



Novel Applications of the H-Cube Technology to the Development of Bioactive Molecules

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Overview

- Introduction
- H-Cube reactor
- Reduction of C=C bonds
- Synthesis of Primary Amines
 - Azide to Amine
 - Nitrile to Amine
 - Nitro to Amine
- Protecting Group Manipulation
 - Deprotection of Benzyloxycarbonyl Groups
 - Deprotection of N-Benzyl or O-Benzyl Groups
- Conclusions
- Acknowledgements



Introduction

- Reasons to use the H-Cube
 - Richard V. Jones presented a new hydrogenation methodology utilizing the H-Cube at the ACS National Meeting in Fall 2005 and subsequently at GSK
 - Richard pointed out many clear advantages that the H-Cube had over traditional hydrogenation tools. These include:
 - Safer for chemists: no cylinders or other external hydrogen sources; no catalyst filtration or direct catalyst contact
 - Efficient: faster optimization, analyze reaction results in a minutes; easy to use with the touch screen
 - Easier workup procedure
 - Compact: only takes half of a standard enclosure
 - Disposable catalyst cartridges: relatively cheap and easier to handle
- We purchased the H-Cube unit in 2006



H-Cube Reactor (Model: HC-2)

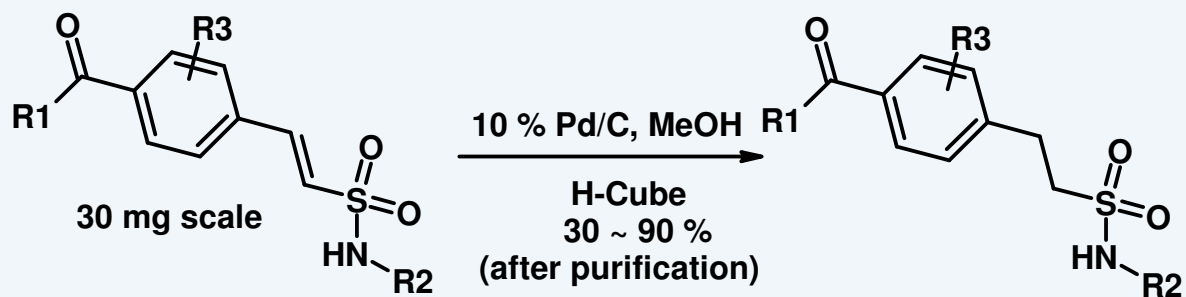
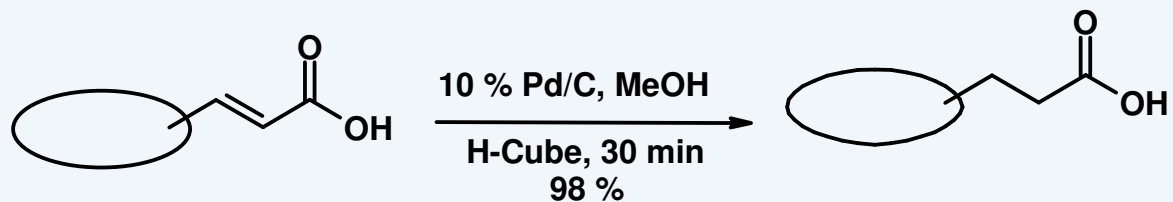


- Standard Conditions
 - Flow: 1 mL/min
 - Cartridge: Pd/C, Pd(OH)₂/C, etc.
 - Temp: 25 °C
 - Pressure: 1 Bar
 - Solvents: Methanol, EtOAc, etc.



Reduction of C=C Bonds

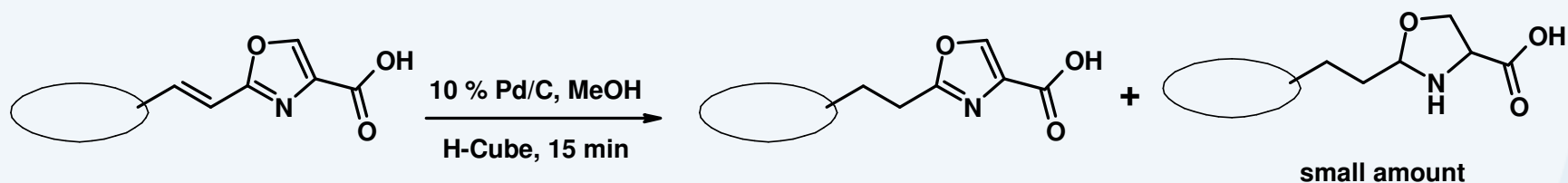
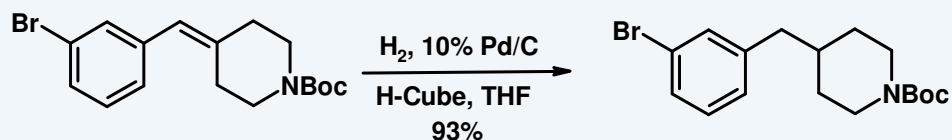
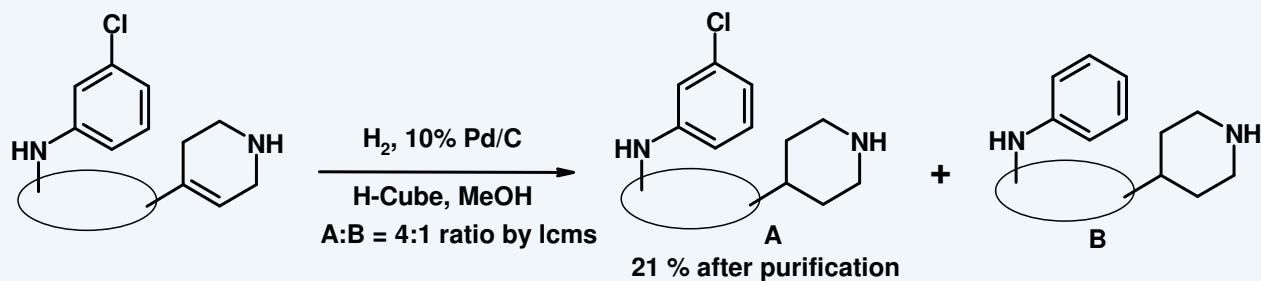
Conjugated Double Bonds





Reduction of C=C Bonds

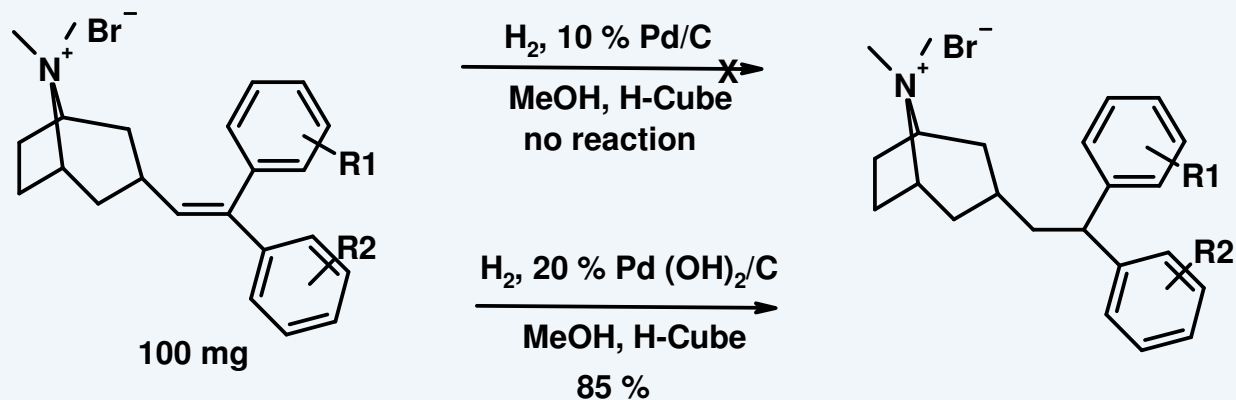
Selectivity





Reduction of C=C Bonds

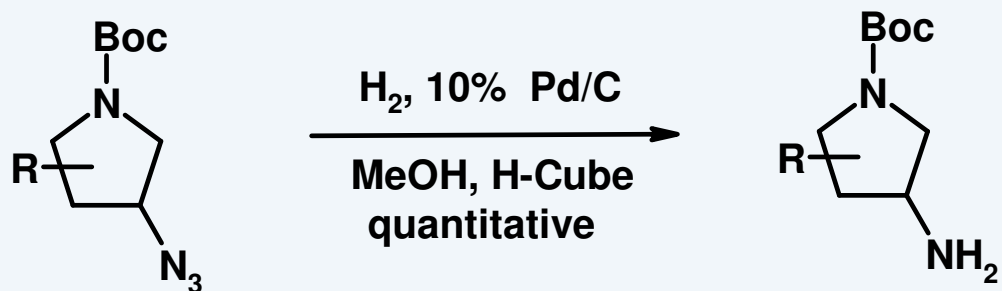
In the Presence of a Quaternary Salt





Synthesis of Primary Amines

Azide to Amine



H-Cube { 100 mg: 30 min
500 mg: 3 h or longer

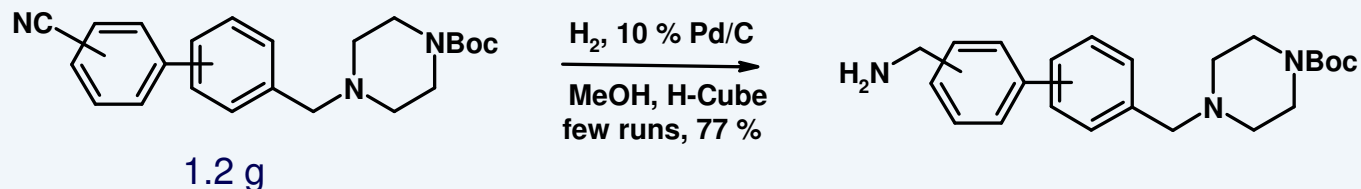
Balloon: 9 gram: using conventional hydrogenation method for 3 h

- Relatively easier to convert azide to amine with H-Cube with Pd/C in a 10 mg to 1 g scale.
- However, conventional hydrogenation was still the preferred method when the scale was more than 2 g

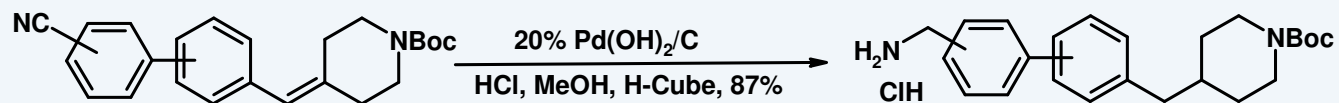


Synthesis of Primary Amines

Nitrile to Amine



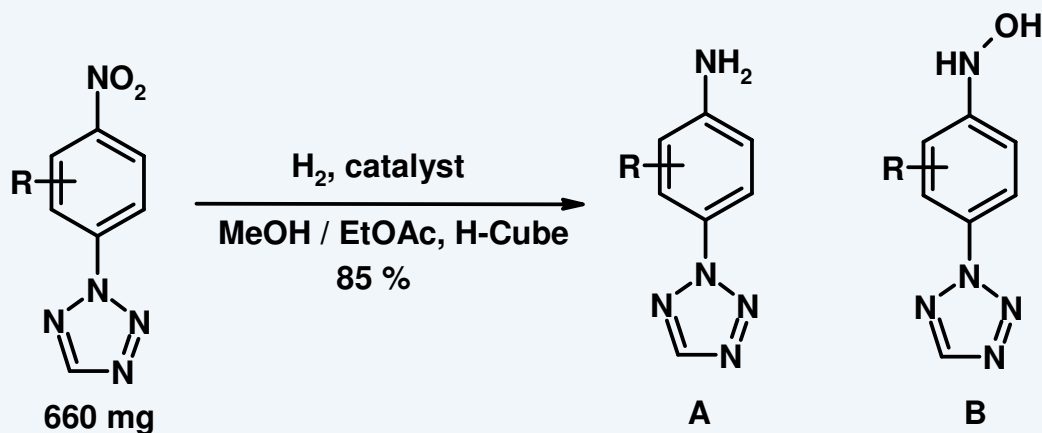
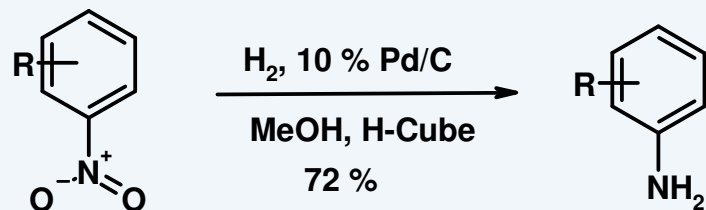
In the presence of a C=C bond:





Synthesis of Primary Amines

Nitro to Amine

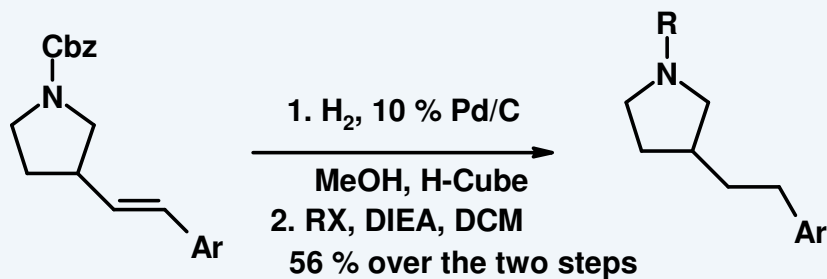
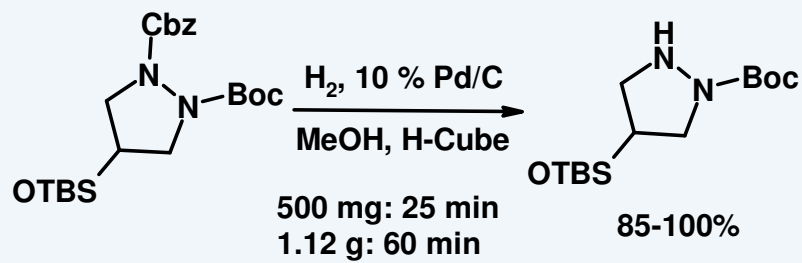
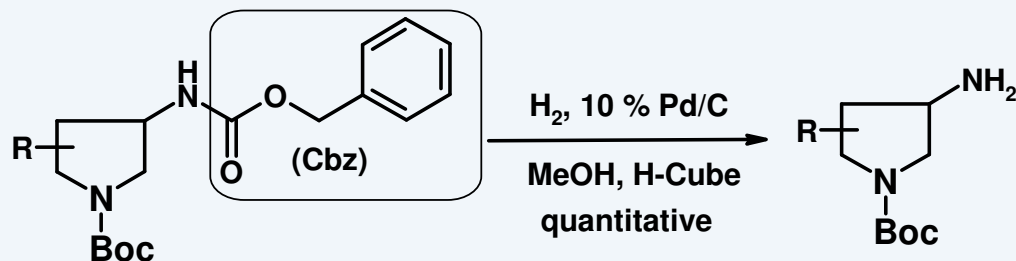


10 % Pd/C: 6.5 h, 1:1.2 ratio of A:B; then switch to
20 % Pd(OH)₂/C: three cycles, complete conversion to A



Protecting Group Manipulation

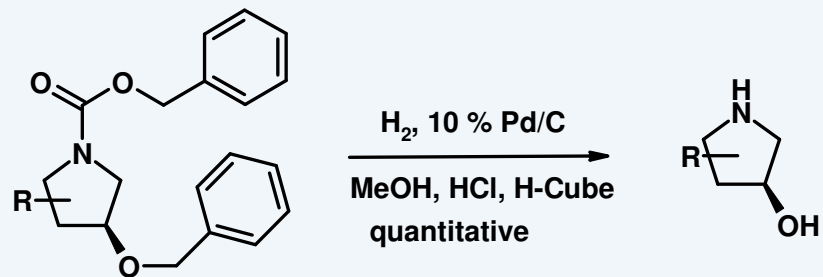
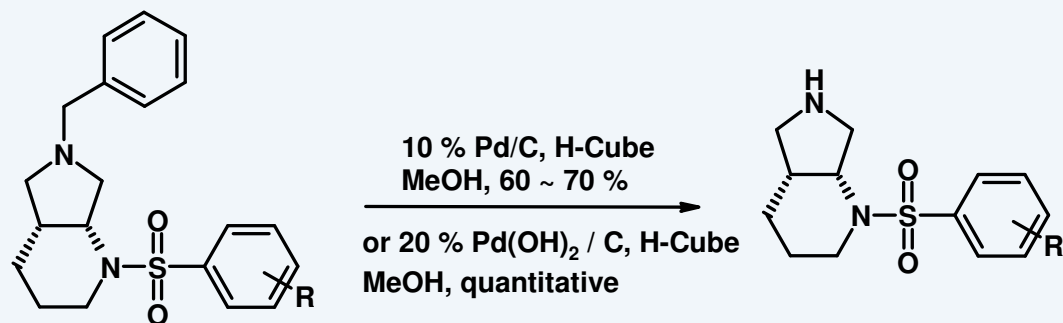
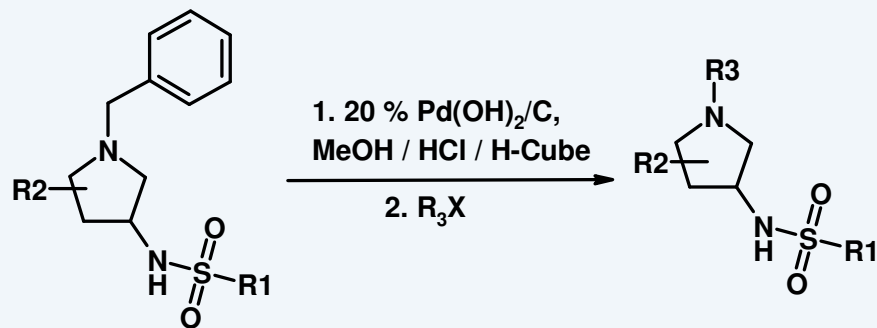
Deprotection of Benzyloxycarbonyl Groups





Protecting Group Manipulation

Deprotection of *N*-Benzyl or *O*-Benzyl Groups





Conclusions

- Generally, researchers in our group found that the H-Cube presented some distinct advantages over conventional methods from small to medium scale (10 mg to 1 g)
 - Safe and convenient
 - Don't have to handle catalyst
 - Installation of the cartridges is straight forward
 - Reactions are easy to monitor and workup
 - As efficient as “conventional” hydrogenations
 - Same reaction scope
 - Comparable yield
- Limitations
 - Lab model HC-2 is not very convenient for larger scale reaction



Acknowledgements

- Chemistry Team in UM Respiratory CEDD
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