Paths of analysis*

C66

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

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

2.1 Path 1

Score: 133.42

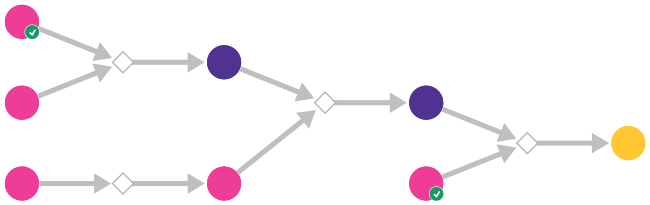
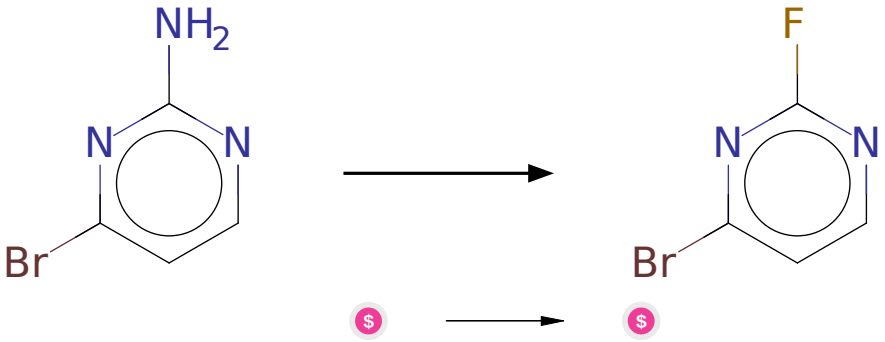


Figure 1: Outline of path 1

2.1.1 Balz-Schiemann Reaction



Substrates:

1. 4-Bromopyrimidin-2-amine - *Combi-Blocks*

Products:

1. 4-Bromo-2-fluoropyrimidine - *Enamine*

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

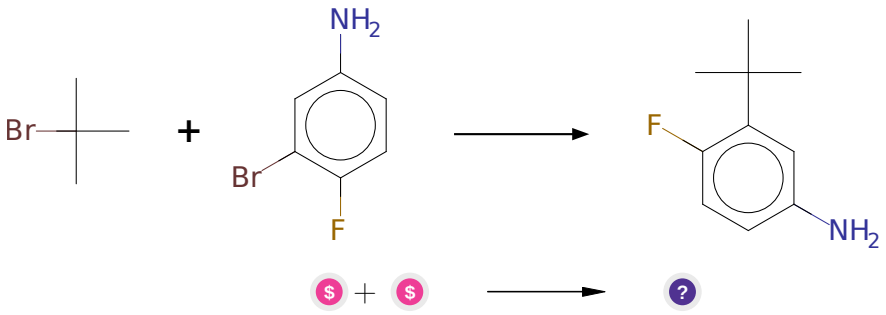
Protections: none

Yield: moderate

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

2.1.2 Photoredox Cross-Electrophile Coupling of Unactivated Alkyl Bromides



Substrates:

1. tert-Butyl bromide - *available at Sigma-Aldrich*
2. 3-Bromo-4-fluoroaniline - *Combi-Blocks*

Products:

1. CC(C)(C)c1cc(N)ccc1F

Typical conditions: [Ir]-photocat.[Ni]-cat.TTMSS.base.blue light

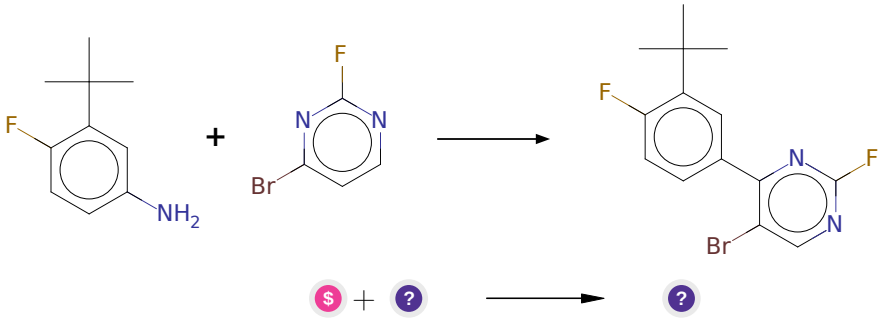
Protections: none

Yield: good

Reference: *10.1021/jacs.6b04818* and *10.1016/j.bbrc.2020.04.028* and *10.1021/acsmedchemlett.8b00183*

Retrosynthesis ID: 31016943

2.1.3 Meerwein coupling of diazonium salt with heteroaryl



Substrates:

1. 4-Bromo-2-fluoropyrimidine - *Enamine*
2. CC(C)(C)c1cc(N)ccc1F

Products:

1. CC(C)(C)c1cc(-c2nc(F)ncc2Br)ccc1F

Typical conditions: 1) HCl.NaNO2 2) [Ru(bpy)3Cl2]*6H2O.45W bulb.H2O.rt

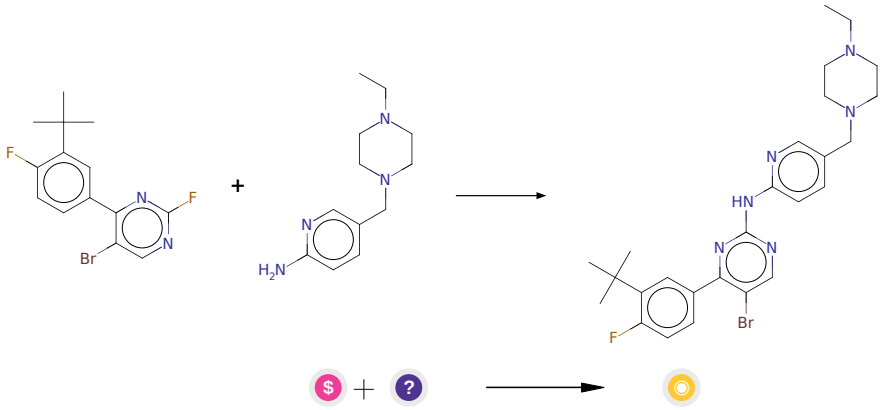
Protections: none

Yield: moderate

Reference: *10.1002/chem.201304120*

Retrosynthesis ID: 10001815

2.1.4 Nucleophilic aromatic substitution



Substrates:

1. 5-((4-Ethylpiperazin-1-yl)methyl)pyridin-2-amine - *available at Sigma-Aldrich*
2. CC(C)(C)c1cc(-c2nc(F)ncc2Br)ccc1F

Products:

1. CCN1CCN(Cc2ccc(Nc3ncc(Br)c(-c4ccc(F)c(C(C)(C)C)c4)n3)nc2)CC1

Typical conditions: Solvent

Protections: none

Yield: good

Reference: *10.1002/9781118093559.ch4*

Retrosynthesis ID: 49476

2.2 Path 2

Score: `185.81`

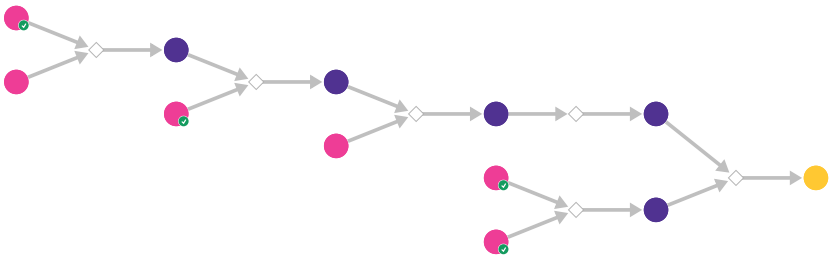
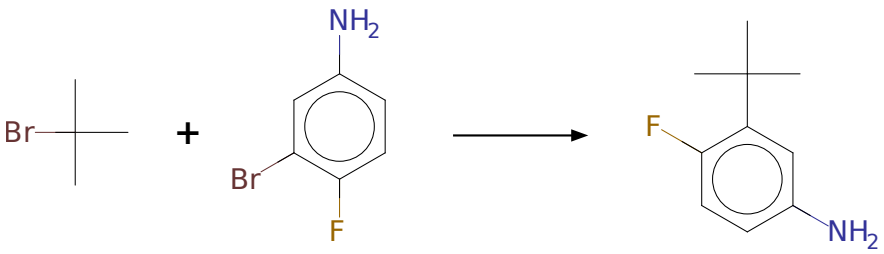
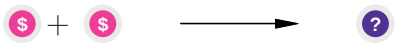


Figure 2: Outline of path 2

2.2.1 Photoredox Cross-Electrophile Coupling of Unactivated Alkyl Bromides





Substrates:

1. tert-Butyl bromide - *available at Sigma-Aldrich*
2. 3-Bromo-4-fluoroaniline - *Combi-Blocks*

Products:

1. CC(C)(C)c1cc(N)ccc1F

Typical conditions: [Ir]-photocat.[Ni]-cat.TTMSS.base.blue light

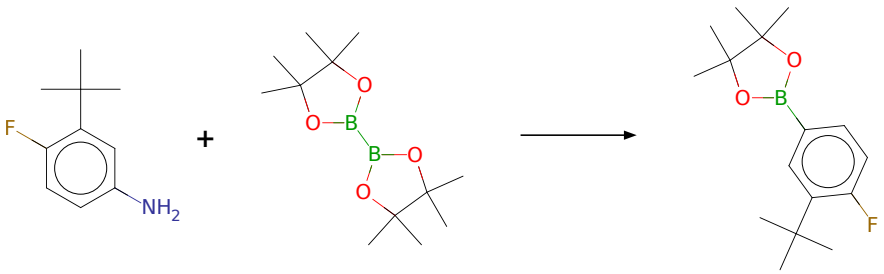
Protections: none

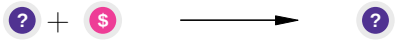
Yield: good

Reference: *10.1021/jacs.6b04818* and *10.1016/j.bbrc.2020.04.028* and *10.1021/acsmedchemlett.8b00183*

Retrosynthesis ID: 31016943

2.2.2 Synthesis of boronic ester derivatives from amines





Substrates:

1. CC(C)(C)c1cc(N)ccc1F
2. Bis(pinacolato)diboron - *available at Sigma-Aldrich*

Products:

1. CC(C)(C)c1cc(B2OC(C)(C)C(C)(C)O2)ccc1F

Typical conditions: eg. HCl. t-BuONO. 0C or photoredox condition

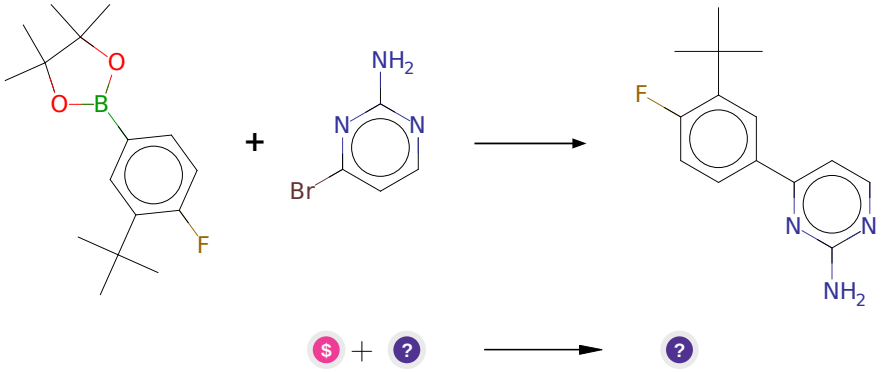
Protections: none

Yield: good

Reference: *10.1021/acs.accounts.7b00566* and *10.1016/j.tetlet.2016.02.097* and *10.1002/anie.200905824* and *10.3184/174751918X15362432558247* and *10.1055/s-0031-1290960* and *10.1016/j.tetlet.2017.08.060* and *10.1021/jo3018878*

Retrosynthesis ID: 2205

2.2.3 Suzuki coupling of arylboronic acids pinacol esters with aryl bromides



Substrates:

1. 4-Bromopyrimidin-2-amine - *Combi-Blocks*
2. CC(C)(C)c1cc(B2OC(C)(C)C(C)(C)O2)ccc1F

Products:

1. CC(C)(C)c1cc(-c2ccnc(N)n2)ccc1F

Typical conditions: Pd catalyst.base.solvent

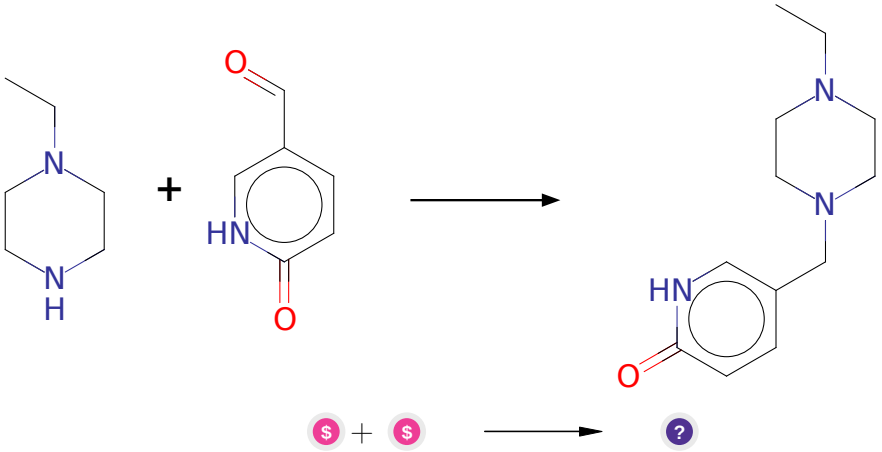
Protections: none

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*

Retrosynthesis ID: 25153

2.2.4 Reductive Amination of Aldehydes with Secondary Amines



Substrates:

1. 6-Oxo-1,6-dihydropyridine-3-carbaldehyde - *available at Sigma-Aldrich*
2. 1-Ethylpiperazine - *available at Sigma-Aldrich*

Products:

1. CCN1CCN(Cc2ccc(=O)[nH]c2)CC1

Typical conditions: NaBH(OAc)3 or NaBH3CN

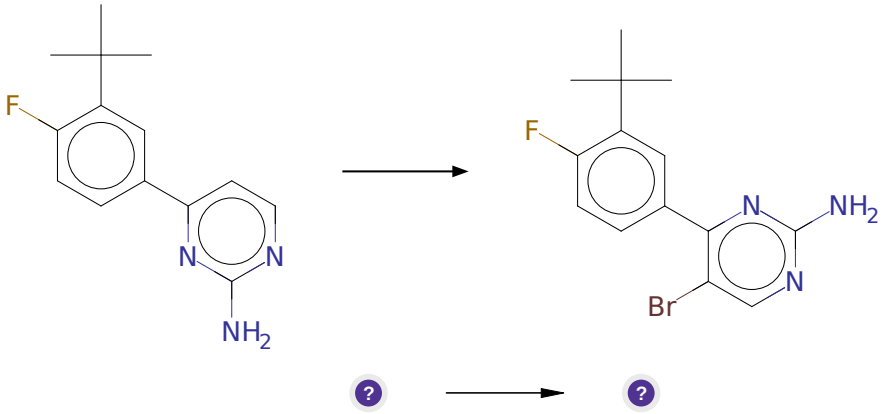
Protections: none

Yield: good

Reference: DOI: *10.1021/jo960057x* and *10.1021/jm7009292* and *10.1073/pnas.1405685111* and *10.1002/ejoc.201101063* and *10.1038/ja.2017.61* and *10.1021/jm4013906*

Retrosynthesis ID: 10019705

2.2.5 Bromination of aromatic compounds



Substrates:

1. CC(C)(C)c1cc(-c2ccnc(N)n2)ccc1F

Products:

1. CC(C)(C)c1cc(-c2nc(N)ncc2Br)ccc1F

Typical conditions: Br2.Fe

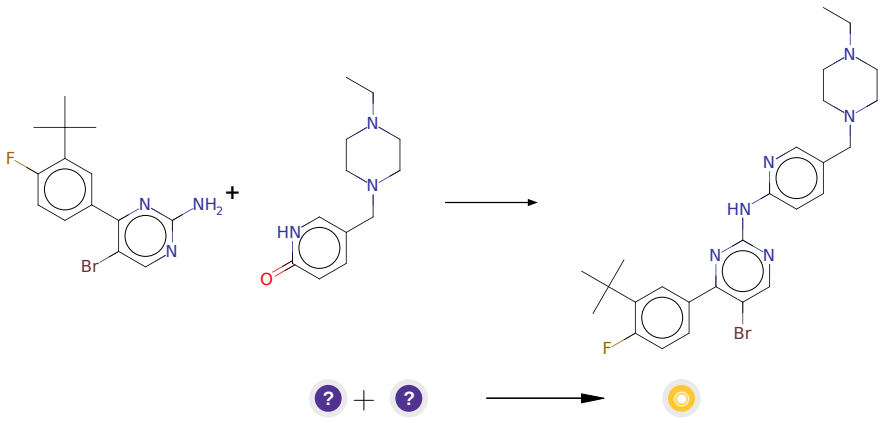
Protections: none

Yield: good

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

Retrosynthesis ID: 7777000

2.2.6 Amination of pyridones



Substrates:

1. CC(C)(C)c1cc(-c2nc(N)ncc2Br)ccc1F
2. CCN1CCN(Cc2ccc(=O)[nH]c2)CC1

Products:

1. CCN1CCN(Cc2ccc(Nc3ncc(Br)c(-c4ccc(F)c(C(C)(C)C)c4)n3)nc2)CC1

Typical conditions: 1.PCl5.2.amine

Protections: none

Yield: moderate

Reference: *10.1021/jm300780p* AND *10.3390/molecules170910902* AND *10.1021/jm00392a017*

Retrosynthesis ID: 14886