Amphoteric Molecules

< Chemistry of Andrei K. Yudin >

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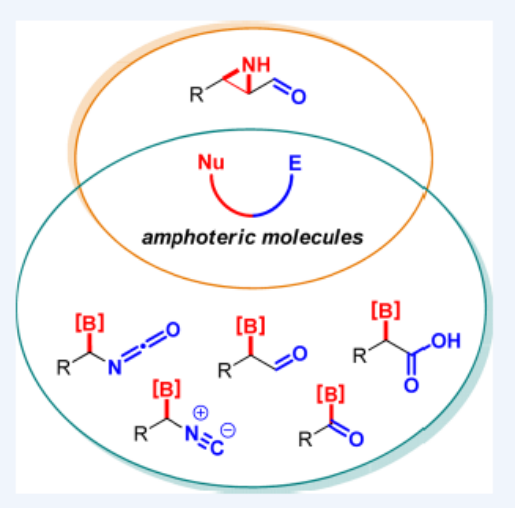
17 JUNE 2014

Amphoteric molecules

- Amphoteric?
  - Greek word “amphoteros” (both of two)
  - Amphoterism in acid/base chemistry
  - Amino acids (thermodynatic amphoterism)

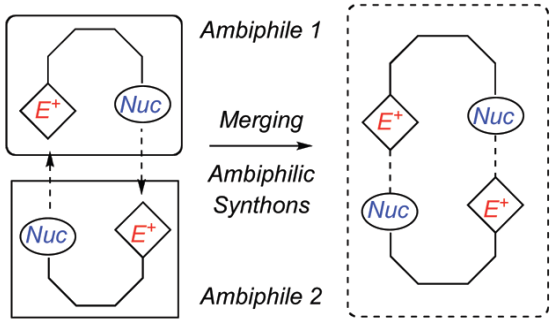
- Amphoteric molecules
  - Contains functional groups that are normally incompatible
  - Yudin and coworkers
  - Nucleophile & electrophile in one molecule
  - Aziridine aldehydes
  - α-Boryl aldehydes

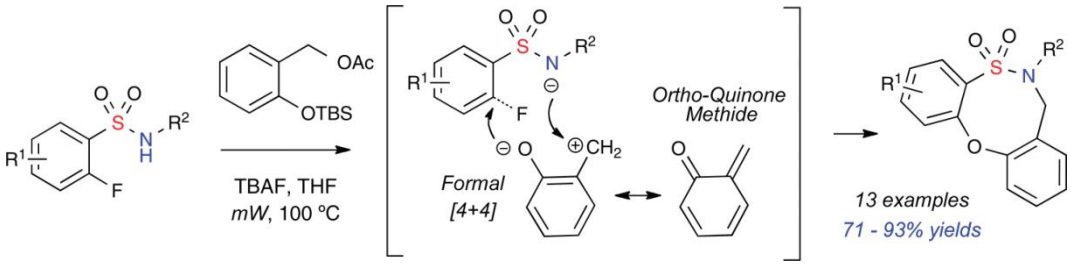


Acc. Chem. Res. **2014**, *47*, 1029−1040.
Chem. Heterocycl. Compd. **2012**, *48*, 191-199.

Other "Amphoteric" molecules

- "Ambiphilic"
  - P. R. Hanson & coworkers
  - [4+4] cyclization of benzosulfonamide with *o*-quinone methide



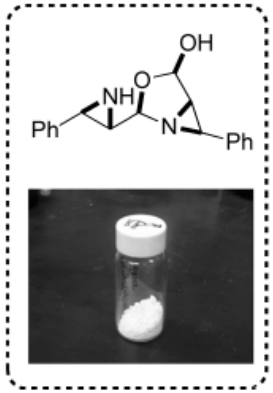


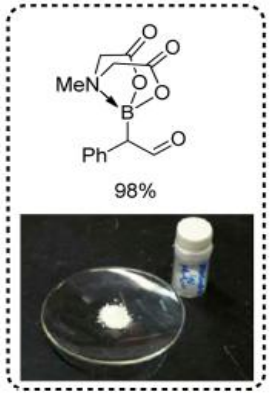
- "Amphiphilic"
  - Y. Yamamoto & coworkers
  - Pd-catalyzed allylation reactions

Org. Lett. **2010**, *12*, 2182–2185.
J. Am. Chem. Soc. **2001**, *123*, 372–377.

Outline

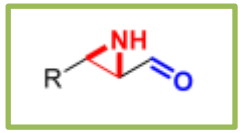
- Aziridine aldehydes
  - [1,3] Amphoteric system
    - Preparation of aziridine aldehydes
    - Reactions on the aldehyde
    - Reactions on both moieties
- α-Boryl aldehydes/carboxylic acids
  - [1,2] Amphoteric system
- α-Boryl cyanate/cyanides
  - [1,3] Amphoteric system
- Acylboronates
  - [1,1] Amphoteric system

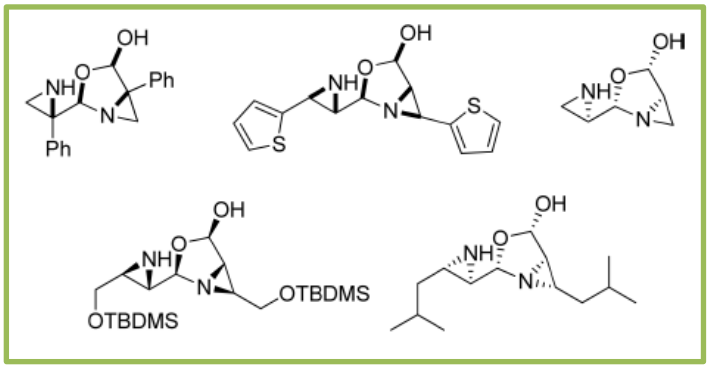




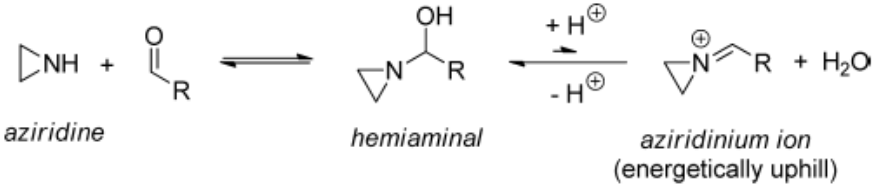
[1,3] Amphoteric System: Aziridine Aldehydes

- Orthogonal functional groups
  - Nucleophile: amine (aziridine)
  - Electrophile: aldehyde

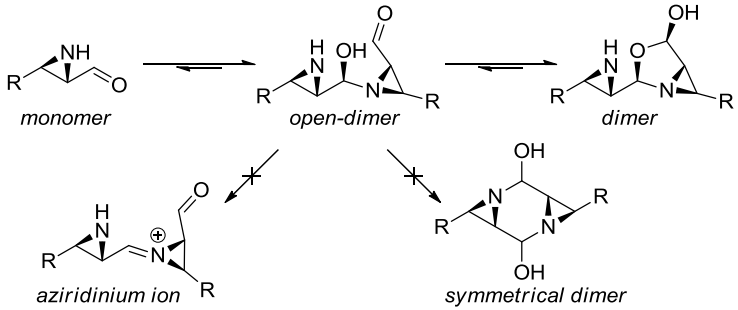


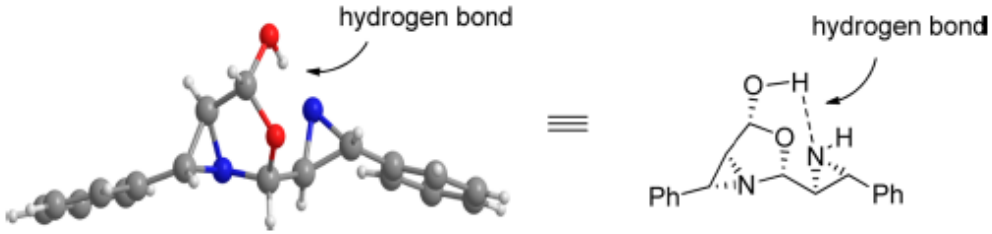


- Stability of α-Amino Aldehyde System
  - Energetically uphill to aziridinium ion



  - Spontaneous Dimerization
  - Fuzed ring of aziridine and 5-oxazolidinol
  - Single diastereomer (X-ray structure)

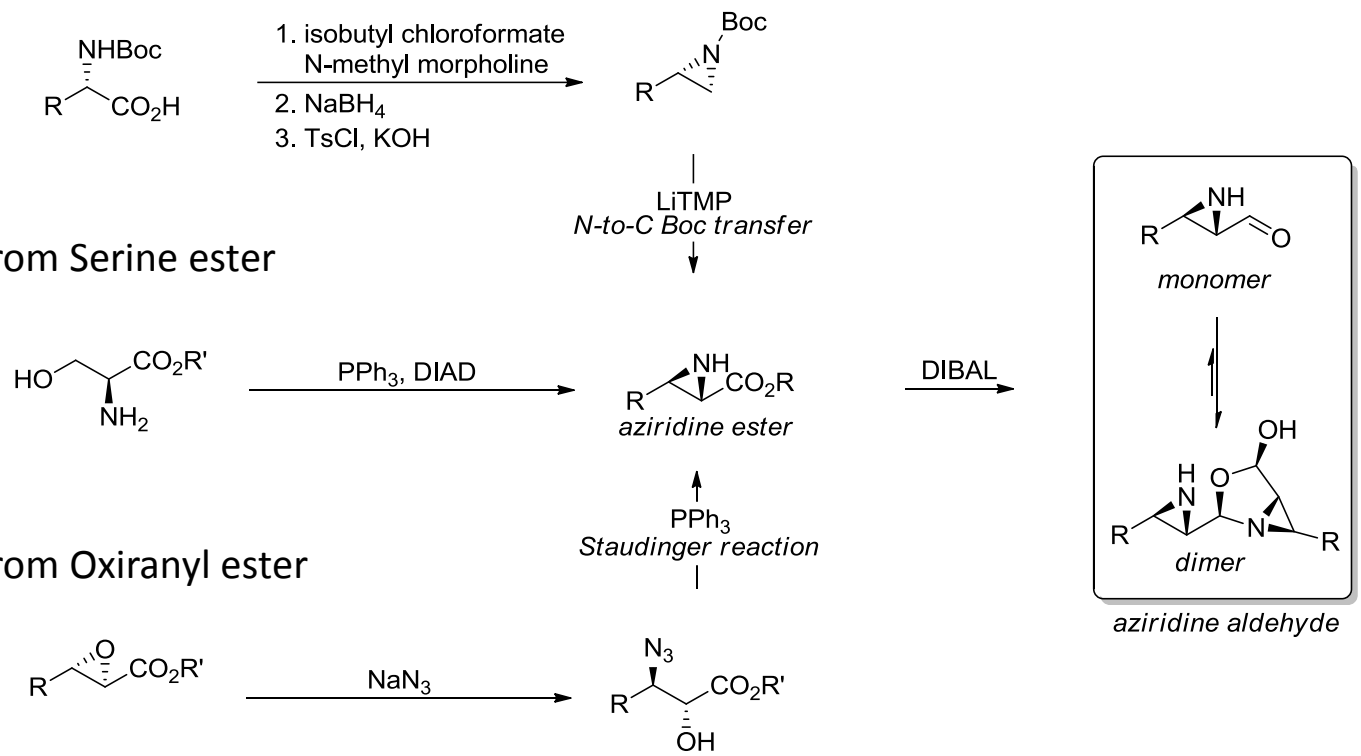




Acc. Chem. Res. **2014**, *47*, 1029–1040.
Chem. Heterocycl. Compd. **2012**, *48*, 191-199.

Preparation of Aziridine Aldehydes

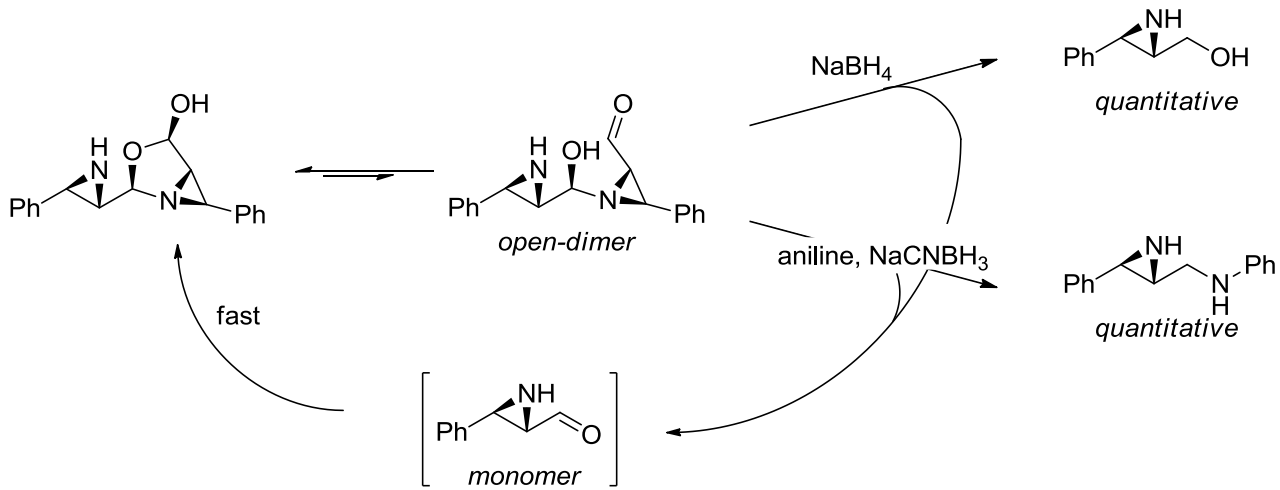
- Synthetic Routes
  - From Boc-amino acids
  - From Serine ester
  - From Oxiranyl ester



Angew. Chem., Int. Ed. **2007**, *46*, 2245–2248.
J. Am. Chem. Soc. **2006**, *128*, 14772–14773.
J. Org. Chem. **2012**, *77*, 5613–5623.

Reactions of Aldehydes

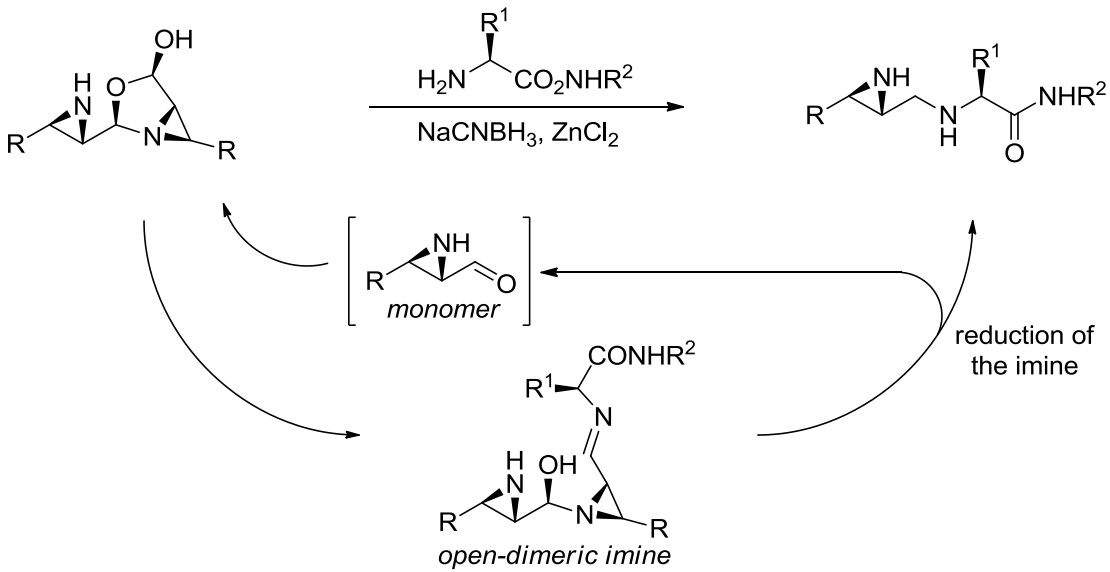
- Reduction / Reductive Amination
  - Quantitative yields with borohydride reagents
  - Proceeds via an open-dimer intermediate
  - Release of monomer / fast redimerization

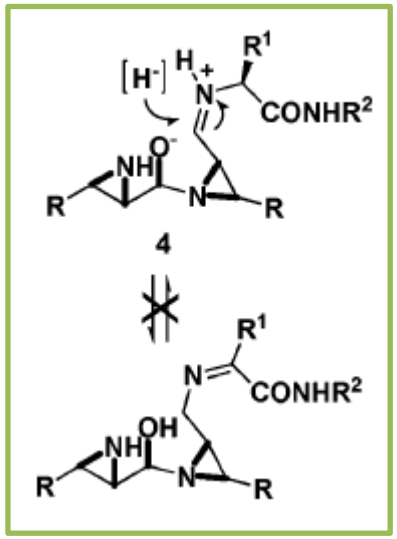


J. Am. Chem. Soc. **2006**, *128*, 14772−14773.
J. Org. Chem. **2012**, *77*, 5613−5623.

Reactions of Aldehydes

- Peptidomimetic Conjugates
  - Preparation of diamine derivatives



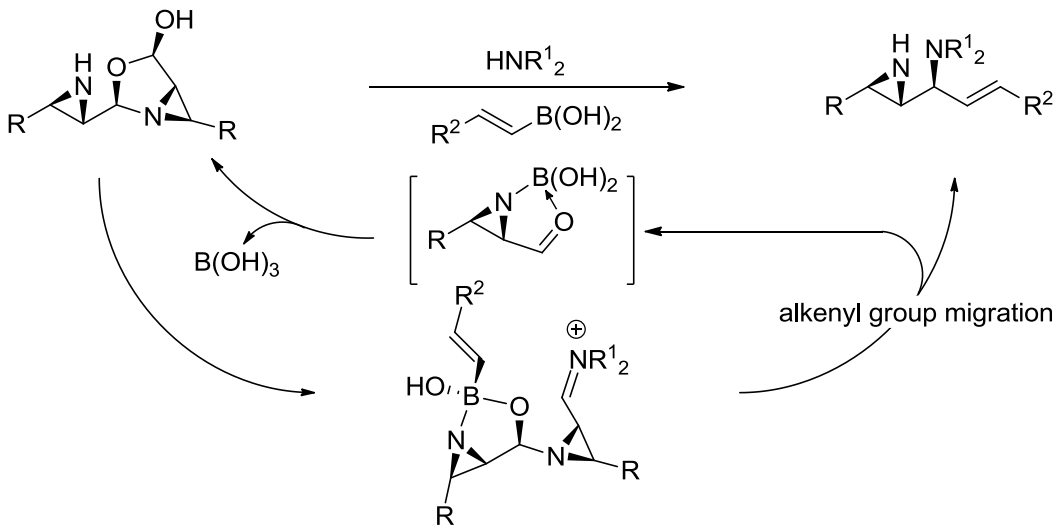


  - No epimerization or overalkylation observed
  - Attributed to the short lifetime of the open-dimeric imine intermediate (ODI)
  - Steric hindrance and low concentration of the ODI prevents overalkylation

J. Am. Chem. Soc. **2007**, *129*, 14152–14153.

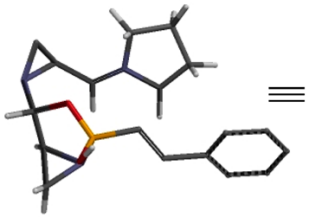
Reactions of Aldehydes

- Borono-Mannich Reaction
  - Vicinal aziridine-containing vinyl diamine

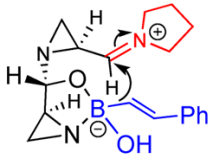


open-dimeric iminium N,O-chelate

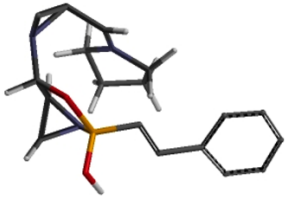
  - Exclusively *syn* selective process
  - Involvement of open-dimeric iminium N,O-chelate
  - Alkenyl group migration onto the *si* face



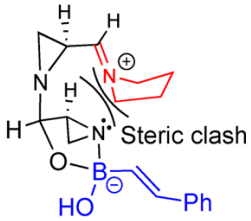
Iminium N,O-Chelate **9' *si***



Si face attack: *syn* product



Iminium N,O-Chelate **9' *re***

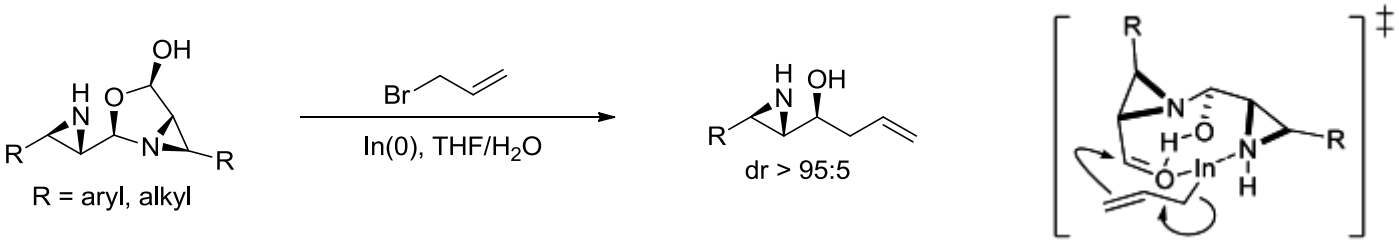


Re face attack: *anti* product

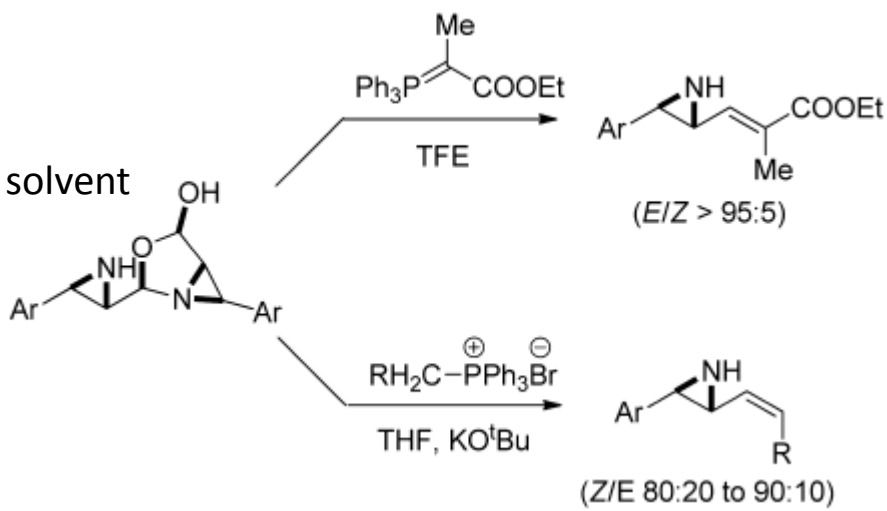
J. Org. Chem. **2013**, *78*, 11637−11645.

Reactions of Aldehydes

- Indium (0)-Mediated Diasteroselective Allylation
  - Organized transition structure accounts for the high diastereoselectivity
  - DFT analysis shows a pocket for Indium surrounded with one N and two O



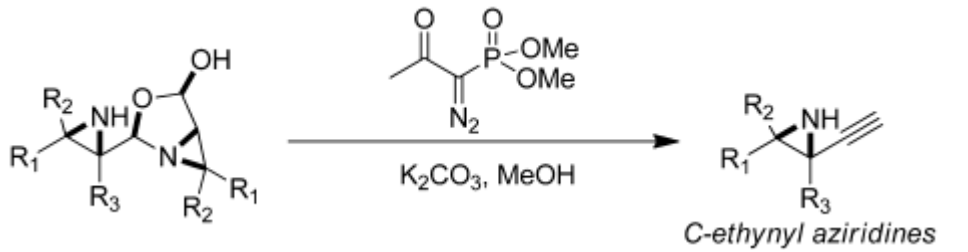
- Wittig Reactions
  - C-vinyl aziridines
  - E/Z controlled by solvent

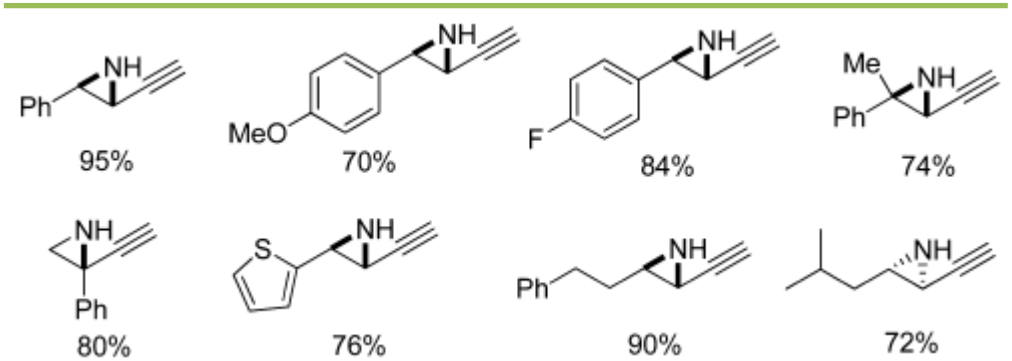


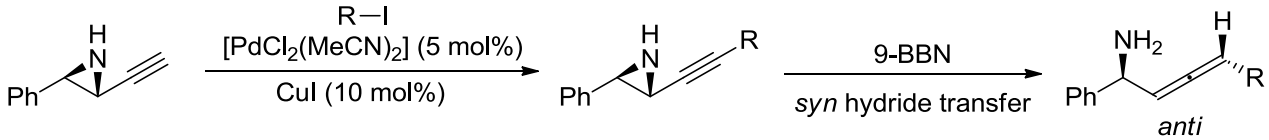
Angew. Chem., Int. Ed. **2008**, *47*, 4188–4191.
Org. Lett. **2010**, *12*, 240–243.

Reactions of Aldehydes

- Seyferth-Gilbert Homologation
  - Bestmann-Ohira reagent
  - C-ethynyl aziridines (strained propargyl amines)
  - α-amino allene formation with 9-BBN



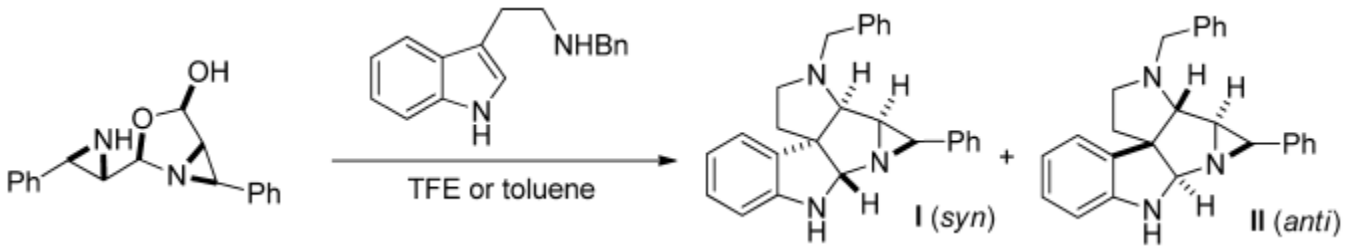




Angew. Chem., Int. Ed. **2010**, *49*, 1607–1610.

Reactions of Aziridines (Group Question)

- Initial Interaction of Aldehydes
- Pictet-Spengler Reaction
  - Access to pentacyclic scaffold through a single cascade reaction



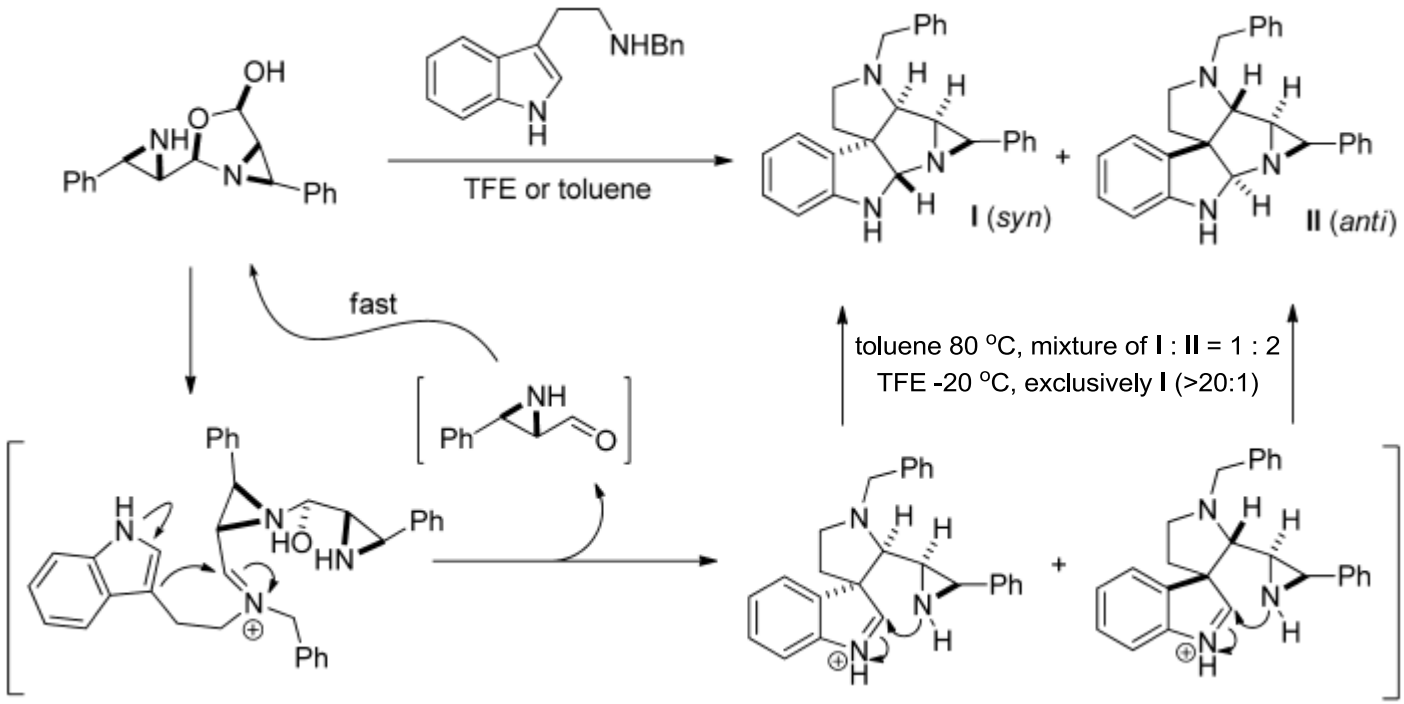
toluene 80 °C, mixture of **I** : **II** = 1 : 2
TFE -20 °C, exclusively **I** (>20:1)

  - Provide the mechanism for the above reaction

J. Am. Chem. Soc. **2006**, *128*, 14772−14773.

Reactions of Aziridines

- Initial Interaction of Aldehydes
- Pictet-Spengler Reaction
  - Access to pentacyclic scaffold through a single cascade reaction

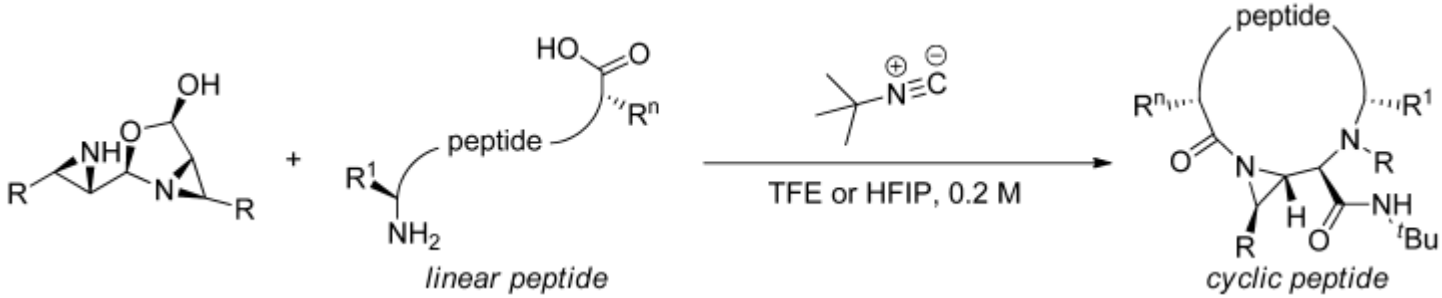


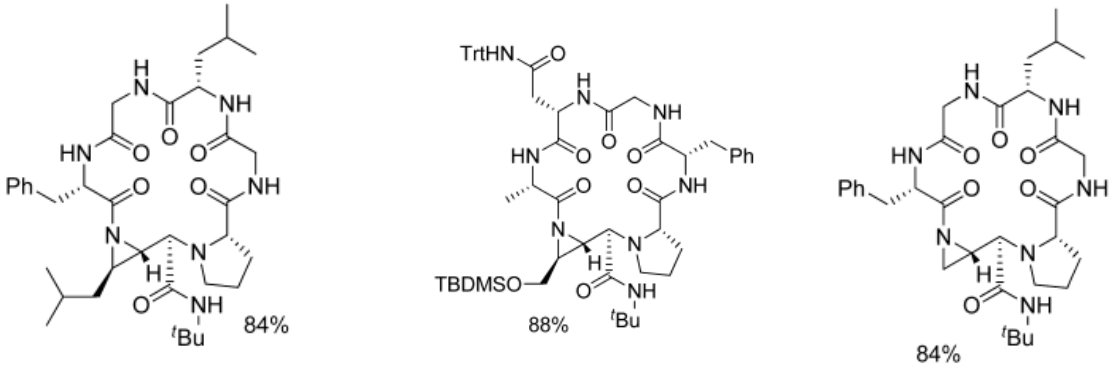
  - Iminium ion formation
  - Intramolecular Ad_EAr followed by intramolecular aziridine attack
  - Solvent and T dependent on diastereoselectivity

J. Am. Chem. Soc. **2006**, *128*, 14772−14773.

Reactions of Aziridines

- Ugi Multi-component Reaction
  - Macrocyclic peptide formation
  - High concentration
  - High diastereoselectivity
  - No epimerization, no dimer/oligomerization observed

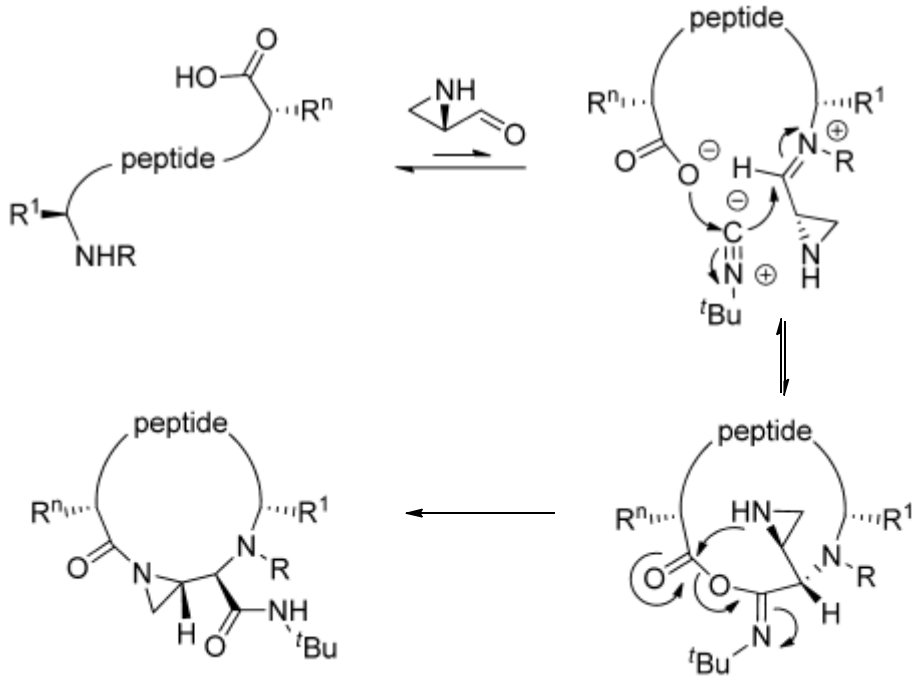




J. Am. Chem. Soc. **2010**, *132*, 2889–2891.

Reactions of Aziridines

- Mechanism for the Ugi Multi-component Reaction

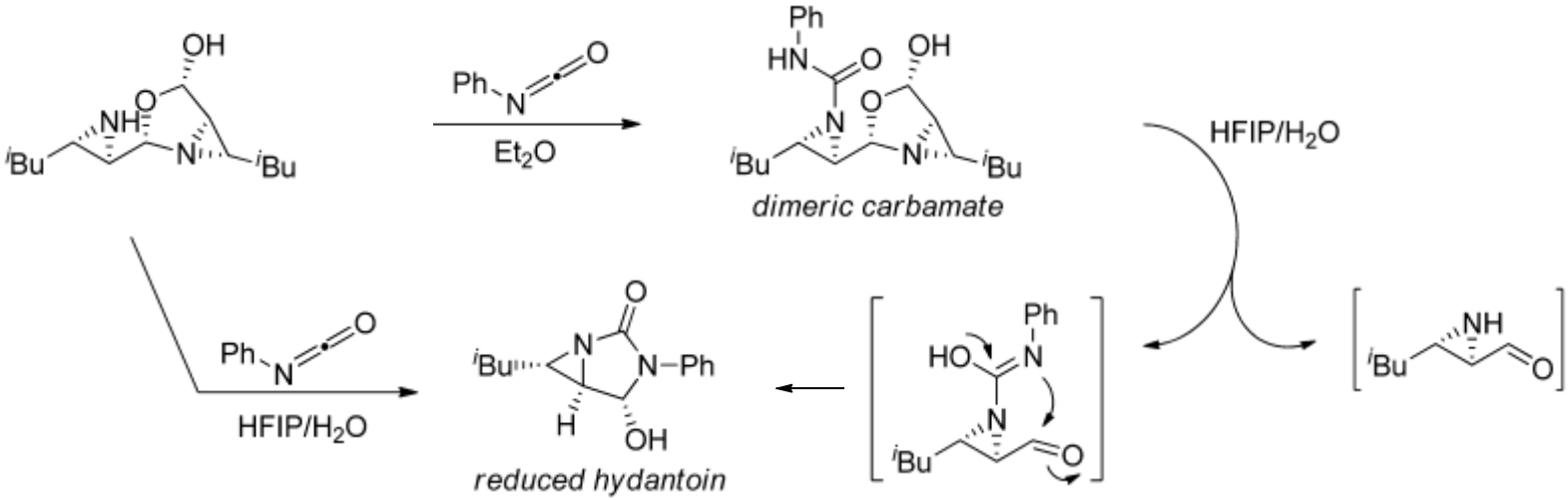


  - Iminium formation
  - Isocyanide α-addition
  - Transannular attack of aziridine
  - Presence of the nucleophilic aziridine at the α-position is responsible for the high yields and high diastereoselectivities

J. Am. Chem. Soc. **2010**, *132*, 2889–2891.

Reactions of Aziridines

- Initial Interaction of Aziridines
- Reaction with Isocyanates

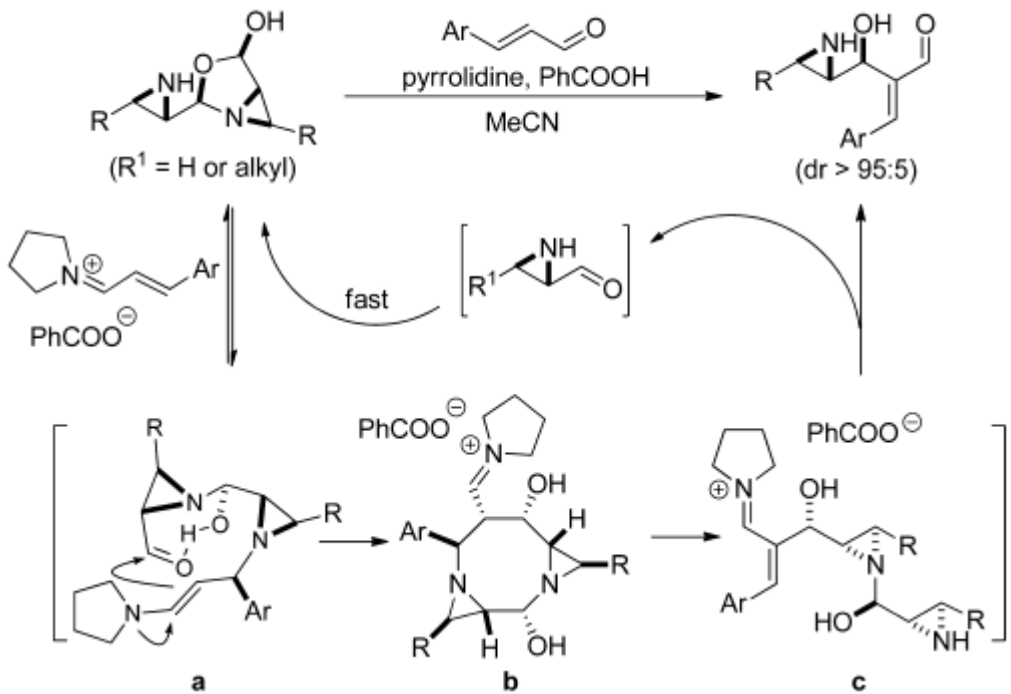


  - Solvent dependent (Et_2O/HFIP)
  - In Et_2O: Dimeric carbamate
  - In HFIP: Reduced fused hydantoin
  - Dimer dissociation under HFIP
  - Hydantoin formed when isolated dimeric carbamate product is treated with HFIP

Angew. Chem., Int. Ed. **2011**, *47*, 11798–11802.

Reactions of Aziridines

- Baylis-Hillman Products
  - Exclusive diastereoselectivity
  - Formation of 8-membered cyclic intermediate (dimeric intermediate)
  - Ring opening by elimination of aziridine



J. Am. Chem. Soc. **2009**, *131*, 16404–16406.

Outline

- Aziridine aldehydes
  - [1,3] Amphoteric system
    - Preparation of aziridine aldehydes
    - Reactions on the aldehyde
    - Reactions on both moieties

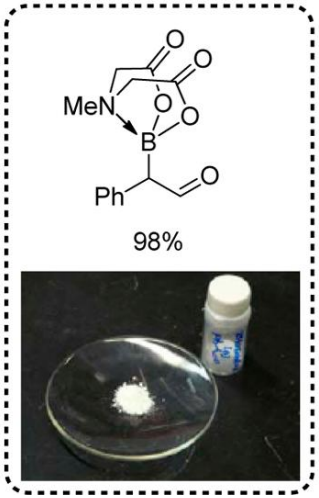
- α-Boryl aldehydes/carboxylic acids
  - [1,2] Amphoteric system

- α-Boryl cyanate/cyanides
  - [1,3] Amphoteric system

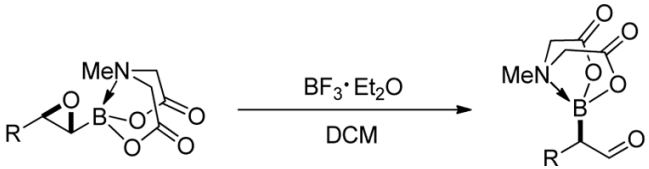
- Acylboronates
  - [1,1] Amphoteric system

[1,2] Amphoteric System: α-Boryl Aldehydes & Carboxylic Acids

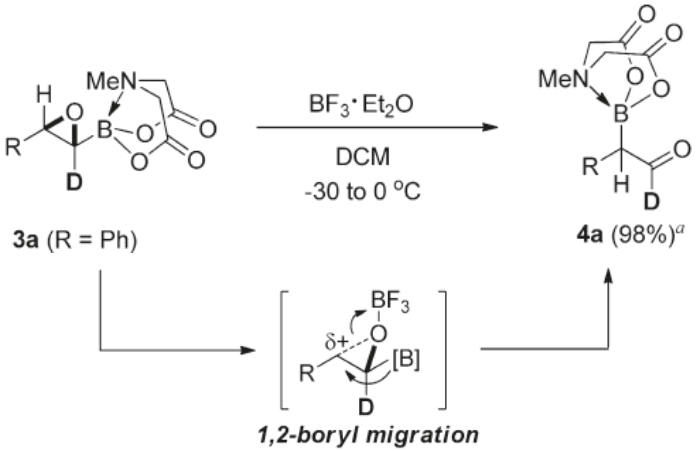
- MIDA (N-methyliminodiacetyl) Boronates
  - Electron-rich boron centers
  - Thermodynamically and kinetically stable C-bound isomer



- Preparation
  - Bench stable white solids
  - IR stretch: 1701 cm^{-1}, ^1H NMR: 9.73 ppm



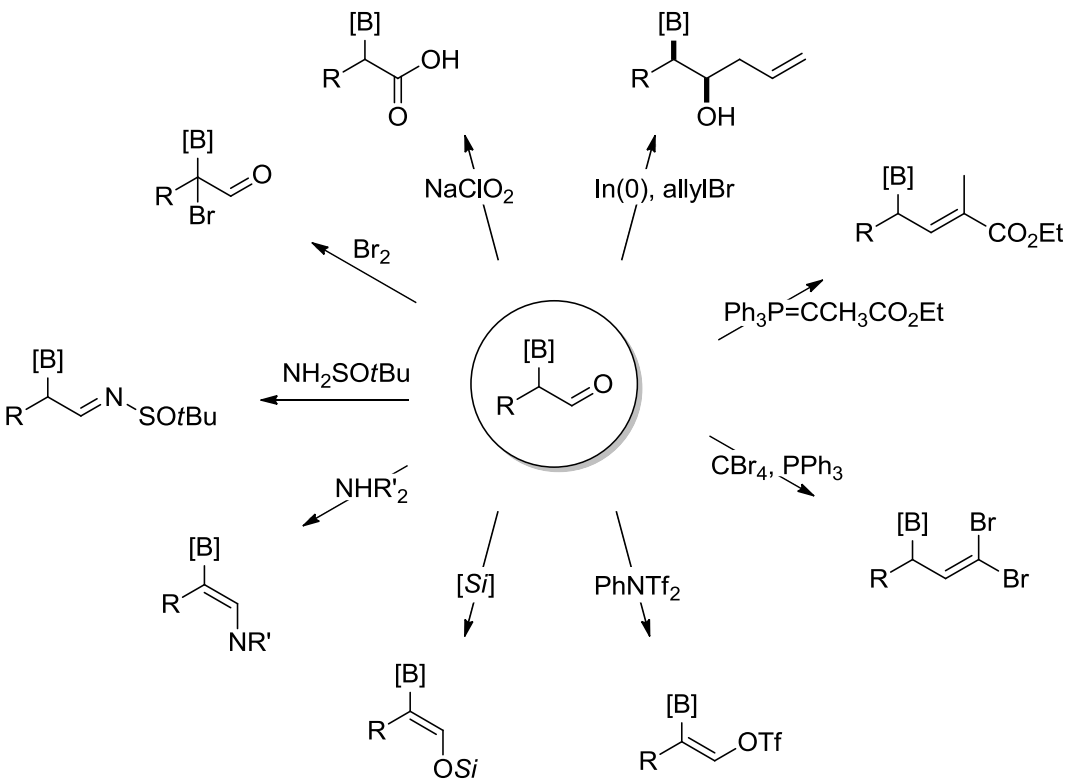
  - Rearrangement of oxiranyl MIDA boronates
  - 1,2-boryl migration (deuterium labeling)



J. Am. Chem. Soc. **2011**, *133*, 13770–13773.

α-Boryl Aldehyde

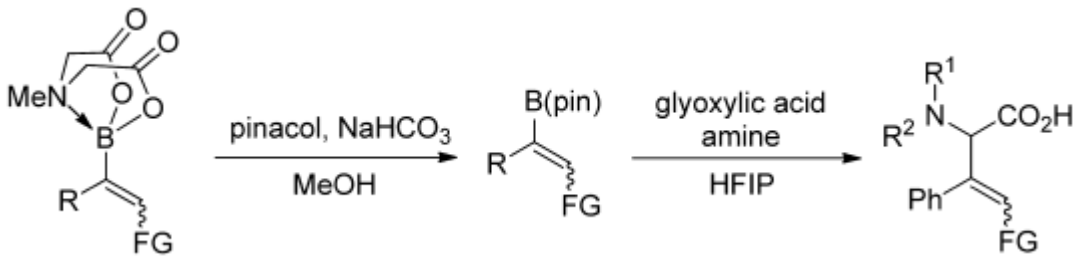
- Various Transformations of the Aldehyde
  - Reaction with amines and amides
  - α-Bromination
  - Pinnick oxidation
  - In-mediated allylation
  - Wittig reaction
  - *gem*-Dibromoalkene
  - Triflate enol ether
  - Silyl enol ether
  - Pd-catalyzed α-allylation



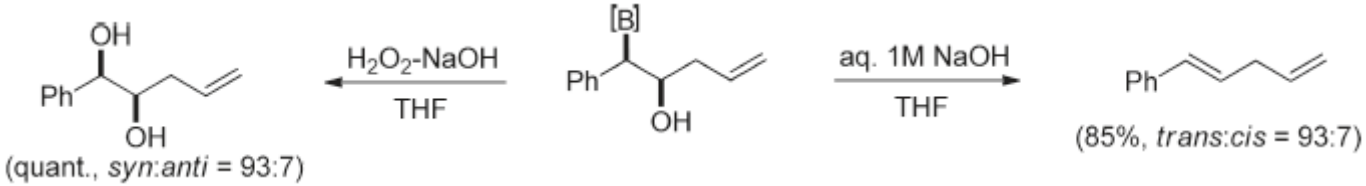
J. Am. Chem. Soc. **2011**, *133*, 13770–13773.

α-Boryl Aldehyde

- Reactions of the Boronate
- Petasis Reaction
  - C-C Bond formation
  - Via pinacolyl boronate intermediate



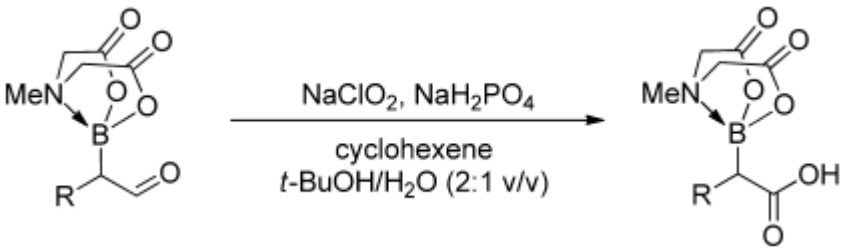
- Allylated α-Boryl Alcohol
  - Oxidation with basic peroxide
  - Skipped diene preparation



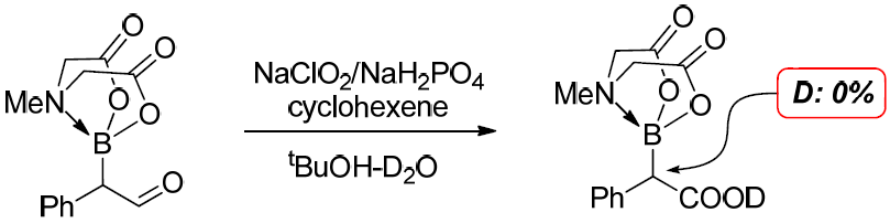
J. Am. Chem. Soc. **2011**, *133*, 13770–13773.

α-Boryl Aldehyde

- Reactions of the Aldehyde
- Pinnick Oxidation
  - α-Boryl Carboxylic Acids
  - Bench stable white solids



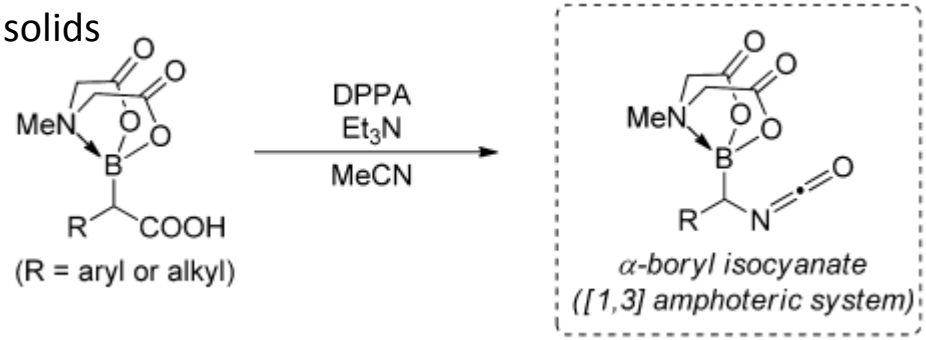
  - Configurational stability at a-position of the acid product
  - Treatment with ^{t}BuOH/D_2O, 0% of deuterium incorporation



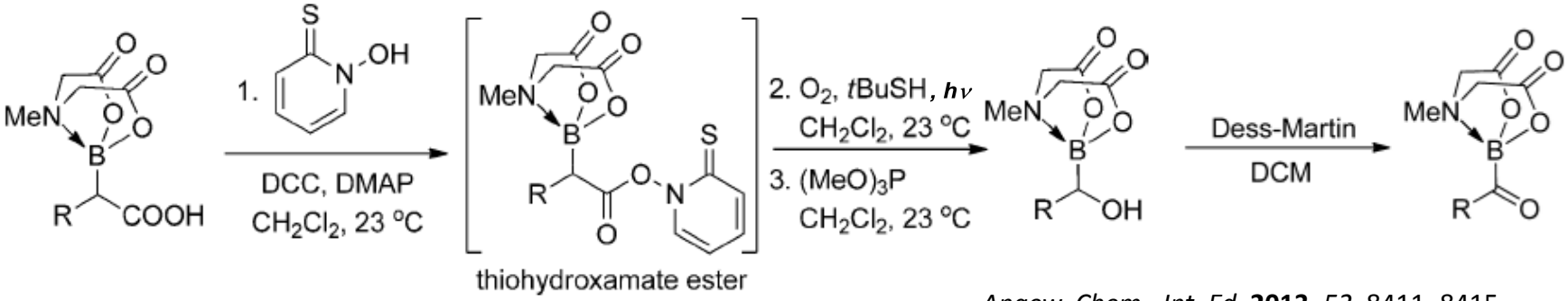
J. Am. Chem. Soc. **2011**, *133*, 13770–13773.

α-Boryl Carboxylic Acid

- Curtius Rearrangement
  - Treatment with DPPA
  - α-boryl isocyanate ([1,3] system)
  - Bench stable white solids



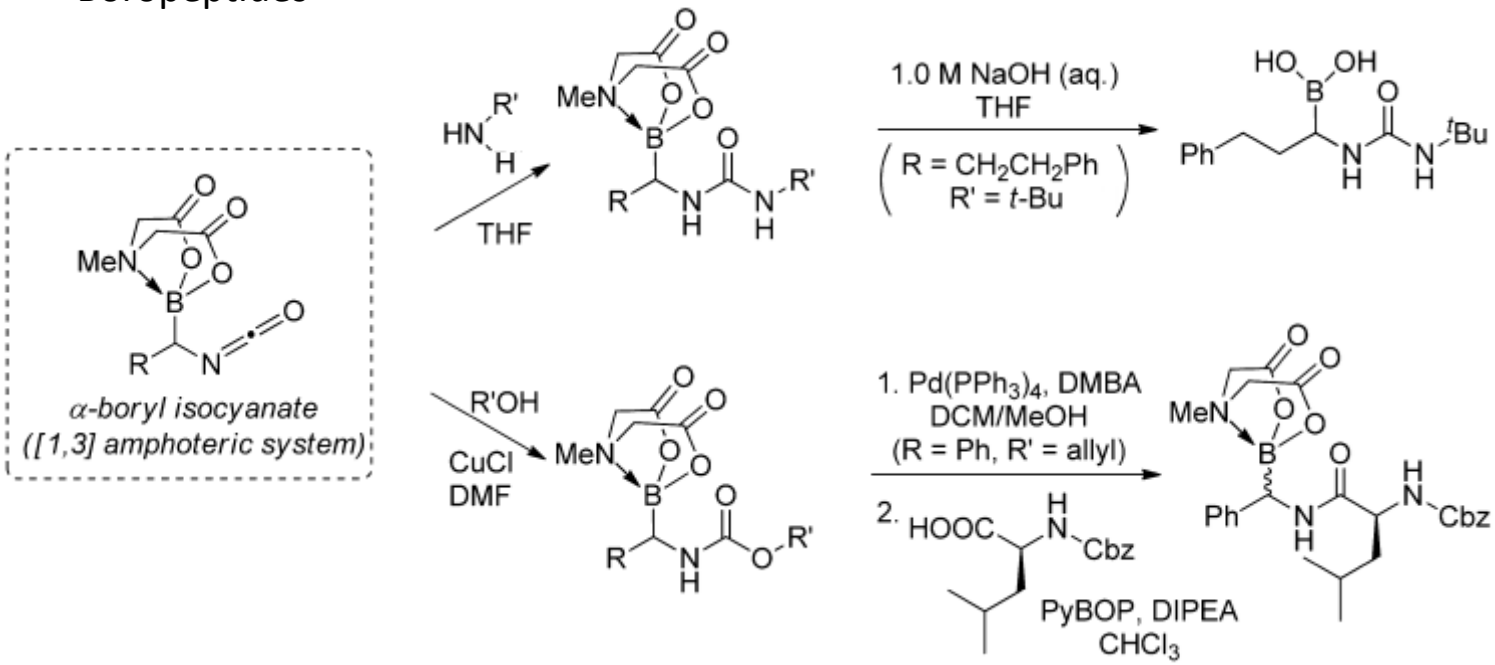
- Barton Radical Decarboxylative Hydroxylation
  - α-hydroboronate formation via thiohydroxamate ester
  - Subsequent oxidation to acylboronates ([1,1] system)



Angew. Chem., Int. Ed. **2013**, *52*, 8411−8415.
Angew. Chem., Int. Ed. **2012**, *51*, 11092−11096.

[1,3] Amphoteric System: α-Boryl Isocyanates

- α-Boryl isocyanate
  - Ureas
  - Manipulation of MIDA group to boronic acid derivatives
  - Carbamates
  - Boropeptides



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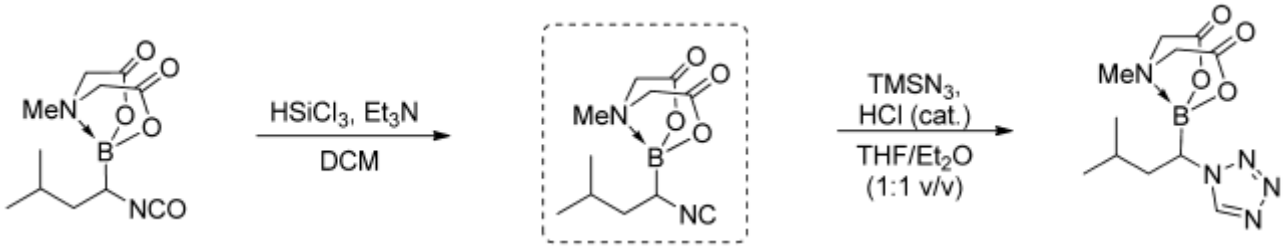
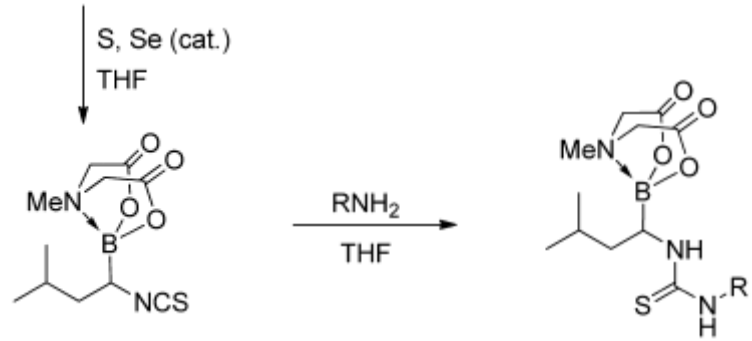
Combined [1,3]/[1,1] Amphoteric System: α-Boryl Isocyanides

- α-Boryl Isocyanide
  - $HSiCl_3$ mediated deoxygenation
  - Combination of two amphoteric systems: [1,3] & [1,1] system



- Other Reactivities
  - Sulfurization to isothiocyanates
  - Reaction with amines (thiourea)
  - Tetrazole formation



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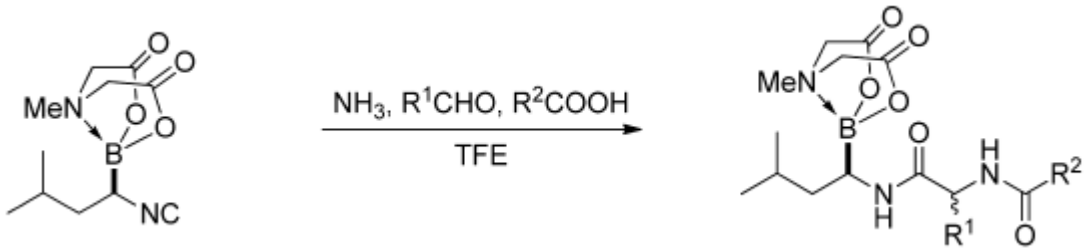
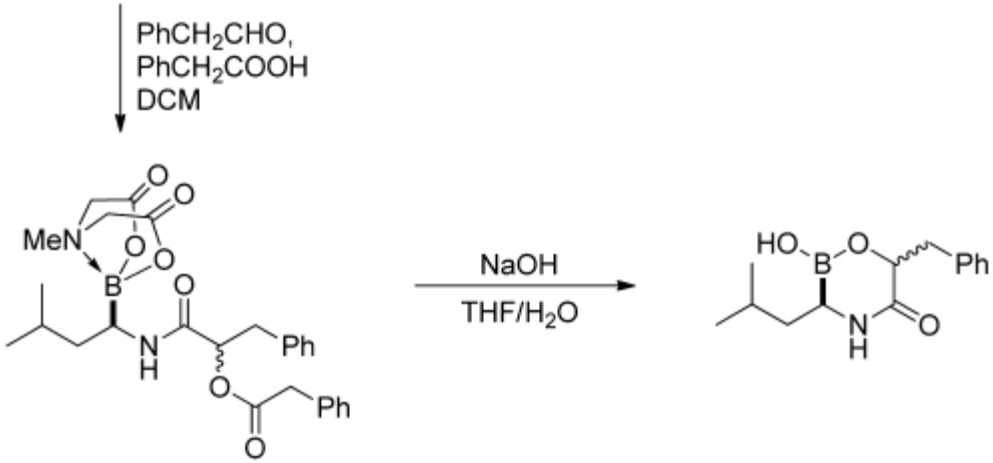
Combined [1,3]/[1,1] Amphoteric System: α-Boryl Isocyanides

- Multicomponent reaction (U4CR/P3CR)
  - Ugi reaction



  - Passerini reaction



  - These borocyclic peptide derivative exhibit comparable results and selectivities to bortezomib

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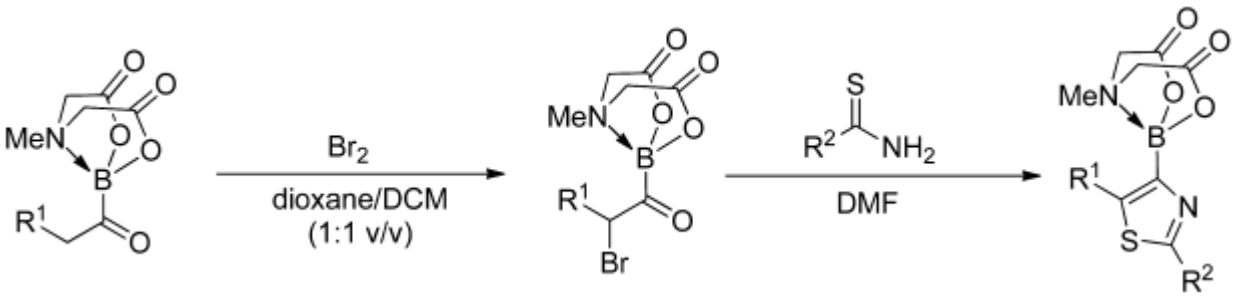
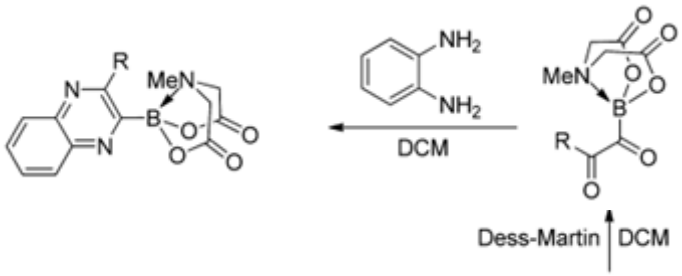
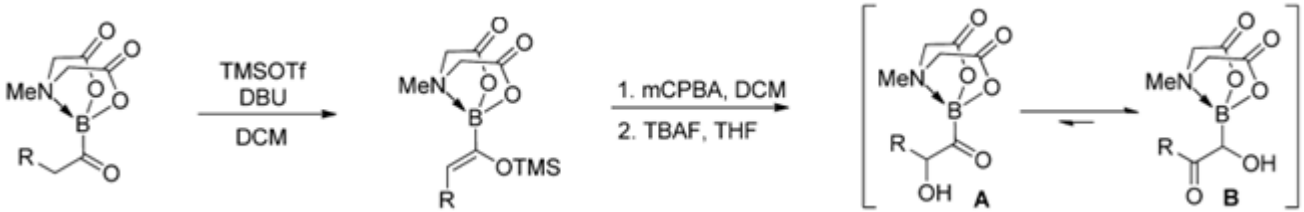
[1,1] Amphoteric System: Acylboronates

- Thiazole Synthesis
  - α-Bromination followed by reaction with thioamides/thioureas
  - Carbon-Boron bond intact



- Quinoxaline Synthesis
  - Silyl enol ether formation
  - Rubottom oxidation
  - α-borylated diketones
  - Subsequent DM oxidation





Angew. Chem., Int. Ed. **2012**, *51*, 11092–11096.

Summary

- The syntheses of compounds with [1,3]-, [1,2]-, and [1,1]-amphoteric systems and its synthetic utility in various reactions have been studied by Yudin and coworkers.

- Amphoteric compounds:
  - are mostly bench stable solids
  - show orthogonality of nucleophilic and electrophilic components.

- Aziridine aldehydes:
  - exists in dimers via self-association
  - benefit high stereoselectivity from having dimeric nature

- α-Boryl aldehydes:
  - Isolable amphoteric metalloids
  - Retention of the C-B bond

Useful References

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