

Catalysis by reversible covalent organoboron interactions

Topic review

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Overview

- ❖ General considerations
- ❖ Catalysis by borinic acid R_2BOH
 - Aldol reactions
 - Monoacylations
 - Selectivity
 - Other monofunctionalisations
 - Mono-glycosylations & application
 - Catalytic cycle & improvements
 - 2,3-epoxy alcohol functionalization
 - Oppenauer Oxidation

- ❖ Catalysis by boronic acid RB(OH)_2
 - Silylations
 - Aza-Michael Addition
 - Aldol reactions
 - Amide formations

General considerations

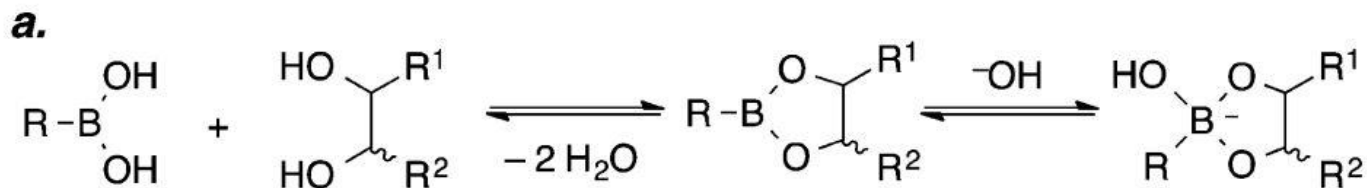
- ❖ Readily available
- ❖ Relatively stable
- ❖ Low toxicity

- ❖ Boronic acids belong to most successful strategy for carbohydrate recognition in aq. Solution
- ❖ Borinic acids have been ignored in this regard



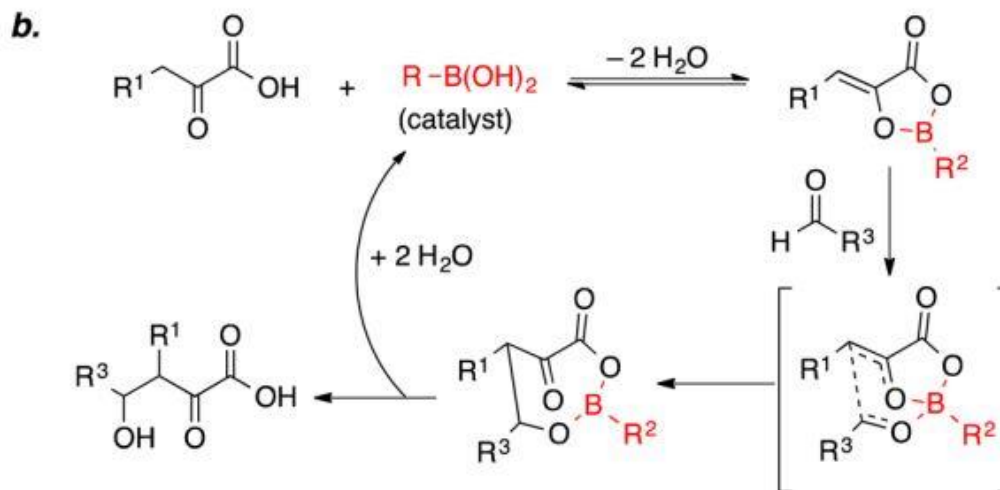
General considerations

- ❖ Selective cis-1,2-diol motif recognition and binding
- ❖ Selectivity in between similar cis-1,2,diol motifs
- ❖ High association constants even in polar protic solvents.
- ❖ Tuneable by pH control:



How the borinic acid catalysis started

- ❖ Initial idea by the group of Mark S. Taylor:
Reversible generation of boron enolates for pyruvic acid aldol condensation under mild conditions.
Interesting because enzymes do it.
Recognition by boronic acid is known from analysis
- ❖ Suggested mechanism:



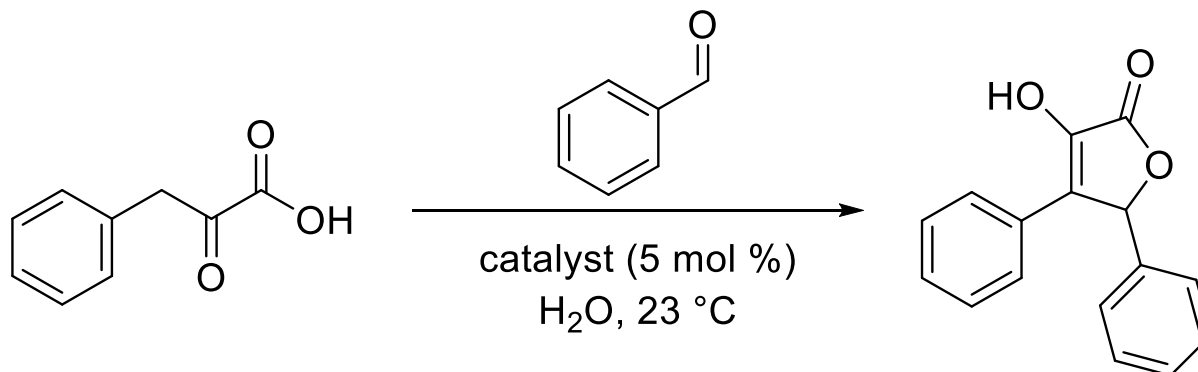
But...

❖ Borinic acid should thus not catalyse the reaction.

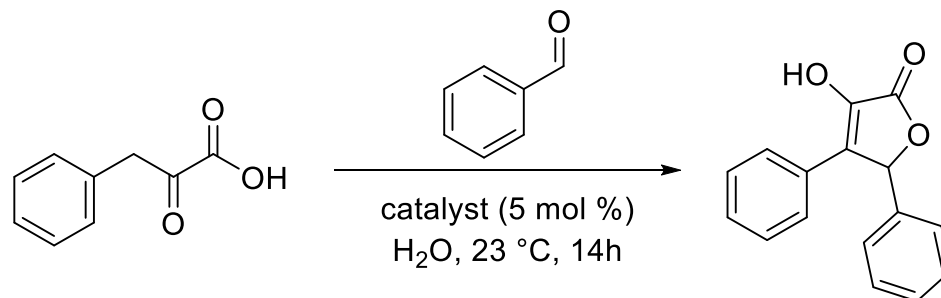
❖ Results

PhB(OH)₂: 19% yield

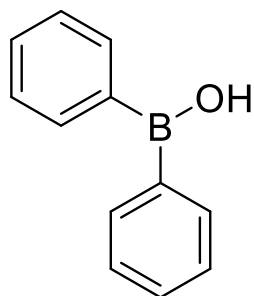
Ph₂BOH: 90% yield



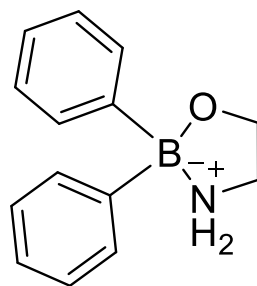
Borinic acid - Aldolreactions



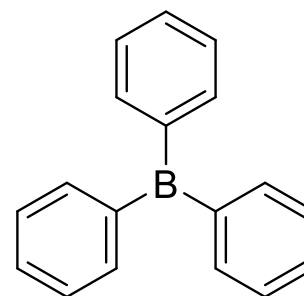
❖ Evaluation of the best catalyst:



1
90%



2
83%



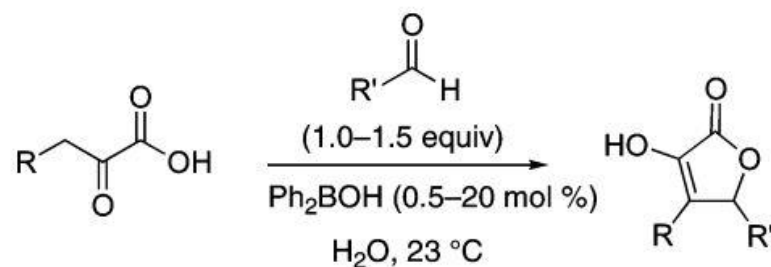
3
87%

Advantage of 2: Crystalline solid, more stable towards oxidation.

Lee, D., Newman, S. G., Taylor, M. S., *Org. Lett.* **2009**, 11, 5486-5489

Borinic acid - Aldolreactions

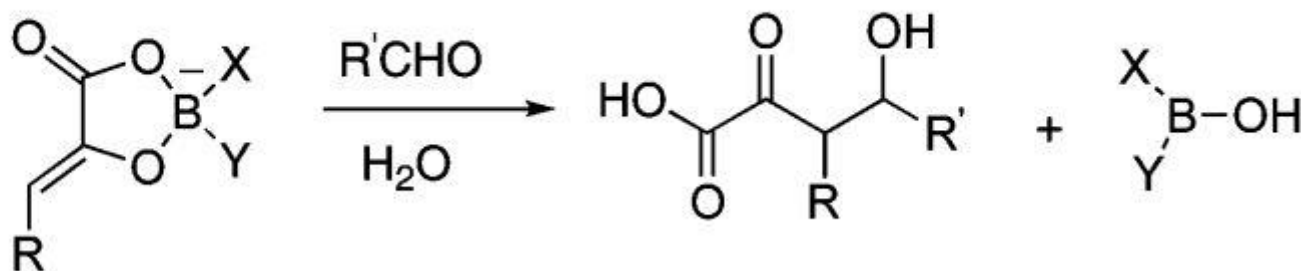
❖ Scope of catalyst 1:



entry	R	R'	product	catalyst (mol %)	yield ^a (%)
1	Ph	Ph	3a	0.5	90
2	Ph	4-MeOC ₆ H ₄	3b	20	70
3	Ph	4-F ₃ CC ₆ H ₄	3c	5	81
4	Ph	2-thienyl	3d	5	82
5	Ph	2-furyl	3e	5	89
6	Ph	<i>n</i> -C ₅ H ₁₁	3f	1	90 ^b
7	Ph	cyclohexyl	3g	5	84

Borinic acid - Aldolreactions

Proposed aldol reaction of boron-pyruvate adducts:



❖ Considerations:

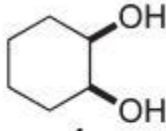
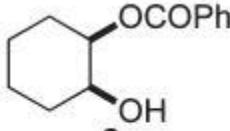
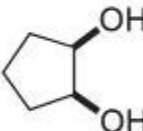
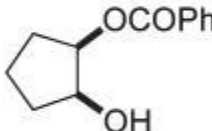
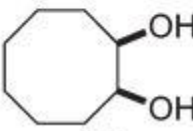
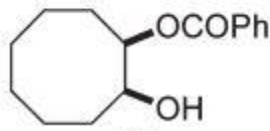
The tetracoordinated boron species has been confirmed = Lewis acidic boron catalysis seems unlikely.

The lactonization step might be catalysed as well.

The lactonization step might improve catalyst turnover, since the carboxylate is no longer available for binding.

The boron ester activates the diol for nucleophilic attack.

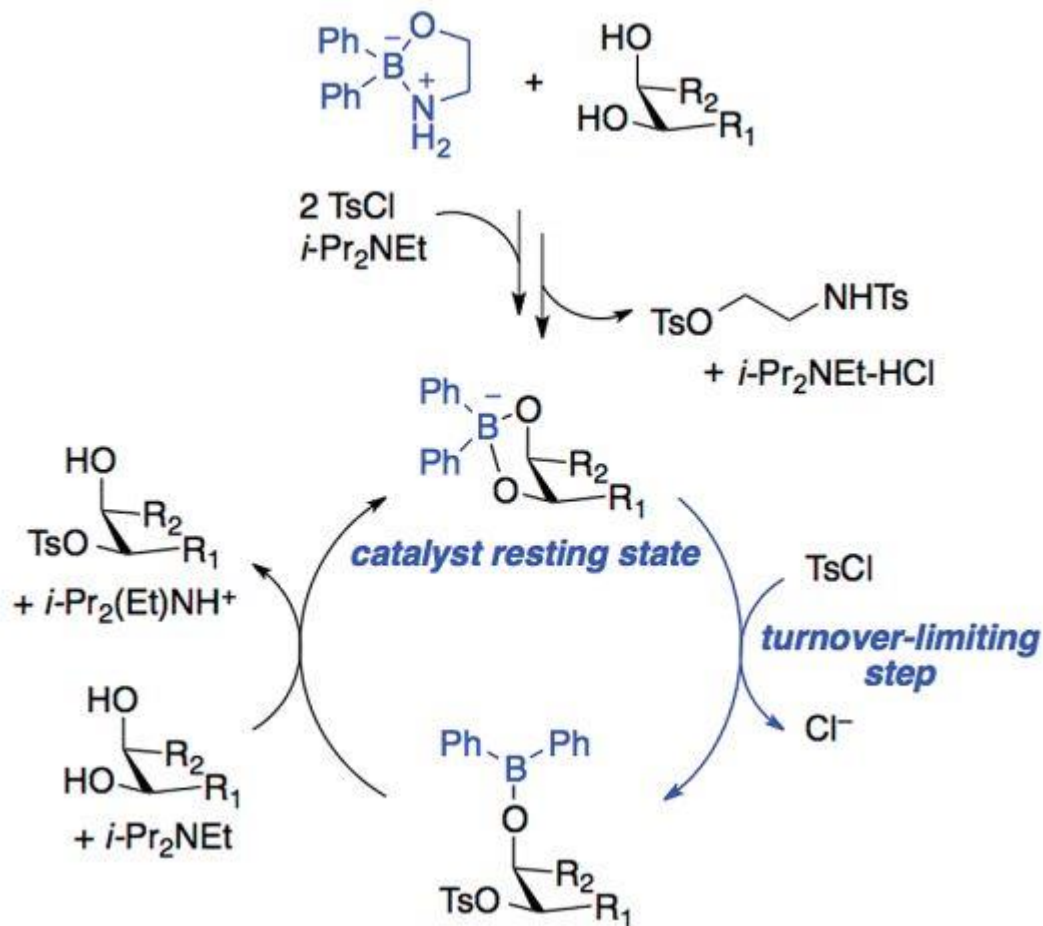
Monoacylations

Entry	Substrate	Product	Yield (%) ^b
1	 1a	 2a	>99 (60)
2	 1c	 2c	94 (50)
3	 1d	 2d	>99 (56)

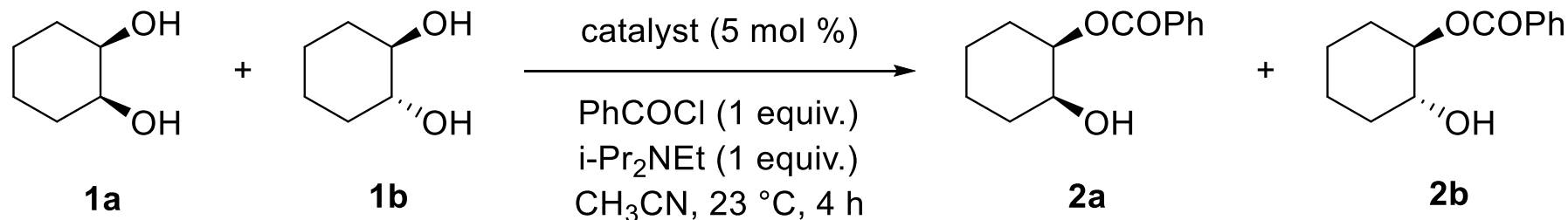
Monoaclyations

Entry	Substrate	Product	Yield (%) ^b
4	<p>5a</p>	<p>6a</p>	91 (<3)
5	<p>5b</p>	<p>6b</p>	80 (64)
6	<p>5c</p>	<p>6c</p>	95 (11)

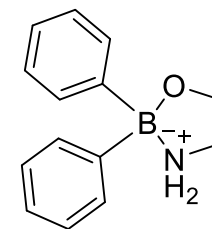
Catalytic cycle



Selectivity I – cis vs. trans



Entry	Catalyst	Yield	Ratio 2a:2b
1	None	<5 %	-
2	Me ₂ SnCl ₂	96 %	1:1
3	PhB(OH) ₂	35 %	3:1
4	2	70 %	11:1
5	Ph ₃ B	47 %	15:1
6	Ph ₂ BOH	70 %	11:1

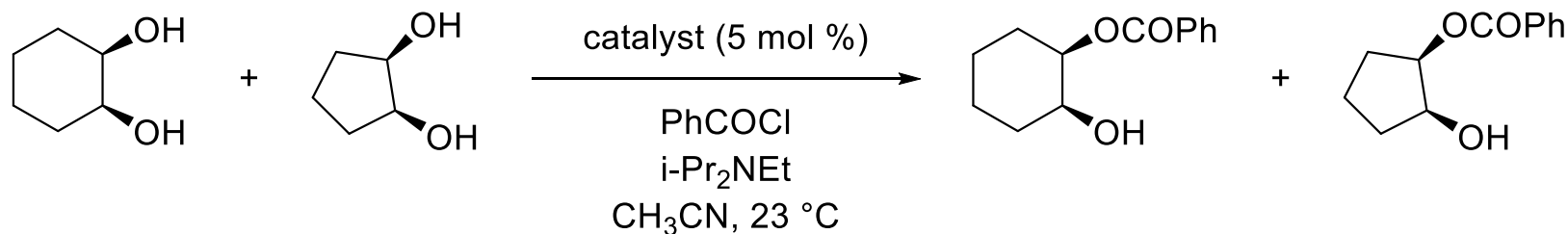


2

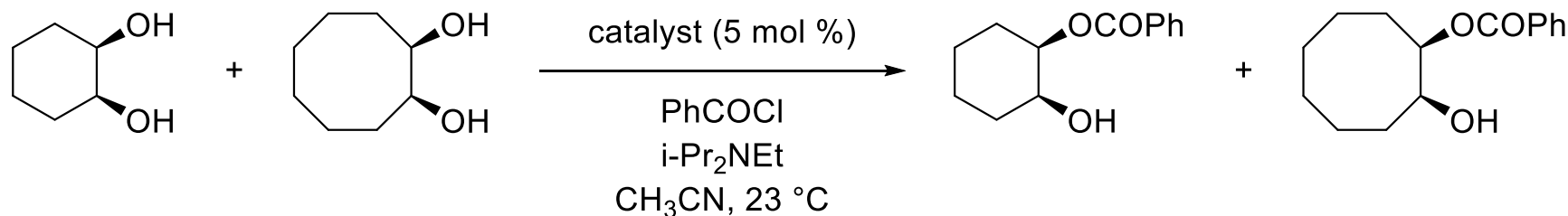
Lee, D., Taylor, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 3724-3727

Iwasaki, F., Maki, T., Onomura, O., Nakashima, W., Matsumura, Y. *J. Org. Chem.* **2000**, *65*, 996-1002

Selectivity II – structural diversity

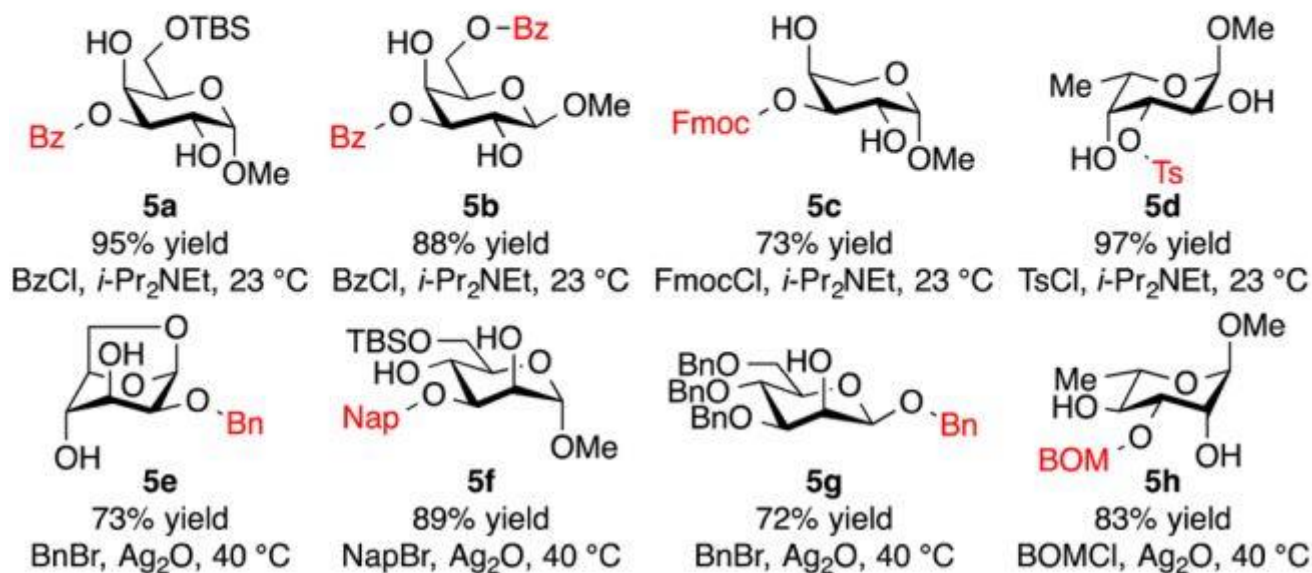
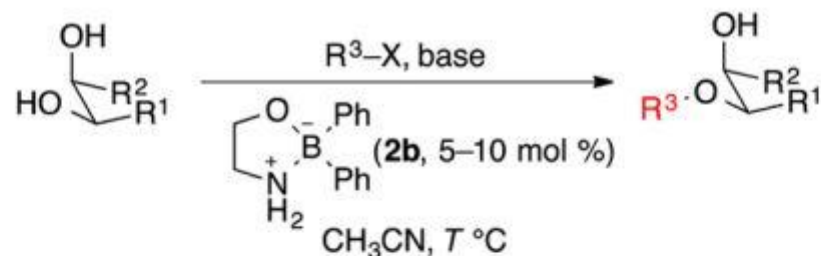


Bu ₂ SnO:	1	4
Catalyst 2:	1	8



Bu ₂ SnO:	1	3
Catalyst 2:	1	>25

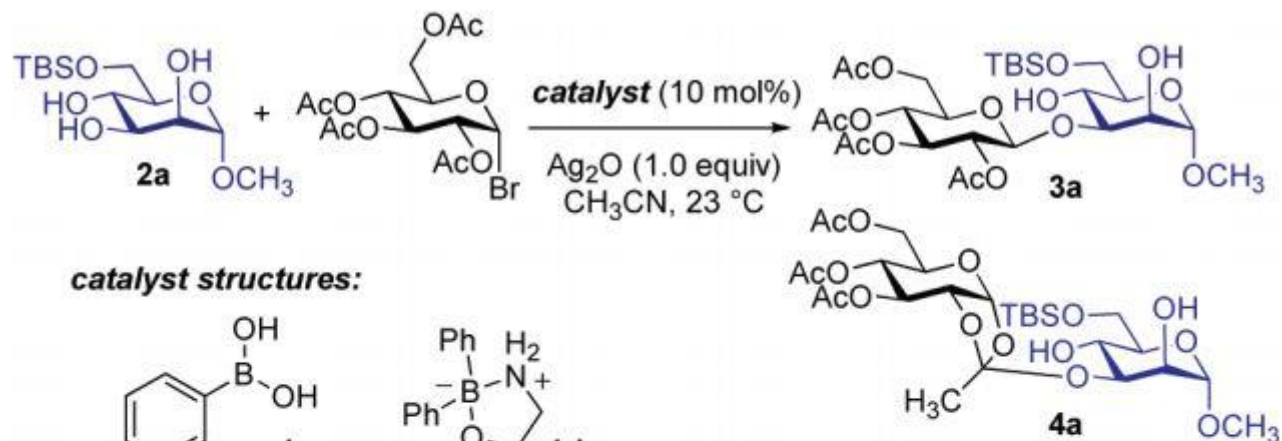
Monofunctionalization



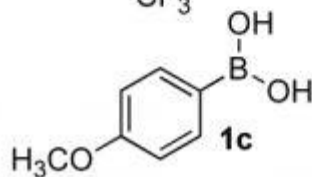
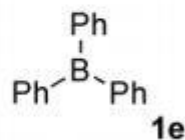
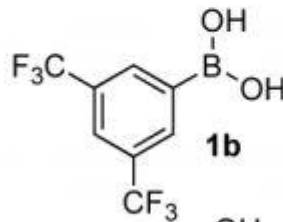
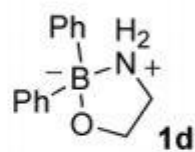
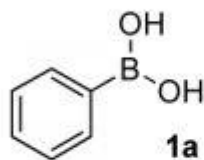
Mono-Glycosylation

- ❖ Important for the total synthesis of some natural products
- ❖ Useful for production of analogues
- ❖ Useful for Structure-Activity relationship determination
- ❖ Outlook: anti-resistance for macrolide antibiotics

Mono-Glycosylation

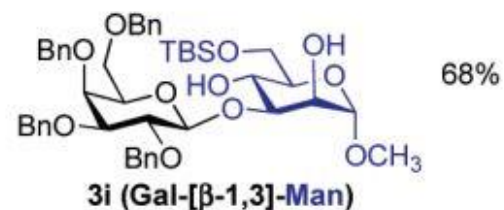
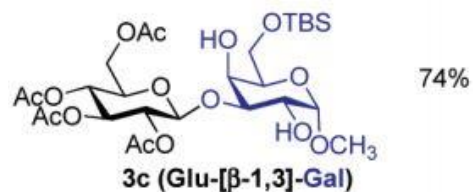
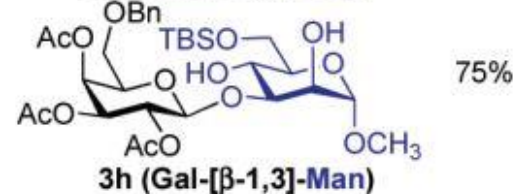
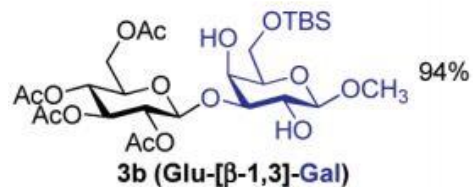
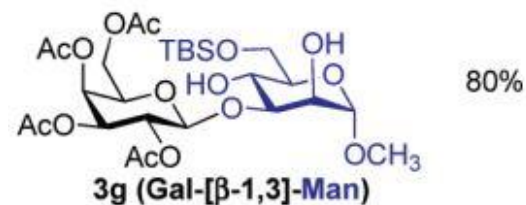
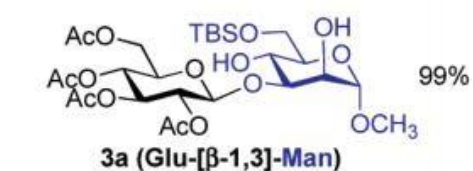
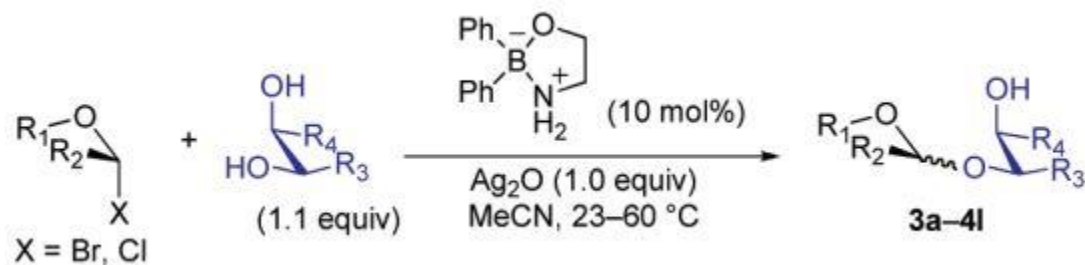


catalyst structures:

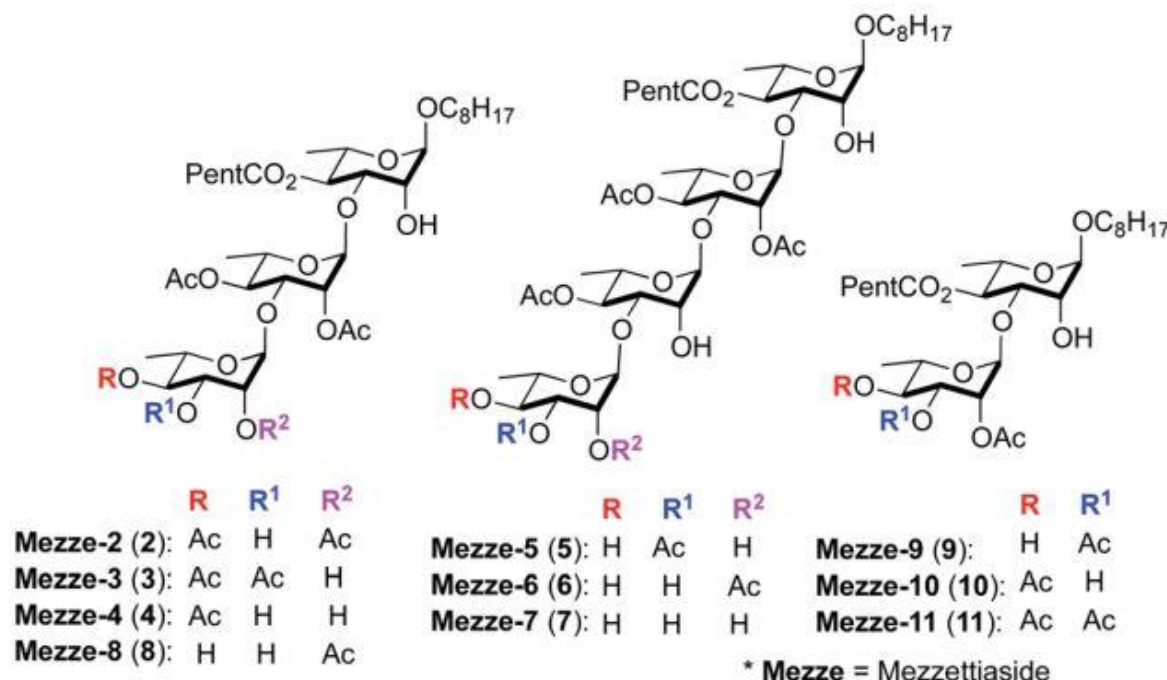


entry	catalyst	yield of 3a ^a
1	none	<5%
2	1a	52%
3	1b	57%
4	1c	50%
5	1d	99%
6	1e	54%

Mono-Glycosylation

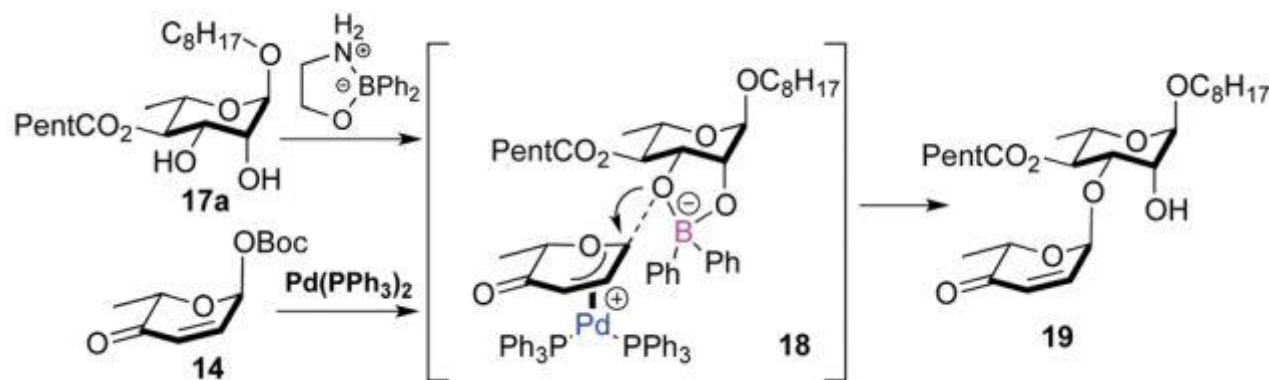


- ❖ *De novo* asymmetric synthesis of the mezzettiaside family of natural products *via* the iterative use of a dual B-/Pd-catalysed glycosylation
- ❖ First synthesis of any and all members of the mezzettiaside family



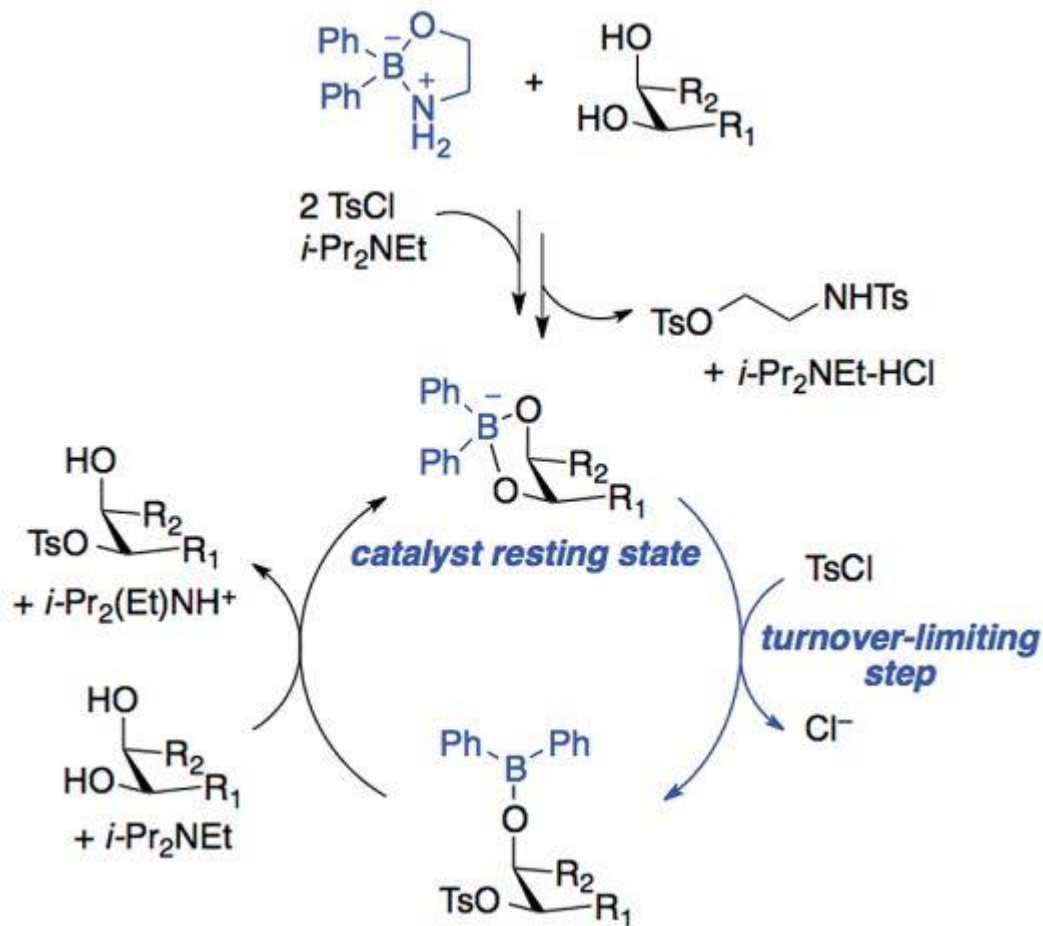
Application

❖ Key coupling step:



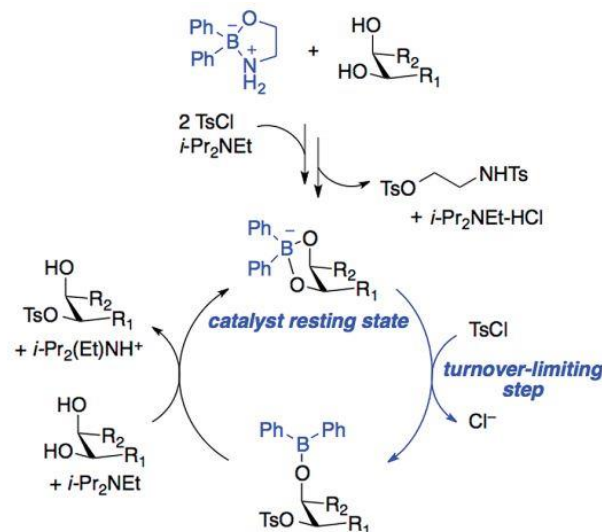
77% yield, 7.5 : 1 regiocontrol (16:1 for the examples where the C4 ester was OAc)

Catalytic cycle



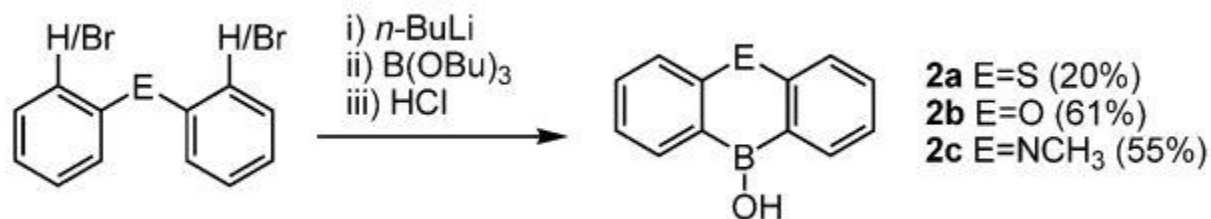
Improvements

- ❖ The turnover (and thus selectivity) limiting step is the nucleophilic attack from the boronate complex
- ❖ More electron rich borinic acid = higher catalytic activity.
- ❖ More electron rich borinic acid = easier oxidation.
- ❖ Ethanolamine complex gives byproducts
- ❖ Diphenylborinic acid was not always recovered (due to oxidation)

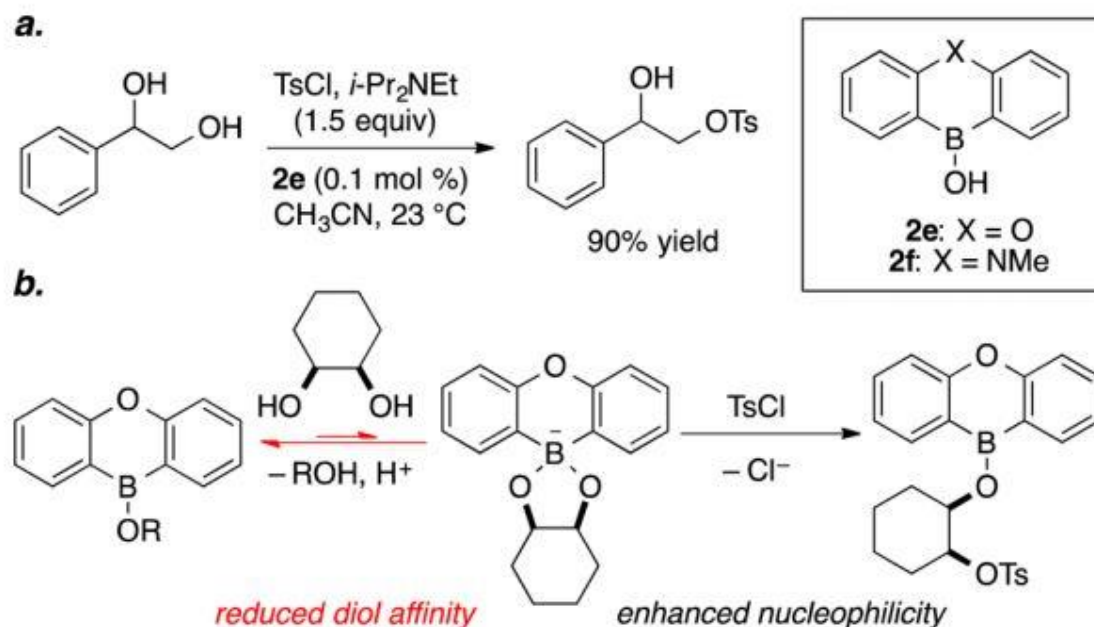


Improvements

- ❖ => Borinic acids based on oxa-, thia- or azaborinine framework
- ❖ Incorporation into a 6π electron system was expected to decrease the Lewis acidity.
- ❖ Literature suggested that these compounds would be resistant to oxidation.



Improvements



Same yield as previous catalyst, with 50 times lower loading.

Although the affinity is lower, the tosylation step more than compensates

2e and 2f can be stored for months in the solid state

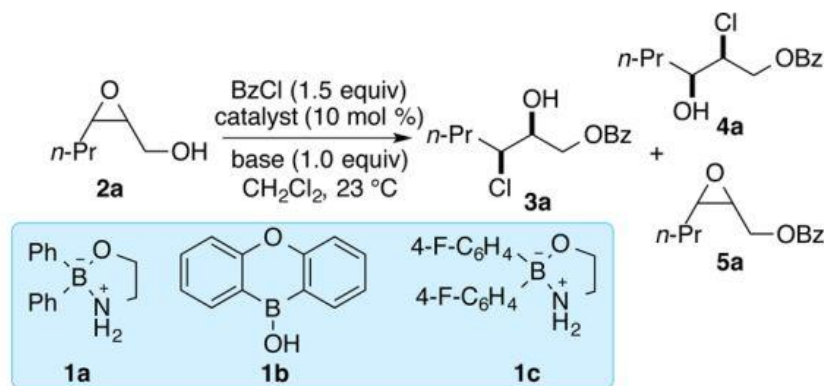
Ethanolamine-derived byproducts are avoided

Dimitrijevic, E., Taylor, M. S. *Chem. Sci.* **2013**, 4, 3298-3304

Functionalization of 2,3-epoxy alcohols

C3 selectivity – cis epoxides

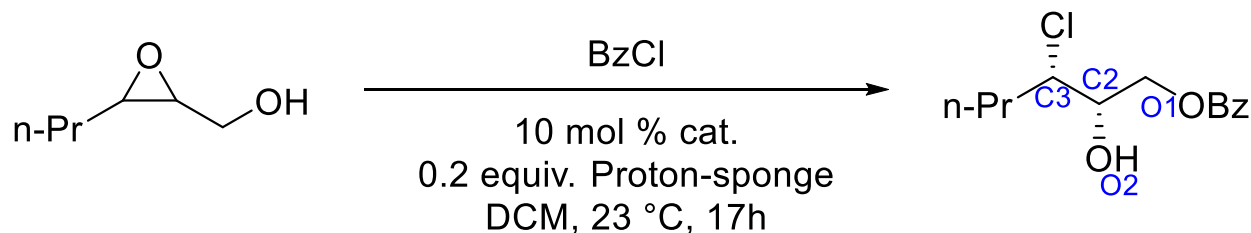
- ❖ Functionalization of 2,3-epoxy alcohols is rather easy – regioselectivity is the challenge.



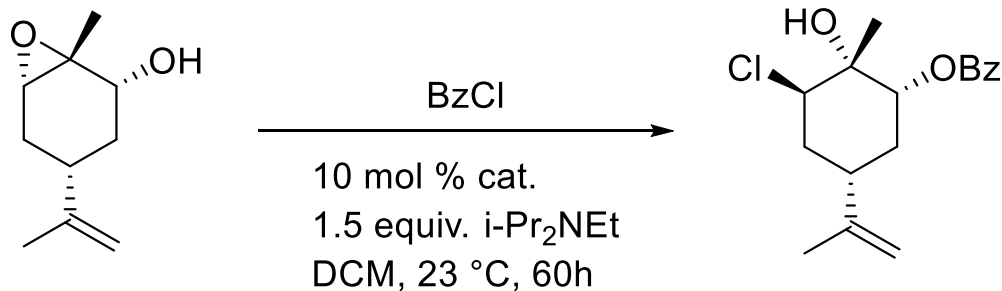
Entry	Catalyst	3a	4a	5a
1	1a	80%	5%	10%
2	1b	35%	10%	35%
3	1c	80%	10%	10%
4	None	<5%	<5%	25%

Functionalization of 2,3-epoxy alcohols

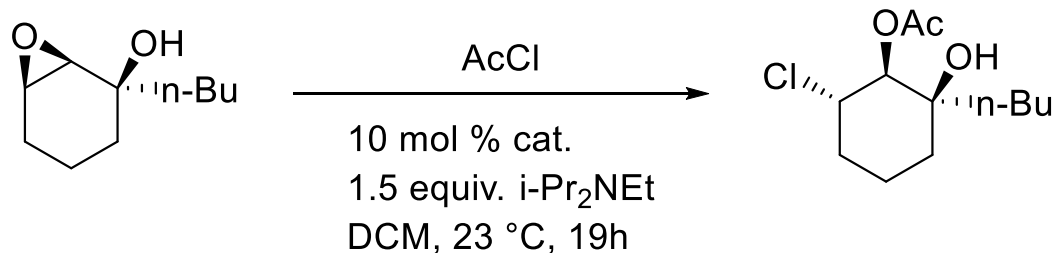
C3 selectivity



19:1 C3:C2 for Cl
 >19:1 O1:O2 for Bz
 70% yield



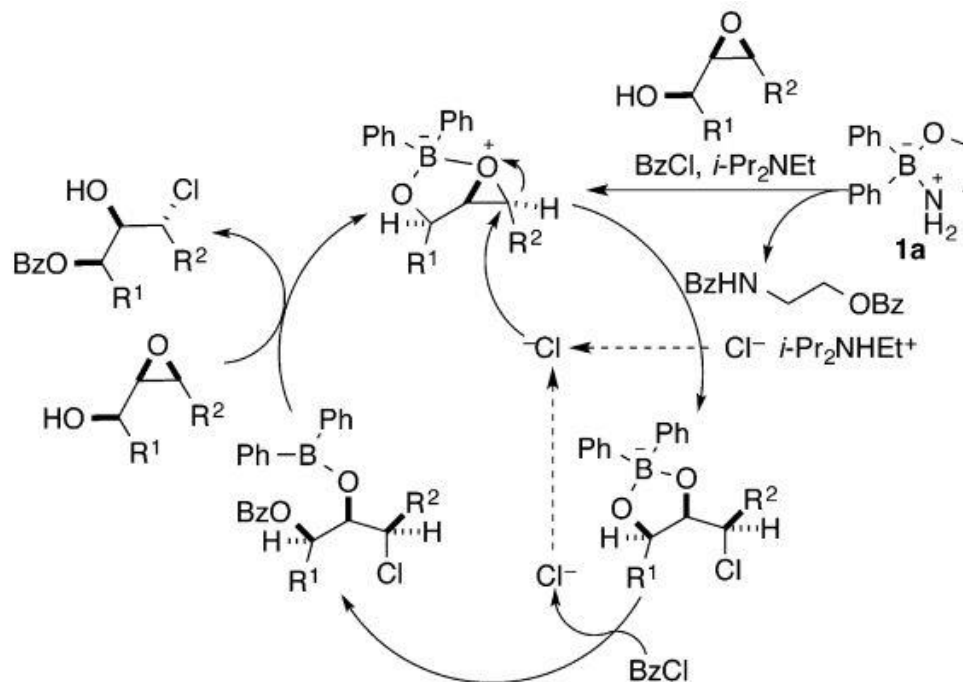
>19:1 C3:C2 for Cl
 >19:1 O1:O2 for Bz
 88% yield



>19:1 C3:C2 for Cl
 1:5.2 O1:O2 for Ac
 70% yield

Functionalization of 2,3-epoxy alcohols

C3 selectivity

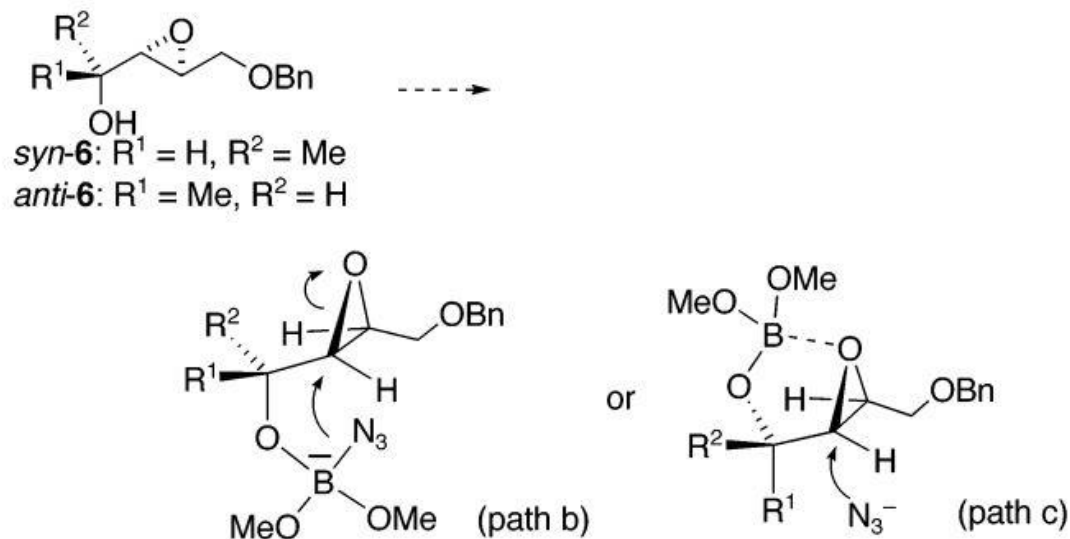


- ❖ Nucleophilic attack at C3 position is favoured by interaction of the catalyst: No reaction if the O1 hydroxy group is protected.
- ❖ Acylation at the lesser sterically hindered alkoxy position
- ❖ Chlorosulfonylation proceeds with less selectivity

Tanveer, K., Jarrah, K., Taylor, M. S. *Org. Lett.* **2015**, 17, 3482-3485

Functionalization of 2,3-epoxy alcohols

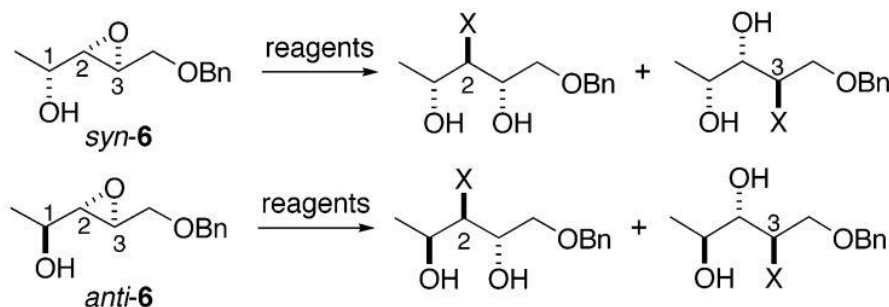
C2 selectivity



- ❖ Ate complex (path b): lower reactivity and selectivity for *syn*, because of steric repulsion (methyl – epoxide).
- ❖ Chelation control (path c): higher selectivity and reactivity for *syn* because of steric hinderance for *anti* (methyl – nucleophile).

Functionalization of 2,3-epoxy alcohols

C2 selectivity

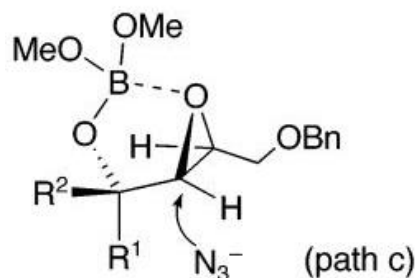


- ❖ Ate complex (path b): lower reactivity and selectivity for syn, because of steric repulsion (methyl – epoxide).
- ❖ Chelation control (path c): higher selectivity and reactivity for syn because of steric hinderance for anti (methyl – nucleophile).

Entry	Reactant	Reagent	Selectivity	Yield
1	syn-6	Me ₂ CuLi	50:50	76 %
2	anti-6	Me ₂ CuLi	79:21	83 %
3	syn-6	NaN ₃ , (CH ₃ O) ₃ B	89:11	92 %
4	anti-6	NaN ₃ , (CH ₃ O) ₃ B	46:54	30%

Functionalization of 2,3-epoxy alcohols

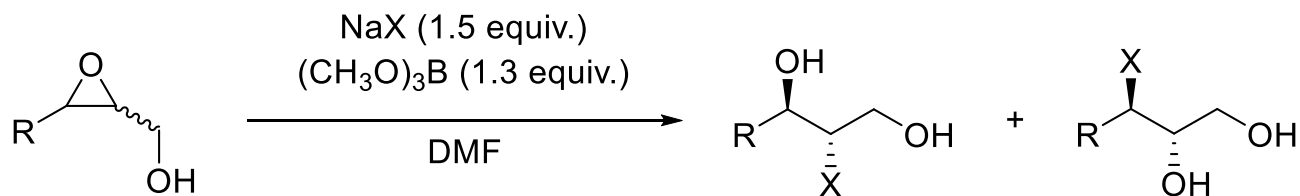
C2 selectivity



- ❖ Chelation control for the boron-catalysed reaction: higher selectivity and reactivity for syn because of steric hindrance for anti (methyl – nucleophile).

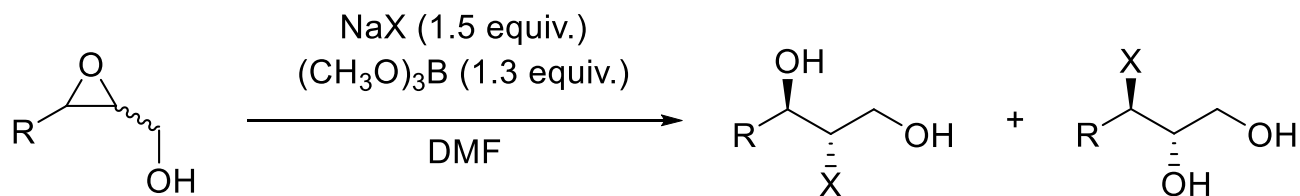
Functionalization of 2,3-epoxy alcohols

C2 selectivity



Entry	Epoxide	X	Selectivity	Yield
1	<i>syn</i> -BnOCH ₂	N ₃	92:8	96 %
2		SPh	95:5	97 %
3	<i>anti</i> -BnOCH ₂	N ₃	73:27	96 %
4		SPh	76:24	90 %
5	<i>syn</i> -nPr	SPh	85:15	97 %
6	<i>anti</i> -nPr	SPh	48:52	85 %

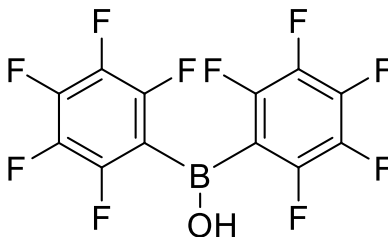
Functionalization of 2,3-epoxy alcohols C2 selectivity



- ❖ Provides a C2 selective alternative for 2,3-epoxy alcohol opening.
- ❖ Selectivity can be achieved with syn and anti epoxides
- ❖ Catalyst not applied in catalytic amount (but much cheaper)

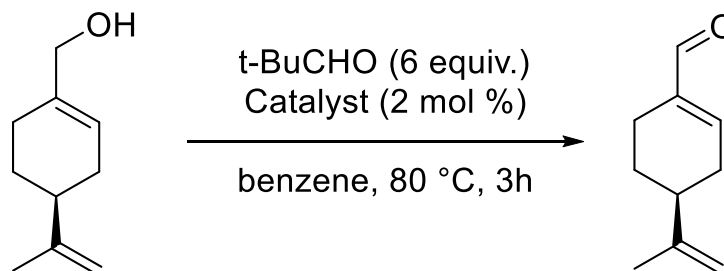
Oppenauer oxidation

- ❖ Organoboron catalysed oxidation of primary and secondary allylic and benzylic alcohols.
- ❖ Oxidation tolerates a range of other functional groups



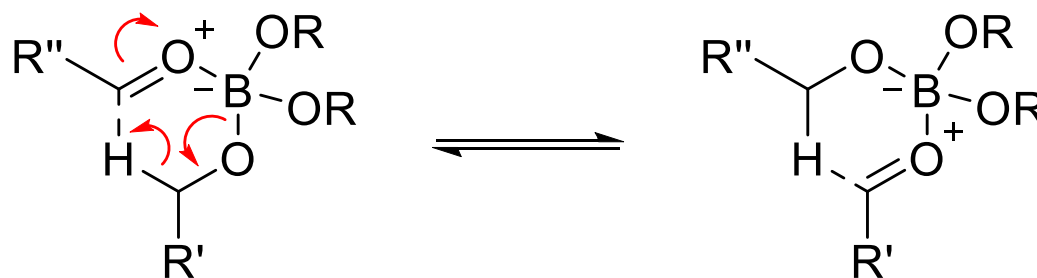
- ❖ Strong electron withdrawing system: more stable
- ❖ The corresponding boronic acid is inactive

Oppenauer oxidation



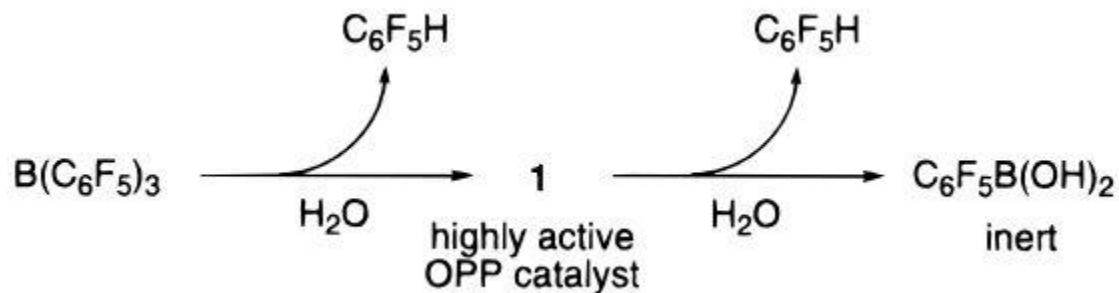
Entry	Catalyst	Yield
1	$C_6F_5B(OH)_2$	0 %
2	$B(C_6F_5)_2(OH)$	> 99 %
3	$B(C_6F_5)_3$	> 99 %

Oppenauer oxidation

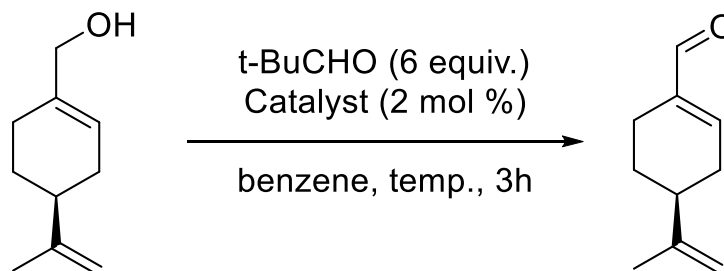


Oppenauer oxidation

Entry	Catalyst	Yield
1	$C_6F_5B(OH)_2$	0 %
2	$B(C_6F_5)_2(OH)$	> 99 %
3	$B(C_6F_5)_3$	> 99 %

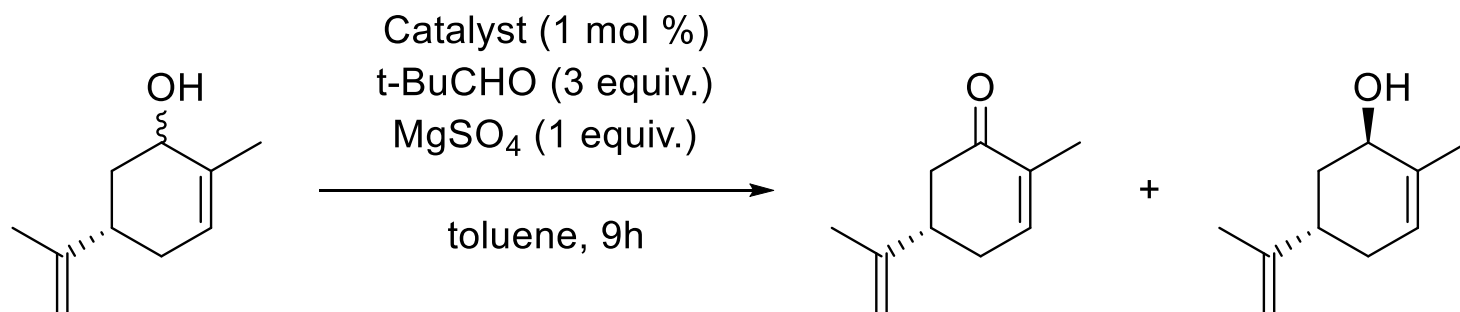


Oppenauer oxidation

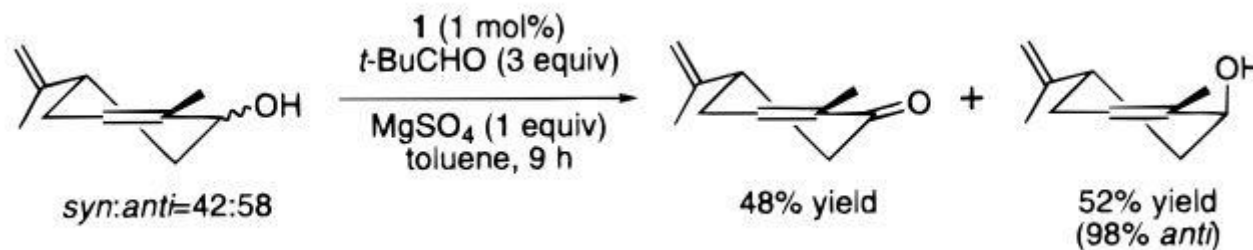
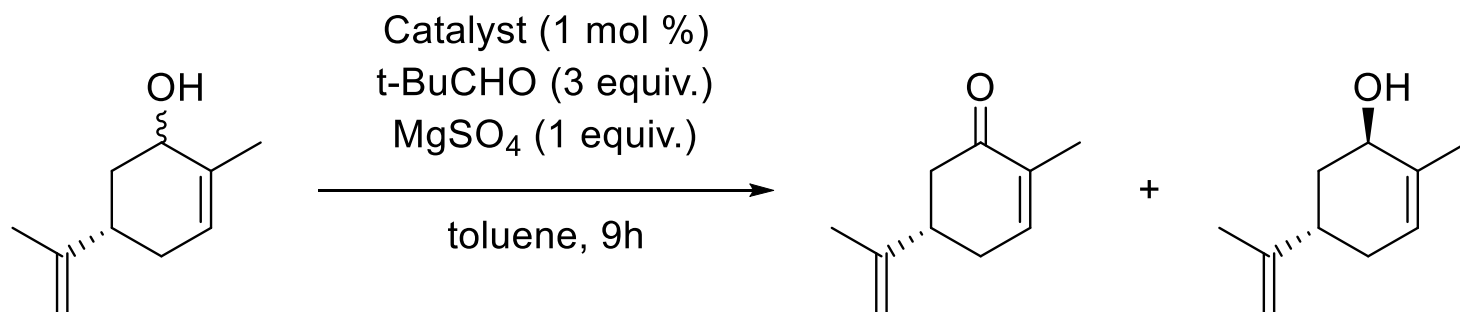


Entry	Additive	Temp.	Yield
1	None	80 ° C	> 99 %
2	None	rt	90 %
3	MgSO ₄	rt	> 99 %
4	MS 4A	rt	< 10 %
5	CHCl ₃	rt	85 %

Oppenauer oxidation



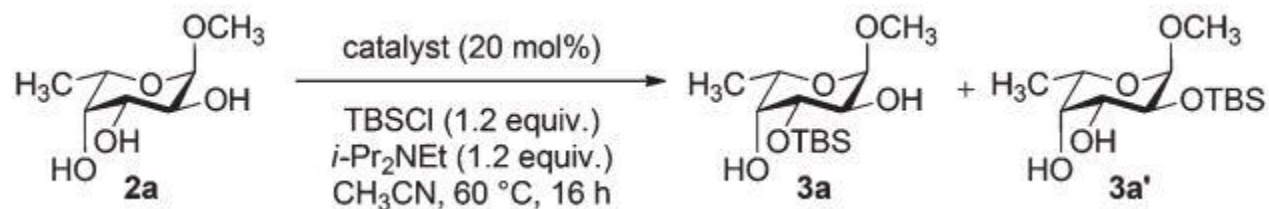
Oppenauer oxidation



Boronic acids

- ❖ More stable than borinic acids
- ❖ Can be applied together with Lewis bases
- ❖ Are better known from molecular recognition
= the association constants are often known
- ❖ For some reactions borinic acids simply don't work

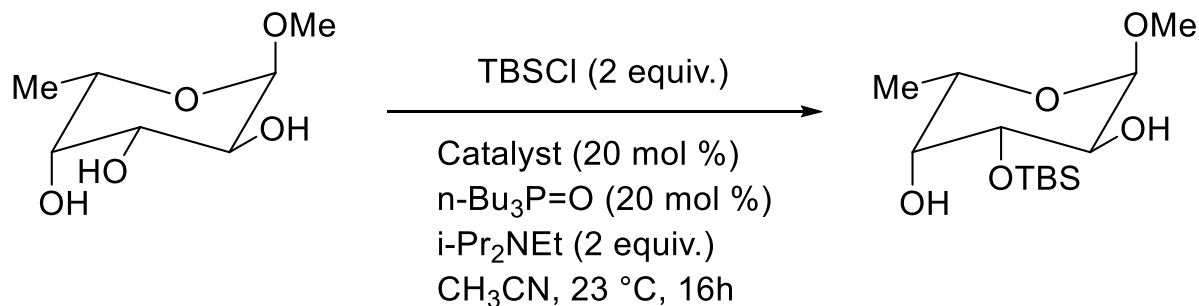
Silylation



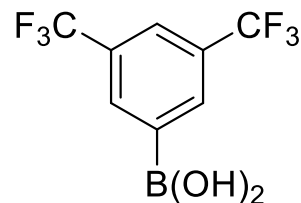
Entry	Catalyst	Yield	Ratio 3a:3a'
1	none	40%	2.6 : 1
2	N-methylimidazole	58%	1 : 1.5
3	Aminoethanol-borinic	27%	3.1 : 1
4	PhB(OH) ₂	40%	6.3 : 1
5	3,5-(CF ₃) ₂ C ₆ H ₃ B(OH) ₂	62%	9.2 : 1

Large influence of solvent ranging from cyclohexane (11% yield) to CH₃CN-toluene 1:1, 89 % yield

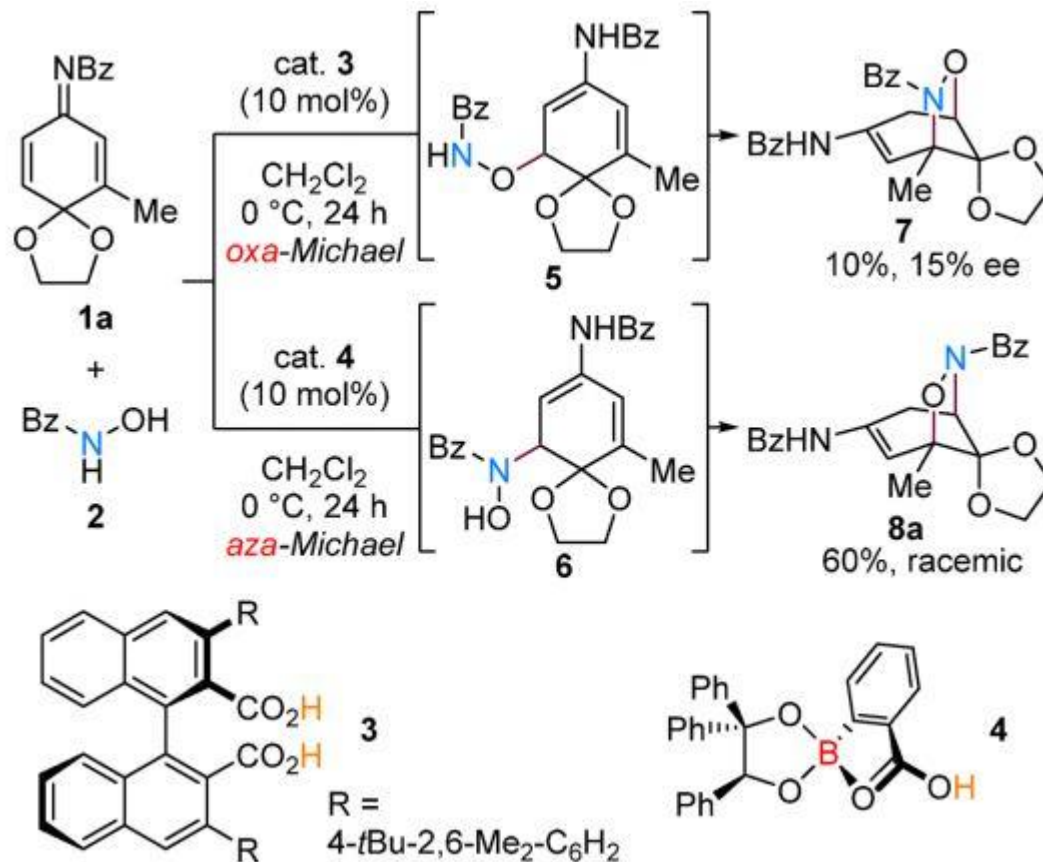
Silylation



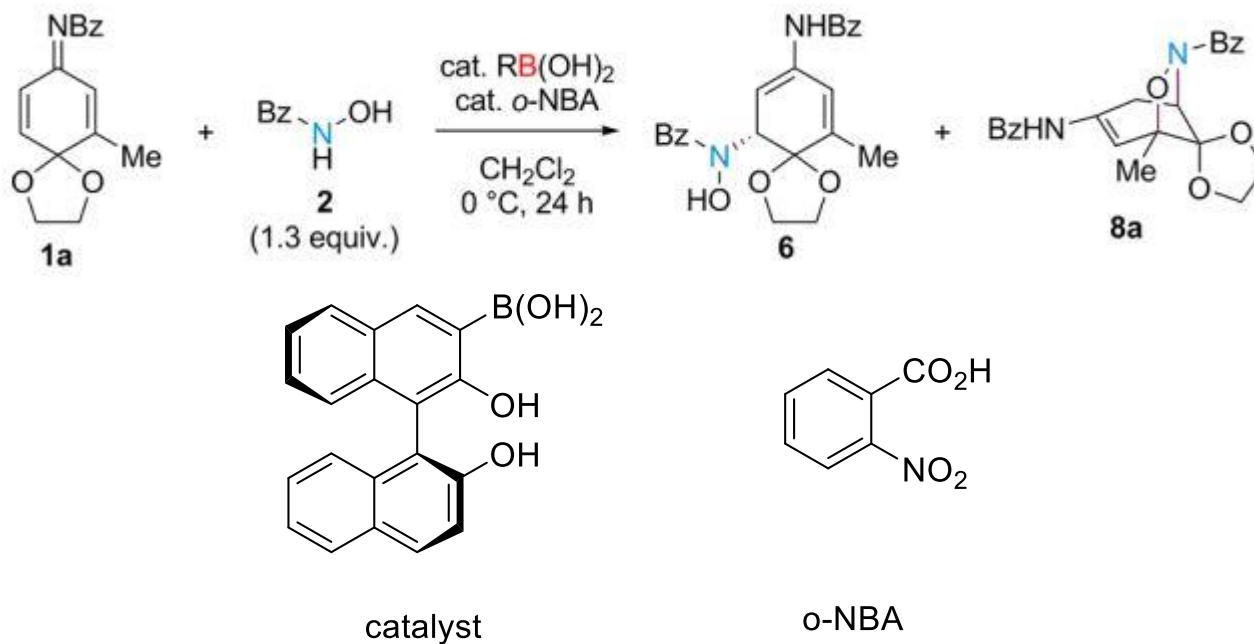
catalysed: 99% yield, >30:1
uncatalysed: 7% yield, 12:1



Aza-Michael Addition



Aza-Michael Addition



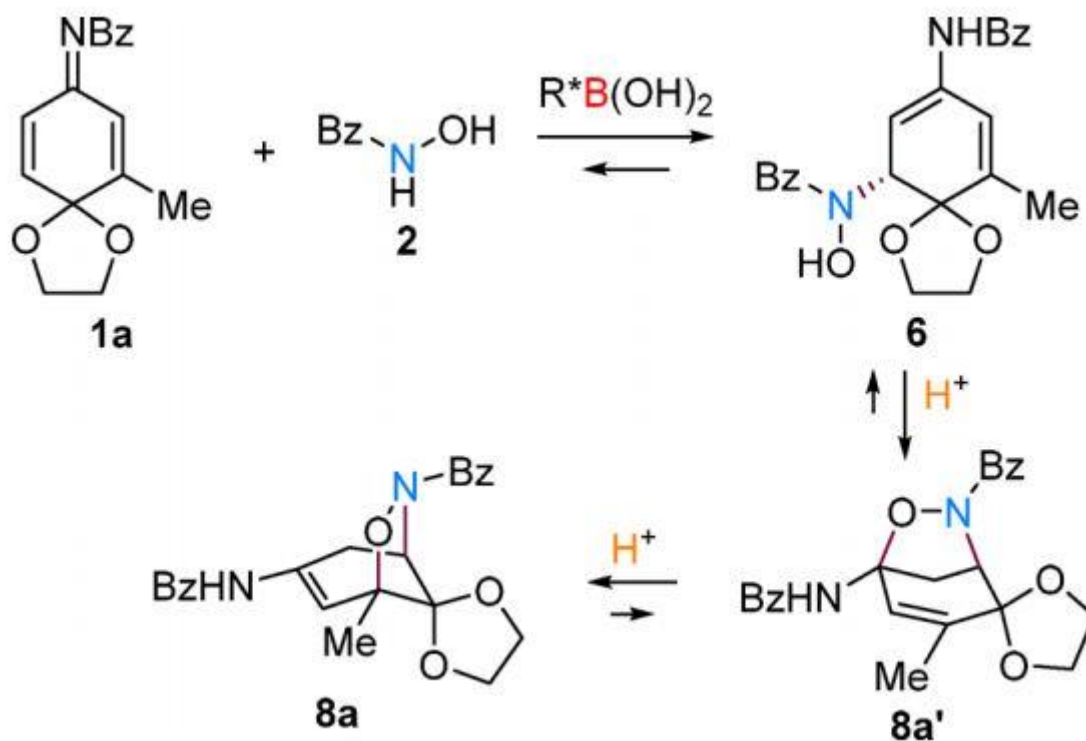
Optimized conditions: 2 mol % catalyst, 30 mol % *o*-NBA.

Traces of **6**, 92% of **8a**, 94% ee

Hashimoto, T., Gálvez, A. O., Maruoka, K. *J. Am. Chem. Soc.*, **2015**, *137*, 16016-16019

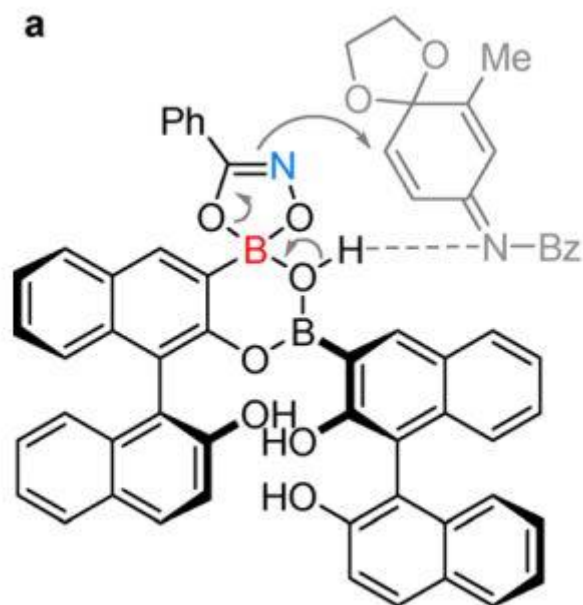
Aza-Michael Addition

❖ Proposed reaction pathway:



Aza-Michael Addition

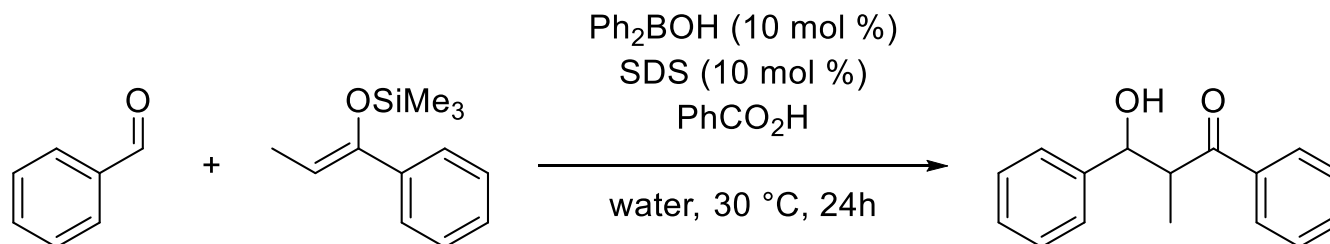
- ❖ Kinetic studies suggest a dimer is the real catalyst:



- ❖ But no inclusion of the nitrobenzoic acid (responsible for cyclization)

Aldol reactions

- ❖ Boronic catalysed aldol-reactions:
Catalytic C-C bond formation in aqueous media



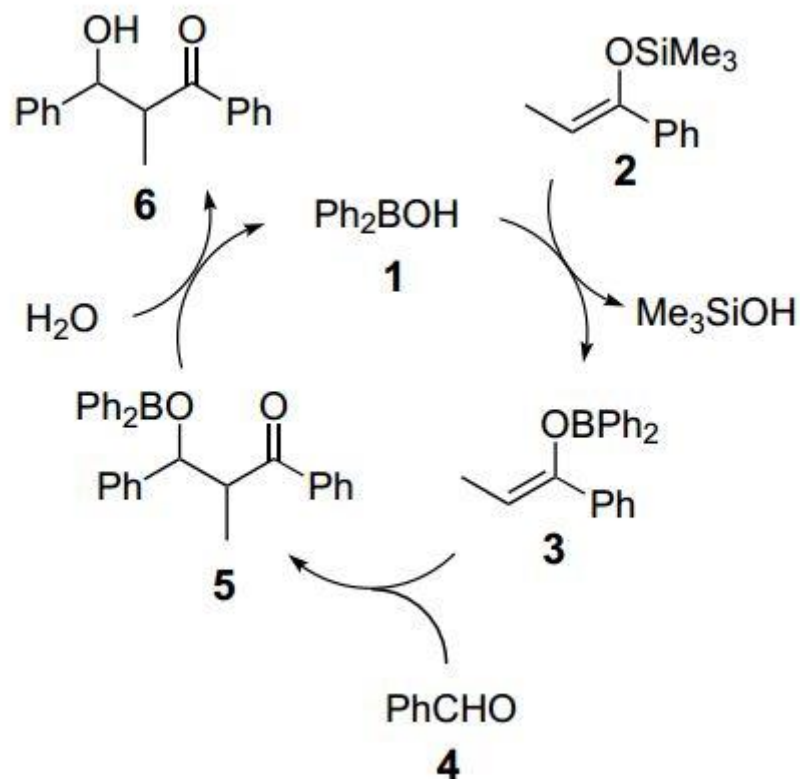
Entry	Solvent	Acid	Yield	Syn/anti
1	Water	None	Trace	-
2	Water	1 mol %	90	92/8
3	Ether	1 mol %	Trace	-
4	DCM	1 mol %	Trace	-
5	none	1 mol %	24	90/10

Mori, Y., Manabe, K., Kobayashi, S. *Angew. Chem. Int. Ed.*, **2001**, 40, 2815-2818

Aldol reactions

- ❖ No stoichiometric amount of boron enolate needed
- ❖ Proceeds in water
- ❖ Much higher syn selectivity than other Lewis acid catalysed Mukaiyama aldol reaction in water. Selectivity consistent with boron-enolate chemistry.

Aldol reactions

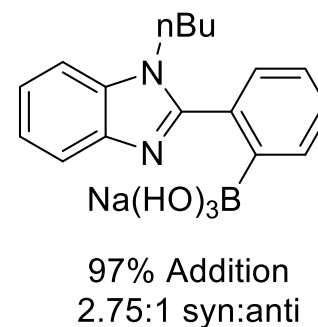
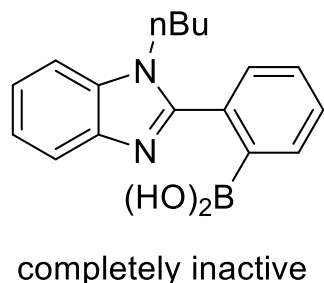
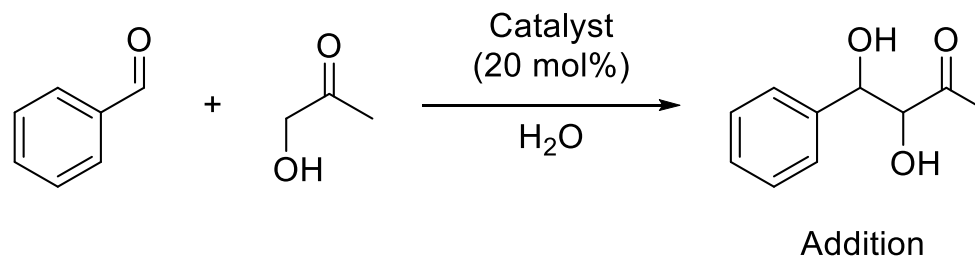


The acid is thought to catalyse the transformation of 1 to 3 and 5 to 1

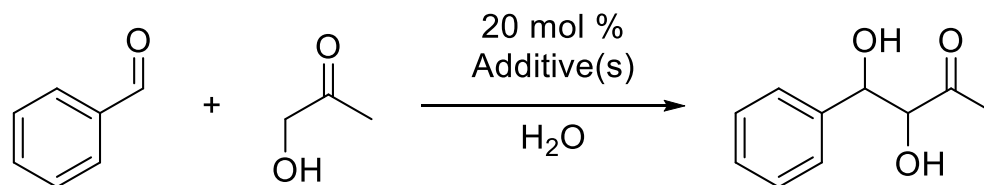
Mori, Y., Manabe, K., Kobayashi, S. *Angew. Chem. Int. Ed.*, **2001**, *40*, 2815-2818

Aldol reactions

- ❖ Boronic catalysed aldol-reactions:
Catalytic C-C bond formation in aqueous media



Aldol reactions



Addition

49% (2.3 : 1)

16M NaOH

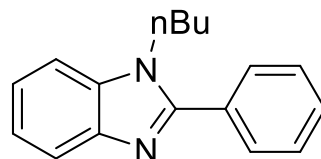
PhB(OH)₂

none

16M NaOH + PhB(OH)₂

none

16M NaOH + PhB(OH)₂ and

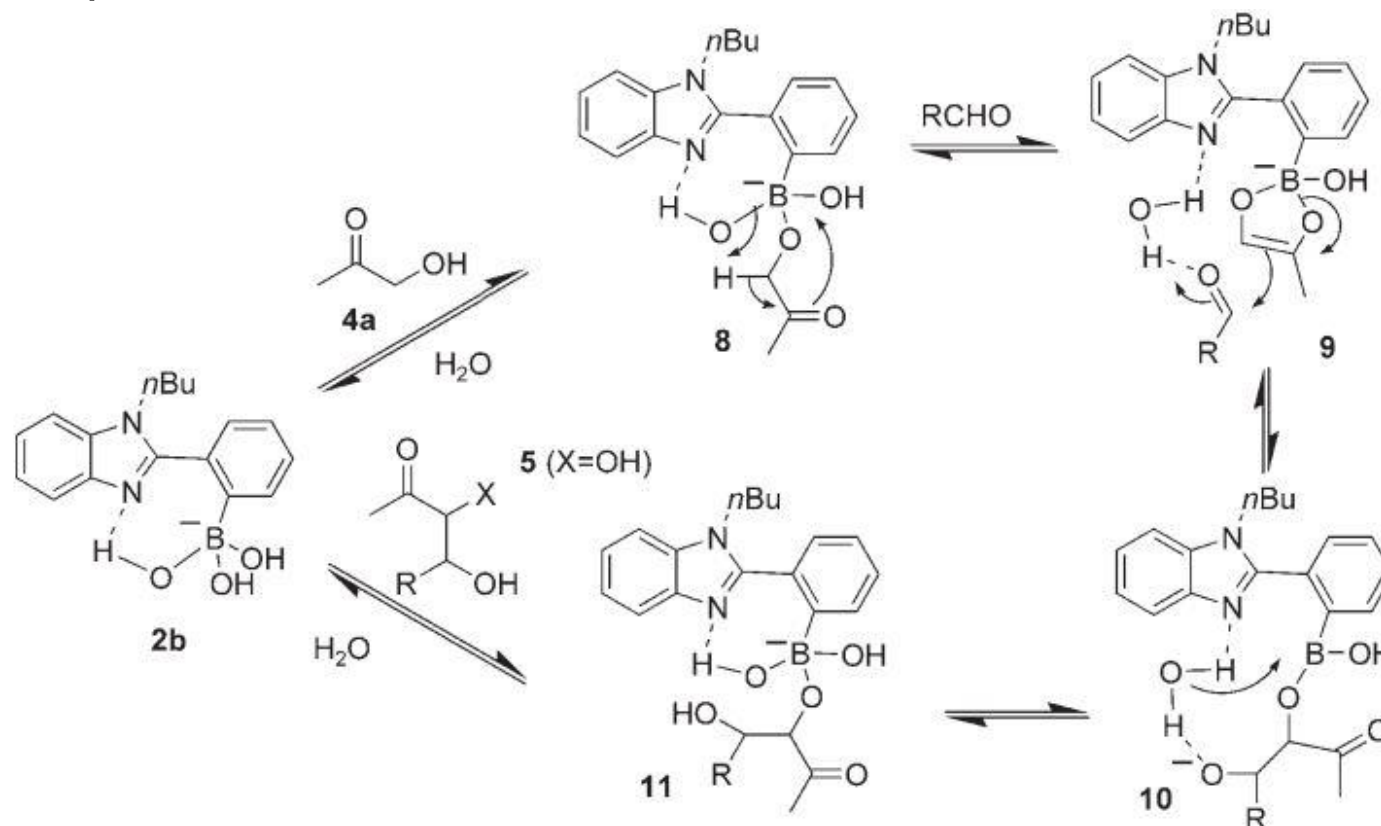


none

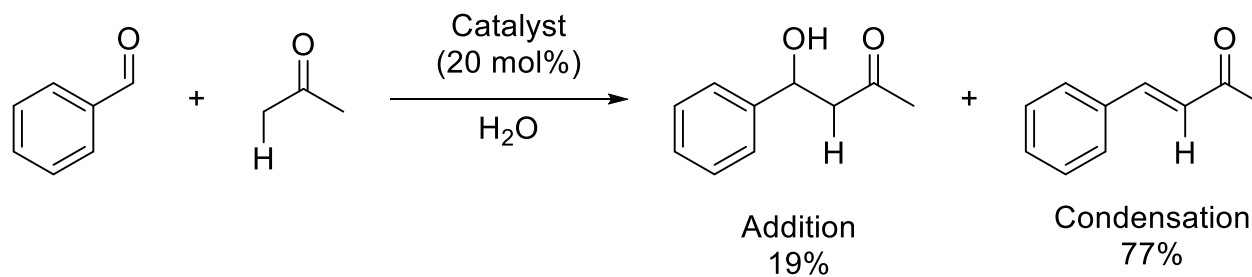
Also kinetic studies suggested that the catalyst does not act as a source of hydroxy ions

Aldol reactions

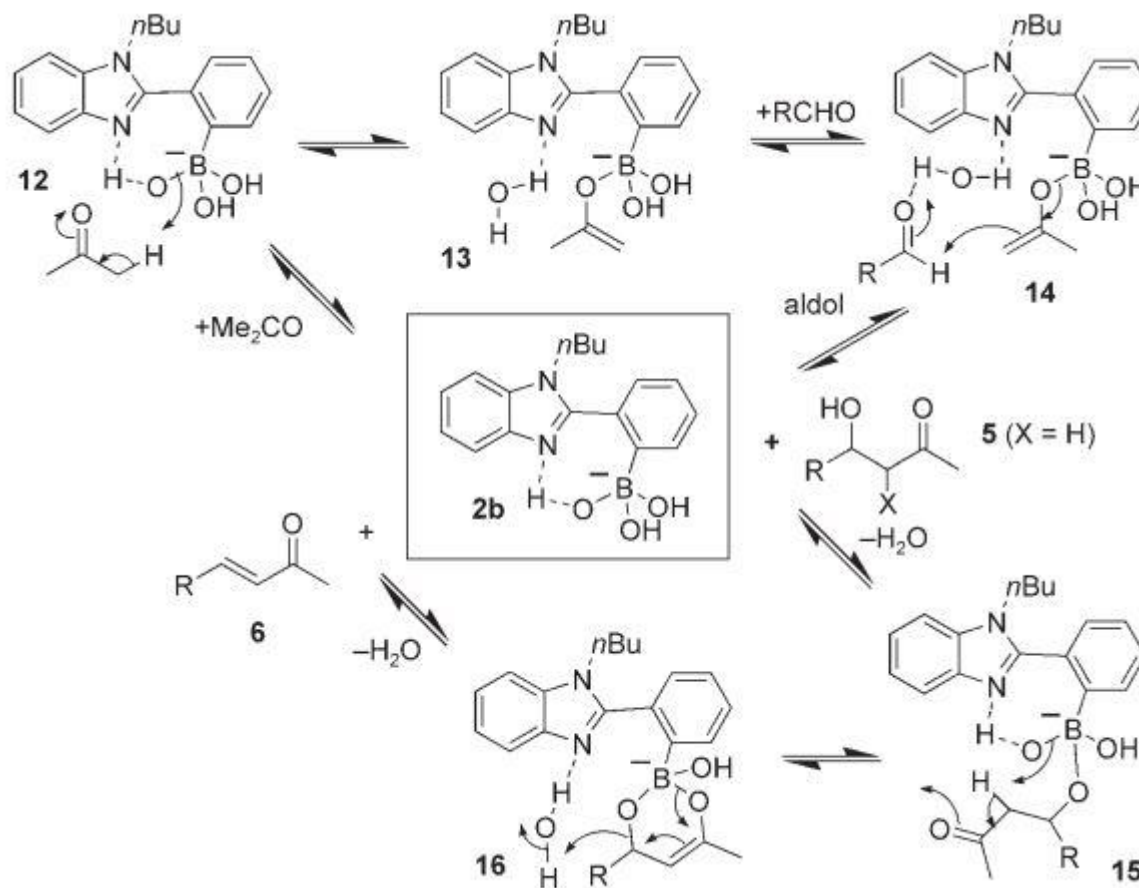
❖ Proposed mechanism:



Aldol reactions

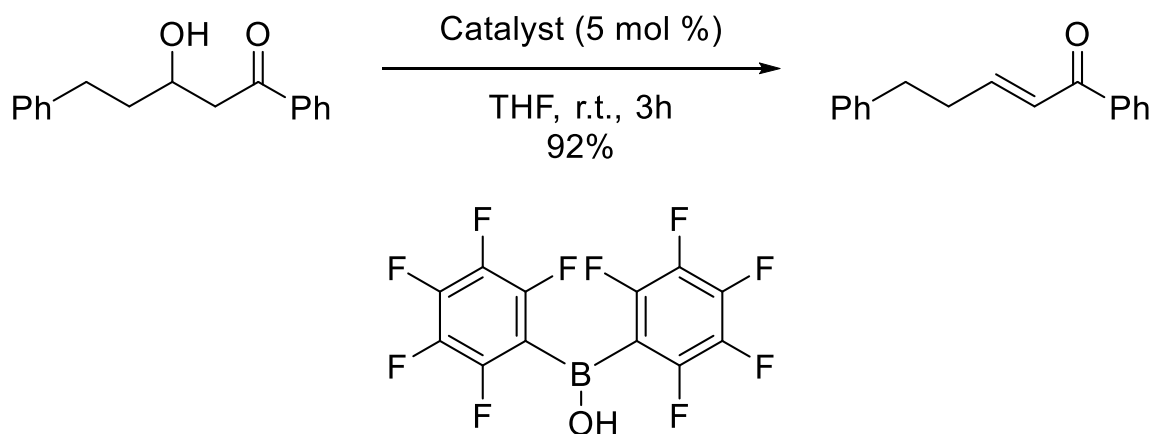


Aldol reactions



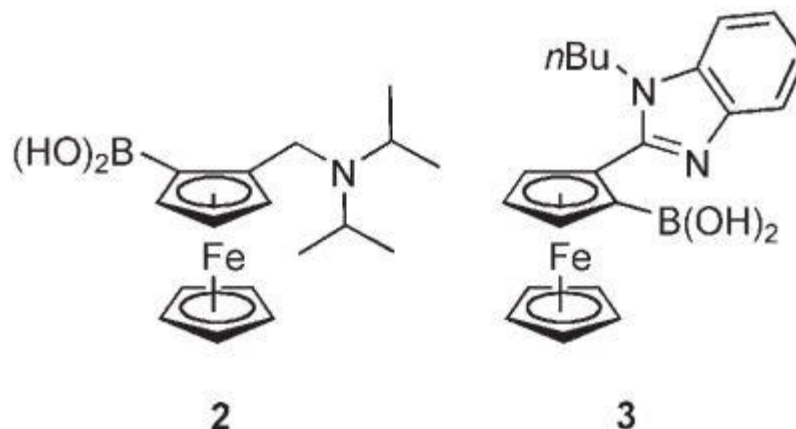
Aldol reactions

- ❖ Only the boronic acid catalyse this reaction
- ❖ While the borinic acid is an ineffective catalyst for the aldol addition, it catalyses the condensation (even more efficient):

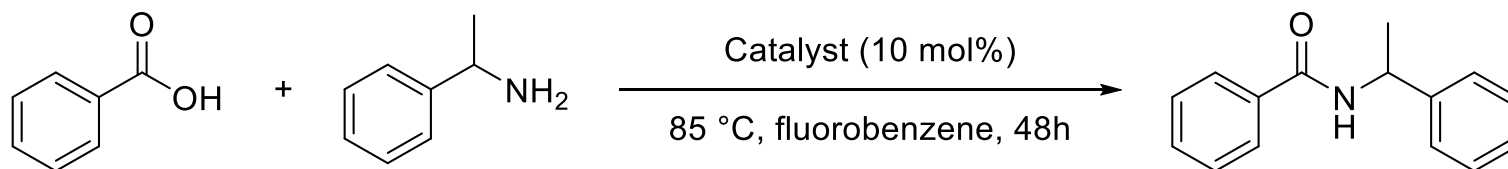


Amide synthesis

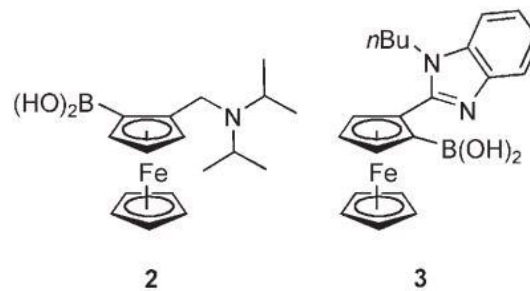
- ❖ First example of asymmetric induction in direct amide synthesis (besides from enzymes)
- ❖ Direct amide synthesis at moderate temperature (85 ° C)



Amide synthesis



Entry	Catalyst	Conversion	ee %
1	none	-	-
2	2	38	0
3	3	21	41 (S)



Amide synthesis

- ❖ Rather low yield, not fully controllable stereochemistry (but proof of principle)
- ❖ Degradation of the catalyst was observed, which might also have led to degradation of ee, because boric acid might catalyse the reaction as well (efficient catalyst at higher temperatures).

Conclusion

- ❖ A broad spectrum of transformations can be catalysed by covalent organoboron interactions
- ❖ The catalysts are most of the time quite selective for one substrate
- ❖ The reactions can sometimes be performed in water

- ❖ One catalyst does often much better than others – predictability for catalyst-choice?
- ❖ Some questions about the mechanisms remain – difficult to improve catalyst