

Paths of analysis*

AS4

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: $\text{TUNNEL_COEF} * \text{FGI_COEF} * \text{STEP} * 20 + 1000000 * (\text{CONFLICT} + \text{NON_SELECTIVITY} + \text{FILTERS} + \text{PROTECT})$

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

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: 2441545.39

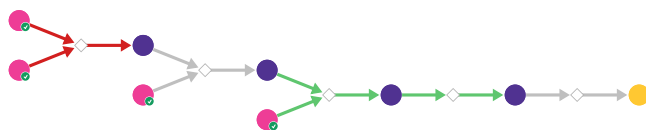
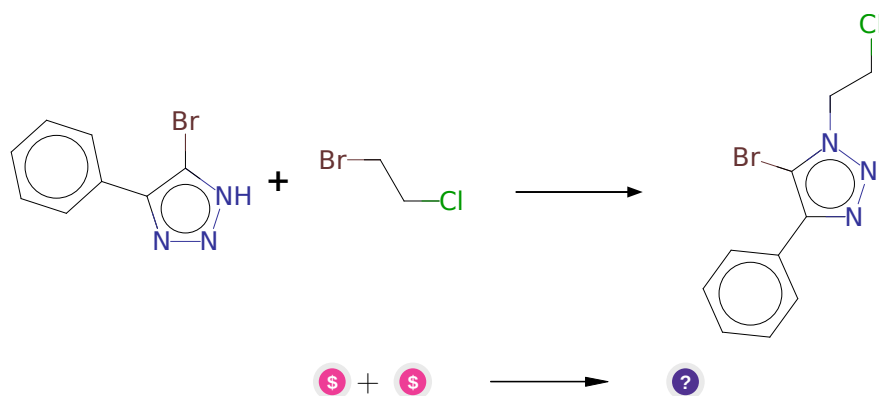


Figure 1: Outline of path 1

2.1.1 N-alkylation of heterocycles



Substrates:

- 1-Bromo-2-chloroethane - *available at Sigma-Aldrich*
- 4-Bromo-5-phenyl-1H-1,2,3-triazole - *available at Sigma-Aldrich*

Products:

1. ClCCn1nnc(-c2ccccc2)c1Br

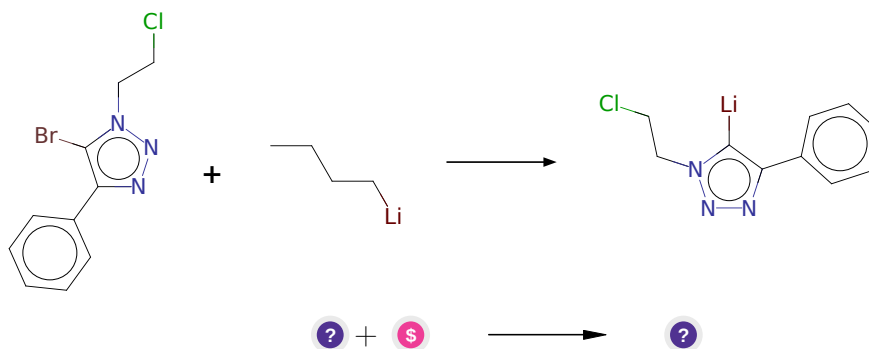
Typical conditions: NaH. DMF

Protections: none

Reference: [10.1016/j.ejmech.2010.11.014](#) or [10.1039/C6OB01149G](#) (SI) or [10.1246/cl.2005.442](#) or [10.1021/ol403570z](#) (SI) or [10.1016/S0040-4020\(01\)00360-X](#)

Retrosynthesis ID: 10000414

2.1.2 Br/Li exchange



Substrates:

1. ClCCn1nnc(-c2ccccc2)c1Br
2. n-BuLi - [available at Sigma-Aldrich](#)

Products:

1. [Li]c1c(-c2ccccc2)nnn1CCCl

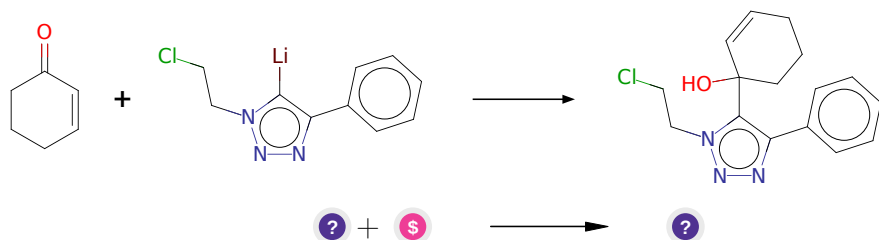
Typical conditions: nBuLi.or.tBuLi.THF.-78C

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

2.1.3 Addition of electrophiles to lithiated arenes/heteroarenes



Substrates:

1. [Li]c1c(-c2ccccc2)nnn1CCCl
2. 2-Cyclohexen-1-one - *available at Sigma-Aldrich*

Products:

1. OC1(c2c(-c3ccccc3)nnn2CCCl)C=CCCC1

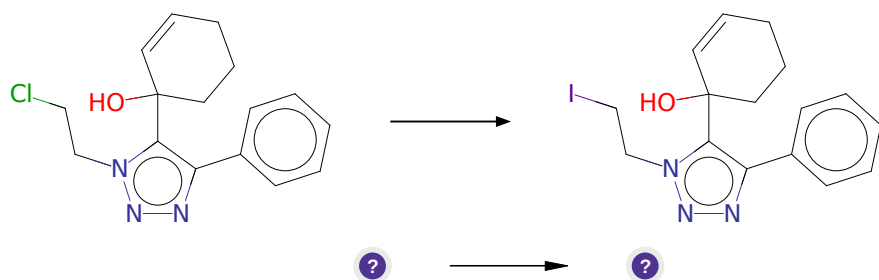
Typical conditions: THF.-78 deg C

Protections: none

Reference: [10.1021/ml300335r](#) and [10.1021/acs.jmedchem.6b00866](#)

Retrosynthesis ID: 31008139

2.1.4 Synthesis of alkyl iodides from alkyl chlorides



Substrates:

1. OC1(c2c(-c3ccccc3)nnn2CCCl)C=CCCC1

Products:

1. OC1(c2c(-c3ccccc3)nnn2CCI)C=CCCC1

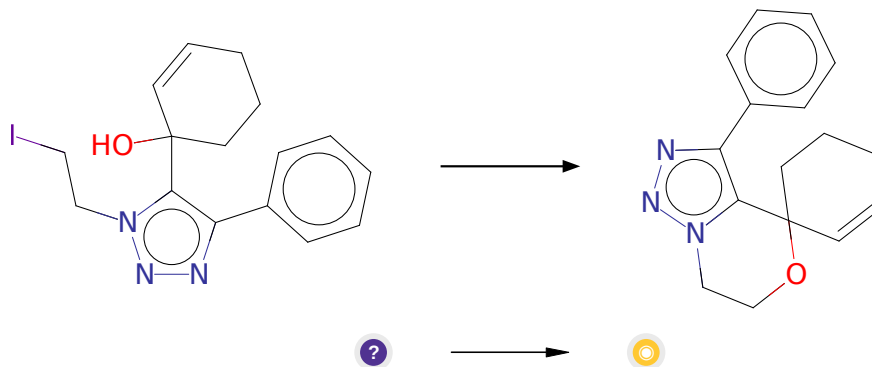
Typical conditions: NaI.acetone.heat

Protections: none

Reference: [10.1039/B812607K](#) and [10.1021/jm030222i](#)

Retrosynthesis ID: 31010848

2.1.5 Alkylation of tertiary alcohols



Substrates:

1. OC1(c2c(-c3ccccc3)nnn2CCI)C=CCCC1

Products:

1. C1=CC2(CCC1)OCCn1nnc(-c3ccccc3)c12

Typical conditions: K₂CO₃.acetone.heat

Protections: none

Reference: [10.1039/P29910000147](#) and [10.1038/ncomms7703](#)

Retrosynthesis ID: 31010959

2.2 Path 2

Score: 2441545.39

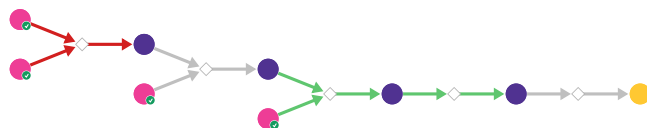
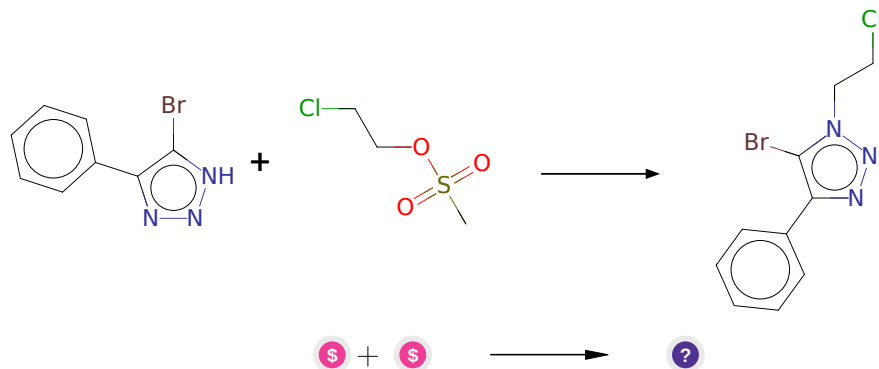


Figure 2: Outline of path 2

2.2.1 Alkylation of N-heterocycles with activated alcohols



Substrates:

- 2-Chloroethyl methanesulfonate - *available at Sigma-Aldrich*
- 4-Bromo-5-phenyl-1H-1,2,3-triazole - *available at Sigma-Aldrich*

Products:

- ClCCn1nnc(-c2ccccc2)c1Br

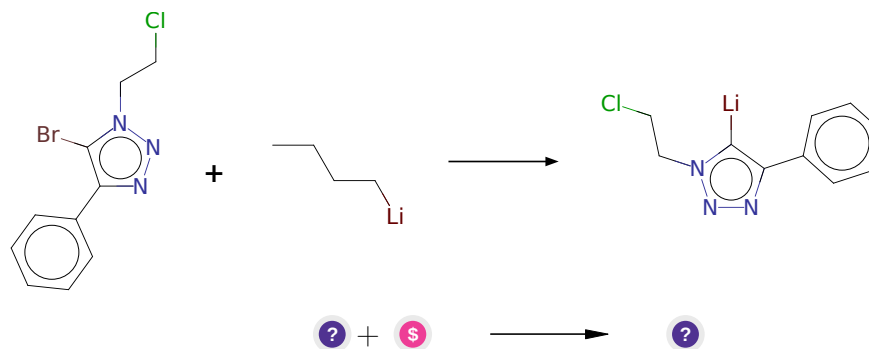
Typical conditions: K₂CO₃.MeCN.heating

Protections: none

Reference: [10.1021/jm200112k](#) (suppl. Info p.27) and WO2013167586A1 p.9 and WO2004/24147 p.23

Retrosynthesis ID: 24133

2.2.2 Br/Li exchange



Substrates:

1. ClCCn1nnc(-c2ccccc2)c1Br
2. n-BuLi - *available at Sigma-Aldrich*

Products:

1. [Li]c1c(-c2ccccc2)nnn1CCCl

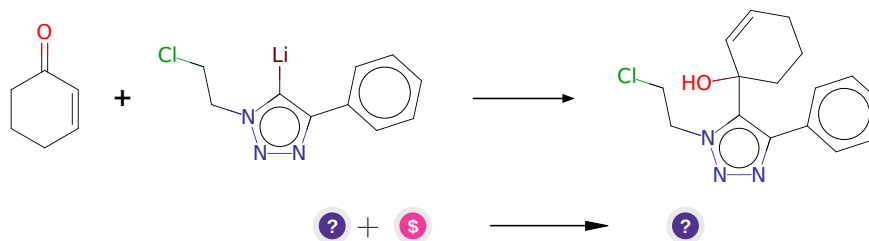
Typical conditions: nBuLi.or.tBuLi.THF.-78C

Protections: none

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

Retrosynthesis ID: 30672

2.2.3 Addition of electrophiles to lithiated arenes/heteroarenes



Substrates:

1. [Li]c1c(-c2ccccc2)nnn1CCCl
2. 2-Cyclohexen-1-one - *available at Sigma-Aldrich*

Products:

1. OC1(c2c(-c3ccccc3)nnn2CCCl)C=CCCC1

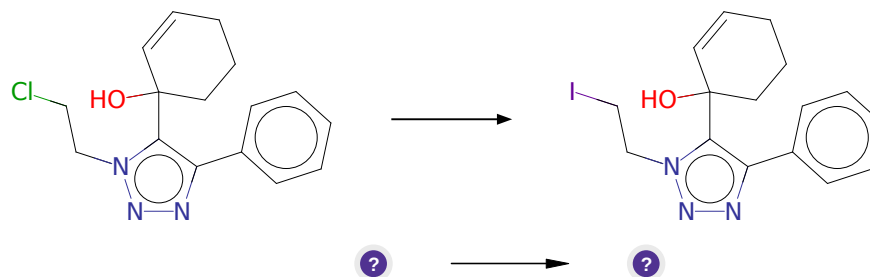
Typical conditions: THF.-78 deg C

Protections: none

Reference: [10.1021/ml300335r](https://doi.org/10.1021/ml300335r) and [10.1021/acs.jmedchem.6b00866](https://doi.org/10.1021/acs.jmedchem.6b00866)

Retrosynthesis ID: 31008139

2.2.4 Synthesis of alkyl iodides from alkyl chlorides



Substrates:

1. OC1(c2c(-c3ccccc3)nnn2CCCl)C=CCCC1

Products:

1. OC1(c2c(-c3ccccc3)nnn2CCI)C=CCCC1

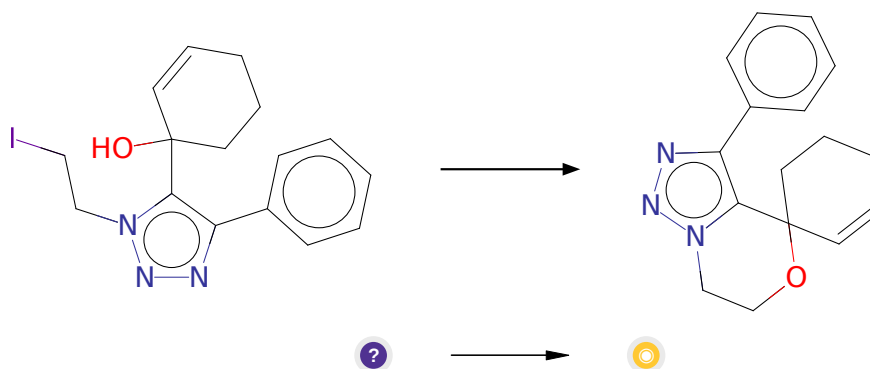
Typical conditions: NaI.acetone.heat

Protections: none

Reference: [10.1039/B812607K](#) and [10.1021/jm030222i](#)

Retrosynthesis ID: 31010848

2.2.5 Alkylation of tertiary alcohols



Substrates:

1. OC1(c2c(-c3ccccc3)nnn2CCI)C=CCCC1

Products:

1. C1=CC2(CCC1)OCCn1nnc(-c3ccccc3)c12

Typical conditions: K₂CO₃.acetone.heat

Protections: none

Reference: [10.1039/P29910000147](#) and [10.1038/ncomms7703](#)

Retrosynthesis ID: 31010959

2.3 Path 3

Score: 2441570.39

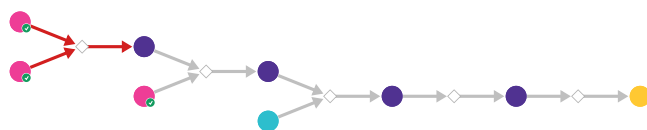
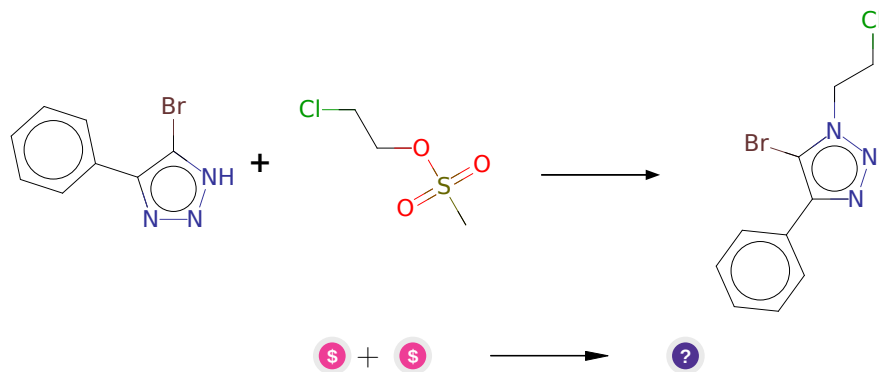


Figure 3: Outline of path 3

2.3.1 Alkylation of N-heterocycles with activated alcohols



Substrates:

1. 2-Chloroethyl methanesulfonate - [available at Sigma-Aldrich](#)
2. 4-Bromo-5-phenyl-1H-1,2,3-triazole - [available at Sigma-Aldrich](#)

Products:

1. ClCCn1nnc(-c2ccccc2)c1Br

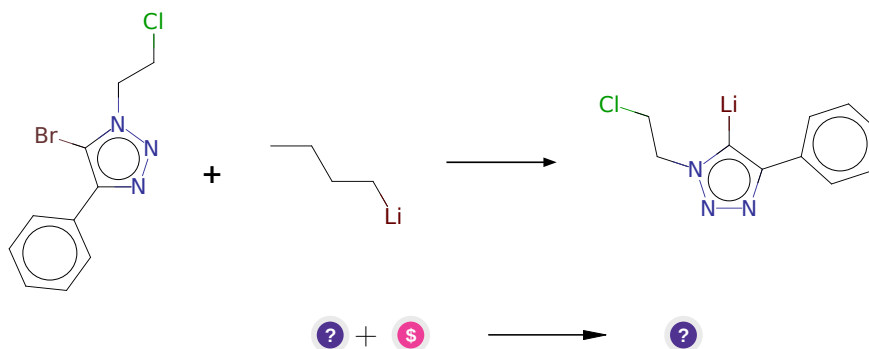
Typical conditions: K₂CO₃.MeCN.heating

Protections: none

Reference: [10.1021/jm200112k](#) (suppl. Info p.27) and WO2013167586A1 p.9 and WO2004/24147 p.23

Retrosynthesis ID: 24133

2.3.2 Br/Li exchange



Substrates:

1. ClCCn1nnc(-c2ccccc2)c1Br
2. n-BuLi - [available at Sigma-Aldrich](#)

Products:

1. [Li]c1c(-c2ccccc2)nnn1CCCl

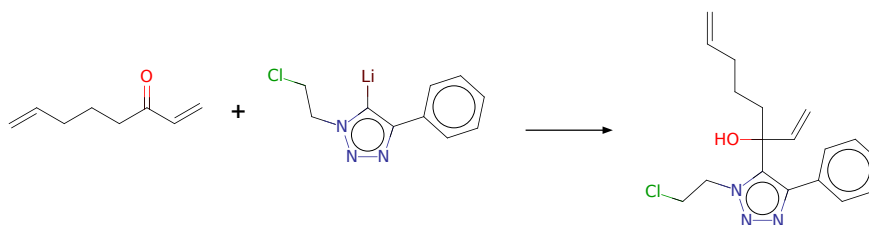
Typical conditions: nBuLi.or.tBuLi.THF.-78C

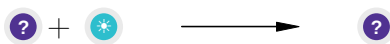
Protections: none

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

2.3.3 Addition of electrophiles to lithiated arenes/heteroarenes





Substrates:

1. [Li]c1c(-c2ccccc2)nnn1CCCl
2. octa-1,7-dien-3-one

Products:

1. C=CCCC(O)(C=C)c1c(-c2ccccc2)nnn1CCCl

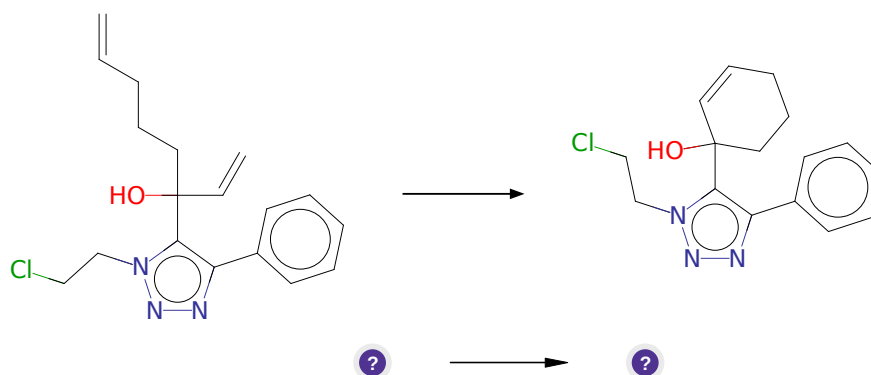
Typical conditions: THF.-78 deg C

Protections: none

Reference: [10.1021/ml300335r](https://doi.org/10.1021/ml300335r) and [10.1021/acs.jmedchem.6b00866](https://doi.org/10.1021/acs.jmedchem.6b00866)

Retrosynthesis ID: 31008139

2.3.4 Ring-Closing Metathesis



Substrates:

1. C=CCCC(O)(C=C)c1c(-c2ccccc2)nnn1CCCl

Products:

1. OC1(c2c(-c3ccccc3)nnn2CCCl)C=CCCC1

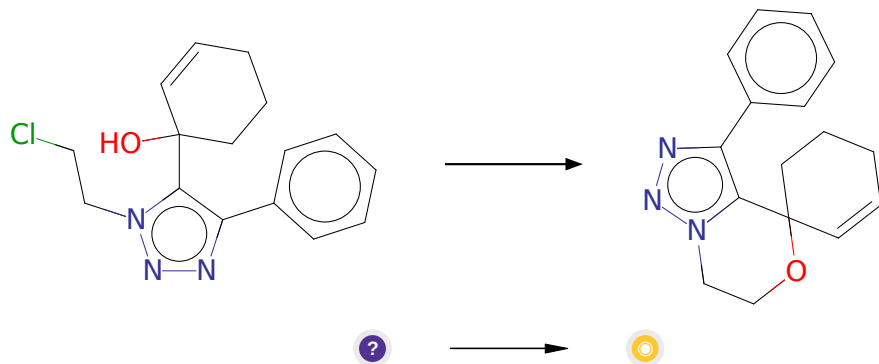
Typical conditions: catalyst e.g. Hoveyda-Grubbs . solvent e.g. CH2Cl2

Protections: none

Reference: DOI: [10.1002/anie.200800693](https://doi.org/10.1002/anie.200800693) and [10.1021/acs.orglett.8b04003](https://doi.org/10.1021/acs.orglett.8b04003) and [10.1021/jo0264729](https://doi.org/10.1021/jo0264729) and [10.1021/ja072334v](https://doi.org/10.1021/ja072334v) and [10.1002/ejoc.201001102](https://doi.org/10.1002/ejoc.201001102)

Retrosynthesis ID: 31014187

2.3.5 Alkylation of tertiary alcohols



Substrates:

1. OC1(c2c(-c3ccccc3)nnn2CCCl)C=CCCC1

Products:

1. C1=CC2(CCC1)OCCn1nnc(-c3ccccc3)c12

Typical conditions: K₂CO₃.acetone.heat

Protections: none

Reference: [10.1016/S0040-4020\(01\)90106-1](#) and [10.1021/acs.analchem.5b04461](#) and [10.3390/molecules24091643](#)

Retrosynthesis ID: 31010930

2.4 Path 4

Score: 2441570.39

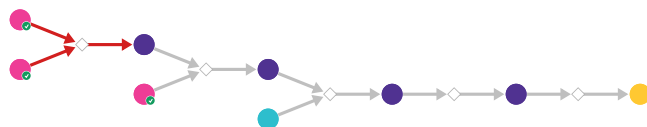
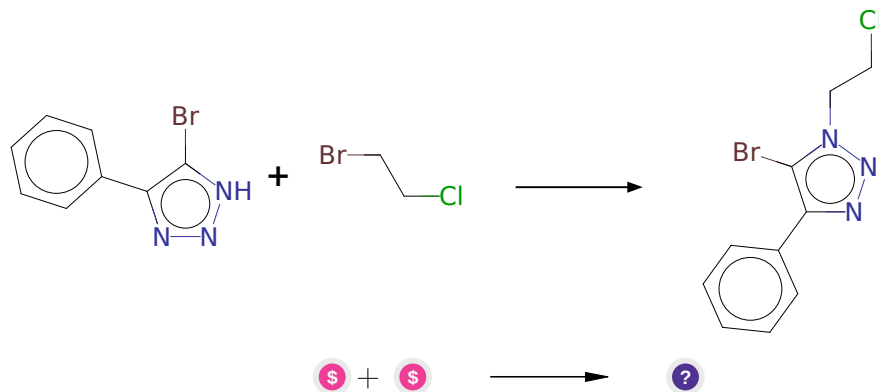


Figure 4: Outline of path 4

2.4.1 N-alkylation of heterocycles



Substrates:

- 1-Bromo-2-chloroethane - *available at Sigma-Aldrich*
- 4-Bromo-5-phenyl-1H-1,2,3-triazole - *available at Sigma-Aldrich*

Products:

- ClCCn1nnc(-c2ccccc2)c1Br

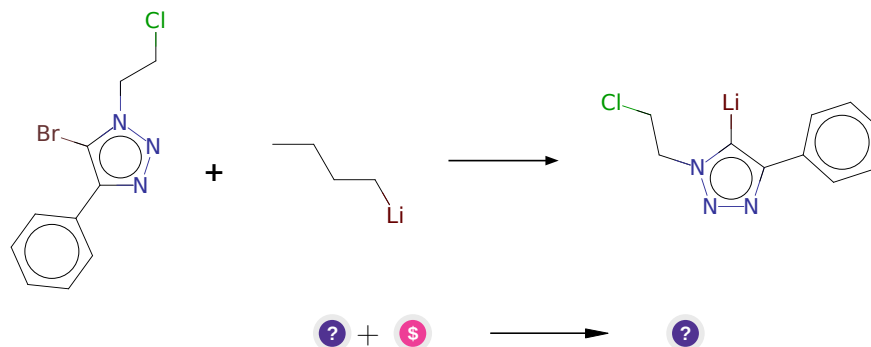
Typical conditions: NaH. DMF

Protections: none

Reference: [10.1016/j.ejmech.2010.11.014](#) or [10.1039/C6OB01149G](#) (SI) or [10.1246/cl.2005.442](#) or [10.1021/o403570z](#) (SI) or [10.1016/S0040-4020\(01\)00360-X](#)

Retrosynthesis ID: 10000414

2.4.2 Br/Li exchange



Substrates:

1. ClCCn1nnc(-c2ccccc2)c1Br
2. n-BuLi - *available at Sigma-Aldrich*

Products:

1. [Li]c1c(-c2ccccc2)nnn1CCCl

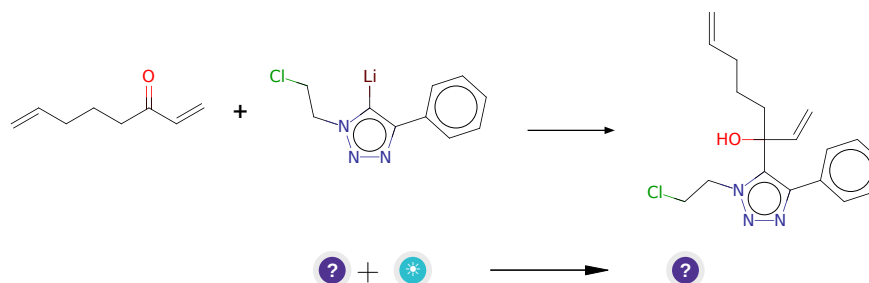
Typical conditions: nBuLi.or.tBuLi.THF.-78C

Protections: none

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

Retrosynthesis ID: 30672

2.4.3 Addition of electrophiles to lithiated arenes/heteroarenes



Substrates:

1. [Li]c1c(-c2ccccc2)nnn1CCCl
2. octa-1,7-dien-3-one

Products:

1. C=CCCCC(O)(C=C)c1c(-c2ccccc2)nnn1CCCl

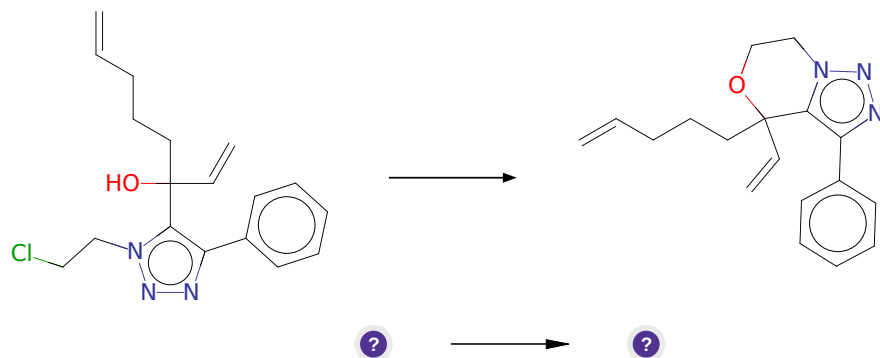
Typical conditions: THF.-78 deg C

Protections: none

Reference: [10.1021/ml300335r](https://doi.org/10.1021/ml300335r) and [10.1021/acs.jmedchem.6b00866](https://doi.org/10.1021/acs.jmedchem.6b00866)

Retrosynthesis ID: 31008139

2.4.4 Alkylation of tertiary alcohols



Substrates:

1. C=CCCCC(O)(C=C)c1c(-c2cccc2)nn1CCCl

Products:

1. C=CCCCC1(C=C)OCCn2nnc(-c3cccc3)c21

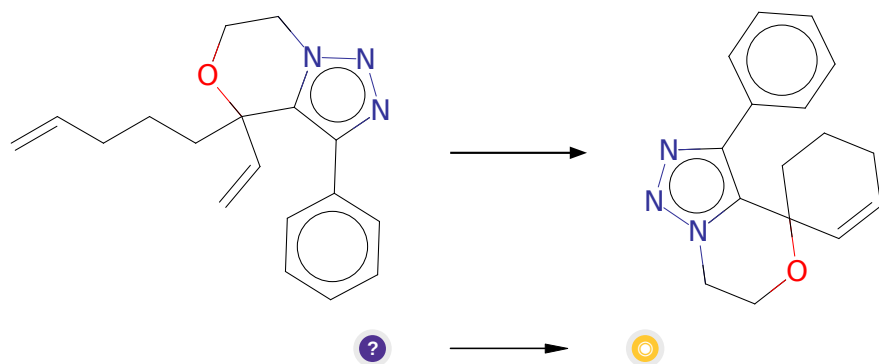
Typical conditions: K₂CO₃.acetone.heat

Protections: none

Reference: [10.1016/S0040-4020\(01\)90106-1](#) and [10.1021/acs.analchem.5b04461](#) and [10.3390/molecules24091643](#)

Retrosynthesis ID: 31010930

2.4.5 Ring-Closing Metathesis



Substrates:

1. C=CCCCC1(C=C)OCCn2nnc(-c3cccc3)c21

Products:

1. C1=CC2(CCC1)OCCn1nnc(-c3ccccc3)c12

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

Protections: none

Reference: DOI: [10.1002/anie.200800693](https://doi.org/10.1002/anie.200800693) and [10.1021/acs.orglett.8b04003](https://doi.org/10.1021/acs.orglett.8b04003) and [10.1021/jo0264729](https://doi.org/10.1021/jo0264729) and [10.1021/ja072334v](https://doi.org/10.1021/ja072334v) and [10.1002/ejoc.201001102](https://doi.org/10.1002/ejoc.201001102)

Retrosynthesis ID: 31014187

2.5 Path 5

Score: 2441570.39

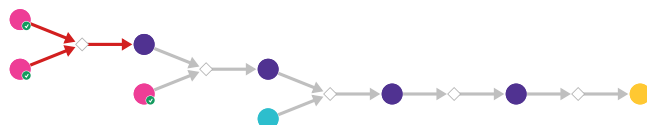
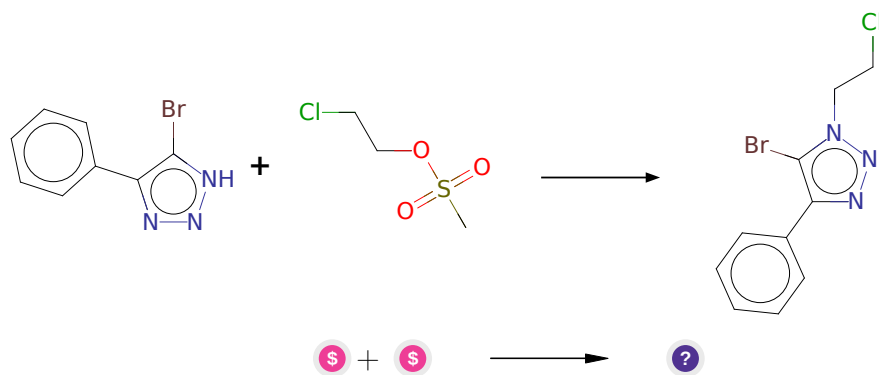


Figure 5: Outline of path 5

2.5.1 Alkylation of N-heterocycles with activated alcohols



Substrates:

1. 2-Chloroethyl methanesulfonate - *available at Sigma-Aldrich*
2. 4-Bromo-5-phenyl-1H-1,2,3-triazole - *available at Sigma-Aldrich*

Products:

1. ClCCn1nnc(-c2ccccc2)c1Br

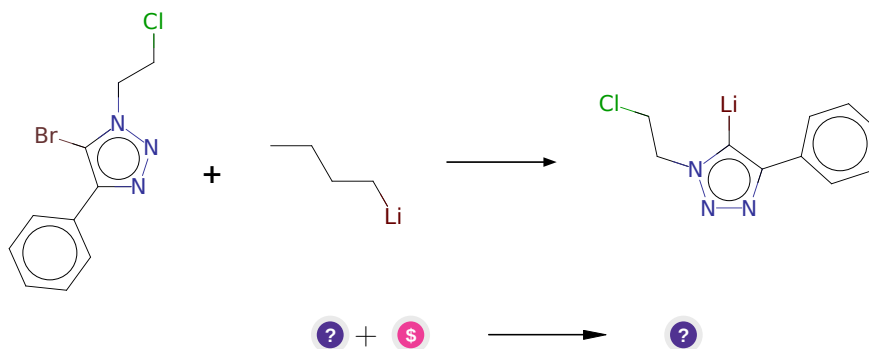
Typical conditions: K₂CO₃.MeCN.heating

Protections: none

Reference: [10.1021/jm200112k](#) (suppl. Info p.27) and WO2013167586A1 p.9 and WO2004/24147 p.23

Retrosynthesis ID: 24133

2.5.2 Br/Li exchange



Substrates:

1. ClCCn1nnc(-c2ccccc2)c1Br
2. n-BuLi - *available at Sigma-Aldrich*

Products:

1. [Li]c1c(-c2ccccc2)nnn1CCCl

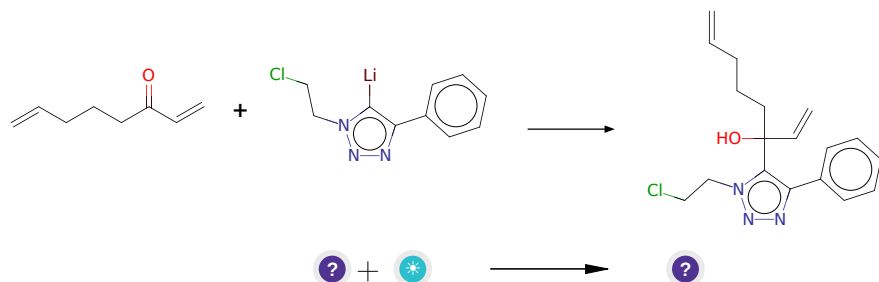
Typical conditions: nBuLi.or.tBuLi.THF.-78C

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

2.5.3 Addition of electrophiles to lithiated arenes/heteroarenes



Substrates:

1. [Li]c1c(-c2ccccc2)nnn1CCCl
2. octa-1,7-dien-3-one

Products:

1. C=CCCCC(O)(C=C)c1c(-c2ccccc2)nnn1CCCl

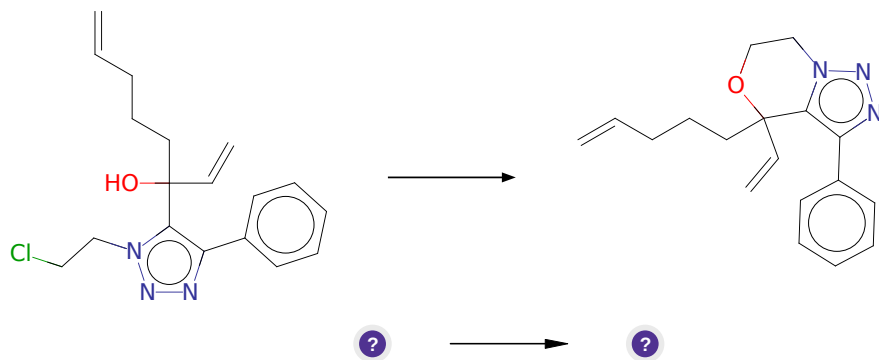
Typical conditions: THF.-78 deg C

Protections: none

Reference: [10.1021/ml300335r](#) and [10.1021/acs.jmedchem.6b00866](#)

Retrosynthesis ID: 31008139

2.5.4 Alkylation of tertiary alcohols



Substrates:

1. C=CCCCC(O)(C=C)c1c(-c2ccccc2)nnn1CCCl

Products:

1. C=CCCCC1(C=C)OCCn2nnc(-c3ccccc3)c21

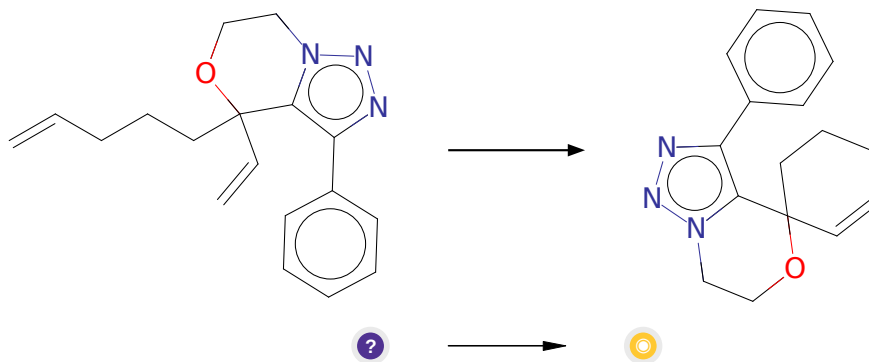
Typical conditions: K₂CO₃.acetone.heat

Protections: none

Reference: [10.1016/S0040-4020\(01\)90106-1](https://doi.org/10.1016/S0040-4020(01)90106-1) and [10.1021/acs.analchem.5b04461](https://doi.org/10.1021/acs.analchem.5b04461) and [10.3390/molecules24091643](https://doi.org/10.3390/molecules24091643)

Retrosynthesis ID: 31010930

2.5.5 Ring-Closing Metathesis



Substrates:

1. C=CCCCC1(C=C)OCCn2nnc(-c3ccccc3)c21

Products:

1. C1=CC2(CCC1)OCCn1nnc(-c3ccccc3)c12

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

Protections: none

Reference: DOI: [10.1002/anie.200800693](https://doi.org/10.1002/anie.200800693) and [10.1021/acs.orglett.8b04003](https://doi.org/10.1021/acs.orglett.8b04003) and [10.1021/jo0264729](https://doi.org/10.1021/jo0264729) and [10.1021/ja072334v](https://doi.org/10.1021/ja072334v) and [10.1002/ejoc.201001102](https://doi.org/10.1002/ejoc.201001102)

Retrosynthesis ID: 31014187