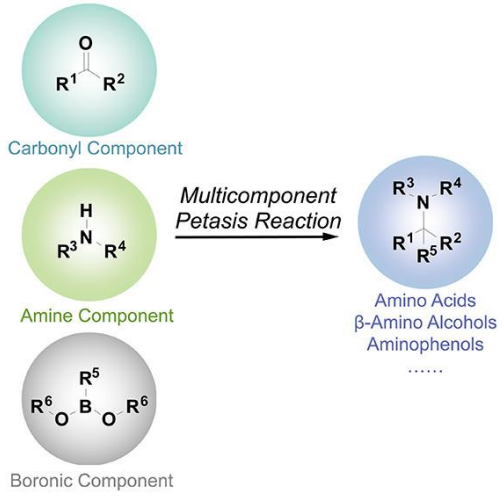
The Boronic Acid Mannich Reaction



Organic Reactions Vol. 83, Chapter 2

Stephen G. Pyne and Minyan Tang

Blake Ocampo

February 16, 2021

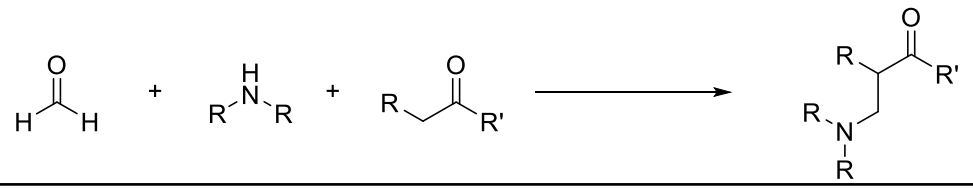
Outline

I. Introduction
II. Uncovering the Mechanism
III. Scope and Applications
    I. α-amino acids
    II. 1,2 amino alcohols
    III. α-amino ketone
    IV. 2-hydroxybenzylamines

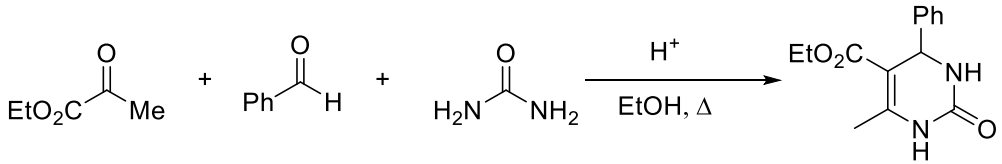
What are Multicomponent Reactions?

- 3 or more reagents in the same flask
- Most atoms of each component are incorporated
- Often robust with very generalizable applications

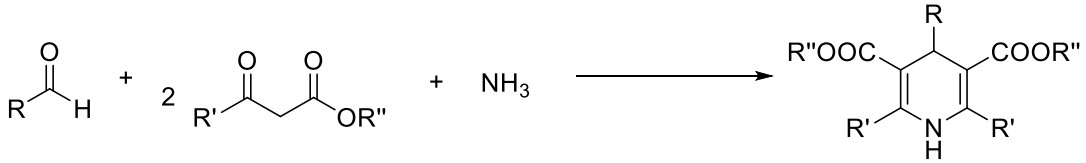
Mannich Reaction



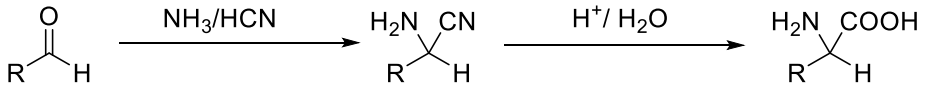
Biginelli Reaction



Hantzsch Dihydropyridine Synthesis

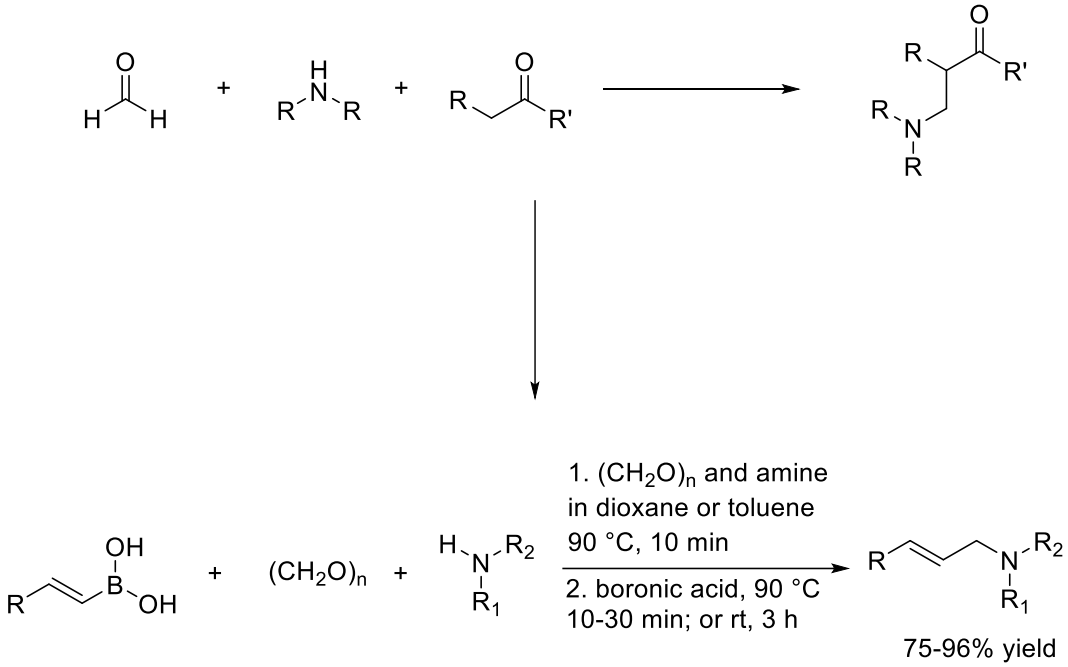


Strecker Synthesis



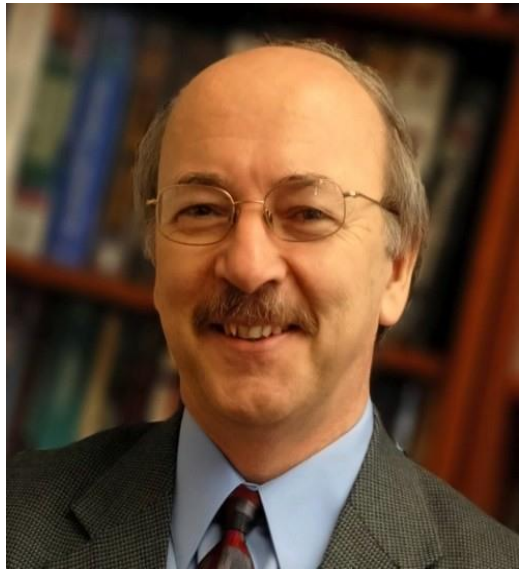
A Modification of the Mannich Reaction

Mannich Reaction



Tetrahedron Lett. **1993**, *34*, 583-586.

Nicos A. Petasis



B.S. 1978 Aristotelian University of Thessaloniki, Greece

Ph.D. 1983 University of Pennsylvania, Philadelphia

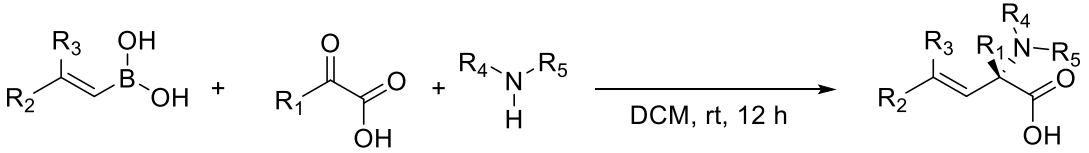
Professor at University of Southern California

Advantage over Mannich Reaction

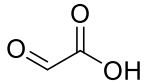
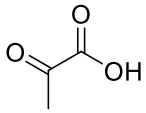
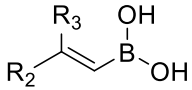
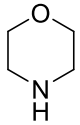
- Vinylic nucleophiles did not work well for allylamines
- Boronic Acids are commercially available
- No loss of configuration

The Petasis Reaction and α-amino acids

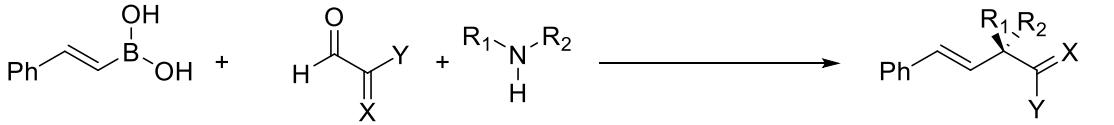
Petasis (1997)



76-94% yield

Carbonyl	Boronic Acids	Amines
 	 R_2 = aryl or Br R_3 = H or Br	$R-NH_2$ R = aryl, benzyl 

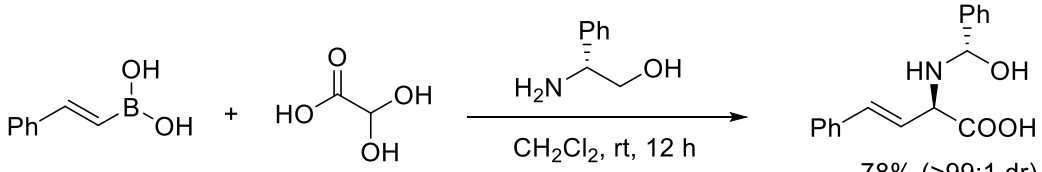
Generalized Form of the Petasis Reaction



X = O, or an H/OH
Z = H, OH, or R

J. Am. Chem. Soc. **1997**, *34*, 445-446.

Stereoselective Example



78% (>99:1 dr)

Advantages over Strecker and Ugi

No Isocyanide!

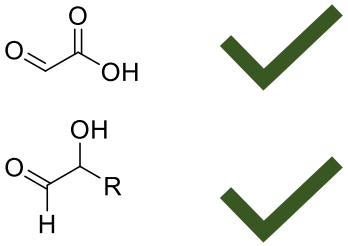
Tolerant of bromo-derivatives

Chiral Amines gave full diastereoselectivity at room temp

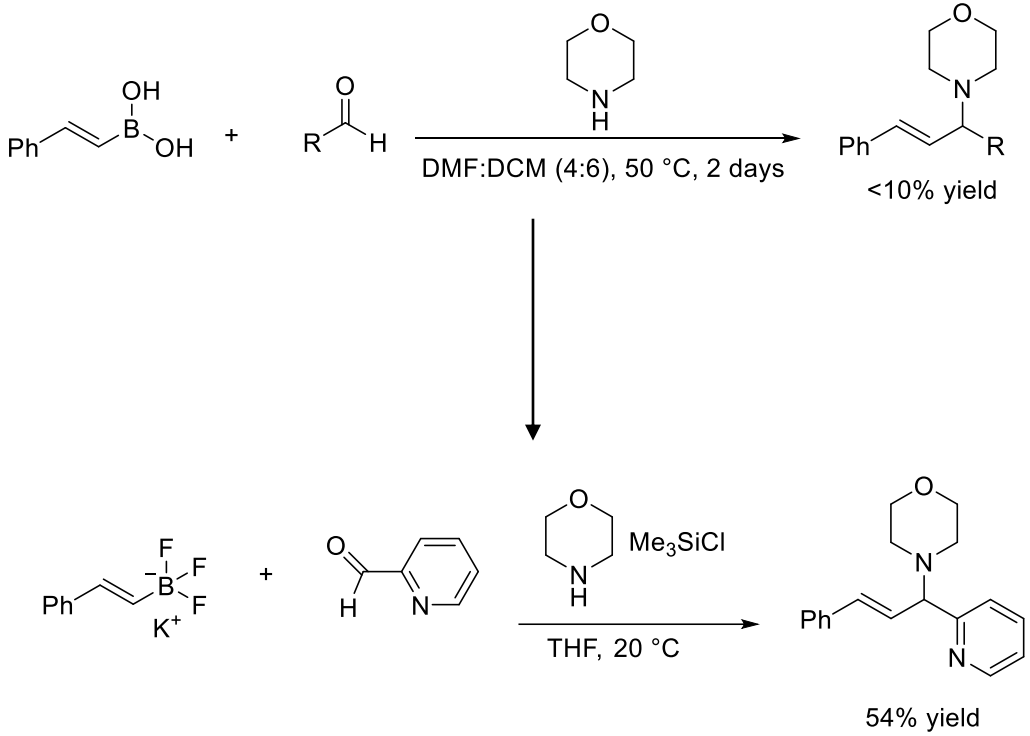
These reagents can be readily prepared

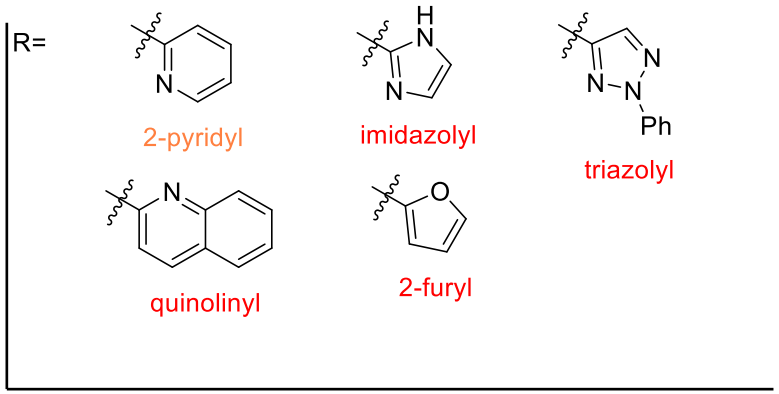
Expanding to Electron Poor α-Aldehydes

Observations



Schlienger (2000)



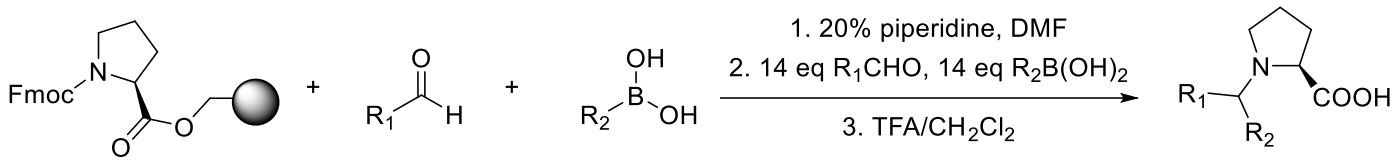


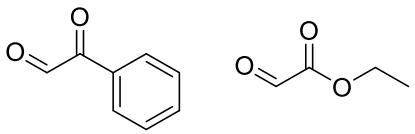
- Electron Rich and Poor α-aldehydes both had poor yield
- Mild Expansion with trifluoroborates, but not significant enough

Tetrahedron Lett. **2000**, *41*, 1303-1305.

Finding a Mechanism with Observations

A Solid Phase Approach for Combinatorial Libraries (Schlienger, 2000)





Work but with lower yields

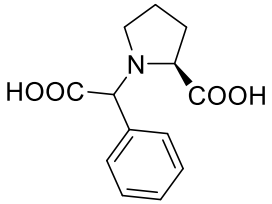
Key Findings

Salicylaldehyde reacted in lesser yield involving more electron rich boronic acids

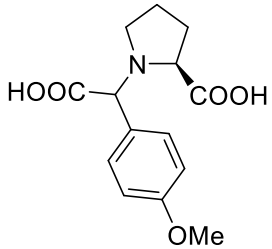
Glyoxylic Acid works in higher yield, but worse dr

Morpholine, Benzylamine, and methylbenzylamine work poorly for solid phase (<37% yield)

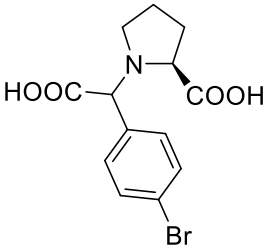
α-heteroatom groups to the carbonyl were required, but implied that highly activated aldehydes were necessary



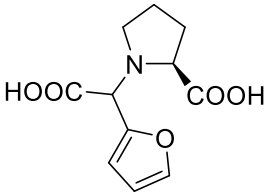
82% yield
88:12 dr
Purity > 95%



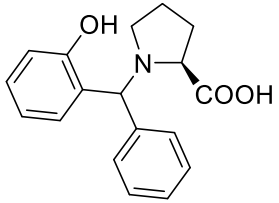
90% yield
70:30 dr
Purity > 95%



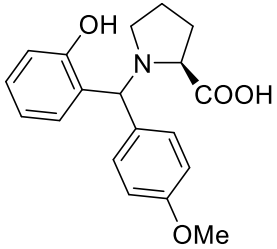
86% yield
73:27 dr
Purity= 92%



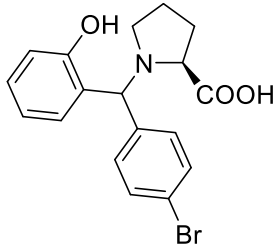
78% yield
54:46 dr
Purity= 90%



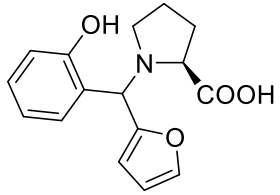
82% yield
70.5:29.5 dr
Purity > 95%



41% yield
87:13 dr
Purity > 84%



81% yield
97.5:2.5 dr
Purity= 95%

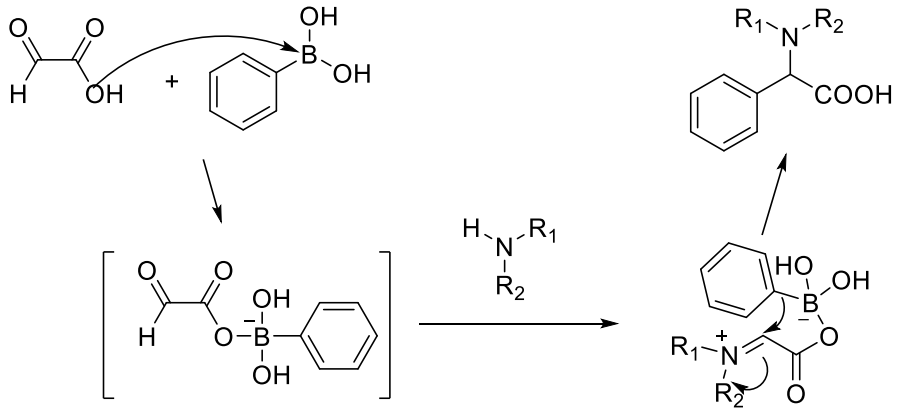


0% yield

Tetrahedron. **2000**, *56,* 10023.
Comprehensive Medicinal Chemistry II. **2007**, 697.

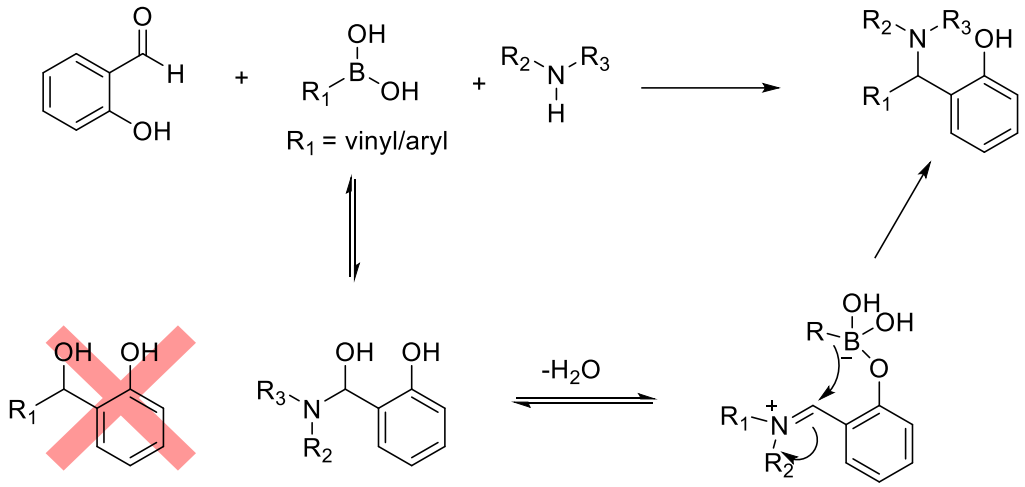
Mechanisms for Glyoxylic Acid and Salicylaldehyde

Mechanism for glyoxylic acid (Schlienger, 2000)



- Vicinal functionality necessary
- ^{11}B NMR shows strong upfield shift from 33.5 to 14.2 ppm in complex
- ^{13}C NMR shows glyoxylic acid monohydrates signals disappear with reappearance at upfield when mixed with phenylboronic acid
- But, with salicylaldehyde, there was no boron shift until secondary amine was added

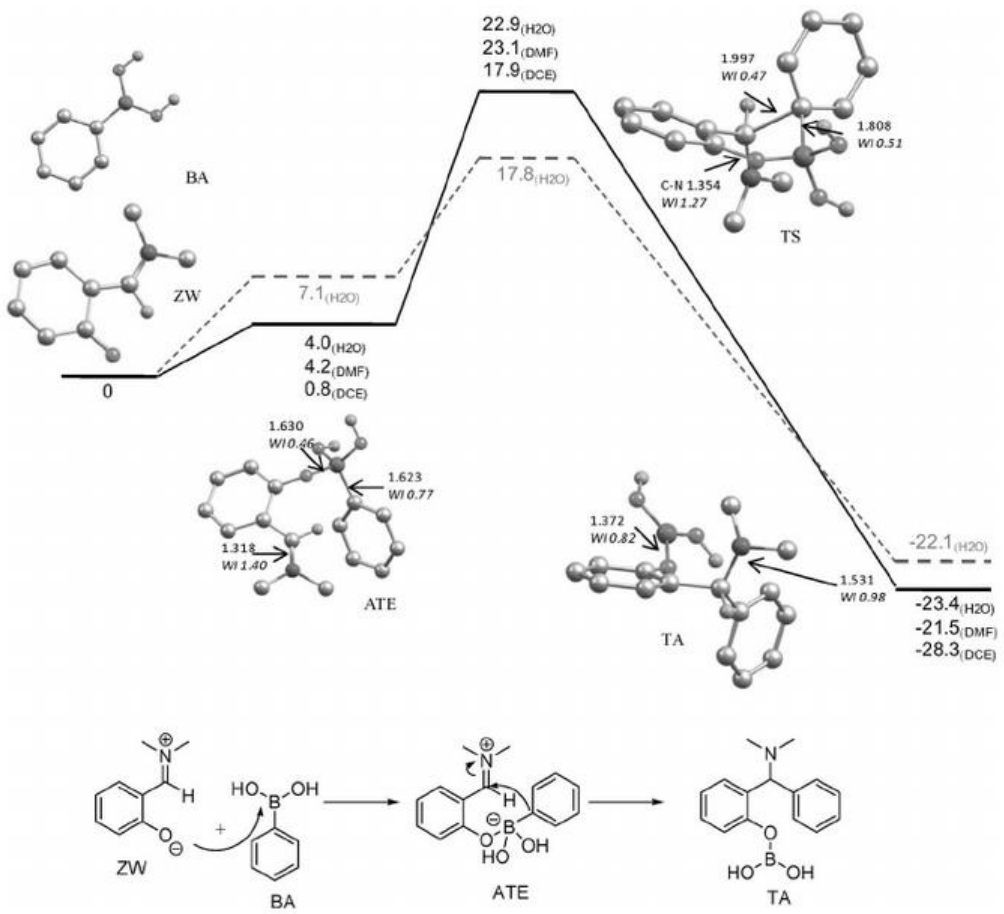
Mechanism for Salicylaldehyde (Petasis, 2001)



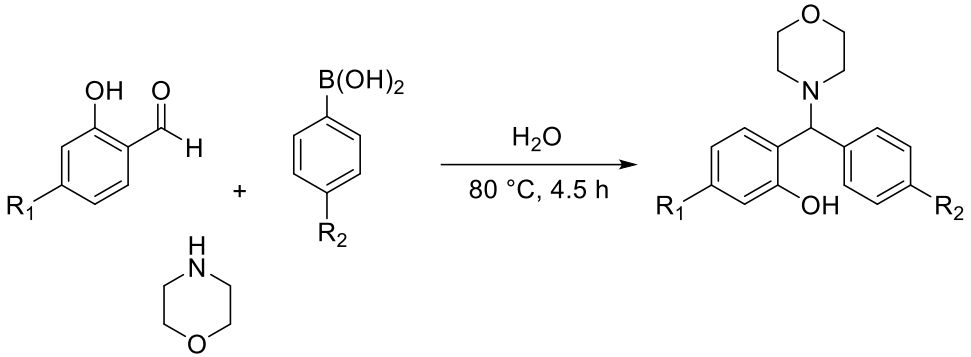
- Boronic acid does not react as nucleophile or electrophile even at high temp
- Requires amine to be present first
- Various aldehydes without a α-heteroatom were ineffective

Tetrahedron Lett. **2000**, *56*, 10023.
Tetrahedron Lett. **2001**, *42*, 539.

A DFT insight in Water for Salicylaldehyde



Candeias (2009)



R_1 = H (75%), Me (70%), OMe (72%)

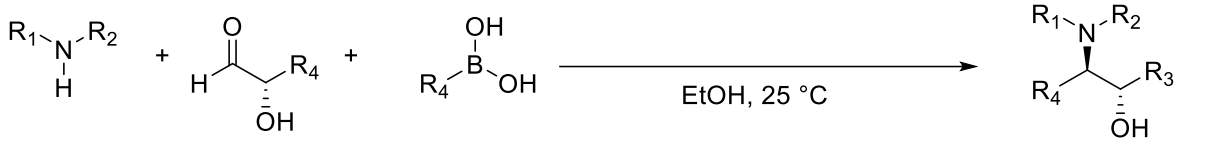
R_2 = F (75%), Me (85%), OMe (81%)

- Salicylaldehyde forms an oil, which dissolves into aqueous upon addition of amines
- No acceleration in water compared to toluene or dichloroethane
- Accounted for solvent effects using polarizable continuum model
- The Zwitterionic TS is 13 kcal/mol less than protonated
- TS indicates early transition state
- Stabilization seen with boronate (ATE) formation

Eur. J. Org. Chem. **2009**, *56*, 1859-1863.

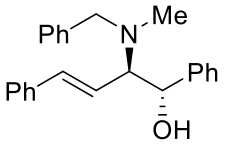
Diastereoselectivity with Chiral Aldehydes

Petasis (1998)

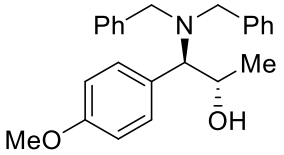


>99:1 dr, >99:1 er

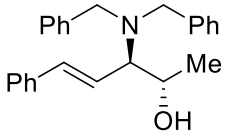
- This high diastereoselectivity is specifically observed only with the synthesis of amino alcohols
- Yield significantly reduced with ammonia
  - This will also be seen later!
- Presence of the alcohol is still needed
- Works with primary amines and secondary amines
- Requires electron rich aryl boronic acid or styryl boronic acids.



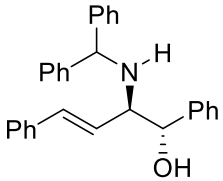
84% yield



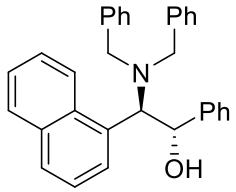
63% yield



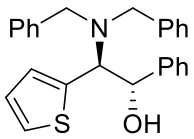
84% yield



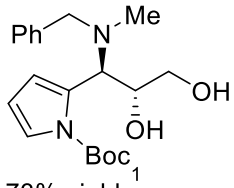
87% yield



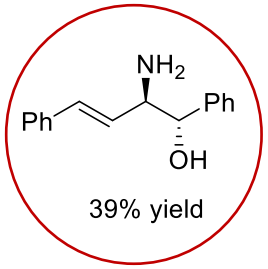
84% yield



86% yield



73% yield

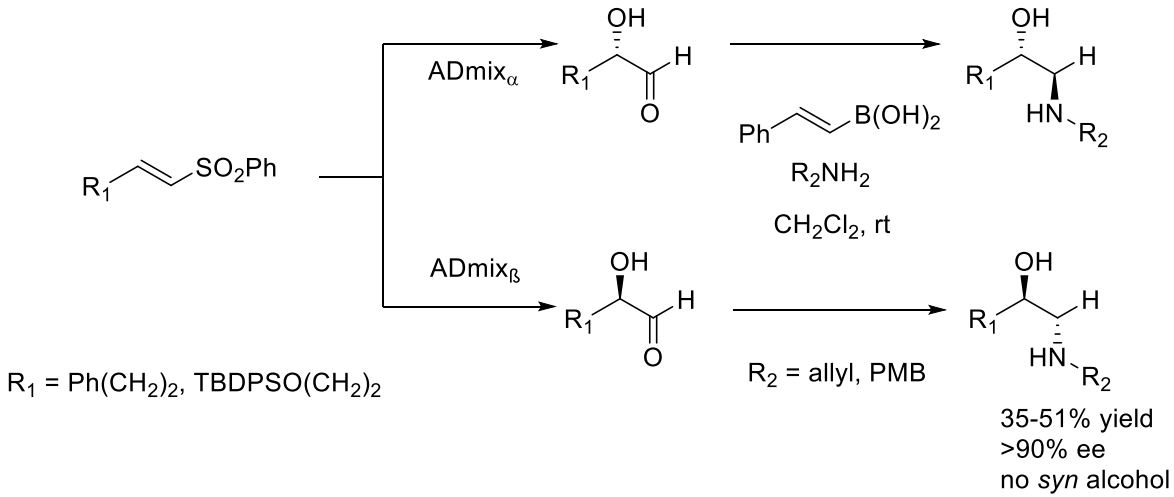


39% yield

J. Am. Chem. Soc. **1998**, 120, *45*, 11798.

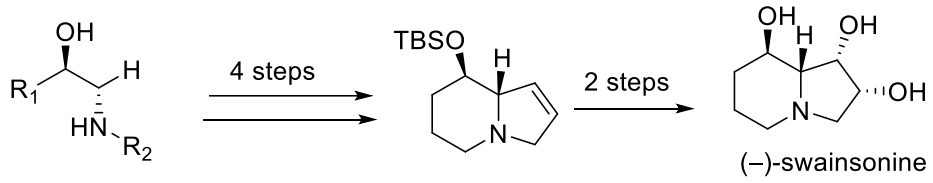
Understanding the Diastereoselectivity

Pyne (2006)

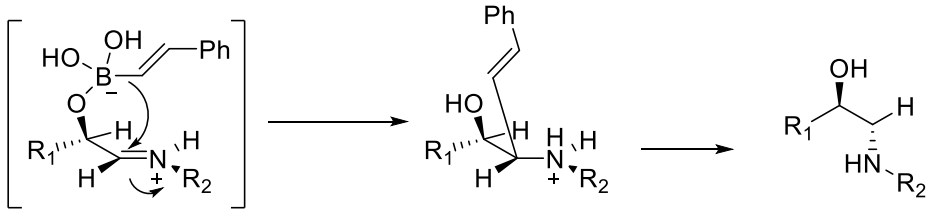


- $PMPNH_2$ and morpholine gave only 12% yield
- No presence of the syn-alcohol and only the anti-diastereomer formed

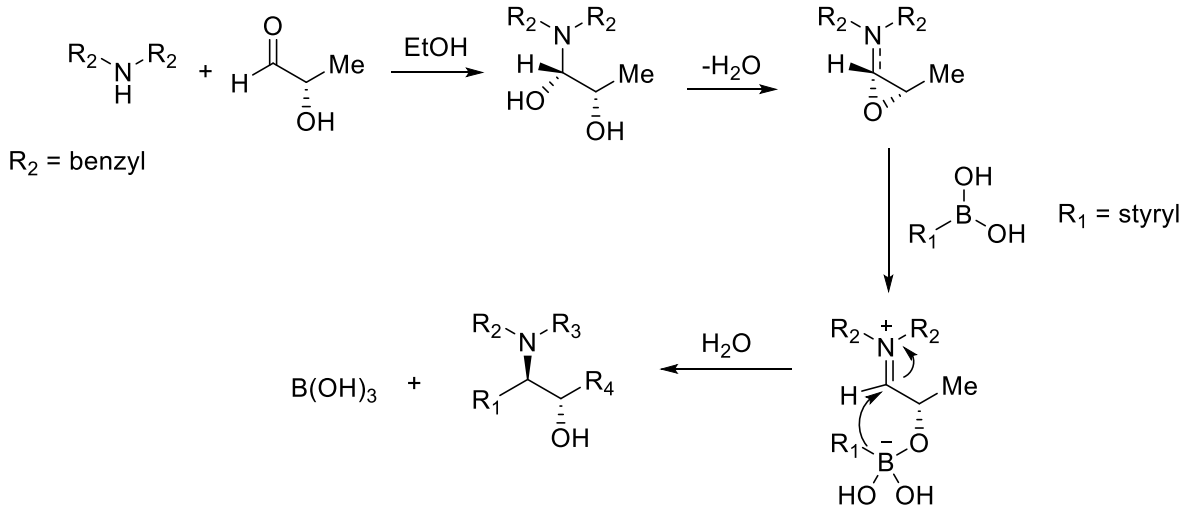
Pyne (2006)



Proposed Mechanism by Pyne (2006)



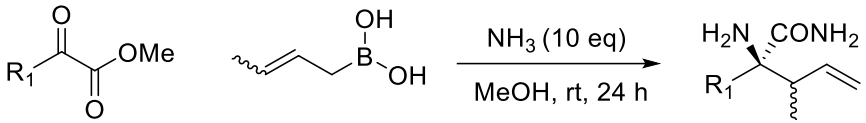
Proposed Mechanism via DFT Shuhua (2010)

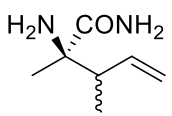


J. Org. Chem. ***2006***, *71*, 7097-7099.
Chin. J. Chem. **2010**, *28*, 41-49.

α-Amino Acid Formation Using Ammonia

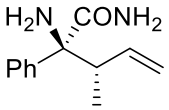
Dhudshia (2005)





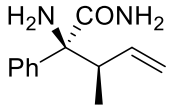
88% yield
60:40 d.r.

(E-crotyl)



92% yield
97:3 d.r.

(E-crotyl)

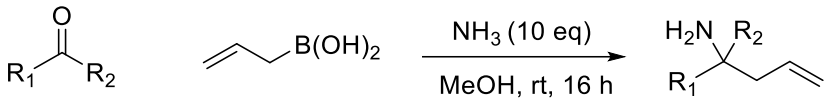


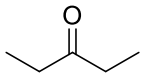
95% yield
97:3 d.r.

(Z-crotyl)

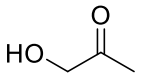
- This mechanism is not encompassed in the previous reactions, but can be plausibly reasoned through with ester group enhancing electrophilicity of intermediate

Demonstrations with non α-heteroatom

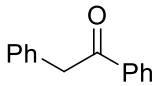




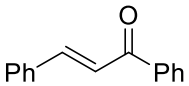
73% yield



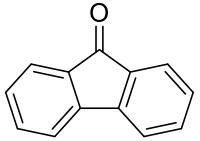
80% yield



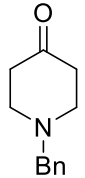
78% yield



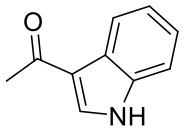
78%% yield



78% yield



92% yield

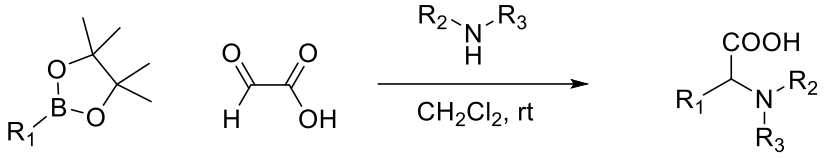


80% yield

Chem. Commun. **2005**, *44*, 5551-5553

Limitations of the Amine with Boronic Esters

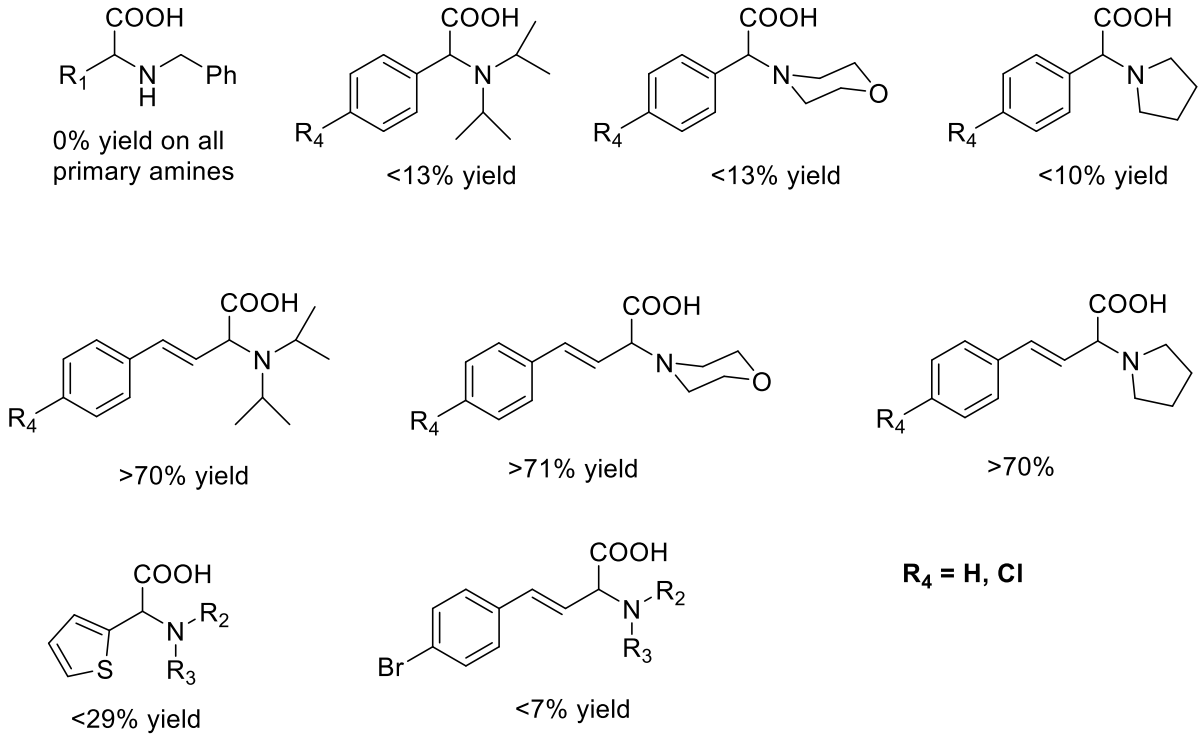
Scobie (2002)



R_1 = vinyl, aryl, or 2-thiophenyl

R_2 = morpholine pyrrolyl, diisopropyl

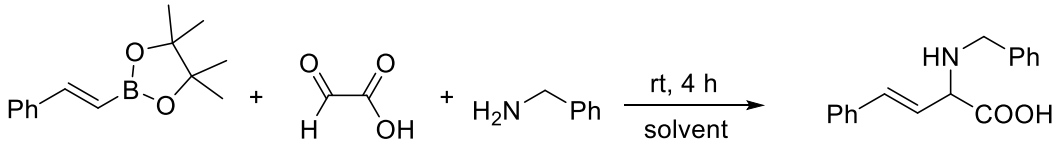
- Primary amines do not work with pinacol boronates
- Benzylamine works up to 67% with 4-methylbenzene boronic acid
- Speculated bis(isopropyl) boronic ester worked for Petasis due to potential for formation of boronic acid due to glyoxylic acid monohydrate being used
- However, this can be altered through the use of solvents



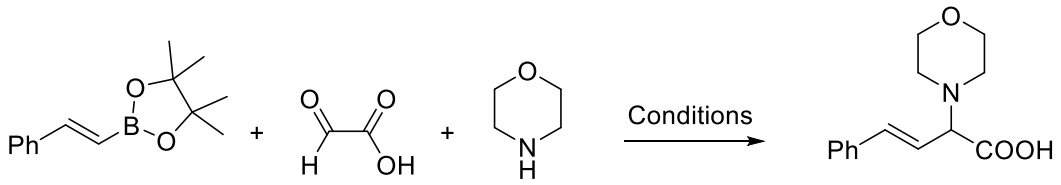
Tetrahedron Lett. **2002**, *43*, 5965-5968

Solvent Effects for α-Amino Acids

Piettre (2005)



Solvent	Yield
toluene, THF, CH_2Cl_2, dioxane	0%
MeOH	52%
EtOH	74%
HFIP	88%



Conditions	Yield
CH_2Cl_2, rt, 4h	12%
MeOH, MW (300 W), 120°, 10 min	21%
HFIP, 4 h	81%

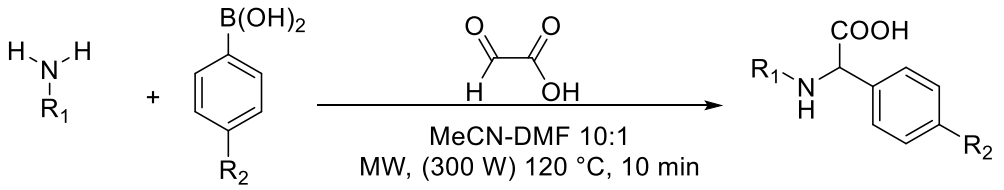
General Notes

- Boronate Esters are the ones that have been studied the most for solvent effects due to issues with reactivity
- Salicylaldehyde with arylboronic acids and morpholine work well with 1,2 DCE (77%) while DMF is less effective (41%).
- In general, the use of polar, organic protic solvents tend to benefit the reaction with styryl boronic acids/esters and glyoxylic acid

Tetrahedron Lett. **2005**, *46*, 8027-8031
Eur. J. Org. Chem. **2009**, *56*, 1859-1863.

Aniline and Heteroaromatic Amines

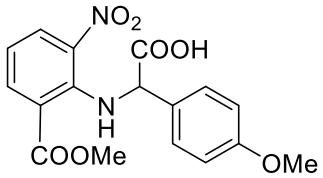
Follmann (2005)



R_1 = heteroaryl

R_2 = H, Cl, OMe

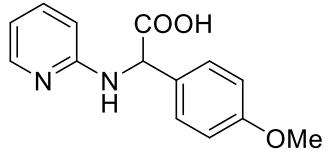
- For the reaction of arylamines with arylboronic acids, the more electron withdrawn the aniline is, the less reactive
- The more electron-withdrawn the arylboronic acid is, the less reactive



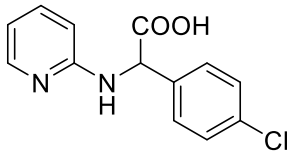
0% yield

Decreasing Electron Density Boronic Acid

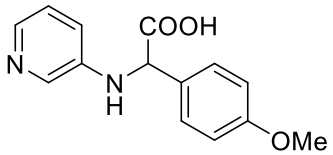
Decreasing Electron Density of Amine



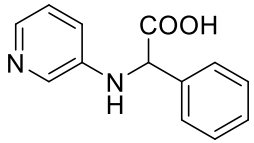
94% yield



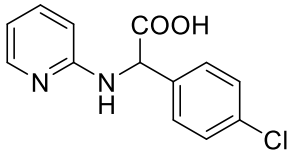
<5% yield



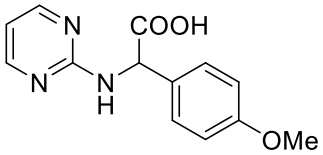
87% yield



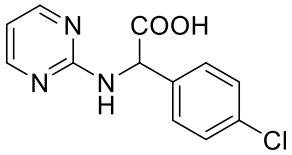
25% yield



<5% yield



86% yield

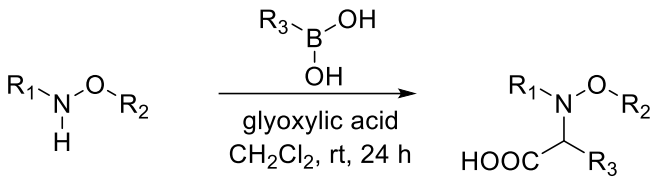


12% yield

Synlett. **2005**, *6*, 1099-1011

Non-Traditional amines with α-amino acids

N-hydroxy and *N*-alkoxy amino acids (Naskar, 2003)



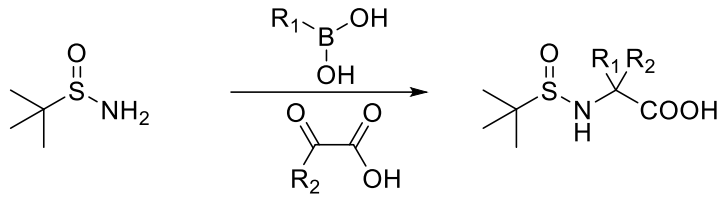
R_1 = methyl, benzyl, t-Bu

R_2 = H, methyl

R_3 = aryl

75-95% yield

N-(*tert*-butyl sulfinyl) amino acids (Naskar, 2003)

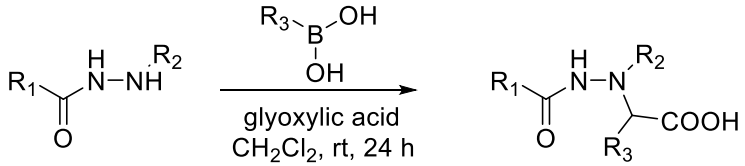


R_1 = aryl, styryl

R_2 = H, methyl

50-73% yield

Hydrazino amino acids (Portlock, 2005)



R_1 = t-BuO, BnO

R_2 = H, aryl, benzyl, alkyl

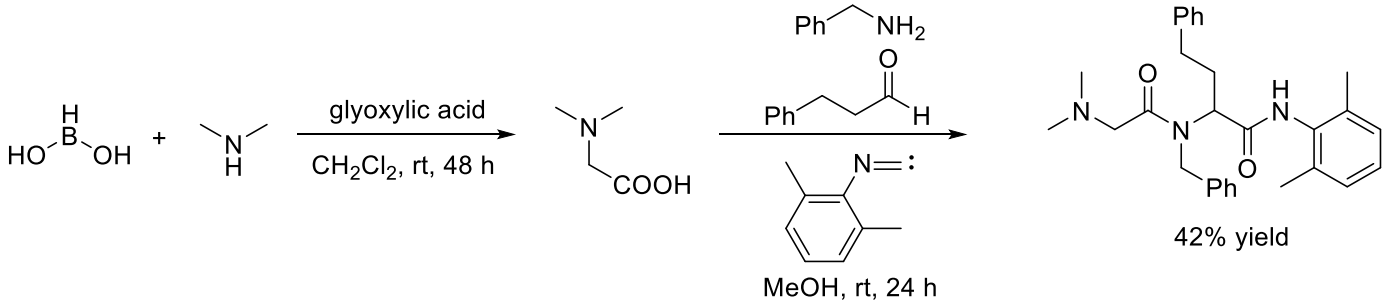
R_3 = aryl, styryl

60-99% yield
non-EWG amines

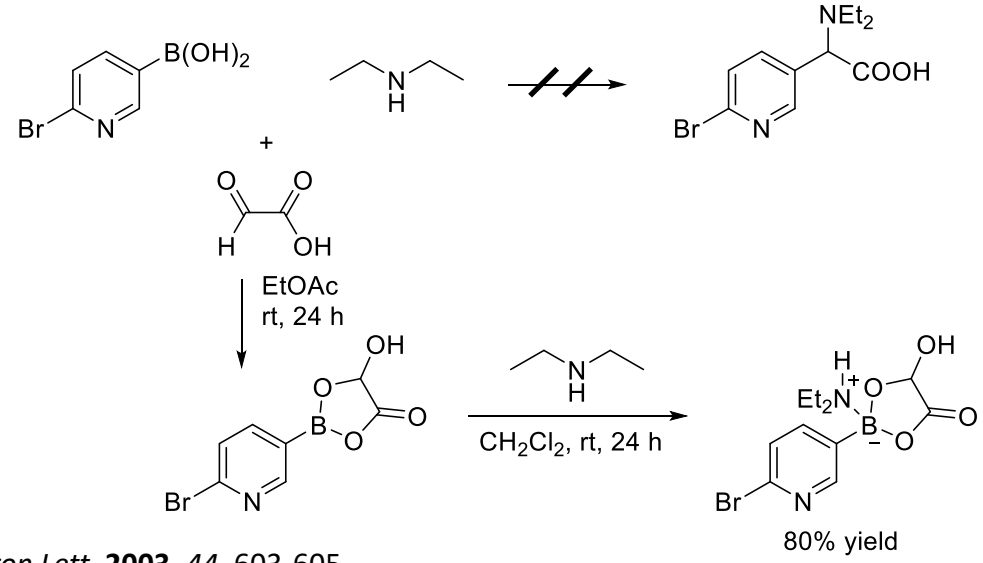
Tetrahedron Lett. **2005**, *43*, 6845-6847
Tetrahedron Lett. **2003**, *44*, 8865-8868

Expanding the Scope of Organoboranes

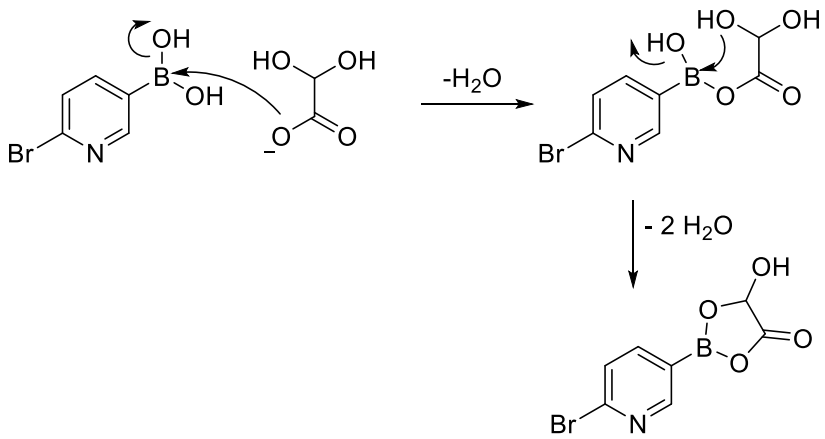
Portlock (2003)



Rault (2006)



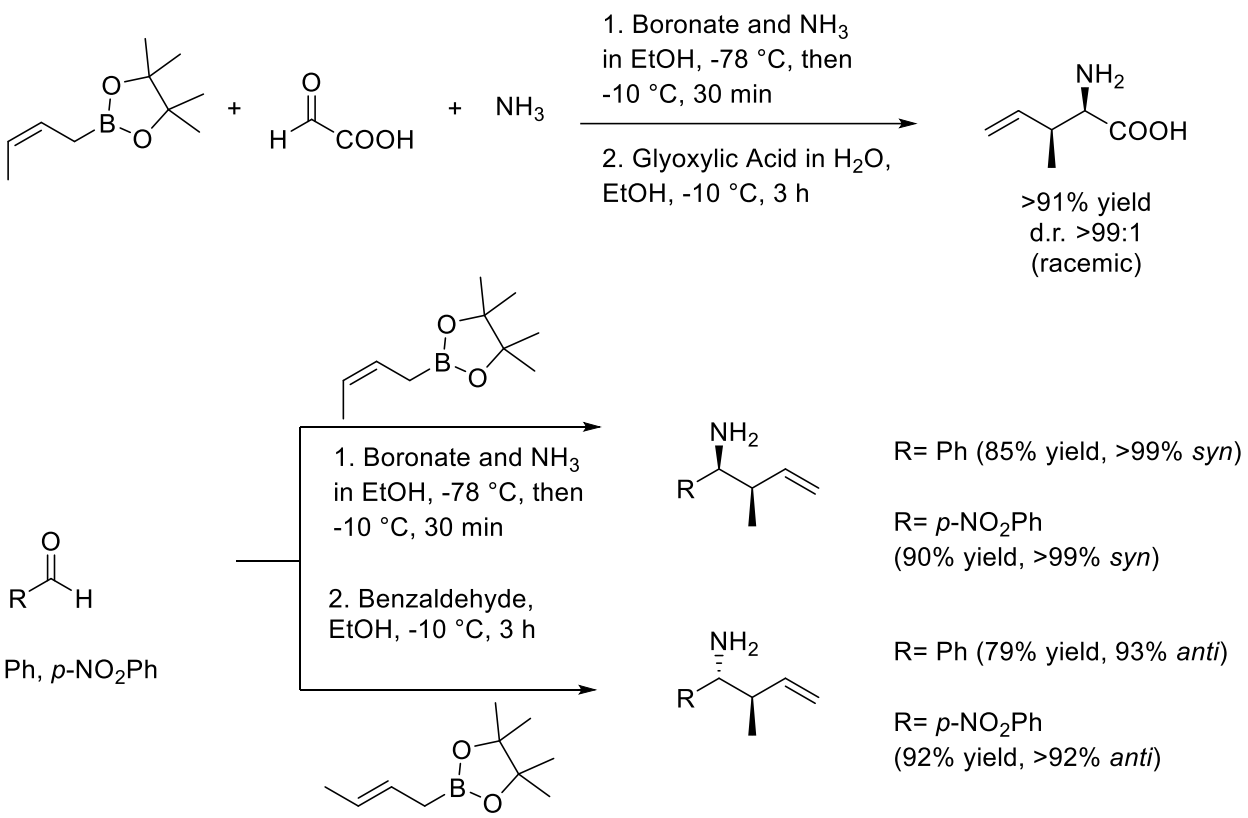
Plausible Mechanism to Explain Formation



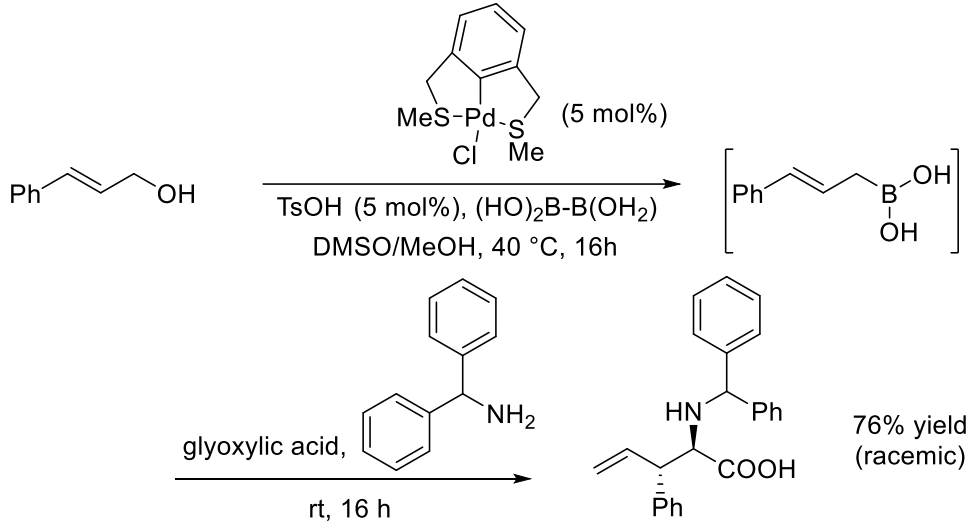
Tetrahedron Lett. **2003**, *44*, 603-605
Tetrahedron Lett. **2006**, *47*, 2165-2169

Pinacol Boronates and Transient Boronic Acids

Crotyl Boronates and Ammonia (Sugiura, 2004)



Transient Boronic Acids (Selander, 2007)

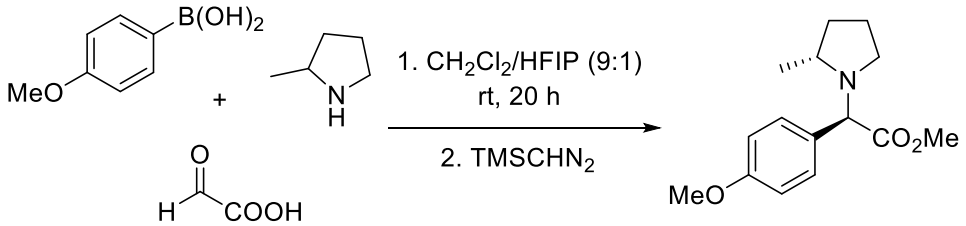


- Some allylboronic acids can rapidly decompose
- This allows for generation of unstable intermediates that still work to generate high yield

J. Am. Chem. Soc. **2004**, *126*, 7182-7183
J. Am. Chem. Soc. **2007**, *129*, 13723-13731

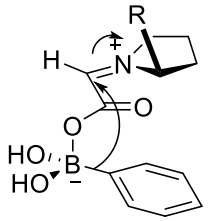
Promoting Diastereoselectivity of α-amino acids

Nanda (2005)

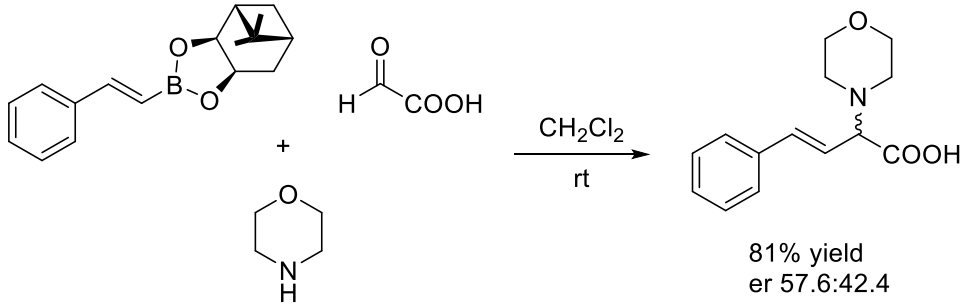


93% yield
dr 94:6
racemic

Proposed Intermediate

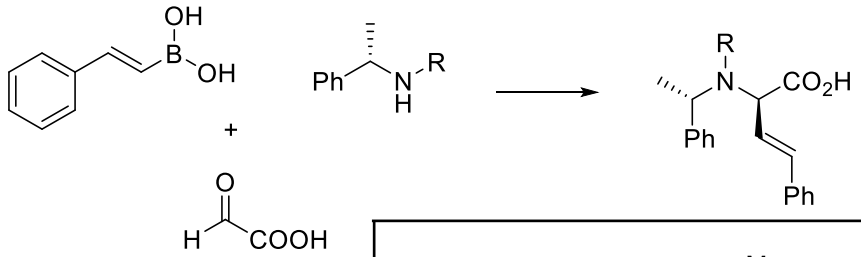


Scobie (2002)

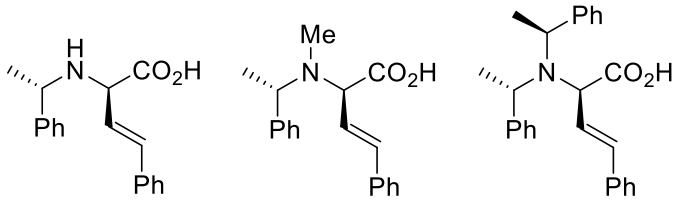


81% yield
er 57.6:42.4

Southwood (2006)



R = H, Me, (*S*)-CH(Me)Ph



81% yield
3.3:1 d.r.

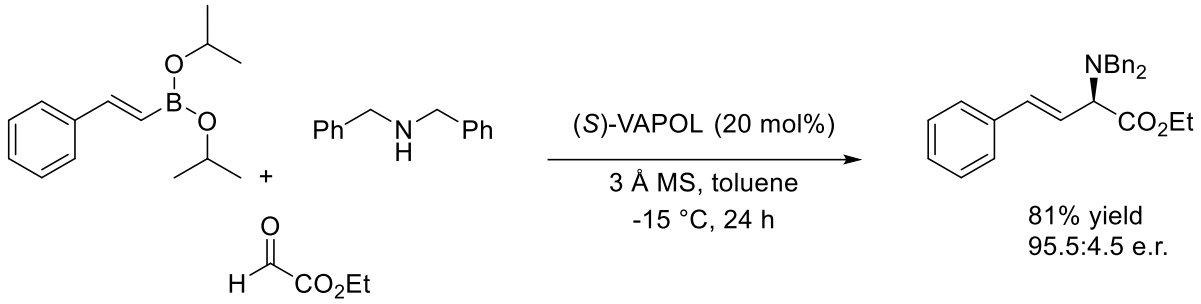
89% yield
>95:5 d.r.

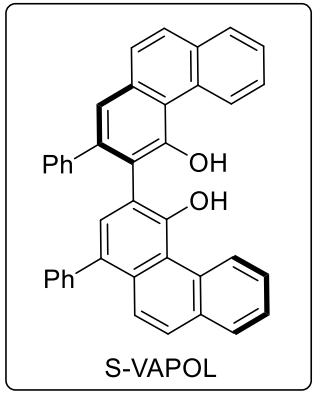
38% yield
>95:5 d.r.

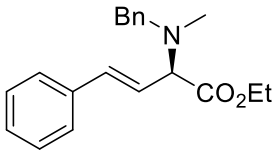
Tetrahedron Lett. **2005**, *46*, 2025-2028
Tetrahedron Lett. **2002**, *43*, 5969-5970
Tetrahedron. **2006**, *62*, 236-242

Asymmetric α-amino acid formation

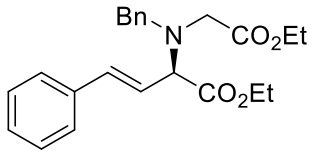
Schaus (2008)



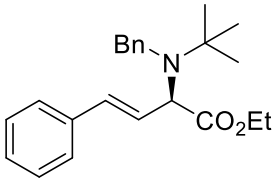




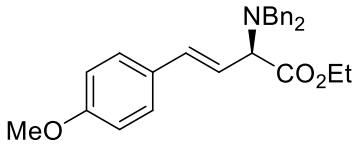
81% yield
95:5 e.r.



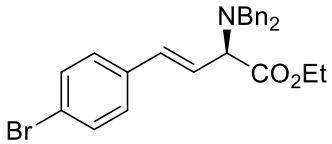
94% yield
95:5 e.r.



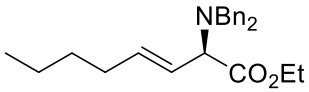
73% yield
93:7 e.r.



84% yield
96:4 e.r.



82% yield
95:5 e.r.



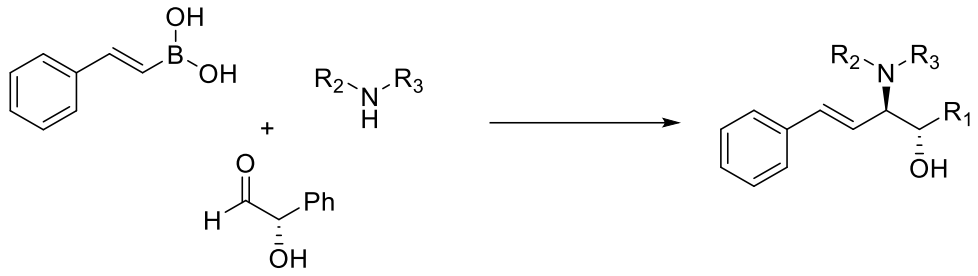
71% yield
93:7 e.r.

- High functional group tolerance across styrenyl boronic acids and amines
- Alkyl substituted boronates were slower but with high selectivity
- One of the first of its kind for the time

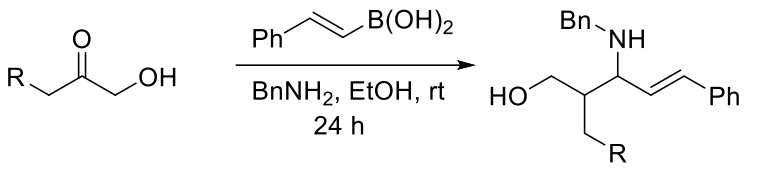
J. Am. Chem. Soc. **2008**, *130* 6922-6923

The Formation of Amino Alcohols

General Form of Amino Alcohols



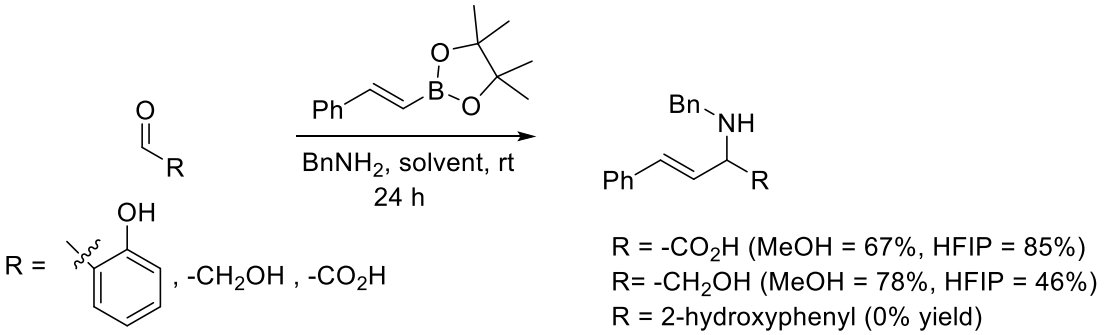
Ishii (2005)



R = H, OH

R = OH (40% yield)
R = H (0% yield)

Piettre (2005)



R = $-CO_2H$ (MeOH = 67%, HFIP = 85%)
R= $-CH_2OH$ (MeOH = 78%, HFIP = 46%)
R = 2-hydroxyphenyl (0% yield)

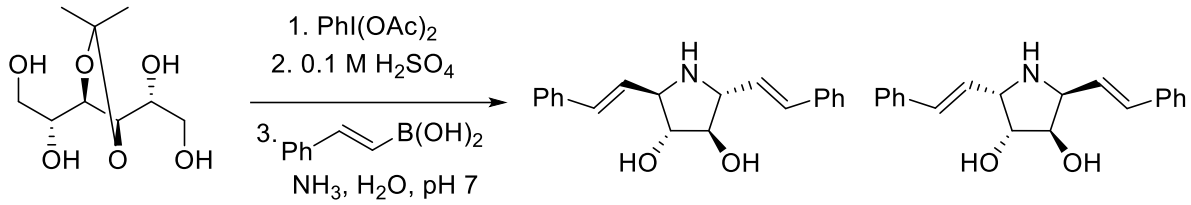
solvent = HFIP or MeOH

- Primary and secondary amines work well
- Boronate esters illustrate comparable reactivity in MeOH to the amino acids, solvent choice plays a pronounced effect on yield

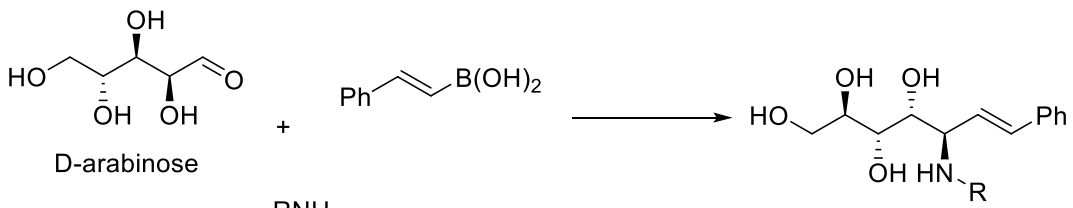
Chem. Pharm. Bull. **2005**, *53*, 100-102
Tetrahedron Lett. **2005**, *46*, 8027-8031

A Special Case of 1,2- Amino Alcohol Formation

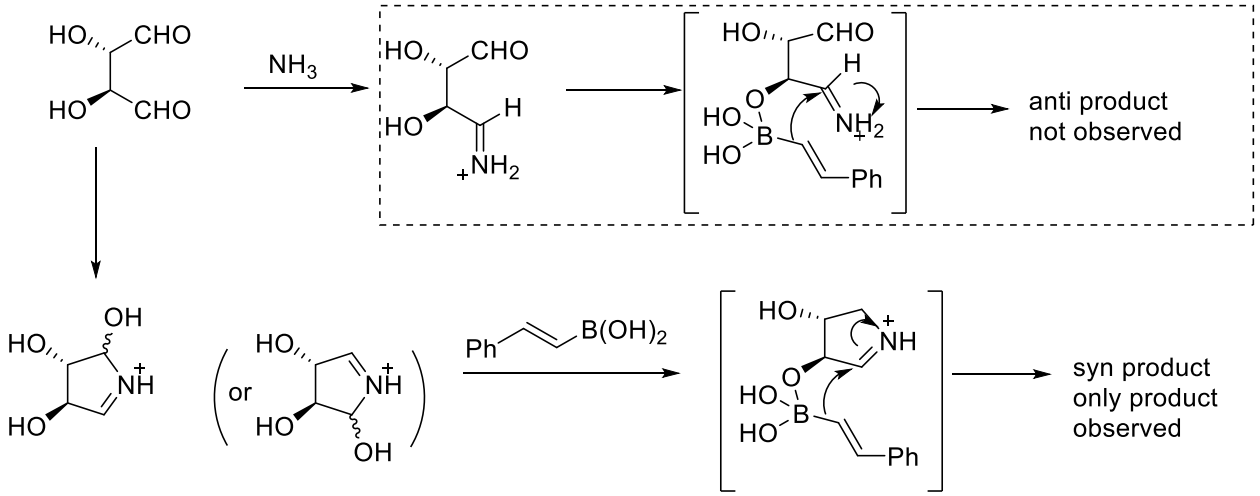
Wong (2009)



Does not work with D-Arabinose



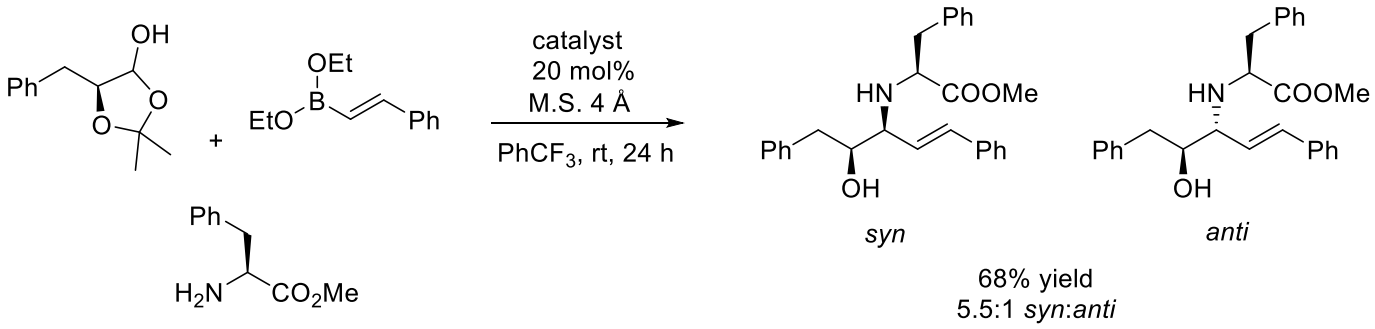
Proposed Explanation

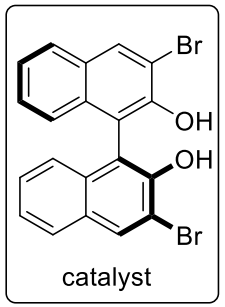


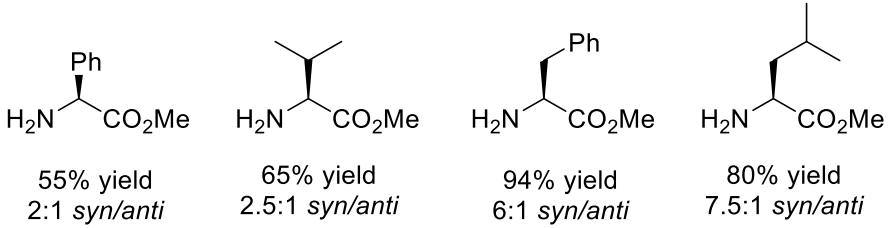
J. Am. Chem. Soc. **2009**, *131*, 8352-8353

Forming *Syn* Amino Alcohols through Asymmetric Catalysis

Schaus (2011)

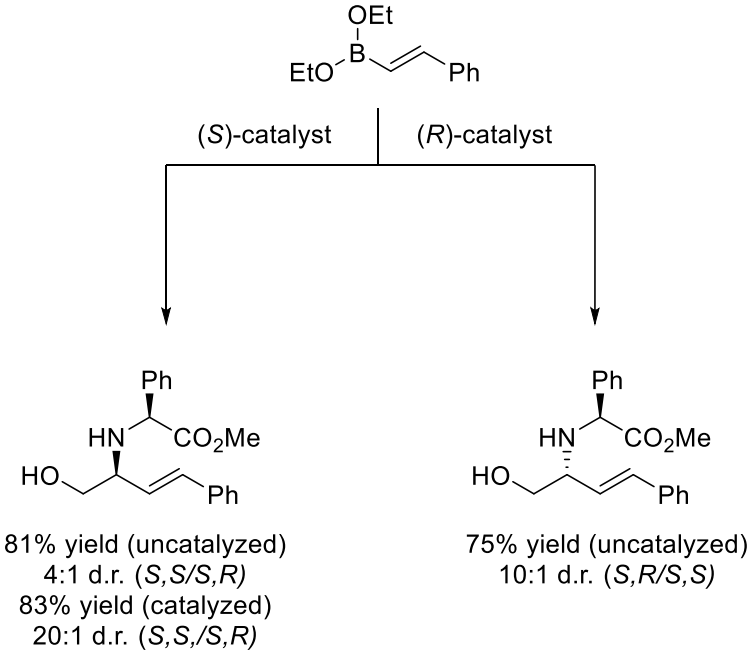






- Designed for selectivity using chiral amino acid derivatives with CH_2 substitution
- Can control diastereoselectivity without chirality of alcohol.
- Works best with boronic acid

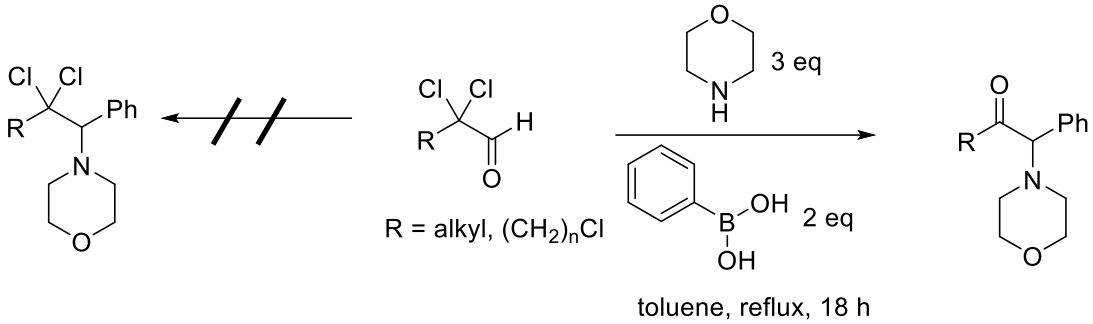
- Catalyst and amine direct selectivity!
- Boronate coordination to α-hydroxy group is critical
  - No reaction without α-hydroxyl

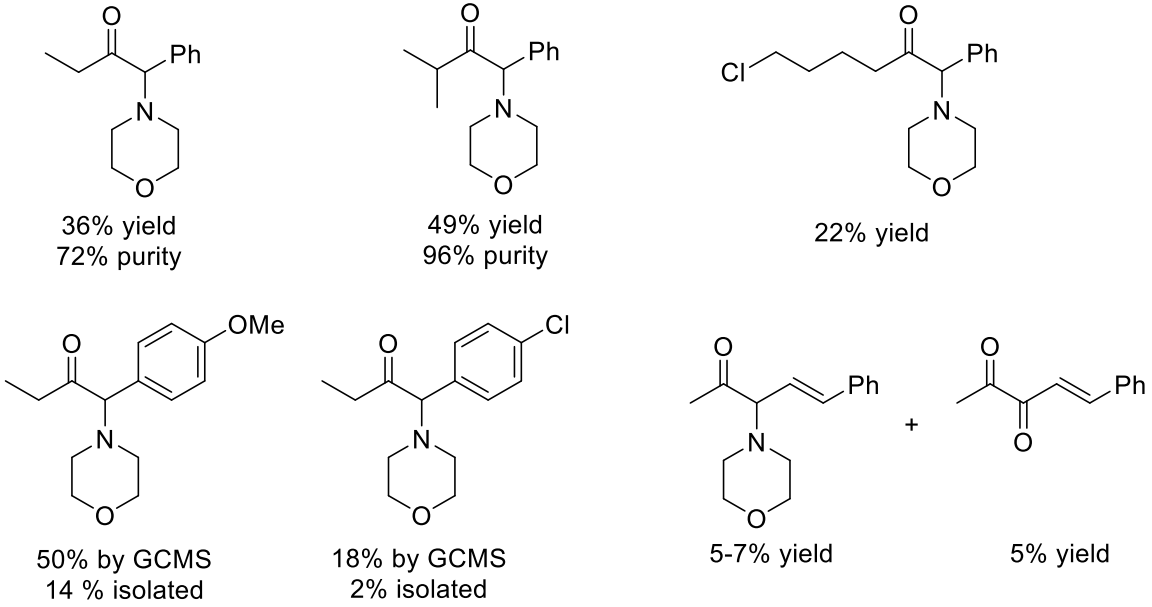


Angew. Chem. Int. Ed. **2011**, *50*, 8172-8175

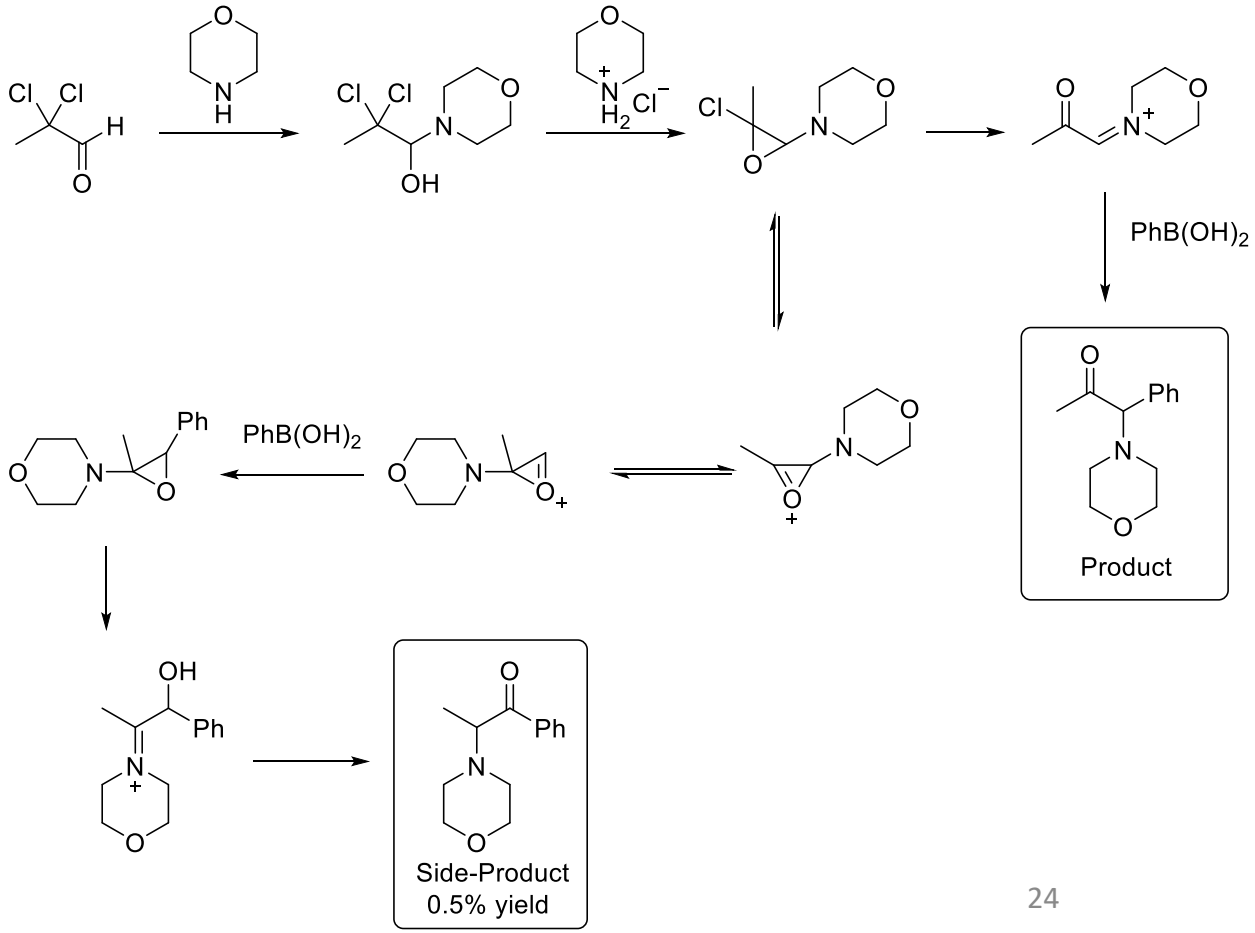
The Lone Example of α-amino ketone formation

Tehrani (2007)





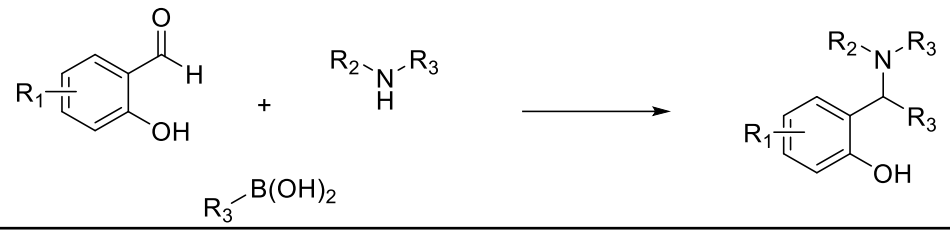
Proposed Mechanism



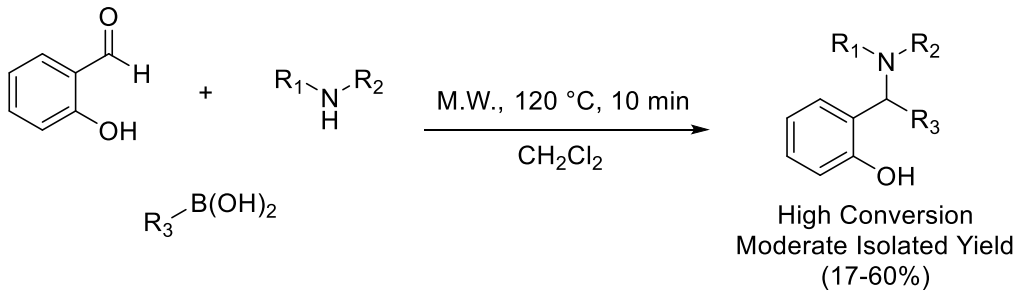
Synthesis, ***2007***, *3*, 433-441

Limitations for the formation of 2-hydroxybenzylamines

Generalized Form

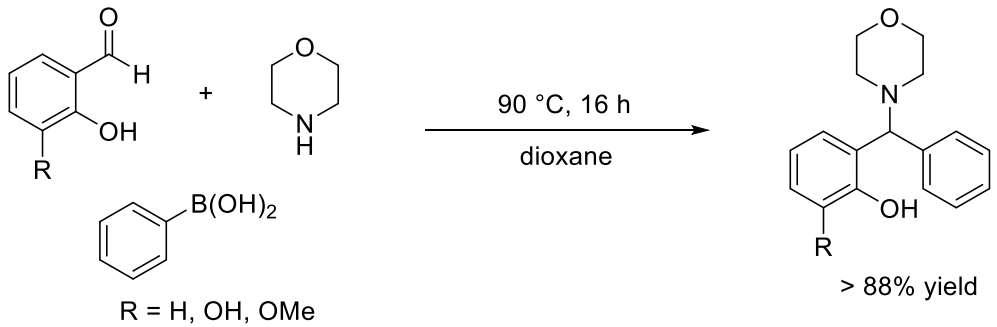


Tye (2004)



- Didn't work with benzylamine or aniline, and primary amines are often limited in success
- Could isolate the imine intermediate!

Finn (2000)



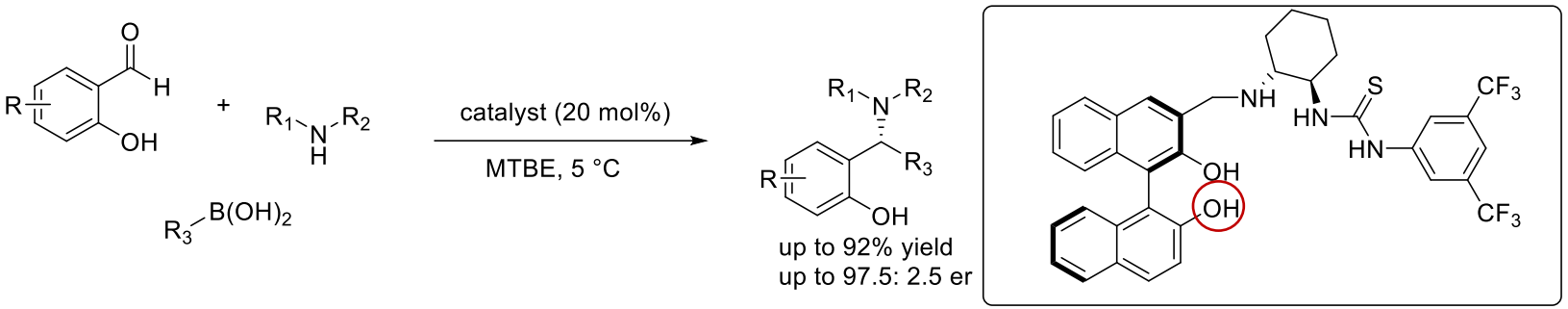
- Does have higher yield than other solvents such as H_2O (53%) and DCE (77%), but those were only 5 h experiments
- Trifluoroborates are underdeveloped, but function less effectively than boronic acids
- Drying agents such as mol. Sieves increase reactivity (think equilibrium of hemiaminal species)

Tetrahedron. Lett. **2004**, *45*, 993-995
Org. Lett. **2000**, *2*, 4063-4065

An Asymmetric Method for Hydroxybenzylamines

Yuan (2012)

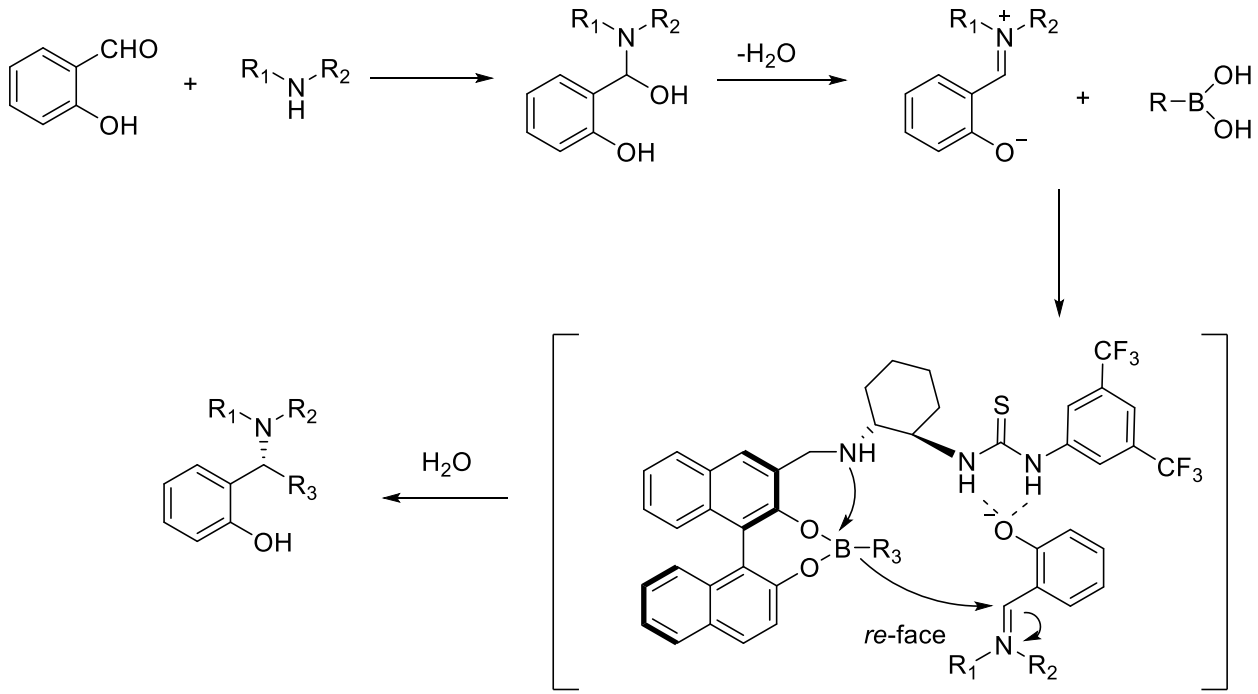
- Inspired by Schaus and Takemoto
- The only one for aromatic aldehydes



Initial Observations

- Methoxy and nitro-aldehydes showed no effect on selectivity or yield
- Cyclic secondary amines work well
- Electron rich and poor arylboronic acids ranged between 86:14- 97.5:2.5 er

Proposed Mechanism



Org. Lett. **2012**, *14*, 976-979

Scope Expansion of Classic Three-Component Petasis Reactions

New Reaction Conditions and Asymmetric Reactions

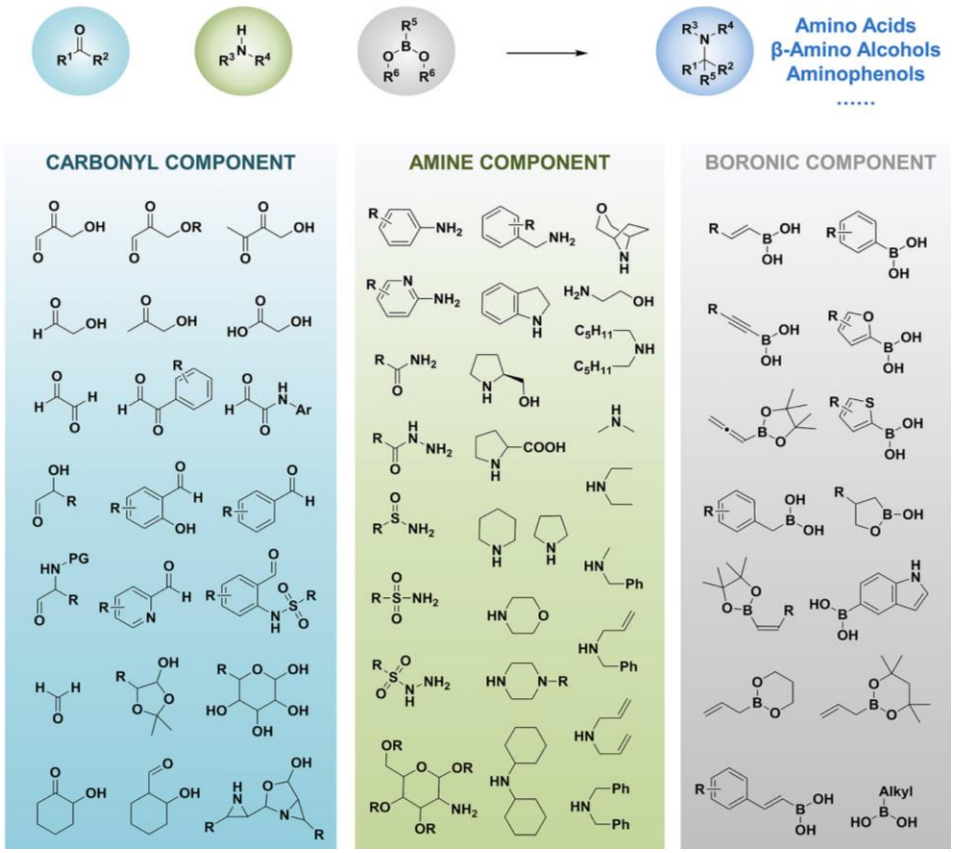
- Four-Component Petasis Reactions
- Petasis-Type Reactions
- Cascade Reactions
- Natural Products Bioactive Molecules

INHERENT MERITS

- High stereoselectivity (products with predictable *anti*-diastereoselectivity)
- Robust and mild reaction conditions (usually insensitive to water and oxygen)
- Easy access to a wide range of reaction substrates
- Minimal need for protecting groups
- Catalyst-free (although catalytic asymmetric reactions have been used to expand scope)
- Rapid access to structural diversity, including natural products, natural product-like compounds, and biologically interesting molecules

COMMON LIMITATIONS

- Only activated carbonyl components or carbonyls with a suitable boron-activating group
- Only electron-rich vinyl- or (hetero)arylboronic acids provide high yields



Chem Rev. **2019**, *119*, 2165-2169

Questions?