino-4-methylthiazole - *available at Sigma-Aldrich*
2. N-Bromosuccinimide - *available at Sigma-Aldrich*

Products:

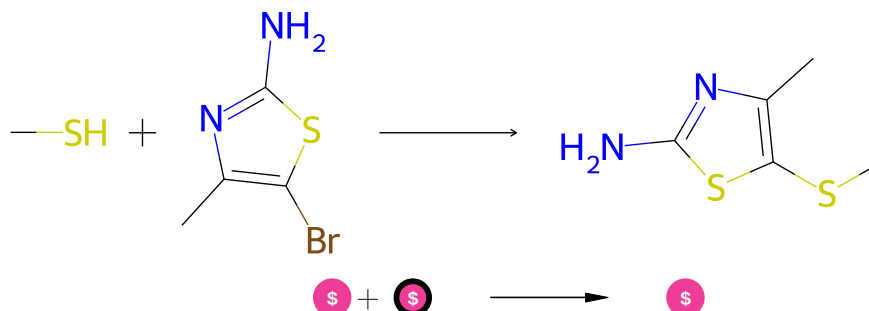
1. 5-Bromo-4-methyl-thiazol-2-amine - *available at Sigma-Aldrich*

Protections: none

Reference: US05369107

Retrosynthesis ID: 6299162

2.1.8 Published reaction



Substrates:

1. 5-Bromo-4-methyl-thiazol-2-amine - *available at Sigma-Aldrich*
2. Methanethiol - *available at Sigma-Aldrich*

Products:

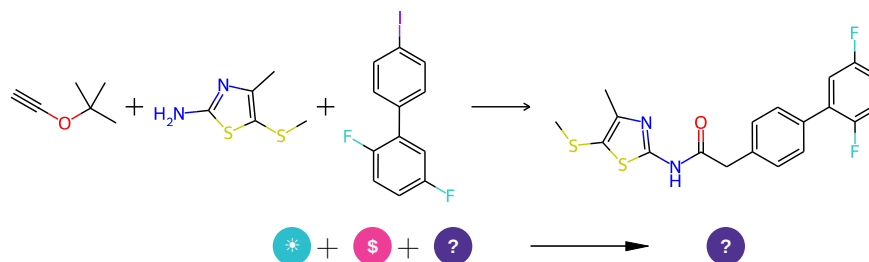
1. 4-Methyl-5-(methylsulfanyl)-1,3-thiazol-2-amine - *available at Sigma-Aldrich*

Protections: none

Reference: US20090143448A1

Retrosynthesis ID: 8454157

2.1.9 Synthesis of amides from aryl iodides through ynol ethers



Substrates:

1. Tert-butoxy-ethyne
2. 4-Methyl-5-(methylsulfanyl)-1,3-thiazol-2-amine - *available at Sigma-Aldrich*
3. Fc1ccc(F)c(-c2ccc(I)cc2)c1

Products:

1. CSc1sc(NC(=O)Cc2ccc(-c3cc(F)ccc3F)cc2)nc1C

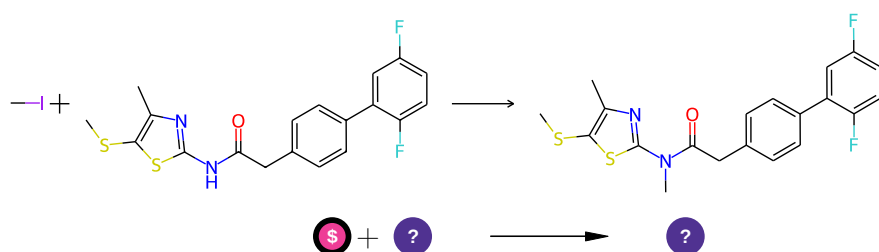
Typical conditions: [Pd2(dba)3].PPh3.CuI.DIPEA.4A MS 2.
amine.75°C.toluene

Protections: none

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

Retrosynthesis ID: 1679

2.1.10 N-alkylation of amides



Substrates:

1. Iodomethane - [available at Sigma-Aldrich](#)
2. CSc1sc(NC(=O)Cc2ccc(-c3cc(F)ccc3F)cc2)nc1C

Products:

1. CSc1sc(N(C)C(=O)Cc2ccc(-c3cc(F)ccc3F)cc2)nc1C

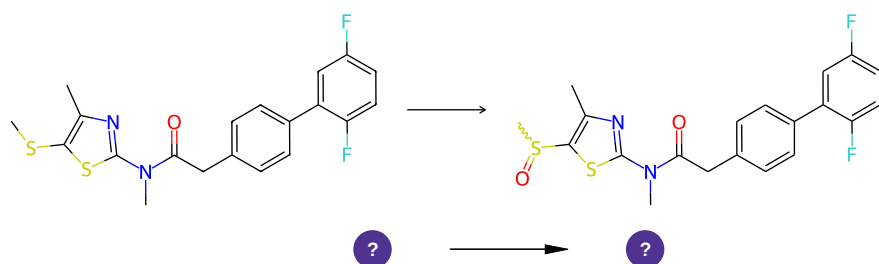
Typical conditions: NaH.DMF

Protections: none

Reference: DOI: [10.1016/j.bmc.2014.03.007](https://doi.org/10.1016/j.bmc.2014.03.007) and [10.1016/j.tetlet.2008.10.057](https://doi.org/10.1016/j.tetlet.2008.10.057)

Retrosynthesis ID: 8841

2.1.11 Oxidation of sulfides to sulfoxides



Substrates:

1. CSc1sc(N(C)C(=O)Cc2ccc(-c3cc(F)ccc3F)cc2)nc1C

Products:

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

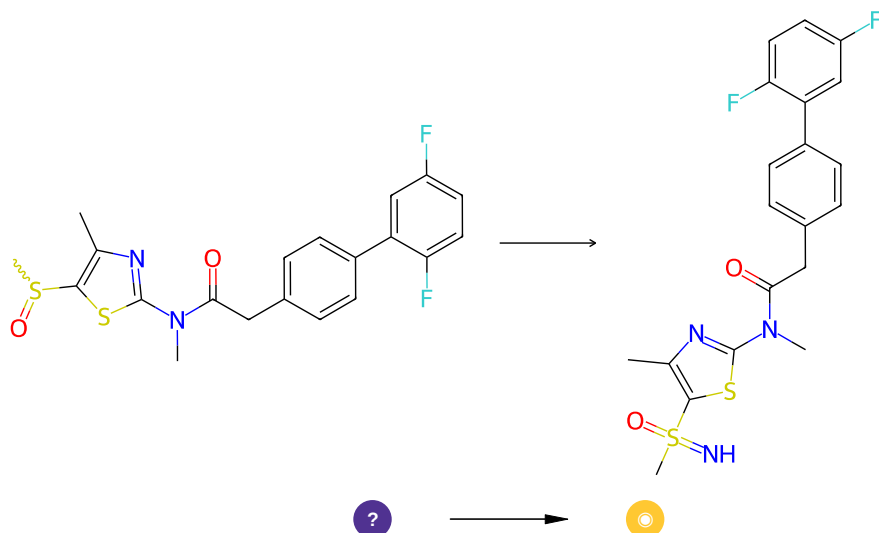
Typical conditions: TaC.H₂O₂.MeOH.45C

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

2.1.12 Synthesis of NH-sulfoximines



Substrates:

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

Products:

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