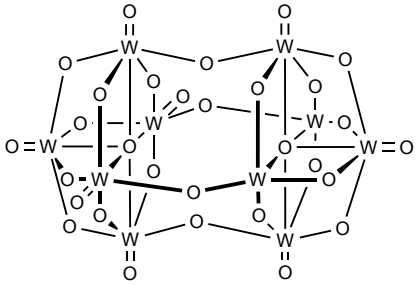
“Stereochemical Editing”



- Photochemical deracemization
- Epimerization of polyols & sugars
- Epimerization of unactivated stereocenters

Not Covered:

- Traditional epimerization methods
- Transformations where stereocenters change alongside other chemical transformations (dynamic resolutions)

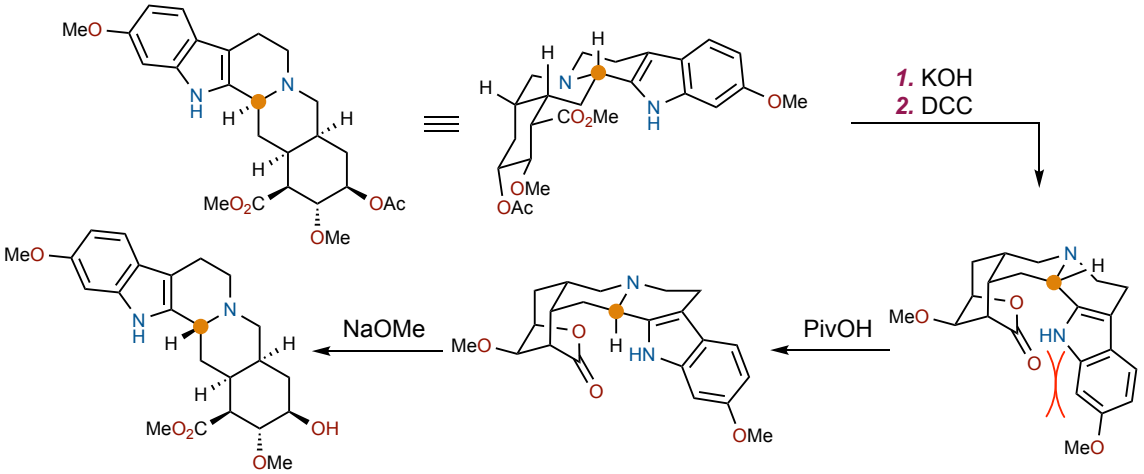
Reviews/perspectives:

Light-empowered contra-thermodynamic stereochemical editing
https://www.nature.com/articles/s41570-022-00441-2

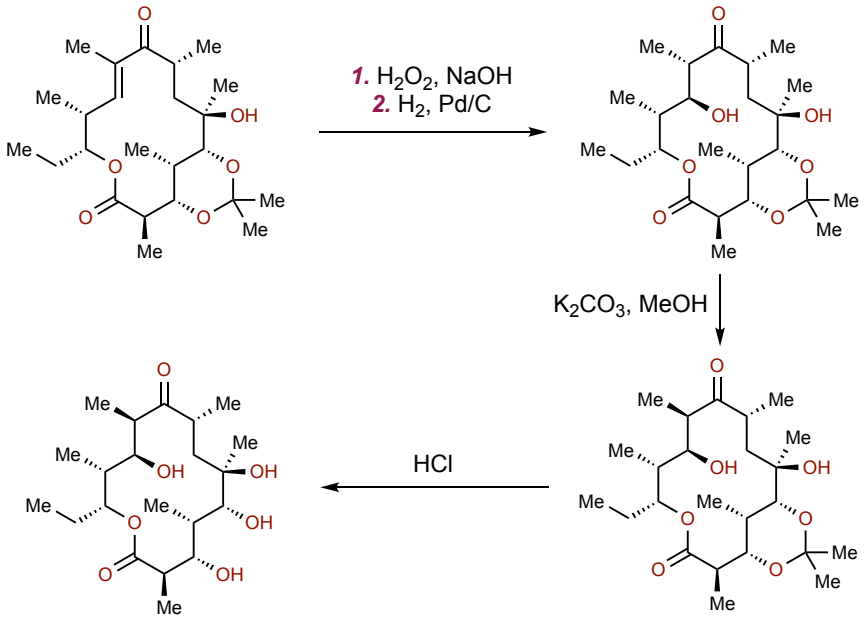
Stereochemical editing
https://onlinelibrary.wiley.com/doi/10.1002/anie.202217840

Resolution topic (TWB)
https://www.sarlahgroup.com/_files/ugd/31ec9c_0e45c50a0d2f4d3c9c3dc27aeafa34ec.pdf

Reserpine – Woodward (1956)

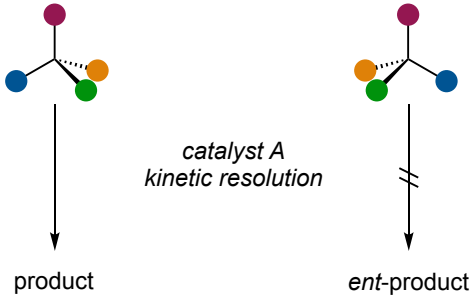


Erythronolide B – Corey (1978)



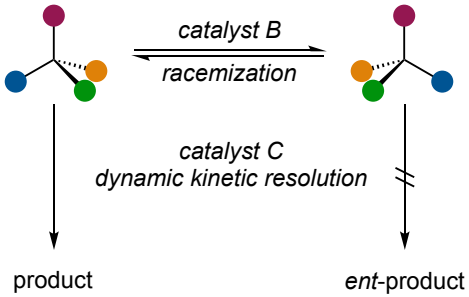
Photochemical Deracemization

Kinetic Resolution



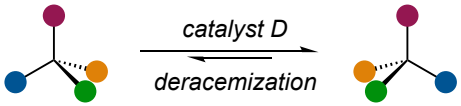
Only 1 enantiomer is transformed by a chiral catalyst

Dynamic Kinetic Resolution



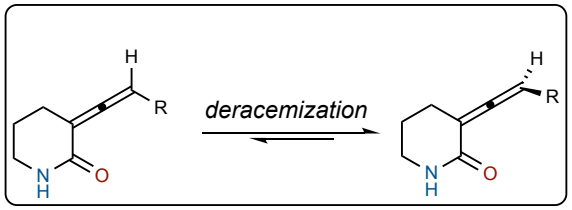
Only 1 enantiomer is transformed by a chiral catalyst; another catalyst racemizes the starting material

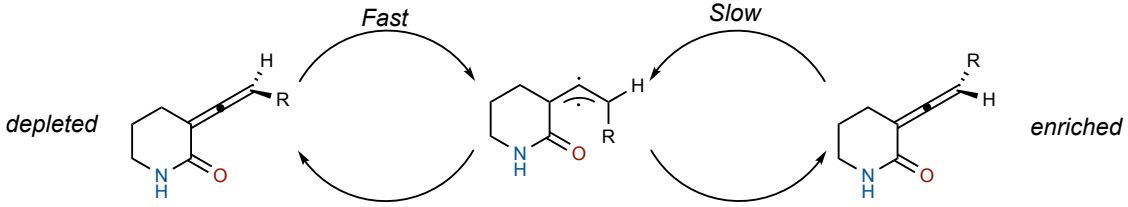
Deracemization



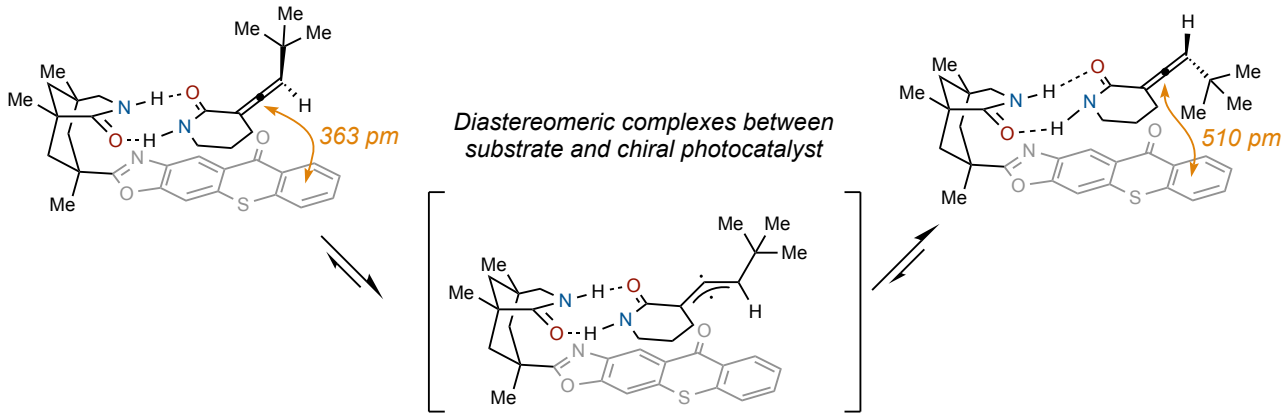
A racemic starting material is made enantioenriched without a chemical transformation

Bach, 2018





diradical collapse is random
(50% of diradical forms product and 50% forms ent-product)

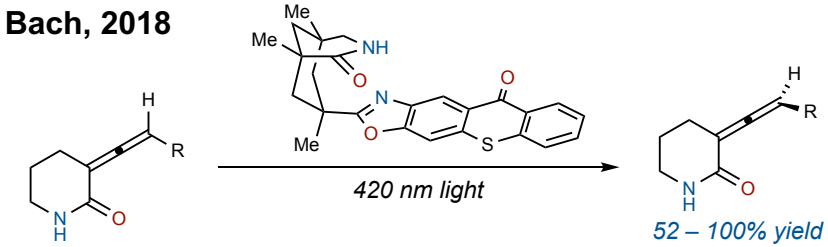


Chiral photocatalyst recruits the substrate through hydrogen bonding
One enantiomer binds more tightly than the other
Efficient triplet energy transfer to only one enantiomer
4-fold difference in K_a between the two enantiomers
Low enantioinduction in methanol

https://doi.org/10.1038/s41586-018-0755-1

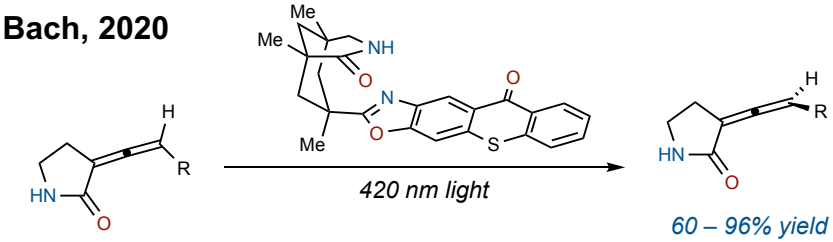
Welcome to the Bach Parade

Bach, 2018



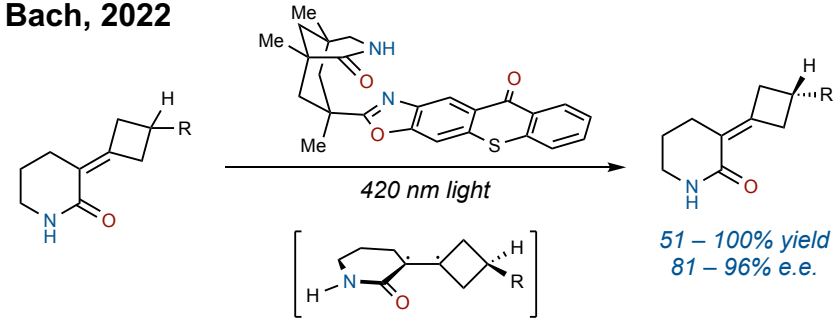
52 – 100% yield
89 – 97% e.e.

Bach, 2020

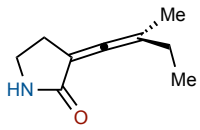


60 – 96% yield
86 – 98% e.e.

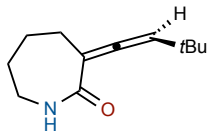
Bach, 2022



51 – 100% yield
81 – 96% e.e.

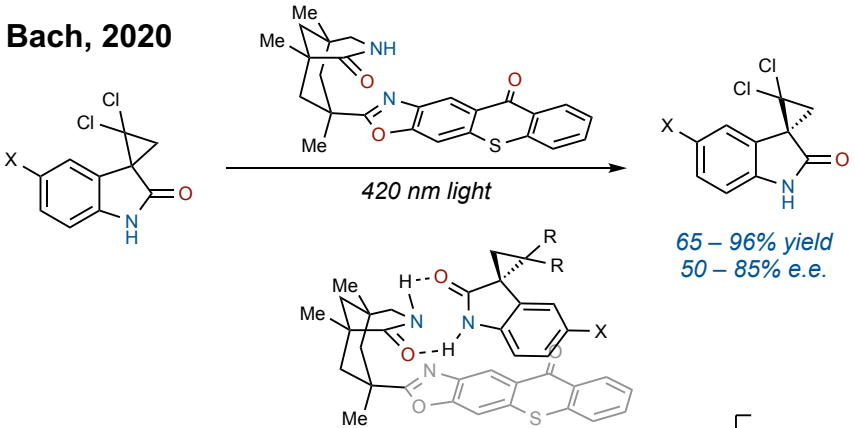


85%, 45% e.e.

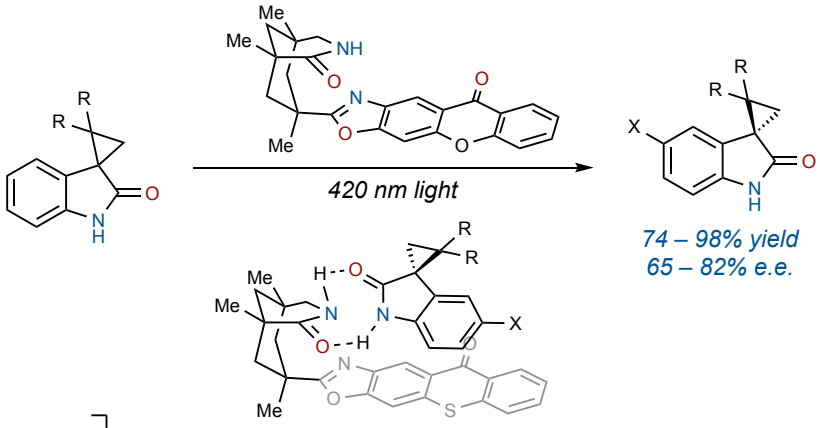


87%, 62% e.e.

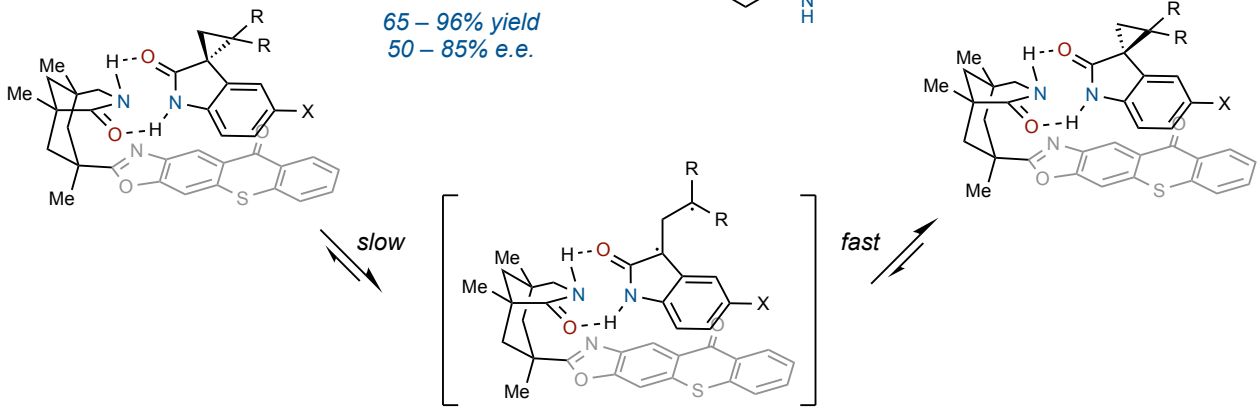
Bach, 2020



65 – 96% yield
50 – 85% e.e.

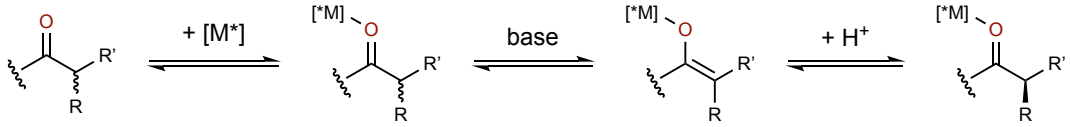


74 – 98% yield
65 – 82% e.e.

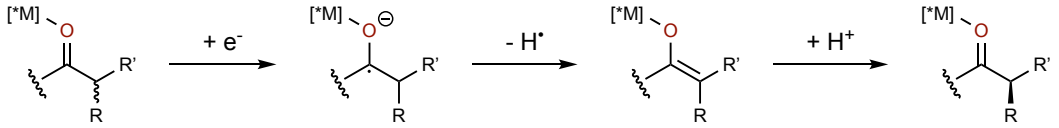


Photochemical Deracemization

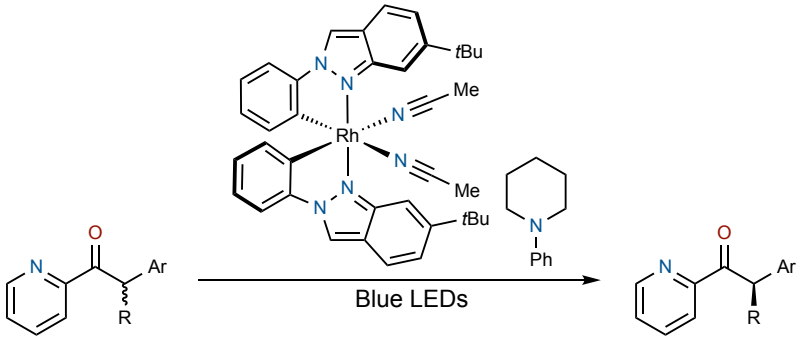
Meggers and Chen, 2021

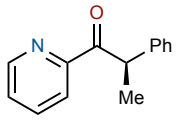


One-pot, catalytic deracemization is challenging because deprotonation and protonation are microscopic reverses
Equilibrium will always form the entropically favored racemate

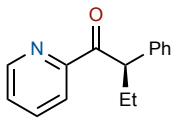


Formal deprotonation through redox process avoids microscopic reversibility problem

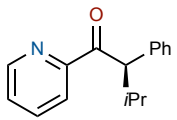




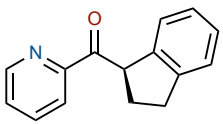
97% yield, 96% e.e.



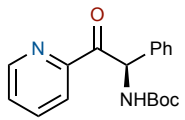
83% yield, 87% e.e.



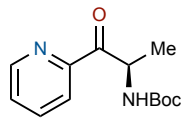
78% yield, 89% e.e.



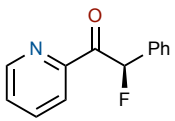
79% yield, 86% e.e.



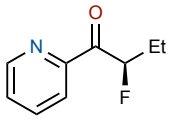
95% yield, 92% e.e.



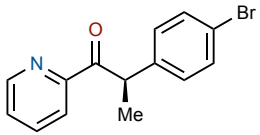
82% yield, 85% e.e.



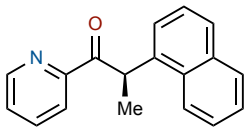
93% yield, 72% e.e.



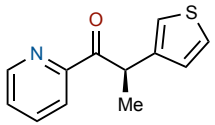
85% yield, 40% e.e.



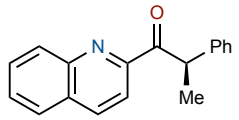
94% yield, 96% e.e.



88% yield, 95% e.e.

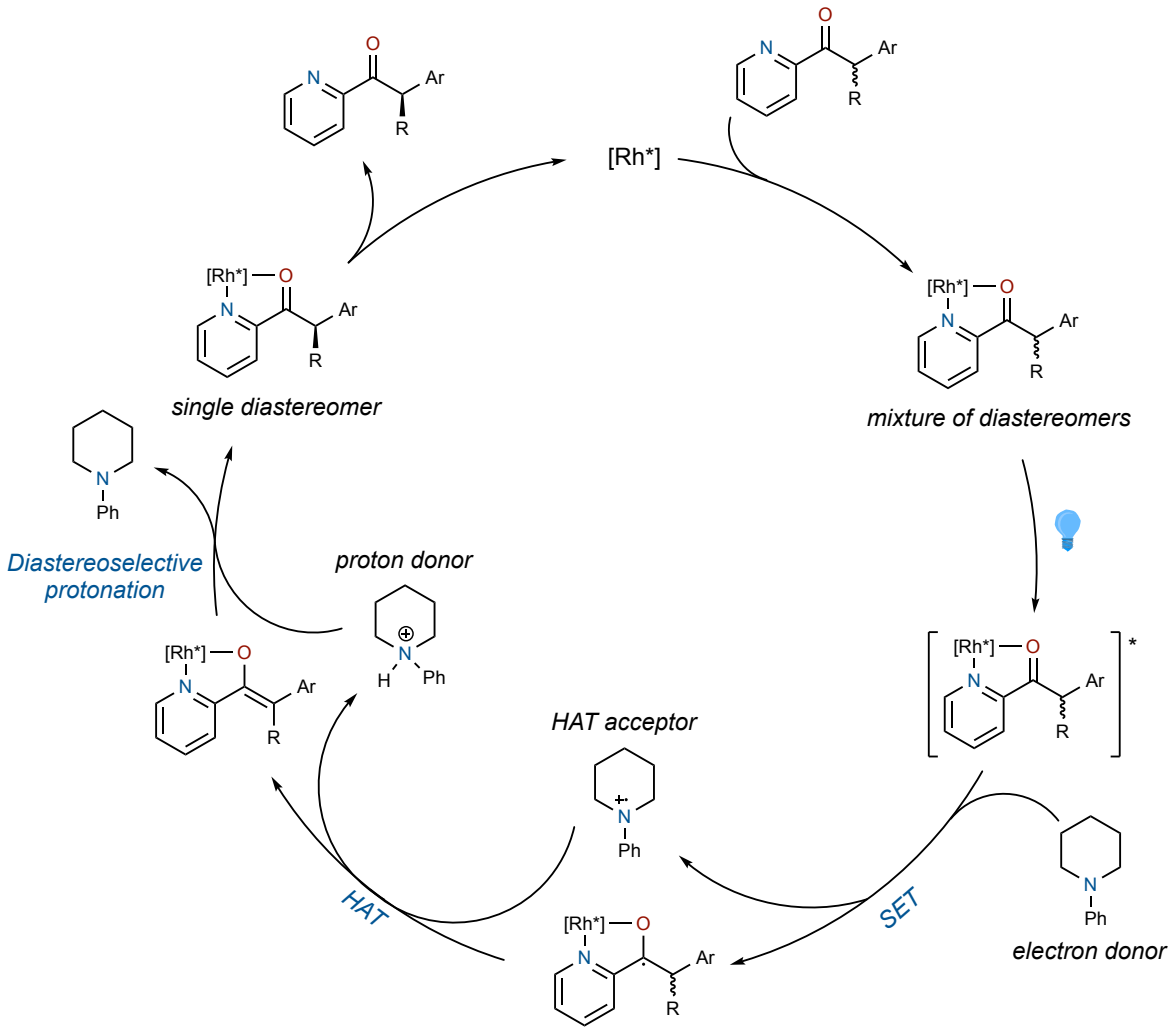


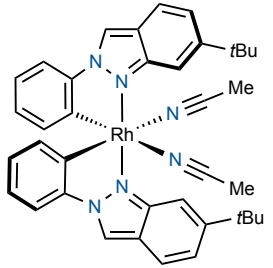
93% yield, 86% e.e.



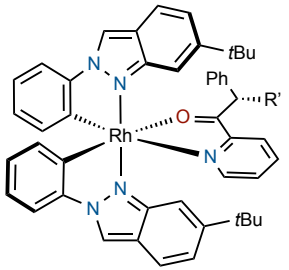
92% yield, 87% e.e.

Photochemical Deracemization

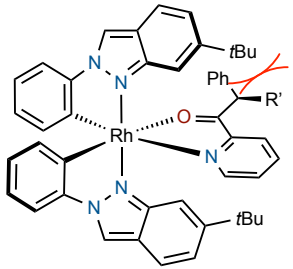




weakly absorbs blue light



matched diastereomeric complex
ΔΔG = 0 kCal/mol



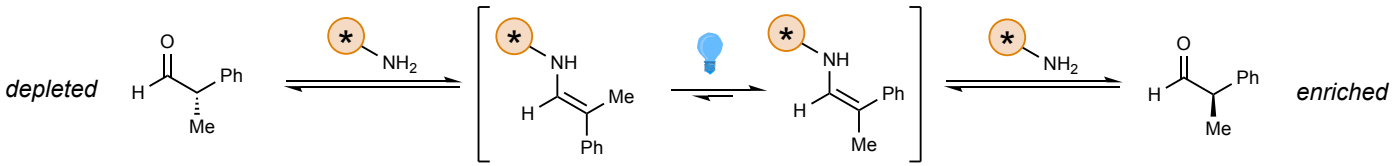
mismatched diastereomeric complex
ΔΔG = 2.9 kCal/mol

Stereoablation through redox enolization allows chiral photocatalyst to control protonation
One enantiomer binds favorably (depleted) and the other binds unfavorably (enriched)
Different mechanisms for protonation and deprotonation enables one-pot deracemization

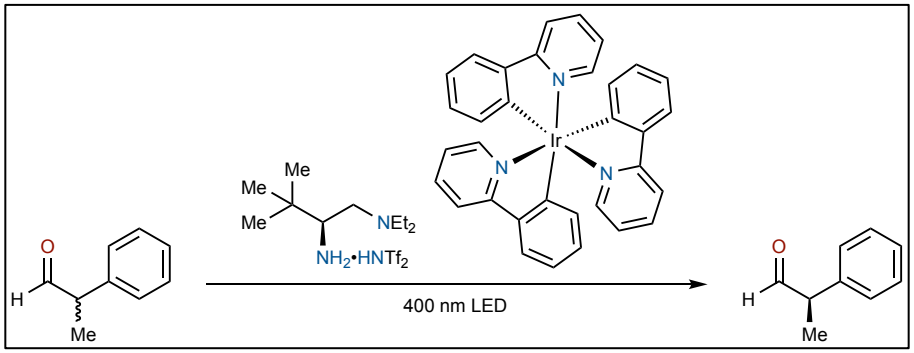
https://doi.org/10.1021/jacs.1c06637

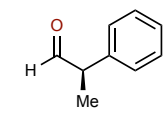
Photochemical Deracemization

Luo, 2022

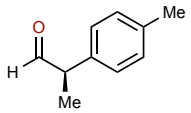


Chiral amine forms different enamines from the two enantiomers
E-enamine isomerizes to *Z*-enamine selectively
Diastereoselective protonation leads to deracemization

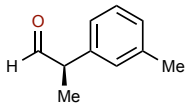




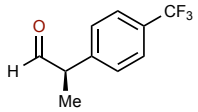
73% yield, 94% e.e.



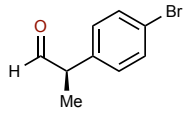
80% yield, 94% e.e.



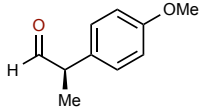
71% yield, 88% e.e.



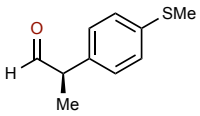
80% yield, 91% e.e.



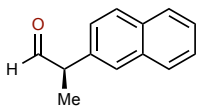
83% yield, 89% e.e.



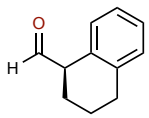
82% yield, 89% e.e.



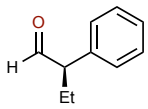
74% yield, 90% e.e.



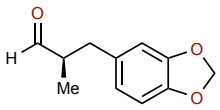
85% yield, 77% e.e.



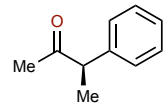
82% yield, 70% e.e.



70% yield, 80% e.e.



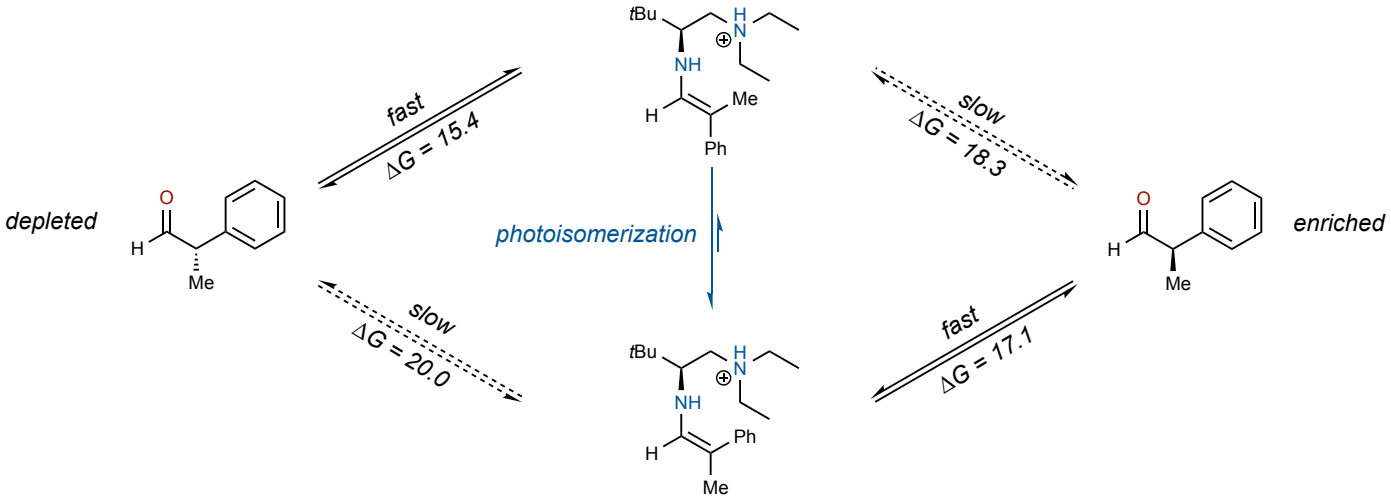
73% yield, 5% e.e.



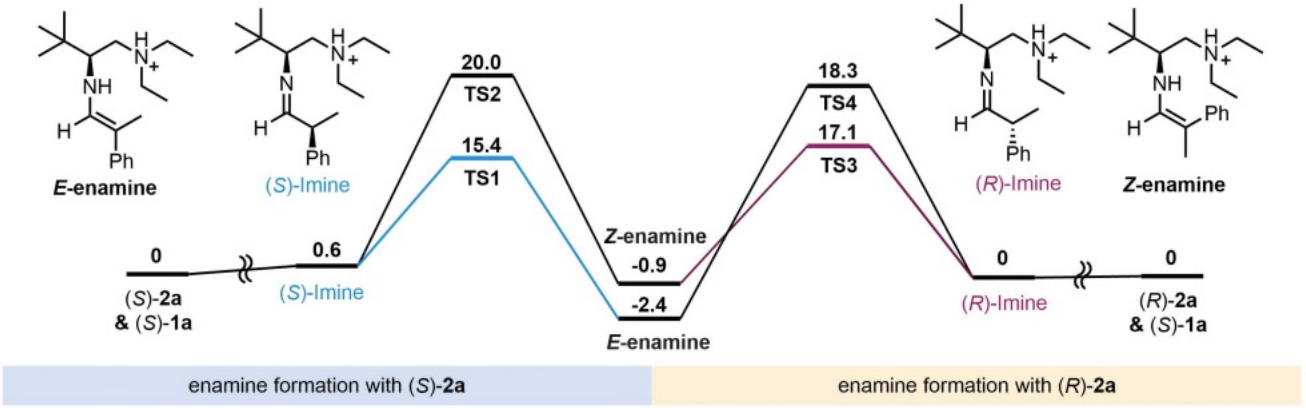
99% yield, 0% e.e.

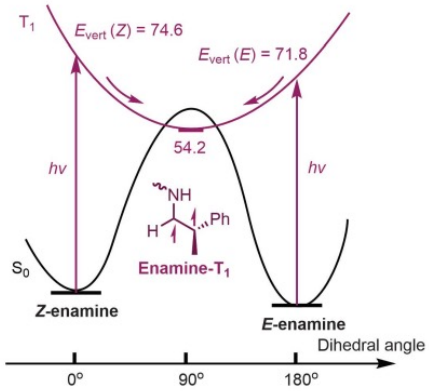
https://doi.org/10.1126/science.abl4922

Photochemical Deracemization



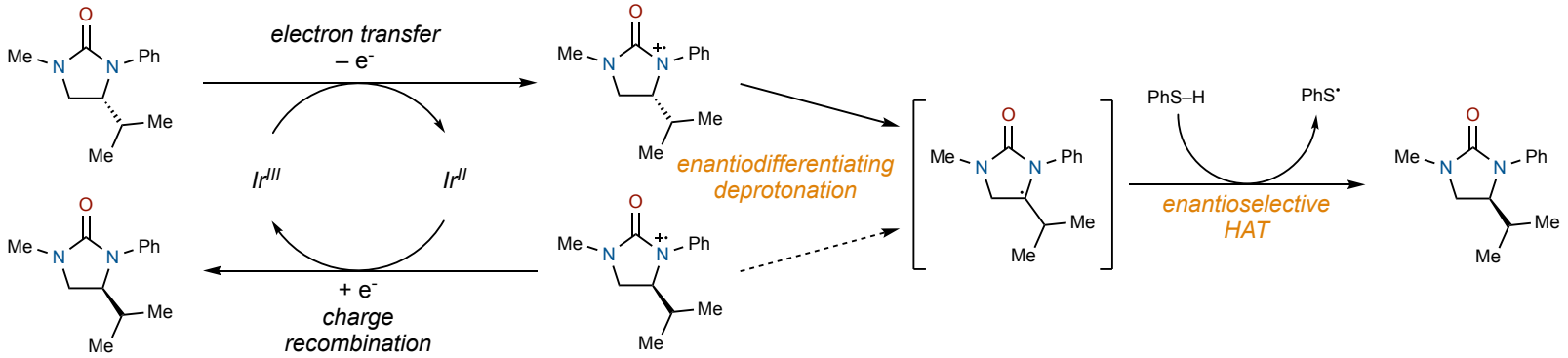
Photocatalyst	E_T (kcal/mol)	$E_{1/2}$	e.e. (%)
$Ru(bpy)_3Cl_2$	46.5	0.77	94
$Ir(ppy)_3$	58.1	0.31	39
E-enamine	54.2	0.73 (E_{ox})	–





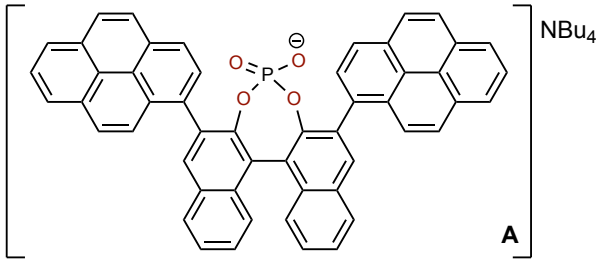
Photochemical Deracemization

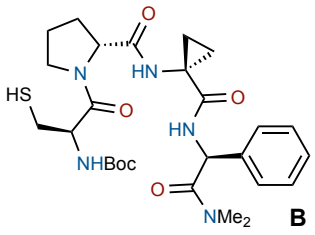
Miller and Knowles, 2021



Differentiation through deprotonation and enantioselective HAT deracemizes cyclic urea
Opportunity for synergistic effects?

Base	Thiol	Additive	Yield (%)	e.r.
A	PhSH	–	84	79:21
A	PhSH	4 Å M.S.	92	86:14
$NBu_4(PhO)_2P(O)O$	**B**	–	97	78:22
$NBu_4(PhO)_2P(O)O$	**B**	4 Å M.S.	95	79:21
A	**B**	4 Å M.S.	96	93:7
A	**B**	Ph_3CH	96	96:4

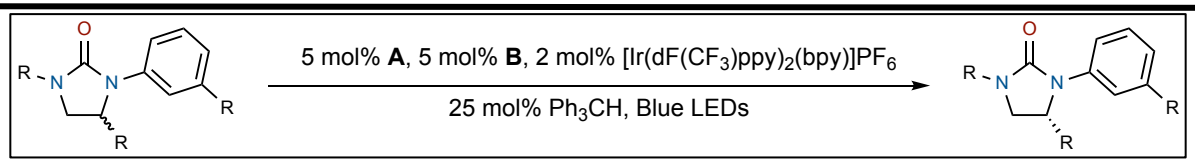


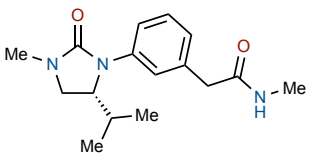


Observed enantiomeric ratio is the product of the e.r. of each catalytic step
Deprotonation • HAT = observed e.r.
(86•79:14•21 = 96:4)

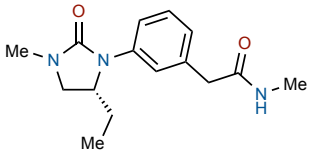
https://doi.org/10.1126/science.aay2204

Photochemical Deracemization

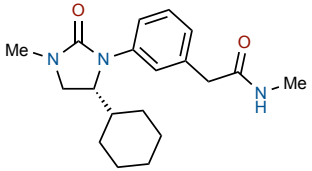




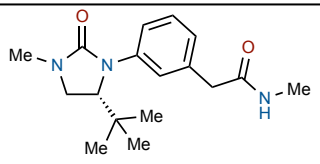
99% yield, 95:5 e.r.



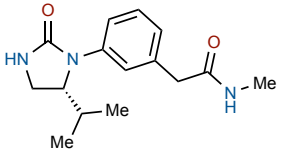
92% yield, 94:6 e.r.



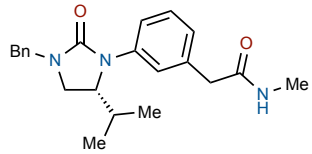
98% yield, 90:10 e.r.



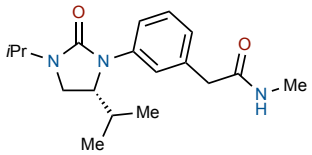
98% yield, 95:5 e.r.



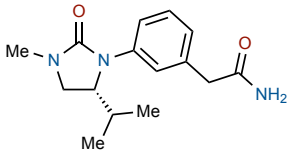
99% yield, 92:8 e.r.



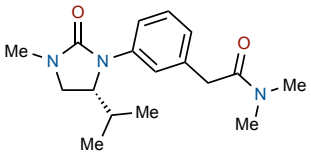
99% yield, 95:5 e.r.



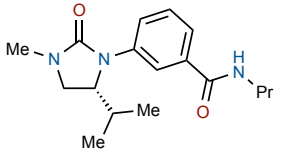
99% yield, 94:7 e.r.



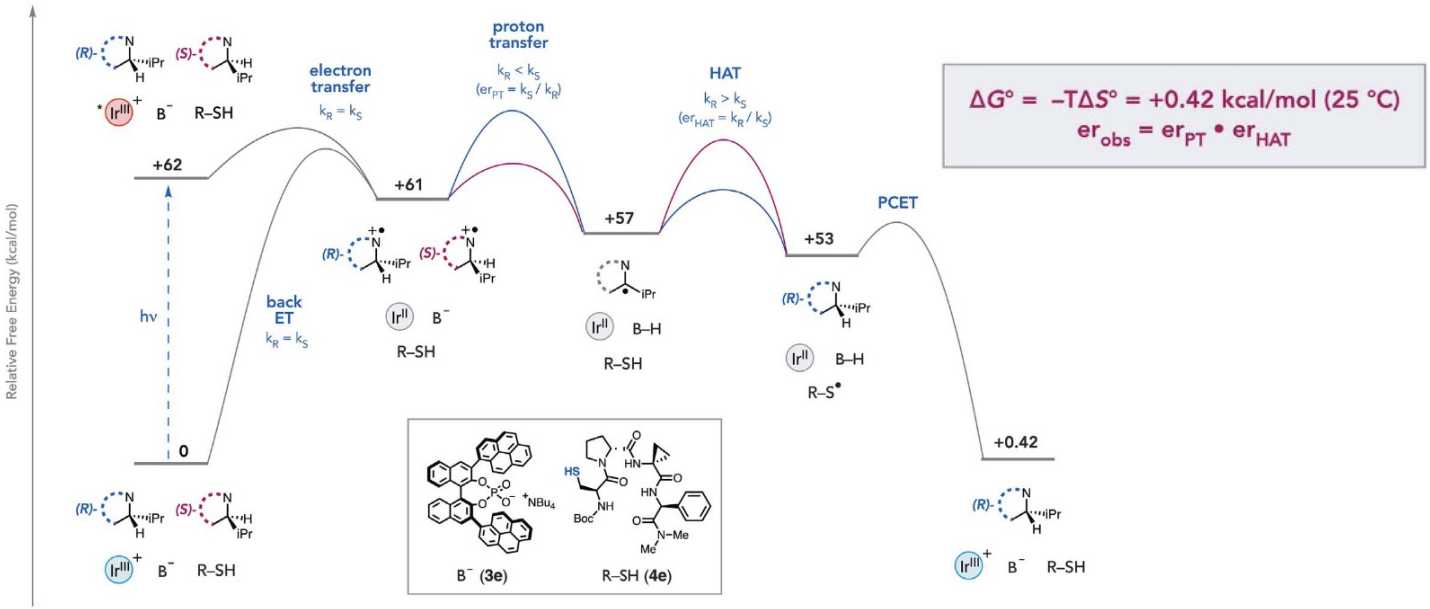
96% yield, 93:7 e.r.



97% yield, 81:19 e.r.

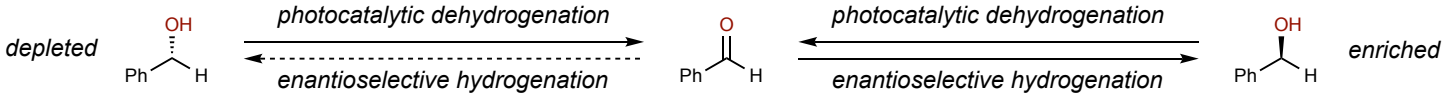


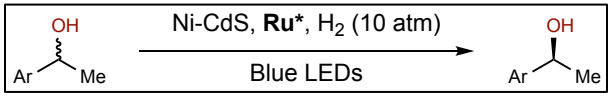
94% yield, 90:10 e.r.



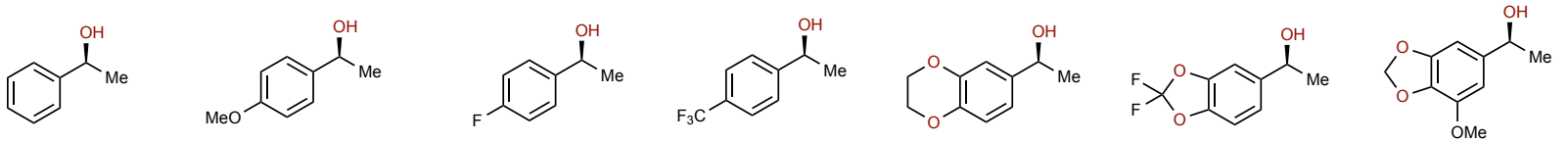
Photochemical Deracemization

Hu, 2021

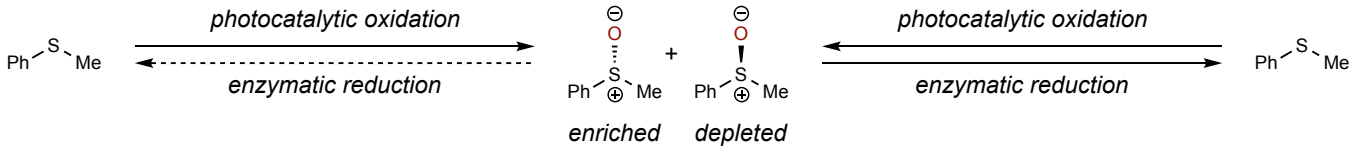




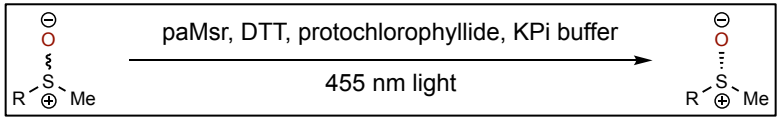
Reaction is finished with 4-24 hours of hydrogenation in the dark

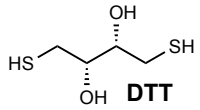


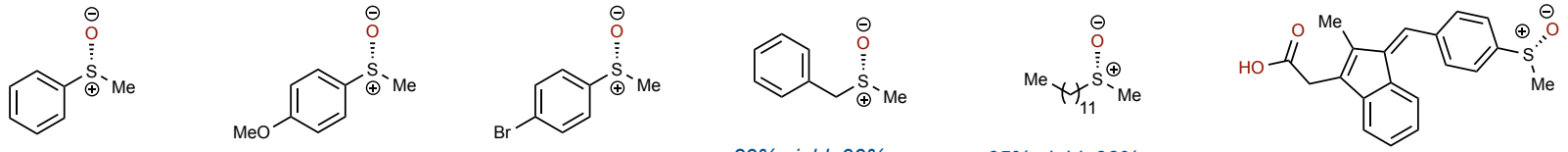
Winkler and Glueck, 2022



Protochlorophyllide is a heme-based PC
paMSR is a methionine sulfoxide reductase



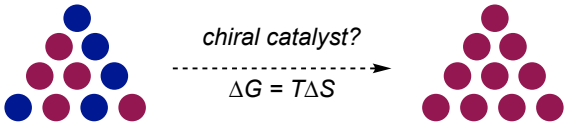




https://doi.org/10.1002/anie.202107570 https://doi.org/10.1002/anie.202117103

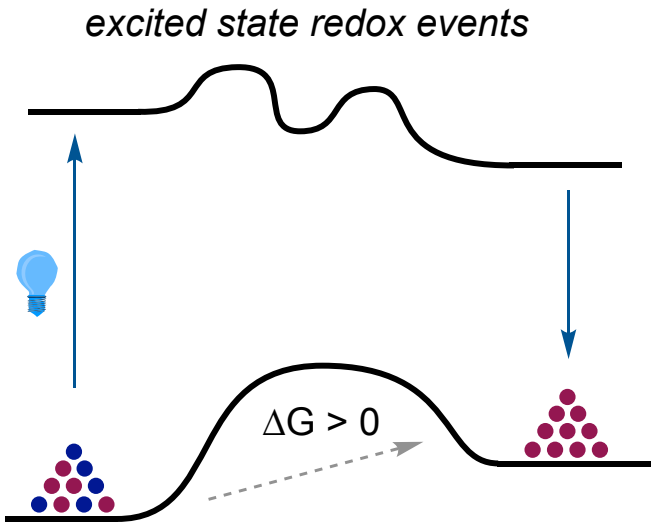
Photochemical Deracemization

Summary



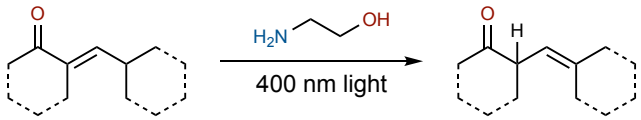
Challenges:
Unfavorable thermodynamics
Overcoming microscopic reversibility

Solutions:
Injecting energy with visible light
Decoupling forward and reverse reactions



Some interesting light-mediated contra-thermodynamic reactions that are not stereochemical editing

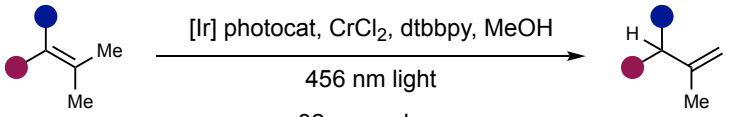
Gilmore and Morack, 2021



20 examples
31-95 % yield
enantioselectivity with cinchona alkaloids

https://doi.org/10.1021/acscatal.1c03089

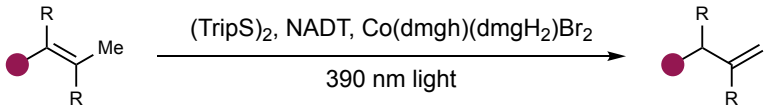
Knowles, 2022



32 examples
75-98% yield

https://doi.org/10.1021/jacs.1c11681

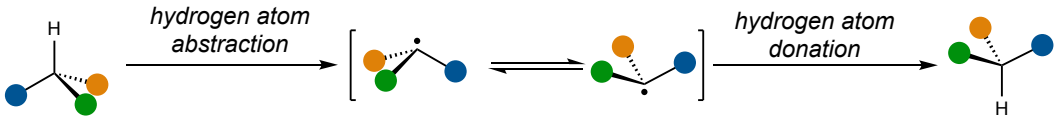
Wendlandt, 2022



33 examples
33-95% yield

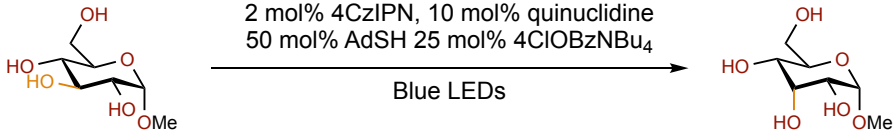
https://doi.org/10.1021/jacs.1c12043

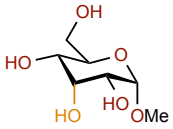
Stereochemical Editing



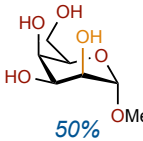
These methods utilize achiral reagents and rely on substrate control to access epimerized products

Wendlandt, 2020

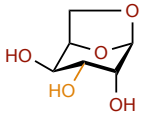




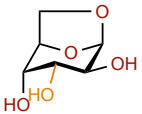
88%
From D-glucose



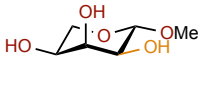
50%
From D-galactose



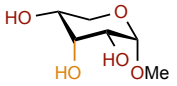
37%
From D-anhydrogalactose



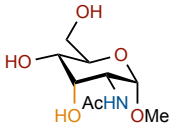
41%
From D-anhydromannose



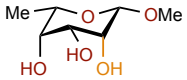
30%
From L-arabinose



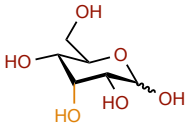
30%
From D-xylose



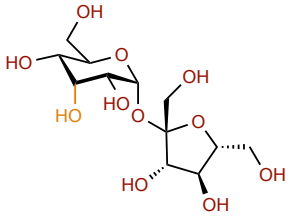
38%
From D-glucosamine



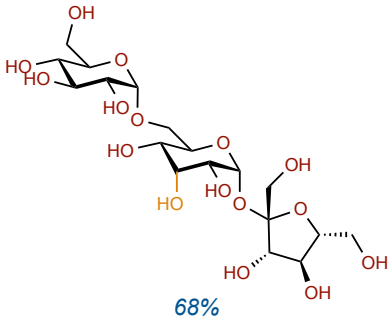
70%
From L-fucose



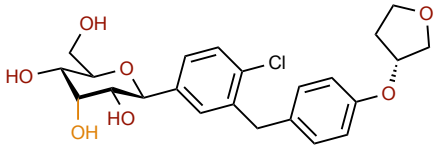
38%
From D-glucose



68%
From D-sucrose



68%
From raffinose

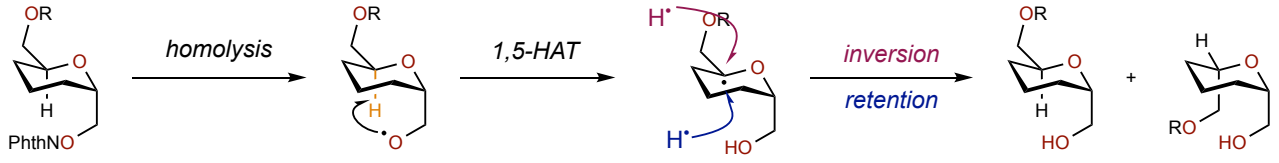


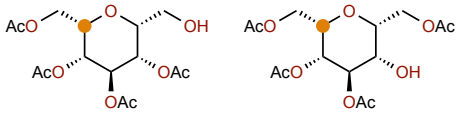
42%
From empagliflozin

https://doi.org/10.1038/s41586-020-1937-1

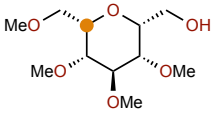
Stereochemical Editing

Suarez, 2022

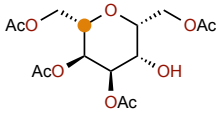




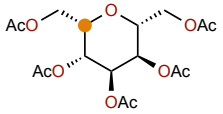
70% combined yield
20% retention



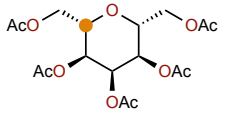
28% yield
43% retention



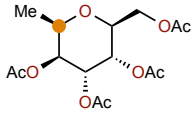
36% yield
33% retention



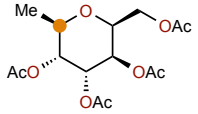
72% yield after acetylation
12% retention



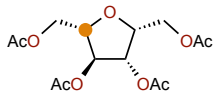
63% yield after acetylation
19% retention



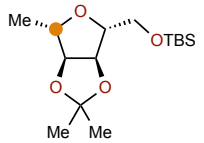
57% yield after acetylation
retention not detected



14% yield after acetylation
14% retention

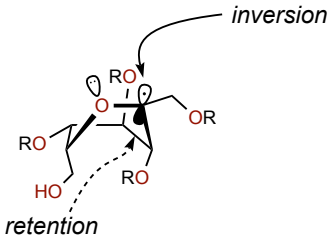


27% yield after acetylation
14% retention

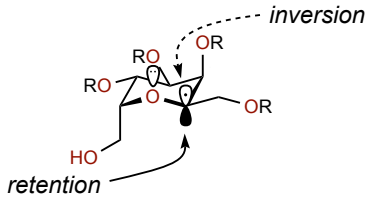


6% yield after silylation
68% retention

Conformation can be predicted by accounting for anomeric and β-oxygen effect



70% yield for inversion

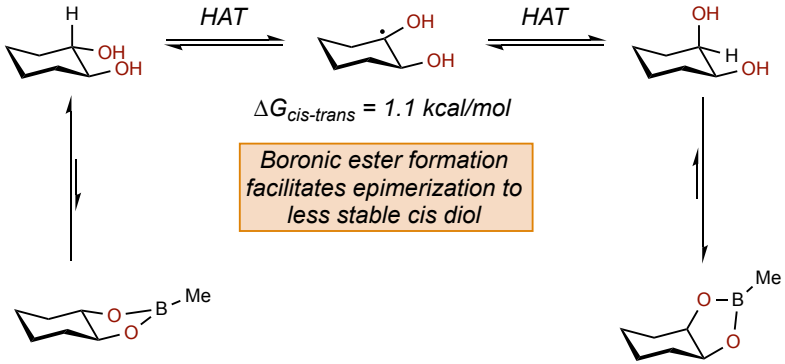


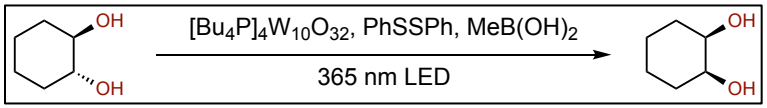
36% yield for inversion

https://doi.org/10.1002/ejoc.202101391

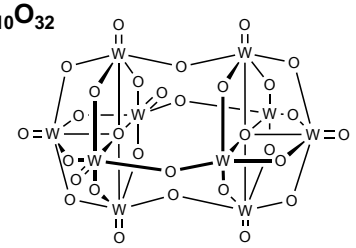
Stereochemical Editing

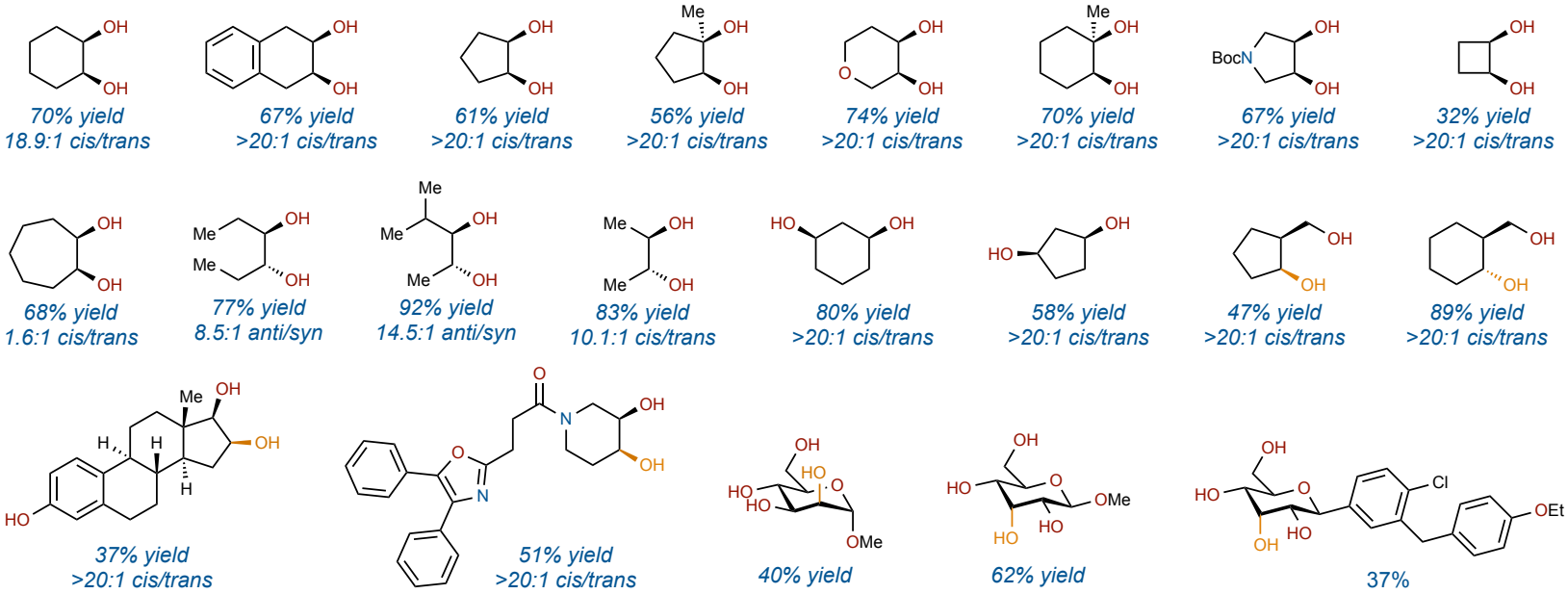
MacMillan, 2022





$W_{10}O_{32}$

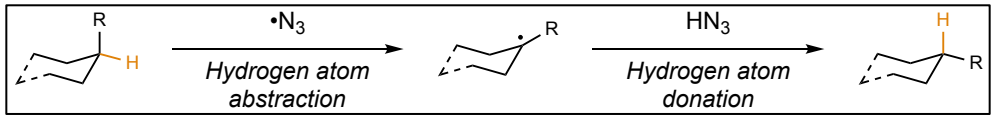


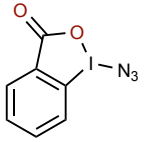


https://doi.org/10.1021/jacs.1c11552

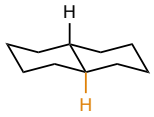
Stereochemical Editing

He, Liu, and Chen, 2018

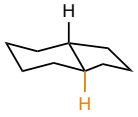




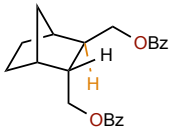
azide source (BIN_3)



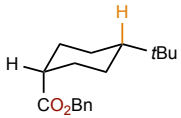
97%



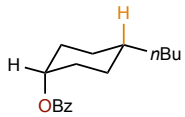
77%
+ 14% cis



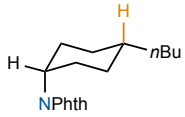
75%
+ 18% cis



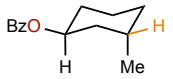
66%
+ 33% cis



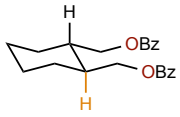
57%
+ 42% cis



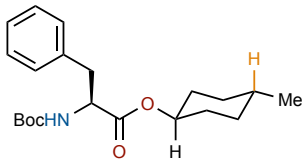
73%
+ 16% cis



26%
+ 71% cis

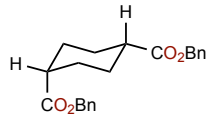


56%
+ 42 % cis

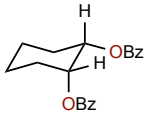


65%
+ 23% cis

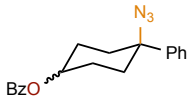
Failed substrates



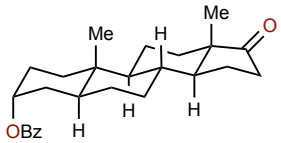
95% RSM

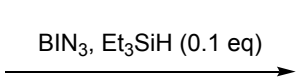


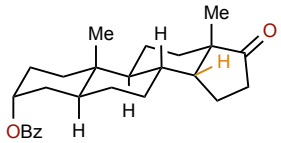
95% RSM

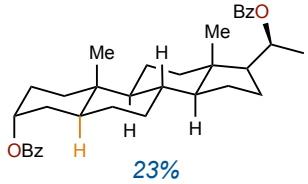


75% azidation
(1:1 d.r.)

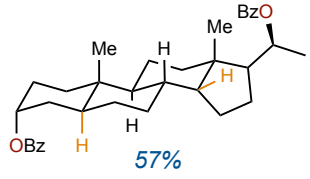






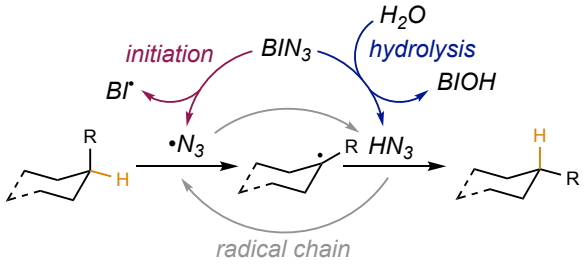


23%



57%

from pregnanediol

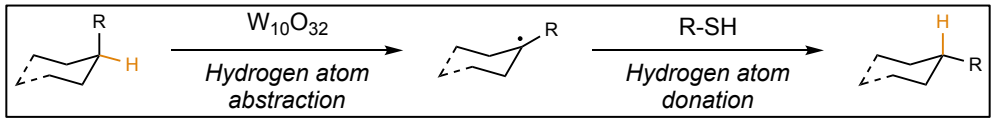


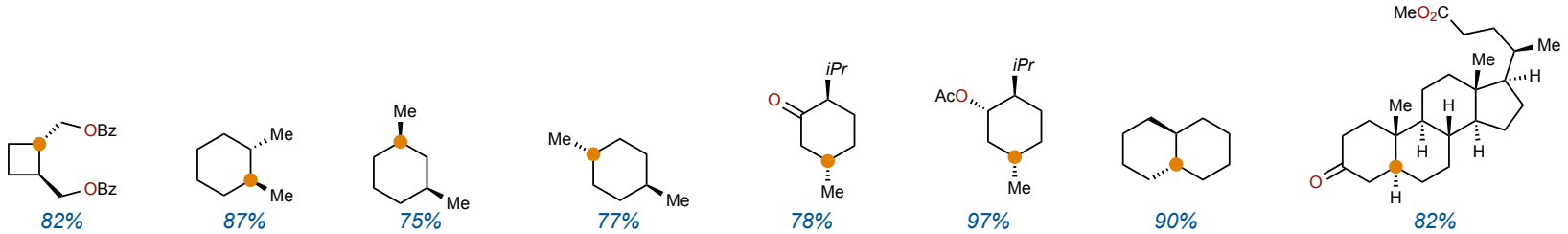
HAA occurs at the weakest tertiary C–H bond! Electron-withdrawing groups prevent HAA at proximal carbons

https://doi.org/10.1021/jacs.8b05753

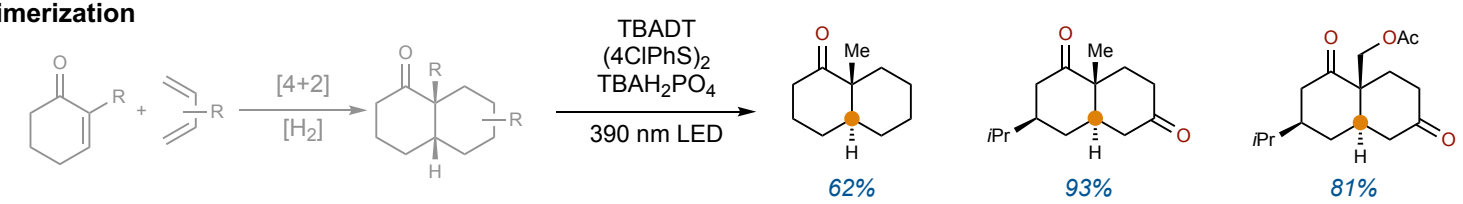
Stereochemical Editing

Wendlandt, 2022

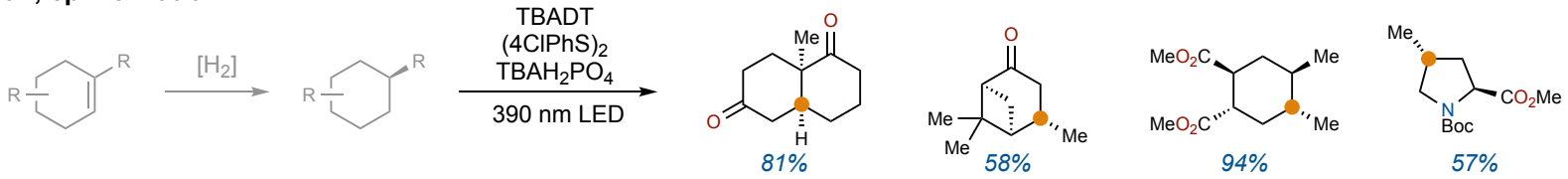




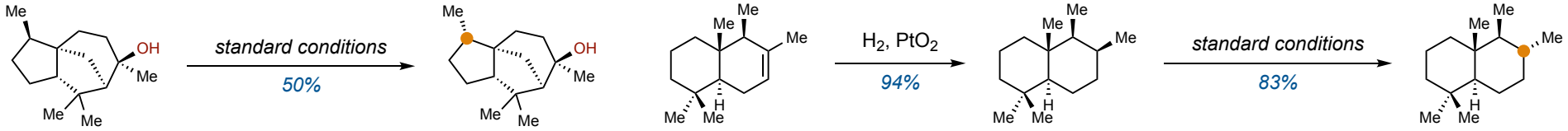
Diels–Alder; epimerization



Hydrogenation; epimerization



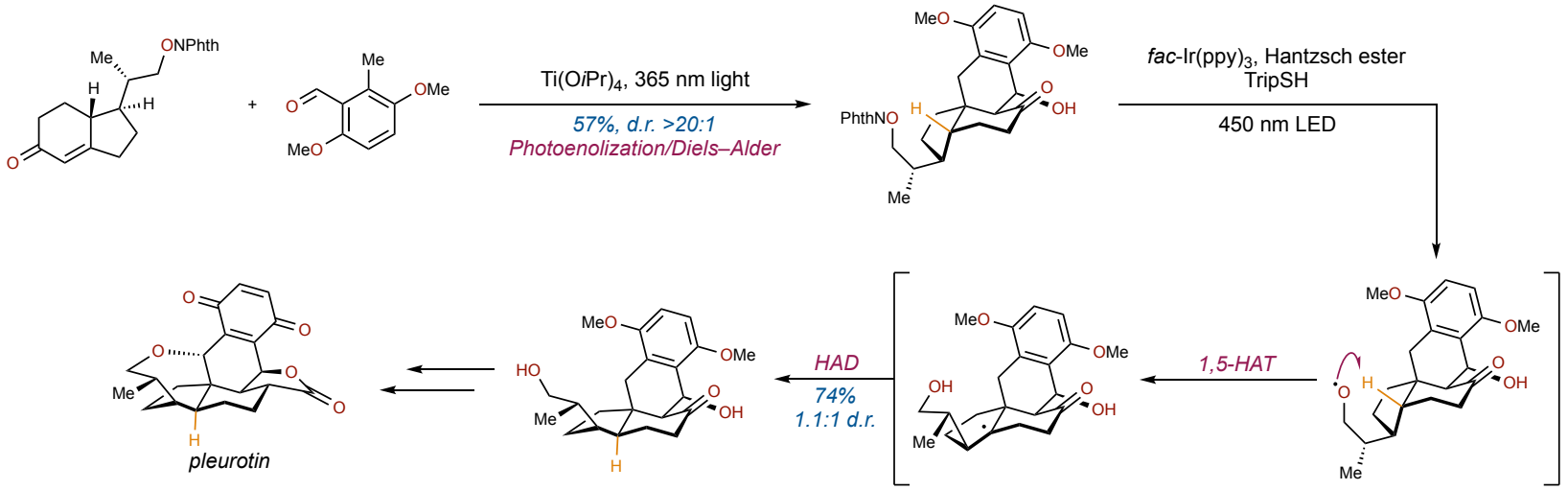
Chiral pool remodeling



https://doi.org/10.1126/science.add6852

Stereochemical Editing

Application in Total Synthesis



Summary, outlook, and my perspective

"Stereochemical Editing" is a sales pitch. It is nothing more than an extension of epimerization tactics to less obvious C–H bonds. Still as an idea, selective epimerization of any C–H bond is an attractive ideal.

The ability to change the stereochemistry of alcohols and tertiary C–H bonds is a potentially powerful new tool

- Relying on the substrate limits the substrate scope to privileged substrates
- Mixtures of stereoisomers could be challenging to deal with
- Where are the olefins?!

External controls (cyclic boronic esters, photocatalysts, amines) can push equilibrium to favor more difficult to access products

Will stereochemical editing lead to a shift in thinking when it comes to retrosynthesis?

- Cyclization phase followed by editing phase
- I think not yet… there is lack of olefin functional groups, poor stereocontrol in complex settings, no predictive model in complex molecules. Still, when an epimer can be easily made and the functionality is amenable to editing, it is a unique disconnection.