

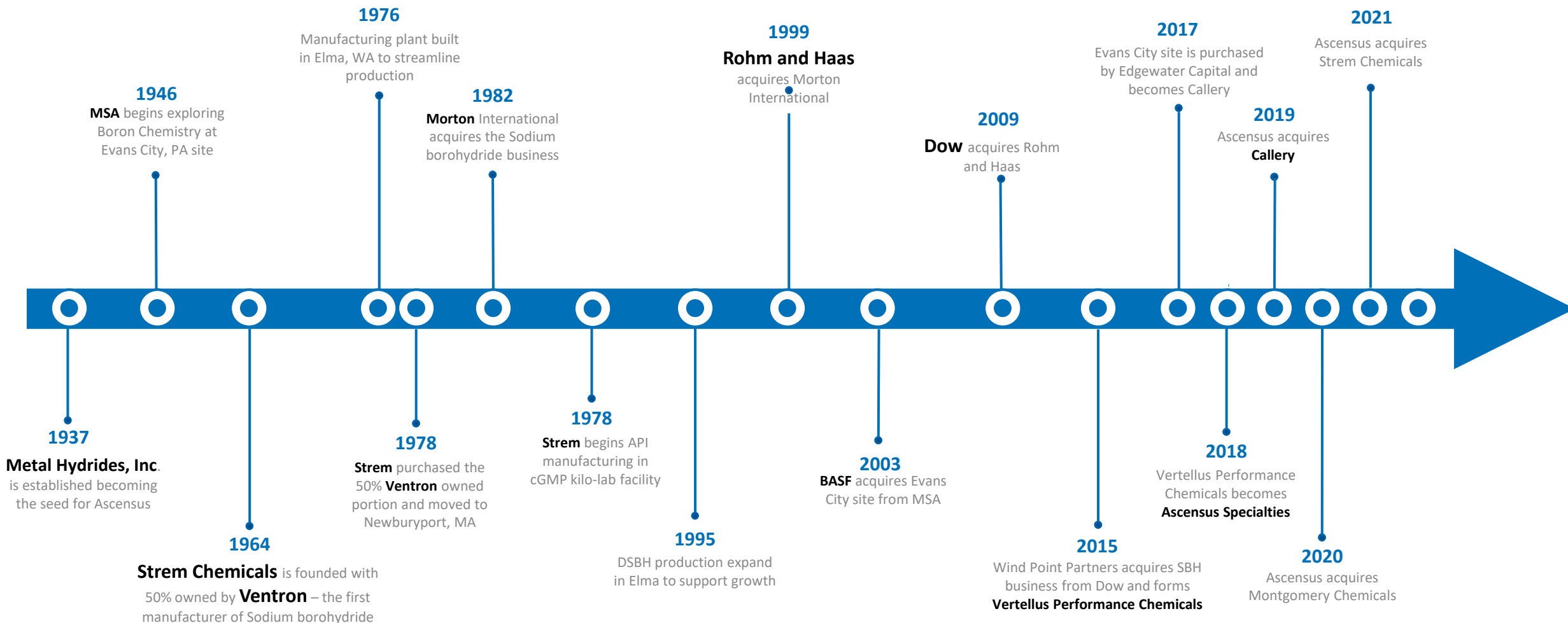


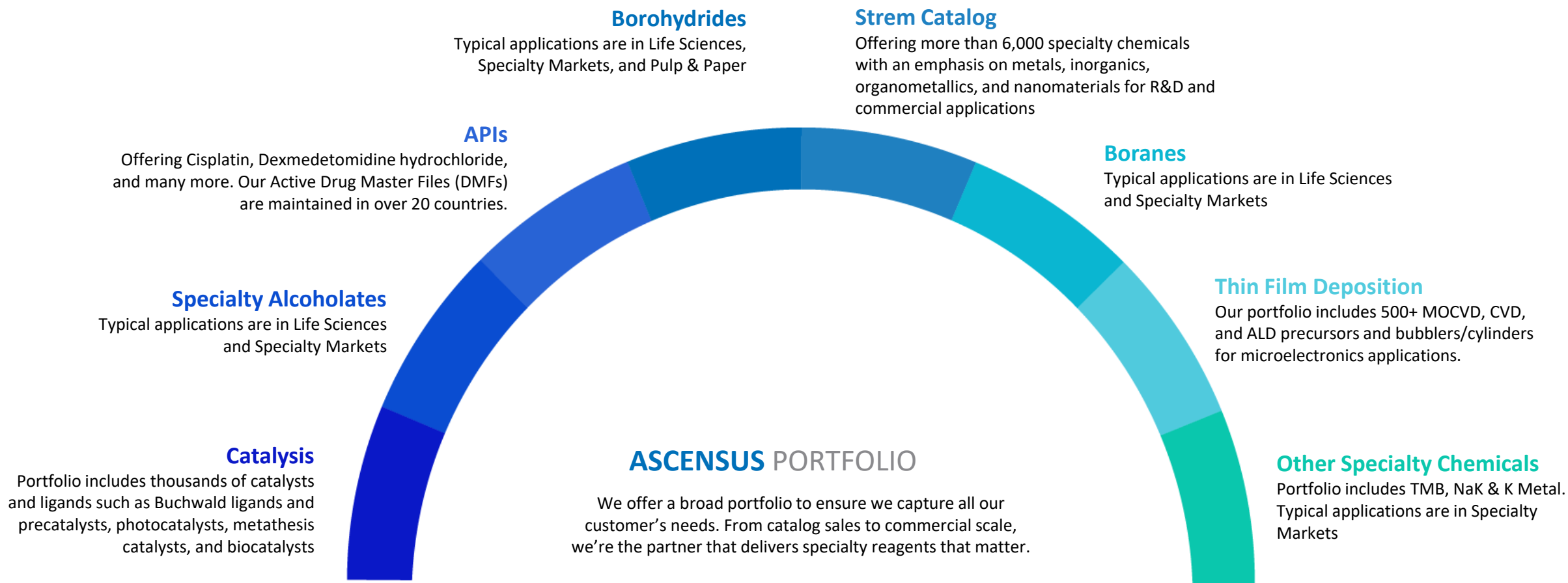
Reliable Methods for Borohydride Reductions

Presenter: Nathan T. Allen PhD

Ascensus Specialties History

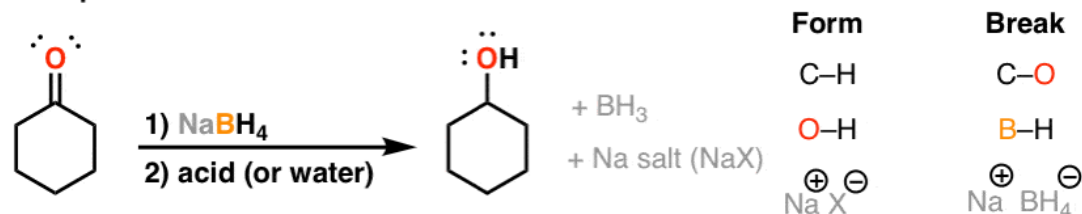
Specialty Chemicals for over 80 years



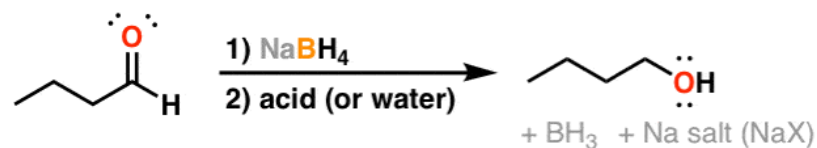


VENPURE Sodium Borohydride

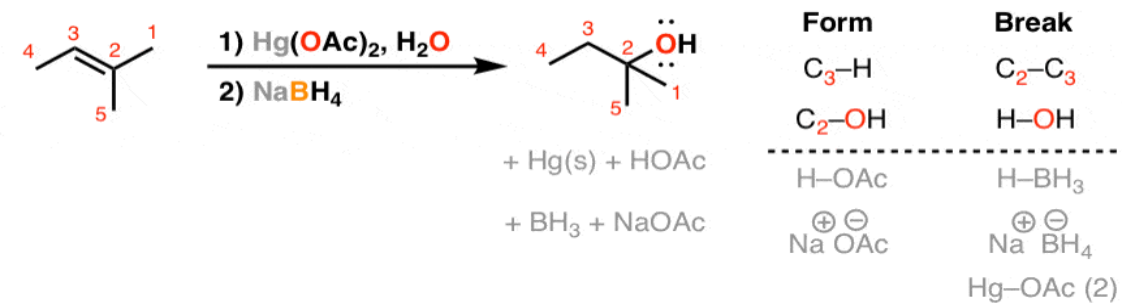
Example 1: Reduction of ketones



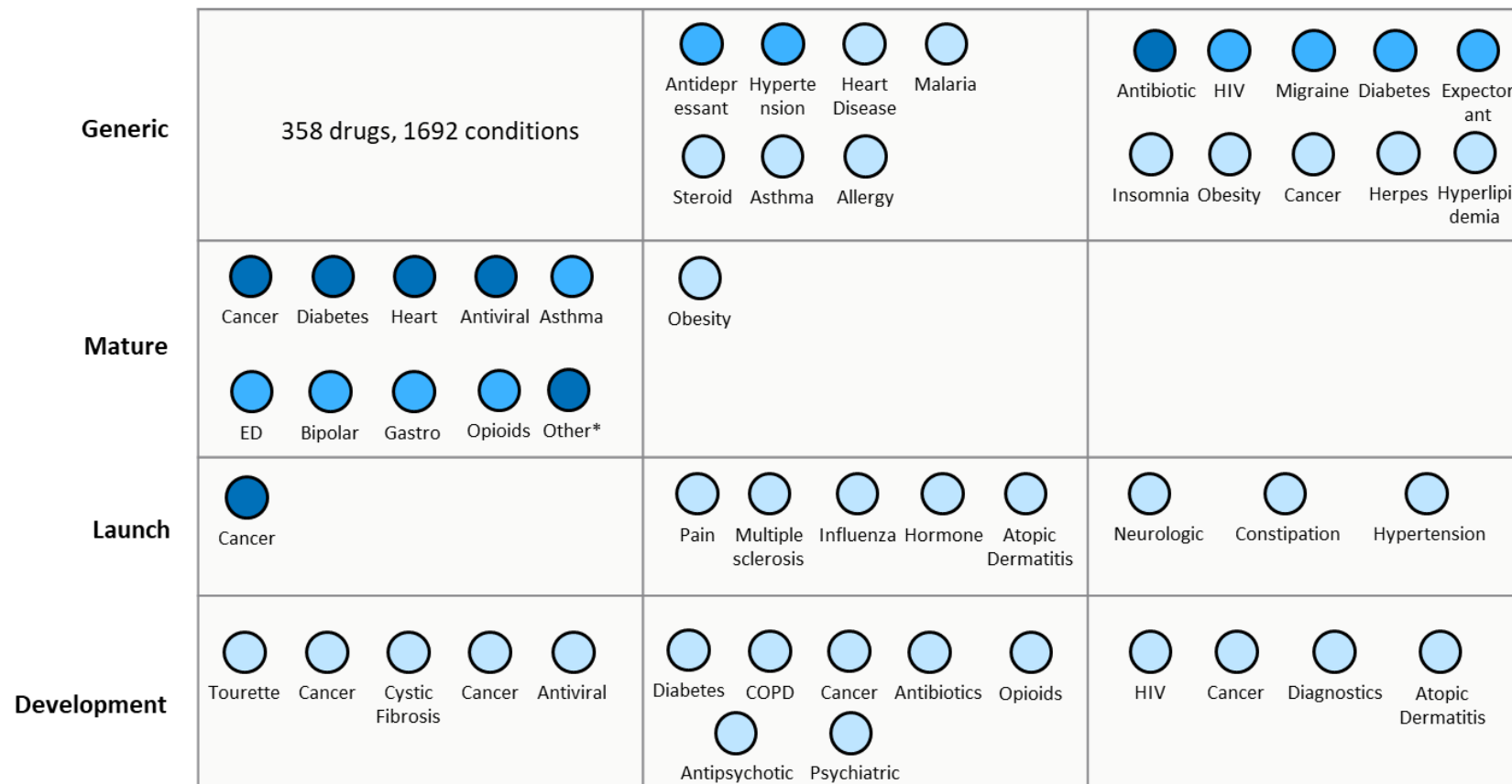
Example 2: Reduction of aldehydes






Example 3: In the second step of the oxymercuration reaction



Wide Application of Borohydride Chemistry

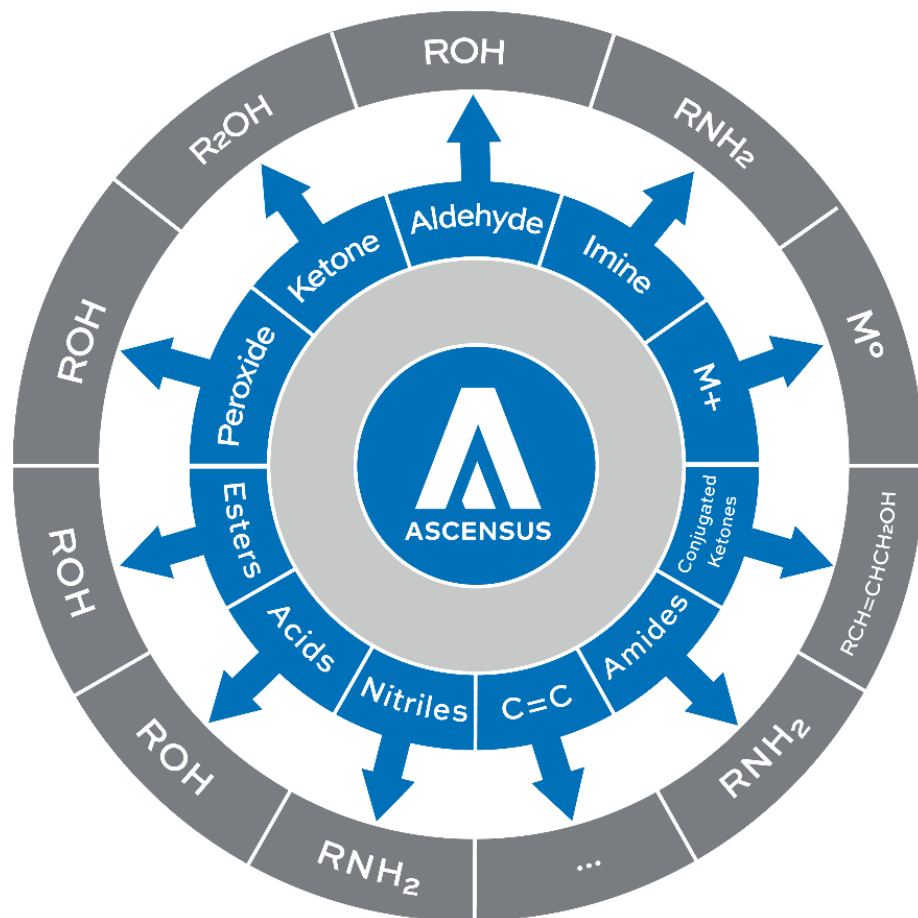


 Single API
  2-5 APIs
  5+ APIs

* Represents 25 additional API's

Borohydride-Based Transformations

Reality is far more complicated



- ▣ 374k Reactions listed in CAS
- ▣ 55k References
- ▣ Begins in 1940's

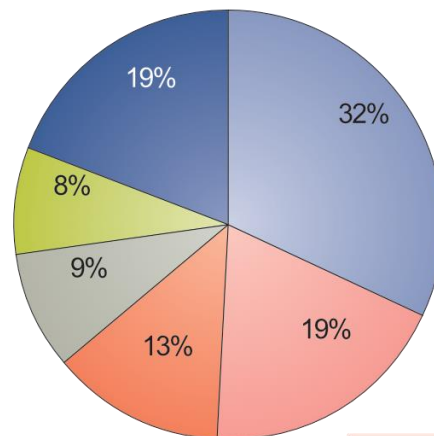
Levels of Believability in Chemistry

Level of R&D	Reported in	Typical Scale	Typical Yields Reported	Typical Reliability
Graduate Student	Lower Organic Chemistry Journals	milligram to gram	80-100%	Well, maybe
Researcher	Process R&D Journals	gram to kilogram	60-90%	It worked, but the project likely died or was a hobby
Lab Researcher	Patents	milligram to gram	50-90%	Their best unoptimized attempt
Process Chemist	Regulatory Documents	kilogram to MT	50-95%	Reality +/- generous error margins
Process Chemist/Engineer	Non-public Technical Conversations	100s kg to MT	50-90%	The Actual Fact

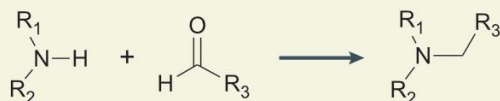
Medicinal Chemistry Toolbox

5 Reactions make up 80% of the Process Steps

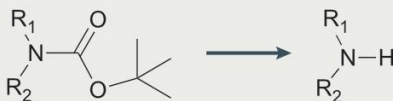
Other reaction types



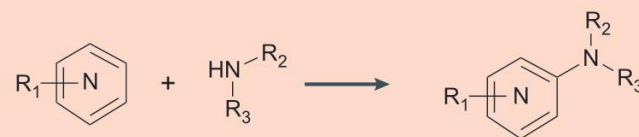
Electrophilic reactions of amines



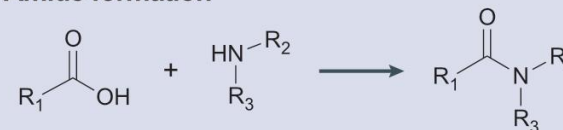
Amine Boc-deprotections



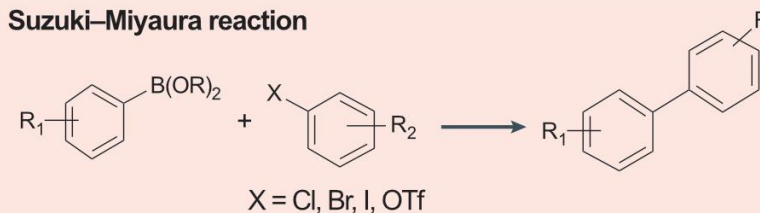
Aromatic nucleophilic substitution reaction (S_NAr)

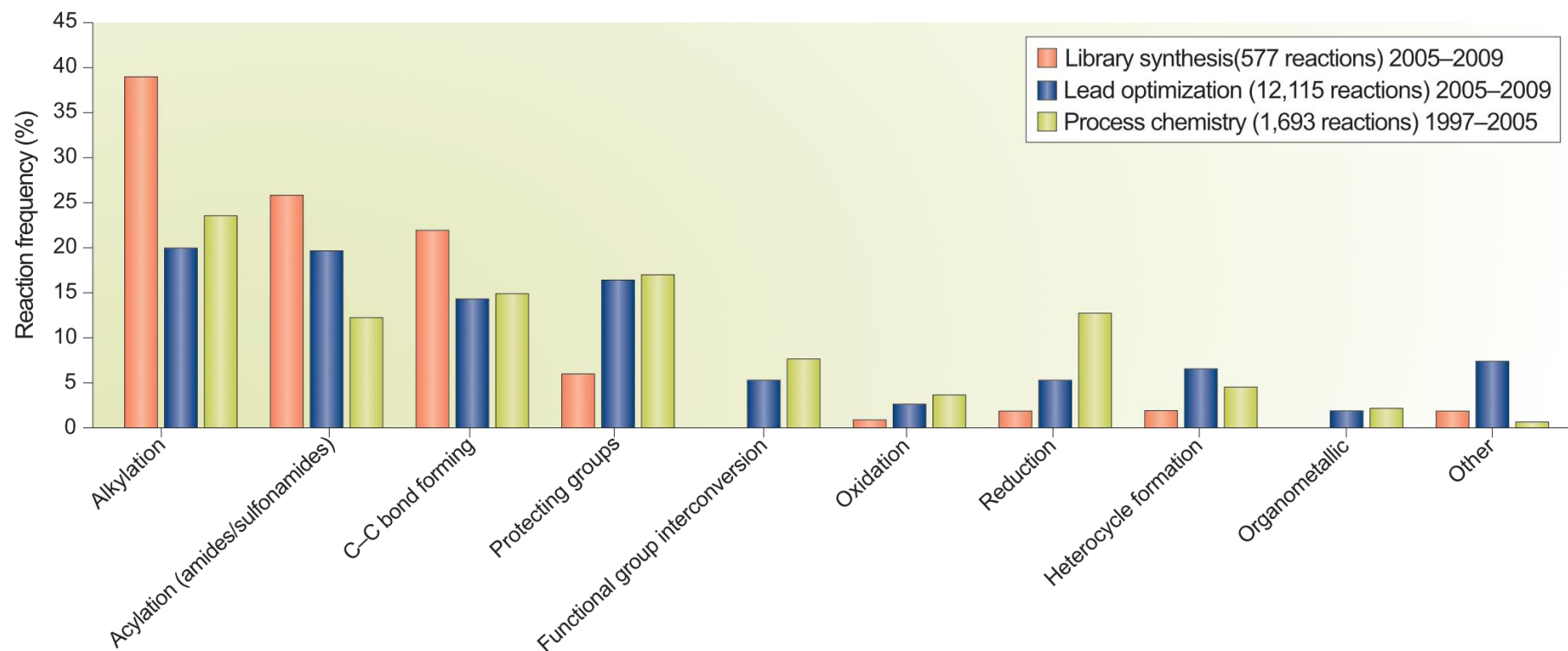


Amide formation



Suzuki-Miyaura reaction





<https://doi.org/10.1038/nrd.2018.116>

Synthetic Transformations at Scale



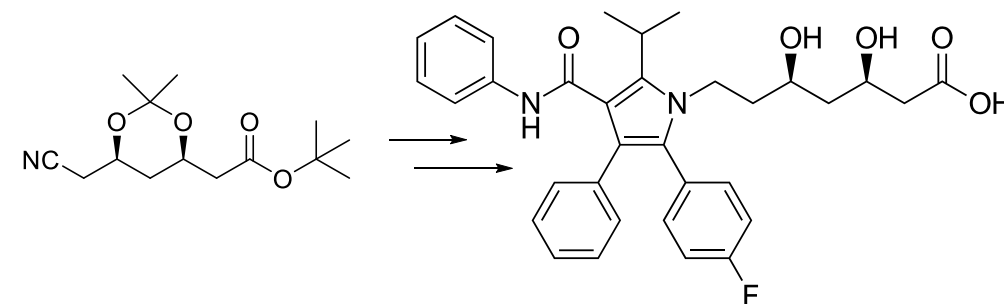
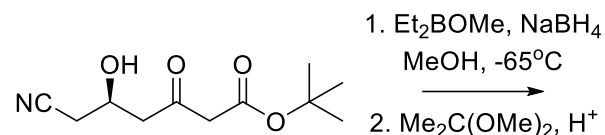
- ▣ Ketone Reductions
- ▣ Reductive Aminations
- ▣ Ester Reductions
- ▣ Carboxylic Acids
- ▣ Deoxygenation
- ▣ Hydrogenations
- ▣ Flow Chemistry

Ketone Reductions

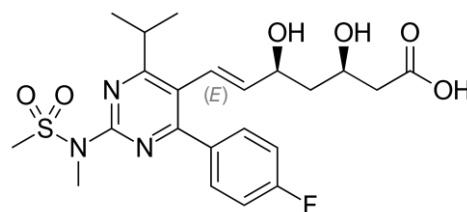
Atorvastatin

Lipitor (Warner-Lambert/Pfizer)

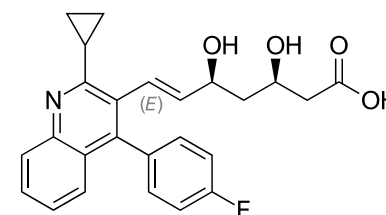
- ▣ Statin medication used to prevent cardiovascular disease
- ▣ World's best-selling medication of all time
- ▣ In 2019, it was the most prescribed medication in the United States, with more than 112 million prescriptions
- ▣ First \$10+ billion API, >\$12 billion in sales in 2005
- ▣ Patented in 1986, and approved for medical use in the United States in 1996
- ▣ Peak API volume >200 MT/yr



Atorvastatin

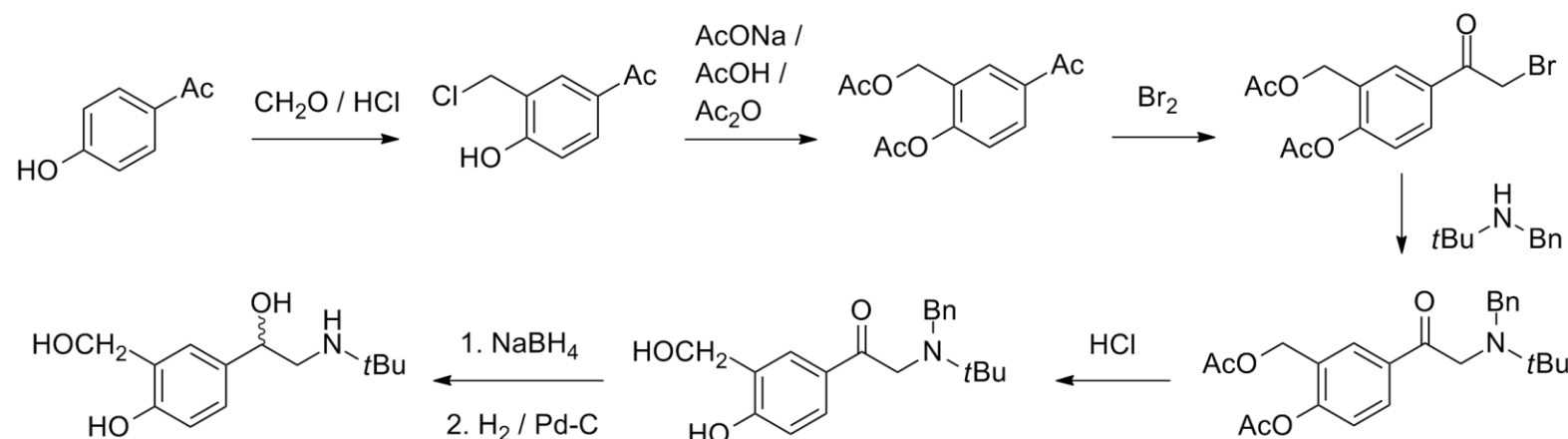


Rosuvastatin (Crestor)

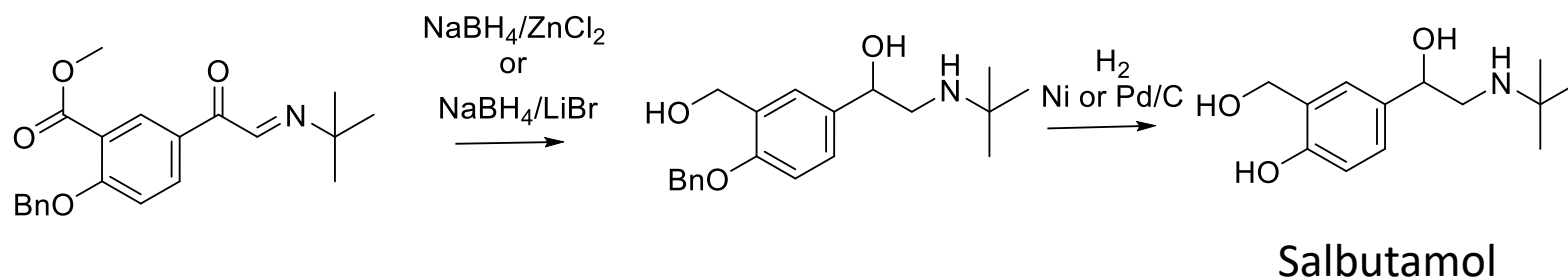


Pitavastatin (Livalo)

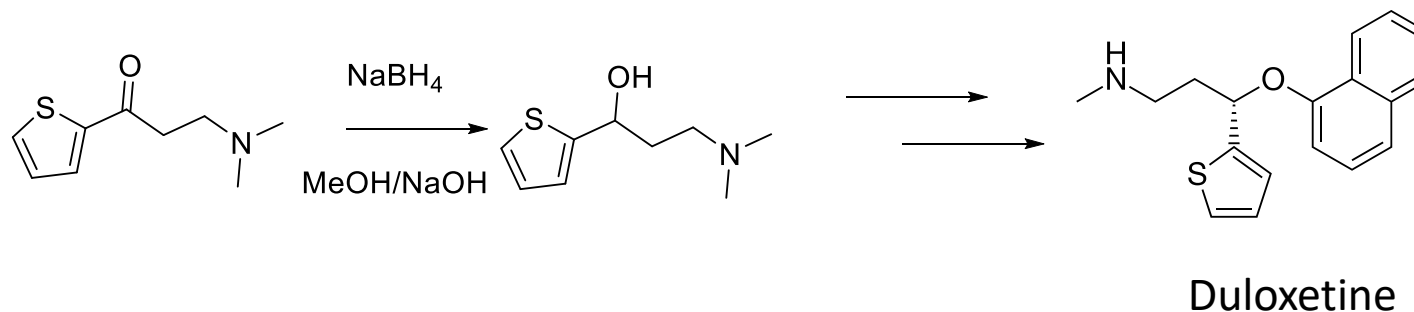
- ▣ Asthma treatment, fast acting inhalers, 7th most prescribed drug in the USA, 60+ million
- ▣ Bronchodilator; β_2 adrenergic receptor agonist
- ▣ Patented in 1966 in Britain and became commercially available in the UK in 1969
- ▣ The original route developed in 1966 at Allen and Hanburys Ltd (UK, GB1838367) still practiced.
- ▣ Approved in the United States in 1982



- ▣ Removes deprotection step
- ▣ Utilizes activated borohydride chemistry
- ▣ Typical ethereal solvents
- ▣ Could also be accomplished with MeOH and heat

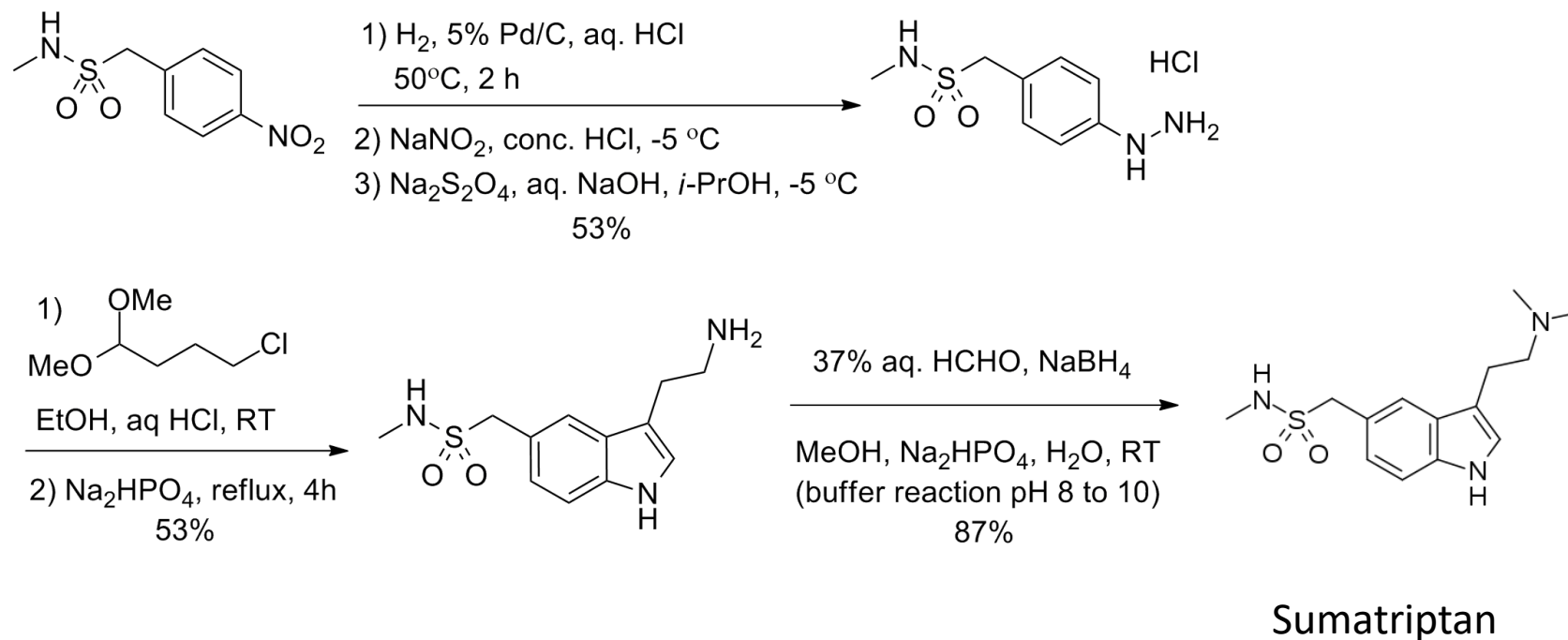


- ▣ Used to treat major depressive disorder, generalized anxiety disorder, fibromyalgia, and neuropathic pain
- ▣ Developed by Eli Lilly in 1986 (Patent US4956388A)
- ▣ 26th most-commonly prescribed medication in the United States, with more than 23 million prescriptions
- ▣ Borohydride reduction 89% at 100 kg batch size (78% in original patent)

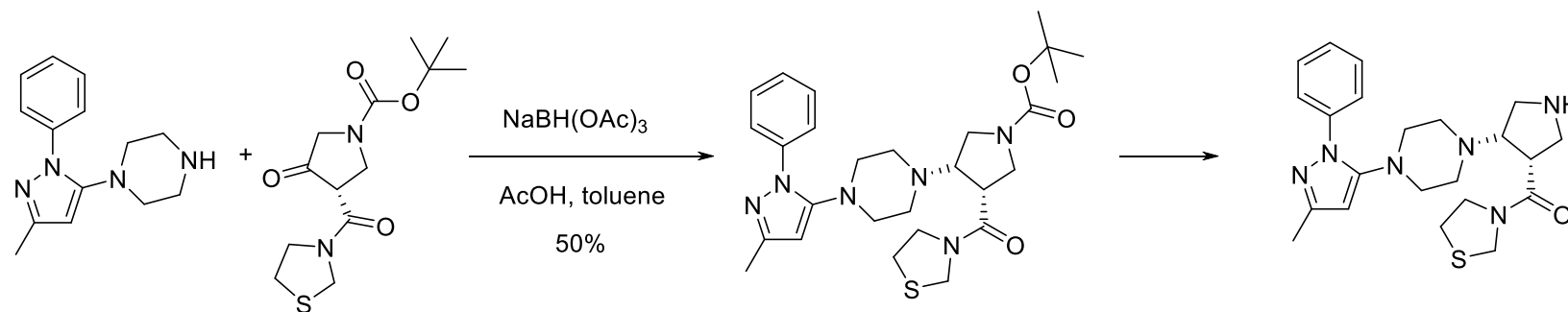


Reductive Aminations

- Patented in 1982 and approved for medical use in 1991
- 98th most-commonly prescribed medication in the United States, with more than 7 million prescriptions
- On the World Health Organization's List of Essential Medicines
- BASF Synthesis
WO2001034561A1
- Similar process step used in Almotriptan and Zolmitriptan



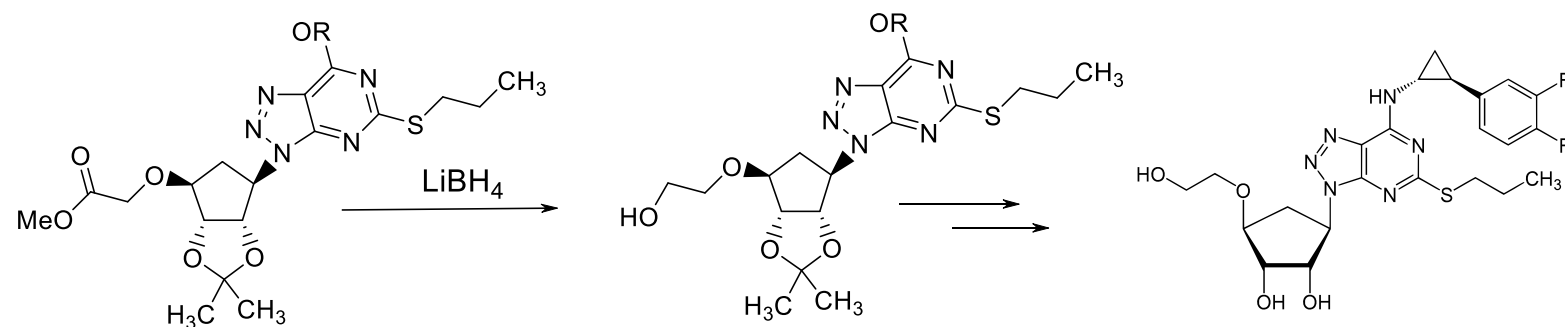
- ▣ Approved in Japan for Treatment of Type 2 Diabetes
- ▣ Patent W02012099915
- ▣ Ascensus STAB is used, but could easily be made in situ



Teneligliptin

Ester Reductions

- ▣ Prevention of stroke, heart attack
- ▣ Approved in USA 2011, EU 2010
- ▣ 216th most prescribed medication in the United States, with more than 2.3 million prescriptions
- ▣ Alternative is DiBAL-H Reduction
- ▣ Options for LiBr/NaBH₄ or LiBH₄
- ▣ Solvents: THF, Diglyme, MeOH, EtOH

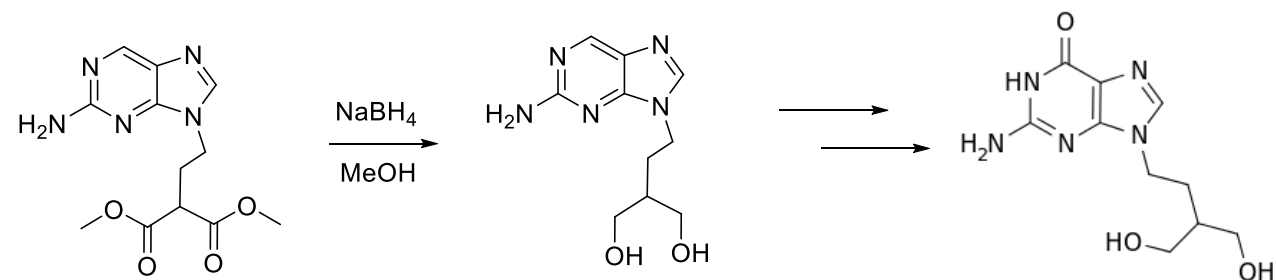


Ticagrelor

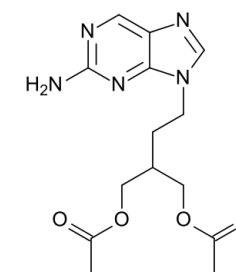
Famciclovir /Penciclovir

Denavir, Vectavir, Fenivir and Famvir (Novartis)

- ▶ Antiviral drug used for the treatment of various herpesvirus
- ▶ Patented in 1983 and approved for medical use in 1994
- ▶ Famciclovir is a prodrug of penciclovir with improved oral bioavailability



Penciclovir

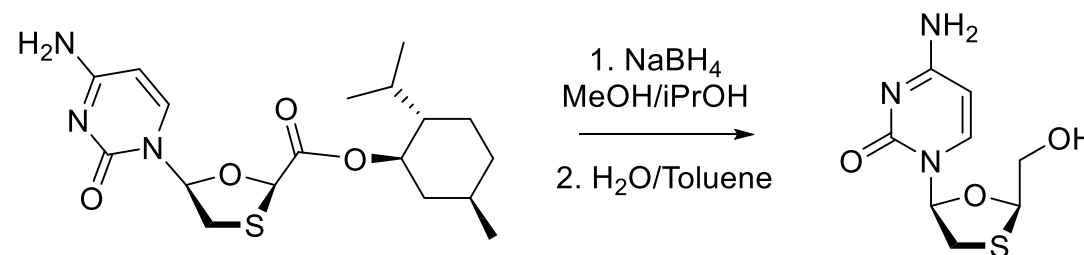


Famciclovir

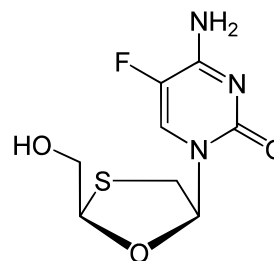
Lamivudine

Epivir, Epivir-HBV, Zeffix, others (Glaxo)

- ▶ 3TC, is an antiretroviral medication used to prevent and treat HIV/AIDS
- ▶ Patented in 1995 and approved for use in the United States in 1995
- ▶ On the World Health Organization's List of Essential Medicines
- ▶ Part of the ARV “drug cocktail”
- ▶ Has saved millions of lives
- ▶ Synthesis done at 500 kg batch size



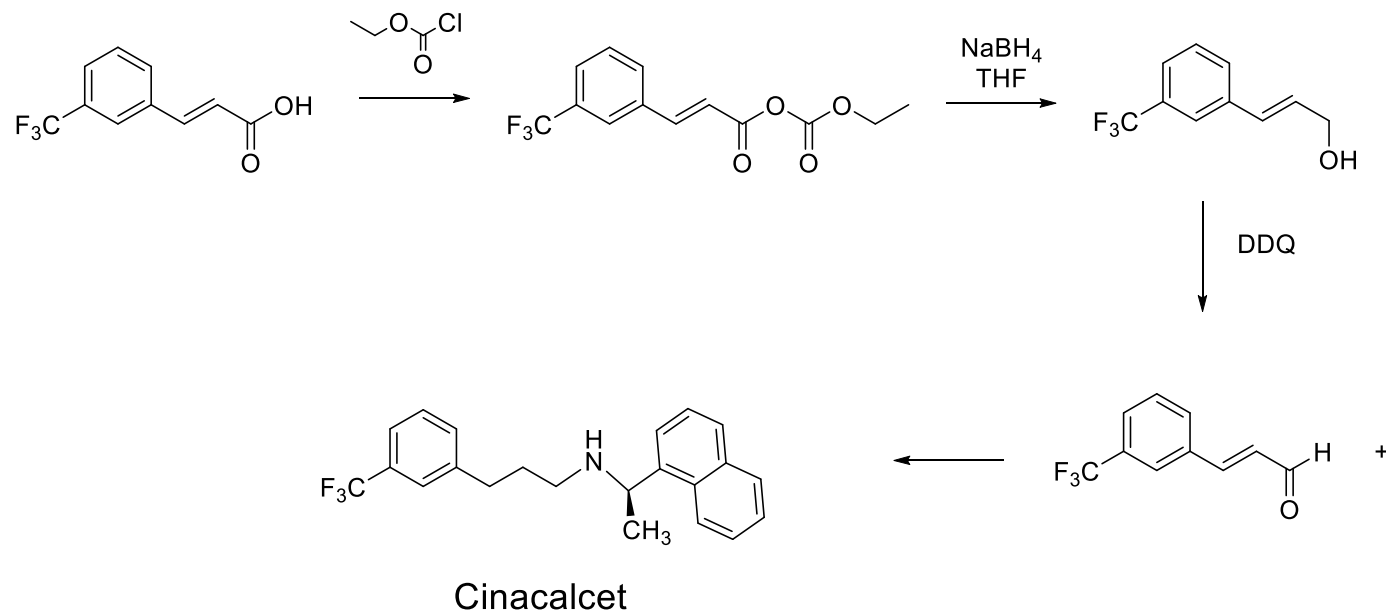
Lamivudine



Emtricitabine

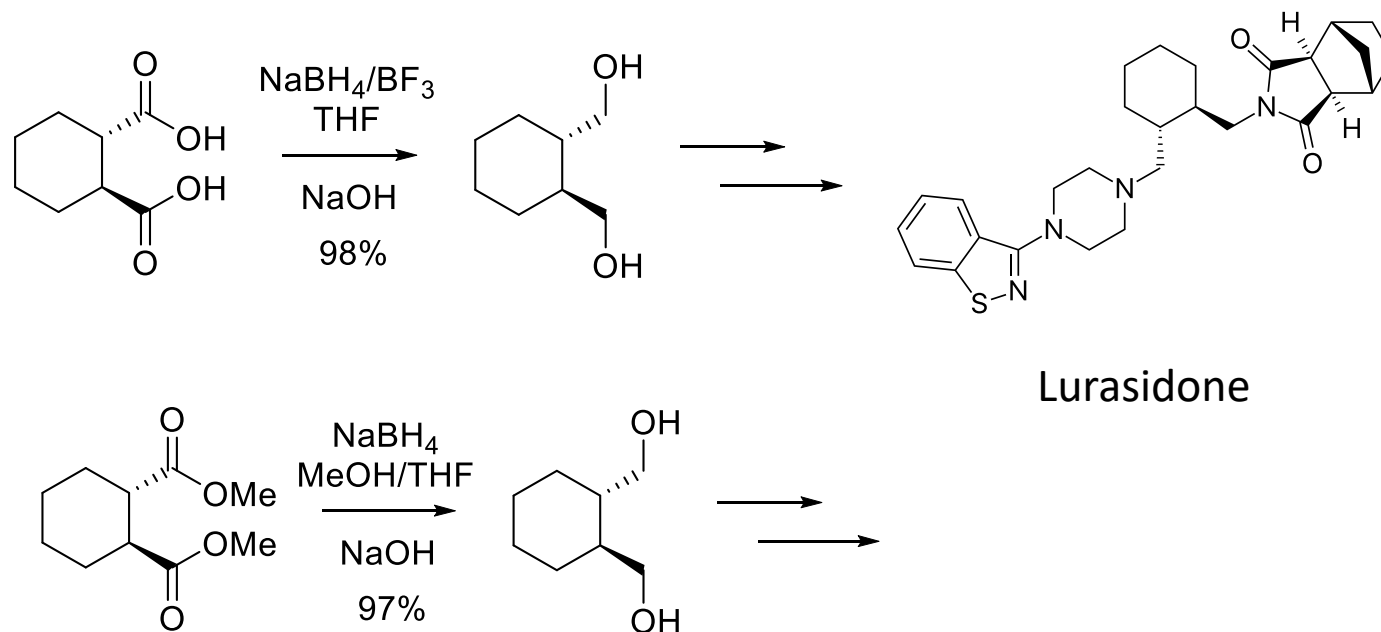
Carboxylic Acid Reduction

- ▣ Used to treat secondary hyperparathyroidism, parathyroid carcinoma, and primary hyperparathyroidism
- ▣ Reduces calcium in blood
- ▣ In 2013, the 76th most prescribed medicine in the United States
- ▣ Originally developed by Amgen (NPS Pharma originated, patent US6211244B1)



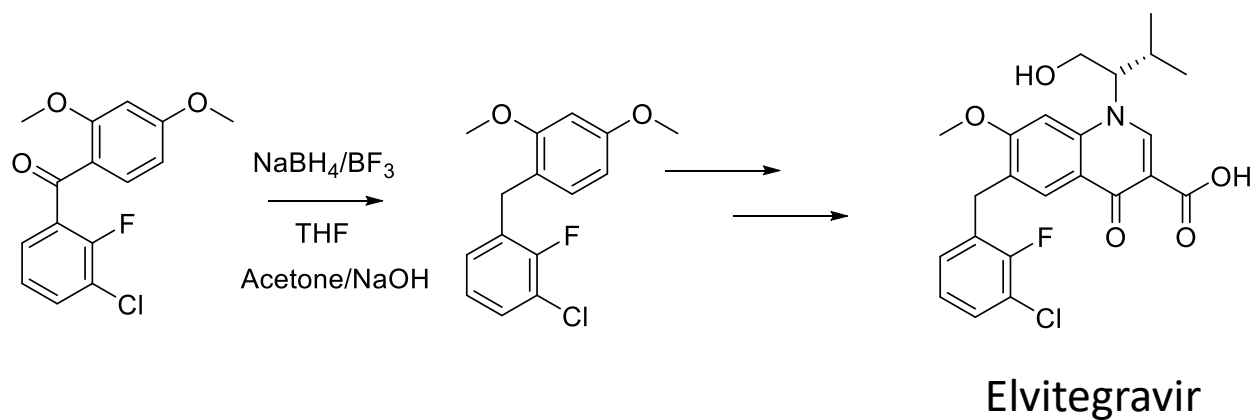
M Barniol-Xicota, et. al.; Syntheses of Cinacalcet: An Enantiopure Active Pharmaceutical Ingredient (API); DOI: 10.1055/s-0035-1561506

- ▶ An antipsychotic medication used to treat schizophrenia and bipolar disorder
- ▶ Approved for medical use in the United States in 2010
- ▶ 220th most prescribed medication in the United States, with more than 2 million prescriptions
- ▶ Patent examples CN102952001A, WO2005090273 A1
- ▶ Commercial batch size 500 kg

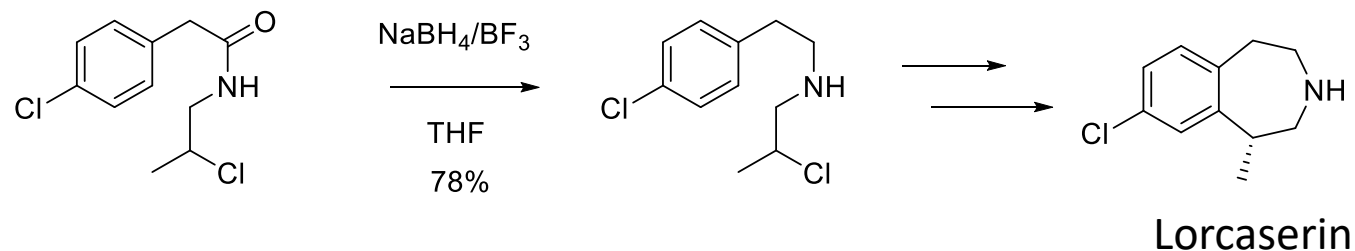


Deoxygenation

- ▶ Integrase inhibitor used to treat HIV infection
- ▶ Gilead Sciences licensed EVG from Japan Tobacco in 2008
- ▶ 2014 the FDA approved
- ▶ BH3-THF is an alternative reagent
- ▶ Synthesis at 100 kg scale

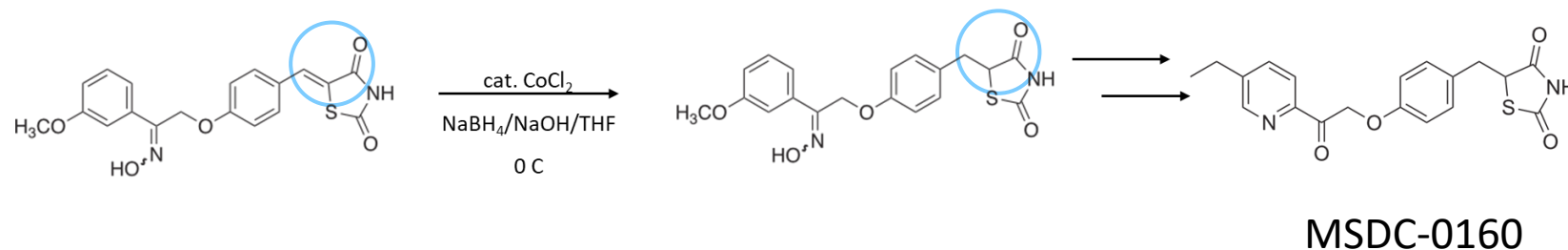


- ▣ Reduces appetite by activating a type of serotonin receptor
- ▣ In 2012, the FDA approved Lorcaserin for use in adults with a body mass index (BMI) of 30
- ▣ Removed from the market in the United States in 2020 due to an increased risk of cancer detected in users
- ▣ BH_3 -THF is an alternative



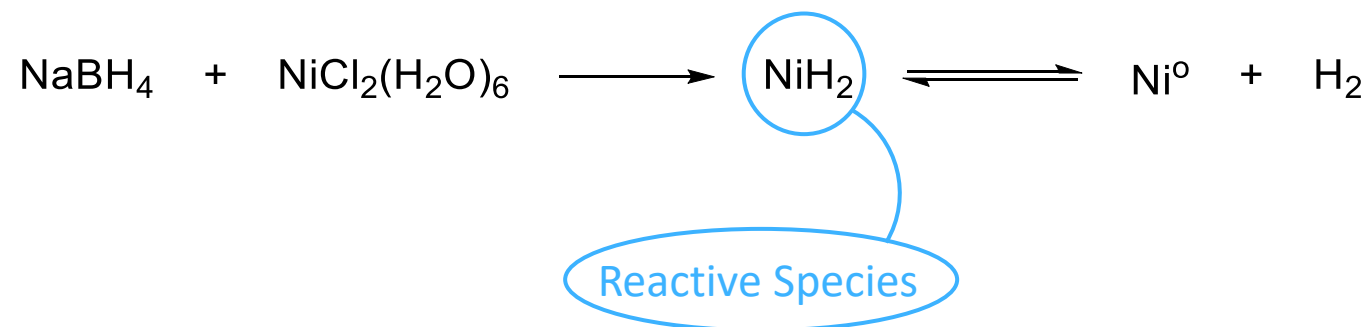
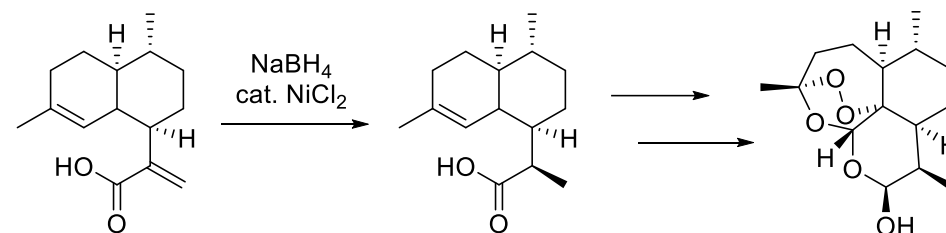
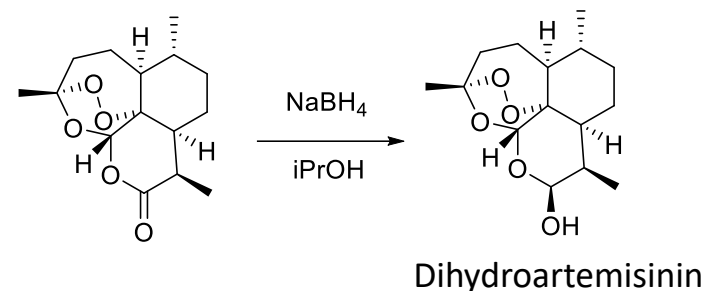
Hydrogenations

- ▣ Phase II Trials for Alzheimer's - Metabolic Solutions, oral insulin sensitizer that works through a new drug target located in the inner mitochondrial membrane
- ▣ Metal-Catalyzed Reductions without hazards of hydrogen gas handling
- ▣ Raney Nickel, Pd/C, Co, Rh, etc...
- ▣ Reaction scale-up simplified
- ▣ Safety – no high pressure H₂ required
- ▣ Low Capex – no catalyst can be run in standard production equipment
- ▣ No specialized reactors needed



Dihydroartemisinin

- ▶ Used to treat Malaria
- ▶ Original chemistry from Brown in 1963, JACS paper on olefin hydrogenation
- ▶ This example from patent CN103193790B
- ▶ Borohydride is a replacement for hydrogen in this case

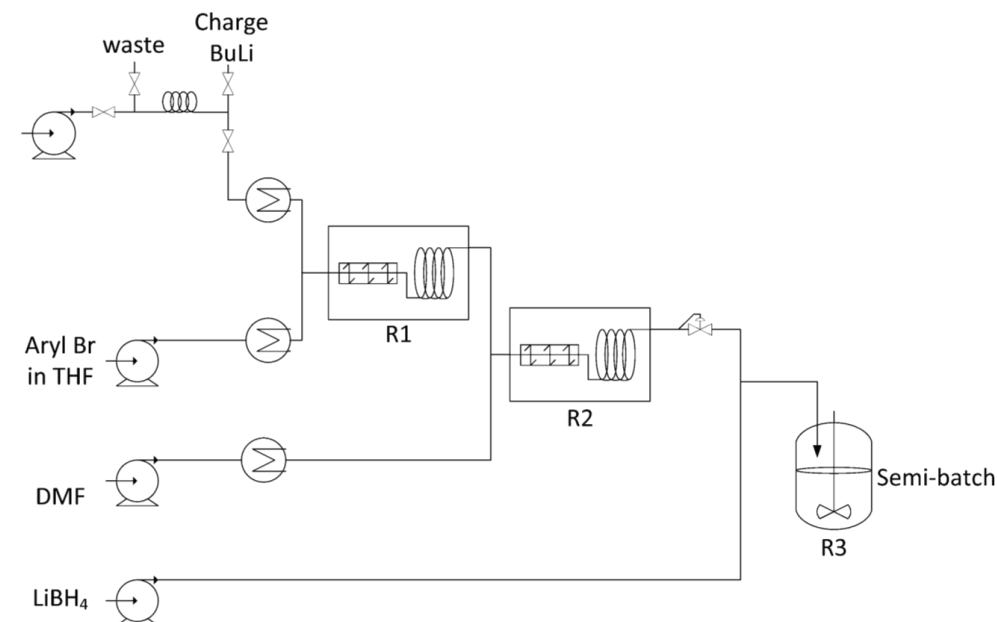
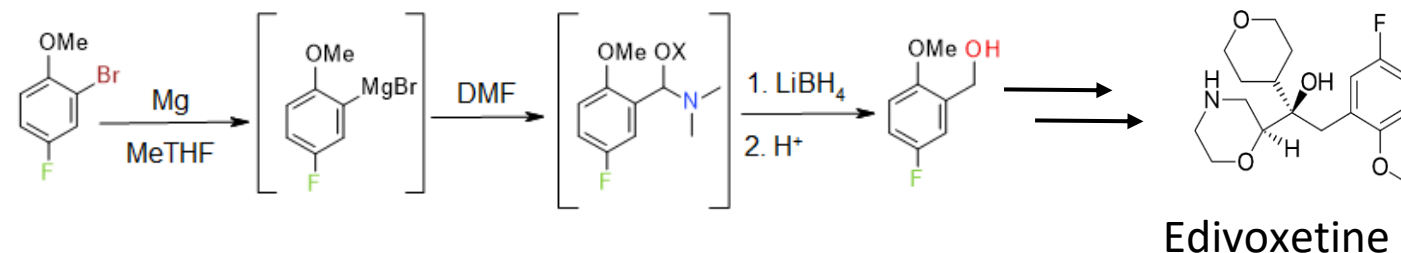


Flow Chemistry

Edivoxetine

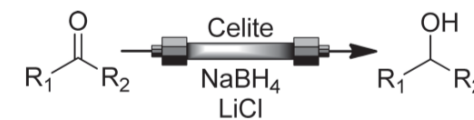
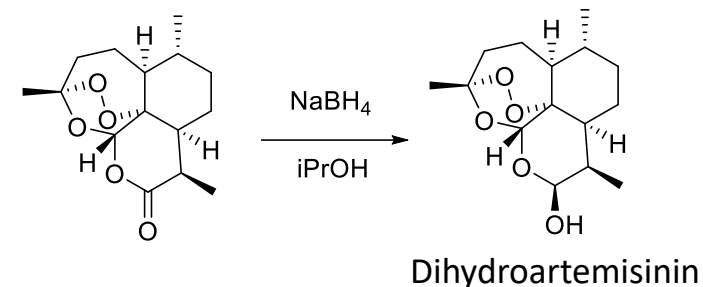
LY-2216684 (Eli Lilly)

- Developed in 2012 for ADD, but failed
- Produces high yield of desired benzyl alcohol
- Soluble in a greater range of aprotic solvents enables use of greener solvents (MeTHF)
- LBH use in flow (continuous) strategy reduces hazards by operation in small volumes and metal activation only once



Dihydroartemisinin

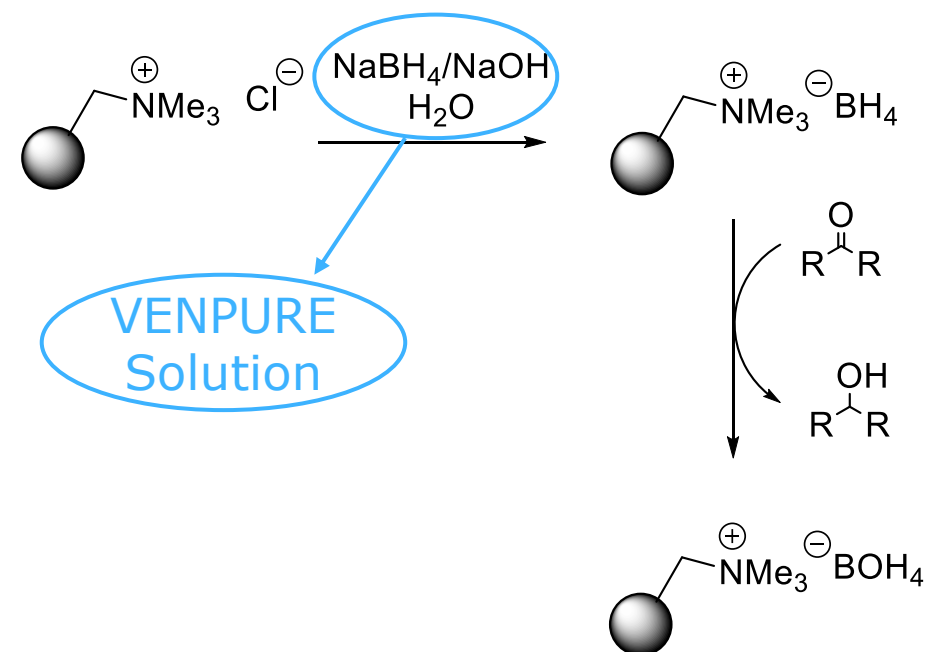
- ▶ Artemisinin - Flow Synthesis Using NaBH_4 Packed Beds
- ▶ High Yields
- ▶ Goal to reduce cost of production



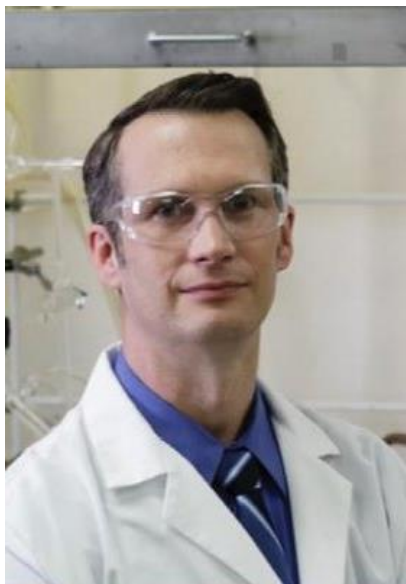
entry	R ₁	R ₂	yield	
1	C ₆ H ₅	H	97%	
2	4-CNC ₆ H ₄	H	99%	
3	(E)-C ₆ H ₅ CHCH	H	94%	
4	CH ₃ (CH ₂) ₄	H	74%	
5	Ph	Ph	83%	
6	CH(Ph) ₂	CH ₃	74%	
7	- C H ₂ (C H ₂) ₃ C H ₂ -			89 %

^aThe column was prepared using (1:1:0.76 w/w) Celite/ NaBH_4 / LiCl . The concentration of aldehyde/ketone was 0.66 M (THF) with 9.5 equiv of MeOH added, run at 0.5 mL/min ($T_{\text{res}} = 5.6$ min).²⁰

- ▣ Amberlite IRA-900Cl or A-26OH Resin
- ▣ Anion exchange resin, simply regenerate with sodium borohydride solution, and rinse.
- ▣ BER alone will easily reduce aldehydes, ketones, allylic aldehydes, nitro, dehalogenation, aryl azide and aryl sulfonyl azides
- ▣ CuSO_4 will allow the reduction of N-oxides, olefins, dehalogenation, azide, and nitro compounds
- ▣ Nickel or cobalt chloride will allow the reduction of halides, olefins, azides and nitro functionalities



Q&A



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Broad Technical Knowledge

Efficiently tackle challenging synthesis goals



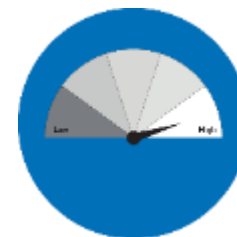
Custom Synthesis

Capabilities, expertise & equipment to rapidly scale up custom products, boranes and specialty alkoxides



Research & Development

Enhanced R&D and application development capabilities



High Pressure

Specialized production equipment (1L to 25-gallon autoclaves) allows for enhanced product offerings



Process Safety

Regulatory and handling expertise to keep your operations and people safe



Analytical

Extensive capabilities assures consistent and reliable testing



Scale Up

Pilot plant capabilities to demonstrate process in larger scale



cGMP

Expertise in manufacturing APIs and intermediates in the USA since 1988

Deliverables that Matter

The Ascensus Difference



