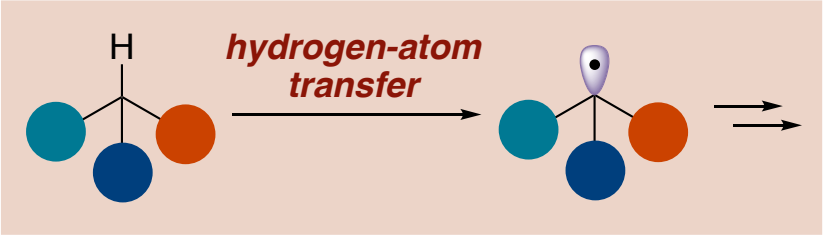
Radical-based C-H Functionalization and Modification of Small and Large Molecules

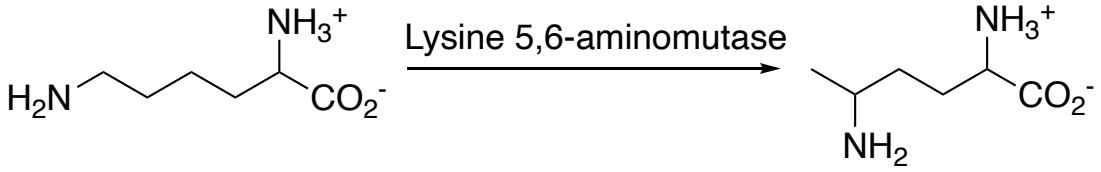


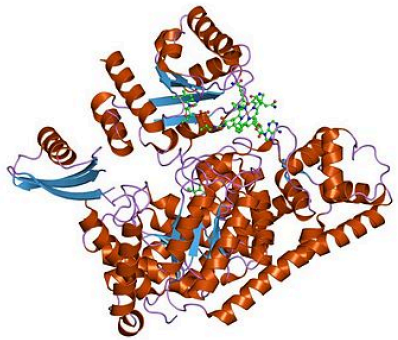
Yumeng Xi
Materials Research Laboratory
University of California, Santa Barbara

1/14/2022
University of Illinois Urbana Champaign

Overview of Proposal #2

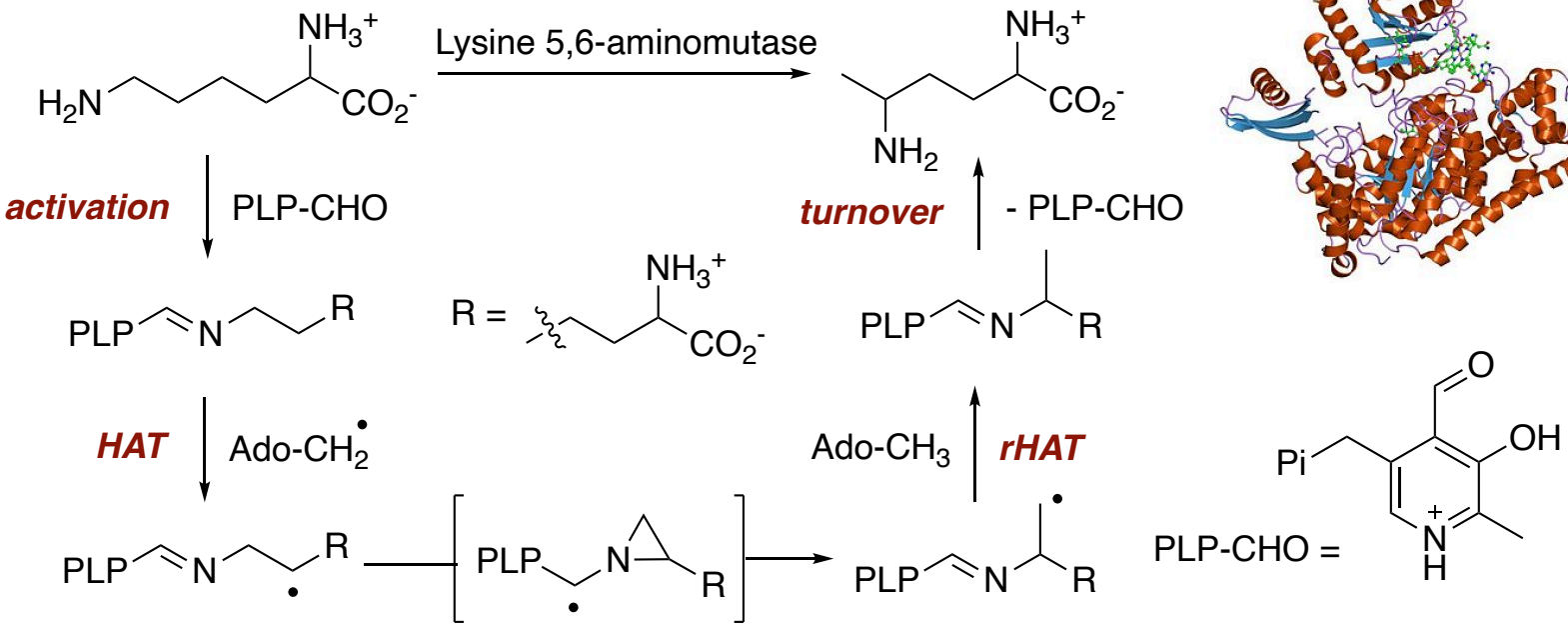
Amine translocation in biology





Overview of Proposal #2

Amine translocation in biology



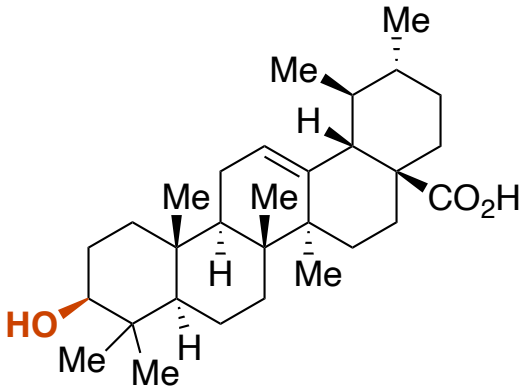
Trends Biotechnol. **2011**, *29*, 352

Overview of Proposal #2

- **Short-term goal**: proving the feasibility of functional group dance strategies; tuning chemo- and site-selectivity; expanding scope

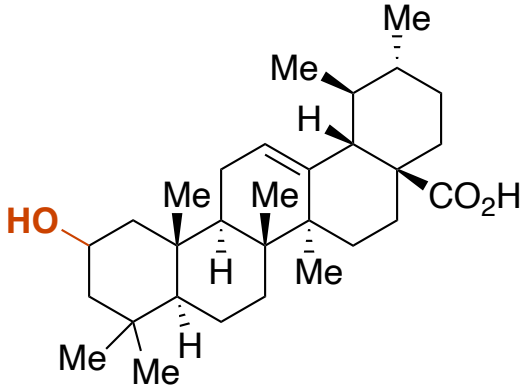
- **Long-term goal**: conducting late-staging editing; establishing FG migratory functionalization; collaborating with synthetic and medicinally chemists on total synthesis and drug discovery

Why Do We Care about FG Dance?



IC_{50} (RMGPa): 15.3 μM

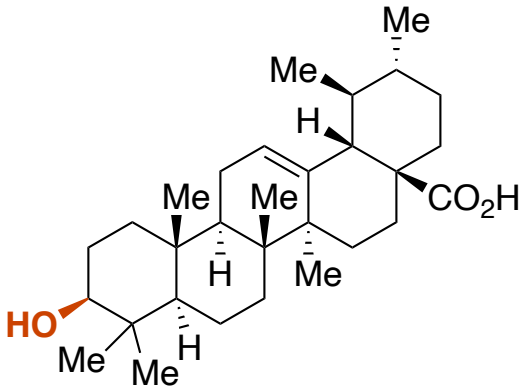
7-steps



R isomer IC_{50} (RMGPa): 5.5 μM
S isomer IC_{50} (RMGPa): 1.2 μM

J. Nat. Prod. **2009**, *72*, 1414.

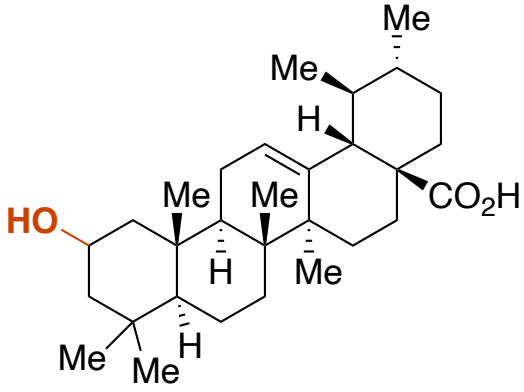
Direct Access to Positional Isomers



IC_{50} (RMGPa): 15.3 μM

1-2 steps?

what about the reverse reaction?



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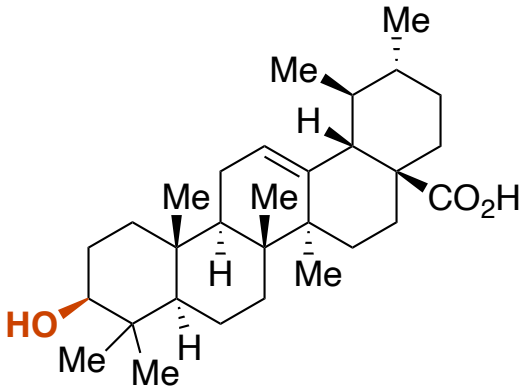
S isomer IC_{50} (RMGPa): 1.2 μM

J. Nat. Prod. **2009**, *72*, 1414.

- ❑ Site-selectivity?
- ❑ Chemoselectivity?
- ❑ Reaction directionality?

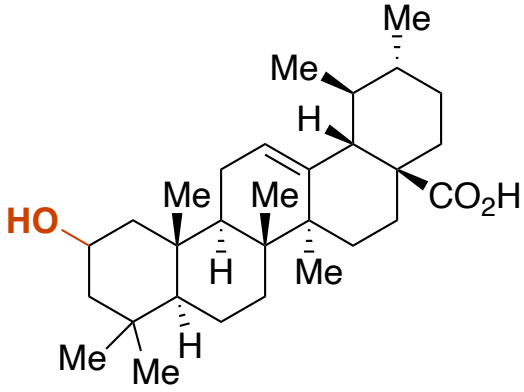
Expedite Synthetic Planning



IC_{50} (RMGPa): 15.3 μM

1-2 steps?

reversibility?



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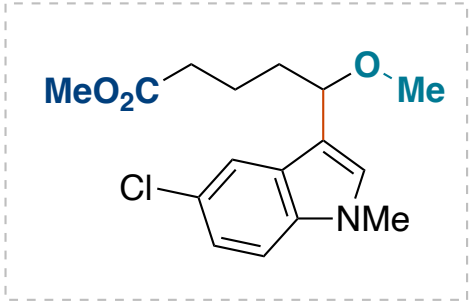
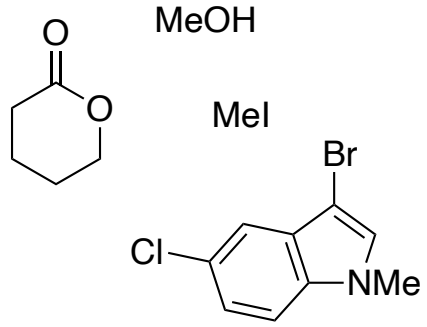
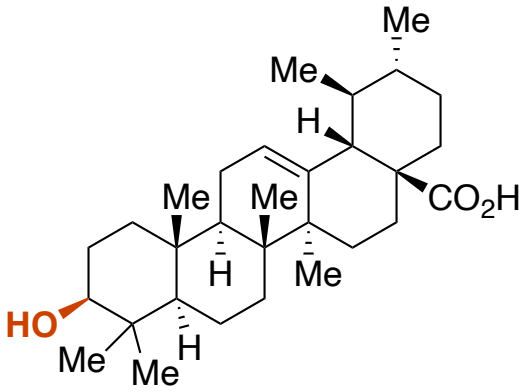


4-5 steps

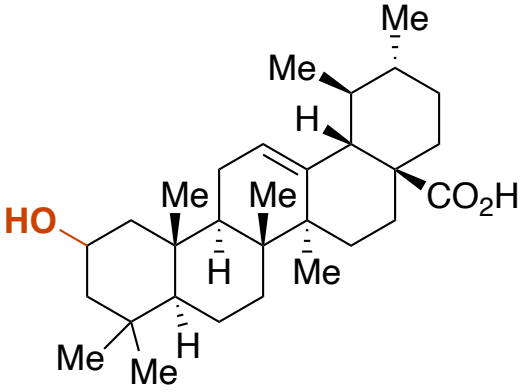


Expedite Synthetic Planning



1-2 steps?

reversibility?



IC_{50} (RMGPa): 15.3 μM

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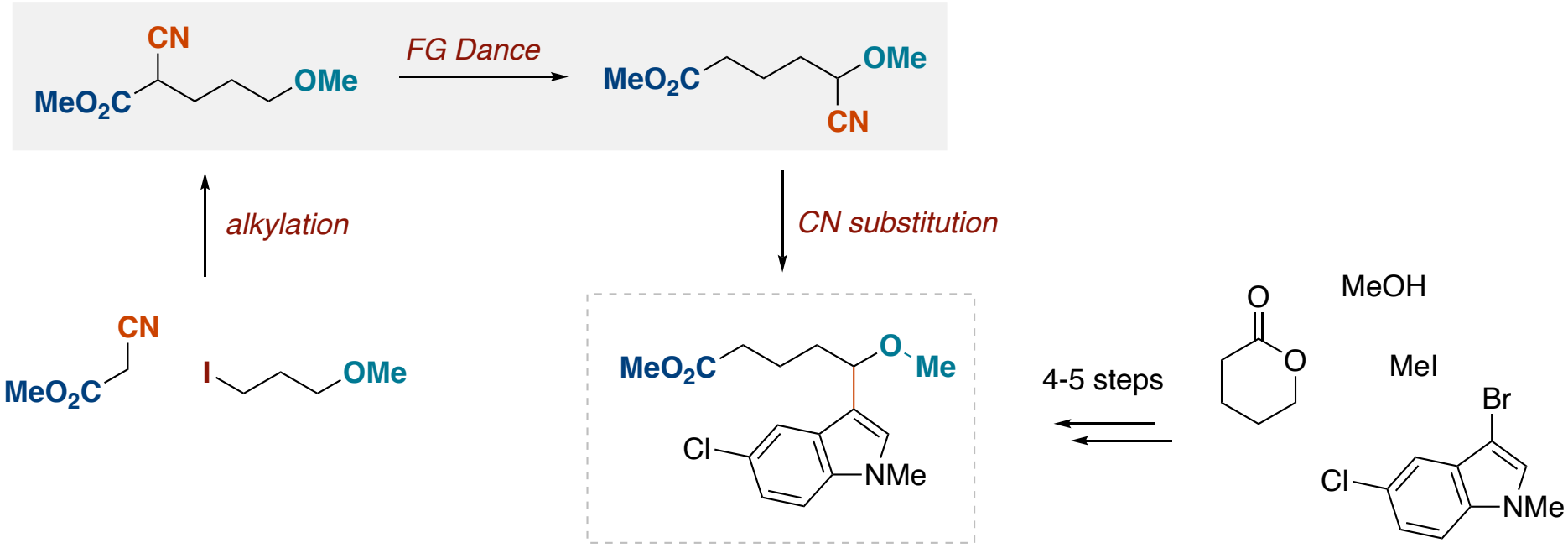
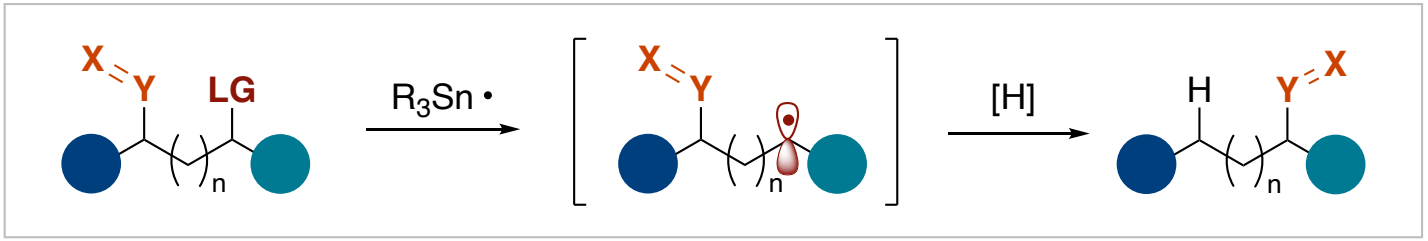
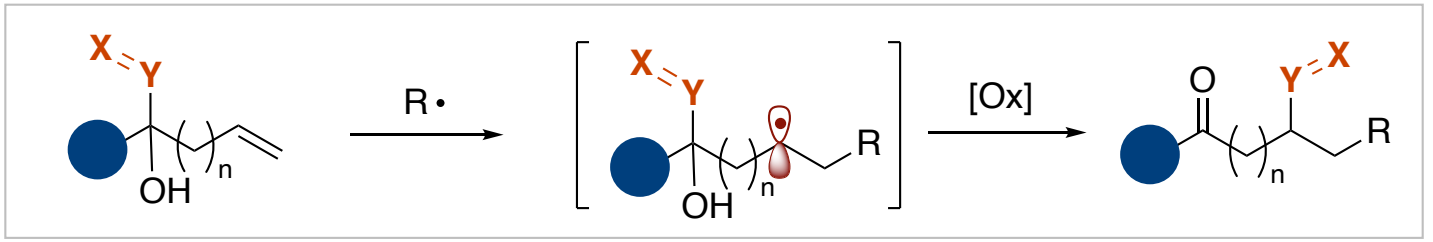
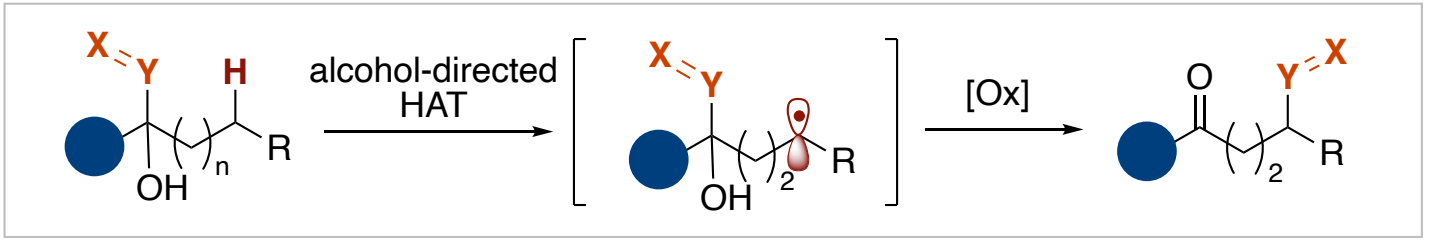
J. Nat. Prod. **2009**, *72*, 1414.



Precedents of Radical Rearrangement Reactions



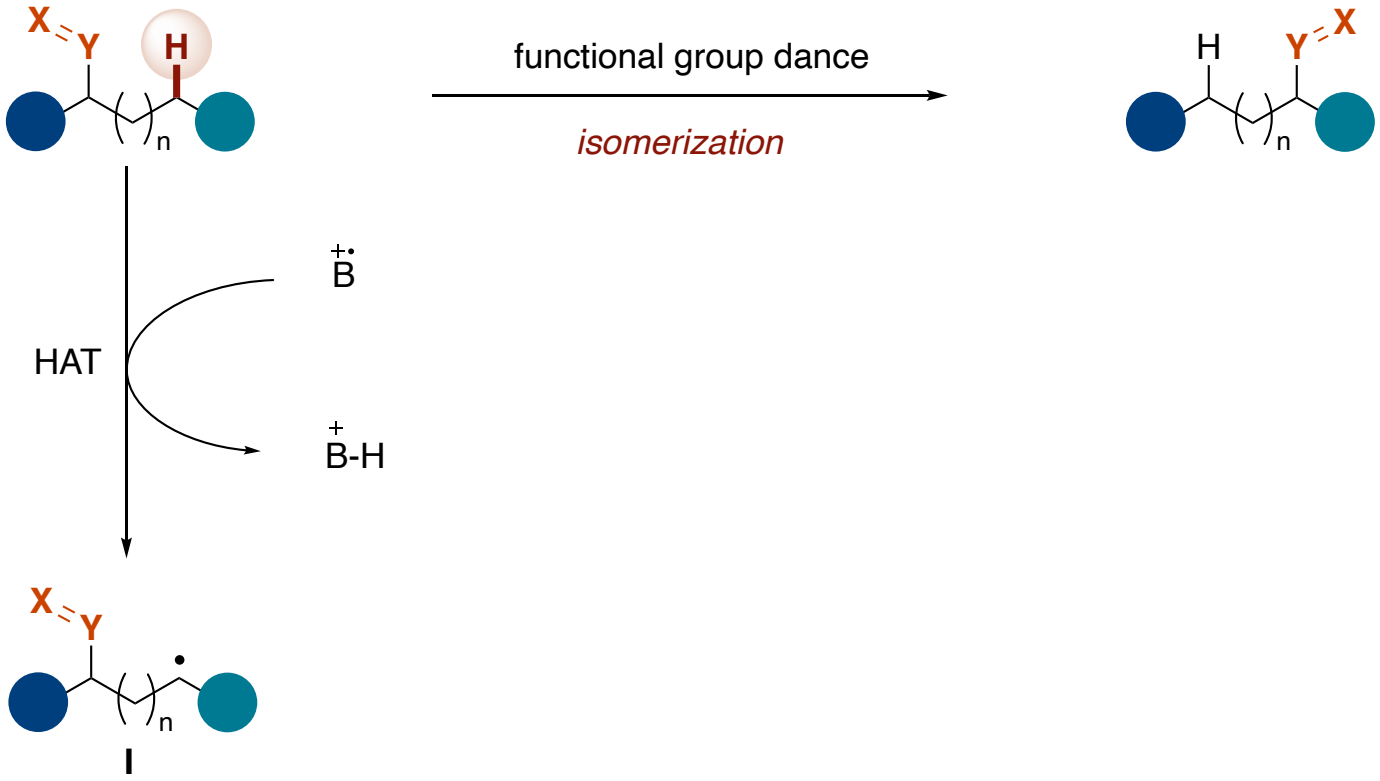




Chem. Soc. Rev. **2021**, *50*, 11577.

Design of Catalytic Systems for Functional Group "Dance"

- The site where FG is migrated to can be tuned by substrates and HAT/rHAT catalysts/reagents.



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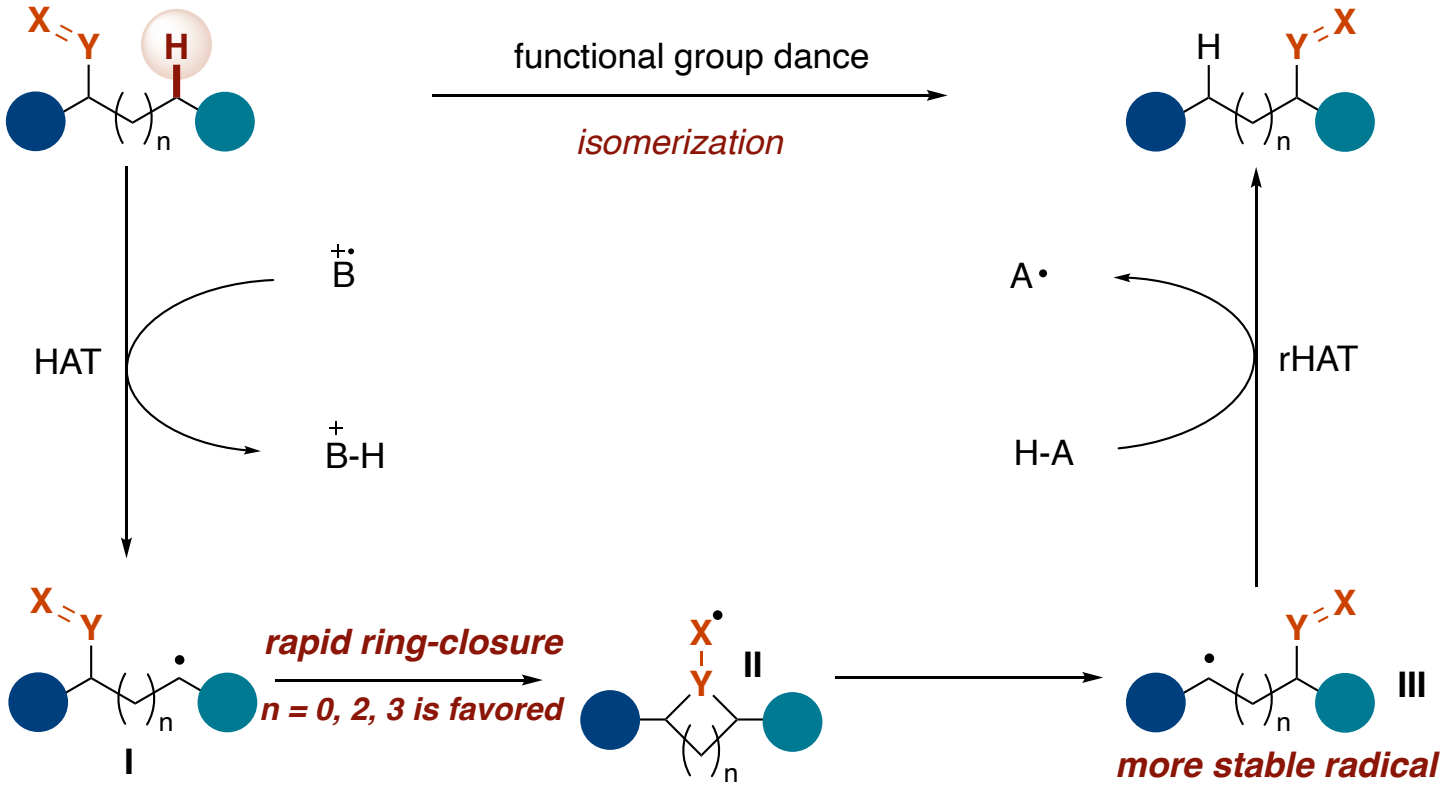
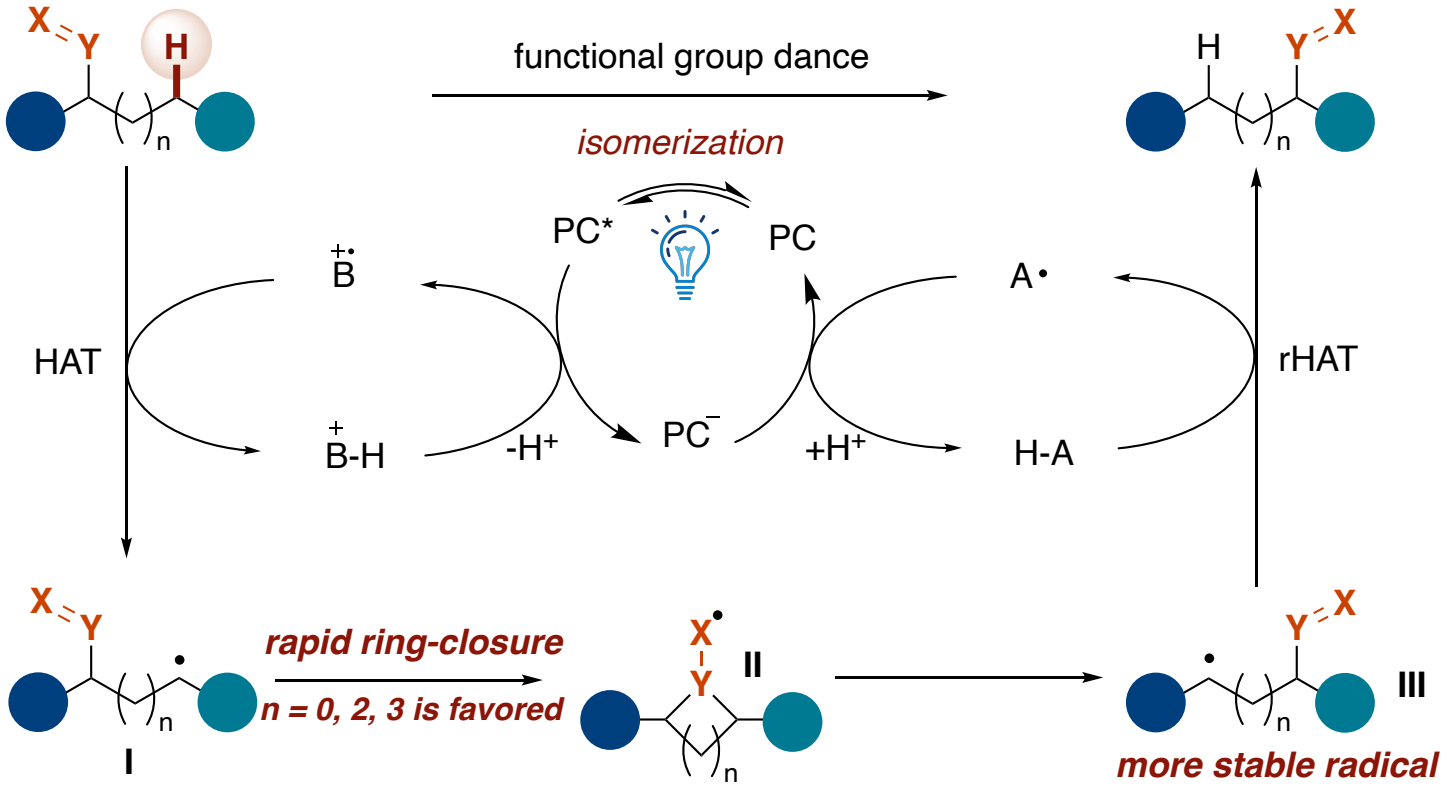


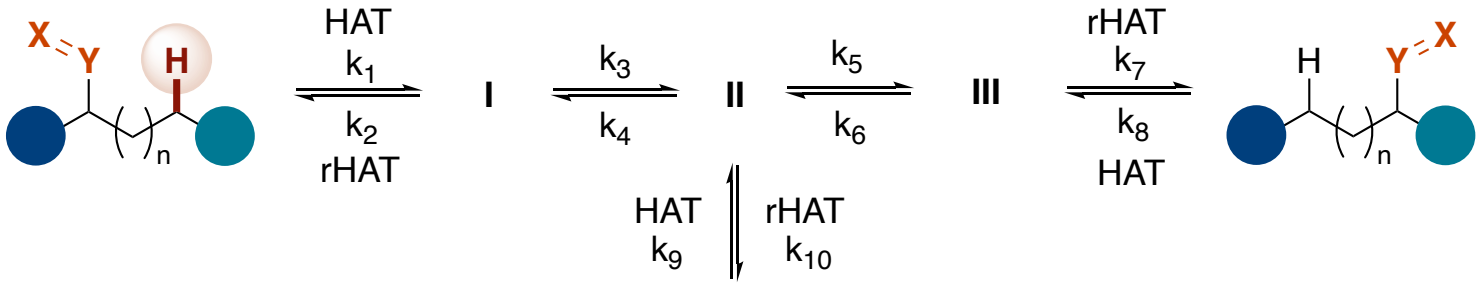
Design of Catalytic Systems for Functional Group "Dance"

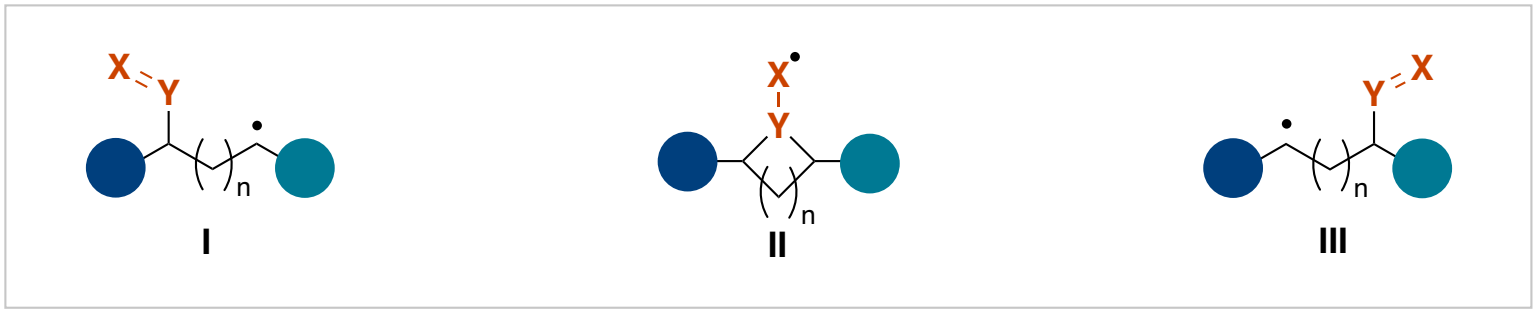
- The site where FG is migrated to can be tuned by substrates and HAT/rHAT catalysts/reagents.



- **Grand challenge**: how to control reaction direction, selectivity and efficiency?

Kinetically Controlled Systems for Functional Group "Dance"

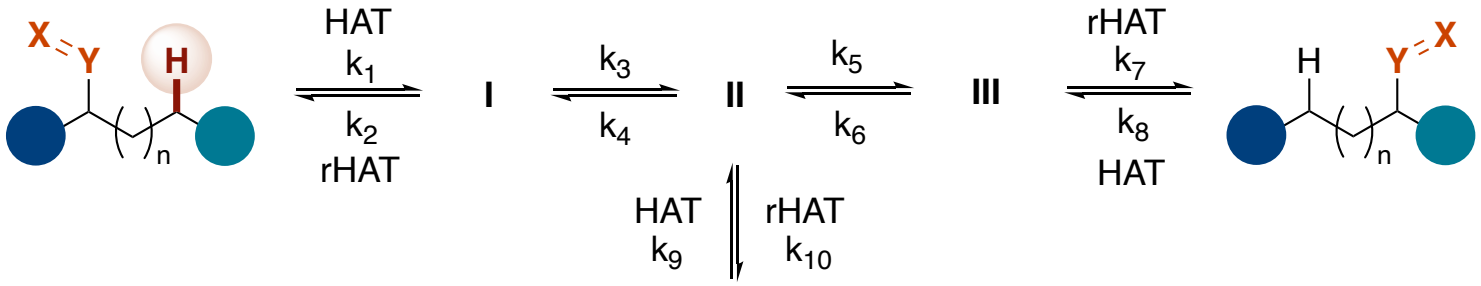




Key criteria for designing kinetically controlled, catalytic systems for functional group dance.

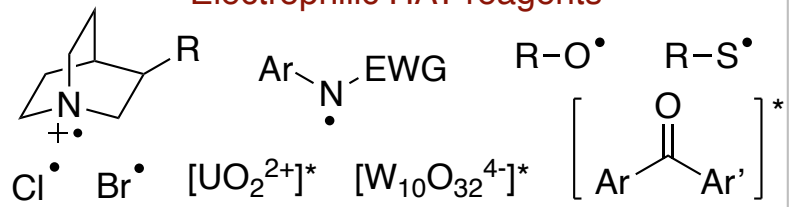
- Rate constant k_8 (backward HAT) is smaller than the overall rate constant for the forward reaction.
- Rate constant k_2 should be on similar magnitude with k_3, if not much smaller, to ensure productive catalysis.
- Transition state for rHAT of intermediate II is high in energy.

Design of Kinetic Systems for Functional Group "Dance"

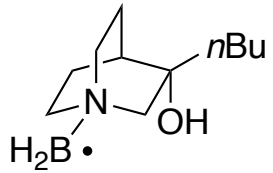


- Pool of HAT reagents

Electrophilic HAT reagents

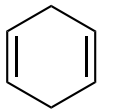


Nucleophilic HAT



rHAT reagents

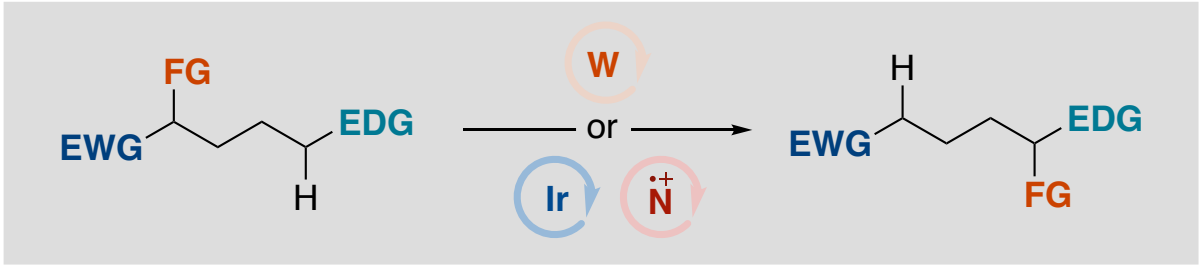
AlkylS-H
Hantzsch ester
ArS-H
$(RO)_2P(O)H$
TMS_3SiH
$PyBH_3$



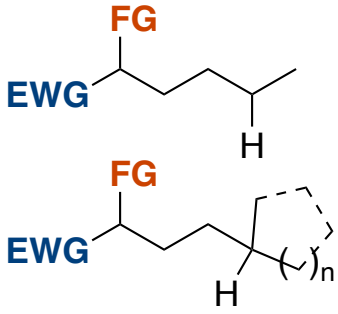
Factors to consider:

- Bond dissociation energy, polarity matching
- Known HAT/rHAT rate constants
- Radical cyclization rate constants

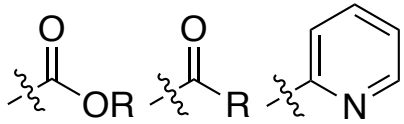
Proof-of-Concept Study using a Biased System



Alternative system

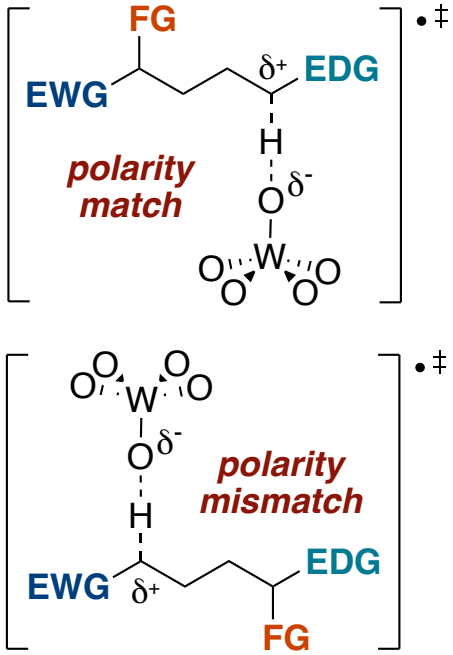


FG = CN

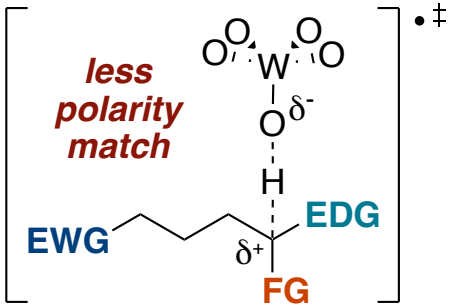
EWG = 

EDG = 

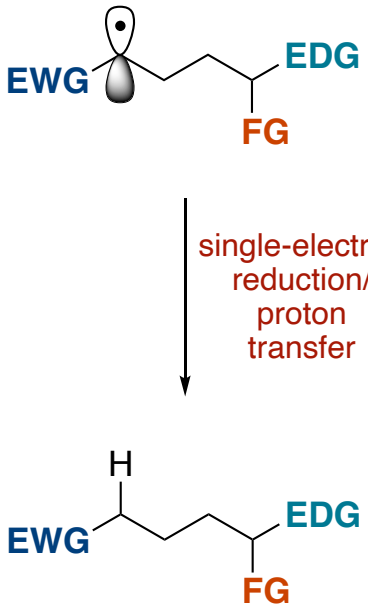
❑ No reverse reaction



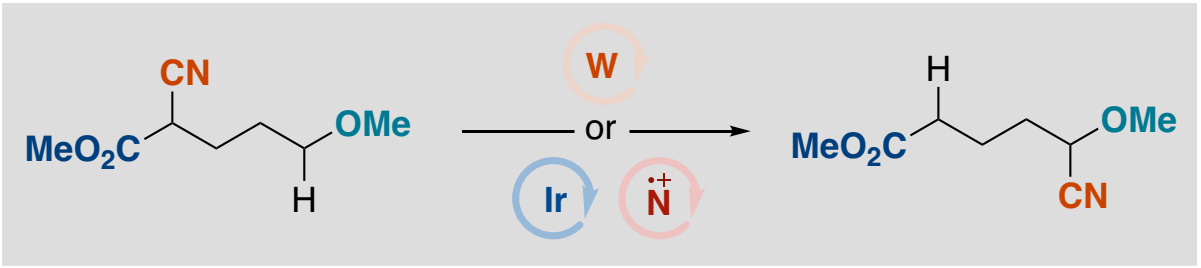
❑ No HAT with products



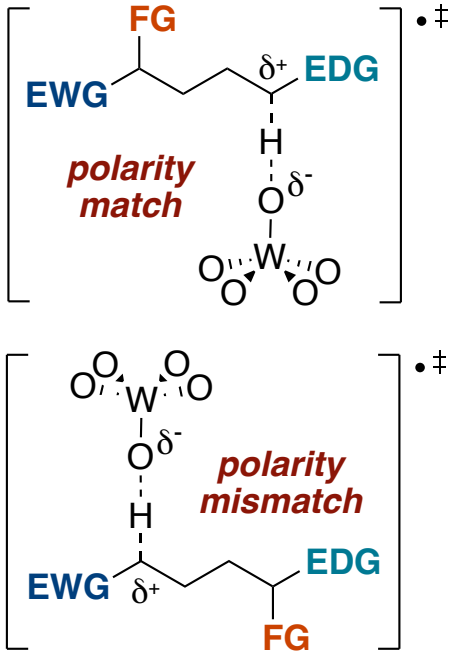
❑ No HAT donor needed



Proof-of-Concept Study using a Biased System



❑ No reverse reaction



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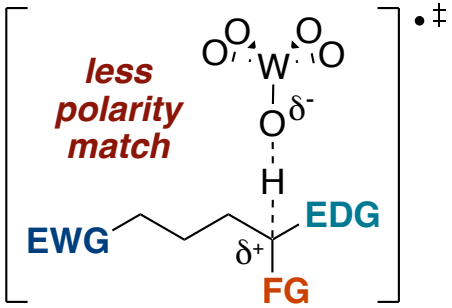

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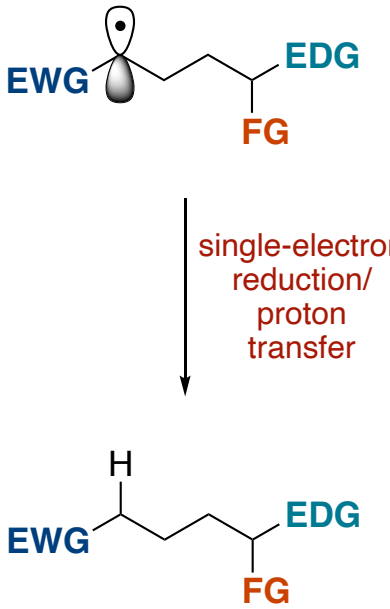
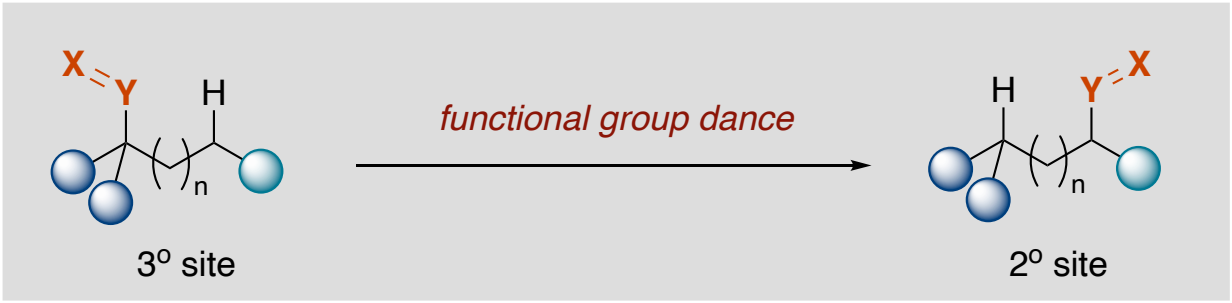
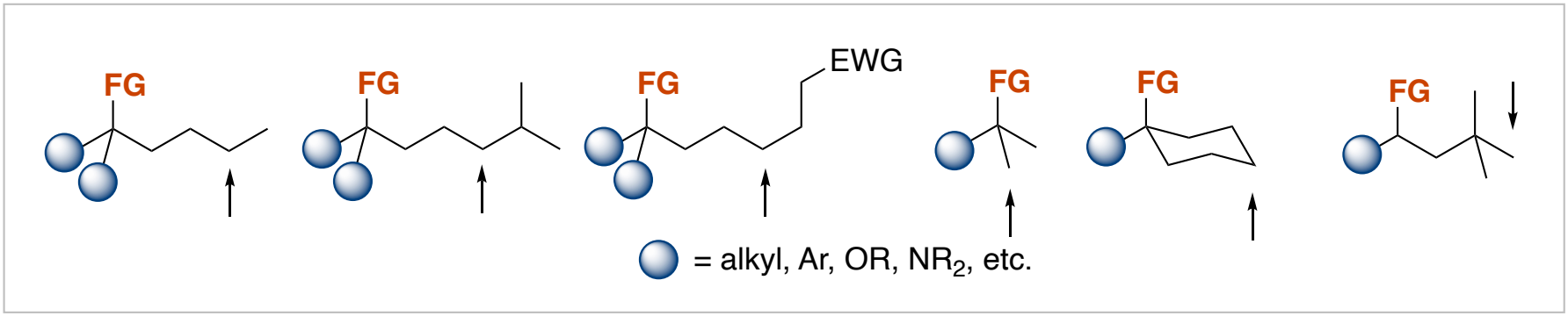
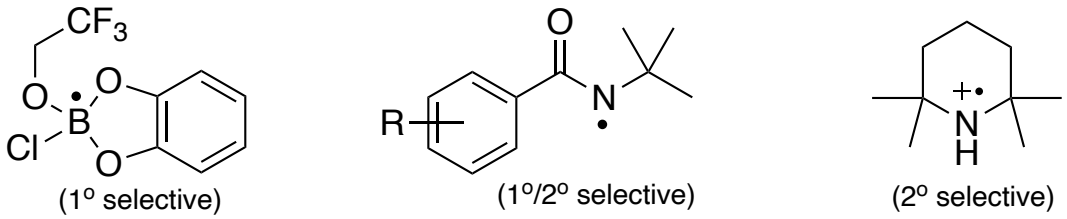


Tuning Selectivity in Unbiased Systems



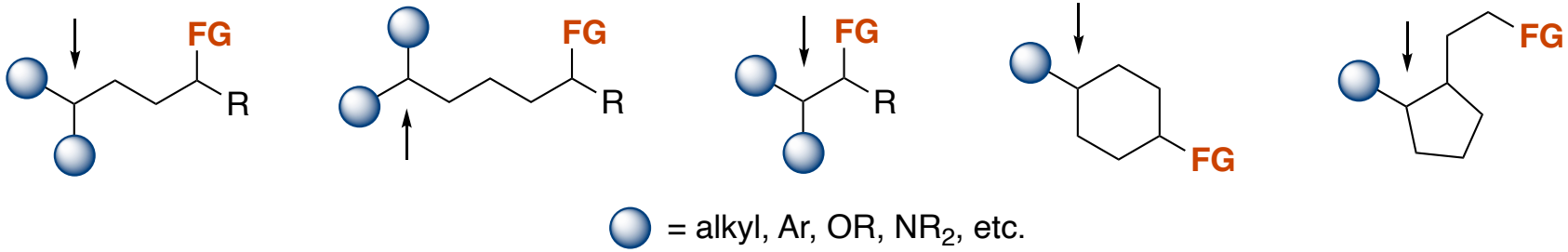


Potential HAT reagent

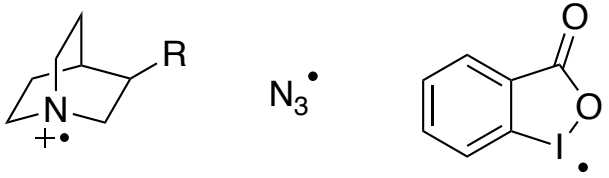


- Reaction direction is driven by 1) HAT selectivity for 1°/2° carbon and 2) formation of a more stable tertiary radical.
- No major difference in rate constants for rHAT of 1°/2°/3° radical with thiols.

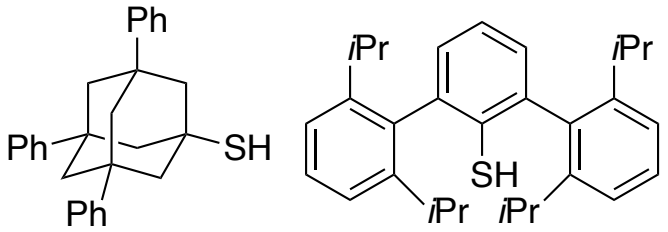
Reversing Selectivity in Unbiased Systems



Potential HAT reagent



Bulky rHAT reagent

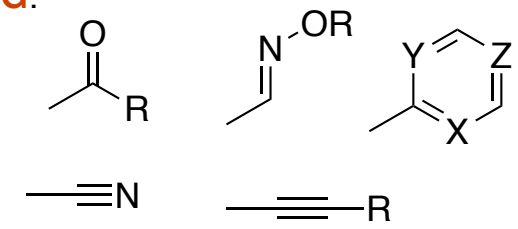


- Reaction direction is in Curtin-Hammett regime and driven by HAT selectivity for 3° carbon.

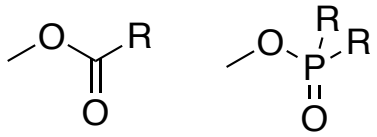
Expanding the Scope of FG Dance

Possible migrating FGs

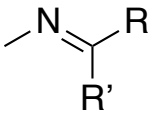
FG:



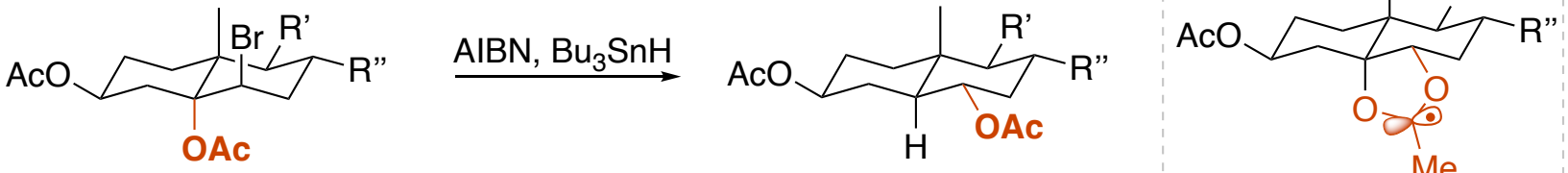
FG (masked alcohol):



FG (masked amine):



R = Ar, CO_2Me



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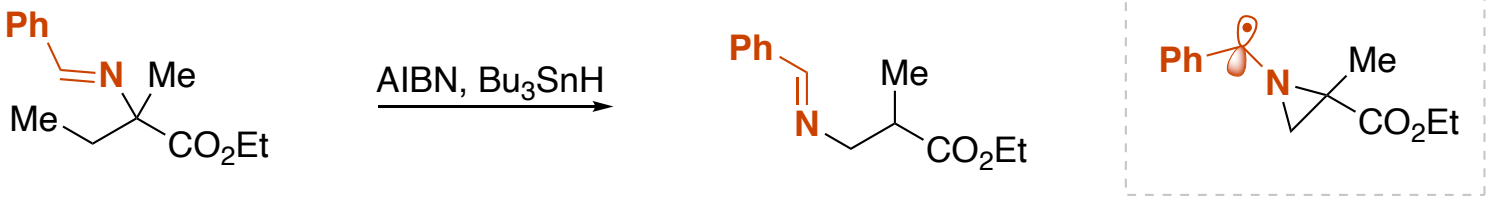

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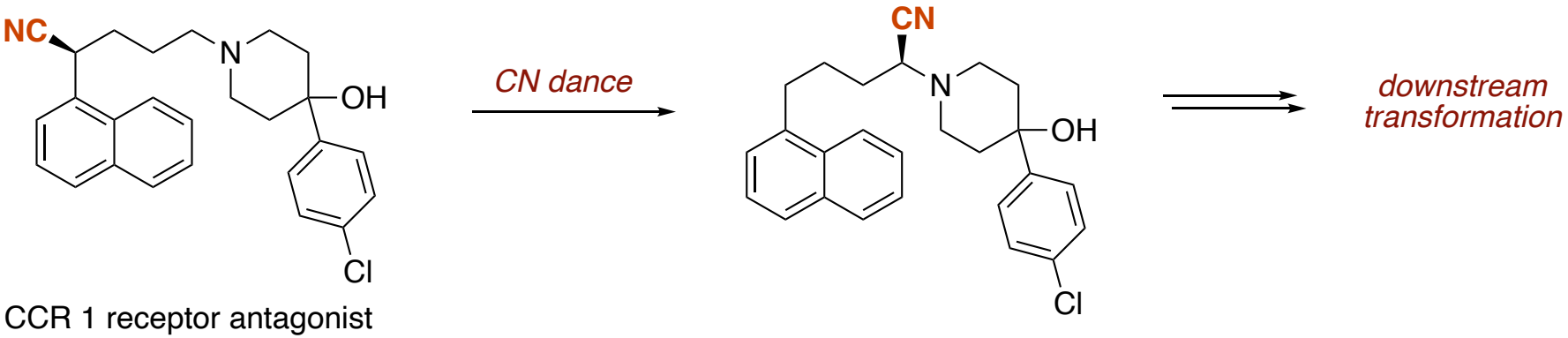
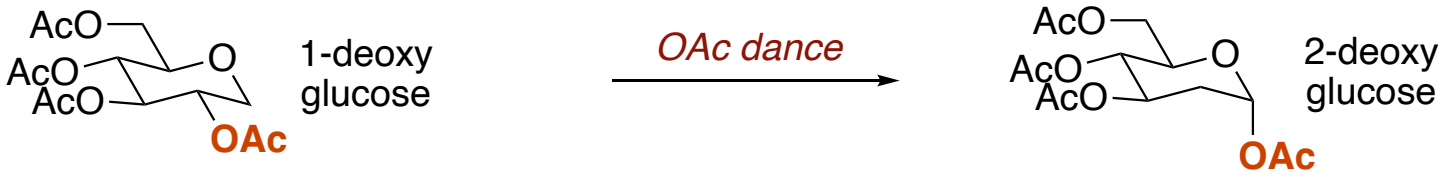
Late-Stage Editing of Complex Molecules using FG Dance

Drug-like molecules



CCR 1 receptor antagonist

Biomolecules



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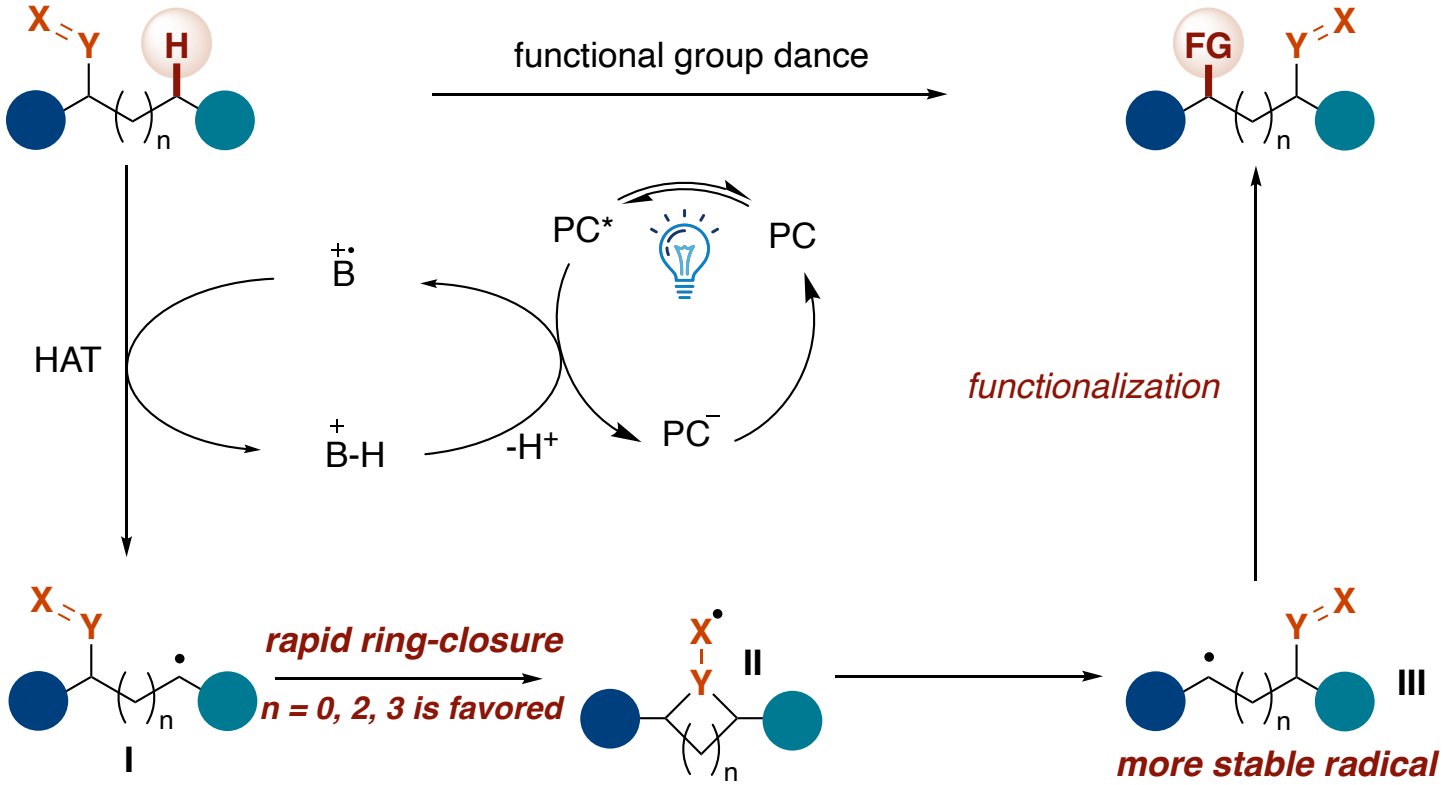
Additional Long-Term Goal: FG Migratory Functionalization



Complex molecule editing