

Paths of analysis*

BMK4

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: 68.83

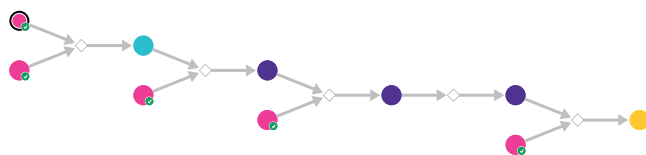
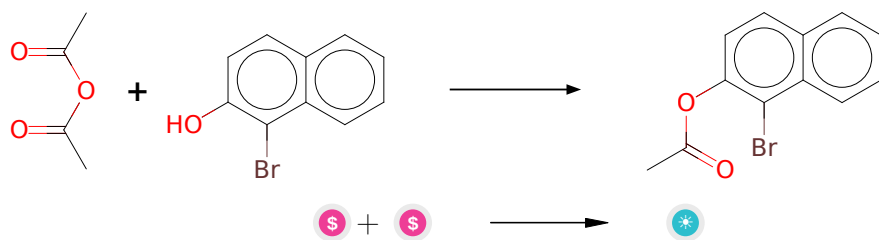


Figure 1: Outline of path 1

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)

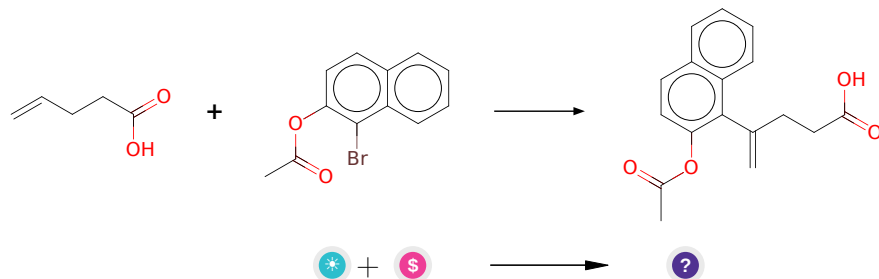
Typical conditions: Cu(II).triflate.DCM.RT

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 Heck Reaction



Substrates:

1. acetic acid-(1-bromo-[2]naphthyl ester)
2. Allylacetic acid - [available at Sigma-Aldrich](#)

Products:

1. C=C(CCC(=O)O)c1c(OC(C)=O)ccc2ccccc12

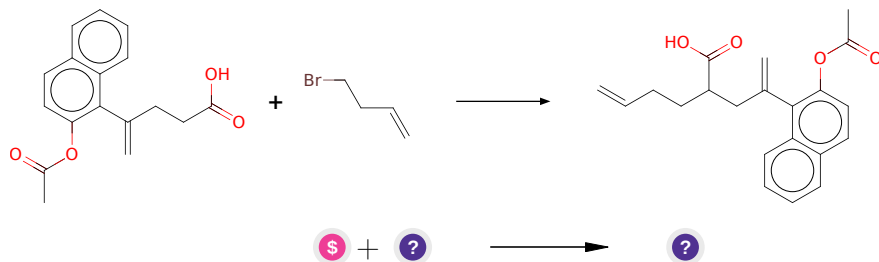
Typical conditions: Pd (cat). Ligand e.g. TXPTS. Base. Temp

Protections: none

Reference: [10.1039/C3CC45911J](https://doi.org/10.1039/C3CC45911J) or [10.1021/ar00049a001](https://doi.org/10.1021/ar00049a001) or [10.1002/anie.201201806](https://doi.org/10.1002/anie.201201806) or [10.1002/9780470716076](https://doi.org/10.1002/9780470716076)

Retrosynthesis ID: 9266

2.1.3 Alkylation of carboxylic acids



Substrates:

1. 4-Bromo-1-butene - [available at Sigma-Aldrich](#)

2. C=C(CCC(=O)O)c1c(OC(C)=O)ccc2ccccc12

Products:

1. C=CCCC(CC(=C)c1c(OC(C)=O)ccc2ccccc12)C(=O)O

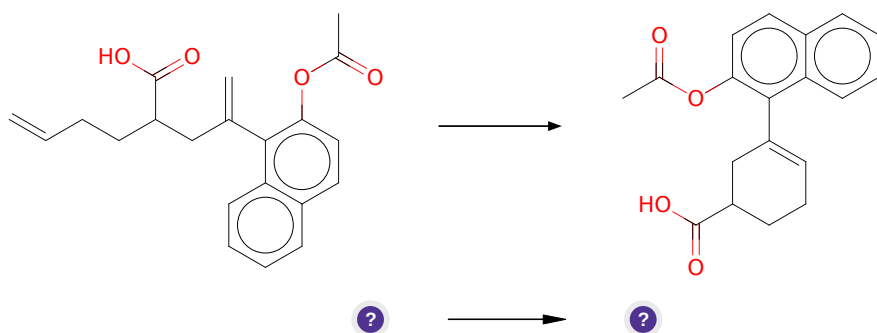
Typical conditions: nBuLi.THF.DIPEA

Protections: none

Reference: [10.1080/15257770.2013.820833](https://doi.org/10.1080/15257770.2013.820833) AND [10.1021/jm00078a017](https://doi.org/10.1021/jm00078a017)
AND [10.1016/j.bmc.2003.12.039](https://doi.org/10.1016/j.bmc.2003.12.039) AND [10.1021/ml500411h](https://doi.org/10.1021/ml500411h)(SI,page 11) AND
[10.1016/j.tet.2010.12.020](https://doi.org/10.1016/j.tet.2010.12.020) AND [10.1016/j.bmcl.2015.07.101](https://doi.org/10.1016/j.bmcl.2015.07.101)

Retrosynthesis ID: 28537

2.1.4 Ring-Closing Metathesis



Substrates:

1. C=CCCC(CC(=C)c1c(OC(C)=O)ccc2ccccc12)C(=O)O

Products:

1. CC(=O)Oc1ccc2ccccc2c1C1=CCCC(C(=O)O)C1

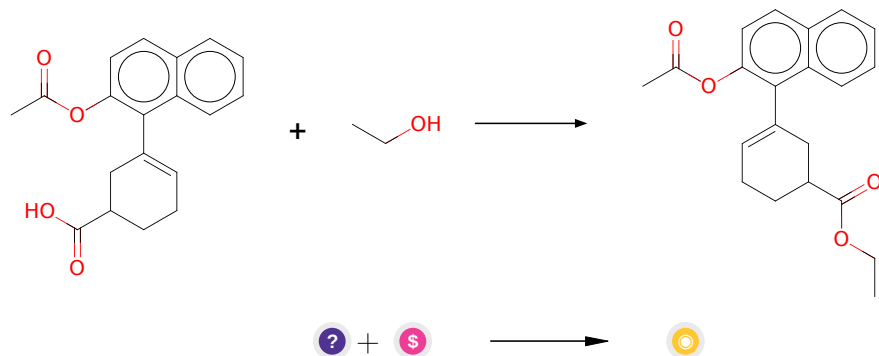
Typical conditions: catalyst e.g. Hoveyda-Grubbs . solvent e.g. CH₂Cl₂

Protections: none

Reference: DOI: [10.1021/ja067870m](https://doi.org/10.1021/ja067870m) and [10.1021/jacs.7b04759](https://doi.org/10.1021/jacs.7b04759) and
[10.1021/jacs.7b13234](https://doi.org/10.1021/jacs.7b13234)(Supporting Info, page S22) and [10.1039/C3CC00316G](https://doi.org/10.1039/C3CC00316G)
and [10.1021/ol9024716](https://doi.org/10.1021/ol9024716)

Retrosynthesis ID: 31014200

2.1.5 Steglich Esterification



Substrates:

1. CC(=O)Oc1ccc2ccccc2c1C1=CCCC(C(=O)O)C1
2. Pure - *available at Sigma-Aldrich*

Products:

1. CCOC(=O)C1CCC=C(c2c(OC(C)=O)ccc3ccccc23)C1

Typical conditions: alcohol.DCC.DMAP.DCM or thiol.DCC.DMAP.DCM

Protections: none

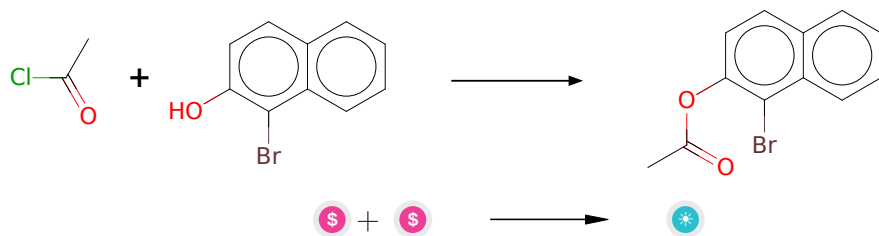
Reference: *10.1002/anie.197805221*

Retrosynthesis ID: 10171

2.2 Path 2

Score: 76.25

2.2.1 Reaction of acyl chlorides with alcohols and phenols



Substrates:

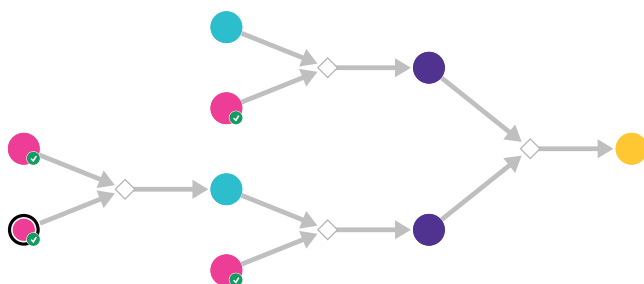


Figure 2: Outline of path 2

- 1-Bromo-2-naphthol - *available at Sigma-Aldrich*
- Acetyl chloride - *available at Sigma-Aldrich*

Products:

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

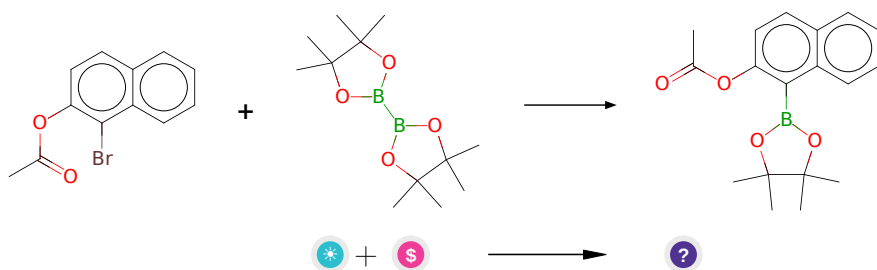
Typical conditions: base.DCM

Protections: none

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

Retrosynthesis ID: 28549

2.2.2 Miyaura Borylation



Substrates:

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

Products:

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

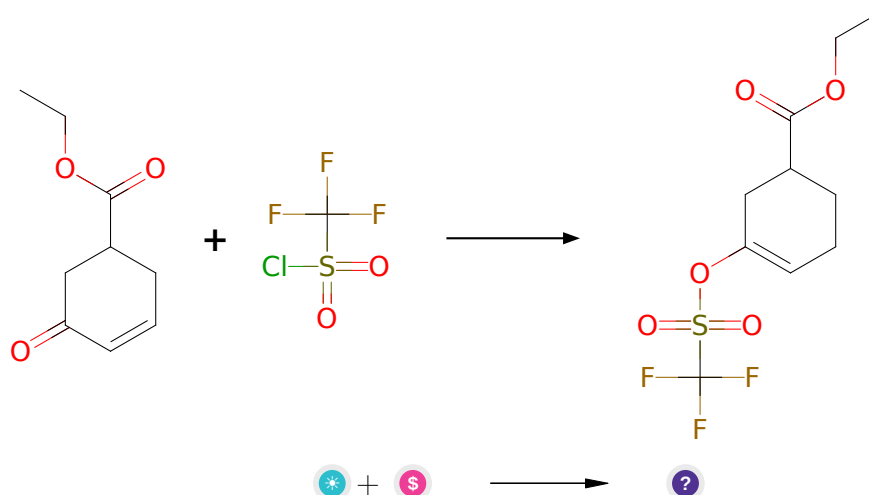
Typical conditions: PdCl₂(dppf)2.KOAc.Dioxane or DMSO.80oC

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

2.2.3 Luche reduction of enones followed by enolate sulfonylation



Substrates:

1. C₉H₁₂O₃
2. Triflyl chloride - [available at Sigma-Aldrich](#)

Products:

1. CCOC(=O)C1CCC=C(OS(=O)(=O)C(F)(F)F)C1

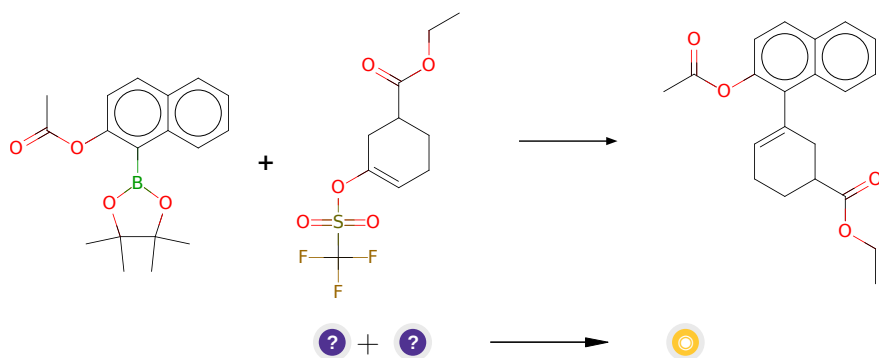
Typical conditions: L-selectridereg.THF

Protections: none

Reference: [10.1055/s-1985-31204](https://doi.org/10.1055/s-1985-31204) and [10.1021/ja00073a057](https://doi.org/10.1021/ja00073a057) and [10.1021/ja057640s](https://doi.org/10.1021/ja057640s) and [10.1021/ol049780x](https://doi.org/10.1021/ol049780x) and [10.1021/ol1023954](https://doi.org/10.1021/ol1023954) and [10.1021/jo062423a](https://doi.org/10.1021/jo062423a)

Retrosynthesis ID: 25238

2.2.4 Suzuki coupling of arylboronic pinacol esters with vinyl triflates



Substrates:

1. CC(=O)Oc1ccc2ccccc2c1B1OC(C)(C)C(C)(C)O1
2. CCOC(=O)C1CCC=C(OS(=O)(=O)C(F)(F)F)C1

Products:

1. CCOC(=O)C1CCC=C(c2c(OC(C)=O)ccc3ccccc23)C1

Typical conditions: Pd catalyst.base.solvent

Protections: none

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: 10841

2.3 Path 3

Score: 76.25

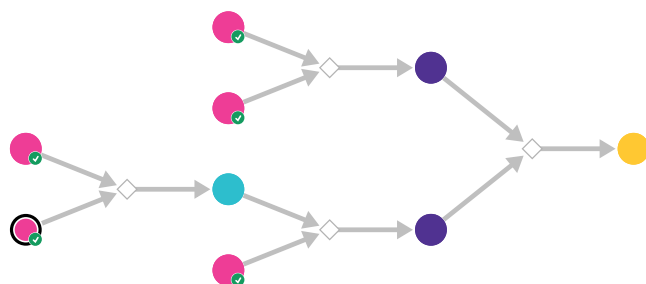
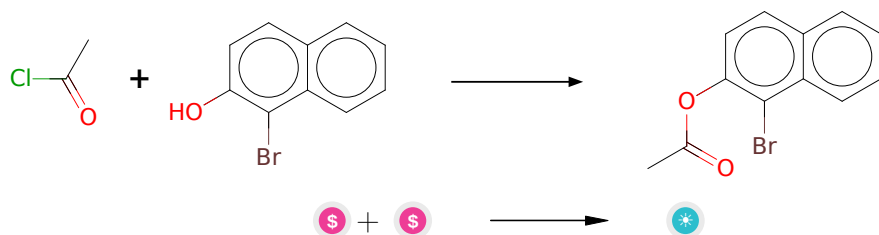


Figure 3: Outline of path 3

2.3.1 Reaction of acyl chlorides with alcohols and phenols



Substrates:

1. 1-Bromo-2-naphthol - *available at Sigma-Aldrich*
2. Acetyl chloride - *available at Sigma-Aldrich*

Products:

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

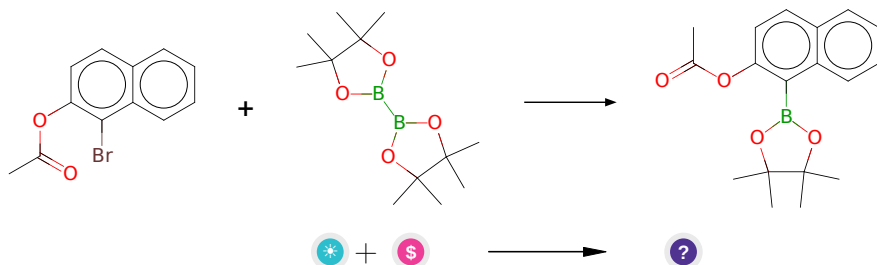
Typical conditions: base.DCM

Protections: none

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

Retrosynthesis ID: 28549

2.3.2 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

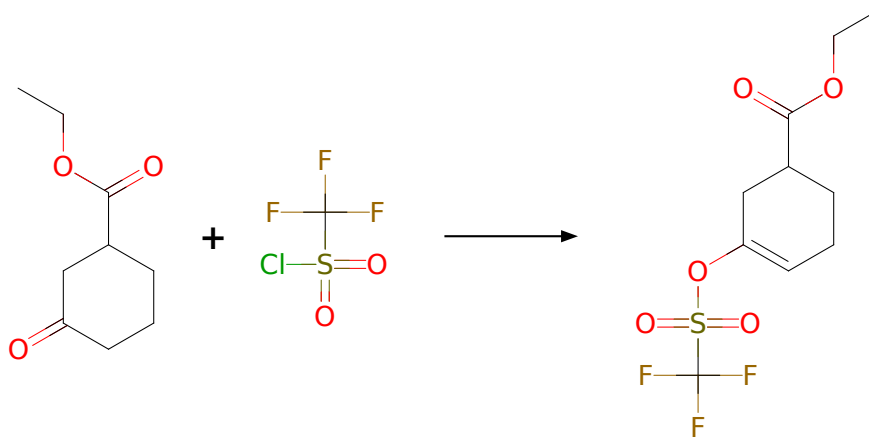
Typical conditions: PdCl₂(dppf)2.KOAc.Dioxane or DMSO.80oC

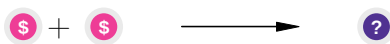
Protections: none

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

2.3.3 Synthesis of enol sulfonates





Substrates:

1. Triflyl chloride - *available at Sigma-Aldrich*
2. Ethyl 3-oxocyclohexane-1-carboxylate - *available at Sigma-Aldrich*

Products:

1. CCOC(=O)C1CCC=C(OS(=O)(=O)C(F)(F)F)C1

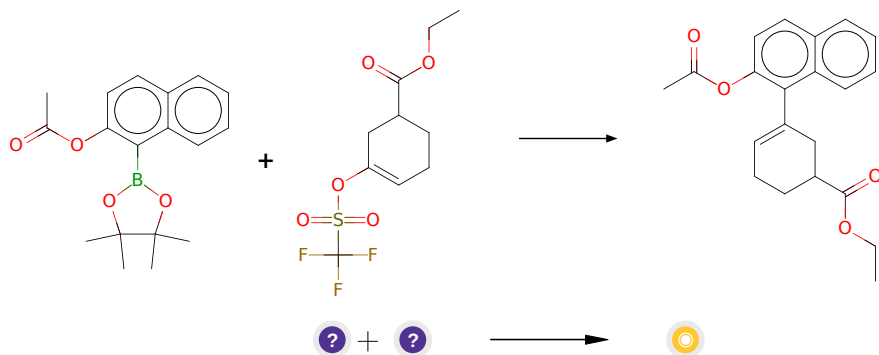
Typical conditions: base.electrophile.THF

Protections: none

Reference: [10.1021/jm960394y](#) and [10.1021/ja068826+](#) and [10.1002/anie.201500112](#) and [10.1021/jacs.6b08608](#)

Retrosynthesis ID: 10004758

2.3.4 Suzuki coupling of arylboronic pinacol esters with vinyl triflates



Substrates:

1. CC(=O)Oc1ccc2ccccc2c1B1OC(C)(C)C(C)(C)O1
2. CCOC(=O)C1CCC=C(OS(=O)(=O)C(F)(F)F)C1

Products:

1. CCOC(=O)C1CCC=C(c2c(OC(C)=O)ccc3ccccc23)C1

Typical conditions: Pd catalyst.base.solvent

Protections: none

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: 10841

2.4 Path 4

Score: 76.25

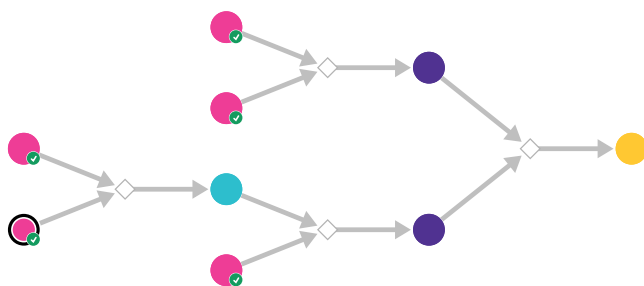
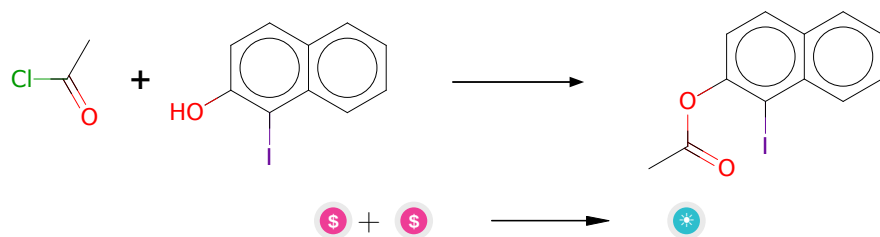


Figure 4: Outline of path 4

2.4.1 Reaction of acyl chlorides with alcohols and phenols



Substrates:

1. 1-Iodo-2-naphthol - *available at Sigma-Aldrich*
2. Acetyl chloride - *available at Sigma-Aldrich*

Products:

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

Typical conditions: base.DCM

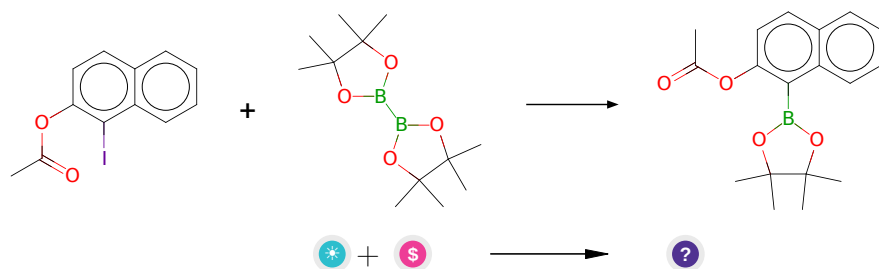
Protections: none

Reference: [10.1016/j.bmcl.2012.03.021](https://doi.org/10.1016/j.bmcl.2012.03.021) AND [10.1021/ja026266i](https://doi.org/10.1021/ja026266i) (SI, hydroperoxides) AND [10.1016/j.tetasy.2004.07.044](https://doi.org/10.1016/j.tetasy.2004.07.044) AND [10.1021/jm1006929](https://doi.org/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

2.4.2 Miyaura Borylation



Substrates:

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

Products:

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

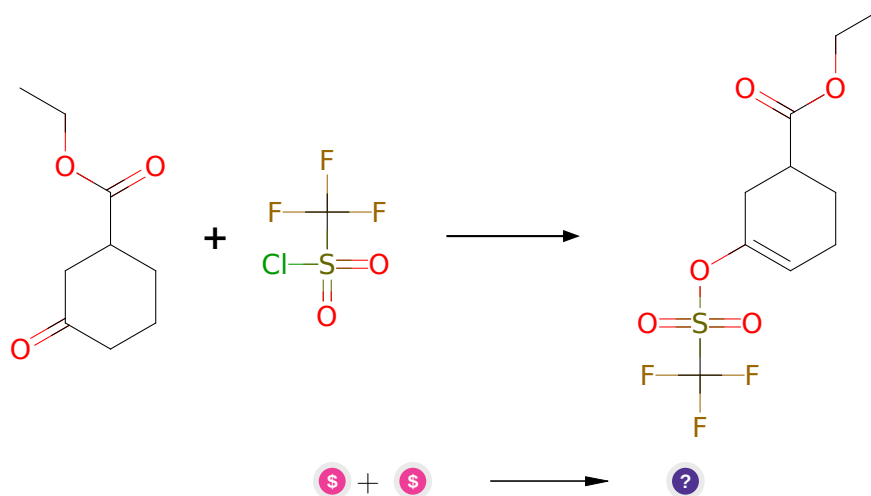
Typical conditions: PdCl₂(dppf)2.KOAc.Dioxane or DMSO.80oC

Protections: none

Reference: DOI: [10.1021/ja503296c](#) and [10.3762/bjoc.10.297](#) and [10.1021/jm0605482](#) and [10.1002/chem.201204055](#) (SI, page 16) and [10.1021/acs.orglett.6b02477](#) (SI, page S4) and [10.1016/j.bmcl.2014.12.067](#)

Retrosynthesis ID: 1210

2.4.3 Synthesis of enol sulfonates



Substrates:

1. Triflyl chloride - *available at Sigma-Aldrich*
2. Ethyl 3-oxocyclohexane-1-carboxylate - *available at Sigma-Aldrich*

Products:

1. CCOC(=O)C1CCC=C(OS(=O)(=O)C(F)(F)F)C1

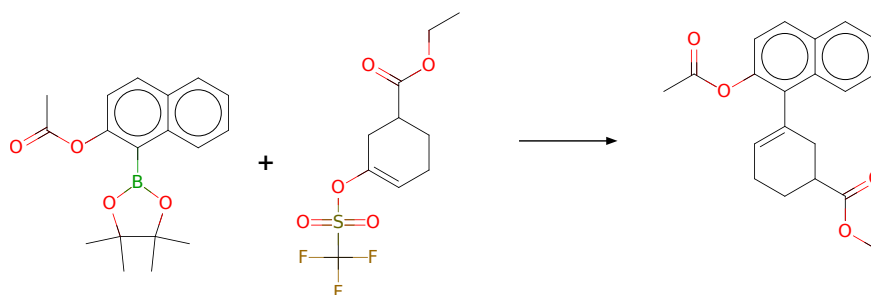
Typical conditions: base.electrophile.THF

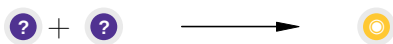
Protections: none

Reference: [10.1021/jm960394y](#) and [10.1021/ja068826+](#) and [10.1002/anie.201500112](#) and [10.1021/jacs.6b08608](#)

Retrosynthesis ID: 10004758

2.4.4 Suzuki coupling of arylboronic pinacol esters with vinyl triflates





Substrates:

1. CC(=O)Oc1ccc2ccccc2c1B1OC(C)(C)C(C)(C)O1
2. CCOC(=O)C1CCC=C(OS(=O)(=O)C(F)(F)F)C1

Products:

1. CCOC(=O)C1CCC=C(c2c(OC(C)=O)ccc3ccccc23)C1

Typical conditions: Pd catalyst.base.solvent

Protections: none

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: 10841

2.5 Path 5

Score: 76.25

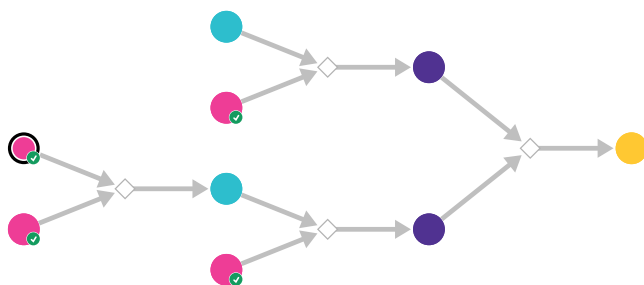
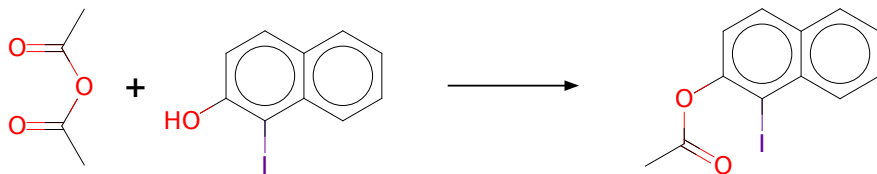
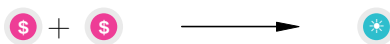


Figure 5: Outline of path 5

2.5.1 Cu(OTf)₂ catalyzed acylation of phenols





Substrates:

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

Products:

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

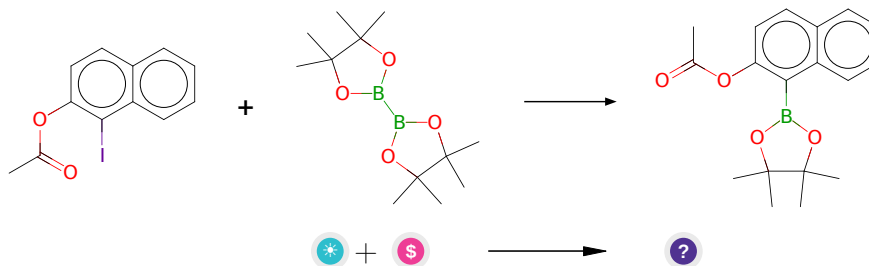
Typical conditions: Cu(II).triflate.DCM.RT

Protections: none

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

Retrosynthesis ID: 11601

2.5.2 Miyaura Borylation



Substrates:

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

Products:

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

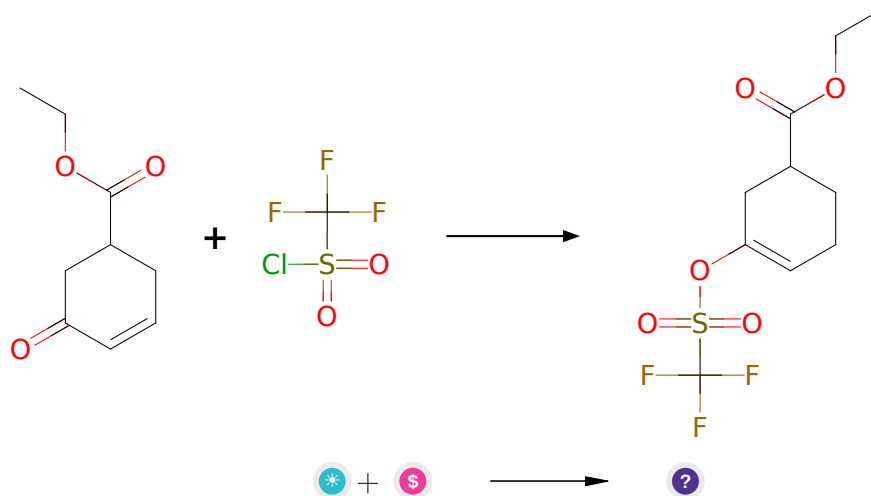
Typical conditions: PdCl₂(dppf)2.KOAc.Dioxane or DMSO.80oC

Protections: none

Reference: DOI: [10.1021/ja503296c](https://doi.org/10.1021/ja503296c) and [10.3762/bjoc.10.297](https://doi.org/10.3762/bjoc.10.297) and [10.1021/jm0605482](https://doi.org/10.1021/jm0605482) and [10.1002/chem.201204055](https://doi.org/10.1002/chem.201204055) (SI, page 16) and [10.1021/acs.orglett.6b02477](https://doi.org/10.1021/acs.orglett.6b02477) (SI, page S4) and [10.1016/j.bmcl.2014.12.067](https://doi.org/10.1016/j.bmcl.2014.12.067)

Retrosynthesis ID: 1210

2.5.3 Luche reduction of enones followed by enolate sulfonylation



Substrates:

1. C₉H₁₂O₃
2. Triflyl chloride - *available at Sigma-Aldrich*

Products:

1. CCOC(=O)C1CCC=C(OS(=O)(=O)C(F)(F)F)C1

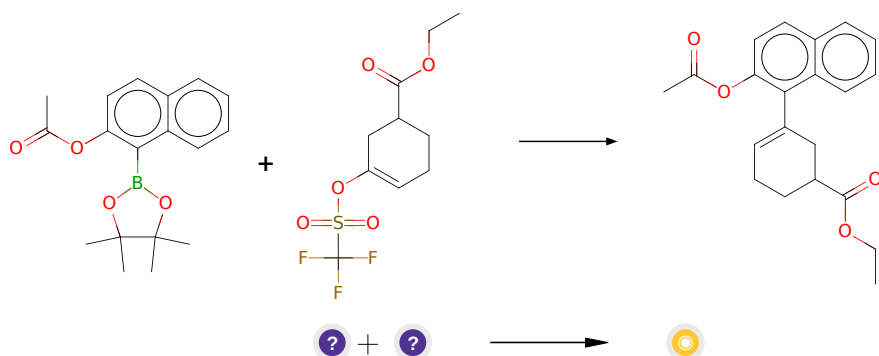
Typical conditions: L-selectridereg.THF

Protections: none

Reference: [10.1055/s-1985-31204](#) and [10.1021/ja00073a057](#) and
[10.1021/ja057640s](#) and [10.1021/ol049780x](#) and [10.1021/ol1023954](#) and
[10.1021/jo062423a](#)

Retrosynthesis ID: 25238

2.5.4 Suzuki coupling of arylboronic pinacol esters with vinyl triflates



Substrates:

1. CC(=O)Oc1ccc2ccccc2c1B1OC(C)(C)C(C)(C)O1
2. CCOC(=O)C1CCC=C(OS(=O)(=O)C(F)(F)F)C1

Products:

1. CCOC(=O)C1CCC=C(c2c(OC(C)=O)ccc3ccccc23)C1

Typical conditions: Pd catalyst.base.solvent

Protections: none

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: 10841