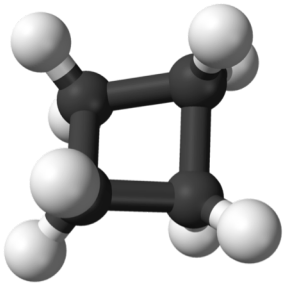
S. Patel

Cyclobutanes in the Pharmaceutical Industry

Burns Lab



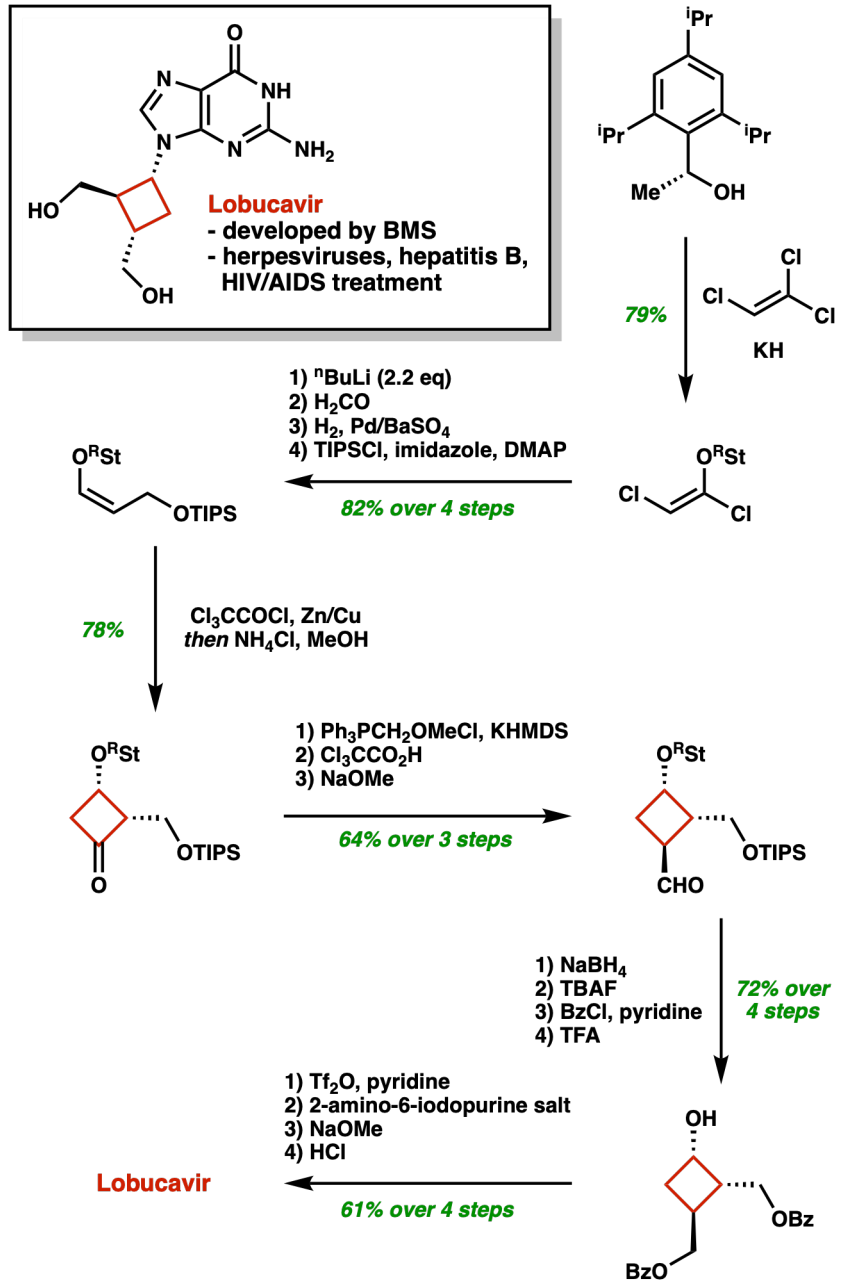
Why Cyclobutanes?
- rigid scaffold, well-defined spatial arrangement of substituents
- move away from arenes as a means to achieve rigid structures
- avoid toxicity arising from arene metabolism

Chem. Soc. Rev. 2011, 40, 5514
Chem. Rev. 2014, 114, 8257

Covered:
- syntheses of pharmaceutically relevant cyclobutane-containing molecules
- primarily process chemistry reports
- some medicinal chemistry reports

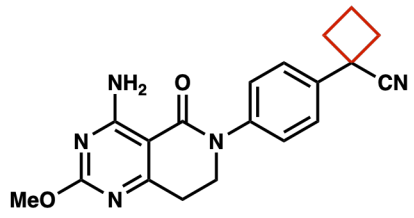
Road Map:
1) syntheses that construct the cyclobutane core
2) syntheses that utilize commercially available cyclobutanes

Not Comprehensively Covered:
- photochemistry
  e.g. *Org. Process Res. Dev.* 2010, 14, 405; *Org. Process Res. Dev.* 2016, 20, 409; *Org. Process Res. Dev.* 2018, 22, 595
- construction of useful intermediates
  e.g. *Org. Process Res. Dev.* 1998, 2, 379; *Org. Process Res. Dev.* 2020, 24, 802
- pinene derivatives

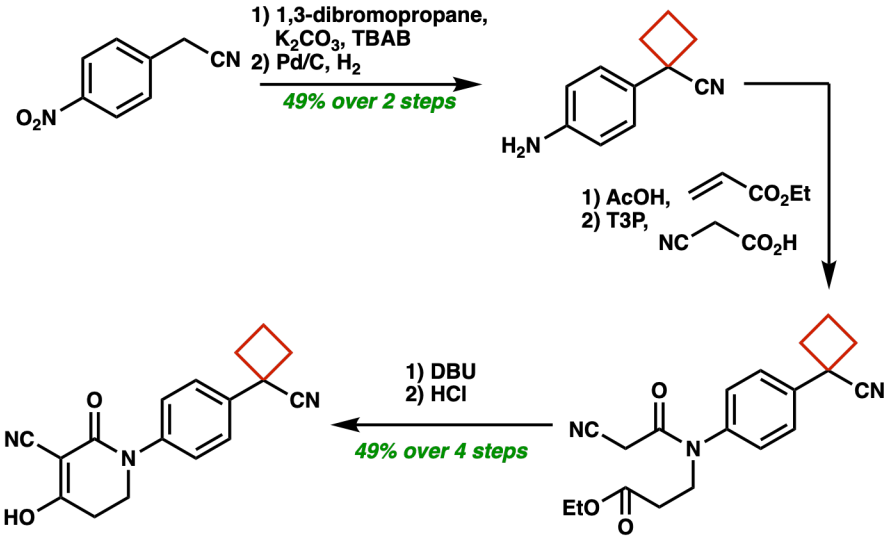


J. Org. Chem. 2012, 77 1710

Cyclobutanes in the Pharmaceutical Industry

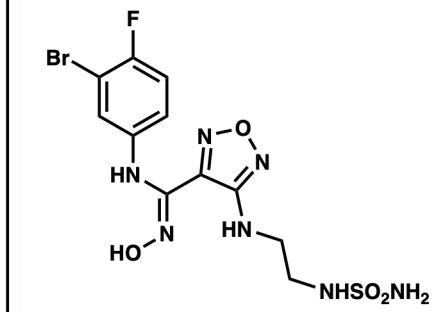


DGAT-1 Inhibitor
- developed by Pfizer
- diacylglycerol acyltransferase-1 (DGAT-1) inhibitor
- Type II diabetes and obesity treatment

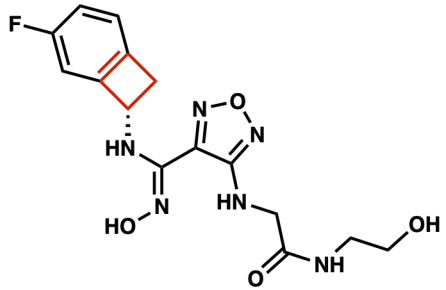


direct treatment of chloride with amine gave lower yield, hydrolysis became an issue

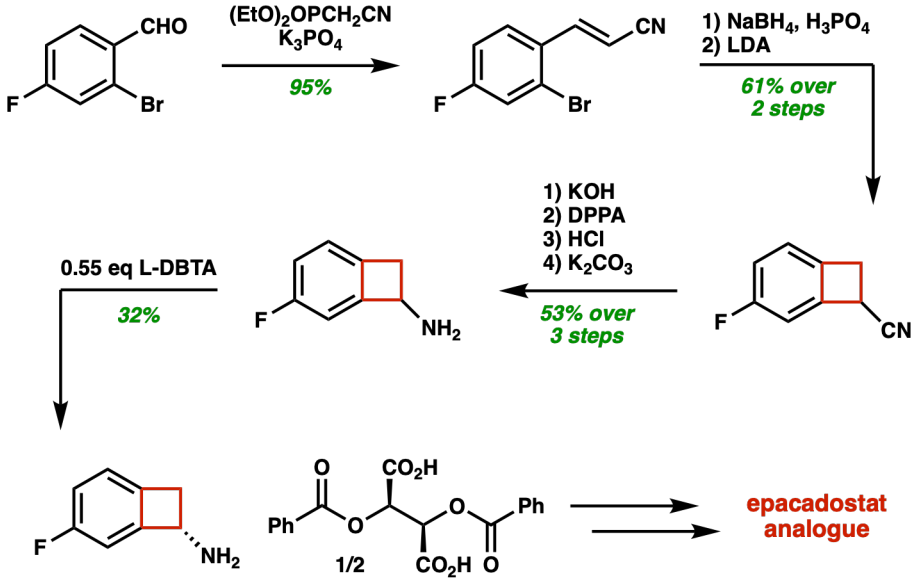
Org. Process Res. Dev. 2013, 17, 1510



epacadostat

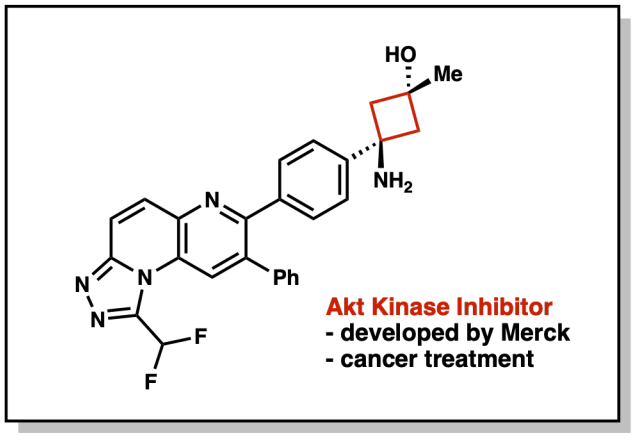


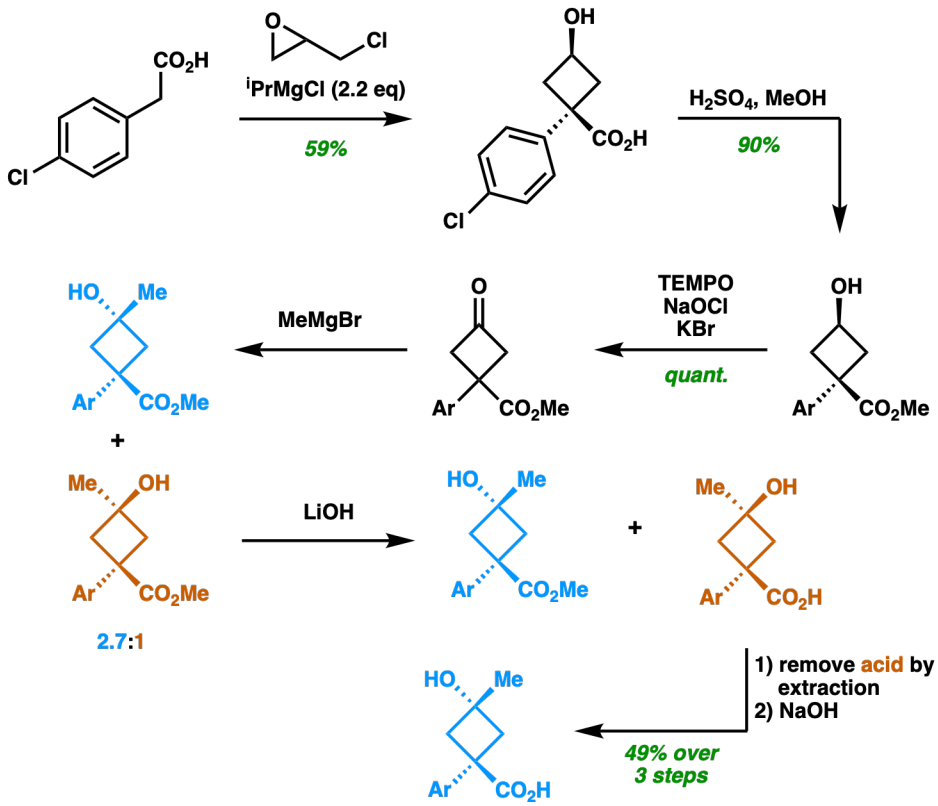
epacadostat analogue
- developed by Merck
- IDO1 inhibitor
- cancer treatment
- used in combination with mAb therapy to prevent drug tolerance

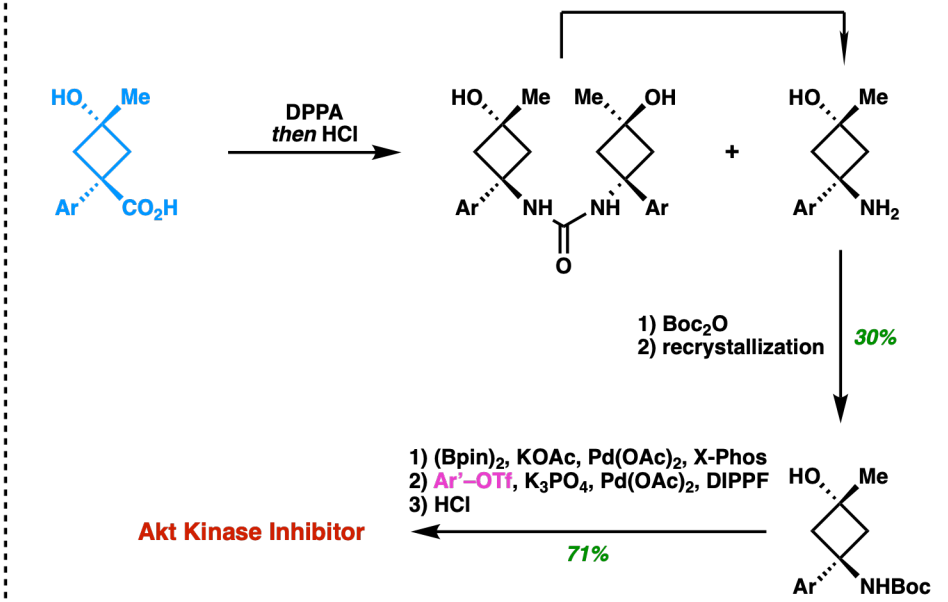


Org. Process Res. Dev. 2019, 23, 1178

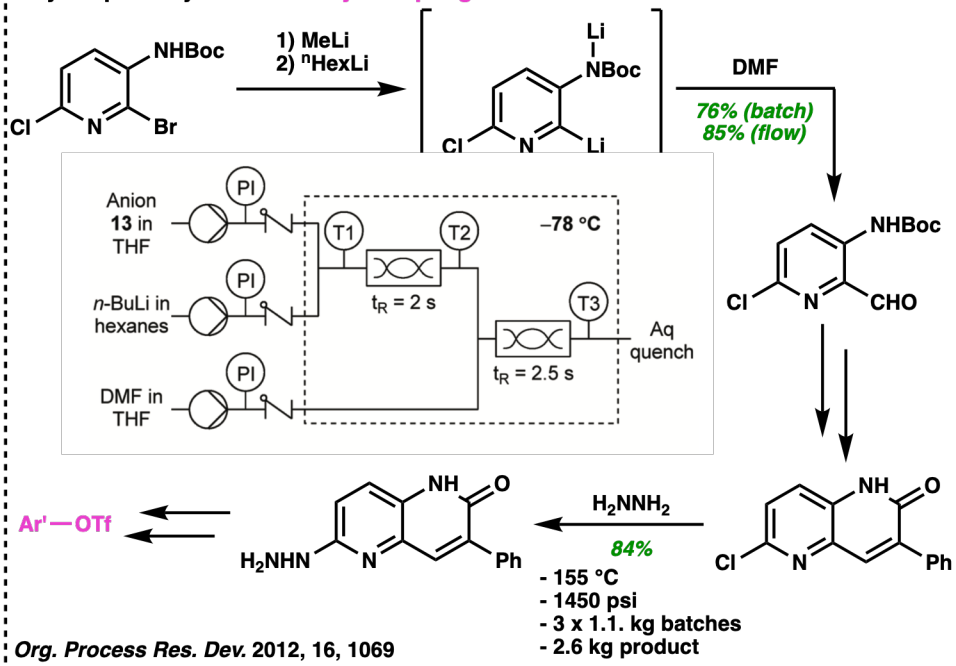
Cyclobutanes in the Pharmaceutical Industry





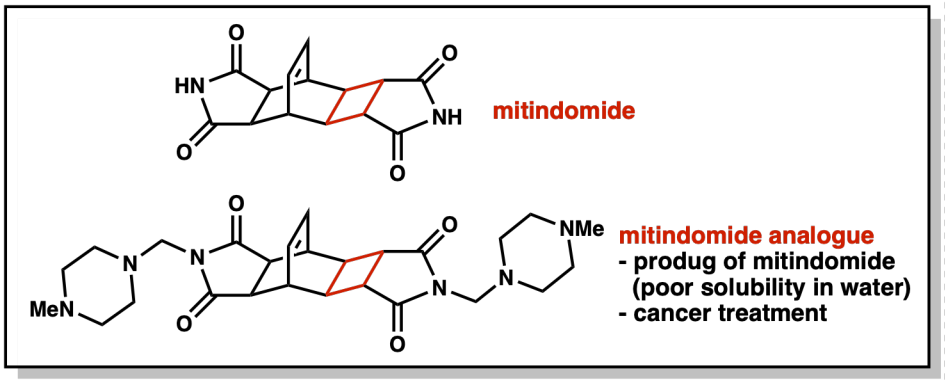


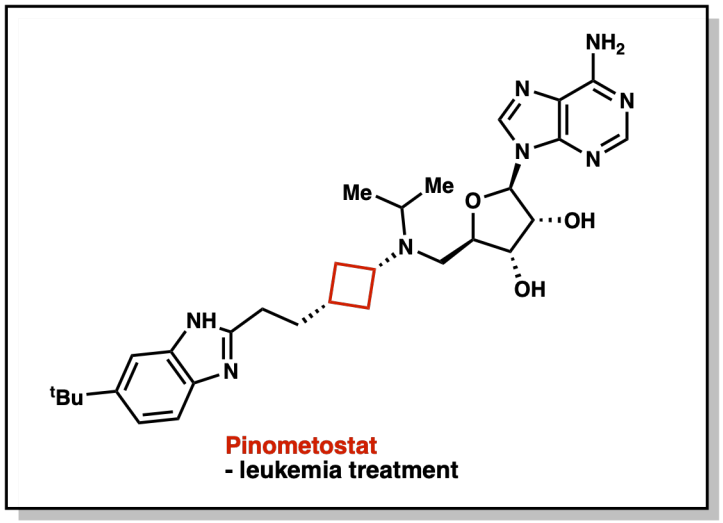
Key Steps in Synthesis of Aryl Coupling Partner

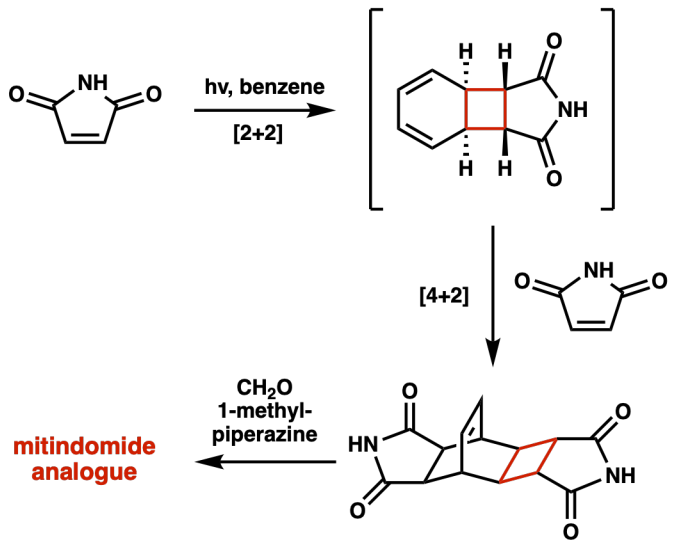


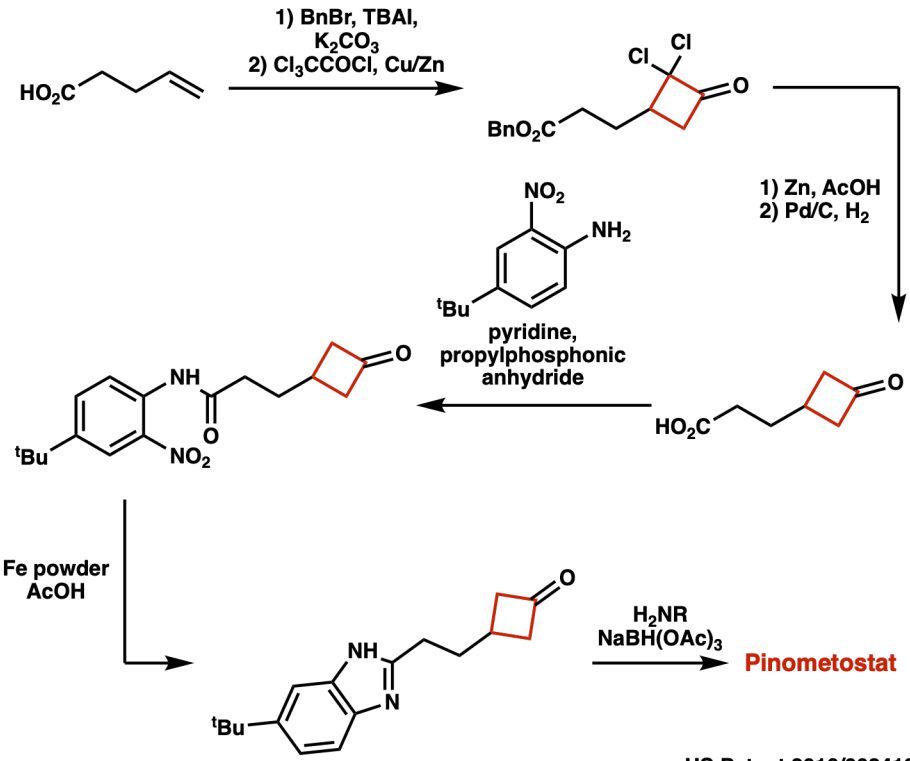
Org. Process Res. Dev. 2012, 16, 1069

Cyclobutanes in the Pharmaceutical Industry







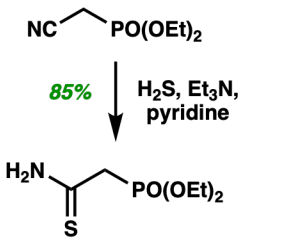


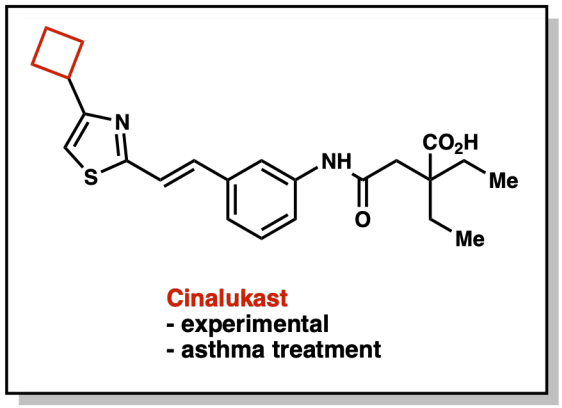
"Both radiation and heating were provided by a 'Hanovia' S 500 mercury-vapour ultraviolet lamp"

J. Med. Chem. 1986, 29, 2164

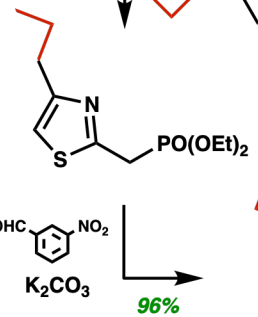
US Patent 2016/0024134

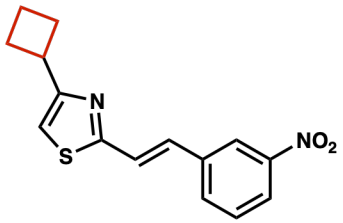
Cyclobutanes in the Pharmaceutical Industry

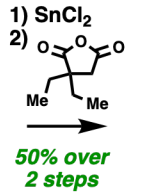




Cinalukast
- experimental
- asthma treatment

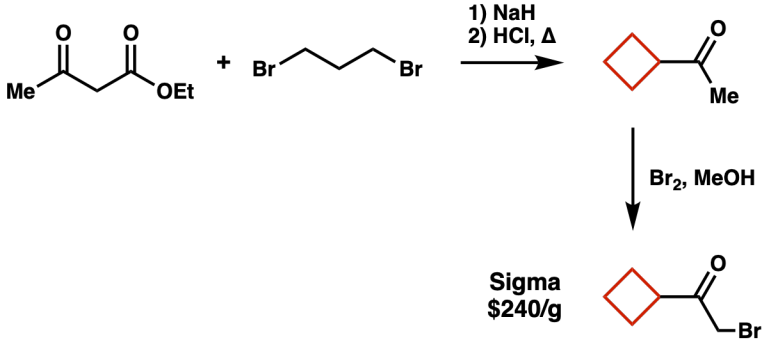




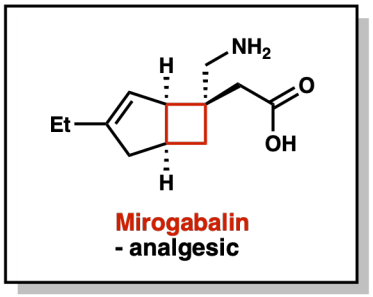


Cinalukast

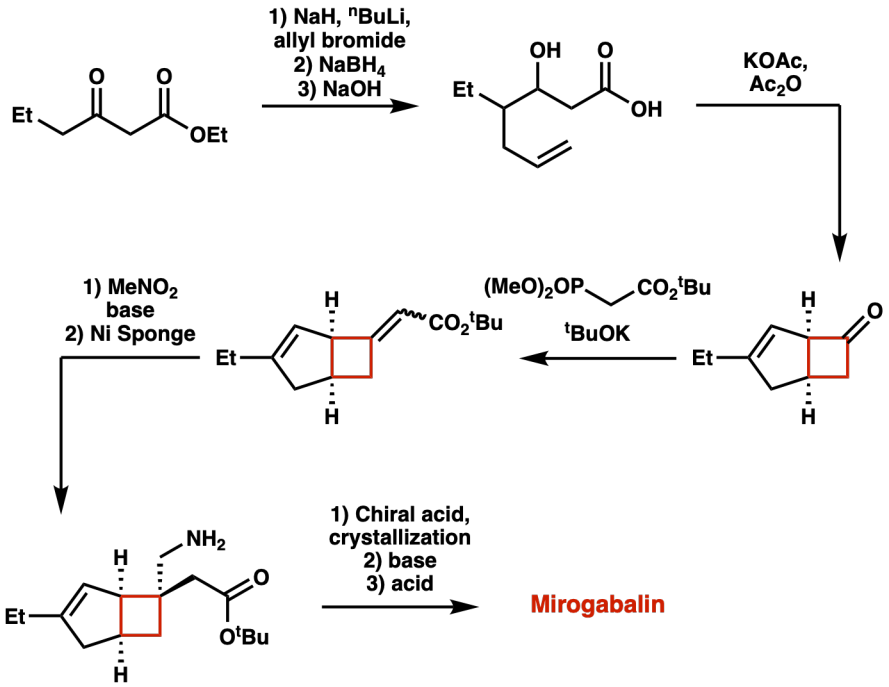
Cyclobutane Source:



Tet. Lett. 1996, 37, 5445

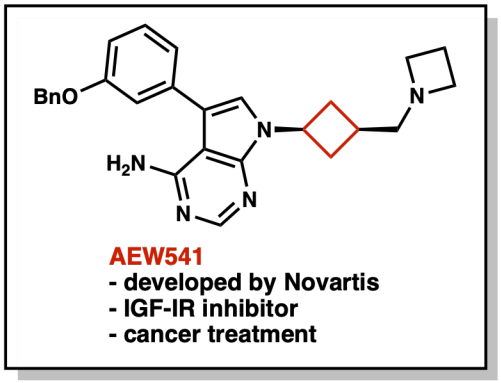


Mirogabalin
- analgesic

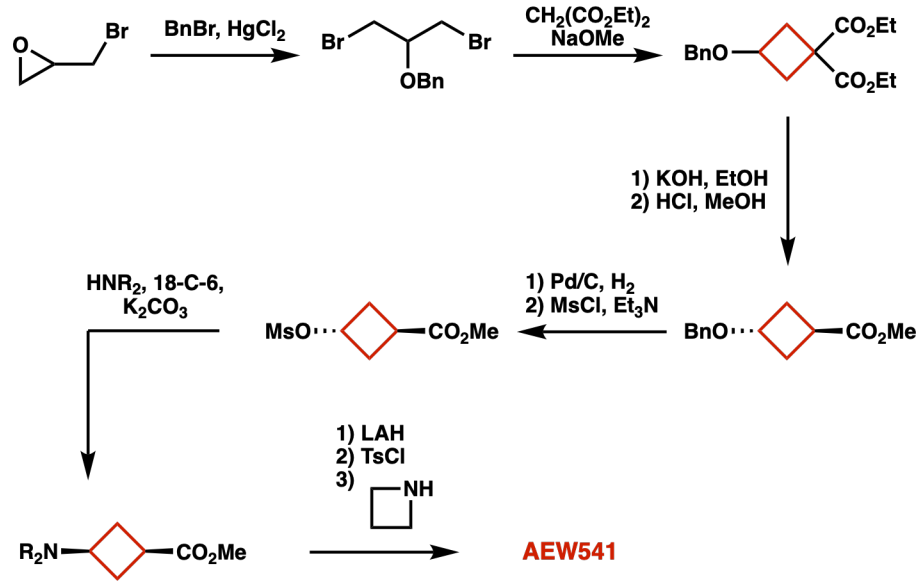


European Patent 2719676
European Patent 2871176

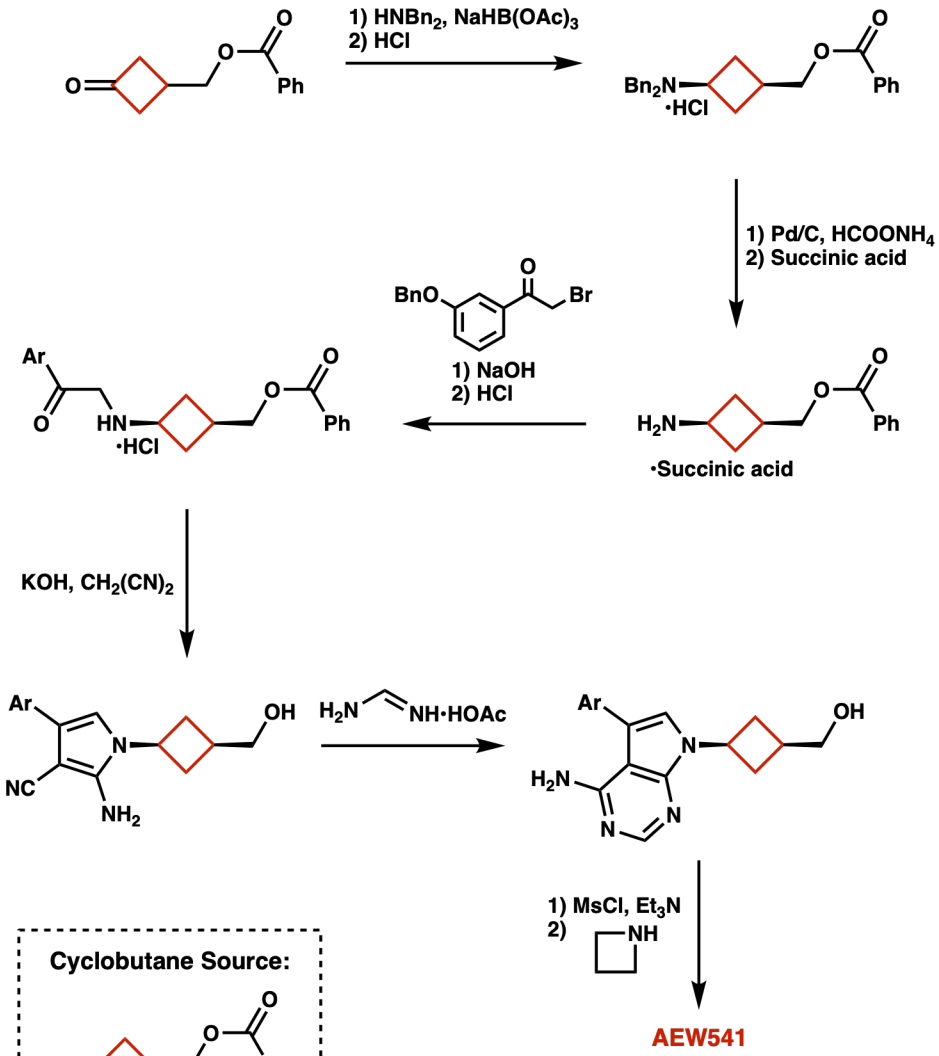
Cyclobutanes in the Pharmaceutical Industry



Discovery Route



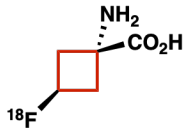
Process Route



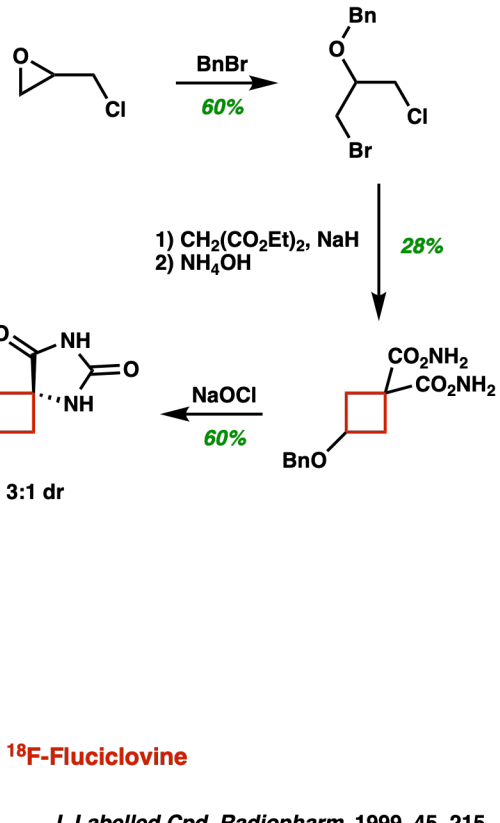
Cyclobutane Source:

PharmaBlock
$77/g

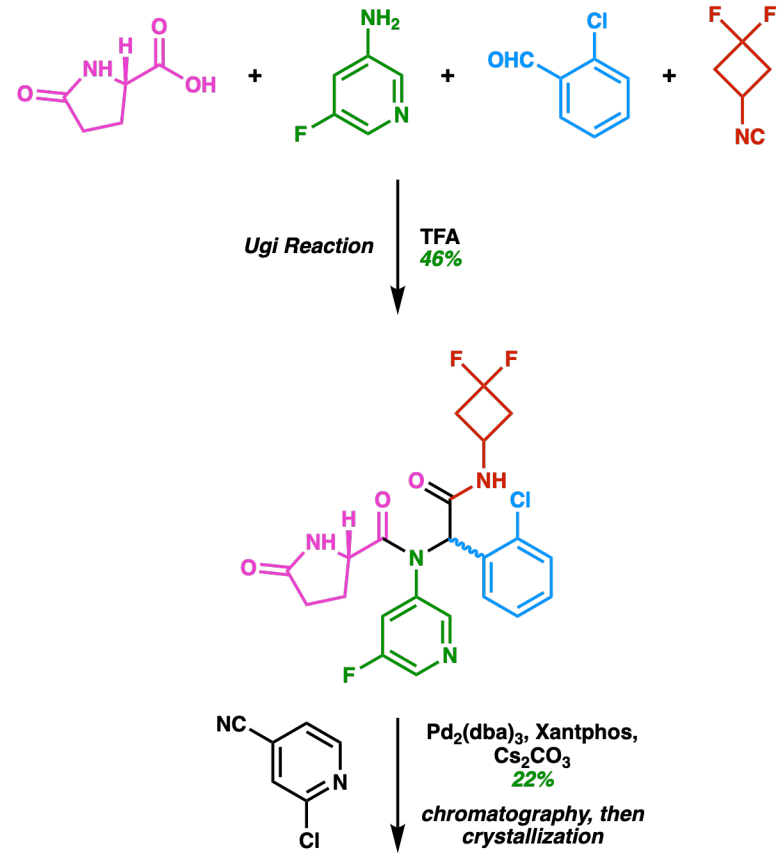
Org. Process Res. Dev. 2007, 11, 825
J. Org. Chem. 1996, 61, 3849



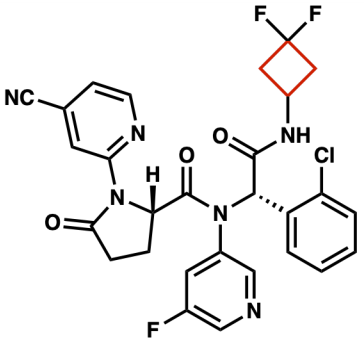
^{18}F-Fluciclovine (Axumin)
- approved in 2016
- PET imaging of prostate cancer



J. Labelled Cpd. Radiopharm. 1999, 45, 215

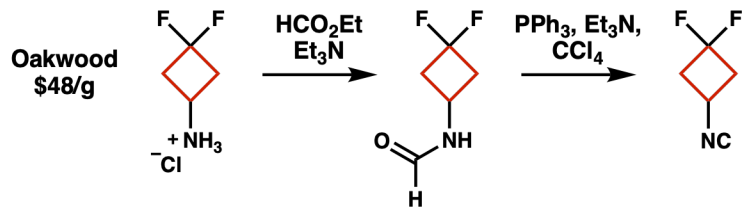


Ivosidenib
99.7% *de*



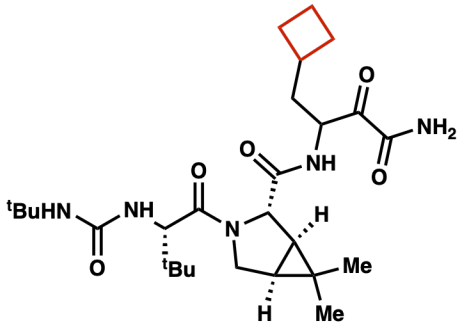
Ivosidenib
- approved in 2019
- mIDH inhibitor
- acute myeloid leukemia treatment

Cyclobutane Source:



ACS Med. Chem. Lett. 2018, 9, 300

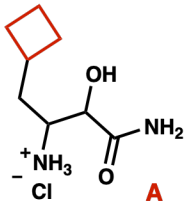
Cyclobutanes in the Pharmaceutical Industry



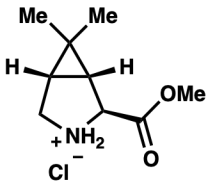
Boceprevir
- protease inhibitor
- Hepatitis C virus (HCV) treatment
- approved in 2011
- developed by Schering-Plough prior to acquisition by Merck

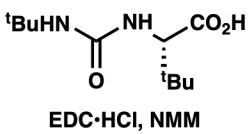
Cyclobutane Source:

PharmaBlock
$533/g



A



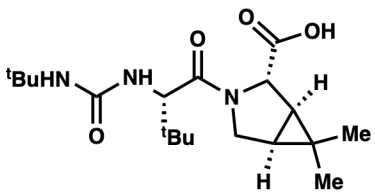


EDC·HCl, NMM
then NaOH
83% over 2 steps

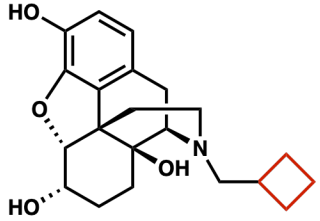
1) EDC·HCl
NMM, A
2) DMP

63% over 2 steps

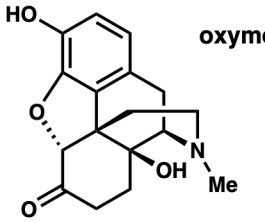
Boceprevir



Org. Process Res. Dev. 2015, 19, 1559

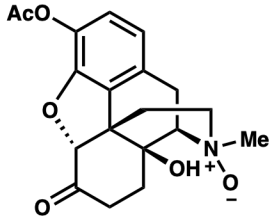


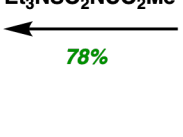
Nalbuphine (Nubain)
- approved in 1979
- analgesic
- synthesized from oxymorphone, a natural opiate



oxymorphone

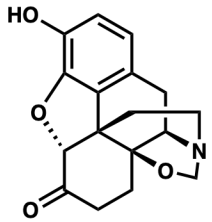
1) Ac_2O, DMAP, Et_3N
2) mCPBA



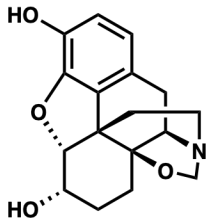


$Et_3\overset{+}{N}SO_2\overset{-}{N}CO_2Me$

78%



$NaBH_4$



ClMg

40% over 2 steps

Nalbuphine

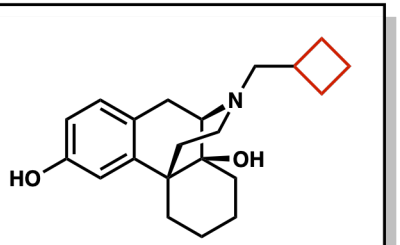
Cyclobutane Source:

Cl

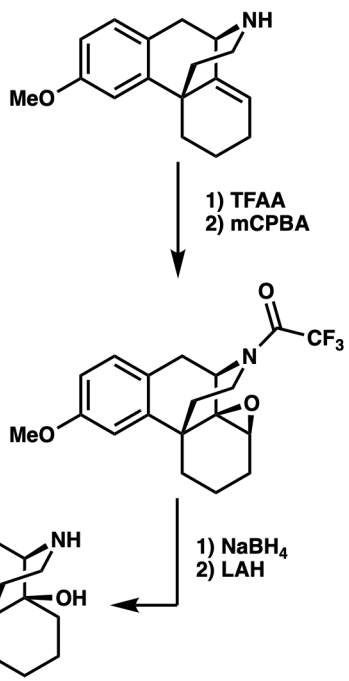
Sigma
$63/g

Adv. Synth. Catal. 2013, 355, 1869

Cyclobutanes in the Pharmaceutical Industry

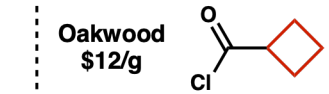


Butorphanol
- opioid analgesic
- developed by Bristol-Myers
- approved in 1979

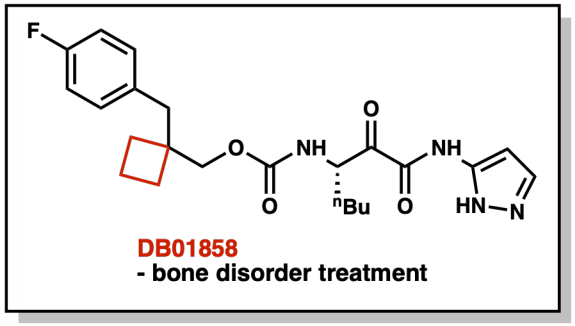


Cyclobutane Source:

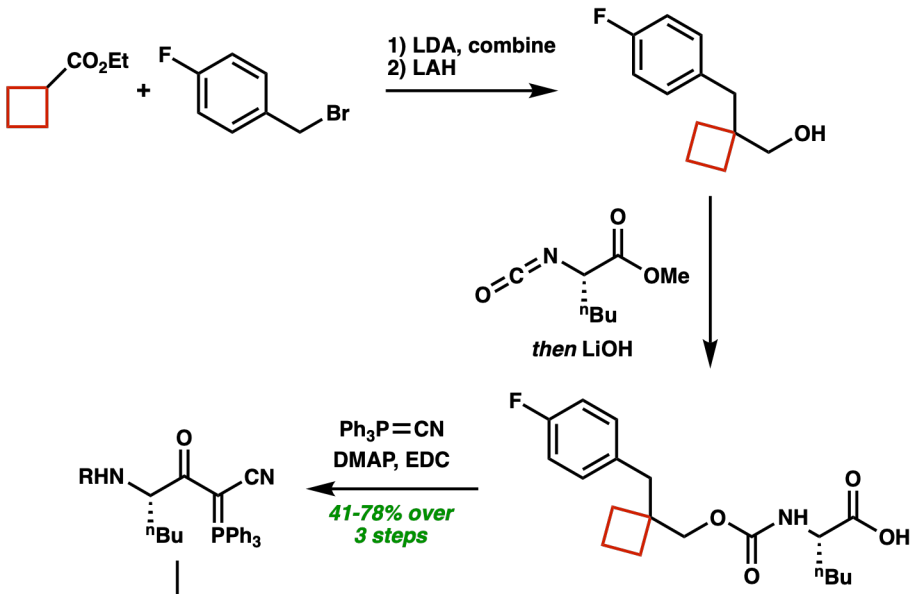
Oakwood
$12/g



US Patent 3819635

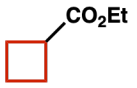


DB01858
- bone disorder treatment



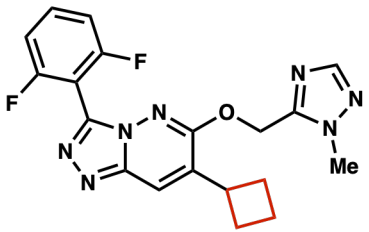
Cyclobutane Source:

Oakwood
$10/g



Bioorg. Med. Chem. Lett. 2004, 14, 4897
WO2003062192

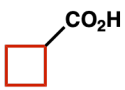
Cyclobutanes in the Pharmaceutical Industry

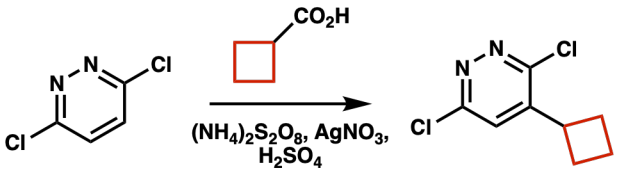


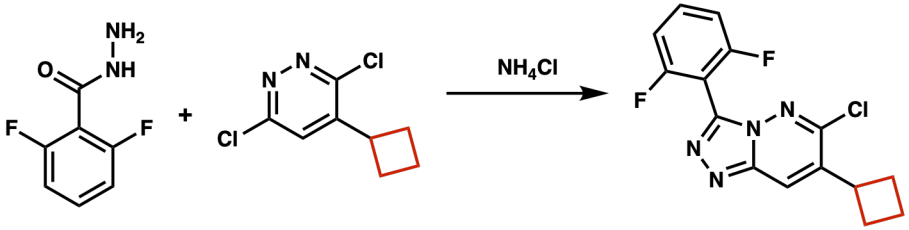
MRK-409
- $GABA_A$ agonist

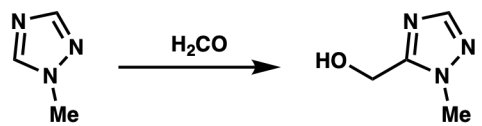
Cyclobutane Source:

Oakwood
$10/g



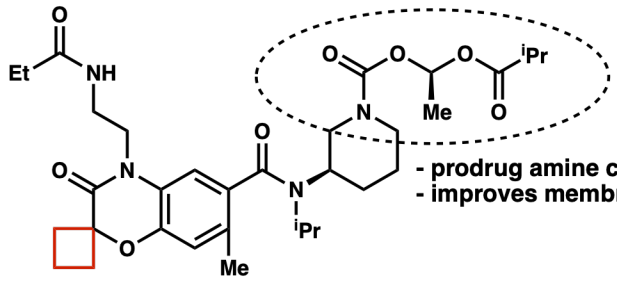






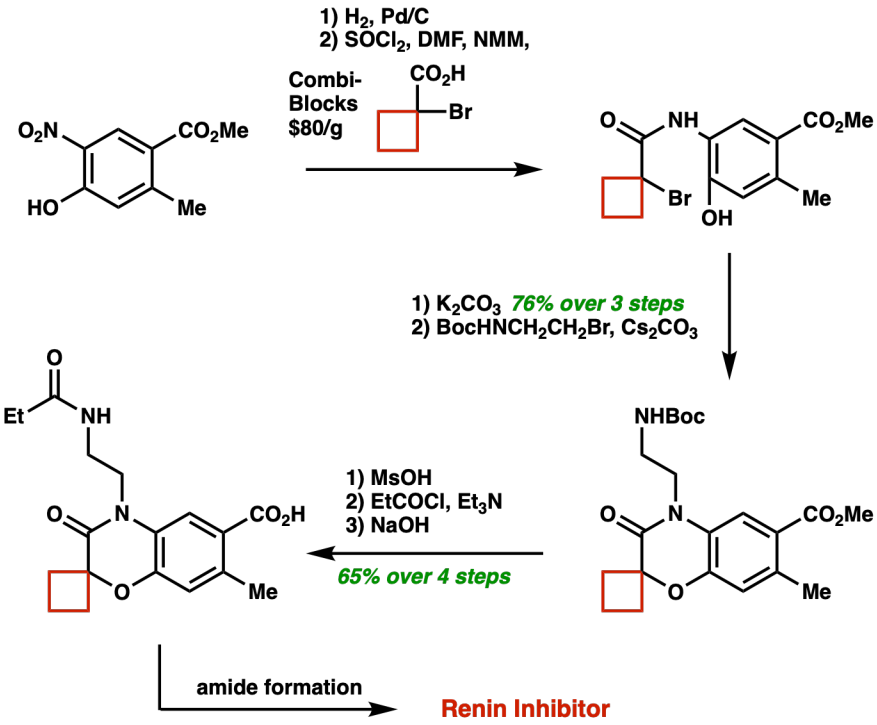
MRK-409

WO 99/37644
J. Med. Chem. 2005, 48, 7089
Journal of Psychopharmacology 2009, 25, 314



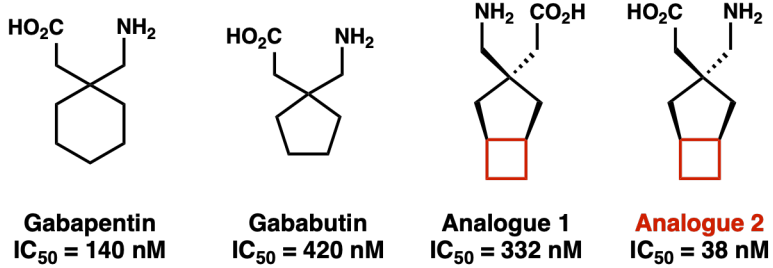
- prodrug amine cap
- improves membrane permeability

Renin Inhibitor
- developed by Sumitomo Dainippon Pharma
- plasma renin activity (PRA) inhibitor
- hypertension treatment

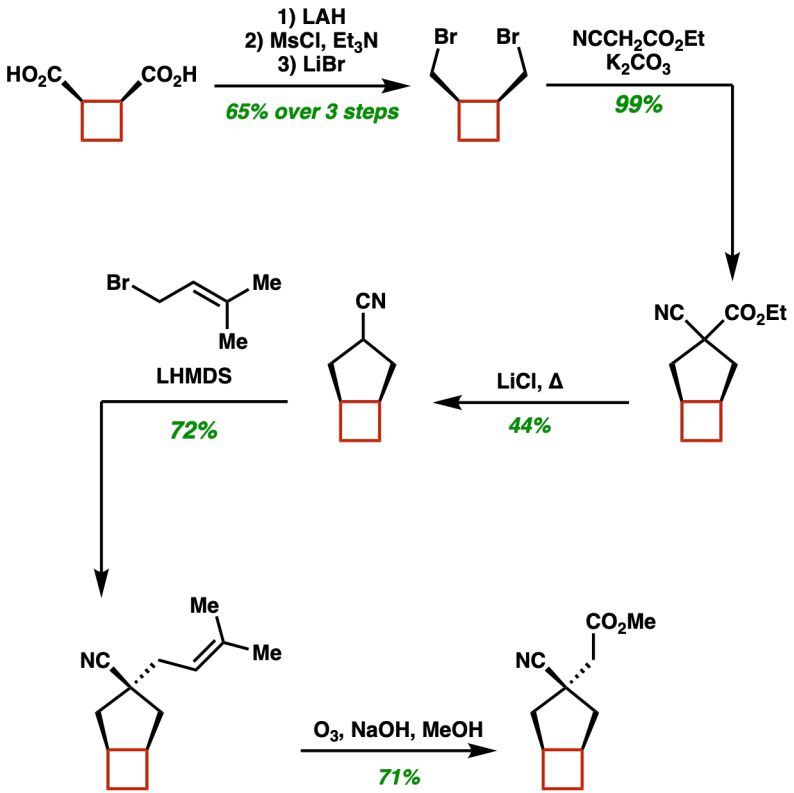


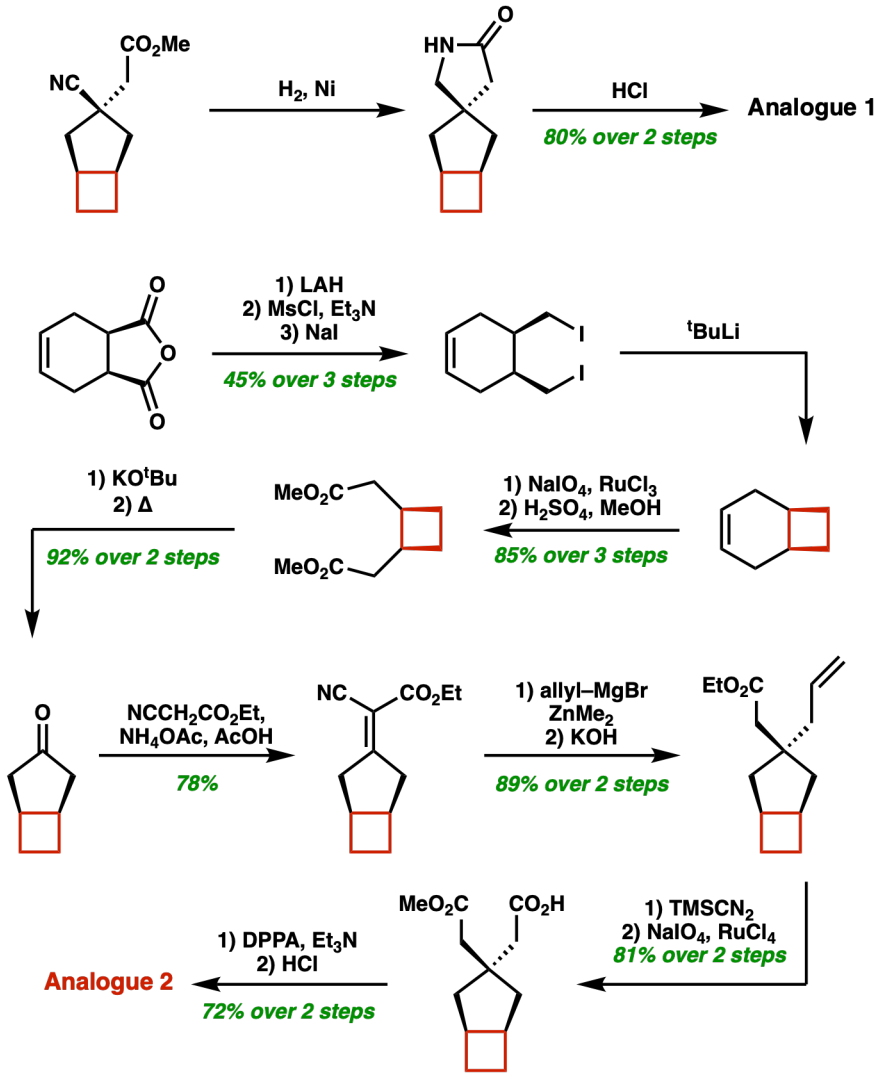
Org. Process Res. Dev. 2019, 23, 499

Cyclobutanes in the Pharmaceutical Industry

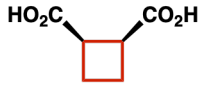


- neuropathic pain and anxiety treatment
- bind to the $\alpha_2\delta$ subunit of a voltage gated Ca channel



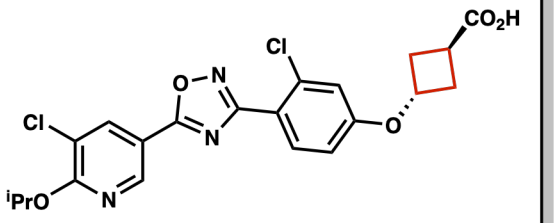


Cyclobutatne Source (Analogue 1): Sigma $207/g



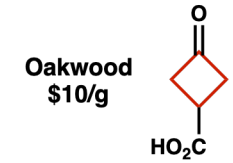
Bioorg. Med. Chem. Lett. 2010, 20, 461

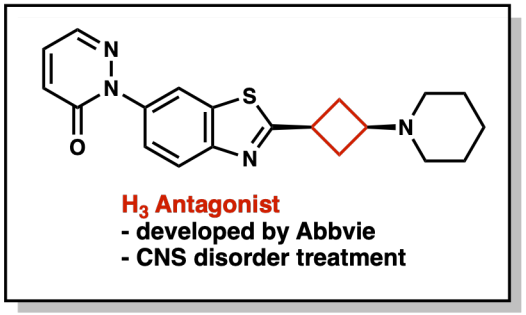
Cyclobutanes in the Pharmaceutical Industry



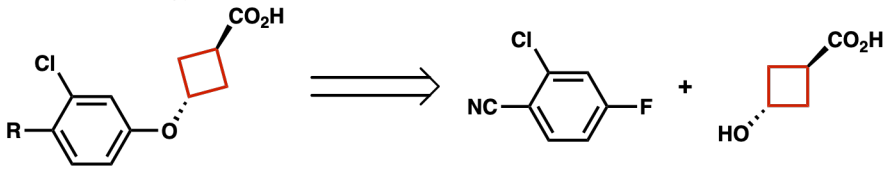
Cyclobutane Source:

Oakwood
$10/g

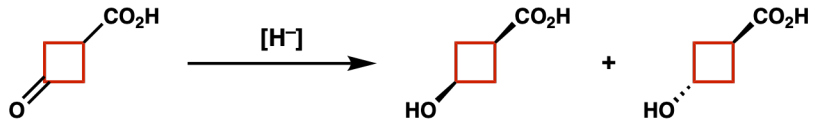




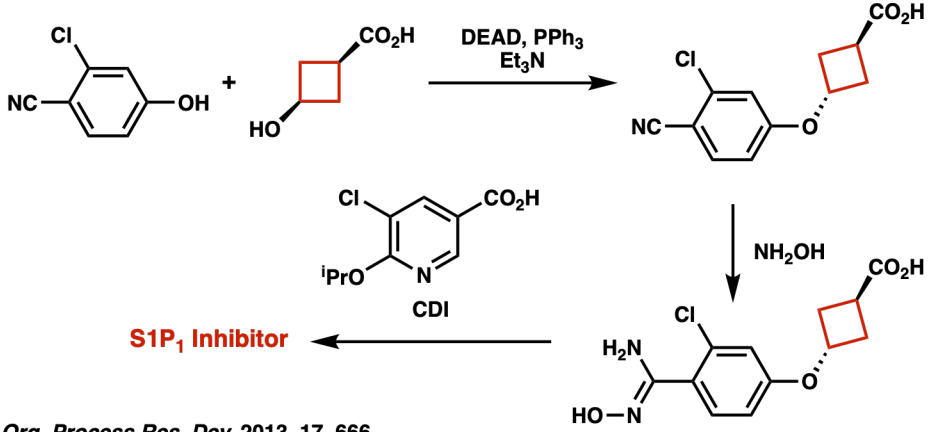
Envisioned Strategy



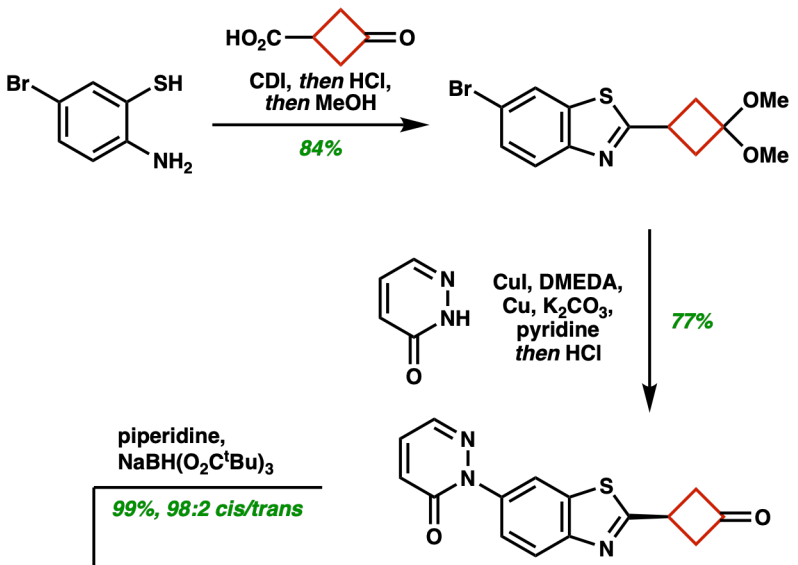
However..



Final Route



Org. Process Res. Dev. 2013, 17, 666



Cyclobutane Source:

Oakwood
$10/g

Org. Process Res. Dev. 2014, 18, 191

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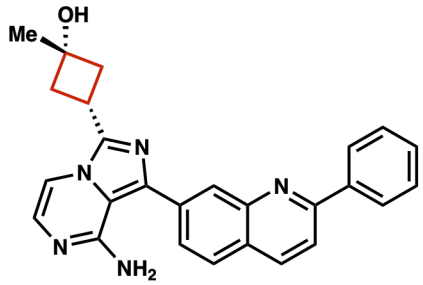
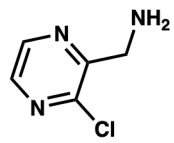
Cyclobutanes in the Pharmaceutical Industry

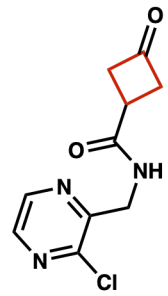
Burns Lab



Linsitinib
- IGF-1R inhibitor
- cancer treatment

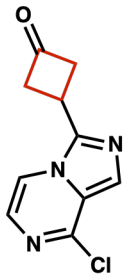


2,5-dioxo-pyrrolidin-1-yl ester,



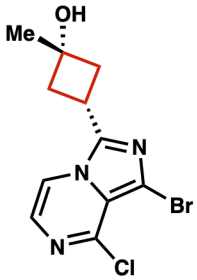
$POCl_3$

75% over 2 steps



1) NBS
2) MeMgCl

65% over 2 steps



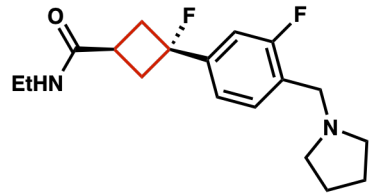
1) NH_3
2) $(RO)_2B-Ar$, $PdCl_2(dppf)$, K_2CO_3

52-71% over 2 steps

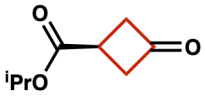
Linsitinib

Cyclobutane Source:

Oakwood
$10/g

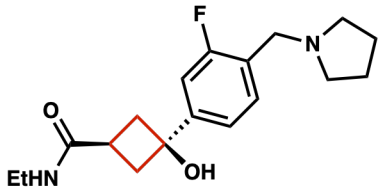


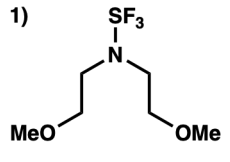
PF-03654746
- Histamine H3 antagonist
- Alzheimer's and daytime sleepiness treatment



1) ArMgLi
2) $EtNH_2$
3) $^iPrOAc/H_2O$ extraction
4) add *n*-heptane, crystallize

55%



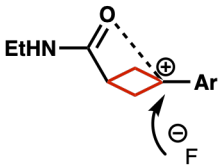


1)

Deoxo-Fluor

2) 2-MeTHF/ H_2O extraction
3) *p*-TsOH

78%



PF-03654746

Cyclobutane Source:

Oakwood
$10/g

US Patent 2013/0123501
ACS Med. Chem. Lett. 2013, 4, 627

Org. Process Res. Dev. 2012, 16, 1393

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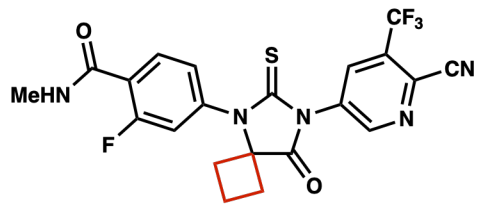
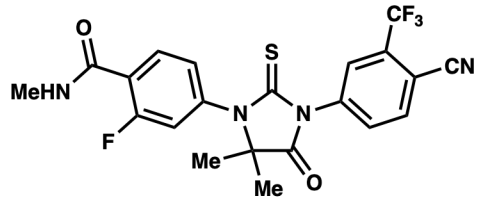
Cyclobutanes in the Pharmaceutical Industry

Burns Lab

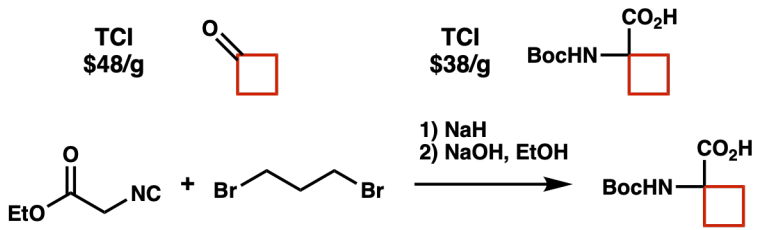


Apalutamide
- antiandrogen drug
- prostate cancer treatment
- discovered by Sawyers and Jung at UCLA
- approved in 2018
- similar to enzalutamide (below), more efficacious and has a lower likelihood of causing seizures (fourfold lower brain penetration in mice)



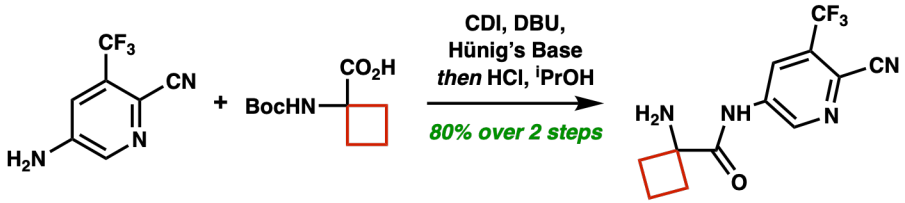
Enzalutamide
- approved in 2012
- predecessor to apalutamide
- key differences include dimethyl group instead of cyclobutane and phenyl group instead of pyrimidyl group on the right-hand portion of the molecule

Cyclobutane Source:

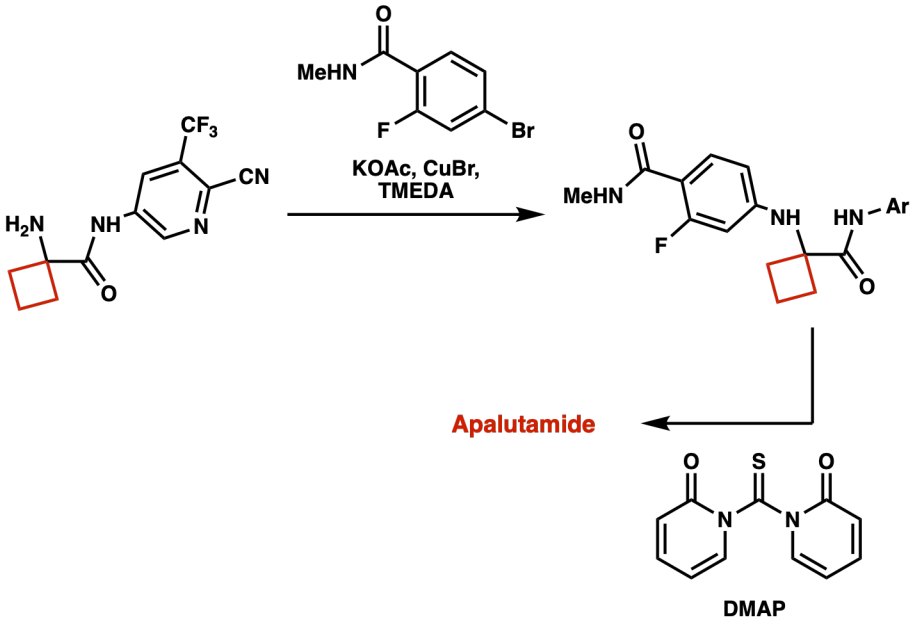


1st Generation Cyclobutane Incoporation (UCLA)

2nd Generation Cyclobutane Incoporation, Avoids Cyanide (Aragon Pharmaceuticals)

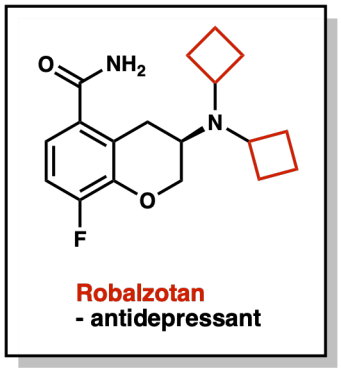


Final Stages of 2nd Generation Route (Aragon)



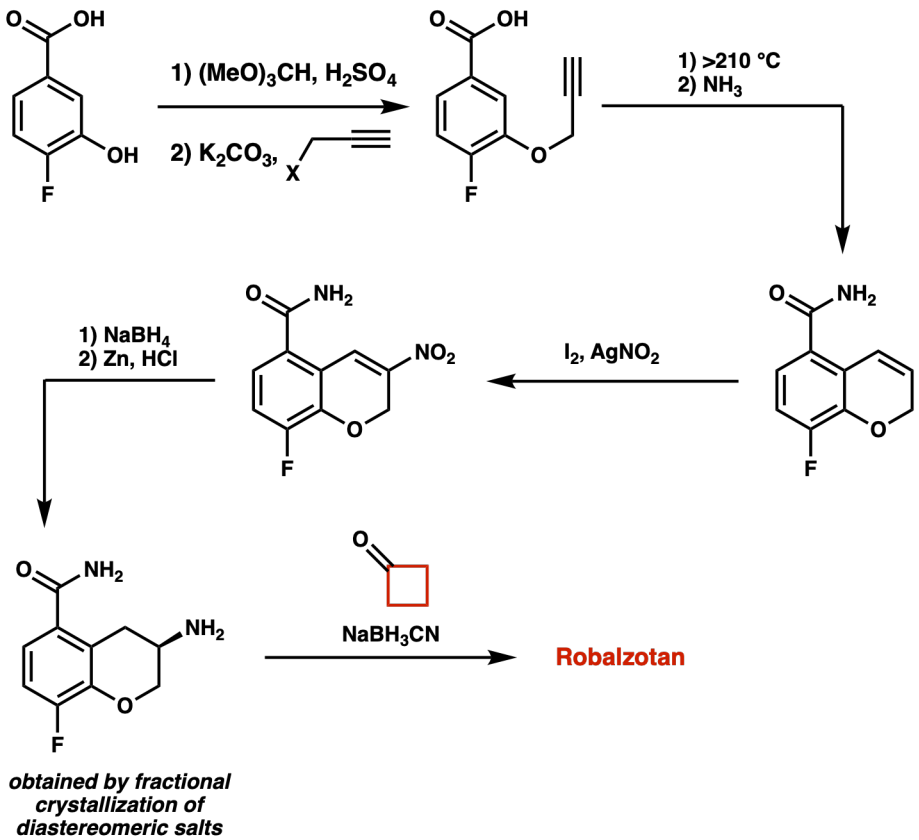
Org. Process Res. Dev. 2020, 24, 347

Cyclobutanes in the Pharmaceutical Industry

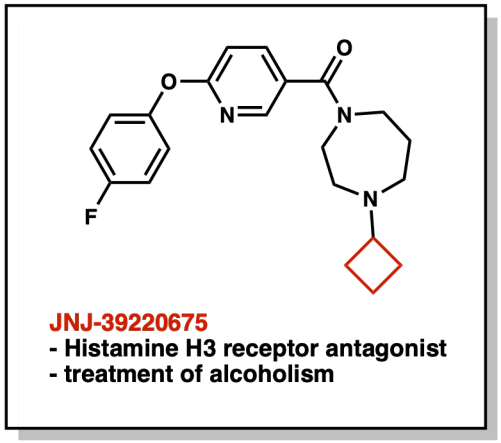


Cyclobutane Source:

TCI
$48/g

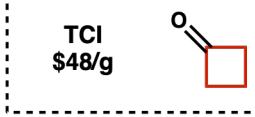


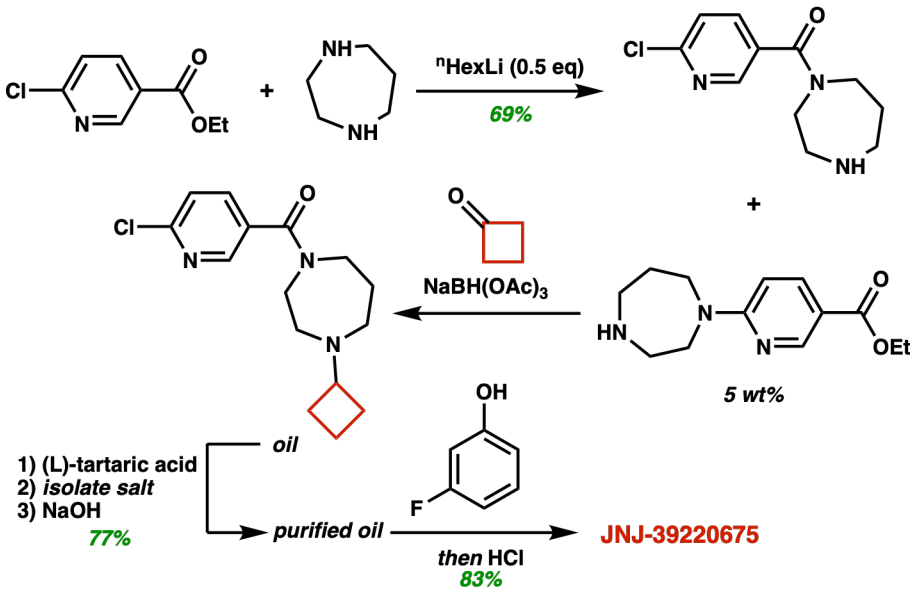
WO 98/46586



Cyclobutane Source:

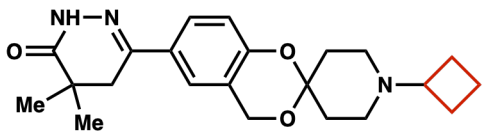
TCI
$48/g





J. Org. Chem. 2010, 75, 4463
Org. Process Res. Dev. 2011, 15, 638

Cyclobutanes in the Pharmaceutical Industry

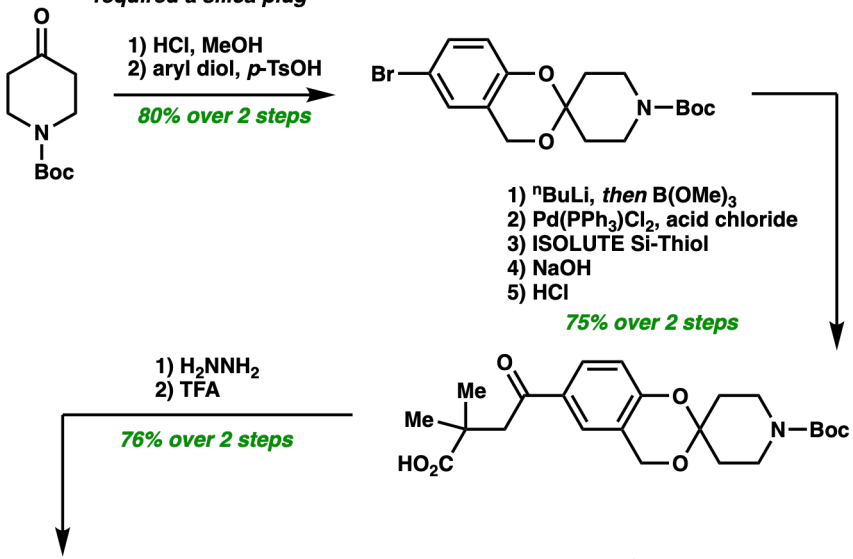


CEP-32215
- developed by Teva Pharmaceuticals
- H_3 receptor antagonist
- CNS disorders treatment

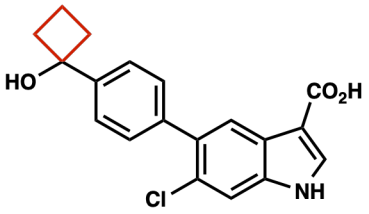
Cyclobutane Source:

TCI
$48/g

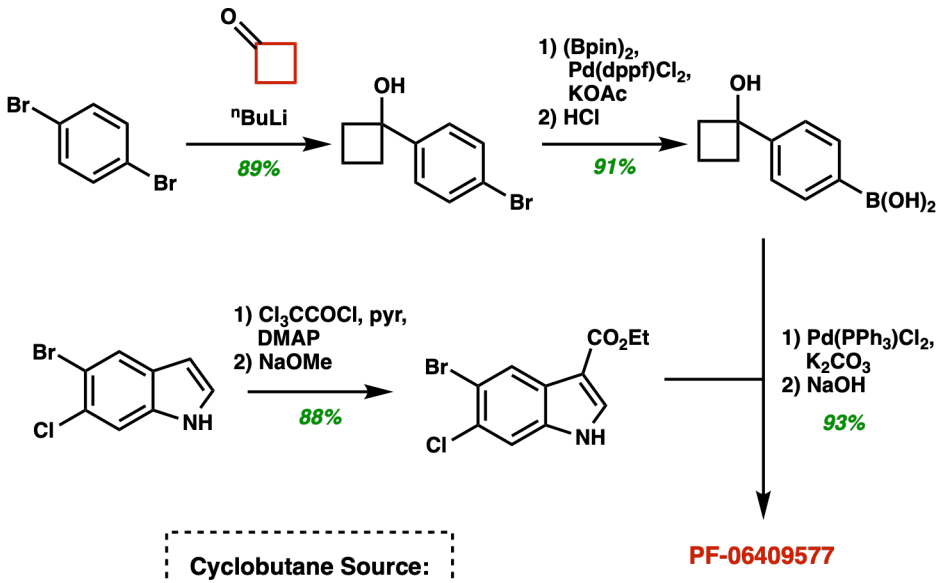
- *direct ketalization required multiple purifications*
- *two-step ketalization only required a silica plug*



Org. Process Res. Dev. 2013, 17, 846



PF-06409577
- developed by Pfizer, Bridge Organics and BoroPharm
- diabetic nephropathy treatment
- AMPK activator

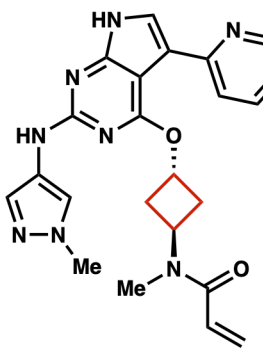


Cyclobutane Source:

TCI
$48/g

Org. Process Res. Dev. 2018, 22, 681

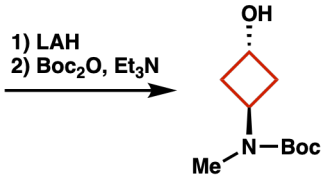
Cyclobutanes in the Pharmaceutical Industry

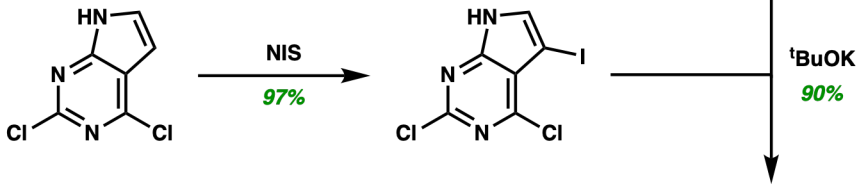


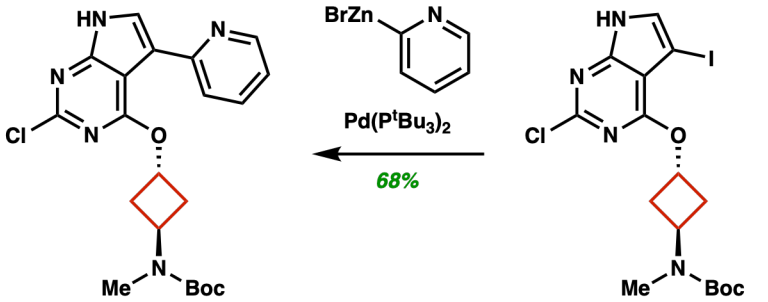
EGFR T790 M Inhibitor
- developed by Pfizer
- lung cancer treatment
- lead candidate against mutant EGFRs that have grown resistance to previous inhibitors

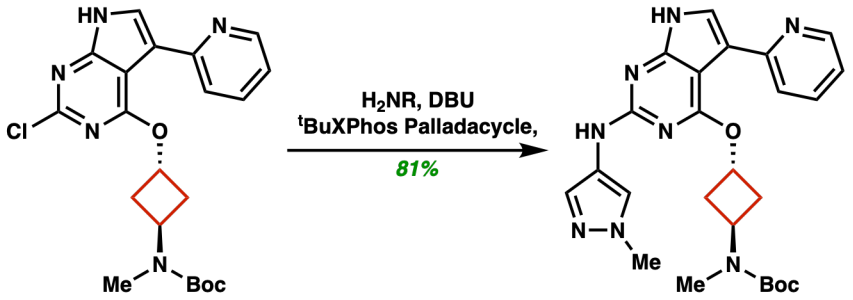
Cyclobutane Source:

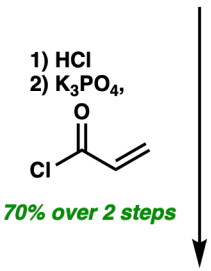
Combi-Blocks
$48/g





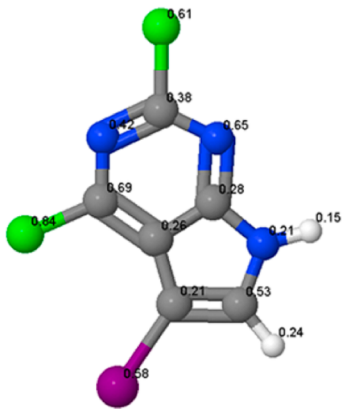






70% over 2 steps

EGFR T790 M Inhibitor



Reactivity Induces – Electrophilicity – in Ether

Atom	Electrophilicity (eV)
C-2	0.38
C-4	**0.69**
C-5	0.21

Note: an electrophilicity index difference between atoms of interest of >0.2 eV is typically indicative of a reasonable selectivity

Org. Process Res. Dev. 2019, 23, 382

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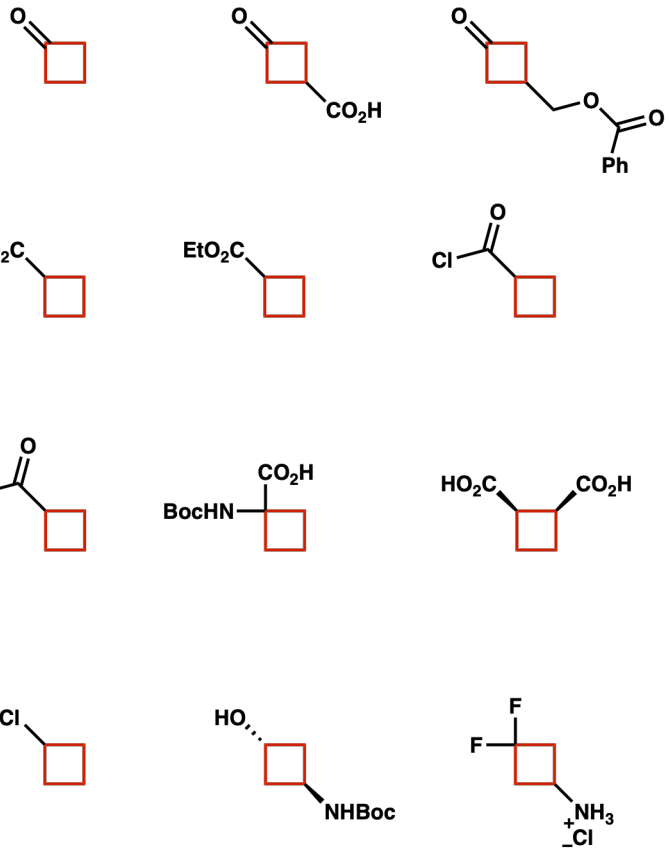
Cyclobutanes in the Pharmaceutical Industry

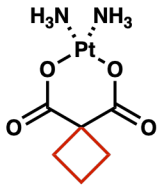
Burns Lab

Concluding Considerations:
- 32% (9 out of 28) of cyclobutanes discussed were synthesized
- 68% (19 out of 28) were accessed via commercial cyclobutanes
- most of the commercial cyclobutanes can be accessed via a photochemical [2+2] or via a ketene [2+2]

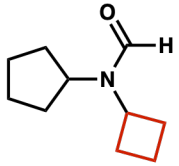
Commercially Available Cyclobutanes Covered:



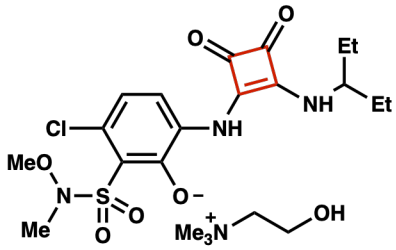
Other drugs not discussed in detail:



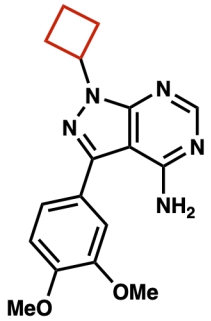
Carboplatin



DB04065



CXCR2 Receptor Antagonist



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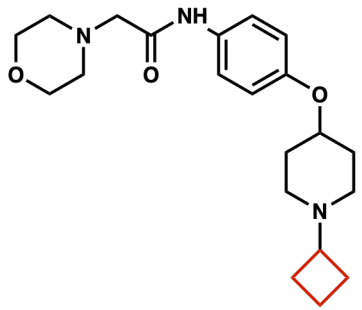
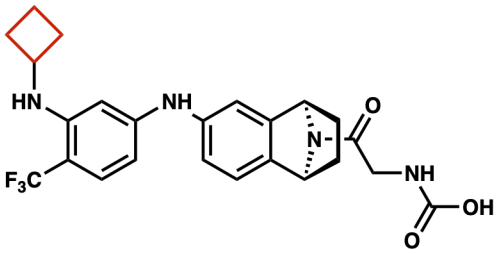


SUVN-G3031



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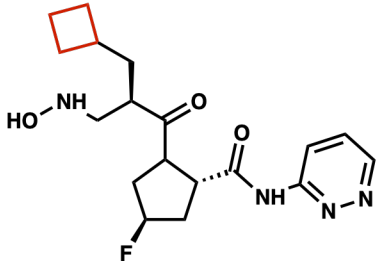

PDF Inhibitor