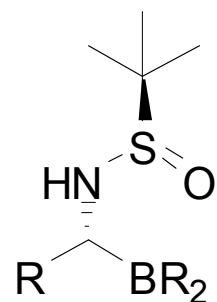


# Asymmetric Copper-Catalyzed Synthesis of $\alpha$ -Amino Boronate Esters from *N*-*tert*-Butanesulfinyl Aldimines



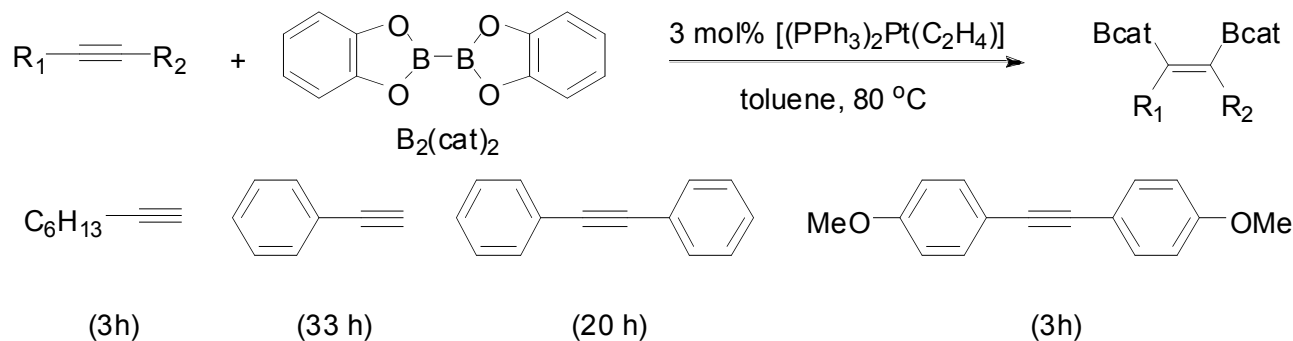
*J. Am. Chem. Soc.* **2008**, *130*, 6910.

Melissa A. Beenen, Chihul An, and Jonathan A. Ellman

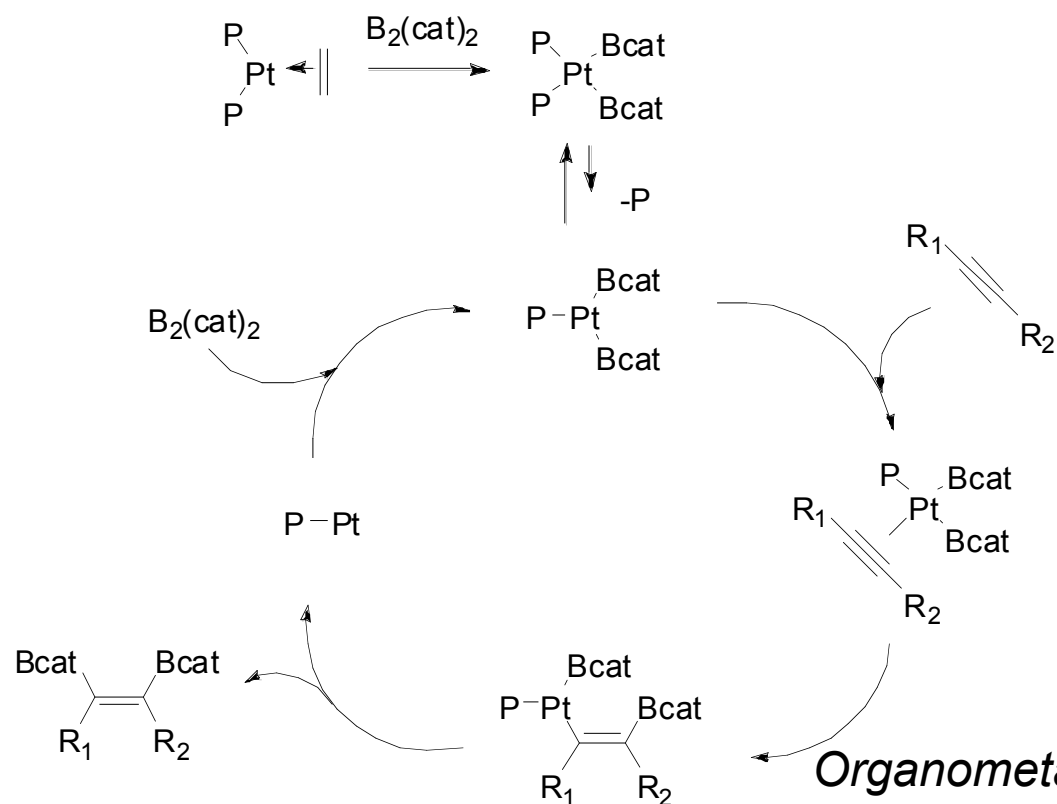
Current Literature: 5/31/08

David Arnold

# Background: Early to Mid 1990's Marked the Initial Investigations of Platinum Catalyzed Diboration of Alkynes

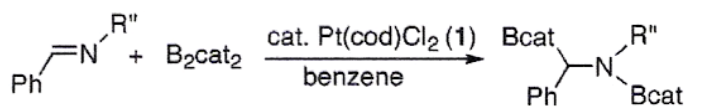


## Mechanism:



*Organometallics* **1996**, *15*, 5137.

# Background: In 2000, the First Example of A Transition-Metal-Catalyzed Diboration of Aldimines to form $\alpha$ -Amino Boronate Esters was Reported

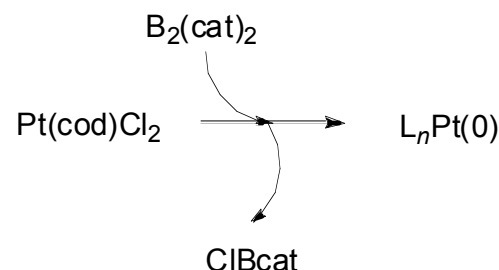


entry	substrate	product	% yield <sup>b</sup>
1			87 (78)
2			95
3			66 <sup>c</sup>

<sup>a</sup> Reaction conditions: 0.25 mM substrate, 1.1 equiv of  $\text{B}_2\text{cat}_2$ , 3–5 mol % of **1**, 3 h at 25 °C in benzene. <sup>b</sup> Yields determined by  $^1\text{H}$  NMR spectroscopy with respect to an internal standard from an average of at least two runs. Yield in parentheses refers to an isolated yield. <sup>c</sup> Reaction was stirred at 55 °C for 3 h.

## Mechanistic Insight:

Reaction is proposed to be catalyzed by an in situ formed  $\text{Pt}(0)$  complex.



## Limitations:

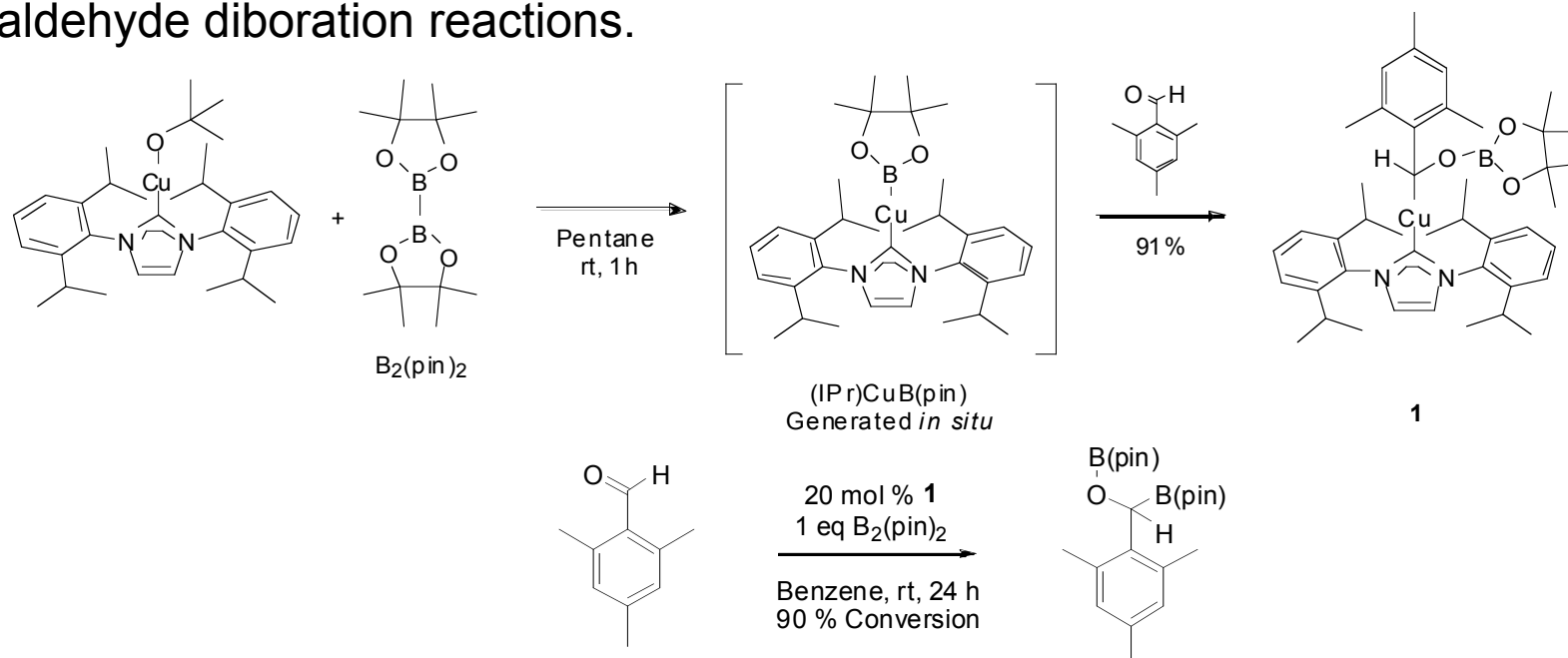
- Racemic synthesis of  $\alpha$ -amino boronate esters
- Selective for diaryl aldimines, reaction is incompatible with aliphatic aldimines
- Selective N-B deboration is problematic

Org. Lett. **2000**, 2, 2105.

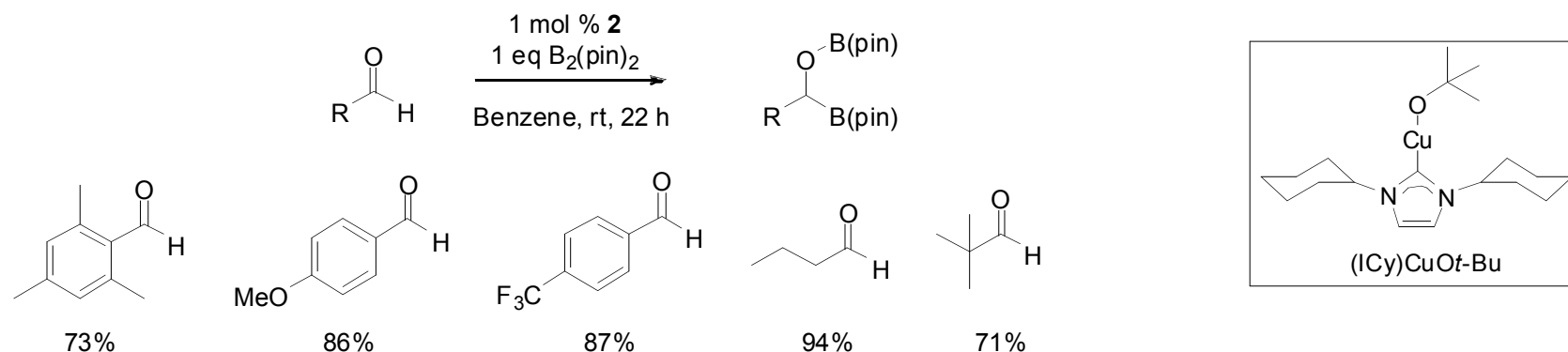
# Background: Movement from Platinum to Copper Catalysis

## Diboration of Aldehydes

- Synthesis of an ( $\alpha$ -Boroxy)benzylcopper complex. A competent precatalyst for aldehyde diboration reactions.

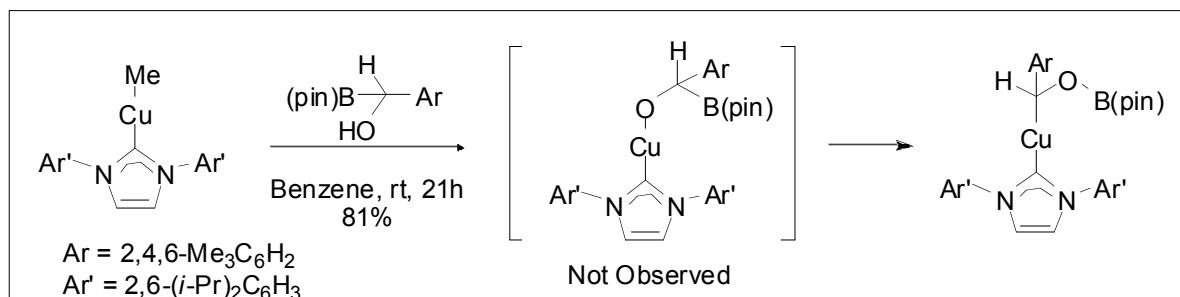
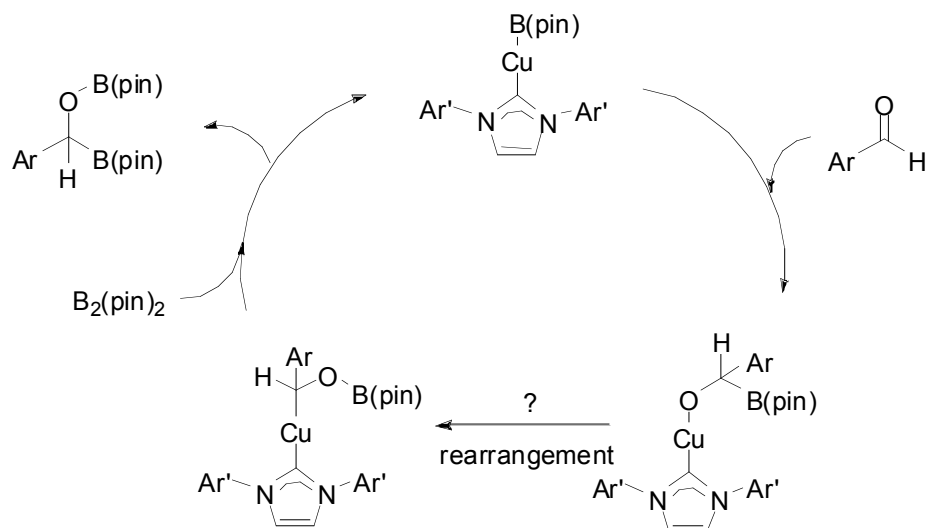


- Precatalyst optimization and reaction scope.



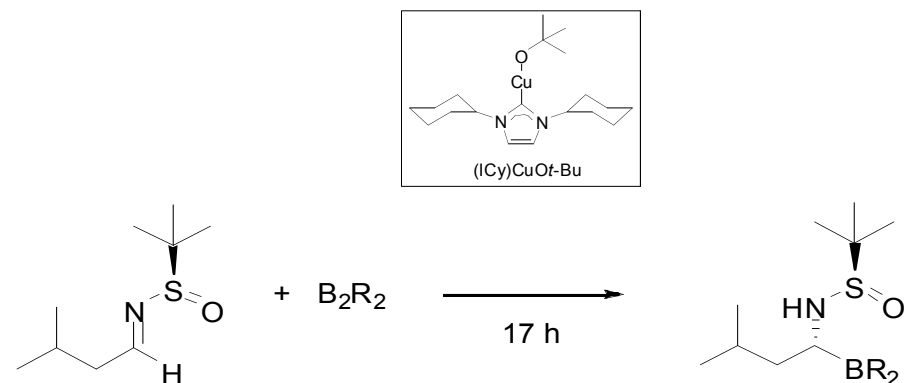
*J. Am. Chem. Soc.* **2006**, *128*, 11036.

# Background: Mechanistic Insights into the (ICy)CuOt-Bu Catalyzed Diboration of Aldehydes



*J. Am. Chem. Soc.* **2006**, *128*, 11036.

# Asymmetric Copper-Catalyzed Synthesis of $\alpha$ -Amino Boronate Esters from *N*-*tert*-Butanesulfinyl Aldimines: Catalyst Screen and Optimization Reactions

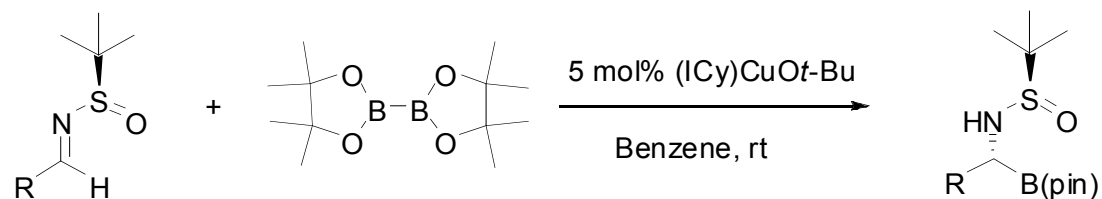


entry	B <sub>2</sub> R <sub>2</sub>	catalyst <sup>a</sup>	temp (°C)	solvent	yield (%) <sup>b</sup>	dr <sup>c</sup>
1	B <sub>2</sub> cat <sub>2</sub>	Pt(cod)Cl <sub>2</sub>	rt	C <sub>6</sub> H <sub>6</sub>	NR	
2	B <sub>2</sub> pin <sub>2</sub>	(ICy)CuOtBu	rt	C <sub>6</sub> H <sub>6</sub>	78	>98:2
3	B <sub>2</sub> pin <sub>2</sub>	none	rt	C <sub>6</sub> H <sub>6</sub>	NR	
4 <sup>d</sup>	B <sub>2</sub> pin <sub>2</sub>	(ICy)CuOtBu	10	C <sub>6</sub> H <sub>6</sub>	71	>98:2
5	B <sub>2</sub> pin <sub>2</sub>	(ICy)CuOtBu	50	C <sub>6</sub> H <sub>6</sub>	54	97:3
6	B <sub>2</sub> pin <sub>2</sub>	(ICy)CuOtBu	rt	toluene	69	>98:2
7	B <sub>2</sub> pin <sub>2</sub>	(ICy)CuOtBu	rt	dioxane	62	98:2
8	B <sub>2</sub> pin <sub>2</sub>	(ICy)CuOtBu	rt	THF	50	99:1

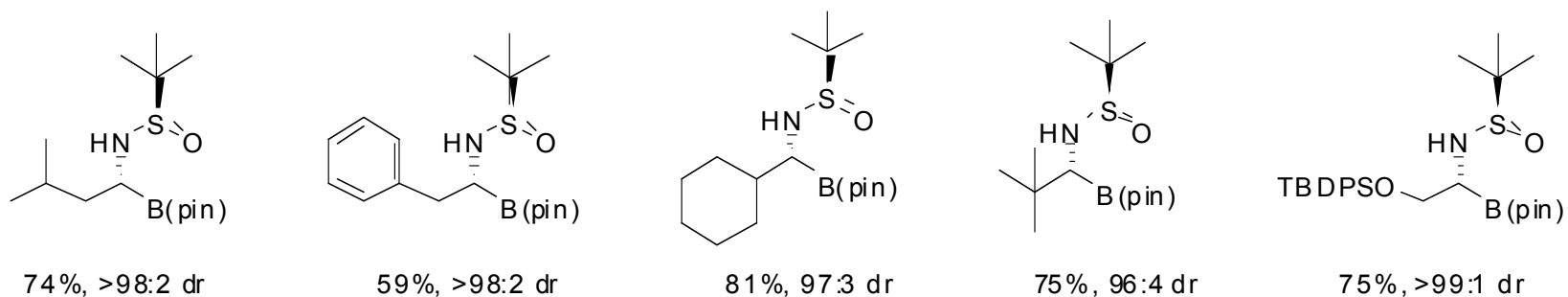
<sup>a</sup> With 5 mol % of catalyst used. <sup>b</sup> Yields were determined by <sup>1</sup>H NMR of the crude material relative to 1,3,5-trimethoxybenzene as an internal standard. <sup>c</sup> Diastereomeric ratio was determined by <sup>19</sup>F NMR of the corresponding (*R*)- and (*S*)-MTPA amides. <sup>d</sup> The reaction time was 30 h.

*J. Am. Chem. Soc.* **2008**, *130*, 6910.

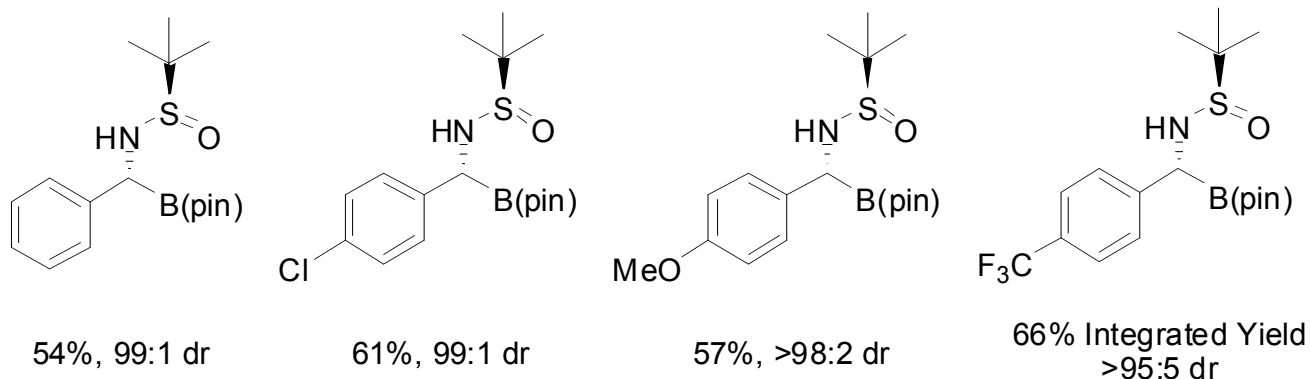
# Substrate Scope



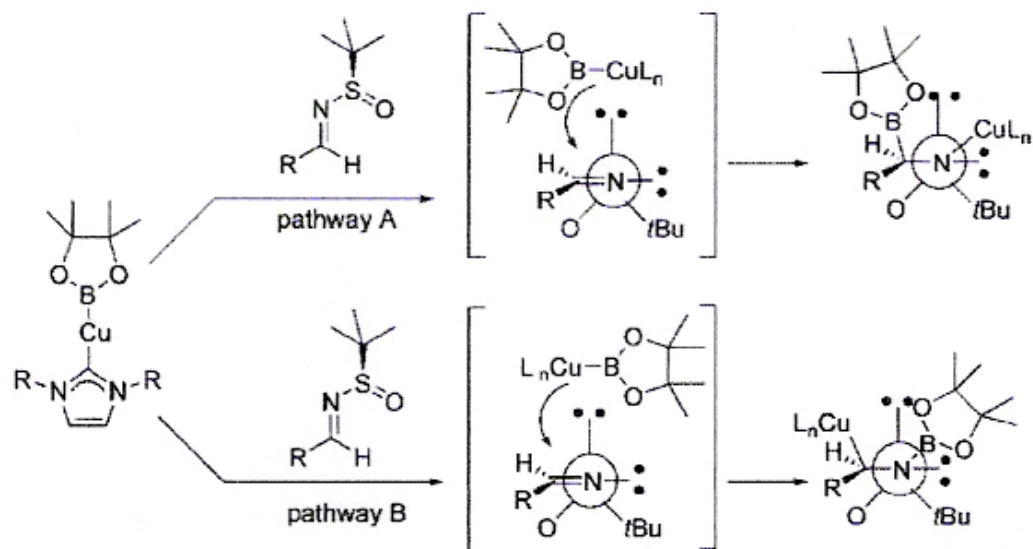
- Synthesis of aliphatic *N*-sulfinyl- $\alpha$ -amino boronate esters.



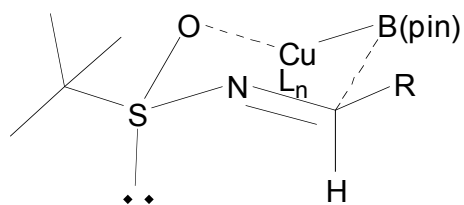
- Synthesis of aromatic *N*-sulfinyl- $\alpha$ -amino boronate esters. Lower yields reflect an increased susceptibility of protodeborylation.



# Rationale for the Observed Sense of Induction



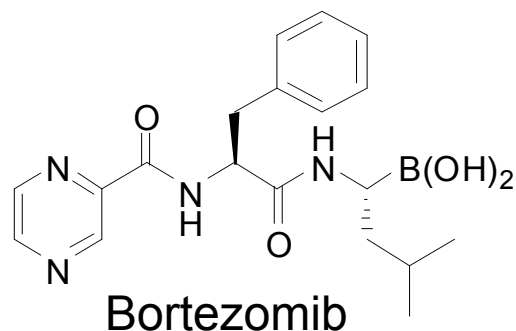
The sense of induction is consistent with an open transition state with the reagent delivered from the least hindered face.



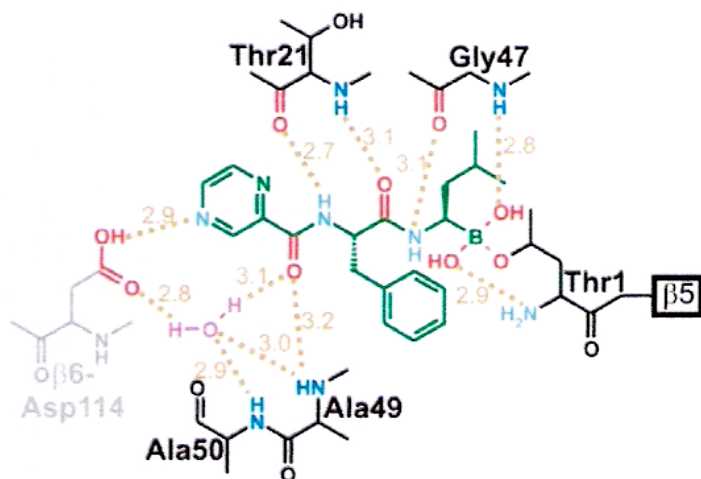
Closed Transition State  
(not observed)



# $\alpha$ -Amino Boronic Acids as Pharmacophores for Protease Inhibition: Bortezomib (Velcade)



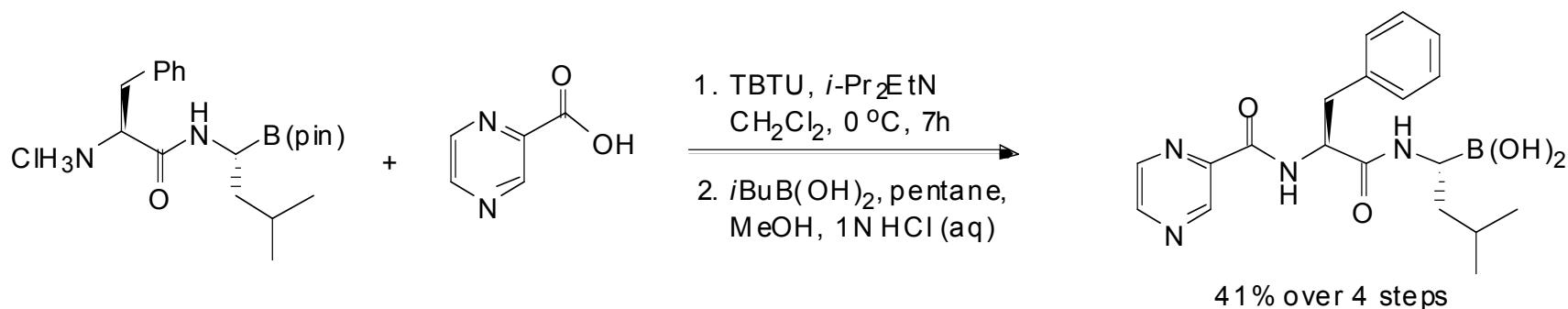
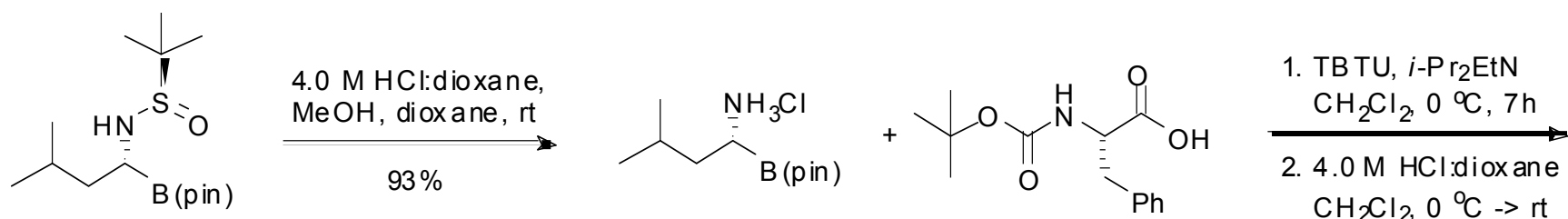
- Bortezomib is currently in clinical use for the treatment of cancers such as multiple myeloma and mantle cell lymphoma.



- Bortezomib is a potent and selective serine protease inhibitor.

*Chem. Rev.* **2007**, *107*, 687.; [www.Velcade.com](http://www.Velcade.com)

# Application of the Asymmetric Copper-Catalyzed Synthesis of $\alpha$ -Amino Boronate Esters: Synthesis of Bortezomib



The authors demonstrate a concise asymmetric synthesis of bortezomib with a 30% yield over 6 steps.

# Conclusion

- The authors have developed the first transition metal catalyzed asymmetric addition of boron to a carbon-heteroatom double bond.
- The utility of this methodology has been showcased by the asymmetric synthesis of the biologically active  $\alpha$ -amino boronic acid: bortezomib.
- This methodology can be easily applied to the synthesis of new  $\alpha$ -amino boronic acid-based protease inhibitors and allows for an alternate route to the generation of  $\alpha$ -chiral-amino boronate esters.

