Lithium & Boron

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Two Elements of Success in High-Performance Fine Chemicals Production

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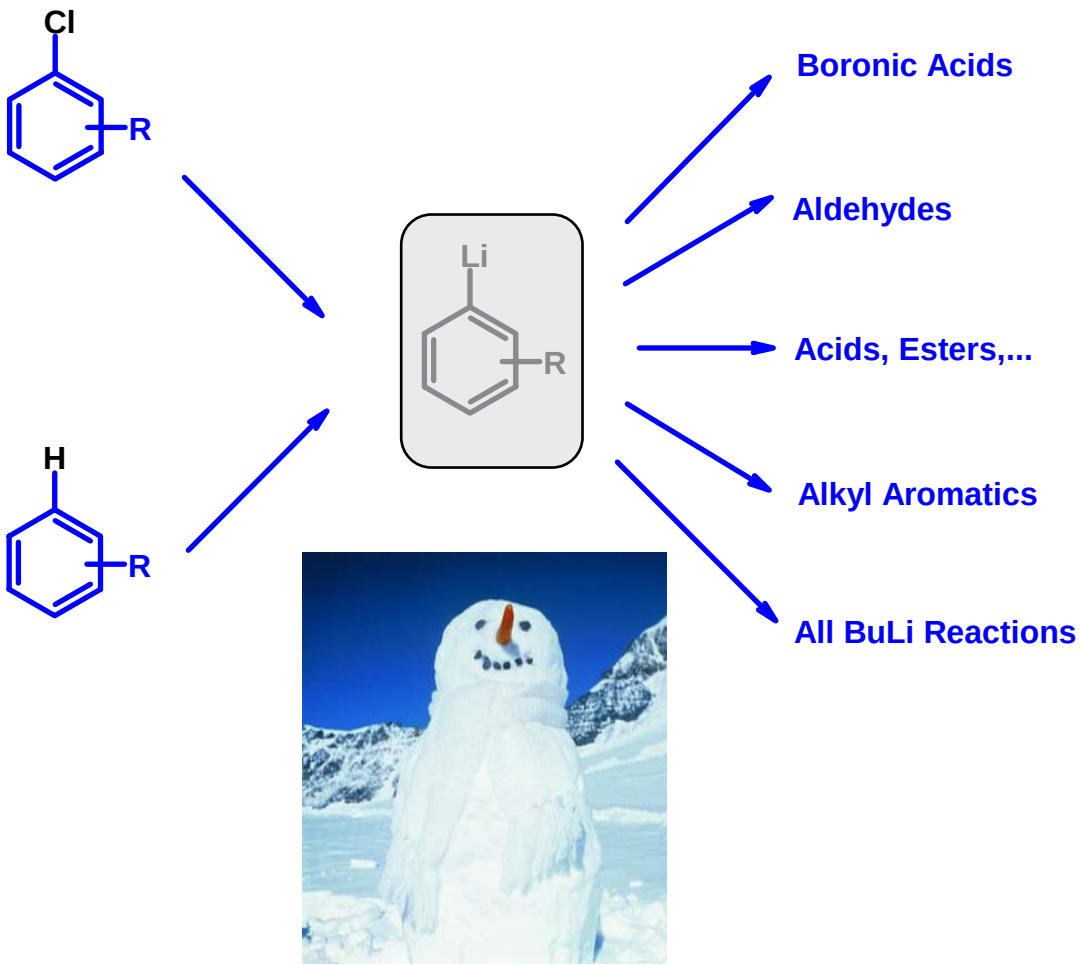
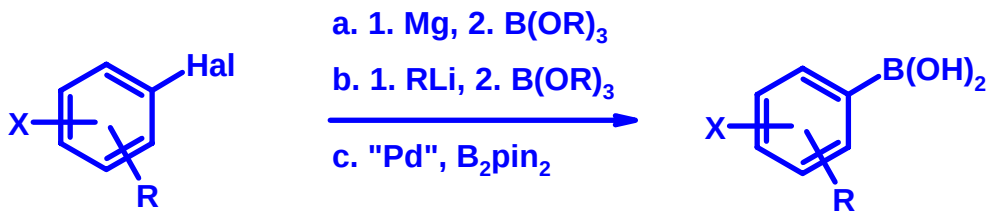
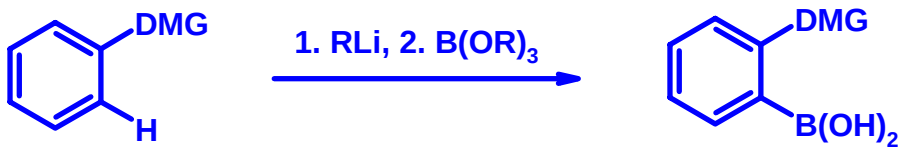
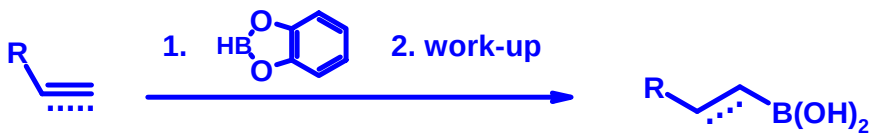
Get the grip…


Cl
R
H
R
Li
R
Boronic Acids
Aldehydes
Acids, Esters,...
Alkyl Aromatics
All BuLi Reactions

Classical Industrial Synthesis of Boronic acids

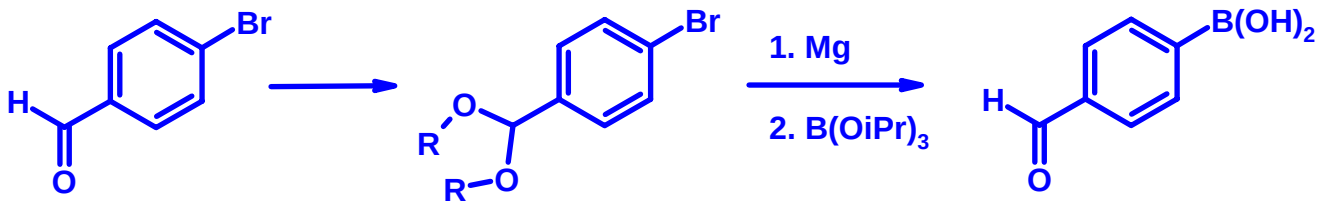




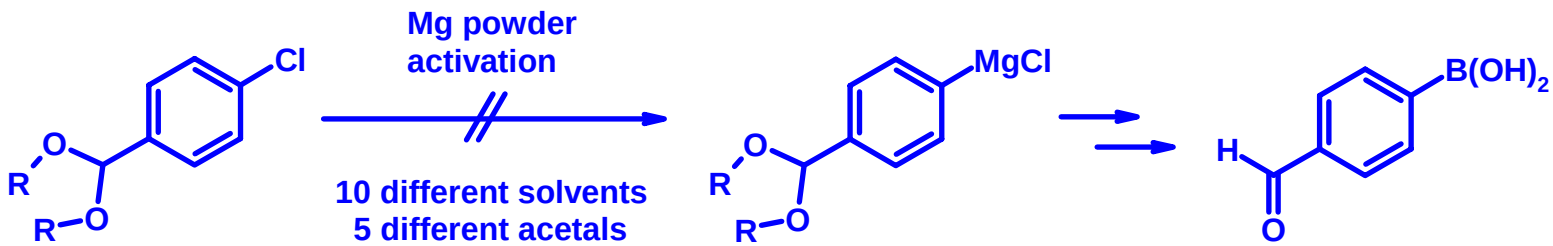


Archimica's Lithium Technology
- 4-Formylphenylboronic acid -

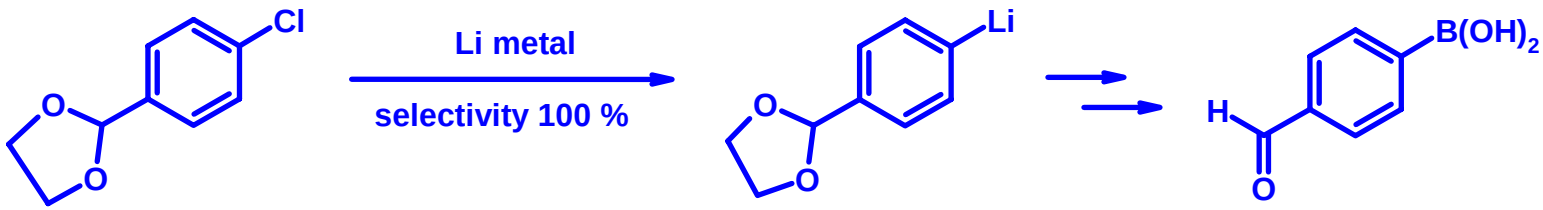
Known synthesis:



Improved economics by starting from 4-Chlorobenzaldehyde?

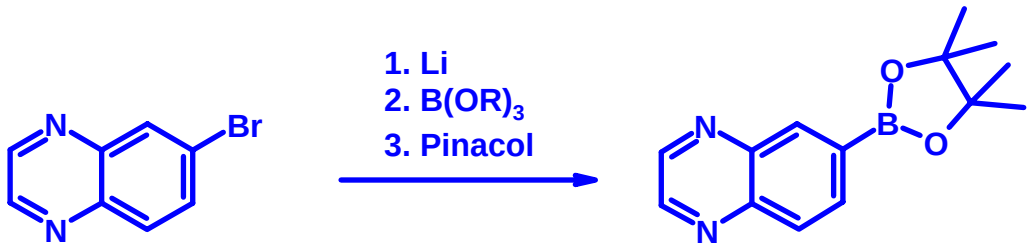


Archimica's Lithium Technology
- 4-Formylphenylboronic acid -



- Reduction of costs and increase in purity at the same time!
- Production volume: several 10 mtons/year

Archimica's Lithium Technology
- Quinoxaline boronic acids -

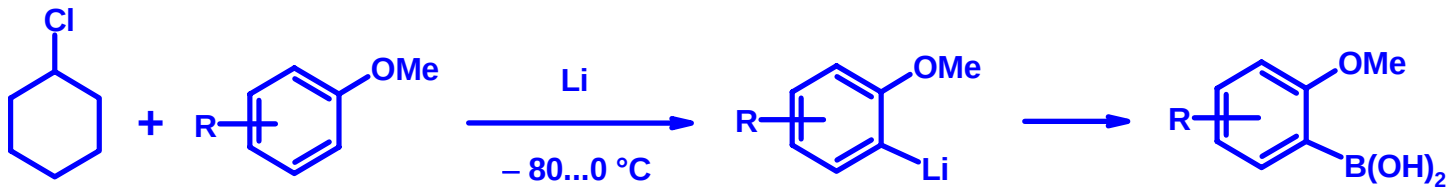


- Mg and RLi – No product formation
- Technical access to high quality product

Archimica's Lithium Technology

- Important core technology
- Unique plant engineering – special cooling system & novel Li granules set-up
- Largest cryogenic capacity in the fine chemicals world (>60 m^3 / -100 °C)
- Cryogenic production facilities (up to 8 m^3 / -100 °C cGMP vessels, 8 full scale lines)
- Lab to PP to multi-ton production: few months

General substitution method for BuLi

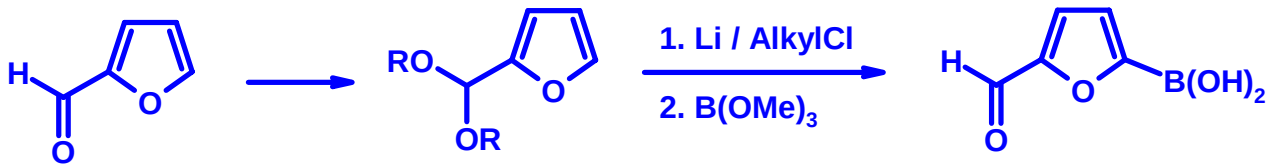


n-BuLi ⟹ **RHal + Li**

- Potential to reduce material costs by up to 50 %
- Fine tuning possible
- Improved yields and purity increase

General substitution method for BuLi
- Furfural boronic acids -

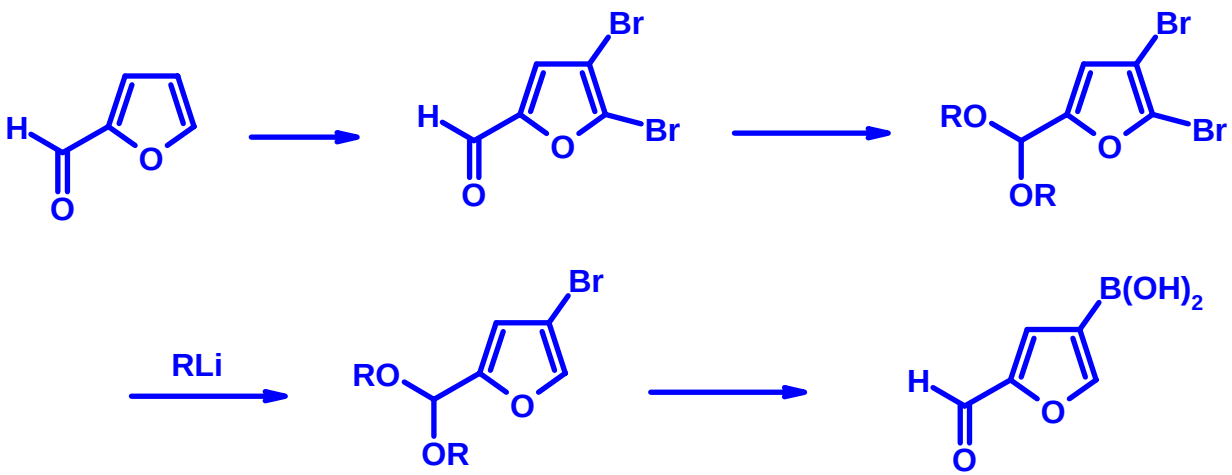
5-Formylfuran-2-boronic acid



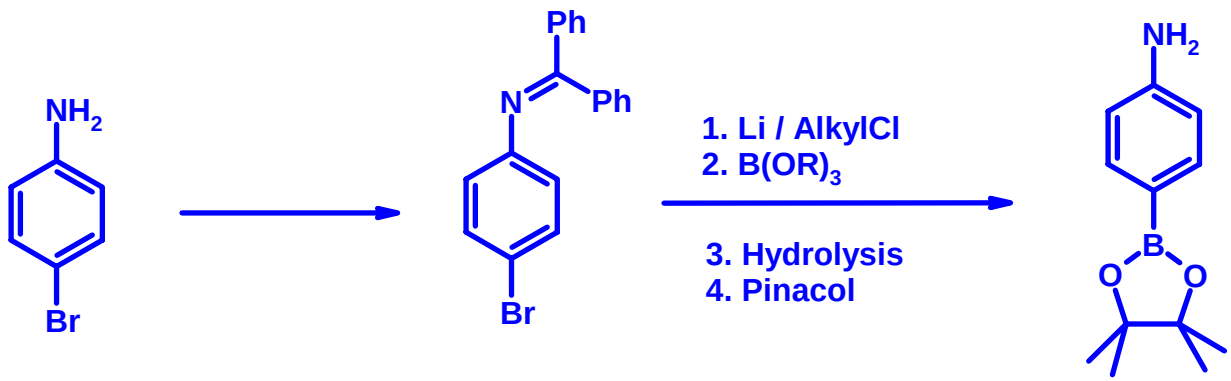
- Lithium technology key to success at scale
- Production scale well at MT level

General substitution method for BuLi
- Furfural boronic acids -

2-Formylfuran-4-boronic acid

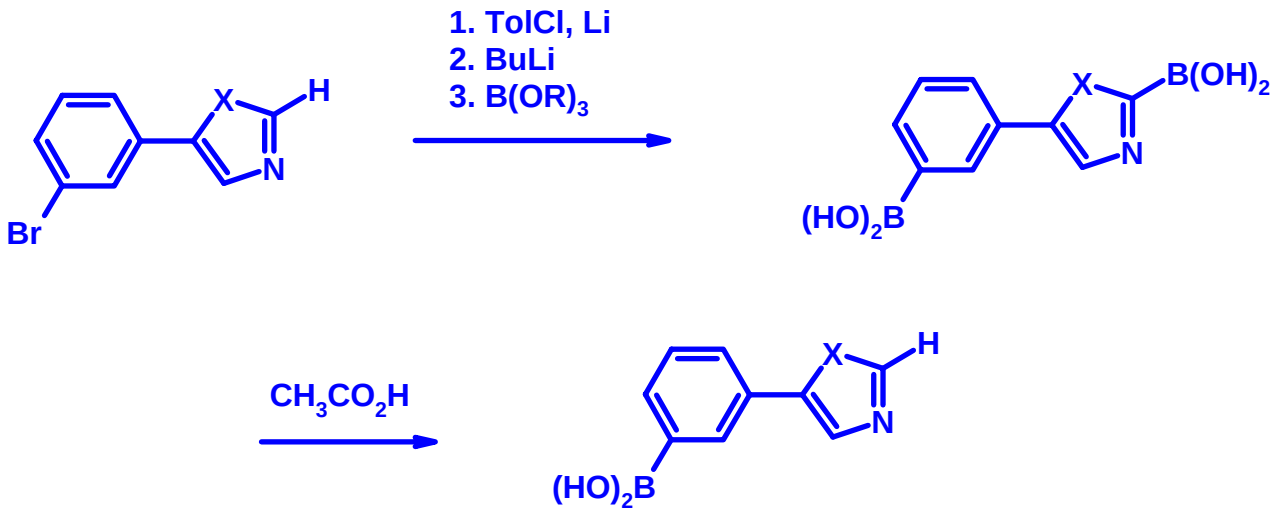


Amino-substituted Aryl boronic acids



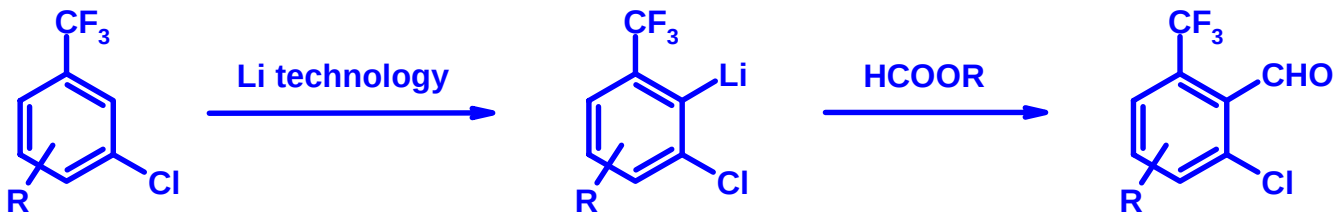
- Protection of Amino groups with Ketones
- High yields, also with Chloro precursor
- Broad functional group tolerance
- Deprotection of Amino group possible *after* Suzuki coupling

Multi-Heteroatom Aryl boronates



- Exploitation of different stabilities of Boronic acids
- Yields > 75 %

Aldehydes via Lithium technology

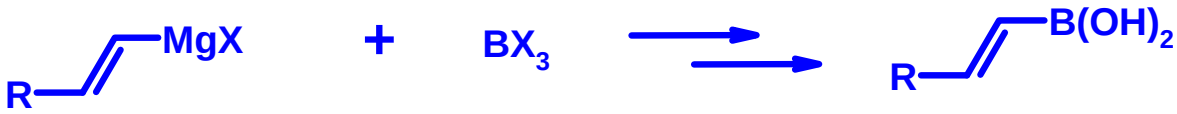


- Li ortho to Cl (possible Aryne formation)
- Attractive yields

Acids / Esters via Lithium technology

- Easily scalable economic access to acids and esters
- Excellent purity
- High yields

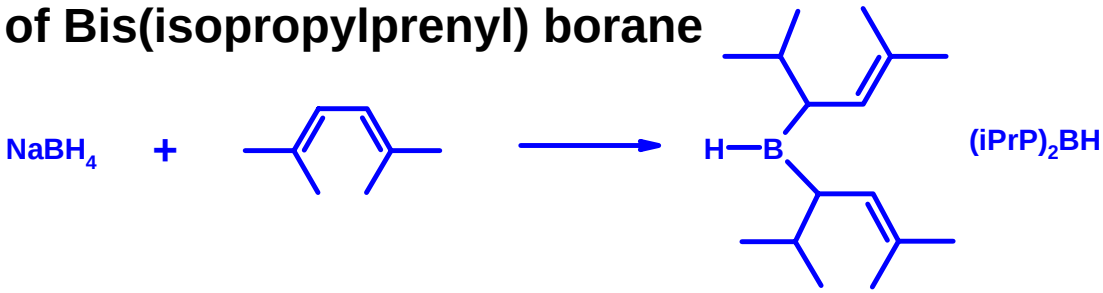
Aliphatic / Vinyl Boronic acids: Literature Synthesis



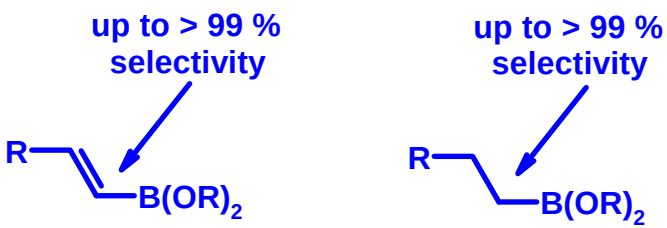
- Typical yields 15 - 25 %
- Highly water-soluble
- Moderate (low) purity products

Aliphatic / Vinyl Boronic acids: A New in-situ Hydroboration Technology

Step 1: Generation of Bis(isopropylprenyl) borane

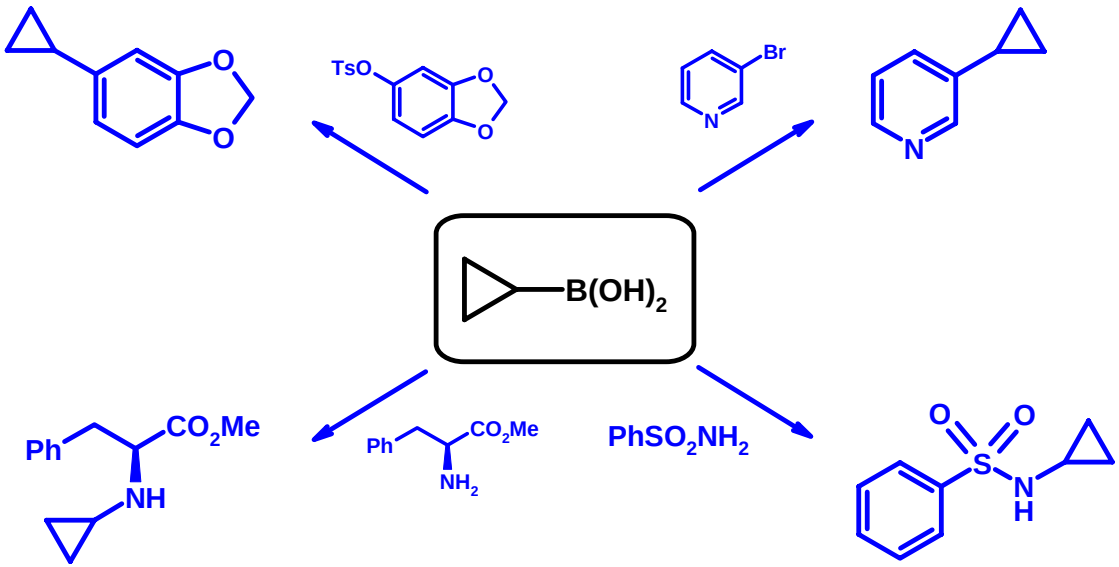


Step 2: Generation of Aliphatic / Vinylic Boronic Acids



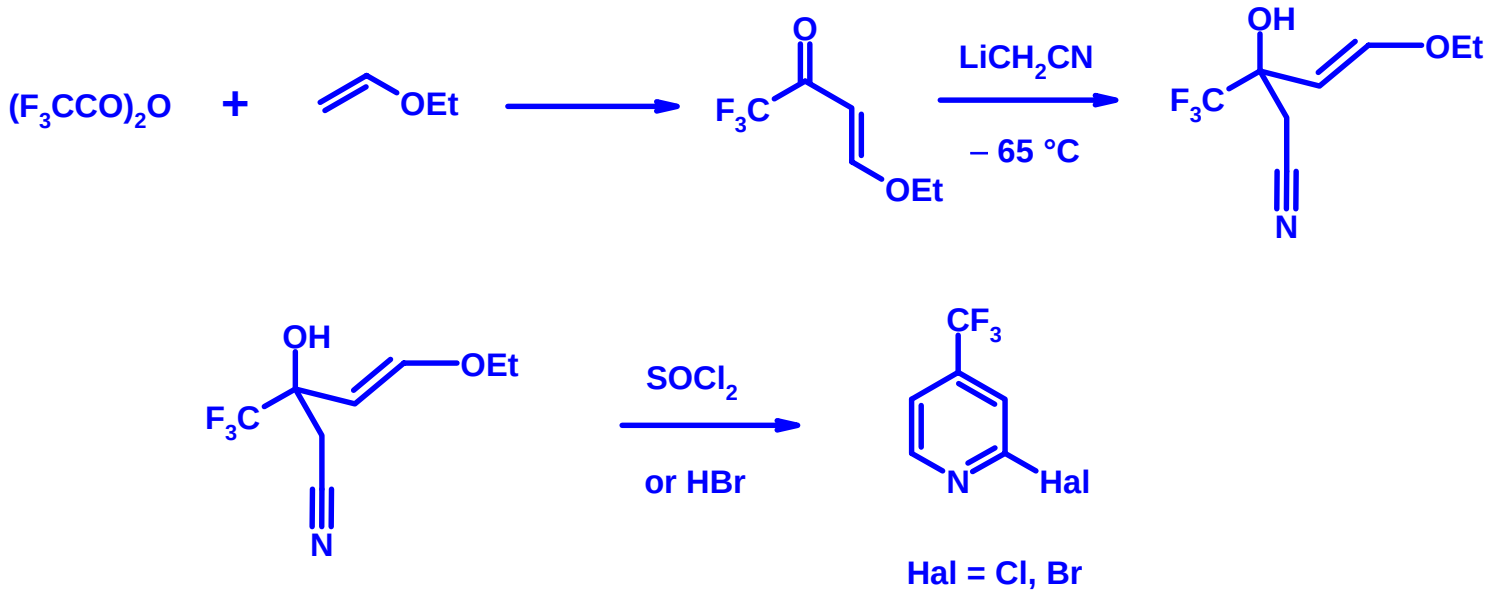
R = Aryl, Alkyl, $SiMe_3$, $CH(OEt)_2$, CH_2OPG

Cyclopropylboronic acid



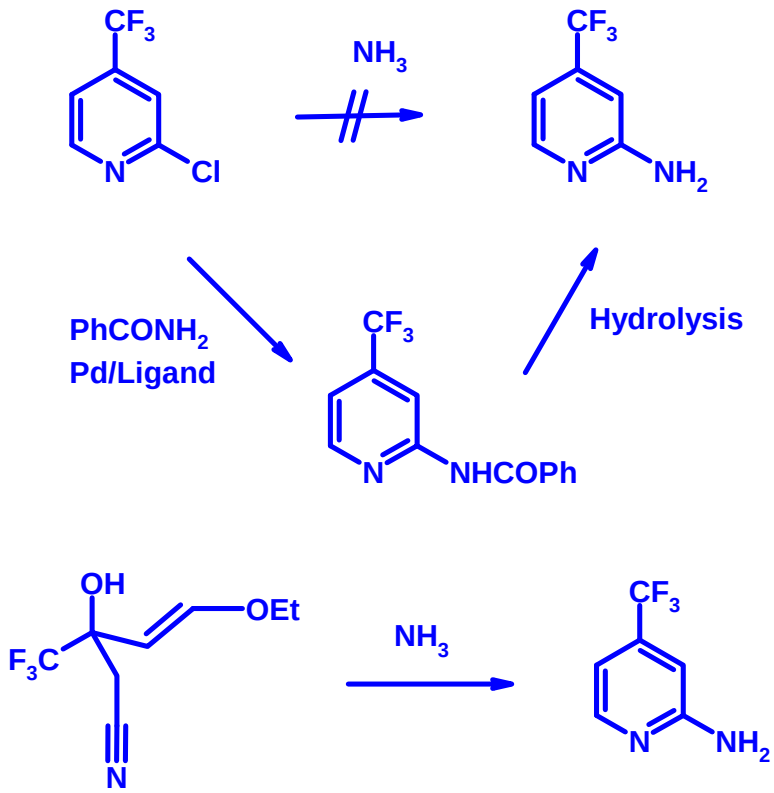
- Versatile building block
- Highly water soluble
- Careful isolation required
- Assay typically >95% (w/w%)

A new Pyridine synthesis (1)



- Innovative technology to „difficult“ substitution patterns
- Easily scalable processes
- Cryogenic + high-performance distillation

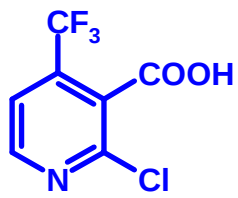
Trifluoromethyl pyridines (2)

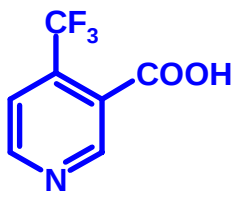


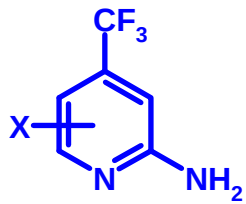
- Completely new route to amino pyridines with CF_3 groups

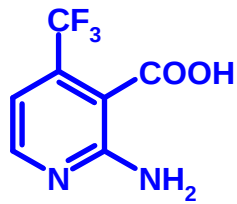
Trifluoromethyl pyridines (3)

- Highly substituted 4-trifluoromethyl pyridine derivatives



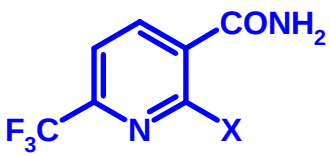


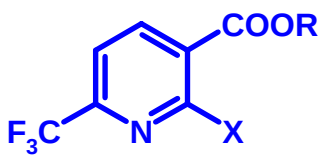


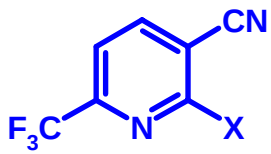


X = Cl, Br, I

- Isomeric 2-/6-trifluoromethyl pyridines are also accessible







X = OH, Cl, H, Alkyl

Summary

- Lithium technology
  - Li metal (granules) as metalation reagent
  - Substitution for Buthyllithium
  - Cost reduction and purity increase
- Large scale cryogenic production (>60 m^3 / -100 °C cGMP vessels)
- Cyclopropylboronic acid (Alkyl-, Alkenyl- and Alkinylboronic acids)
- Innovative synthesis to Trifluoromethyl pyridines

Thank you!

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