

Paths of analysis*

BMK2

Synthia

October 10, 2022

1 Analysis parameters

Analysis type: Automatic Retrosynthesis

Rules: none selected

Filters: Exclude Diastereoselective reactions, Tunnels, FGI, FGI with protections

Max. paths returned: 50

Max. iterations: 2000

Commercial:

1. Max. molecular weight - 1000 g/mol
2. Max. price - 1500 \$/g

Published:

1. Max. molecular weight - 1000 g/mol
2. Popularity - 5

My Stockroom:

1. Max. molecular weight - 1000 g/mol

Reaction scoring formula: $TUNNEL_COEF * FGI_COEF * STEP * 20 + 1000 * (CONFLICT + NON_SELECTIVITY + FILTERS + PROTECT)$

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

Min. search width: 400

Max. reactions per product: 60

*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.

Strategies: none selected

FGI Coeff: 0

Tunnels Coeff: 0

JSON Parameters: {}

2 Paths

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

2.1 Path 1

Score: 109.06

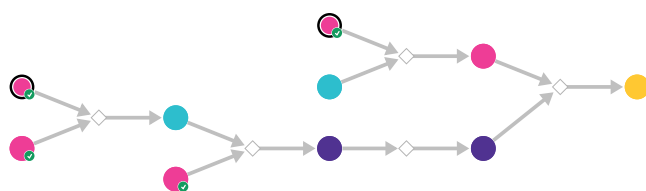
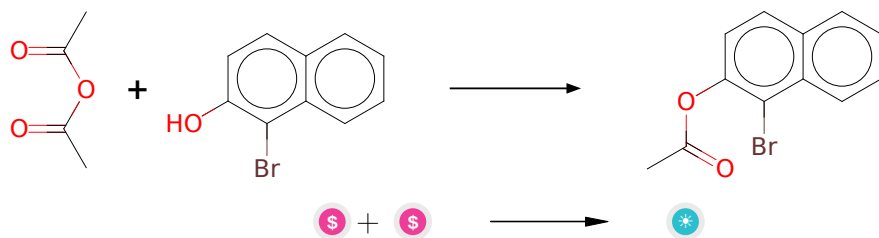


Figure 1: Outline of path 1

2.1.1 Cu(OTf)₂ catalyzed acylation of phenols



Substrates:

1. Acetic anhydride - *available at Sigma-Aldrich*
2. 1-Bromo-2-naphthol - *available at Sigma-Aldrich*

Products:

1. acetic acid-(1-bromo-[2]naphthyl ester)

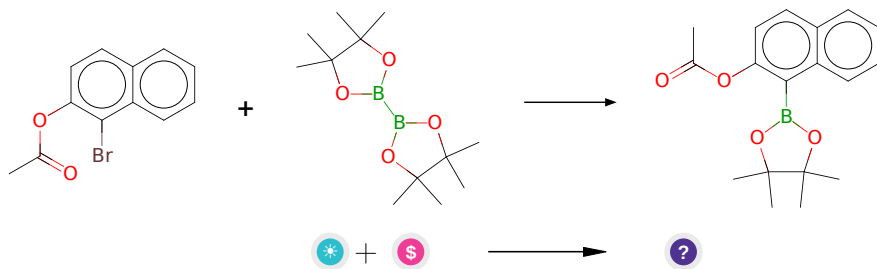
Typical conditions: Cu(II).triflate.DCM.RT

Protections: none

Reference: DOI: [10.1016/S0040-4020\(01\)01229-7](https://doi.org/10.1016/S0040-4020(01)01229-7)

Retrosynthesis ID: 11601

2.1.2 Miyaura Borylation



Substrates:

1. acetic acid-(1-bromo-[2]naphthyl ester)
2. Bis(pinacolato)diboron - *available at Sigma-Aldrich*

Products:

1. CC(=O)Oc1ccc2ccccc2c1B1OC(C)(C)C(C)(C)O1

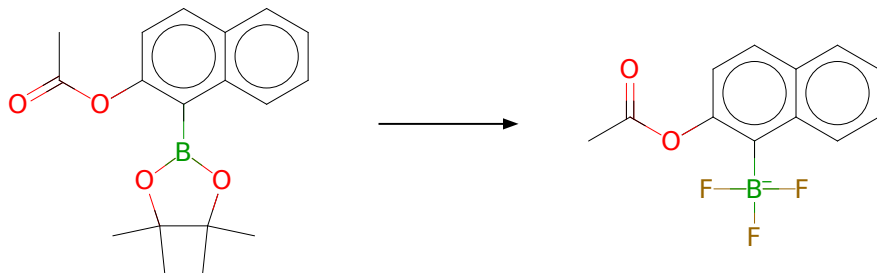
Typical conditions: PdCl₂(dppf)2.KOAc.Dioxane or DMSO.80oC

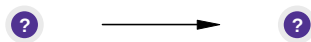
Protections: none

Reference: DOI: [10.1021/ja509198w](https://doi.org/10.1021/ja509198w) and [10.1021/jm800832q](https://doi.org/10.1021/jm800832q) and [10.1021/jm401499g](https://doi.org/10.1021/jm401499g) and [10.1039/C1CC12020D](https://doi.org/10.1039/C1CC12020D) (SI, page S4) and [10.1055/s-0035-1561355](https://doi.org/10.1055/s-0035-1561355) (SI, page 12) and [10.1021/ol2000556](https://doi.org/10.1021/ol2000556) and [10.1021/jo102070e](https://doi.org/10.1021/jo102070e) and WO2010/75270 A1, 2010 (page 37)

Retrosynthesis ID: 1209

2.1.3 Synthesis of organotrifluoroborate salts in mild conditions





Substrates:

1. CC(=O)Oc1ccc2ccccc2c1B1OC(C)(C)C(C)(C)O1

Products:

1. CC(=O)Oc1ccc2ccccc2c1[B-](F)(F)F

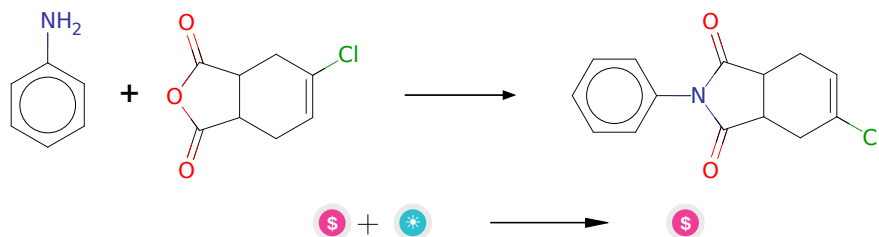
Typical conditions: KF.tartaric acid.CH₃CN.THF.H₂O.rt

Protections: none

Reference: DOI: [10.1002/anie.201203930](https://doi.org/10.1002/anie.201203930)

Retrosynthesis ID: 6072

2.1.4 Synthesis of imides from anhydrides



Substrates:

1. Aniline - *available at Sigma-Aldrich*
2. 4-chloro-1,2,3,6-tetrahydro-phthalic anhydride

Products:

1. 5-chloro-2-phenyl-3a,4,7a-tetrahydro-isoindole-1,3-dione - *Vitas-MLaboratory*

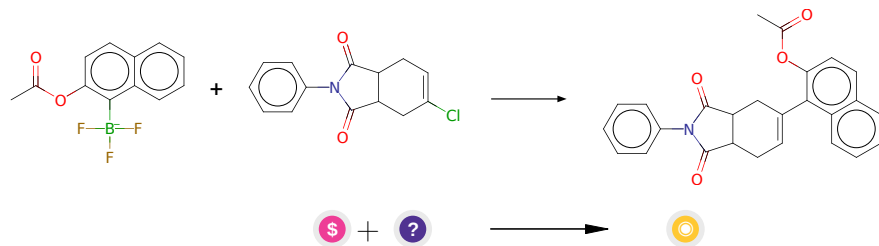
Typical conditions: AcOH

Protections: none

Reference: [10.1080/00397910802474966](https://doi.org/10.1080/00397910802474966) and [10.1021/ja9024676](https://doi.org/10.1021/ja9024676) (SI) and [10.1002/ejoc.201402202](https://doi.org/10.1002/ejoc.201402202)

Retrosynthesis ID: 8178

2.1.5 Suzuki Coupling of aryltrifluoroborates with alkenyl chlorides



Substrates:

1. 5-chloro-2-phenyl-3a,4,7,7a-tetrahydro-isindole-1,3-dione - *Vitas-MLaboratory*
2. CC(=O)Oc1ccc2ccccc2c1[B-](F)(F)F

Products:

1. CC(=O)Oc1ccc2ccccc2c1C1=CCC2C(=O)N(c3ccccc3)C(=O)C2C1

Typical conditions: PdCl₂(dppf).K₂CO₃.toluene.reflux

Protections: none

Reference: [10.1002/chem.200900425](https://doi.org/10.1002/chem.200900425) and [10.1016/j.tetlet.2014.10.078](https://doi.org/10.1016/j.tetlet.2014.10.078)

Retrosynthesis ID: 10034105

2.2 Path 2

Score: 118.83

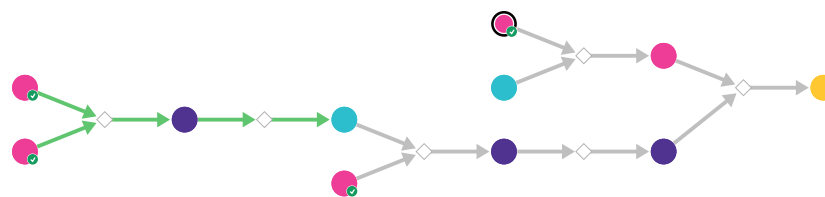
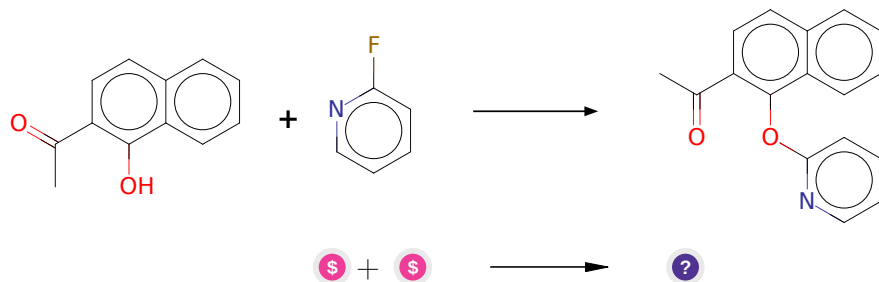


Figure 2: Outline of path 2

2.2.1 Nucleophilic aromatic substitution



Substrates:

1. 2-Fluoropyridine - *available at Sigma-Aldrich*
2. 2-Acetyl-1-naphthol - *available at Sigma-Aldrich*

Products:

1. CC(=O)c1ccc2ccccc2c1Oc1ccccn1

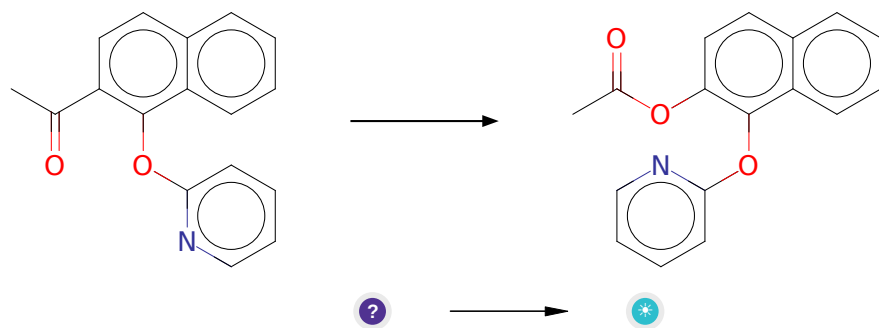
Typical conditions: NaH.THF.0-80 C or K₂CO₃.DMF.110 C

Protections: none

Reference: [10.1016/j.tetlet.2015.10.008](#) p. 6479, 6483 and [10.1016/j.ejmech.2016.06.056](#) p. 82, 85

Retrosynthesis ID: 49475

2.2.2 Bayer-Villiger oxidation



Substrates:

1. CC(=O)c1ccc2ccccc2c1Oc1ccccn1

Products:

1. C₁₇H₁₃NO₃

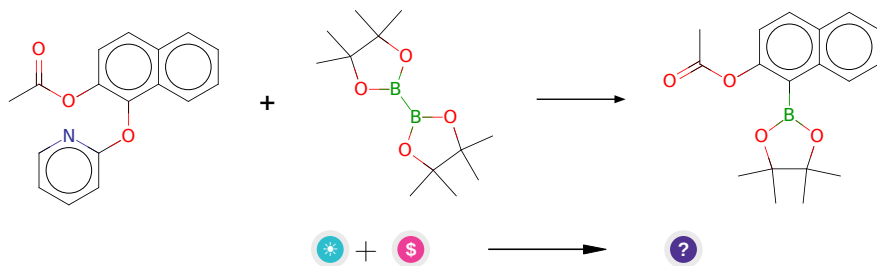
Typical conditions: mCPBA.NaHCO₃.DCM

Protections: none

Reference: [10.1021/ol702571c](#) and [10.1021/ja00272a051](#) and [10.1080/00397910801997835](#)

Retrosynthesis ID: 4811

2.2.3 Rh-catalyzed borylation of aryl pyridyl ethers



Substrates:

1. C₁₇H₁₃NO₃
2. Bis(pinacolato)diboron - [available at Sigma-Aldrich](#)

Products:

1. CC(=O)Oc1ccc2ccccc2c1B1OC(C)(C)C(C)(C)O1

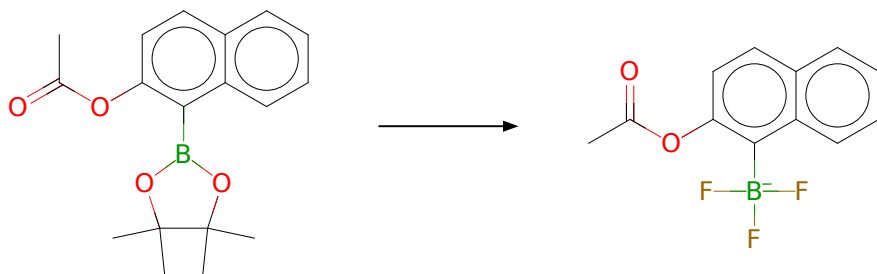
Typical conditions: [RhCl(cod)]₂.PCy₃.100°C

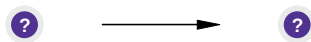
Protections: none

Reference: DOI: [10.1021/ja511622e](#)

Retrosynthesis ID: 9950

2.2.4 Synthesis of organotrifluoroborate salts in mild conditions





Substrates:

1. CC(=O)Oc1ccc2ccccc2c1B1OC(C)(C)C(C)(C)O1

Products:

1. CC(=O)Oc1ccc2ccccc2c1[B-](F)(F)F

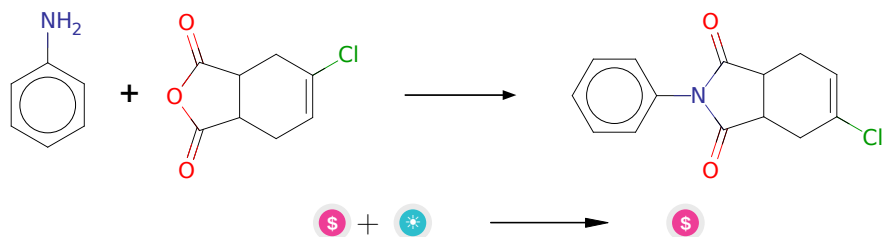
Typical conditions: KF.tartaric acid.CH₃CN.THF.H₂O.r.t

Protections: none

Reference: DOI: [10.1002/anie.201203930](https://doi.org/10.1002/anie.201203930)

Retrosynthesis ID: 6072

2.2.5 Synthesis of imides from anhydrides



Substrates:

1. Aniline - [available at Sigma-Aldrich](#)
2. 4-chloro-1,2,3,6-tetrahydro-phthalic anhydride

Products:

1. 5-chloro-2-phenyl-3a,4,7a-tetrahydro-isoindole-1,3-dione - [Vitas-MLaboratory](#)

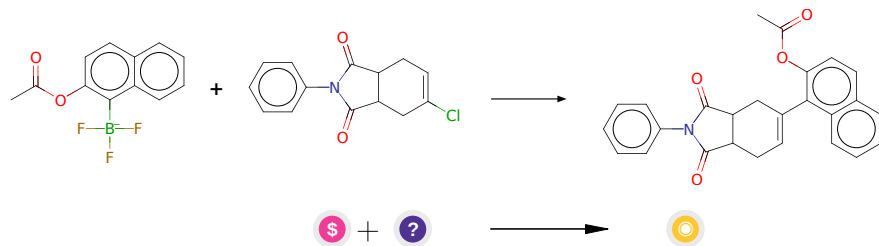
Typical conditions: AcOH

Protections: none

Reference: [10.1080/00397910802474966](https://doi.org/10.1080/00397910802474966) and [10.1021/ja9024676](https://doi.org/10.1021/ja9024676) (SI) and [10.1002/ejoc.201402202](https://doi.org/10.1002/ejoc.201402202)

Retrosynthesis ID: 8178

2.2.6 Suzuki Coupling of aryltrifluoroborates with alkenyl chlorides



Substrates:

1. 5-chloro-2-phenyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione - *Vitas-MLaboratory*
2. CC(=O)Oc1ccc2ccccc2c1[B-](F)(F)F

Products:

1. CC(=O)Oc1ccc2ccccc2c1C1=CCC2C(=O)N(c3ccccc3)C(=O)C2C1

Typical conditions: PdCl₂(dppf).K₂CO₃.toluene.reflux

Protections: none

Reference: [10.1002/chem.200900425](#) and [10.1016/j.tetlet.2014.10.078](#)

Retrosynthesis ID: 10034105

2.3 Path 3

Score: 118.83

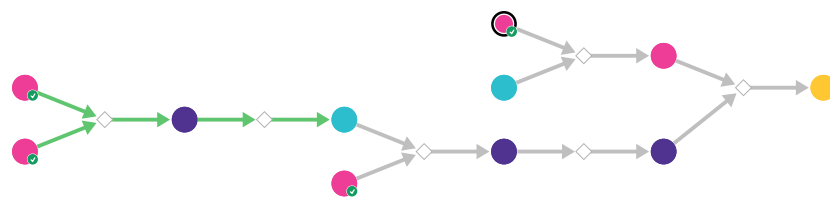
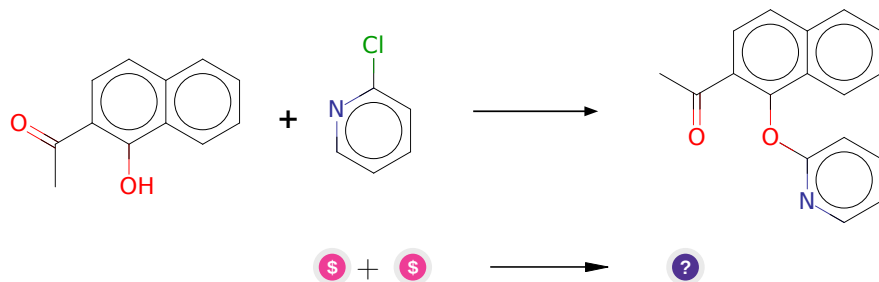


Figure 3: Outline of path 3

2.3.1 Nucleophilic aromatic substitution



Substrates:

1. 2-Chloropyridine - *available at Sigma-Aldrich*
2. 2-Acetyl-1-naphthol - *available at Sigma-Aldrich*

Products:

1. CC(=O)c1ccc2ccccc2c1Oc1cccn1

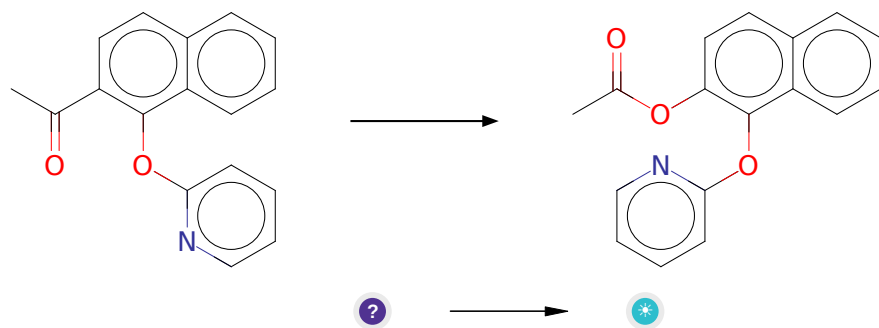
Typical conditions: K₂CO₃.DMAc

Protections: none

Reference: [10.1021/jm400463q](https://doi.org/10.1021/jm400463q) and [10.1016/j.bmc.2015.06.048](https://doi.org/10.1016/j.bmc.2015.06.048) and [10.1007/s00044-013-0839-2](https://doi.org/10.1007/s00044-013-0839-2) and [10.1021/jm2013453](https://doi.org/10.1021/jm2013453)

Retrosynthesis ID: 29655

2.3.2 Bayer-Villiger oxidation



Substrates:

1. CC(=O)c1ccc2ccccc2c1Oc1cccn1

Products:

1. C₁₇H₁₃NO₃

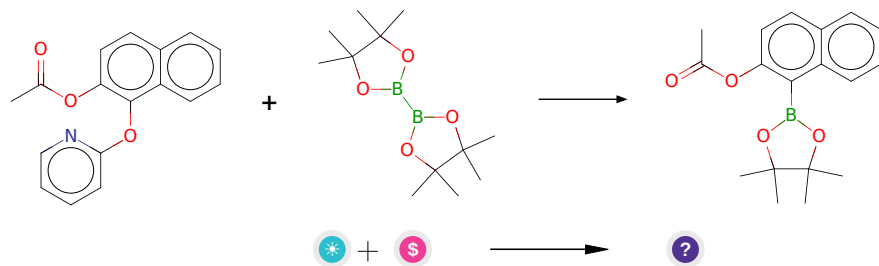
Typical conditions: mCPBA.NaHCO₃.DCM

Protections: none

Reference: [10.1021/ol702571c](#) and [10.1021/ja00272a051](#) and [10.1080/00397910801997835](#)

Retrosynthesis ID: 4811

2.3.3 Rh-catalyzed borylation of aryl pyridyl ethers



Substrates:

1. C₁₇H₁₃NO₃
2. Bis(pinacolato)diboron - [available at Sigma-Aldrich](#)

Products:

1. CC(=O)Oc1ccc2ccccc2c1B1OC(C)(C)C(C)(C)O1

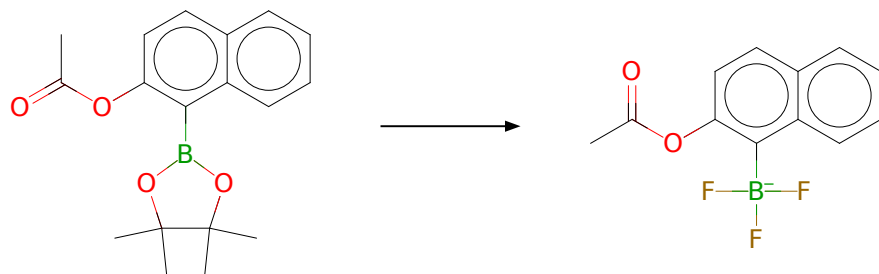
Typical conditions: [RhCl(cod)]₂.PCy₃.100°C

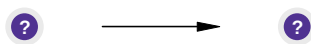
Protections: none

Reference: DOI: [10.1021/ja511622e](#)

Retrosynthesis ID: 9950

2.3.4 Synthesis of organotrifluoroborate salts in mild conditions





Substrates:

1. CC(=O)Oc1ccc2ccccc2c1B1OC(C)(C)C(C)(C)O1

Products:

1. CC(=O)Oc1ccc2ccccc2c1[B-](F)(F)F

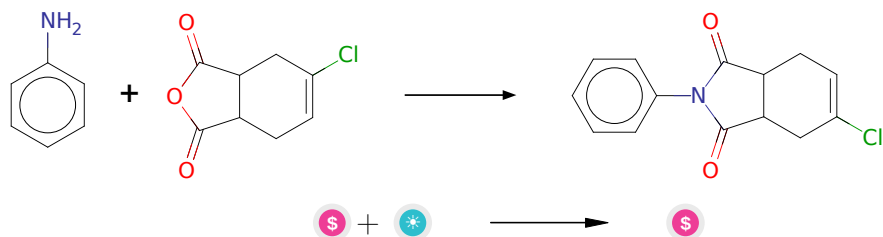
Typical conditions: KF.tartaric acid.CH₃CN.THF.H₂O.r.t

Protections: none

Reference: DOI: [10.1002/anie.201203930](https://doi.org/10.1002/anie.201203930)

Retrosynthesis ID: 6072

2.3.5 Synthesis of imides from anhydrides



Substrates:

1. Aniline - *available at Sigma-Aldrich*
2. 4-chloro-1,2,3,6-tetrahydro-phthalic anhydride

Products:

1. 5-chloro-2-phenyl-3a,4,7a-tetrahydro-isoindole-1,3-dione - *Vitas-MLaboratory*

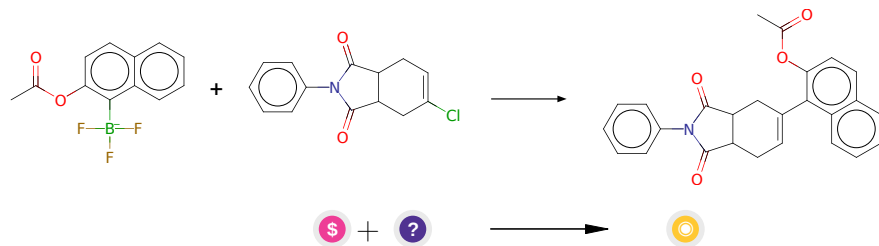
Typical conditions: AcOH

Protections: none

Reference: [10.1080/00397910802474966](https://doi.org/10.1080/00397910802474966) and [10.1021/ja9024676](https://doi.org/10.1021/ja9024676) (SI) and [10.1002/ejoc.201402202](https://doi.org/10.1002/ejoc.201402202)

Retrosynthesis ID: 8178

2.3.6 Suzuki Coupling of aryltrifluoroborates with alkenyl chlorides



Substrates:

1. 5-chloro-2-phenyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione - *Vitas-MLaboratory*
2. CC(=O)Oc1ccc2ccccc2c1[B-](F)(F)F

Products:

1. CC(=O)Oc1ccc2ccccc2c1C1=CCC2C(=O)N(c3ccccc3)C(=O)C2C1

Typical conditions: PdCl₂(dppf).K₂CO₃.toluene.reflux

Protections: none

Reference: [10.1002/chem.200900425](#) and [10.1016/j.tetlet.2014.10.078](#)

Retrosynthesis ID: 10034105

2.4 Path 4

Score: 129.38

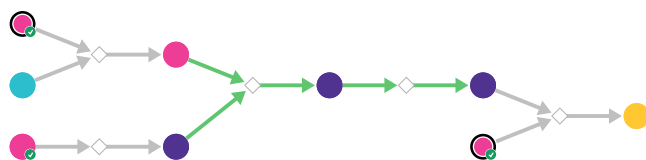
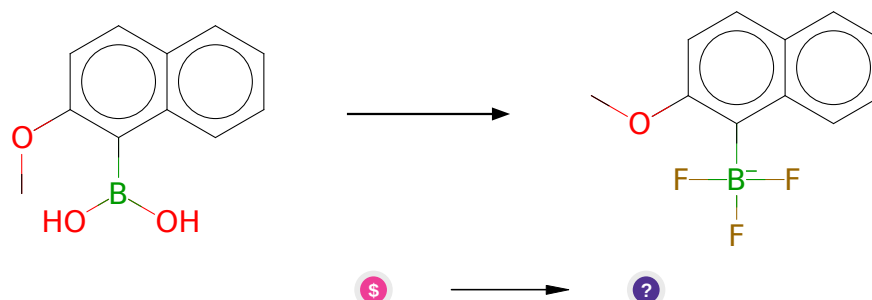


Figure 4: Outline of path 4

2.4.1 Synthesis of aromatic trifluoroborates from boronic acids



Substrates:

- 1-(2-Methoxynaphthyl)boronic acid - *available at Sigma-Aldrich*

Products:

- COc1ccc2ccccc2c1[B-](F)(F)F

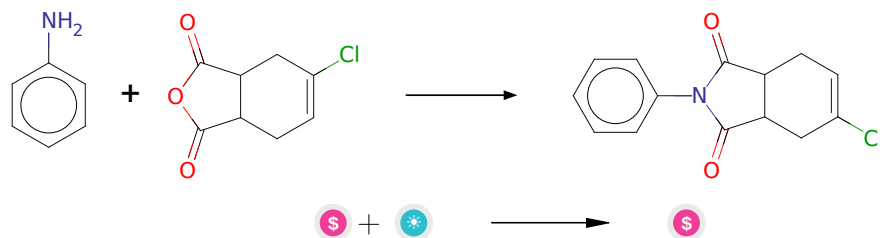
Typical conditions: H₂O.MeOH.KHF₂

Protections: none

Reference: DOI: [10.1021/jo00115a016](https://doi.org/10.1021/jo00115a016)

Retrosynthesis ID: 1282

2.4.2 Synthesis of imides from anhydrides



Substrates:

- Aniline - *available at Sigma-Aldrich*
- 4-chloro-1,2,3,6-tetrahydro-phthalic anhydride

Products:

- 5-chloro-2-phenyl-3a,4,7a-tetrahydro-isoindole-1,3-dione - *Vitas-MLaboratory*

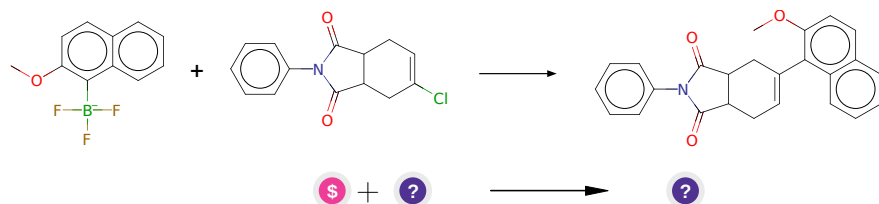
Typical conditions: AcOH

Protections: none

Reference: [10.1080/00397910802474966](#) and [10.1021/ja9024676](#) (SI) and [10.1002/ejoc.201402202](#)

Retrosynthesis ID: 8178

2.4.3 Suzuki Coupling of aryltrifluoroborates with alkenyl chlorides



Substrates:

- 5-chloro-2-phenyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione - *Vitas-MLaboratory*
- COc1ccc2ccccc2c1[B-](F)(F)F

Products:

- COc1ccc2ccccc2c1C1=CCC2C(=O)N(c3ccccc3)C(=O)C2C1

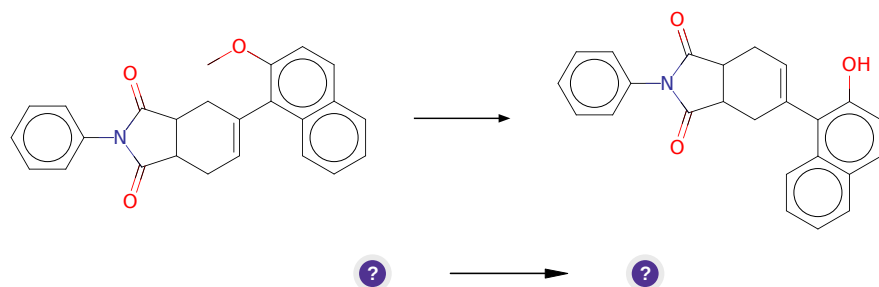
Typical conditions: PdCl₂(dppf).K₂CO₃.toluene.reflux

Protections: none

Reference: [10.1002/chem.200900425](#) and [10.1016/j.tetlet.2014.10.078](#)

Retrosynthesis ID: 10034105

2.4.4 Demethylation of Phenols



Substrates:

1. COc1ccc2ccccc2c1C1=CCC2C(=O)N(c3ccccc3)C(=O)C2C1

Products:

1. O=C1C2CC=C(c3c(O)ccc4ccccc34)CC2C(=O)N1c1ccccc1

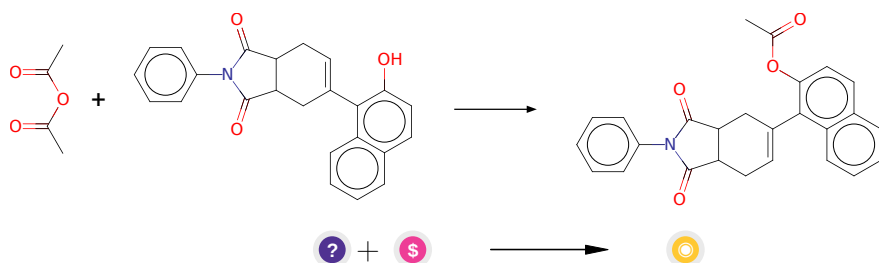
Typical conditions: BBr₃.CH₂Cl₂

Protections: none

Reference: DOI: [10.1021/ja00105a021](https://doi.org/10.1021/ja00105a021) and [10.1021/jm00176a011](https://doi.org/10.1021/jm00176a011) and [10.1021/jm970277i](https://doi.org/10.1021/jm970277i) and [10.1021/ja0106164](https://doi.org/10.1021/ja0106164) and Patent: US2010/16298, 2010, A1, page 185

Retrosynthesis ID: 10011837

2.4.5 Cu(OTf)₂ catalyzed acylation of phenols



Substrates:

1. O=C1C2CC=C(c3c(O)ccc4ccccc34)CC2C(=O)N1c1ccccc1
2. Acetic anhydride - *available at Sigma-Aldrich*

Products:

1. CC(=O)Oc1ccc2ccccc2c1C1=CCC2C(=O)N(c3ccccc3)C(=O)C2C1

Typical conditions: Cu(II).triflate.DCM.RT

Protections: none

Reference: DOI: [10.1016/S0040-4020\(01\)01229-7](https://doi.org/10.1016/S0040-4020(01)01229-7)

Retrosynthesis ID: 11601

2.5 Path 5

Score: 129.38

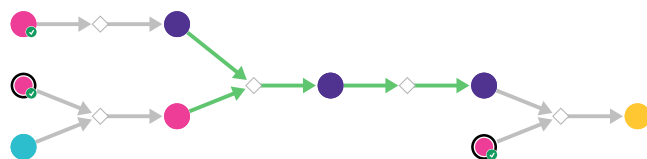
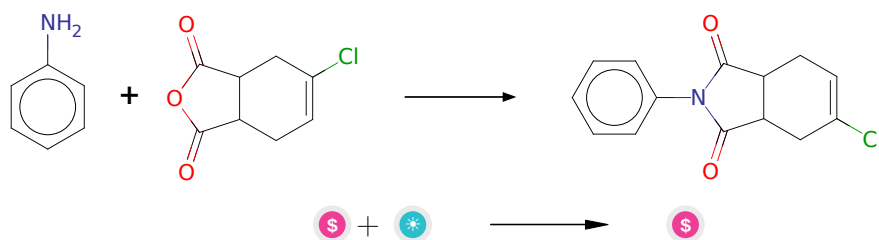


Figure 5: Outline of path 5

2.5.1 Synthesis of imides from anhydrides



Substrates:

1. Aniline - *available at Sigma-Aldrich*
2. 4-chloro-1,2,3,6-tetrahydro-phthalic anhydride

Products:

1. 5-chloro-2-phenyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione - *Vitas-MLaboratory*

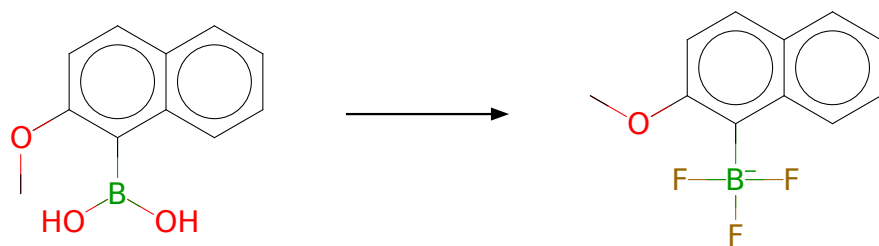
Typical conditions: AcOH

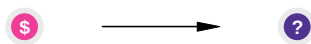
Protections: none

Reference: [10.1080/00397910802474966](#) and [10.1021/ja9024676](#) (SI) and [10.1002/ejoc.201402202](#)

Retrosynthesis ID: 8178

2.5.2 Synthesis of aromatic trifluoroborates from boronic acids





Substrates:

1. 1-(2-Methoxynaphthyl)boronic acid - *available at Sigma-Aldrich*

Products:

1. COc1ccc2ccccc2c1[B-](F)(F)F

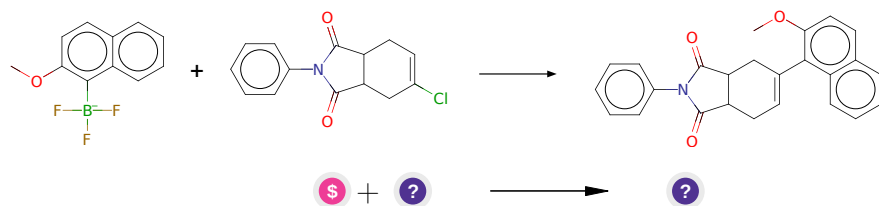
Typical conditions: H₂O.MeOH.KHF₂

Protections: none

Reference: DOI: [10.1021/jo00115a016](https://doi.org/10.1021/jo00115a016)

Retrosynthesis ID: 1282

2.5.3 Suzuki Coupling of aryltrifluoroborates with alkenyl chlorides



Substrates:

1. 5-chloro-2-phenyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione - *Vitas-MLaboratory*
2. COc1ccc2ccccc2c1[B-](F)(F)F

Products:

1. COc1ccc2ccccc2c1C1=CCC2C(=O)N(c3ccccc3)C(=O)C2C1

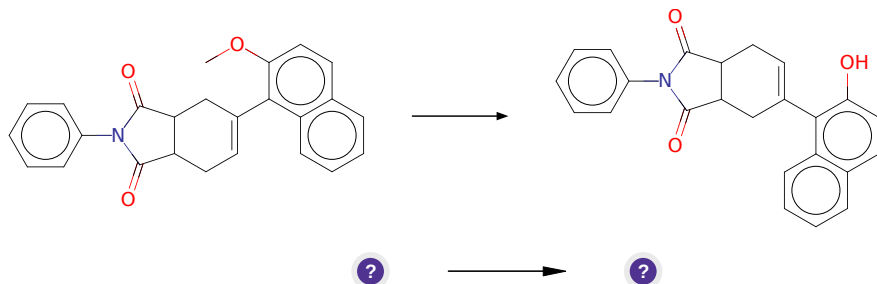
Typical conditions: PdCl₂(dppf).K₂CO₃.toluene.reflux

Protections: none

Reference: [10.1002/chem.200900425](https://doi.org/10.1002/chem.200900425) and [10.1016/j.tetlet.2014.10.078](https://doi.org/10.1016/j.tetlet.2014.10.078)

Retrosynthesis ID: 10034105

2.5.4 Demethylation of Phenols



Substrates:

1. COc1ccc2ccccc2c1C1=CCC2C(=O)N(c3ccccc3)C(=O)C2C1

Products:

1. O=C1C2CC=C(c3c(O)ccc4ccccc34)CC2C(=O)N1c1ccccc1

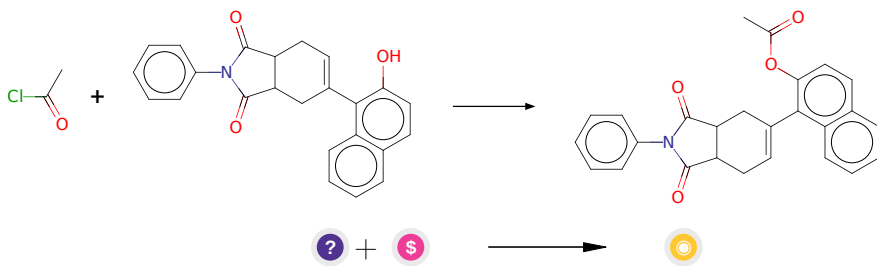
Typical conditions: BBr₃.CH₂Cl₂

Protections: none

Reference: DOI: [10.1021/ja00105a021](https://doi.org/10.1021/ja00105a021) and [10.1021/jm00176a011](https://doi.org/10.1021/jm00176a011) and [10.1021/jm970277i](https://doi.org/10.1021/jm970277i) and [10.1021/ja0106164](https://doi.org/10.1021/ja0106164) and Patent: US2010/16298, 2010, A1, page 185

Retrosynthesis ID: 10011837

2.5.5 Reaction of acyl chlorides with alcohols and phenols



Substrates:

1. O=C1C2CC=C(c3c(O)ccc4ccccc34)CC2C(=O)N1c1ccccc1
2. Acetyl chloride - *available at Sigma-Aldrich*

Products:

1. CC(=O)Oc1ccc2ccccc2c1C1=CCC2C(=O)N(c3ccccc3)C(=O)C2C1

Typical conditions: base.DCM

Protections: none

Reference: [10.1016/j.bmcl.2012.03.021](#) AND [10.1021/ja026266i](#) (SI, hydroperoxides) AND [10.1016/j.tetasy.2004.07.044](#) AND [10.1021/jm1006929](#) (SI) AND [10.1016/j.tet.2011.05.017](#) AND [10.1016/j.tetasy.2012.09.002](#) AND [10.1021/ol016268s](#) (SI) AND [10.1021/jo801116n](#) AND [10.1021/jo00279a041](#) AND WO2013/64518 A1, 2013 (page 102)

Retrosynthesis ID: 28549