Selective Epimerization of Sugars Inspired by Radical-Based Synthetic Mechanisms

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Literature Seminar

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2022/6/9

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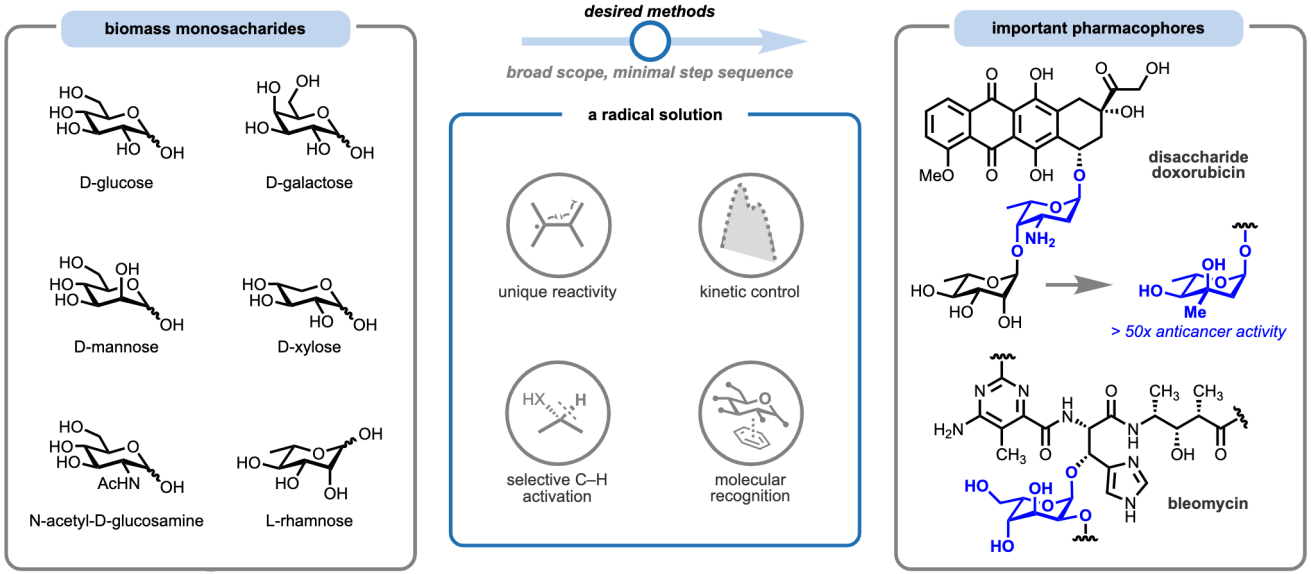
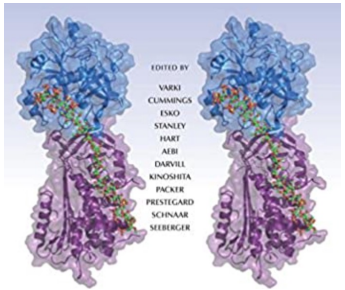
Importance of Synthesizing Rare Sugars



Carolyn E. Suh *et al.* *ACS Chem.* **2021**, *16, 1814*−1828.



Rare Sugars

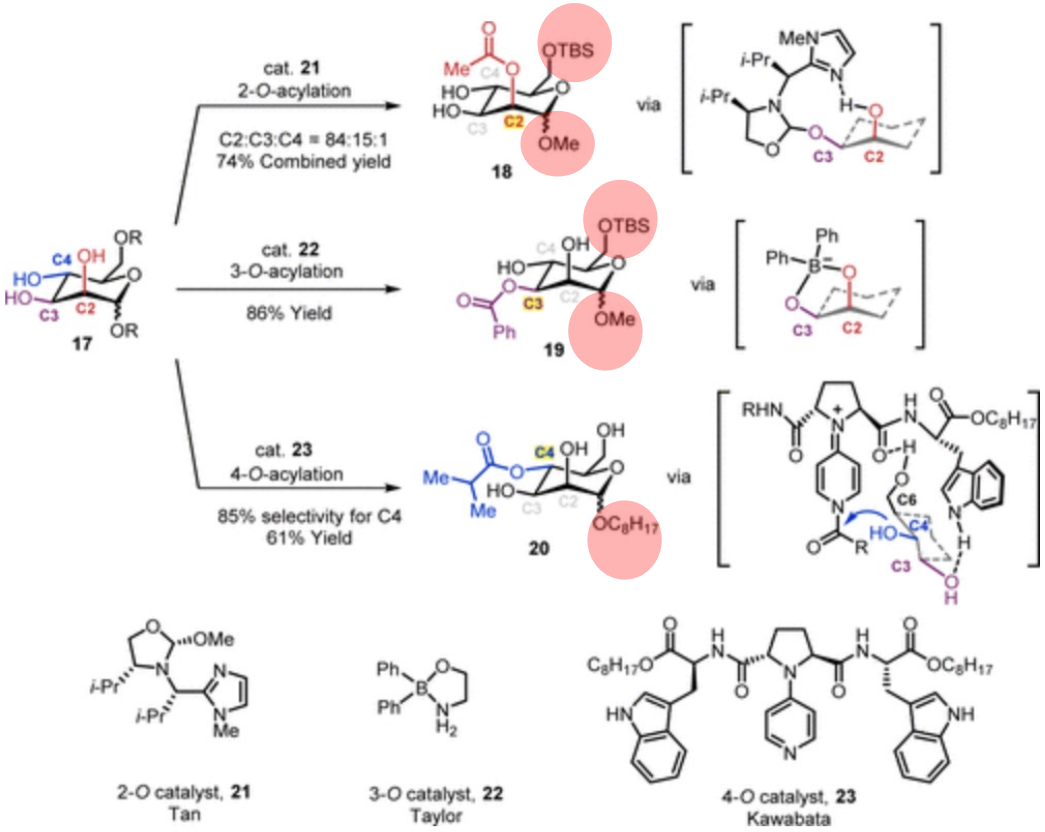
Glycosylated natural products
and
Pharmaceuticals

Synthesis Using Protecting Groups

✓ Previous research using **protecting groups**

The use of **protecting groups** is unnecessary synthetic steps

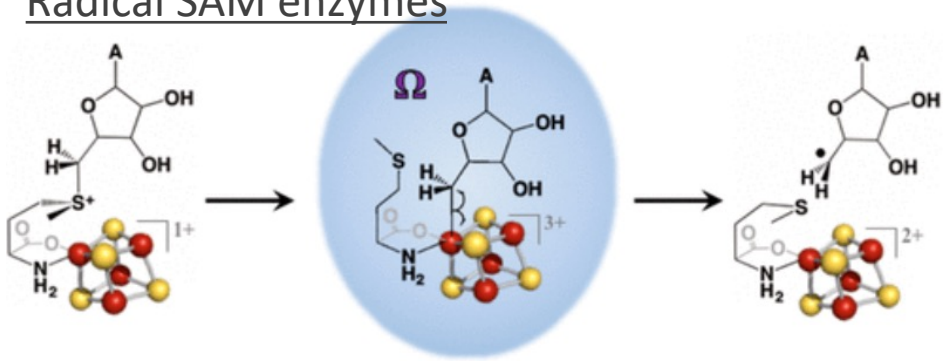
The direct transformation is efficient
But too difficult



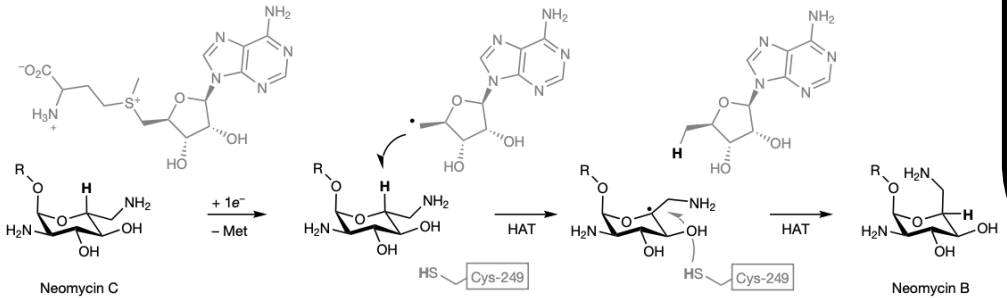
Huang, Z. *et al. Acc. Chem.* **2017**, *50(3), 465*−471.

SAM (Radical Enzymes)

Radical SAM enzymes



Mechanism



✓ Previous research using radical SAM enzymes

Microbial sugar biosynthesis has diverse **radical** pathways

Broderick, W. E. *et al. Acc. Chem.* **2018**, *51(11), 2611*−2619.

Advantages and Challenges of Radical Pathways

Advantages

✓ Reactivity at unconventional sites

✓ No unnecessary substrate activation

✓ Easy translation from enzymatic to synthetic systems

✓ Irreversible

Challenges

Reagents or harsh conditions

Prefunctionalization is necessary

Advantages and Challenges of Radical Pathways

Advantages

✓ Reactivity at unconventional sites

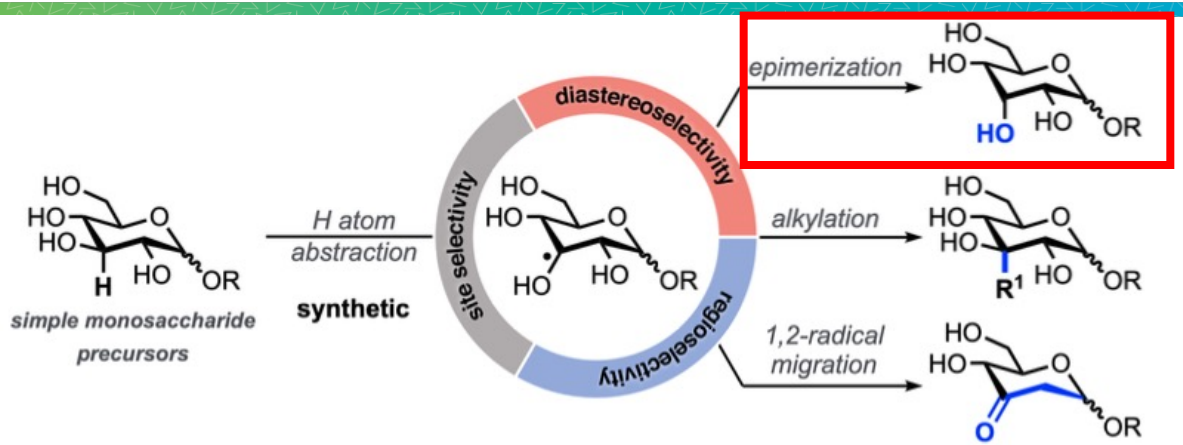
✓ No unnecessary substrate activation

✓ Easy translation from enzymatic to synthetic systems

✓ Irreversible

Photochemistry

Photochemistry



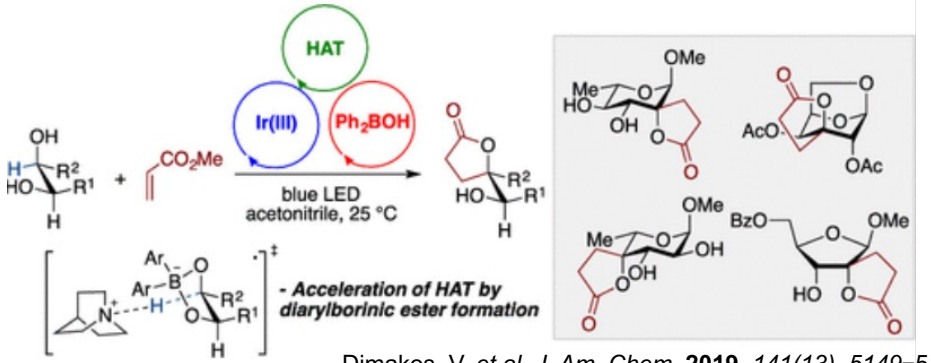
Carolyn E. Suh *et al. ACS Chem.* **2021**, *16, 1814*−1828.

Advantages of Photochemistry

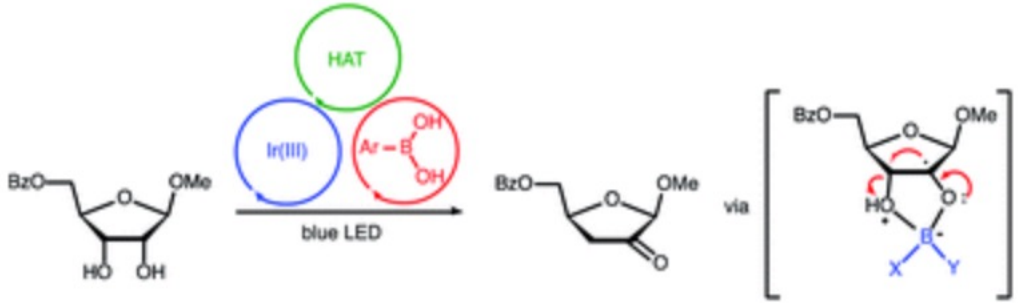
- ✓ No prefunctionalization
- ✓ Mild conditions
- ✓ Selective reaction
- ✓ No reagents
- ✓ Minimally Protecting groups

Epimerization is Possible ??

✓ Alkylation and 1,2-radicalmigration is possible



Dimakos, V. *et al. J. Am. Chem.* **2019**, *141(13), 5149*−5153.



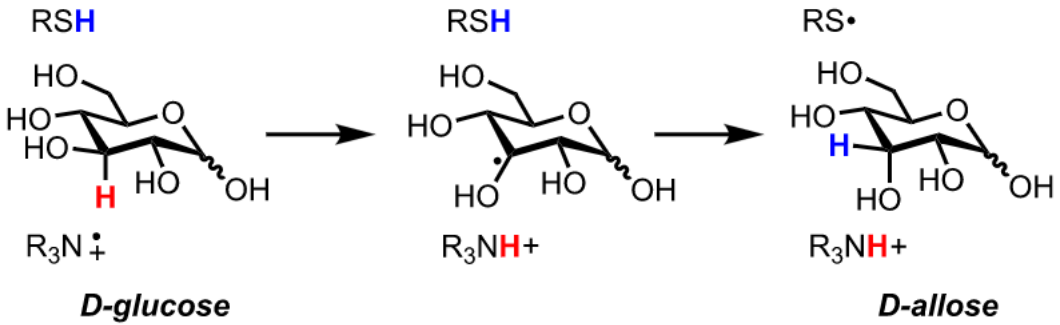
Dimakos, V. *et al. Chemical Science.* **2020**, *11(6), 1531*−1537.

Epimerization Is Possible ??

Contents

Epimerization via Kinetic Control

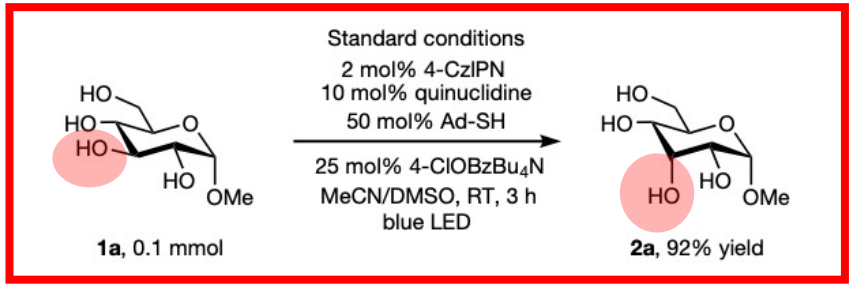
Synthesis of rare sugar isomers through site-selective epimerization



Yong Wang *et al. Nature.* **2020**, *578, 403*−408.

- ✓ Kinetically controlled mechanism
- ✓ High selectivity
- ✓ Single step
- ✓ High yield
- ✓ Site-selective

Condition Optimization for Sugar Epimerization



Entry	Variation from standard conditions	Percentage yield (% RSM)
1	No photocatalyst	0% (99%)
2	No quinuclidine	< 1% (99%)
3	No thiol	0% (98%)
4	No blue LED	0% (99%)
5	No 4-ClOBzBu$_4$N	29% (71%)
6	Bu$_4$NOBz instead of 4-ClOBzBu$_4$N	63% (35%)
7	1% Ir[(dF(CF$_3$)ppy)$_2$(dtbpy)]PF$_6$ instead of 4-CzIPN	88% (2%)
8	DABCO instead of quinuclidine	0% (99%)
9	Hydrogen atom source[a]	0% (99%)

Yong Wang *et al. Nature.* **2020**, *578, 403*−408.

Optimized reaction !!

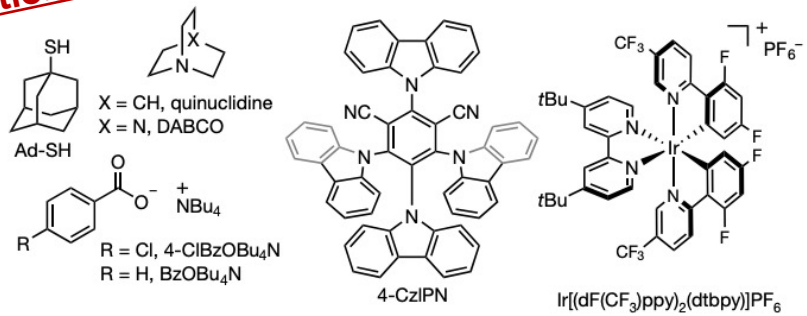


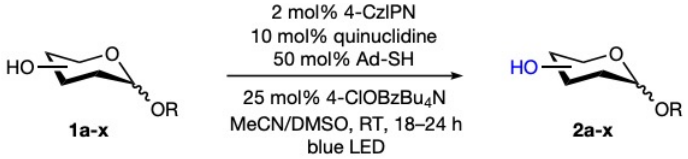
Fig. 2 | Epimerization of α-methylglucose to α-methylallose. Effect of changes to optimized reaction conditions. Yields determined by proton nuclear magnetic resonance (^{1}H NMR) analysis using 4-fluoroanisole as internal standard. RSM, recovered starting material; MeCN, acetonitrile; DMSO, dimethylsulfoxide; RT, room temperature; LED, light-emitting diode; Me, methyl; DABCO, 1,4-diazabicyclo[2,2,2]octane; Ad-SH, adamantane thiol; Bz, benzoyl. [a]See Supplementary Information sections 5 and 8 for full experimental details.

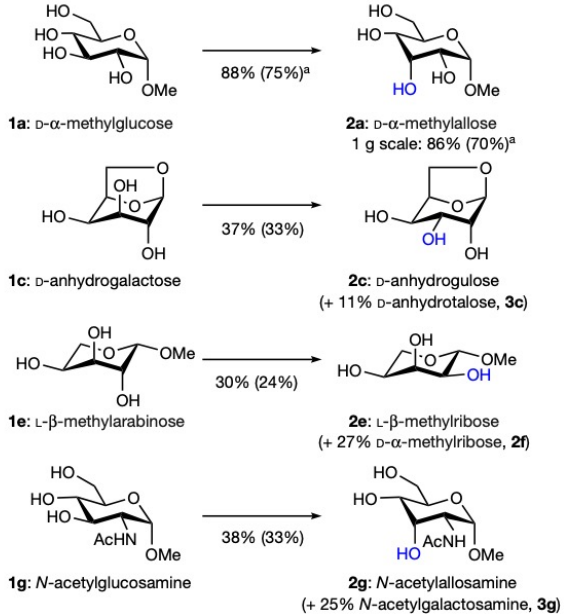
C3 selectivity

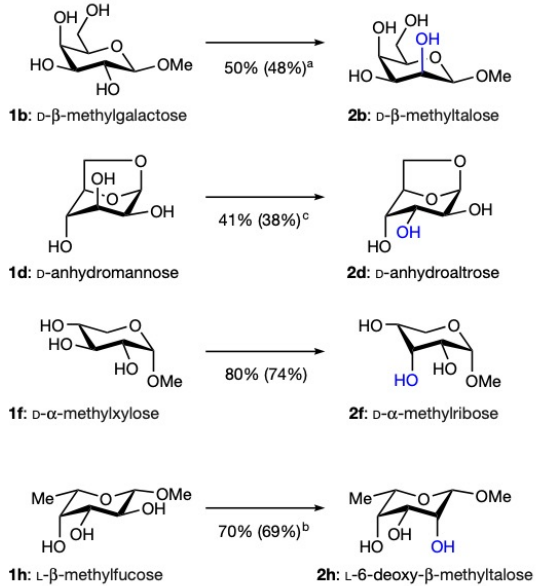
↑

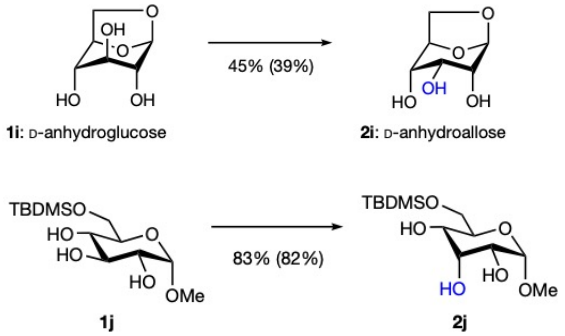
Hydrogen bond between 1a and the base

Substrate Scope of Protected Monosaccharides









This Strategy provides **rare sugars**

1f, 1e (pentose sugars)
→ C3 and C2 epimerization

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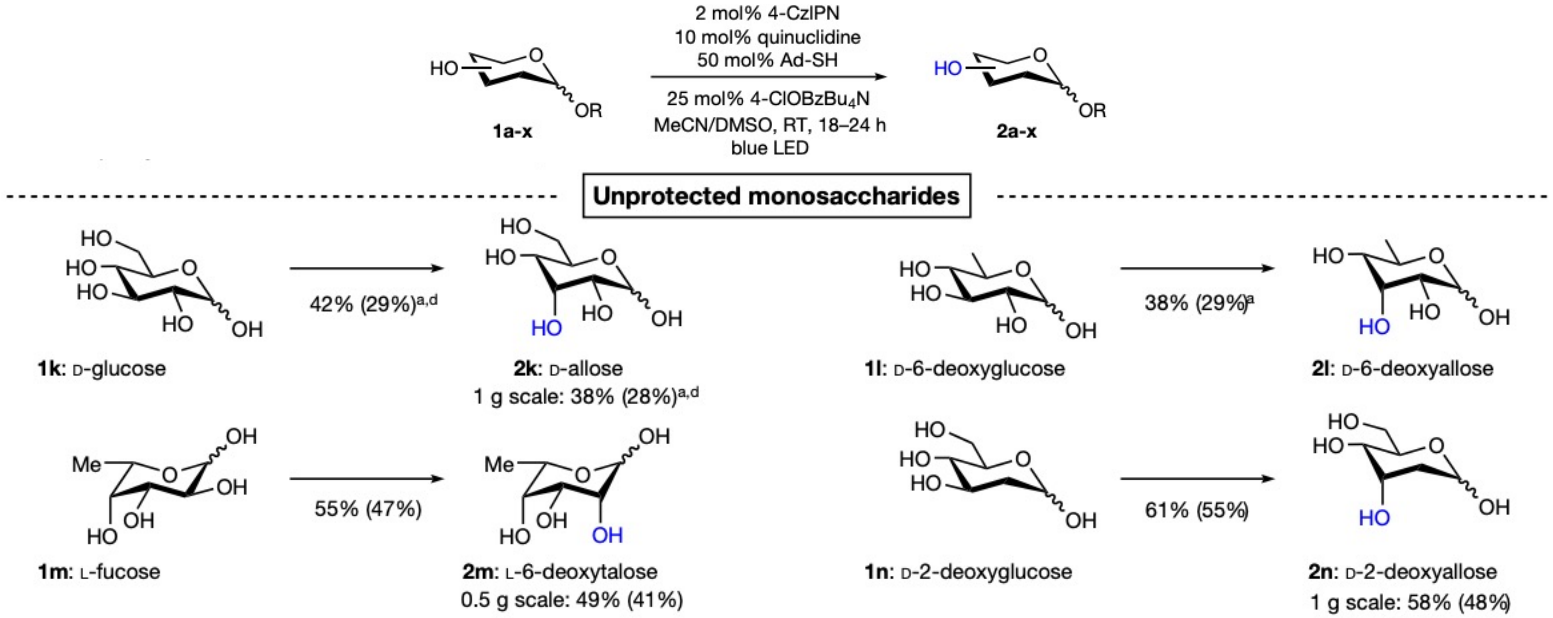
Substrate Scope of Unprotected Monosaccharides

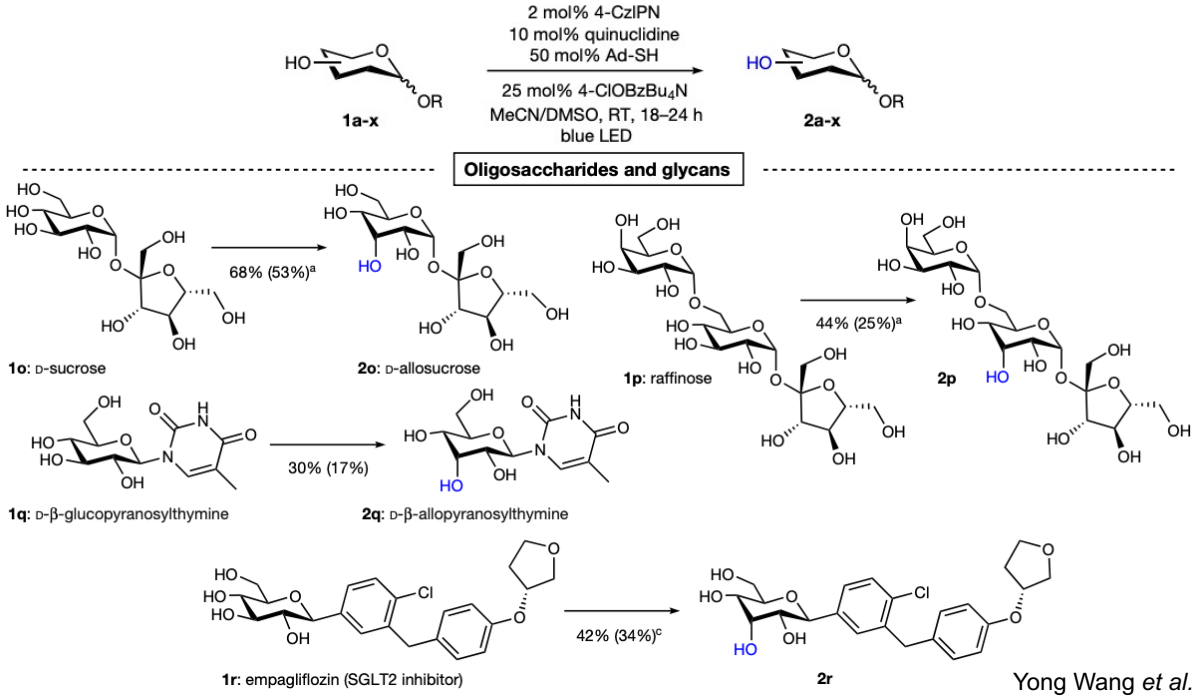


Epimerization of unprotected monosaccharides is successful

The only reaction of epimerization of 2-deoxygenated sugars

Yong Wang *et al. Nature.* **2020**, *578, 403*−408.

Substrate Scope of Oligosaccharides and Glycans



Yong Wang *et al. Nature.* **2020**, *578, 403*−408.

Epimerization of oligosaccharides and glycans is successful
→ **High selectivity**, **High functional group compatibility**

Mechanistic Studies of Sugar Epimerization

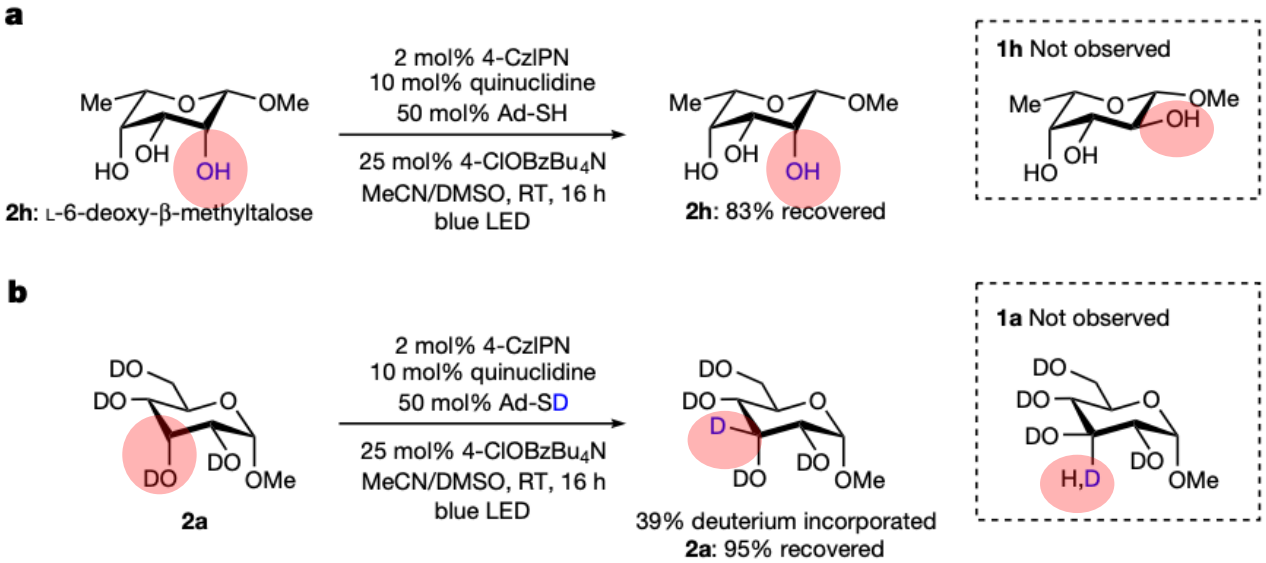
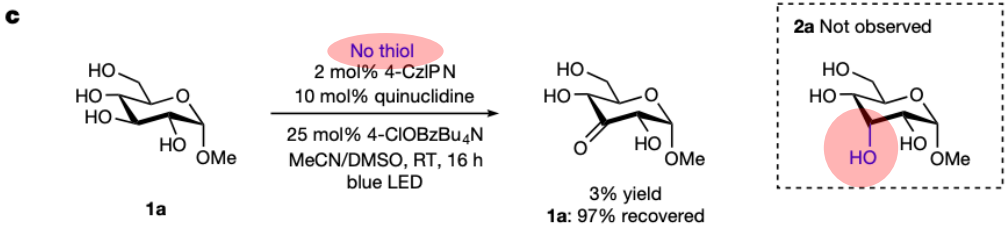


Fig. 4 | Mechanistic studies and proposed mechanism. a, No epimerization is observed when reaction products are re-subjected to the standard reaction conditions. **b**, Deuterium labelling studies indicate that the reaction product reacts under standard reaction conditions, but both epimers converge to a common product.

a : No reverse epimerization
b : Hydrogen-atom abstraction is occurred
↓
Not simple equilibrium control

Yong Wang *et al. Nature.* **2020**, *578, 403*−408.

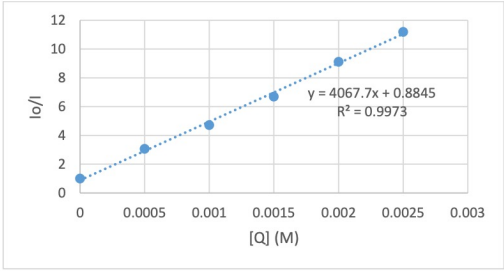
Mechanistic Studies of Photocatalyst and Quinuclidine



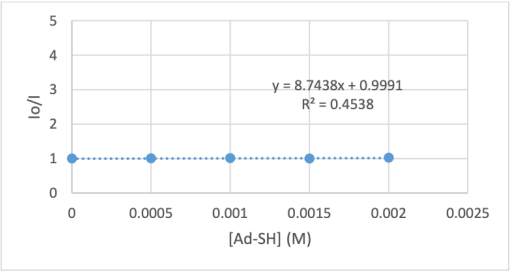
Graph:
Photocatalyst is quenched by quinuclidine
c :
No thiol → No epimerization

Photocatalyst and quinuclidine :
Sufficient for C-H cleavage (irreversible)
Insufficient for epimerization

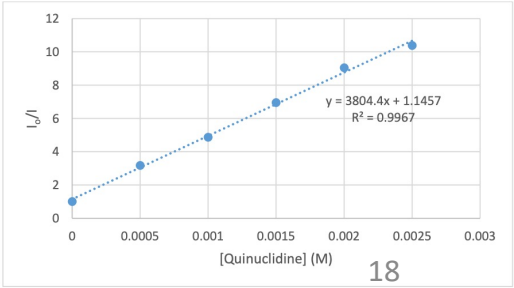
Quinuclidine



Ad-SH



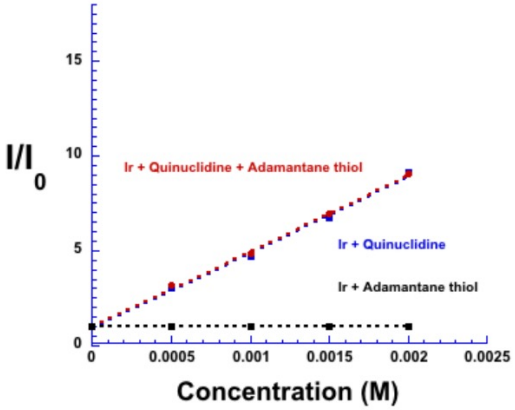
Constant Ad-SH
and
Variable Quinuclidine



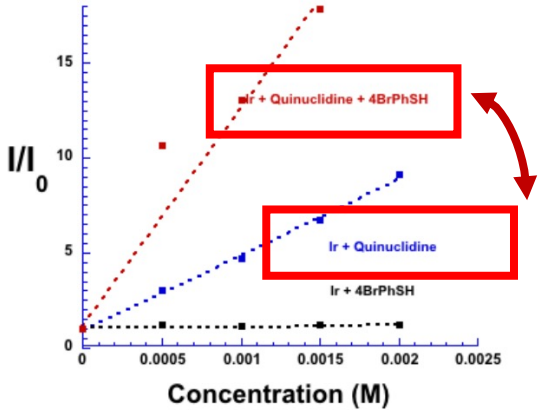
Yong Wang *et al. Nature.* **2020**, *578, 403*−408.

Mechanistic Studies of Thiol Co-Catalyst

A : Productive epimerization conditions
(Ad-SH)



B : Non-productive conditions
(4BrPhSH)



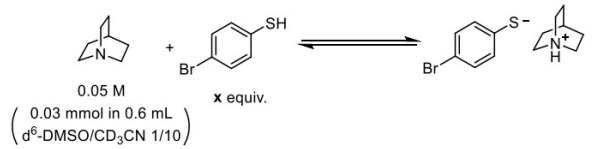
Yong Wang *et al. Nature.* **2020**, *578, 403*–408.

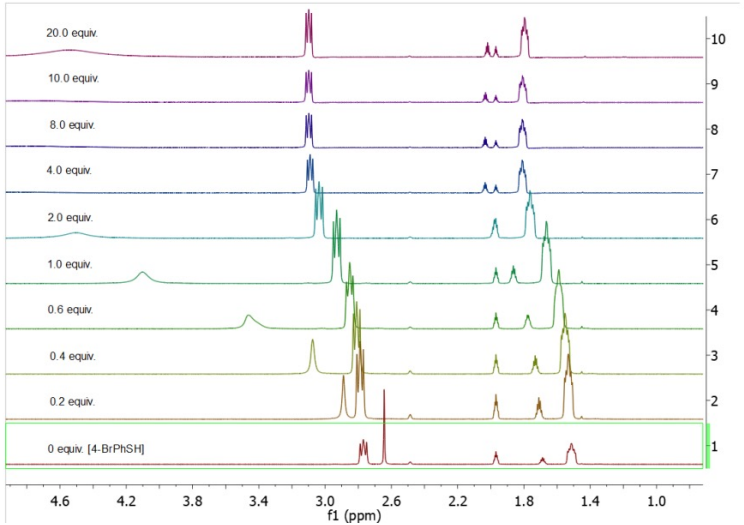
Fluorescence quenching (B) :
Quinuclidine + 4BrPhSH >> Only Quinuclidine
Why ??

Oxidation of thiolate enhanced fluorescence quenching ??

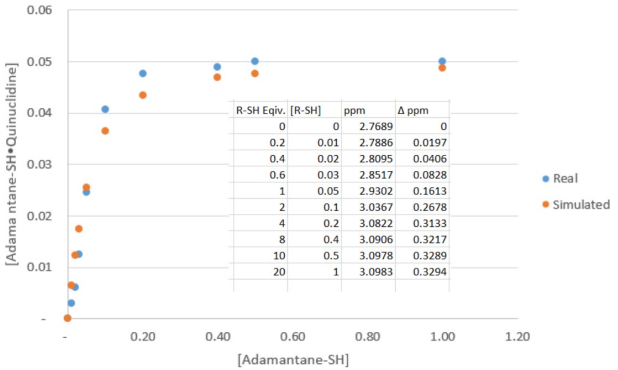
Interaction between Quinuclidine and Thiol

Equilibrium Constant between 4-BrPhSH and Quinuclidine





Equilibrium Binding Curve between 4-BrPhSH and Quinuclidine



R-SH Eqiv.	[R-SH]	ppm	Δ ppm
0	0	2.7689	0
0.2	0.01	2.7886	0.0197
0.4	0.02	2.8095	0.0406
0.6	0.03	2.8517	0.0828
1	0.05	2.9302	0.1613
2	0.1	3.0367	0.2678
4	0.2	3.0822	0.3133
8	0.4	3.0906	0.3217
10	0.5	3.0978	0.3289
20	1	3.0983	0.3294

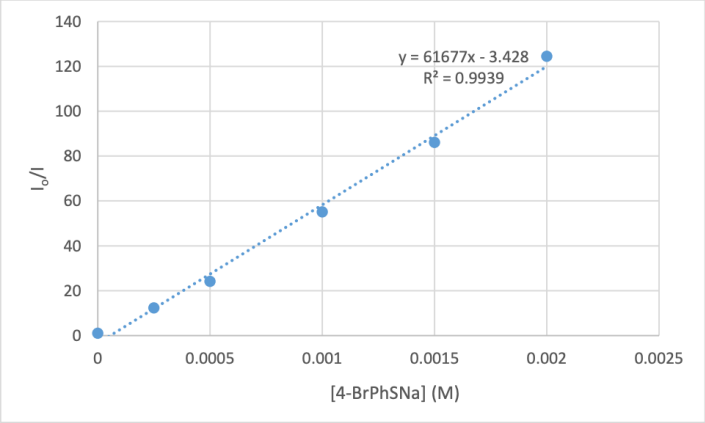
Equilibrium interaction between 4-BrPhSH and Quinuclidine

Quinuclidine deprotonate acidic thiols to form **thiolate salts**

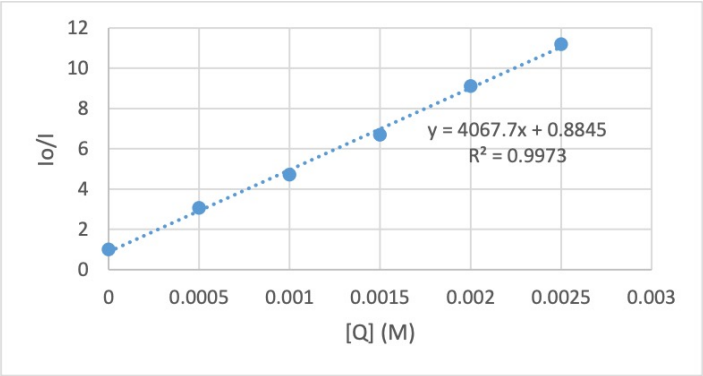
Yong Wang *et al. Nature.* **2020**, *578, 403*−408.

Interaction between Quinuclidine and Thiol

4-BrPhSNa



Quinuclidine



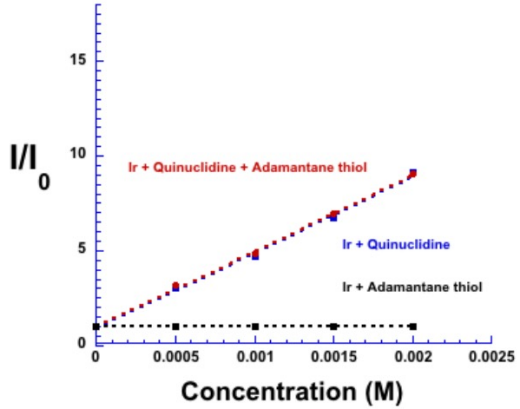
Yong Wang *et al. Nature.* **2020**, *578, 403*−408.

Fluorescence quenching :
4-BrPhSHNa > Only Quinuclidine

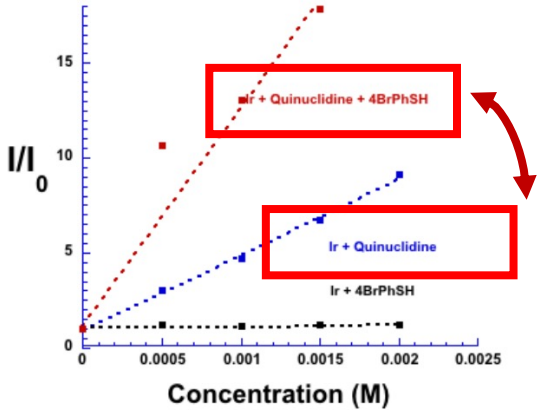
Oxidation of thiolate enhanced fluorescence quenching

Mechanistic Studies of Thiol Co-Catalyst

A : Productive epimerization conditions
(Ad-SH)



B : Non-productive conditions
(4BrPhSH)



Yong Wang *et al. Nature.* **2020**, *578, 403*−408.

A (Ad-SH) : Sufficient acidic

Quenching of the photo-catalyst :
Thiol < Quinuclidine

↓

C-H cleavage

B (4BrPhSH) : Too acidic

Quinuclidine deprotonate acidic thiols to form **thiolate salt**

↓

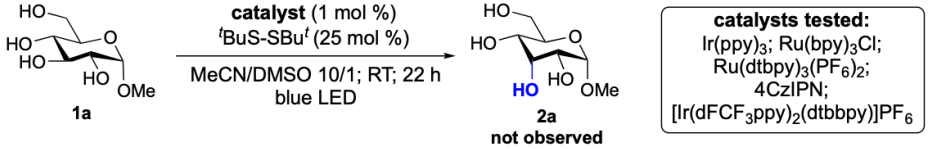
Quenching of the photo-catalyst :
Thiolate salt > Quinuclidine

↓

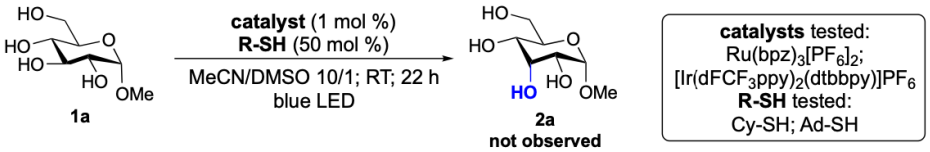
Formation of thiyl radicals

Mechanistic Studies of Thiol Co-Catalyst

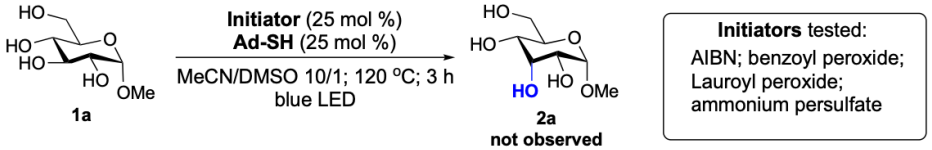
a. Epimerization of 1a under Photo-Reductive Conditions through the In-Situ Generation of Thiyl Radical [18]



b. Epimerization of 1a under Photo-Oxidative Conditions through the In-Situ Generation of Thiyl Radical [19]



c. Epimerization of 1a under Thermal Conditions [20,21]



Thiyl radical
≠ hydrogen-atom abstraction

Thiol co-catalyst
= irreversible HAT to sugar radical
(Second step)

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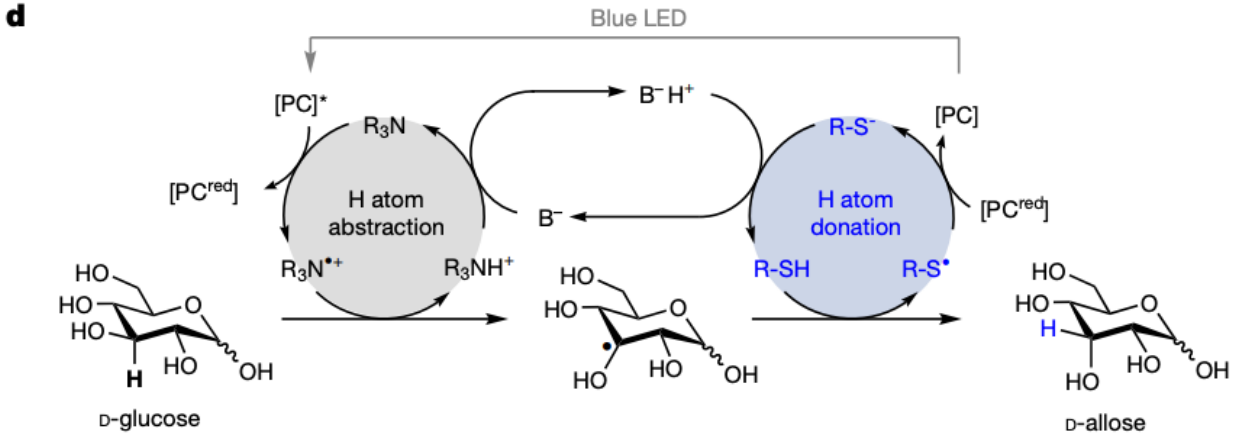
Mechanism of Sugar Epimerization



Yong Wang *et al. Nature.* **2020**, *578, 403*−408.

2 steps
1 : Hydrogen-atom abstraction by quinuclidinium radical cation
2 : HAT from thiol

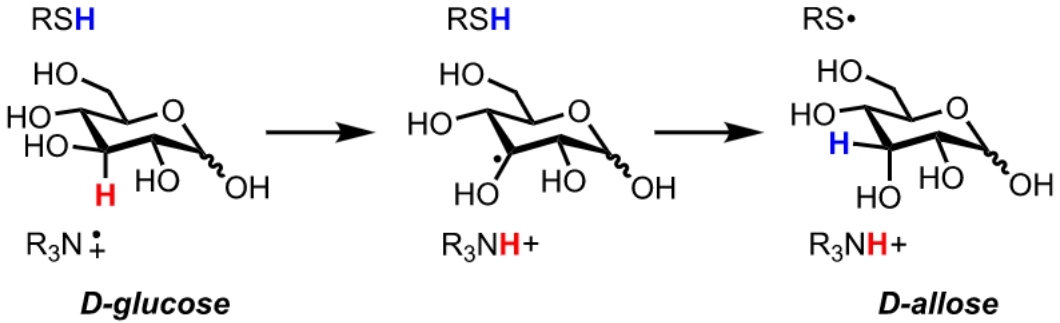
Kinetically controlled

↑

Irreversible and diastereoselective HAT from thiol

Short Summary

Synthesis of rare sugar isomers through site-selective epimerization



D-glucose ***D-allose***

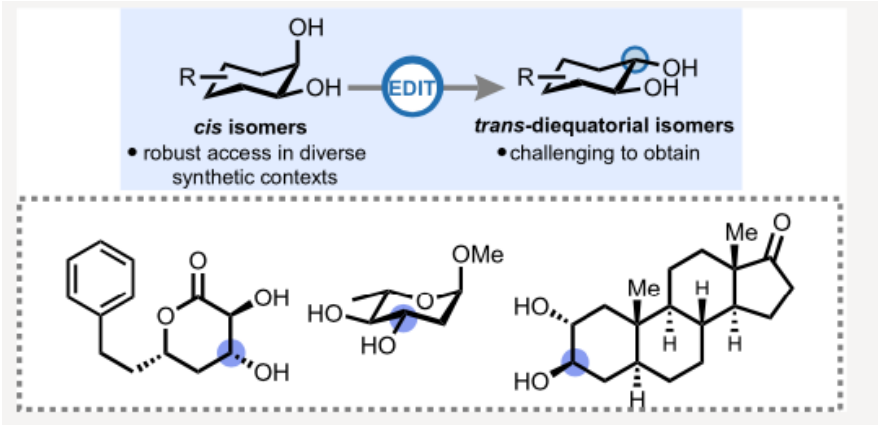
Yong Wang *et al. Nature.* **2020**, *578, 403*−408.

- ✓ Kinetic control
- ✓ Sequential steps of HAT
- ✓ HAT mediated by two distinct catalysts
- ✓ Concise and potentially extensive access to rare sugars

Contents

Epimerization via Thermodynamic Control

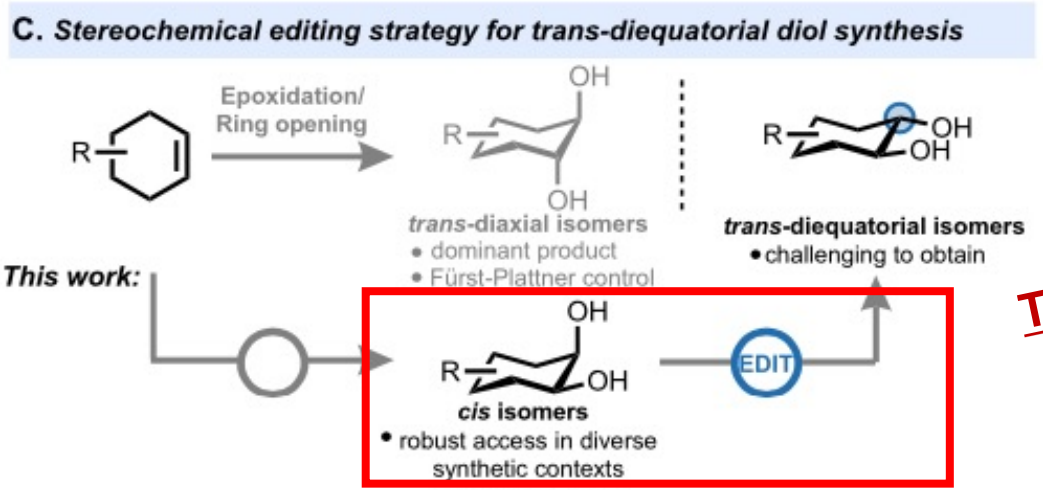
A Change from Kinetic to Thermodynamic Control Enables Trans-Selective Stereochemical Editing of Vicinal Diols



Yu-An Zhang *et al. J. Am. Chem.* **2022**, *144*, *599*−605.

- ✓ Ph_3SiSH as a HAT catalyst
- ✓ Chemoselective
- ✓ Thermodynamic
- ✓ Mild condition
- ✓ Broadly functional group tolerant
- ✓ Concise access to trans-diol products

Problem Presentation



This reaction!!

Yu-An Zhang *et al. J. Am. Chem.* **2022**, *144*, *599*−605.

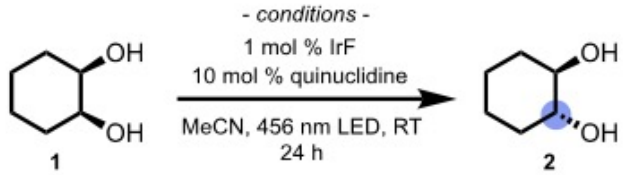
The access to cis- and trans-diaxial isomers
→ Many methods

The access to trans-diequatorial isomers
→ Limited

This research :
Catalytic reaction to access trans-diequatorial vicinal diols directly from cis-diols

Condition Optimization

A



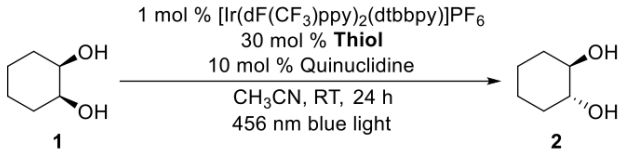
Entry	conditions	Yield 2 *(RSM)*	Final ratio *(trans/cis)*
1	30 mol % **AdSH**	38% (51%)	1.0 : **1.3**
2	30 mol % **Ph_3SiSH**	69% (22%)	**3.2** : 1.0
3	no IrF *-or-* no Blue LED *-or-* no thiol	N. R.	—

Figure 2. Reaction conditions optimization. (A) Isomerization of cyclohexanediol. Conditions: 0.1 mmol scale, 1 mol % IrF, 10 mol % quinuclidine, 30 mol % "thiol", 0.2 M CH_3CN, 23 °C, 24 h, 456 nm blue LED; yield of **2** and recovered **1** were determined by ^1H NMR with nitrobenzene as internal standard; IrF, $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$; RSM, recovered starting material; N.R., no reaction. (B) Reaction timecourse data carried out under Ph_3SiSH- and AdSH-catalyzed conditions.

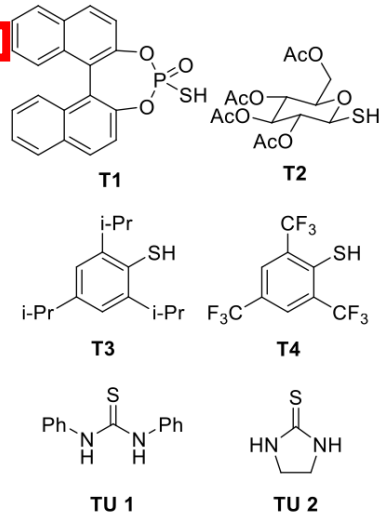
2: **Ph_3SiSH** is best thiol catalyst

3: No IrF, No Blue LED, No thiol
→ No reaction

Table S1. Effect of Different Thiol Catalysts in the Presence of Quinuclidine.



Thiol	Yield
Ph_3SiSH	69%
iPr_3SiSH	40%
$C_{10}H_{21}SH$	48%
Cyclohexanethiol	44%
AdSH	38%
*t*BuSH	33%
Thiobenzoic acid	26%
T1	12%
AcSH	20%
T2	25%
Methyl thioglycolate	4%
Ph_3CSH	0
Thiophenol	0
T3	17%
T4	0
Thiourea	2%
N,N'-Dimethylthiourea	0
TU1	2%
TU2	0



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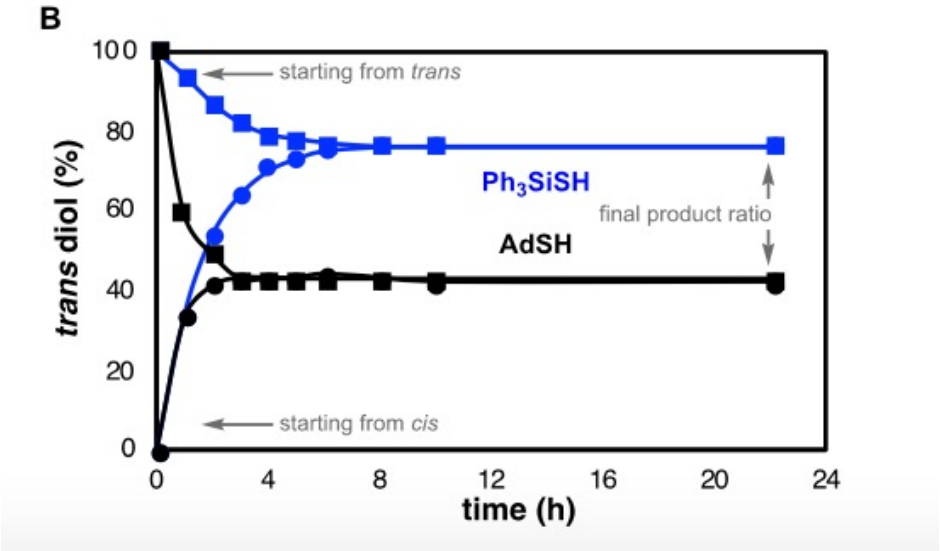
Reaction Timecourse



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The cis- / trans- isomer starting substrate
→ Same final product ratio

The thiol catalyst dictates
the final equilibrium product ratio

PhSiSH > Ad-SH

Comparison between Ph_3SiSH and Quinuclidine

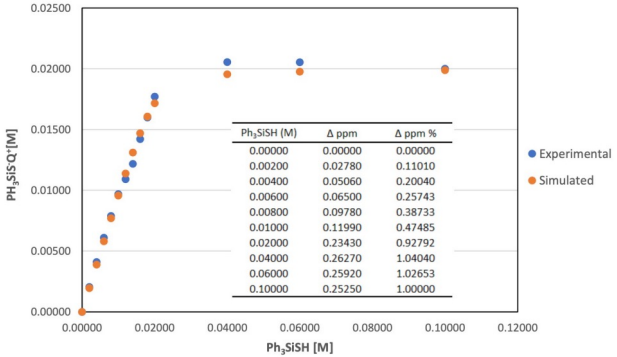

Figure S10. NMR titration of Ph_3SiSH and quinuclidine. Fitting based on the peak shift of C-H of quinuclidine, $K_{fit} = 2131\ M^{-1}$.

The interaction between Ph_3SiSH and Quinuclidine

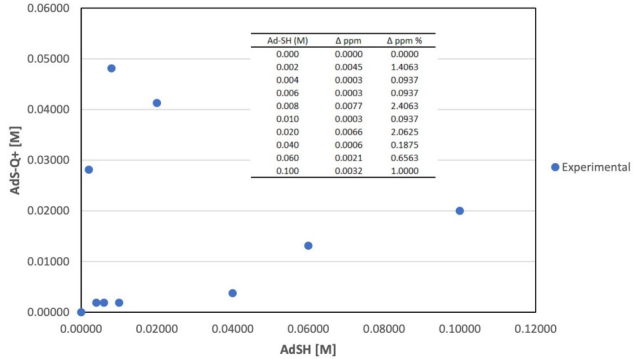

Figure S11. NMR titration of AdSH and quinuclidine reveals no significant binding interaction.

No interaction between Ad-SH and Quinuclidine

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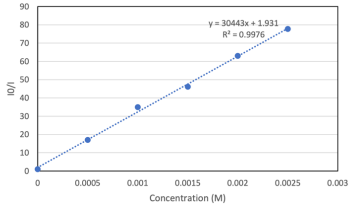
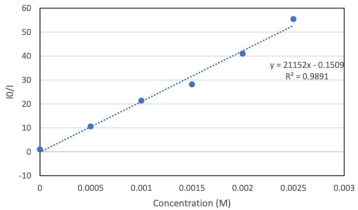
Comparison between Ph_3SiSH and Quinuclidine

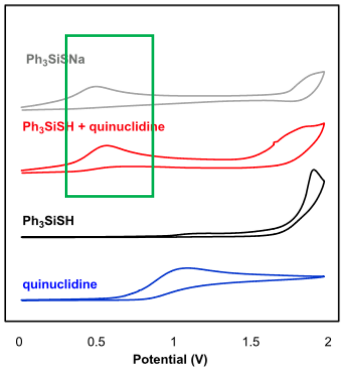
Ph_3SiSH

Ph_3SiSNa



Ph_3SiSH and DABCO (base)



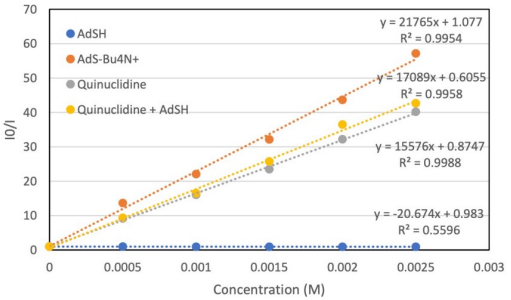


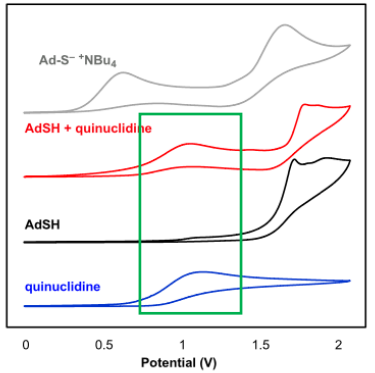
Single electron oxidation potential
Only Ph_3SiSNa = Quinuclidine + Ph_3SiSH

Fluorescence quenching
Thiolate salt > DABCO (base)

Quinuclidine → **Base**

Ad-SH





Single electron oxidation potential
Only Quinuclidine = Quinuclidine + AdSH

Fluorescence quenching
Thiolate < Quinuclidine

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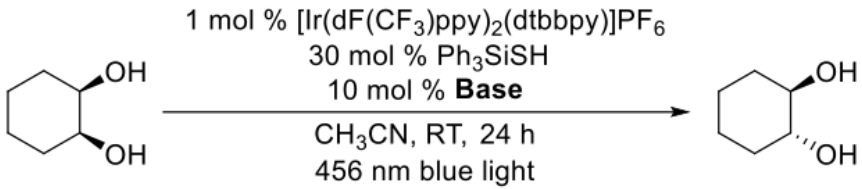
Comparison between Ph_3SiSH and Quinuclidine

Optimization of base (Ph_3SiSH)



Best base

Base	Yield
DABCO	69%
quinuclidine	69%
2,2,6,6-tetramethylpiperidine	69%
piperidine	60%
Et_3N	5%
diisopropylethylamine	9%
$NaHCO_3$	68%
Cs_2CO_3	7%
K_2CO_3	17%
TBAOAc	3%
$TBAH_2PO_4$	3%
no base	10-20%

Ph_3SiSH

Quinuclidine :
replaced with DABCO, NaHCO3, or other basic additives

↓

Not HAT

Ad-SH

Quinuclidine :
Not replaced with DABCO, NaHCO3, or other basic additives

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Mechanism of the Epimerization

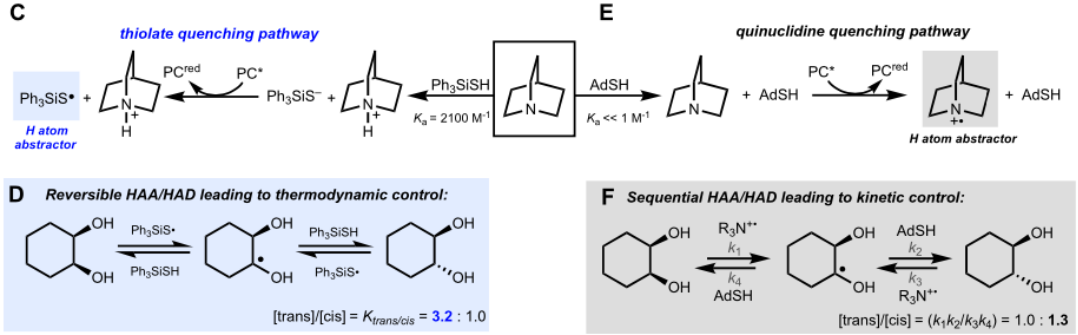

Figure 3. Mechanistic experiments and proposed mechanism. (A) Cyclic voltammetry studies interrogating Ph_3SiSH-catalyzed conditions. (B) Cyclic voltammetry studies interrogating AdSH-catalyzed conditions. Proposed (C) thiolate and (E) quinuclidine quenching mechanisms. (D) Reversible HAA/HAD leads to thermodynamic control. (F) Sequential HAA/HAD leads to kinetic control. See Supporting Information for full experimental details.

Ph_3SiSH

Ph_3SiSH :
Both H atom abstraction and donation

↓

The reaction is reversible

↓

Thermodynamic product !!

Ad-SH

Quinuclidine and Ad-SH:
Both H atom abstraction and donation

↓

Kinetic product !!

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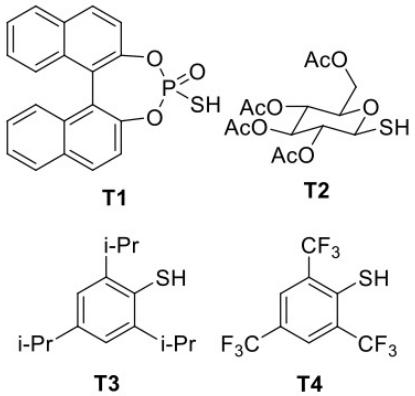
Optimization of Thiol in the Presence of DABCO

Optimization

Table S2. Effect of Different Thiol Catalysts in the Presence of DABCO.

Thiol	Yield
Ph_3SiSH	69%
iPr_3SiSH	53%
Thiobenzoic acid	15%
AcSH	18%
T1	12%
AdSH	0
T2	0
Thiophenol	0
T3	0
T4	0
$C_{10}H_{21}SH$	0
Cyclohexanethiol	0
*t*BuSH	0
Methyl thioglycolate	0
Ph_3CSH	0



Reaction timecourse

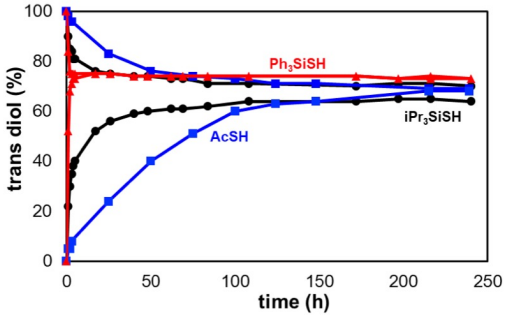


Figure S8. Timecourse studies results (0-240 h) using Ph_3SiSH, iPr_3SiSH and AcSH as the thiol catalysts.

Electron-rich / -deficient thiophenol derivatives
→ No reaction

Reaction speed : AcSH << Ph_3SiSH
Equilibrium ratio : iPr_3SiSH << Ph_3SiSH

↓

Ph_3SiSH is Best !!

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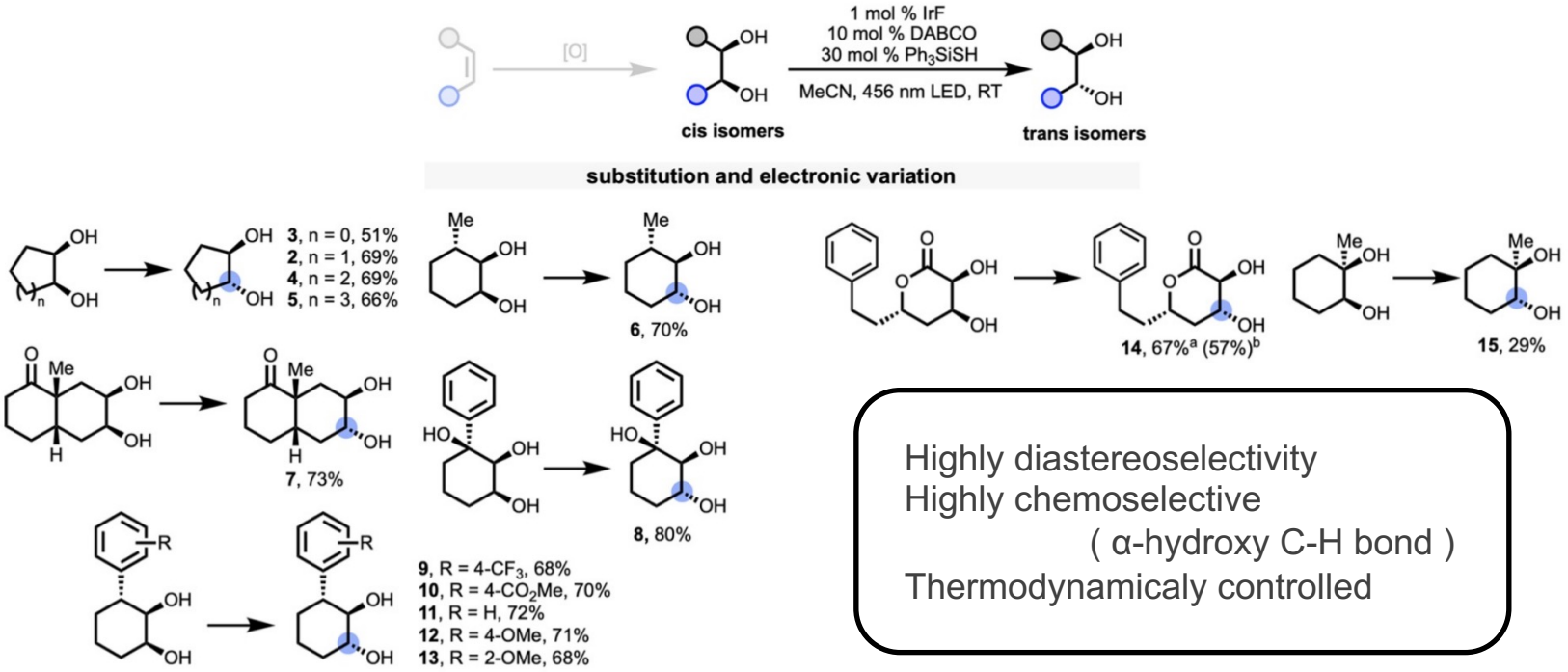
Substrate Scope



Highly diastereoselectivity
Highly chemoselective
(α-hydroxy C-H bond)
Thermodynamicaly controlled

Figure 4. Synthetic scope of *cis*/*trans* epimerization of vicinal diols. Standard conditions: 0.1−1.0 mmol scale, 1 mol % IrF, 10 mol % DABCO, 30 mol % Ph_3SiSH, 0.2 M MeCN, 23 °C, 24 h, 456 nm blue LED. Percent yields reported are isolated yields (average of two runs). See the Supporting Information for full experimental details. [a]Reaction was performed with 1 mol % IrF, 10 mol % quinuclidine, 50 mol % AdSH, 0.2 M MeCN, 23 °C, 24 h, 456 nm blue LED. [b]Reaction was performed under standard conditions. Number in parentheses is ^{1}H NMR yield with nitrobenzene as internal standard. [c]Reaction was performed with the *trans*-diaxial diol isomer **25** under standard conditions for 48 h. Number in parentheses is ^{1}H NMR yield with nitrobenzene as internal standard. [d]The identity of the major and minor diastereomer was not determined.

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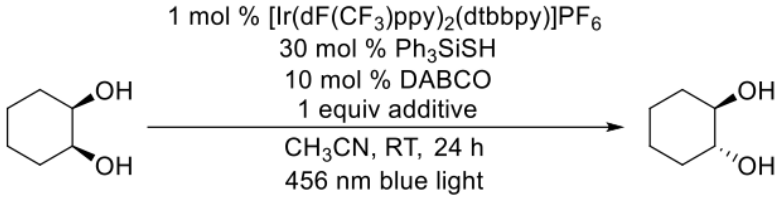
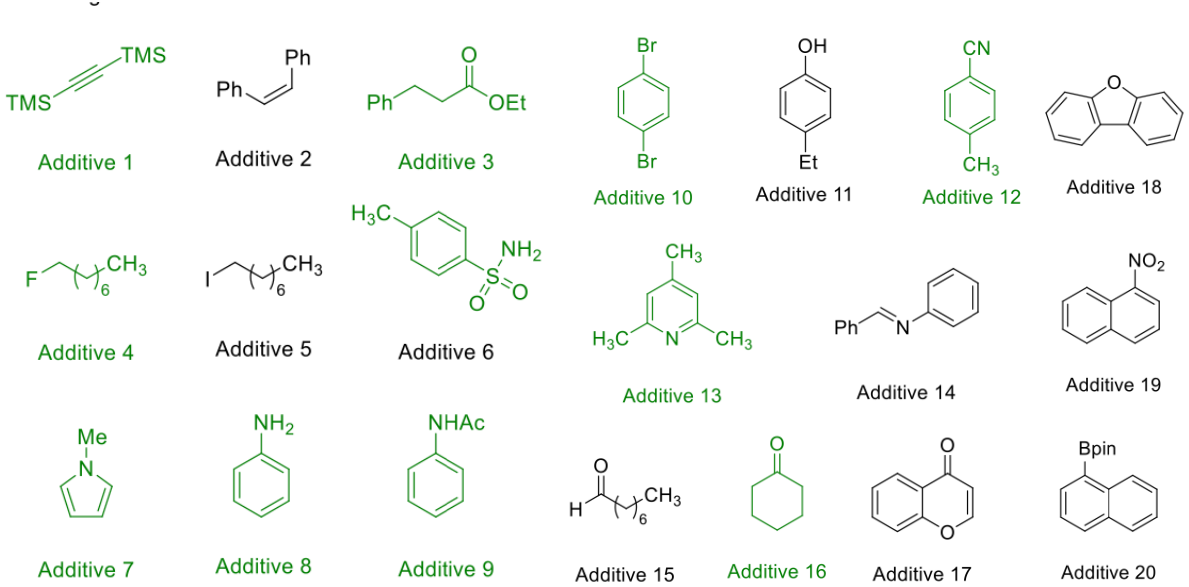
Functional Group Compatibility





Additive	Additive Recovery	Yield
Additive 1	100%	72%
Additive 2	28%	32%
Additive 3	87%	54%
Additive 4	92%	66%
Additive 5	45%	29%
Additive 6	100%	72%
Additive 7	72%	67%
Additive 8	91%	71%
Additive 9	94%	59%
Additive 10	100%	69%
Additive 11	97%	8%
Additive 12	97%	62%
Additive 13	97%	68%
Additive 14	72%	0%
Additive 15	3%	0%
Additive 16	100%	70%
Additive 17	82%	30%
Additive 18	100%	29%
Additive 19	63%	0%
Additive 20	97%	0%

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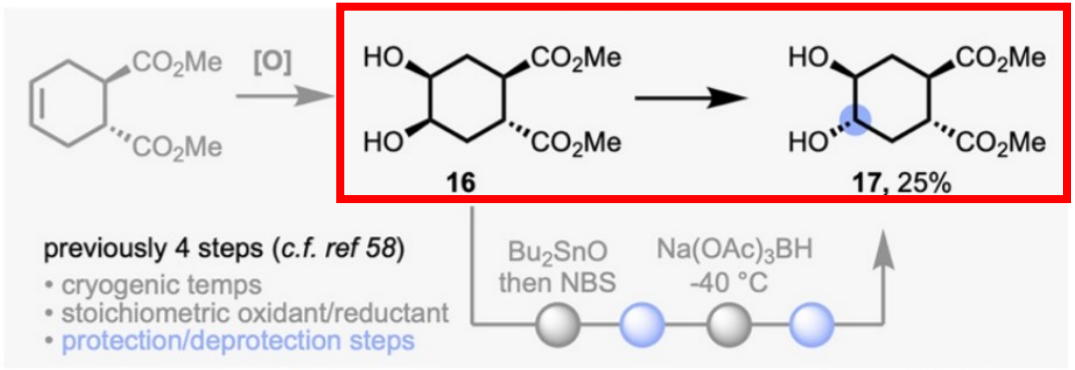
Comparison with Previous Synthetic Strategies



One Step !!

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Previous methods

✓ 4 steps
✓ Cryogenic temperature
✓ Stoichiometric oxidant / reductant
✓ Use of protecting groups

This method

✓ **Only 1** step
✓ **No** cryogenic temperature
✓ **No** stoichiometric oxidant / reductant
✓ **No** use of protecting groups

Substrate Scope of Sugars / Steroid

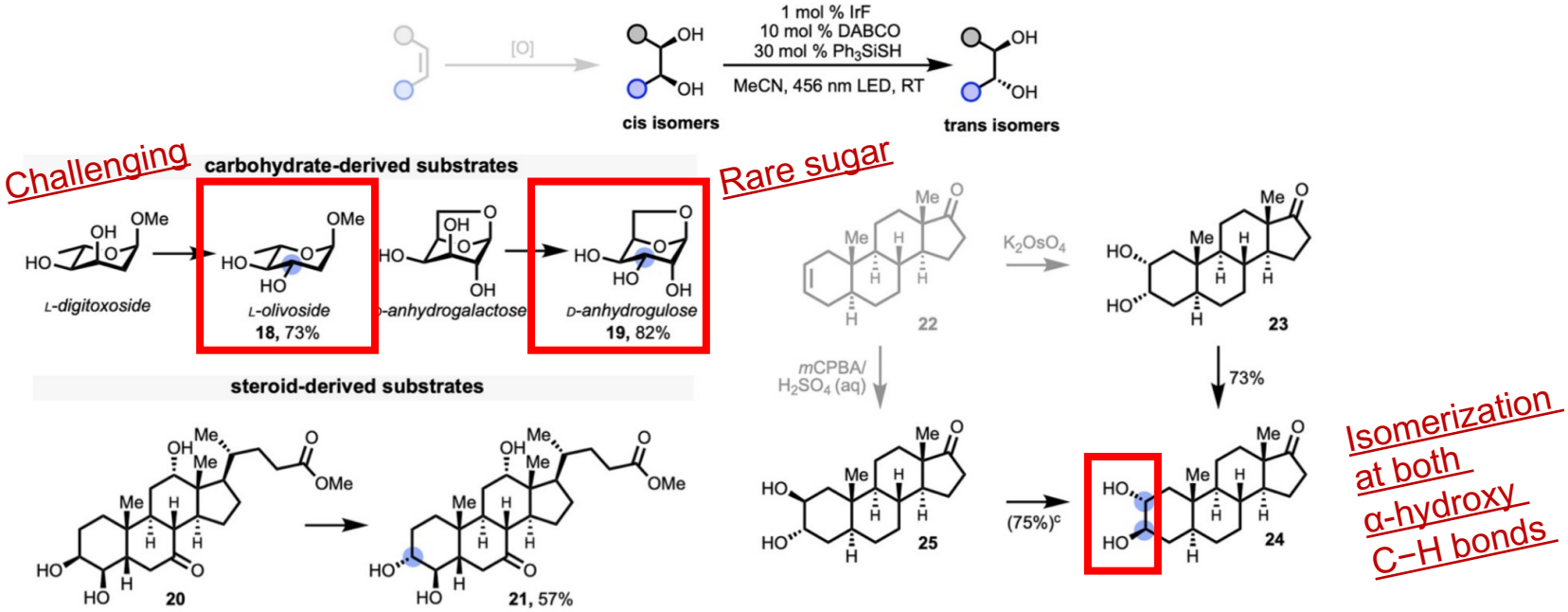

Figure 4. Synthetic scope of *cis*/*trans* epimerization of vicinal diols. Standard conditions: 0.1−1.0 mmol scale, 1 mol % IrF, 10 mol % DABCO, 30 mol % Ph_3SiSH, 0.2 M MeCN, 23 °C, 24 h, 456 nm blue LED. Percent yields reported are isolated yields (average of two runs). See the Supporting Information for full experimental details. [a]Reaction was performed with 1 mol % IrF, 10 mol % quinuclidine, 50 mol % AdSH, 0.2 M MeCN, 23 °C, 24 h, 456 nm blue LED. [b]Reaction was performed under standard conditions. Number in parentheses is ^{1}H NMR yield with nitrobenzene as internal standard. [c]Reaction was performed with the *trans*-diaxial diol isomer **25** under standard conditions for 48 h. Number in parentheses is ^{1}H NMR yield with nitrobenzene as internal standard. [d]The identity of the major and minor diastereomer was not determined.

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Substrate Scope of Cis-Diol Mixtures

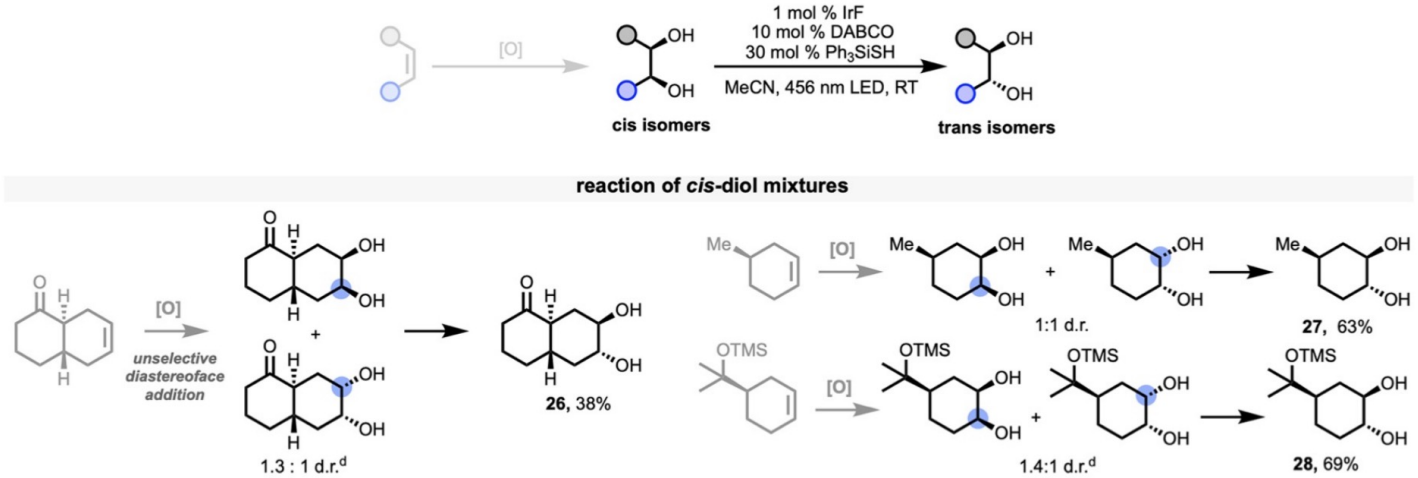

Figure 4. Synthetic scope of *cis*/*trans* epimerization of vicinal diols. Standard conditions: 0.1−1.0 mmol scale, 1 mol % IrF, 10 mol % DABCO, 30 mol % Ph_3SiSH, 0.2 M MeCN, 23 °C, 24 h, 456 nm blue LED. Percent yields reported are isolated yields (average of two runs). See the Supporting Information for full experimental details. [a]Reaction was performed with 1 mol % IrF, 10 mol % quinuclidine, 50 mol % AdSH, 0.2 M MeCN, 23 °C, 24 h, 456 nm blue LED. [b]Reaction was performed under standard conditions. Number in parentheses is ^{1}H NMR yield with nitrobenzene as internal standard. [c]Reaction was performed with the *trans*-diaxial diol isomer **25** under standard conditions for 48 h. Number in parentheses is ^{1}H NMR yield with nitrobenzene as internal standard. [d]The identity of the major and minor diastereomer was not determined.

The reaction from mixtures of cis-diols to the only 1 desired trans-diequatorial diastereomer is successful

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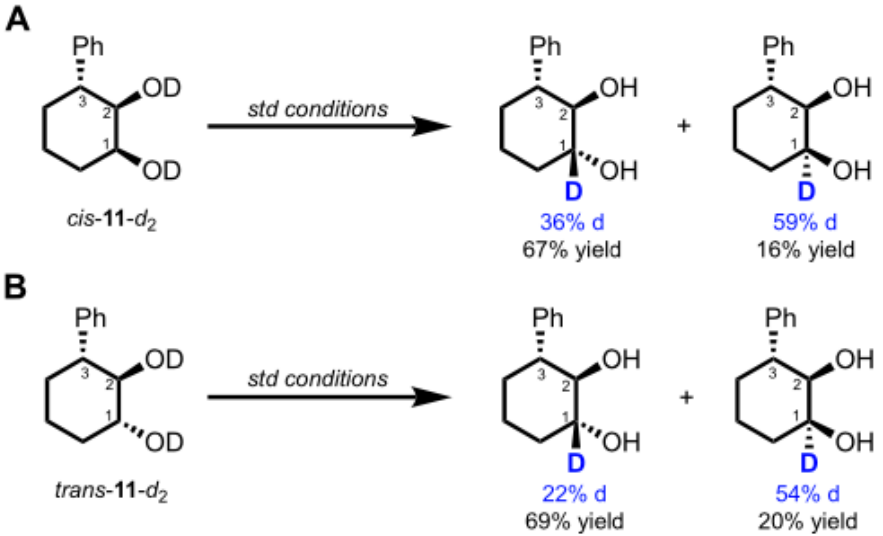
Selectivity of α-hydroxy C-H Bond



Calc. BDE (kcal/mol)	
C_1-H	93.4
C_2-H	92.8
C_3-H	90.6

Calc. BDE (kcal/mol)	
C_1-H	94.7
C_2-H	93.6
C_3-H	91.7

Figure 5. Deuterium incorporation studies showing selective α-hydroxy C−H bond isomerization starting from (A) *cis*-diol, and (B) *trans*-diol substrates.

BDE calculation
→ C1~C3 is mostly same

Deuterium incorporation
→ Only C1

Both equatorial
and axial C−H bonds
undergo activation

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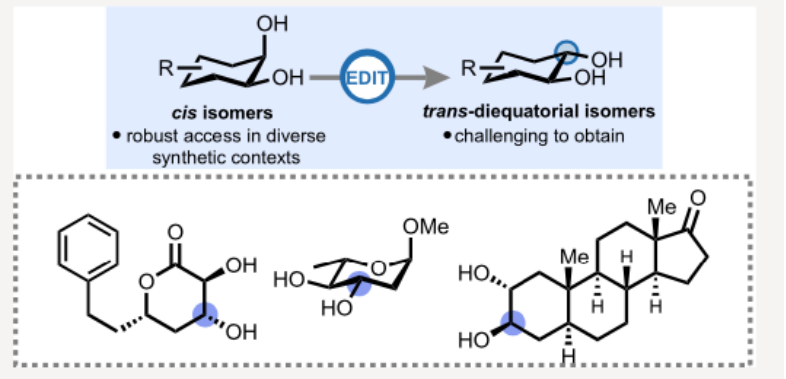
Short Summary

A Change from Kinetic to Thermodynamic Control Enables Trans-Selective Stereochemical Editing of Vicinal Diols



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✓ Catalyst system of direct access from cis-vicinical to trans-diequatorial vicinial diols

✓ Ph_3SiSH promotes reversible HAT and thermodynamic control

✓ Mild tools capable of tuning stereogenic centers

Contents

Nobel Prize in Chemistry

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シュテファン・ヘル
Stefan Hell

ウィリアム・モーナー
William E. Moerner

トマス・リンダール
Tomas Lindahl

ポール・モドリッチ
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グレゴリー・ウィンター
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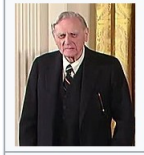

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Benjamin List

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David MacMillan

Epimerization via Transient Thermodynamic Control

Selective Isomerization via Transient Thermodynamic Control: Dynamic Epimerization of trans to cis Diols

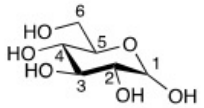
Christian, J. Oswood *et al. J. Am. Chem.* **2022**, *144, 93*−98.

✓ Boronic acid mediator
✓ Selectivity
✓ C2 site-selectivity
✓ Epimerization of trans to cis Diols
✓ Transient thermodynamic control

Problem Presentation

Stereochemistry of glycosides

C1 stereocenter:
methods for inversion

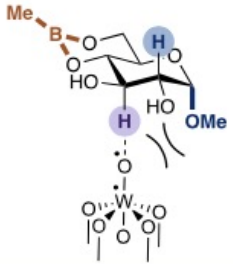


Other stereocenters:
manipulation
remains challenging

This reaction!!

Source of α-anomer C2 site-selectivity

axial OMe hinders C3 abstraction



Christian, J. Oswood *et al. J. Am. Chem.* **2022**, *144*, 93−98.

C1 stereocenter
→ Many methods

Other stereocenters
→ Limited

This research :

New site-selectivity

Reaction Design of the Selective Epimerization

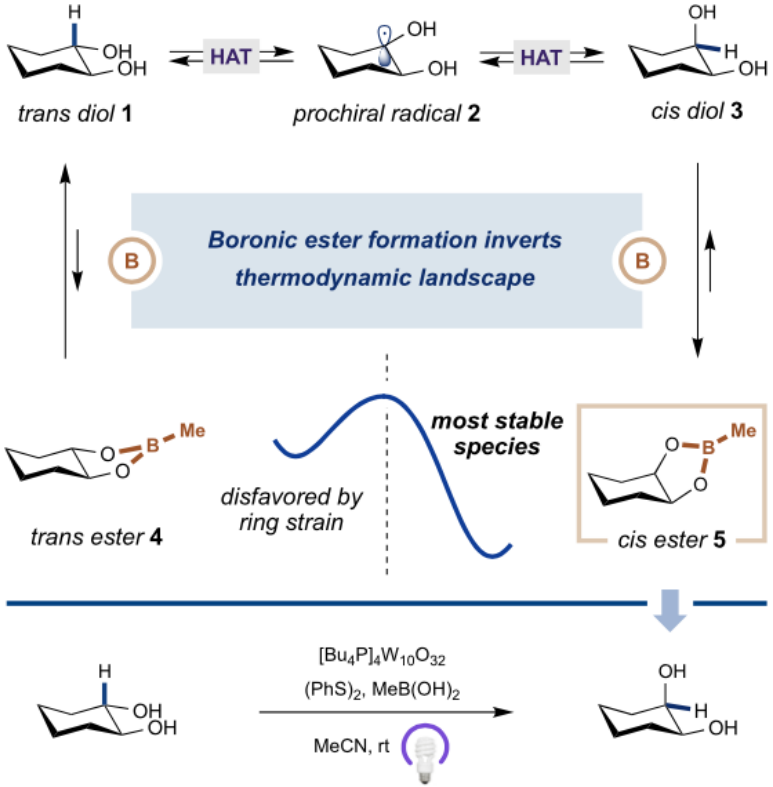
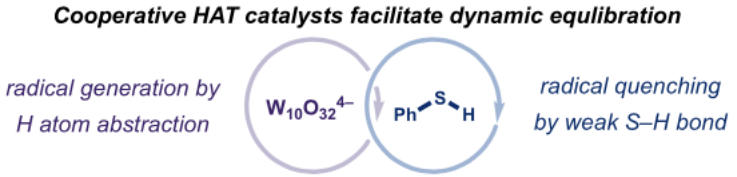


Figure 2. Reaction design of the selective epimerization.



$W_{10}O_{32}^{4-}$: Radical generation by H atom abstraction
PhSH : Radical quenching by weak S-H bond

Equilibrium ratio :

trans boronic ester (ring strain) > trans diol 1

cis boronic ester (most stable) < cis diol 3

cis boronic ester is predominant

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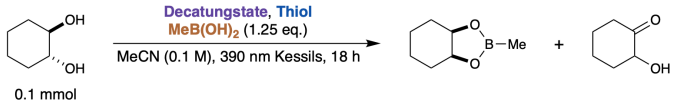
Optimization of the Selective Epimerization

Supplementary Table S1. Optimization of epimerization reaction conditions



Entry	Decatungstate	Thiol	*cis* diol	*trans* diol/esters	***cis* ester**	hydroxyketone
1	$(Bu_4N)_4W_{10}O_{32}$ (1 mol%)	PhSH (20 mol%)	0%	61%	34%	5%
2	$(Bu_4N)_4W_{10}O_{32}$ (1 mol%)	$(PhS)_2$ (50 mol%)	0%	9%	71%	5%
3	$(Bu_4P)_4W_{10}O_{32}$ (0.5 mol%)	$(PhS)_2$ (50 mol%)	0%	4%	70%	4%
4*	$(Bu_4P)_4W_{10}O_{32}$ (0.5 mol%)	$(PhS)_2$ (50 mol%)	0%	5%	74%	5%

* 3 h irradiation with PennOptical Integrated Photoreactor

S-S bonds homolyze with blue light

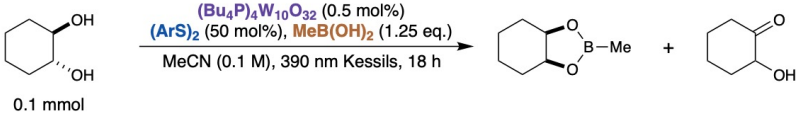
Disulfide → 2 × active thiophenol HAT catalyst

→ More rate of $W_{10}O_{32}$ turnover

→ $(PhS)_2$ > PhSH

$(Bu_4P)_4W_{10}O_{32}$: Better soluble

Supplementary Table S5: Evaluation of disulfides for the epimerization



Entry	Disulfide	*cis* diol	*trans* diol/esters	***cis* ester**	hydroxyketone
1	$(PhS)_2$	0%	4%	**70%**	4%
2	$(4\text{-}MeC_6H_4S)_2$	0%	4%	**66%**	2%
3	$(2,4,6\text{-}Me_3C_6H_2S)_2$	0%	5%	**60%**	3%
4	$(2,4,6\text{-}i\text{Pr}C_6H_2S)_2$	0%	3%	**57%**	0%
5	$(1\text{-naphthyl}S)_2$	0%	39%	**41%**	3%
6	$(4\text{-}(MeO)C_6H_4S)_2$	7%	42%	**26%**	8%
7	$(2,4\text{-}F_2C_6H_3S)_2$	0%	21%	**47%**	5%
8	$(2,6\text{-}Cl_2C_6H_3S)_2$	0%	5%	**18%**	2%
9	$(4\text{-}CF_3C_6H_4S)_2$	0%	4%	**68%**	4%
10	$(3,5\text{-}dCF_3C_6H_3S)_2$	0%	3%	**54%**	5%

Best

If necessary, disulfides were prepared from the corresponding thiols by perborate oxidation.[21]

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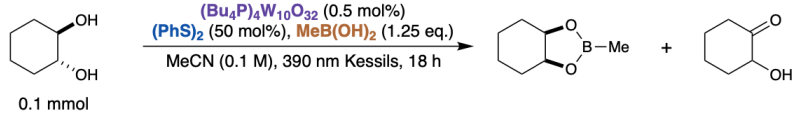
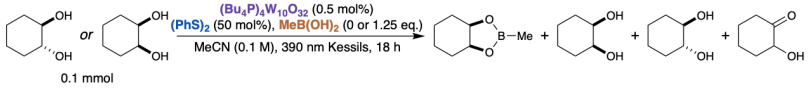
Optimization of the Selective Epimerization

Supplementary Table S2. Control reactions



Entry	Deviation	*cis* diol	*trans* diol/esters	***cis* ester**	hydroxyketone
1	none	0%	4%	**70%**	4%
2	no decatungstate	0%	100%	**0%**	0%
3	no $(PhS)_2$	0%	80%	**13%**	6%
4	no $MeB(OH)_2$	25%	47%	–	20%
5	no light	0%	100%	**0%**	0%

Supplementary Table S3. Convergence of diol isomers in boronic-acid-free epimerization



Boronic acid?	Starting diol	*cis* diol	*trans* diol/esters	***cis* ester**	hydroxyketone
Yes	*trans*	0%	4%	70%	4%
Yes	*cis*	0%	2%	82%	2%
No	*trans*	25%	46%	–	25%
No	*cis*	27%	45%	–	23%

Supplementary Table S4: Evaluation of boron chelators for the epimerization

Entry	Boron	*cis* diol	*trans* diol/esters	***cis* ester**	hydroxyketone
1	$MeB(OH)_2$	0%	4%	**70%**	4%
2	$cPrB(OH)_2$	0%	7%	**68%**	10%
3	$PhB(OH)_2$	0%	12%	**64%**	4%
4	$(4\text{-}t\text{Bu})C_6H_4B(OH)_2$	0%	15%	**51%**	7%
5	$(4\text{-MeO})C_6H_4B(OH)_2$	0%	9%	**65%**	10%
6	$(2,4,6\text{-Me})C_6H_2B(OH)_2$	0%	19%	**49%**	17%
7	$(4\text{-}CF_3)C_6H_4B(OH)_2$	0%	5%	**61%**	10%
8	$(3,5\text{-d}CF_3)C_6H_3B(OH)_2$	0%	23%	**34%**	14%
9	$(MeBO)_3$*	0%	10%	**59%**	8%
10	Ph_2BOH	0%	30%	**33%**	0%
11	$B(OMe)_3$	0%	16%	**53%**	17%
12	$B(OH)_3$	0%	22%	**42%**	21%

Best

S2 : $(PhS)_2$, $(Bu_4P)_4W_{10}O_{32}$, $MeB(OH)_2$, Light → Necessary

S3 : Boronic acid → trans - selectivity

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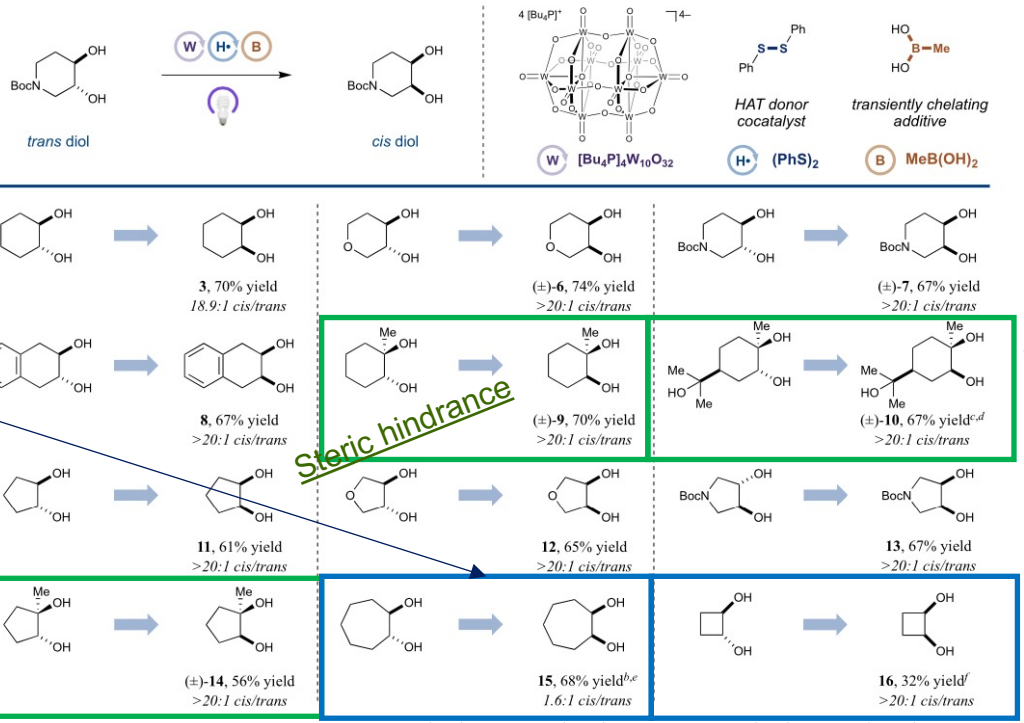
Substrate Scope of trans- 1,2-Diols

Table 1. Scope Evaluation of *trans*-1,2-Diols[a]



7 ring (small stability)

Steric hindrance

Steric hindrance

Steric hindrance

4 ring

[a]Standard conditions: 0.5 mmol of *trans* diol, 1.25 equiv of $MeB(OH)_2$, 0.5 mol % $(PBu_4)_4W_{10}O_{32}$, 50 mol % $(PhS)_2$, MeCN (0.1 M), 12–36 h of irradiation with a 365 nm LED plate in the Integrated Photoreactor at 20–30 °C then 1.5 equiv of pinanediol, 5 equiv of K_2CO_3, 4–24 h. See Supporting Information for full experimental details. All yields are isolated as single diastereomers unless noted otherwise. [b]Isolated as a mixture of diastereomers. [c]4 h of irradiation. [d]Analytical yield from ^1H NMR vs mesitylene. [e]35 equiv of H_2O added. [f]1 mol % $(PBu_4)_4W_{10}O_{32}$. [g]Acyclic diol conditions: 0.1 mmol scale, 1% $(PBu_4)_4W_{10}O_{32}$, 24 h irradiation, isolated as a mixture of diastereomers from five combined reactions. [h]2 mol % $(PBu_4)_4W_{10}O_{32}$, 4:1 MeCN/*t*-BuOH (0.02 M) as solvent.

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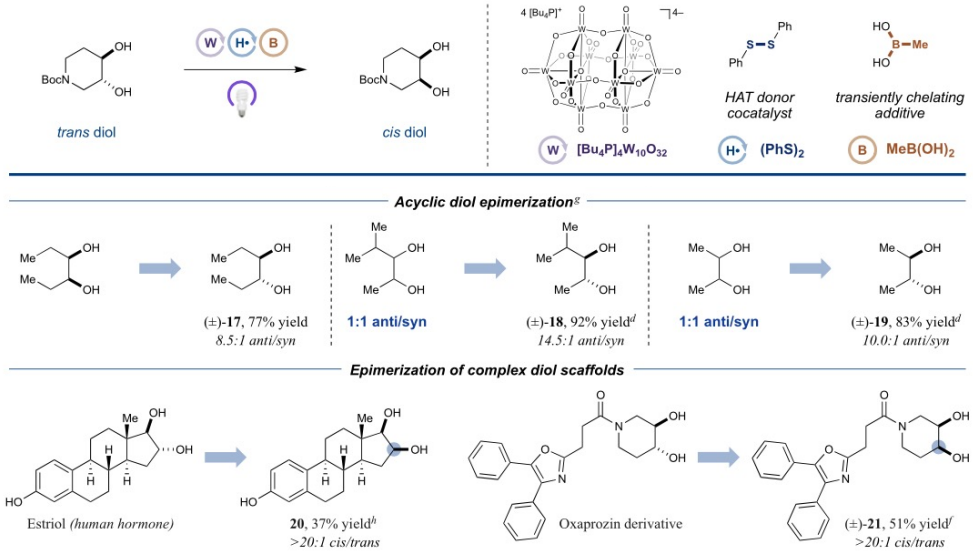
Substrate Scope of trans- 1,2-Diols

Table 1. Scope Evaluation of *trans*-1,2-Diols[a]



[a]Standard conditions: 0.5 mmol of *trans* diol, 1.25 equiv of $MeB(OH)_2$, 0.5 mol % $(PBu_4)_4W_{10}O_{32}$, 50 mol % $(PhS)_2$, MeCN (0.1 M), 12–36 h of irradiation with a 365 nm LED plate in the Integrated Photoreactor at 20–30 °C then 1.5 equiv of pinanediol, 5 equiv of K_2CO_3, 4–24 h. See Supporting Information for full experimental details. All yields are isolated as single diastereomers unless noted otherwise. [b]Isolated as a mixture of diastereomers. [c]4 h of irradiation. [d]Analytical yield from ^1H NMR vs mesitylene. [e]35 equiv of H_2O added. [f]1 mol % $(PBu)_4W_{10}O_{32}$. [g]Acyclic diol conditions: 0.1 mmol scale, 1% $(PBu_4)_4W_{10}O_{32}$, 24 h irradiation, isolated as a mixture of diastereomers from five combined reactions. [h]2 mol % $(PBu_4)_4W_{10}O_{32}$, 4:1 MeCN/*t*-BuOH (0.02 M) as solvent.

Acyclic diol :
anti configuration is stable
Synthetic utility

20 :
Human hormone

21 :
diol- containing derivative of the pharmaceutical compound

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Substrate Scope of 1,3-Diols

Table 2. Scope Evaluation of 1,3-Diols[a]

trans diol → *cis* diol

cyclic 1,3-diols

***cis* favored**

22, 80% yield
>20:1 cis/trans

trans disfavored

23, 58% yield
4.8:1 cis/trans

5-membered exocyclic diols

***cis* favored**

(±)-**24**, 77% yield
4.0:1 cis/trans

trans disfavored

(±)-**25**, 47% yield
>20:1 cis/trans

6-membered exocyclic diols

cis disfavored

(−)-**26**, 89% yield[b]
13.0:1 trans/cis

***trans* favored**

(±)-**27**, 70% yield
10.3:1 trans/cis

[a]See Supporting Information for experimental details. All yields are isolated. [b]Isolated as a mixture of diastereomers.

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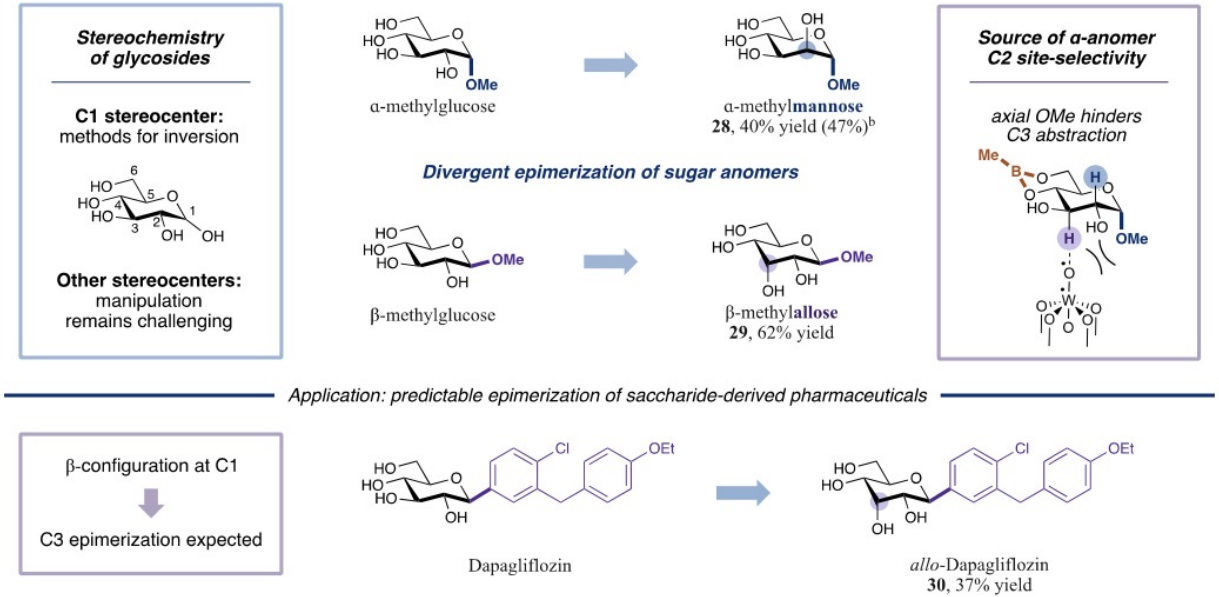
Substrate Scope of Glycosides

Table 3. Divergent Epimerization of Glycosides[a]



[a]See Supporting Information for experimental details. All yields are isolated unless noted otherwise. [b]Assay yield from ^{1}H NMR vs mesitylene.

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Site-selectivity ↑
$W_{10}O_{32}^{-4}$ abstract from less sterically hindered C−H sites

30 (Pharmaceuticals) : β-configuration at C1

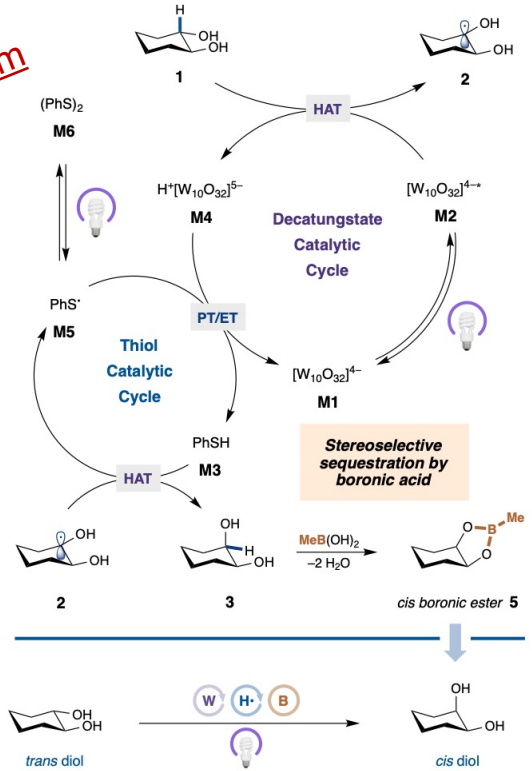
↓

C3 epimerization (less sterically hindered C−H sites

Kinetic selectivity !!

Short Summary

Proposed Mechanism



Supplementary Figure S6. Proposed reaction mechanism

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Selective Isomerization via Transient Thermodynamic Control: Dynamic Epimerization of trans to cis Diols

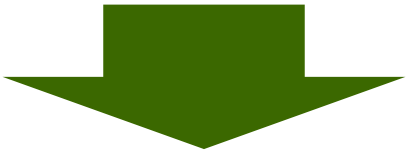
- ✓ Epimerization of trans to cis Diols
- ✓ Transient thermodynamic control
- ✓ Methylboronic acid as a key chelating additive
- ✓ C2 site-selectivity

Contents

Summary

Advantages of photoredox catalysis

✓ No Prefunctionalization
✓ No reagents
✓ Mild conditions
✓ Minimally Protecting groups
✓ Selective reaction (site-, chemo-, diastereoselectivity)



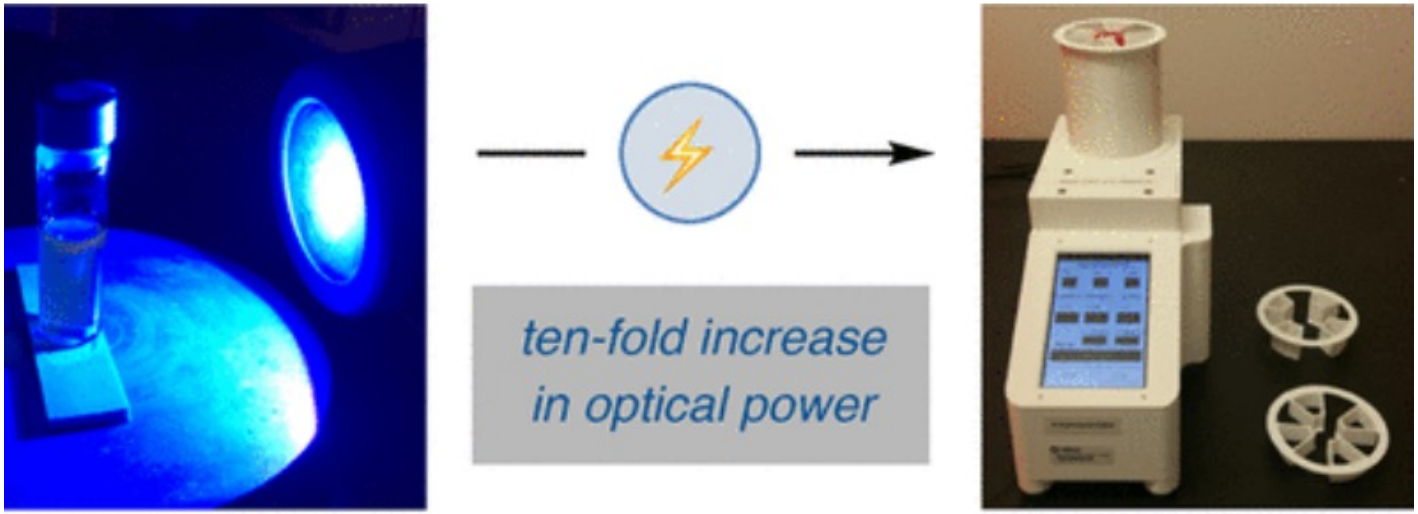
Vision

✓ Carbohydrate synthesis without protecting groups
✓ New glycan synthesis

Thank you for your attention !!

Appendix

The Integrated Photoreactor

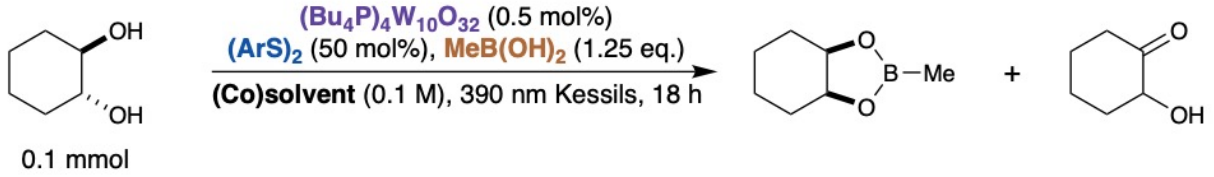


Standardization and Acceleration of Photocatalytic Reactions

Chi "Chip" Le et al. ACS Cent Sci. **2017**, *3, 6, 647*−653.

Optimization of Solvent

Supplementary Table S6: Evaluation of solvents and cosolvents for the epimerization



Entry	(Co)solvent	*cis* diol	*trans* diol/esters	***cis* ester**	hydroxyketone
1	MeCN	0%	4%	**70%**	4%
2	*t*BuCN	0%	45%	**40%**	7%
3	PhCN	0%	3%	**40%**	3%
4	acetone	0%	21%	**62%**	0%
5	*t*BuOAc	0%	98%	**2%**	0%
6	MeCN/*t*BuOH (9:1)	0%	93%	**5%**	3%
9	MeCN/*t*BuOAc (1:1)	0%	8%	**61%**	7%
10	MeCN/DCM (1:1)	0%	33%	**44%**	19%
11	MeCN/$CHCl_3$ (1:1)	0%	78%	**14%**	7%
12	MeCN/$PhCF_3$ (1:1)	0%	38%	**39%**	11%
13	MeCN/*o*-$C_6H_4F_2$ (1:1)	0%	31%	**51%**	11%
14	MeCN/*p*-$C_6H_4F_2$ (1:1)	0%	89%	**10%**	4%
15	MeCN/HFIP (1:1)	0%	55%	**15%**	15%
16	MeCN/$MeNO_2$ (1:1)	0%	12%	**20%**	7%

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