Why would you use computational chemistry?

Robert T. Martin

Group Meeting

March 7th, 2025

Why do we use experimental chemistry?

Why do we use experimental chemistry?

Why do we use experimental chemistry?

Where do experiments fall short?

Where do experiments fall short?

"The file-drawer problem"

Positive results

$p < 0.05$

Negative results

$p > 0.05$

Where do experiments fall short?

"The file-drawer problem"

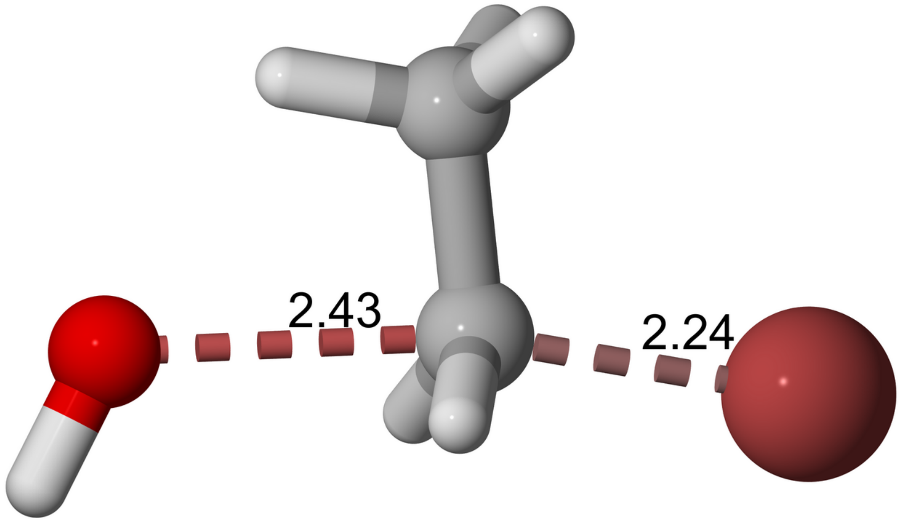
Positive results

$p < 0.05$

Negative results

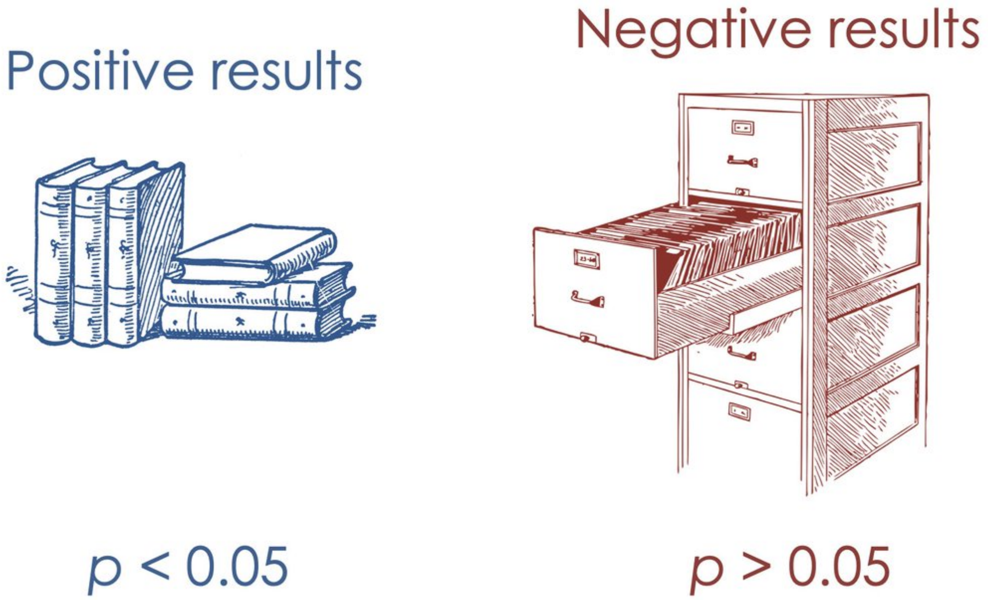
$p > 0.05$

Transition states

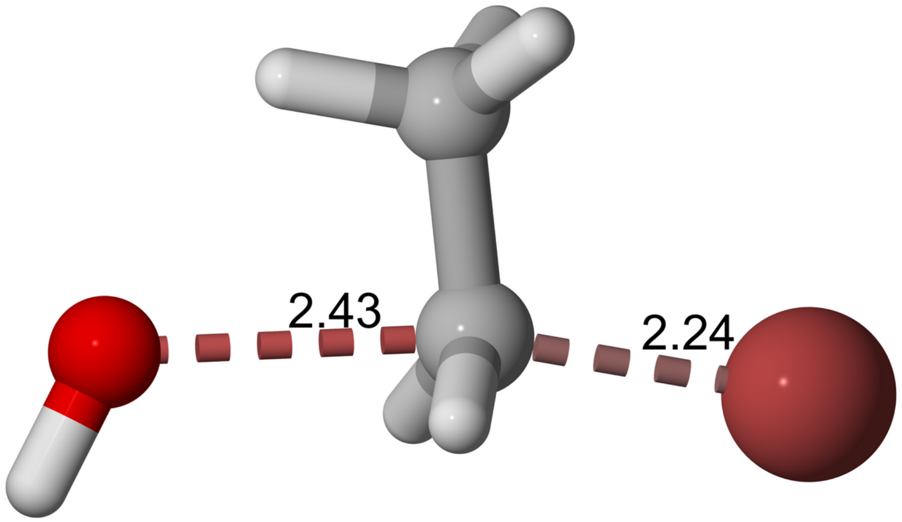


Where do experiments fall short?

"The file-drawer problem"



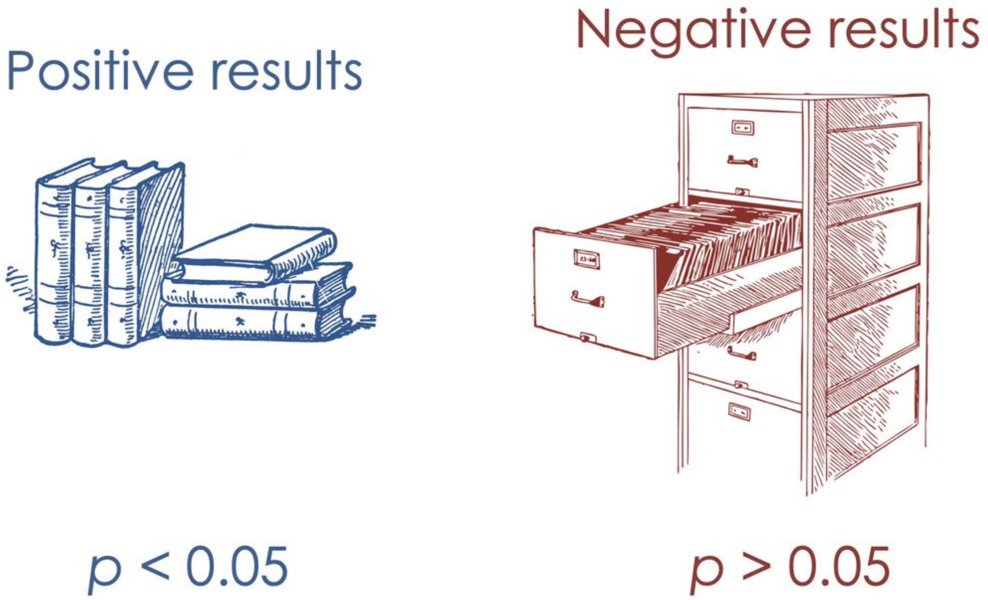
Transition states



Cost, sustainability, and time

Where do experiments fall short?

"The file-drawer problem"



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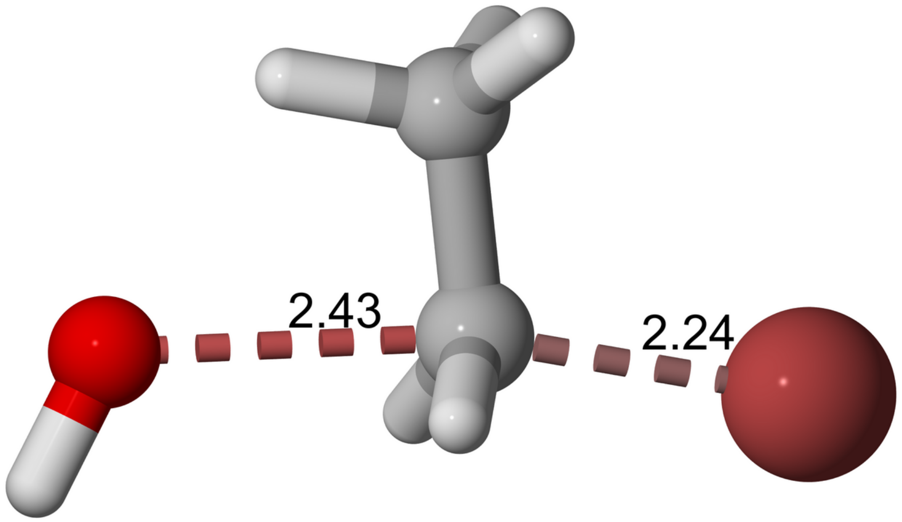
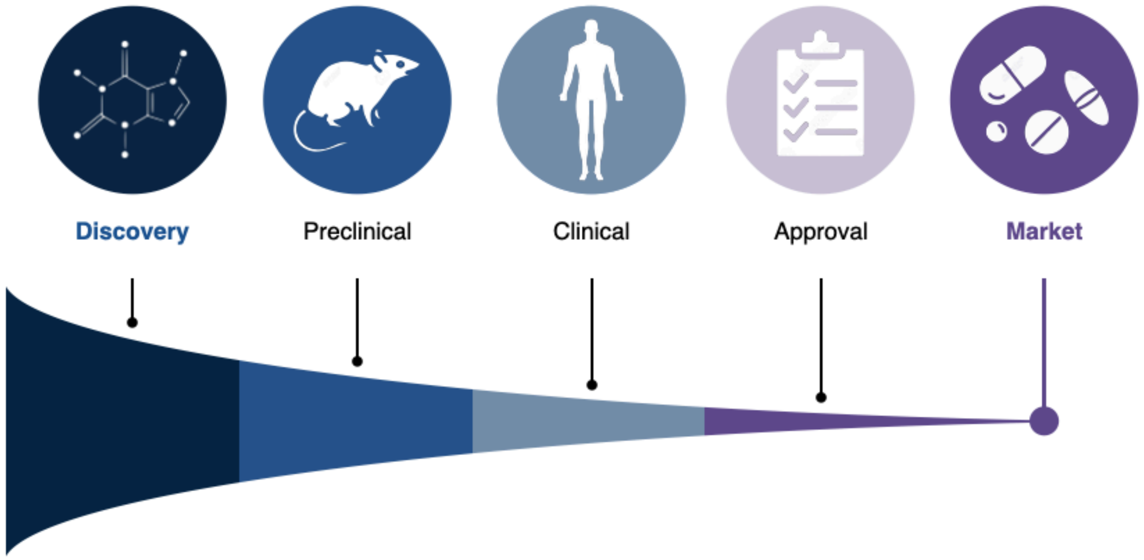


Cost, sustainability, and time



What can computational chemistry do for you?

What can computational chemistry do for you?

Understanding how molecules act

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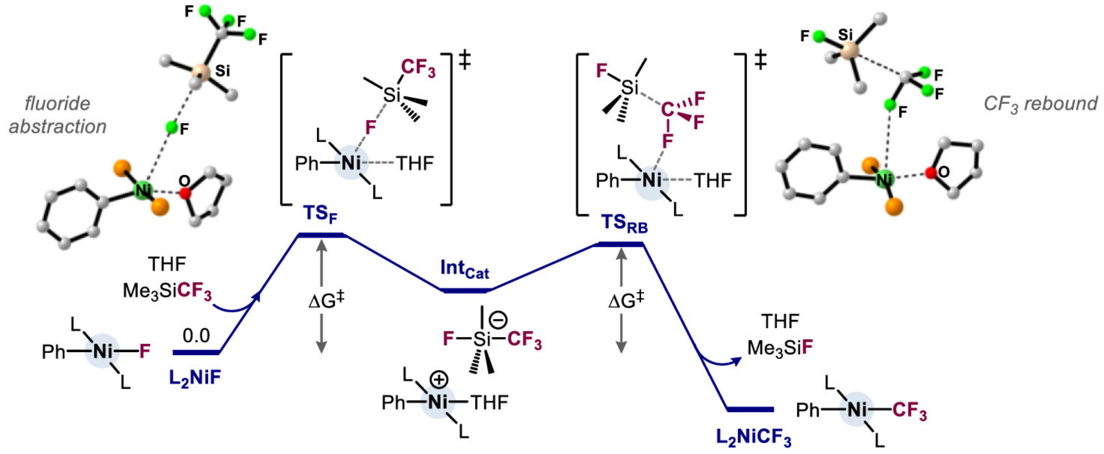
Understanding how molecules act

Predicting how molecules should act

What can computational chemistry do for you?

Understanding how molecules act

Density functional theory



Predicting how molecules should act

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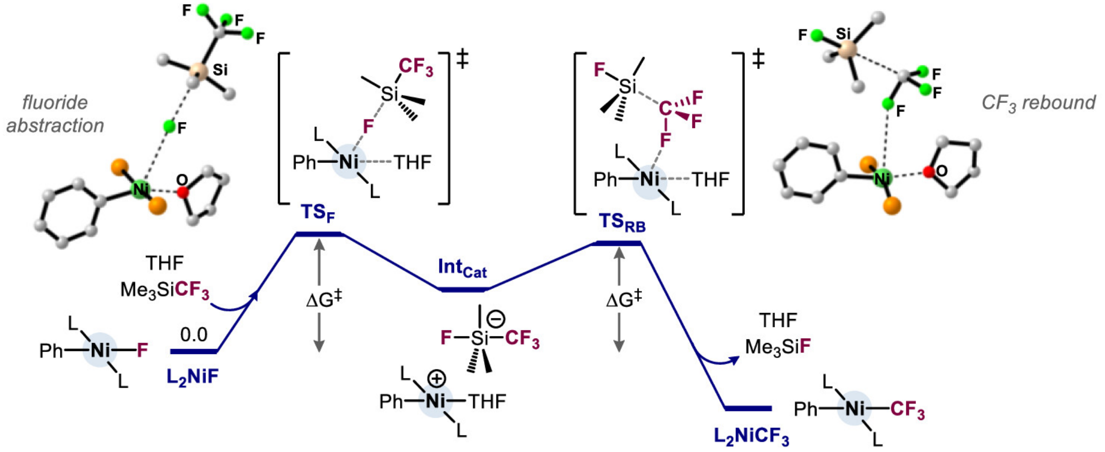
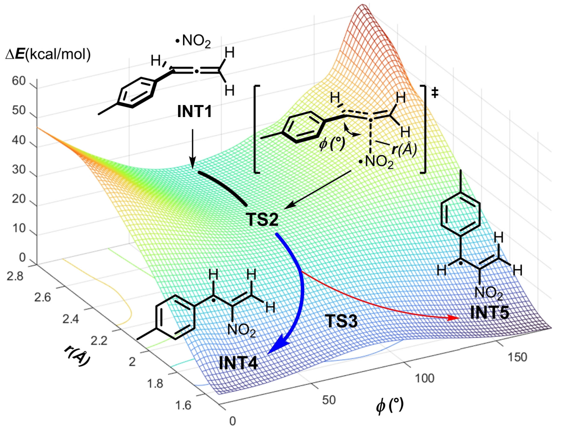
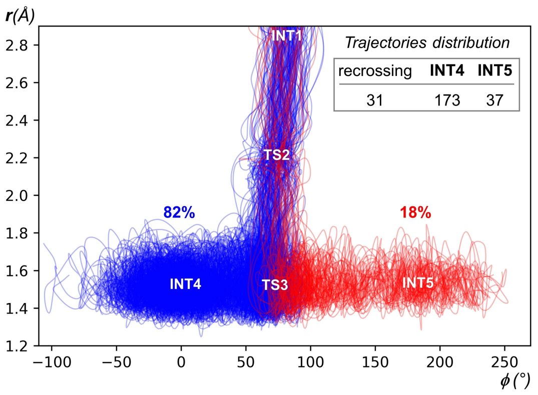


Dynamics Simulations





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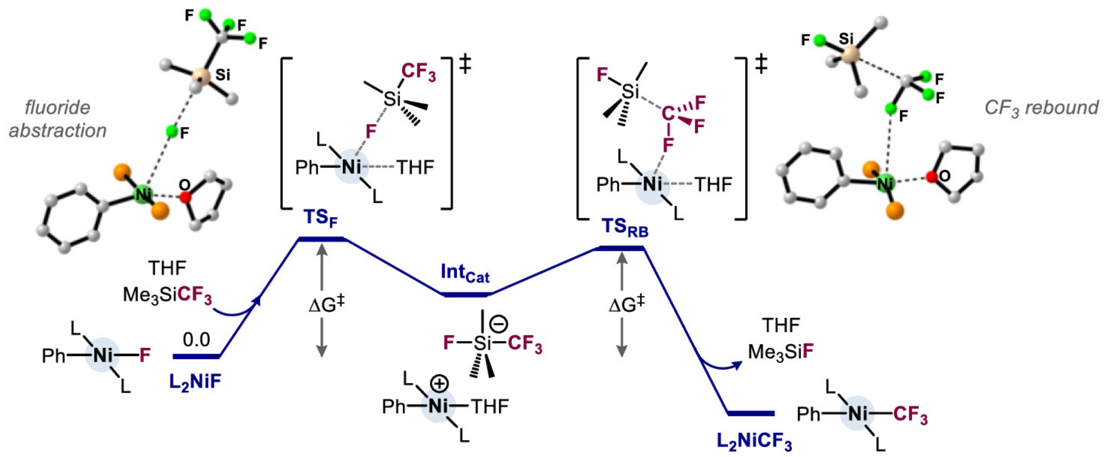

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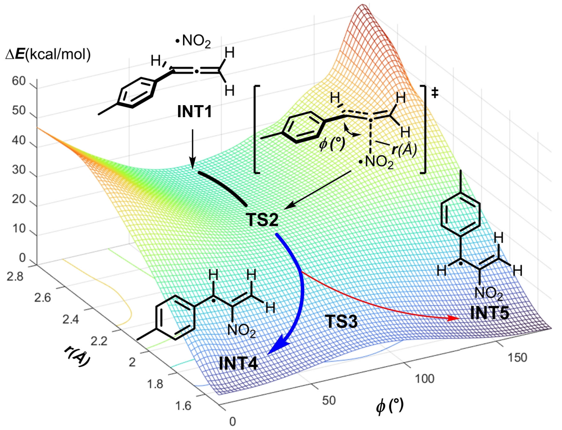
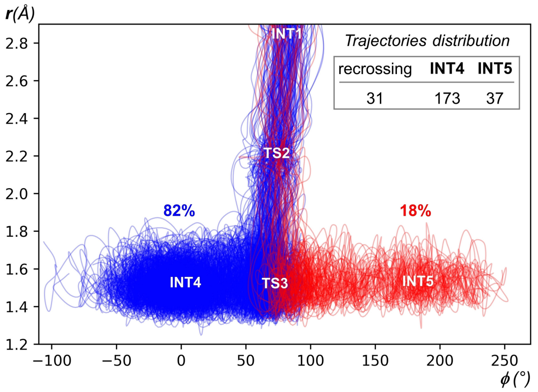
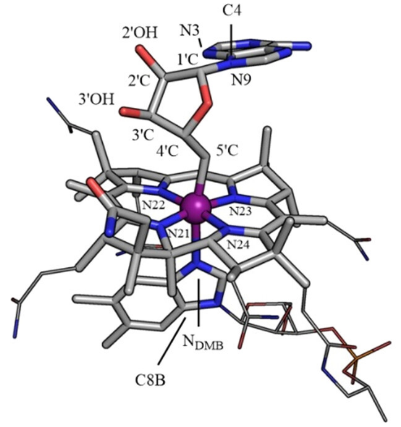
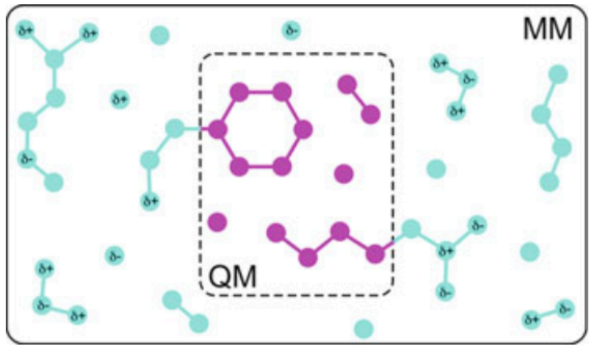




QM/MM





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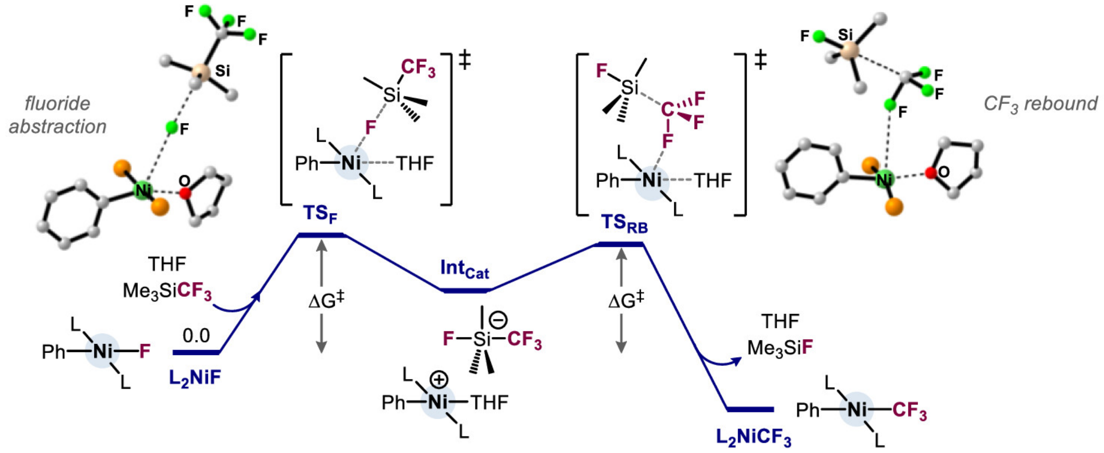

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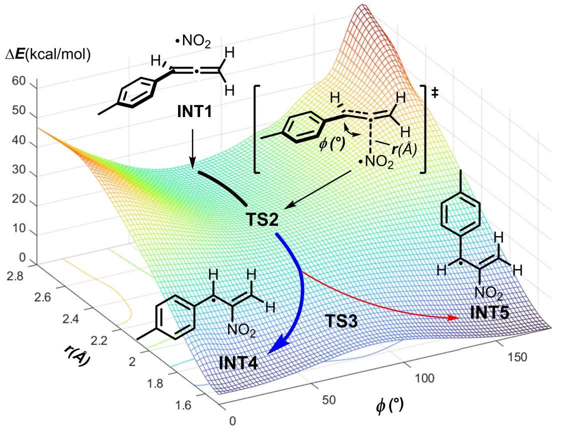

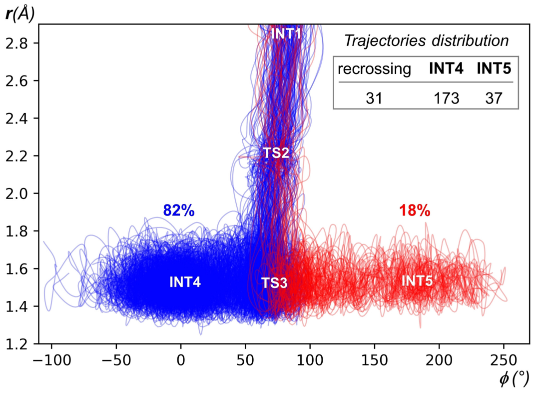

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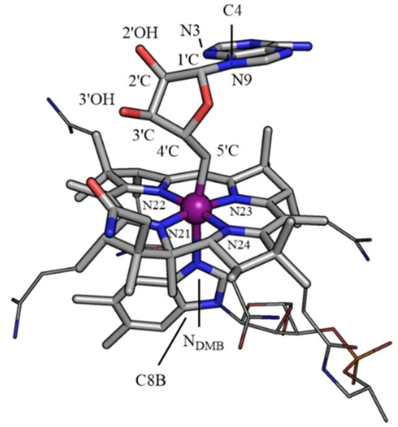
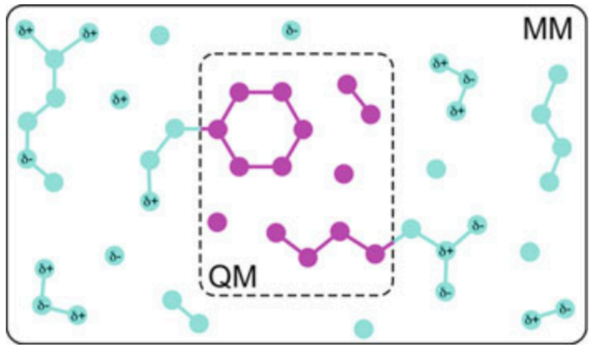
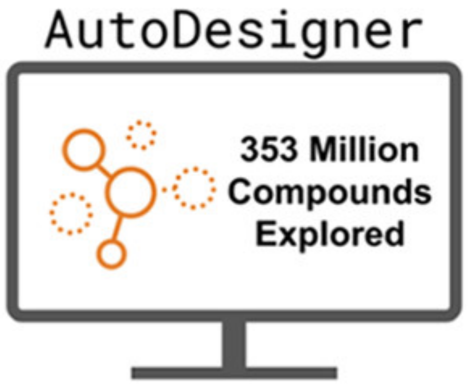
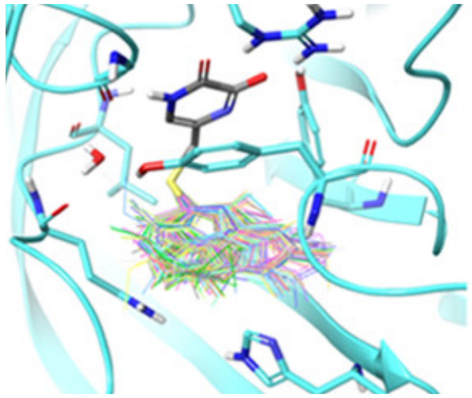




Predicting how molecules should act

Machine learning





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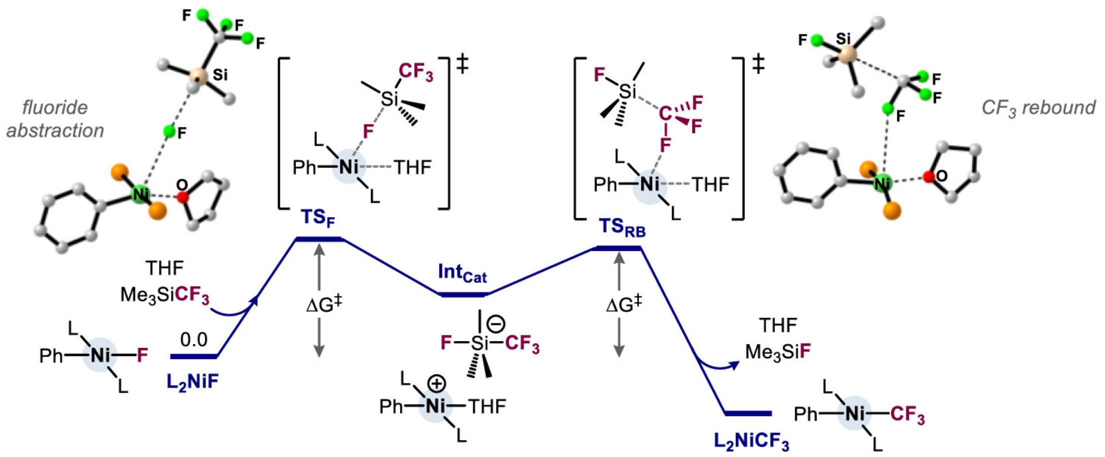
Density functional theory



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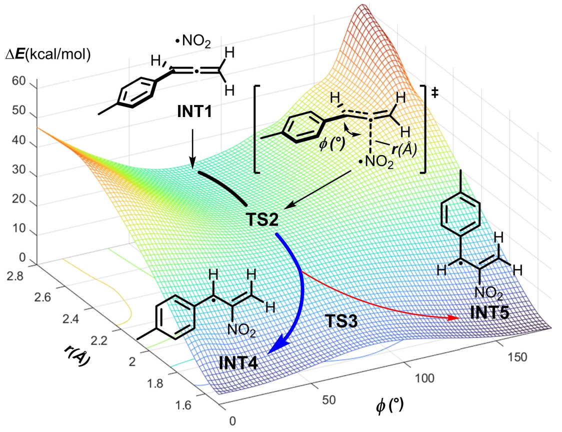

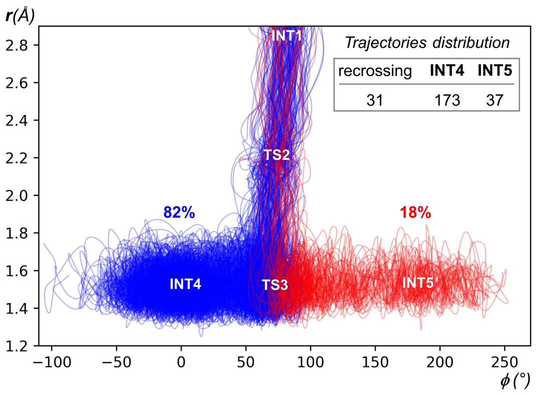

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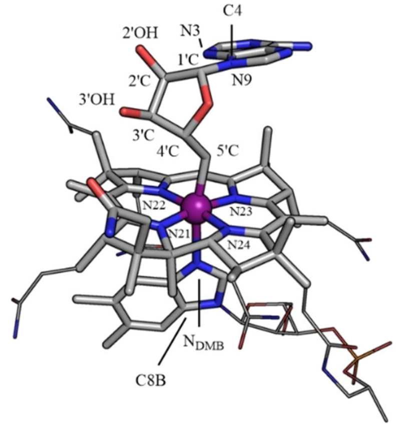

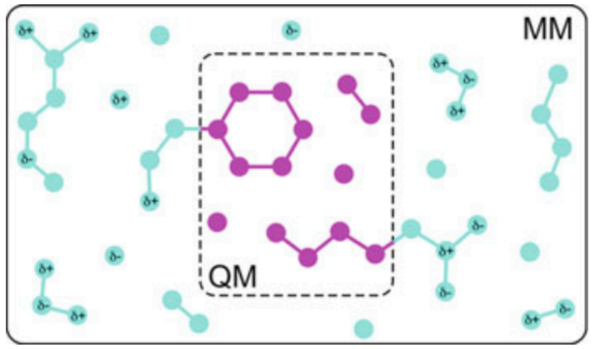

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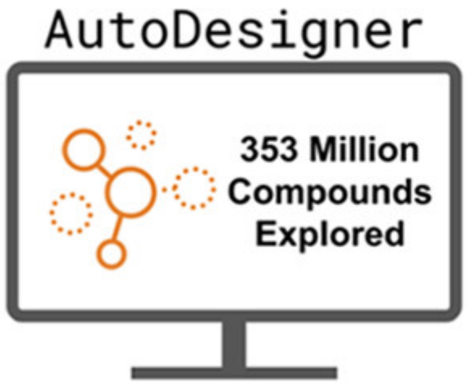
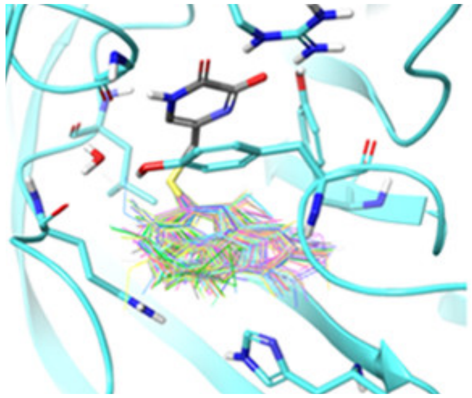
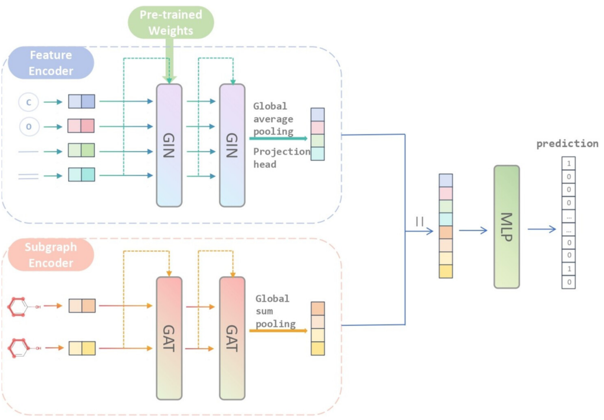
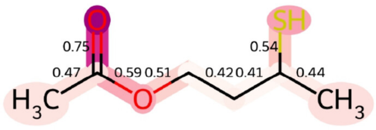




Neural networks

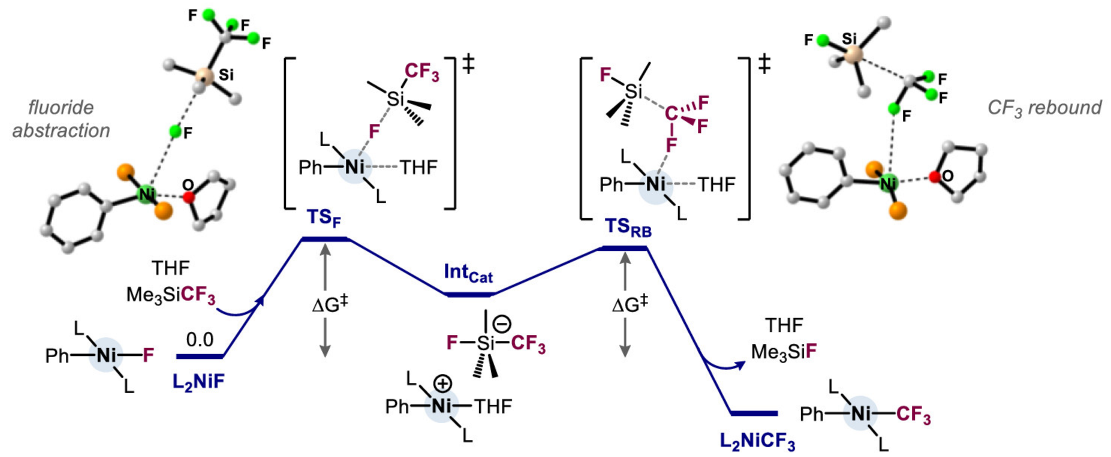




What can computational chemistry do for you?

Understanding how molecules act

Density functional theory



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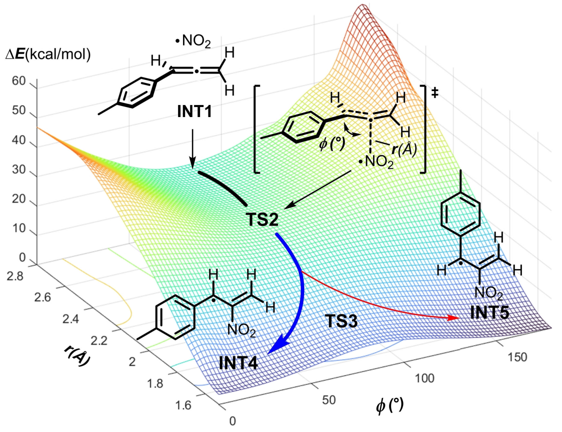

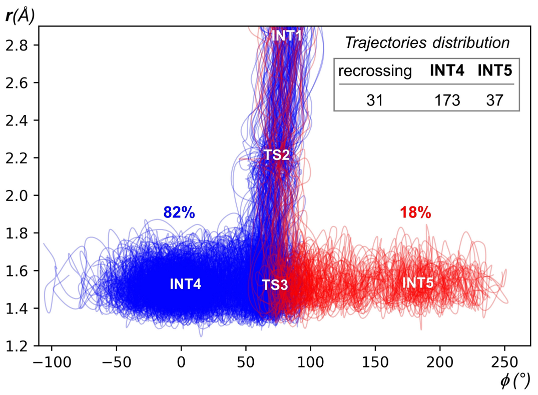

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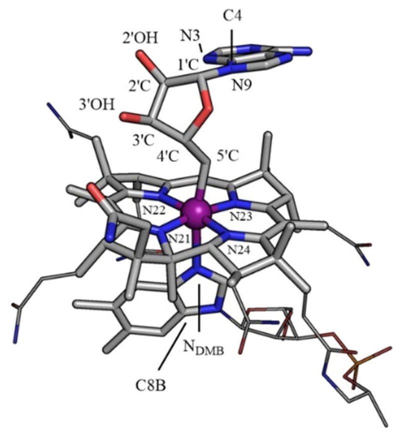

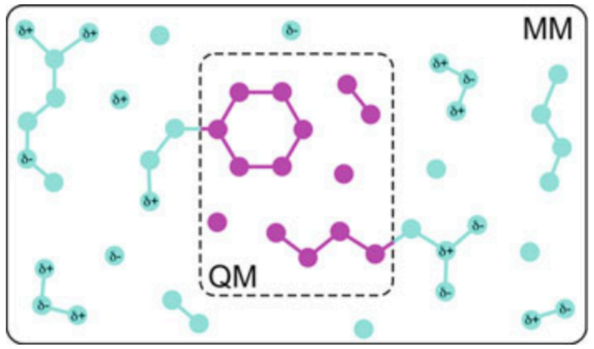

Predicting how molecules should act

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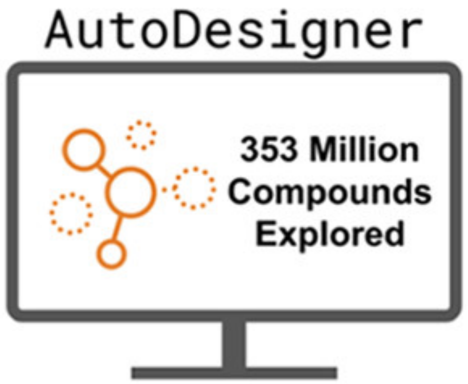

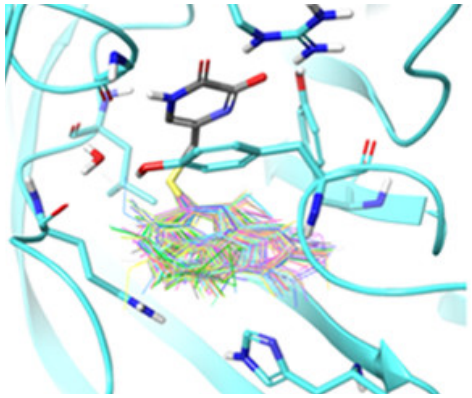

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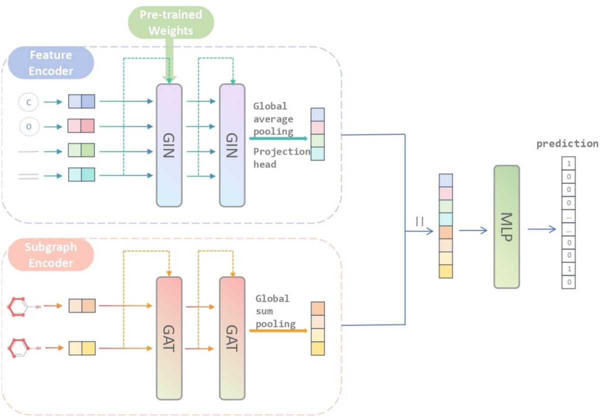
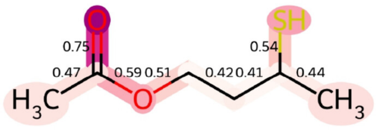
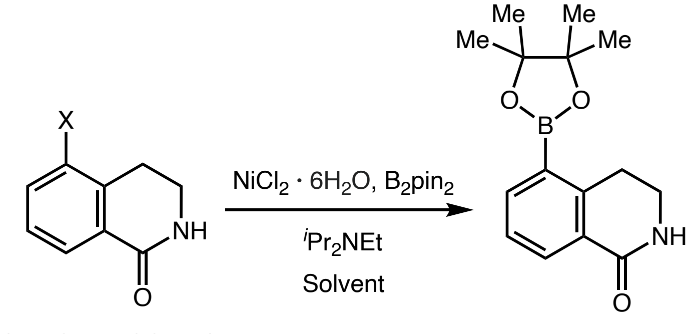




Data Science

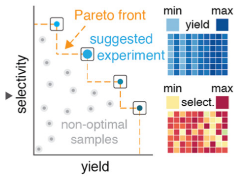


$NiCl_2 \cdot 6H_2O$, B_2pin_2

$^iPr_2NEt$

Solvent

(X = Cl, Br, SO_2Me)

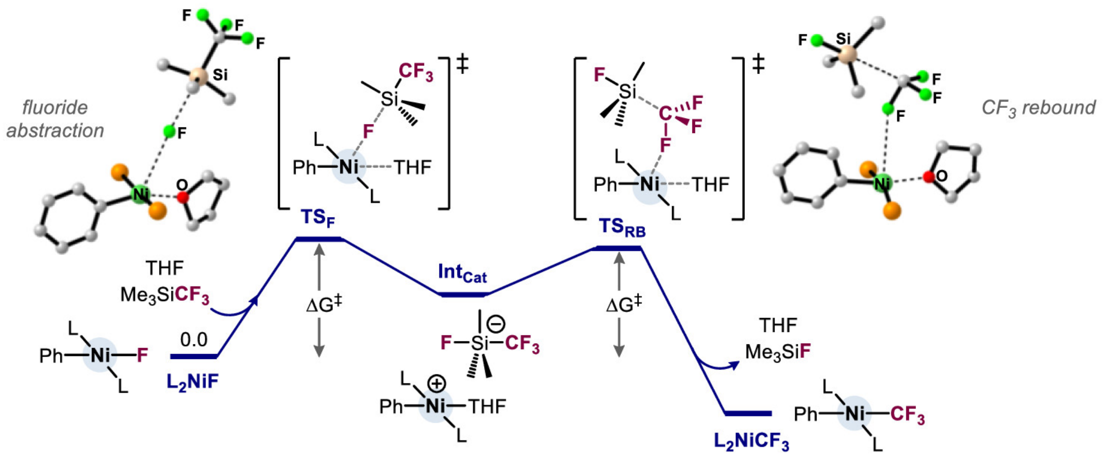


Multi-objective acquisition function

What can computational chemistry do for you?

Understanding how molecules act

Density functional theory



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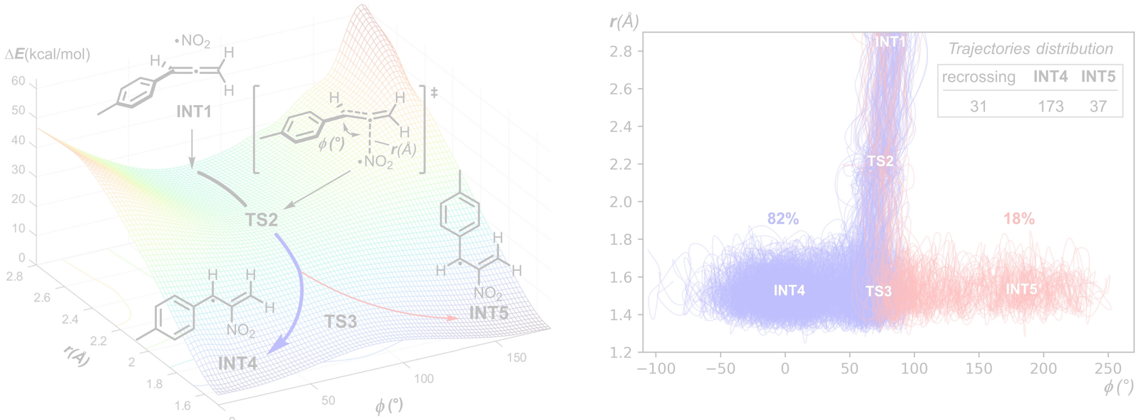

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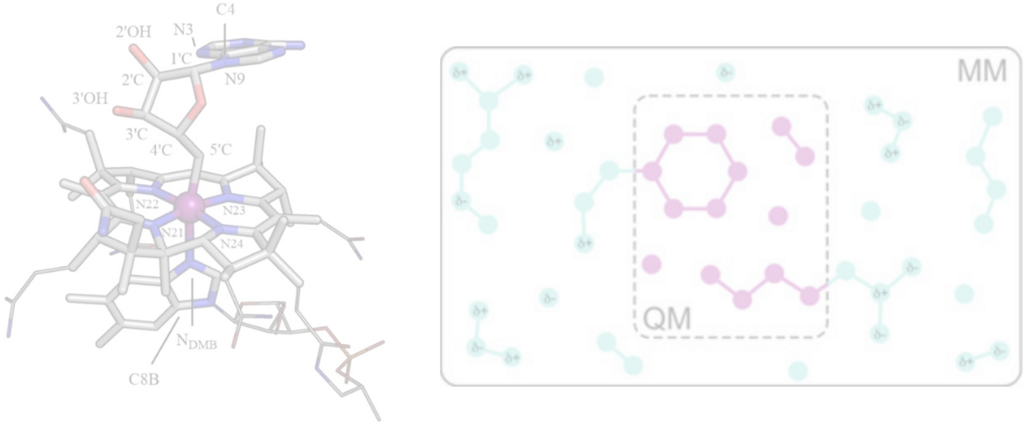

Predicting how molecules should act

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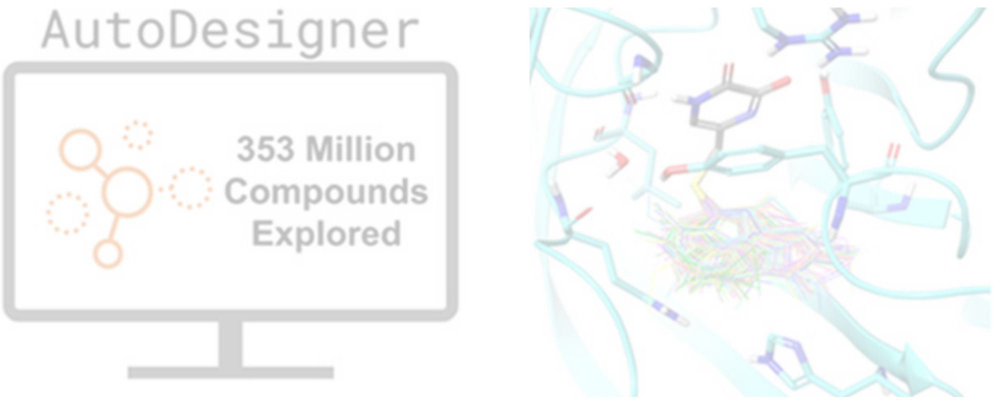
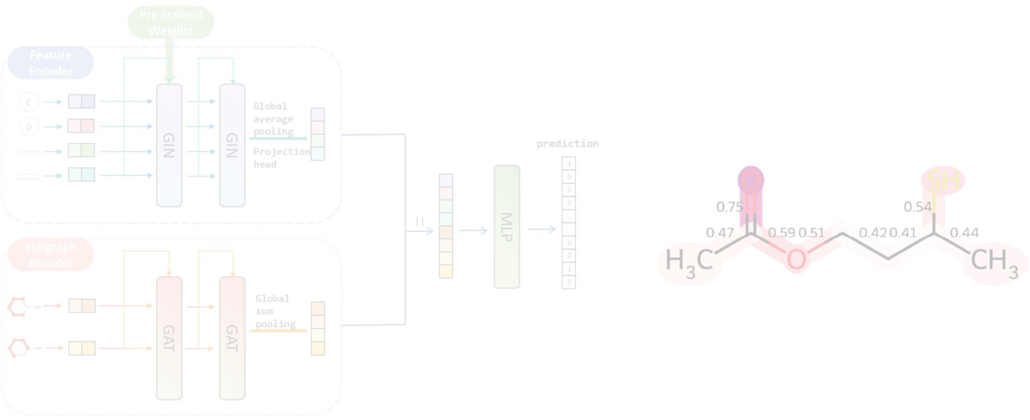


Neural networks



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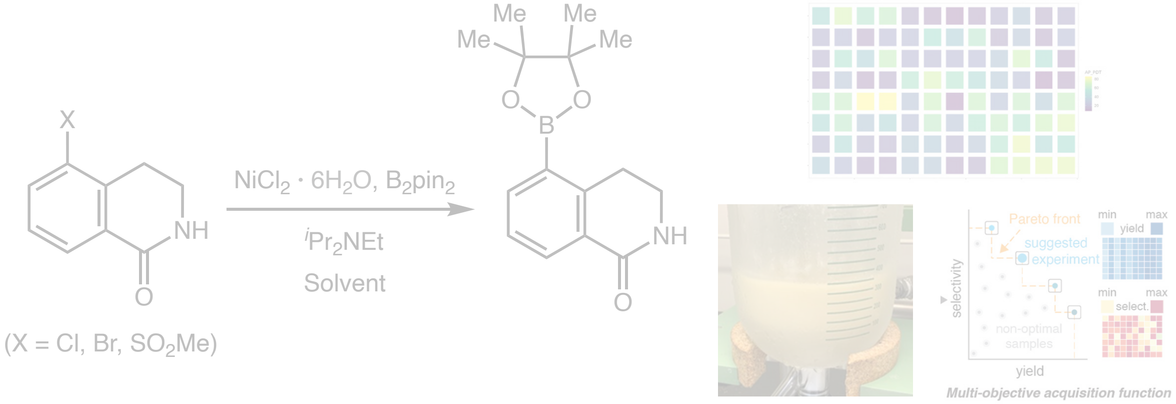

Understanding how molecules act

The Schrödinger Equation

We want to be able to determine the energies and the molecular/atomic orbitals of molecules of interest

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$$\hat{H}\Psi = E\Psi$$

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Hamiltonian operator

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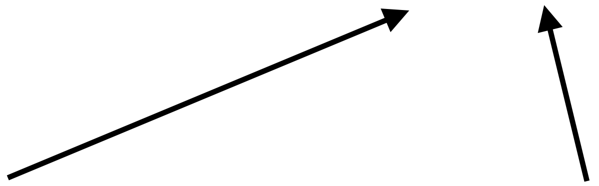

Hamiltonian operator

Wavefunction
(gives us the orbitals)

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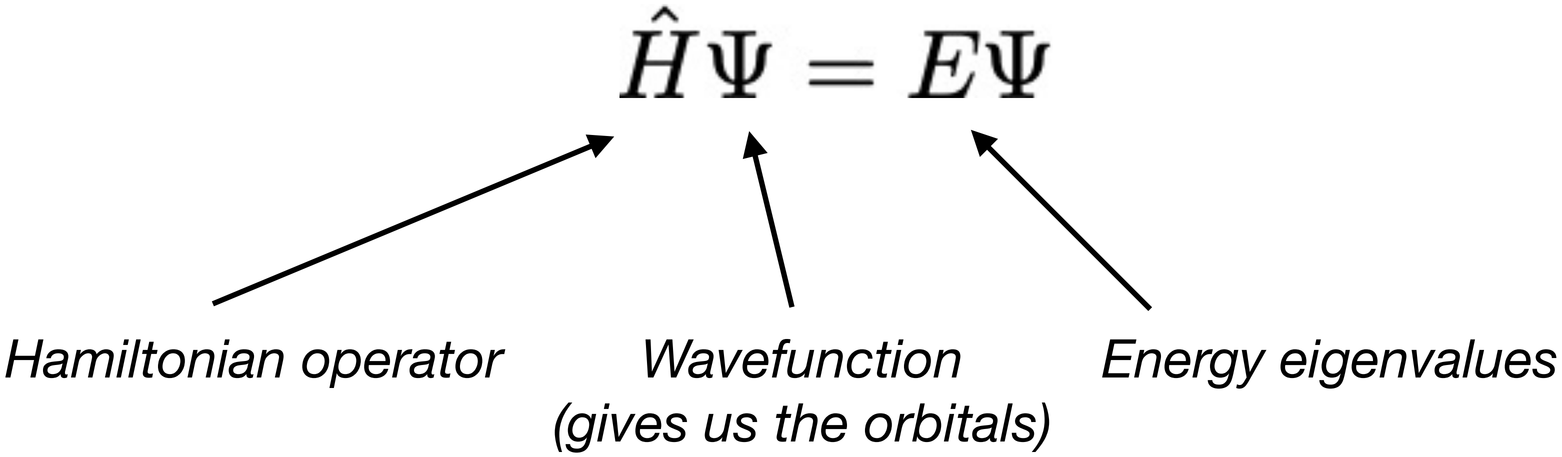

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kinetic
energy

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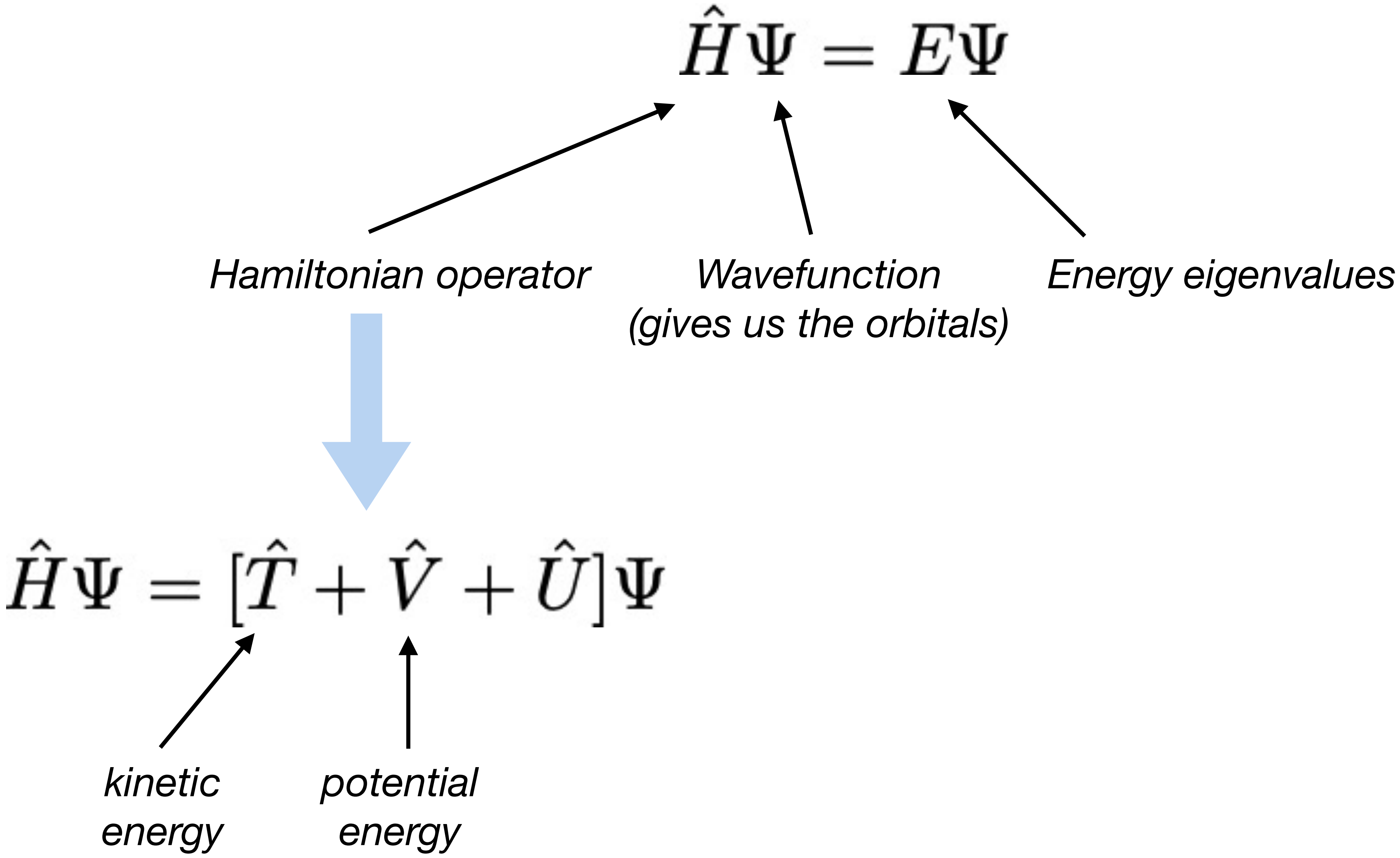

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kinetic energy

potential energy

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electron-electron interaction energy

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Consider the H atom:

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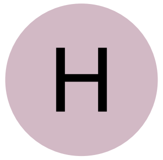

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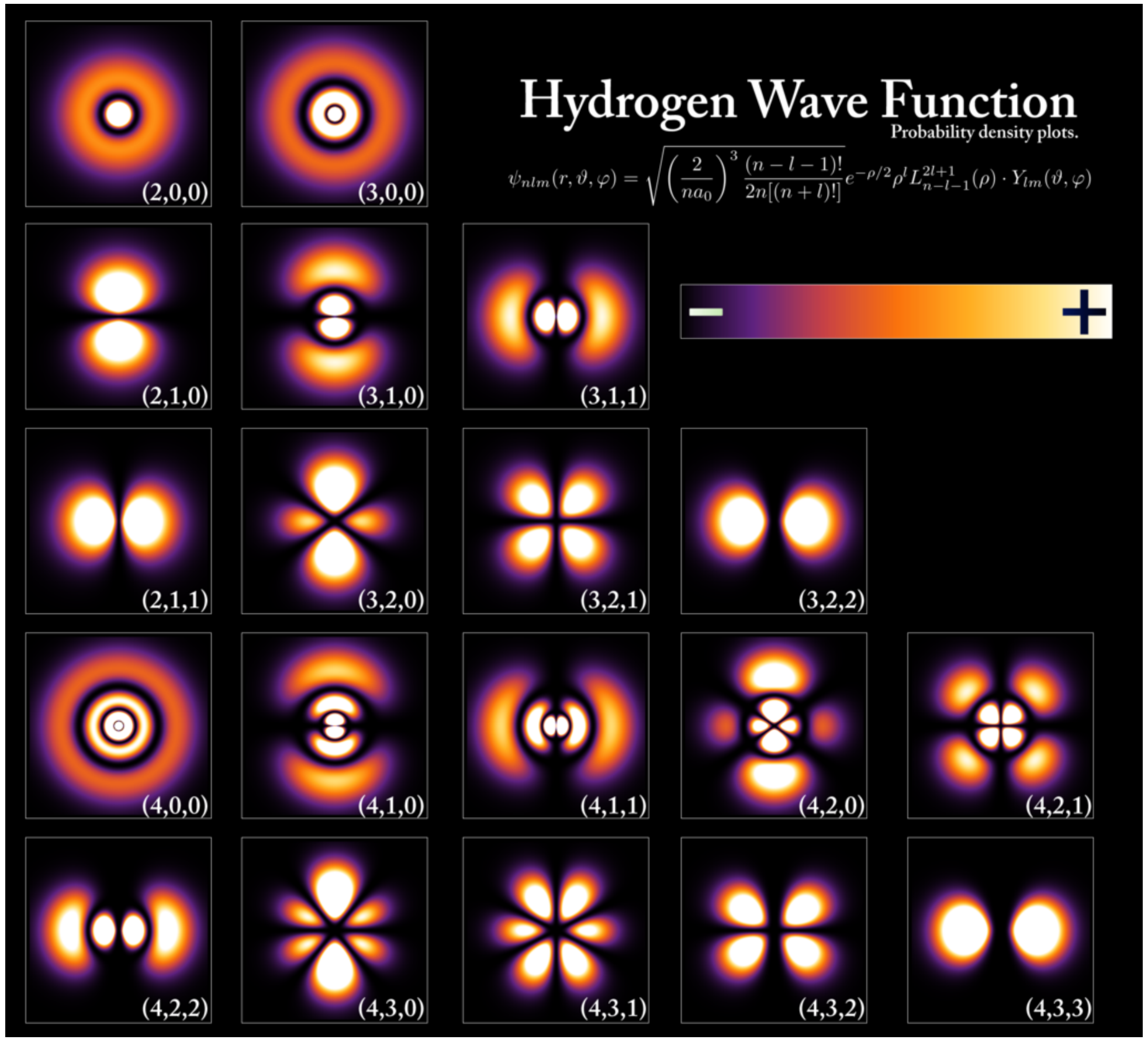
H

$$\Psi_{n\ell m}(r,\theta,\phi) = \sqrt{\left(\frac{2}{na_0}\right)^3 \frac{(n-\ell-1)!}{2n[(n+\ell)!]}} e^{-r/na_0} \left(\frac{2r}{na_0}\right)^{\ell} L_{n-\ell-1}^{2\ell+1}\left(\frac{2r}{na_0}\right) \cdot Y_{\ell}^{m}(\theta,\phi)$$

$$E_n = \frac{-13.6\text{eV}}{n^2}$$



Understanding how molecules act

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But for any larger molecular system, the Schrödinger equation is non-analytic (i.e. only numerically solvable)

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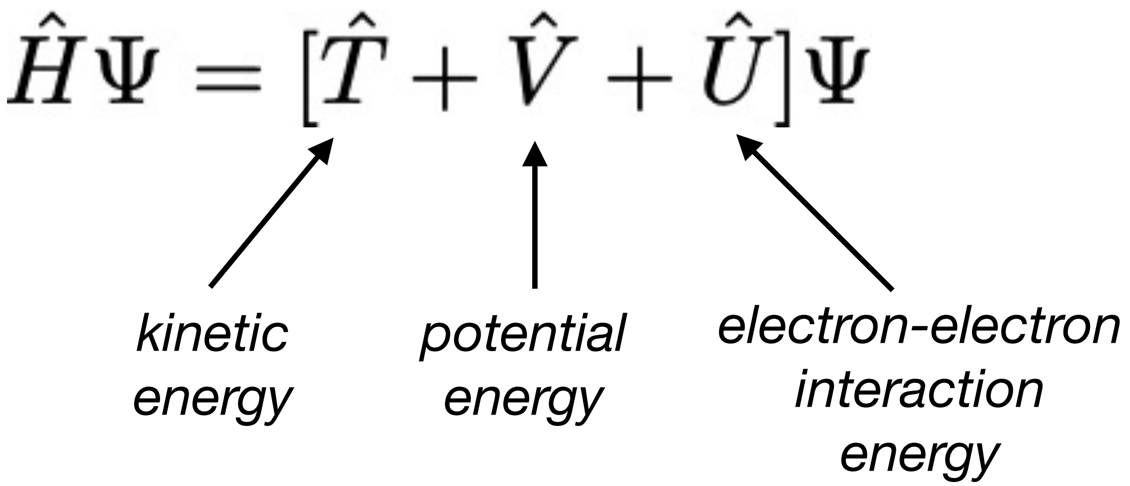

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kinetic energy

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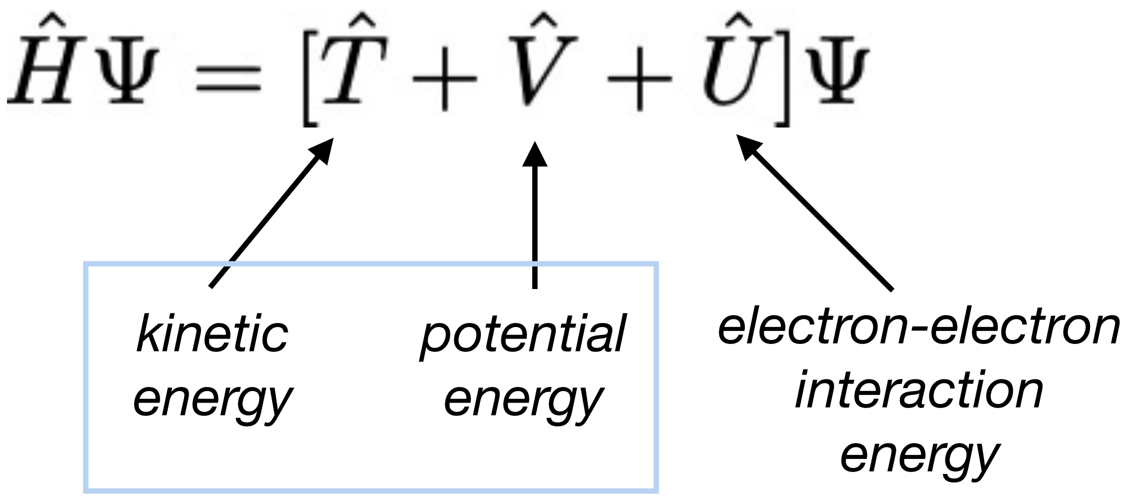

$$\hat{H}\Psi = [\hat{T} + \hat{V} + \hat{U}]\Psi$$

kinetic energy

potential energy

electron-electron interaction energy

Universal operators

(same for any n-electron system)

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kinetic energy

potential energy

electron-electron interaction energy

Universal operators

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Problematic with many-body problems

Understanding how molecules act

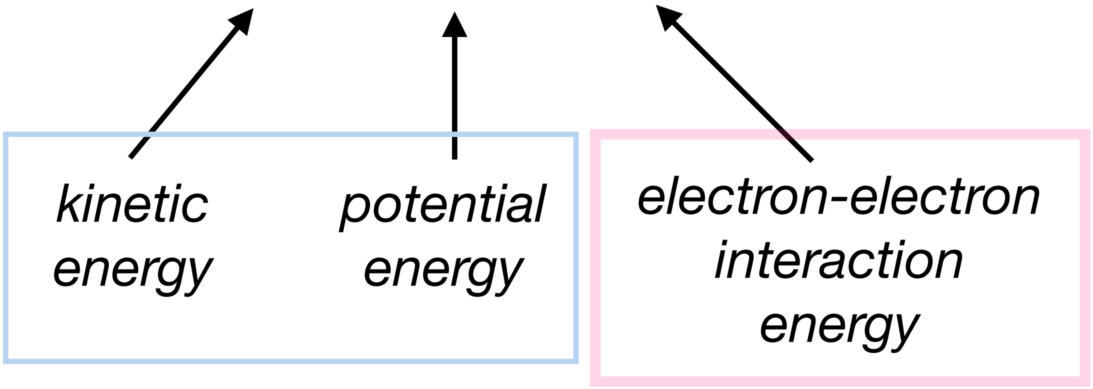
The Schrödinger Equation

We want to be able to determine the energies and the molecular/atomic orbitals of molecules of interest

$$\hat{H}\Psi = E\Psi$$

But for any larger molecular system, the Schrödinger equation is non-analytic (i.e. only numerically solvable)

$$\hat{H}\Psi = [\hat{T} + \hat{V} + \hat{U}]\Psi$$



kinetic energy

potential energy

electron-electron interaction energy

Universal operators

(same for any n-electron system)

Problematic with many-body problems

Doing these calculations with common techniques (HF or post-HF) is computationally difficult

Understanding how molecules act

Basics of density functional theory

We want to be able to determine the energies and the molecular/atomic orbitals of molecules of interest

$$\hat{H}\Psi = E\Psi$$

Understanding how molecules act

Basics of density functional theory

We want to be able to determine the energies and the molecular/atomic orbitals of molecules of interest

$$\hat{H}\Psi = E\Psi$$

Density Functional Theory (DFT)

Treat each electron as experiencing all other electrons as an "electron density" function (ρ(r))

$$E[\rho(\mathbf{r})] = T_{ni}[\rho(\mathbf{r})] + V_{ne}[\rho(\mathbf{r})] + V_{ee}[\rho(\mathbf{r})] \\ + \Delta T[\rho(\mathbf{r})] + \Delta V_{ee}[\rho(\mathbf{r})]$$

Understanding how molecules act

Basics of density functional theory

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$$\begin{aligned} E[\rho(\mathbf{r})] = T_{ni}[\rho(\mathbf{r})] + V_{ne}[\rho(\mathbf{r})] + V_{ee}[\rho(\mathbf{r})] \\ + \Delta T[\rho(\mathbf{r})] + \Delta V_{ee}[\rho(\mathbf{r})] \end{aligned}$$

This allows for greatly simplified calculations of energies and wavefunctions

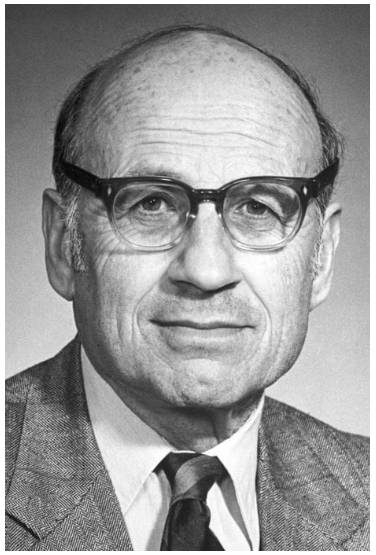
Understanding how molecules act

Basics of density functional theory

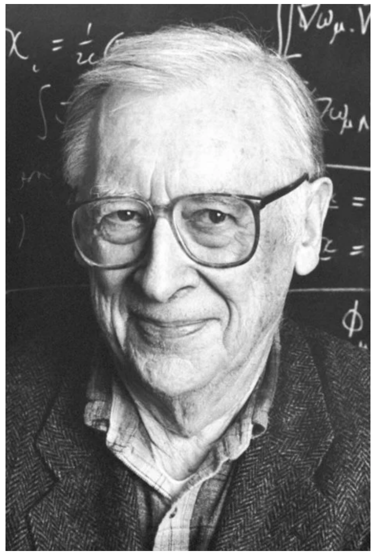
We want to be able to determine the energies and the molecular/atomic orbitals of molecules of interest

$$\hat{H}\Psi = E\Psi$$

The Nobel Prize in Chemistry 1998



Walter Kohn
UCSB
"for his development of the density-functional theory"



John A. Pople
Northwestern
"for his development of computational methods in quantum chemistry"

Understanding how molecules act

What can DFT do for us?

Understanding how molecules act

What can DFT do for us?

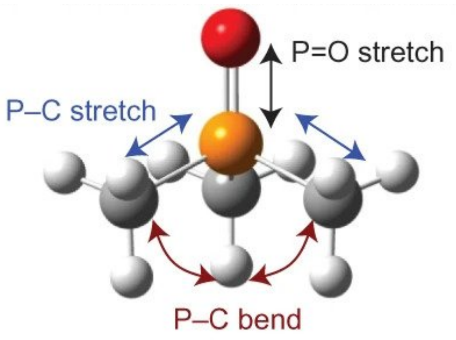
Molecular Properties

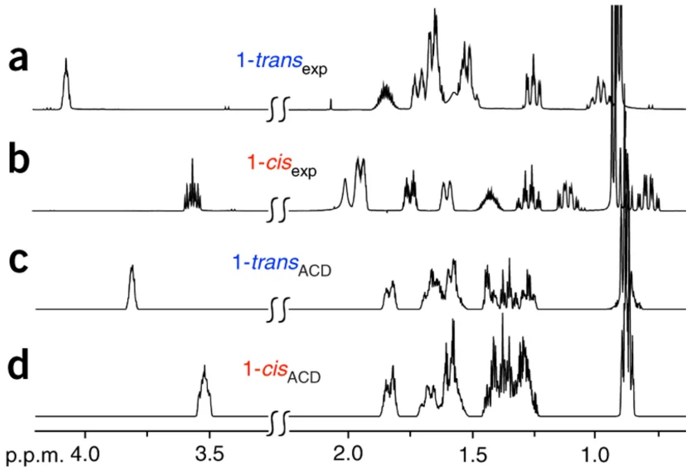
Understanding how molecules act

What can DFT do for us?

Molecular Properties

predicted spectral data





Understanding how molecules act

What can DFT do for us?

Molecular Properties

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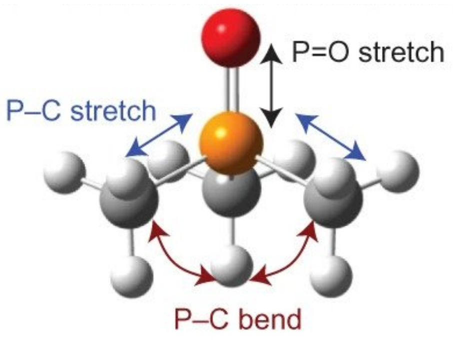
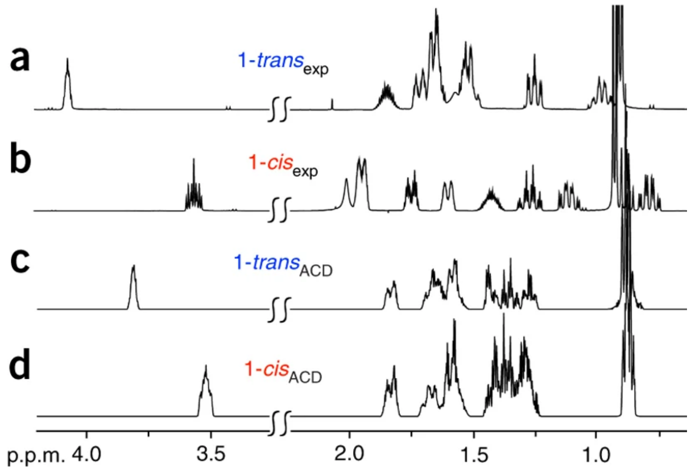
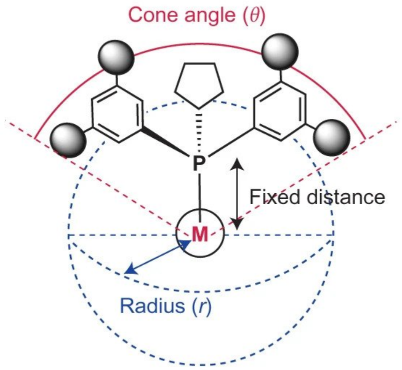
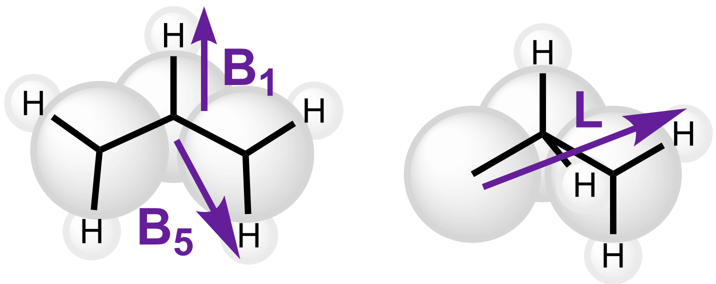




steric parameters





Understanding how molecules act

What can DFT do for us?

Molecular Properties

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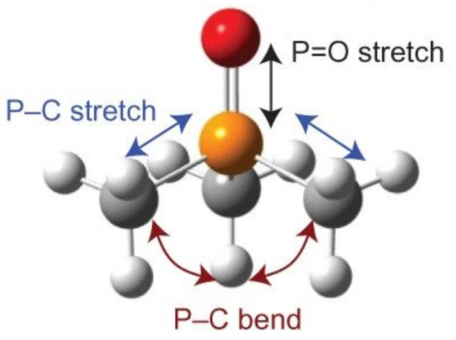

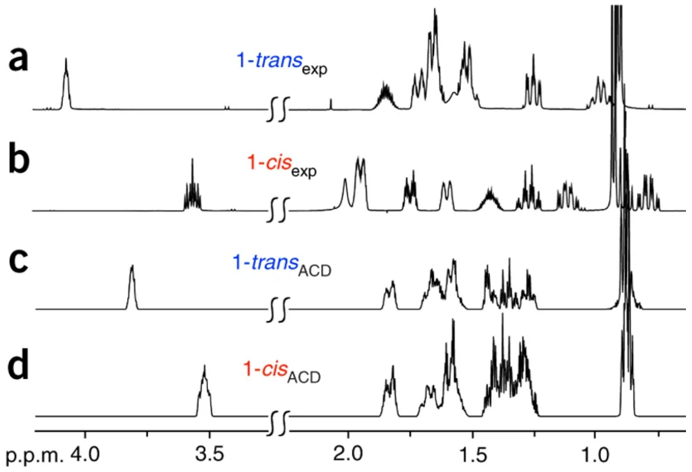

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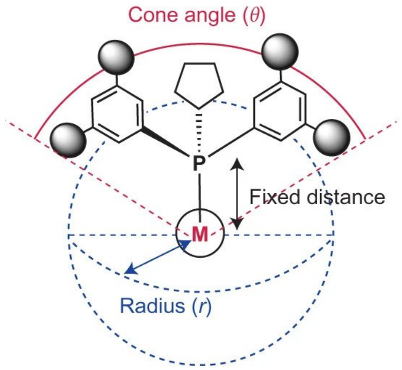
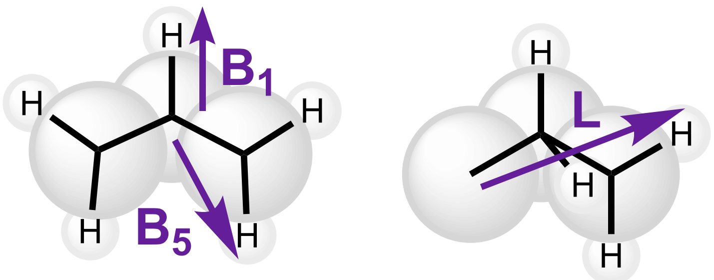
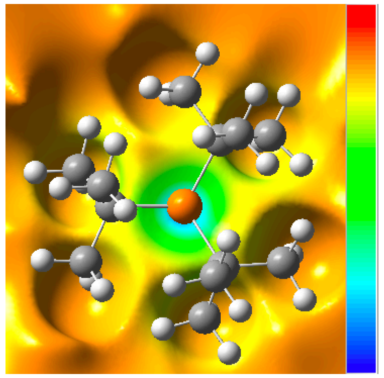
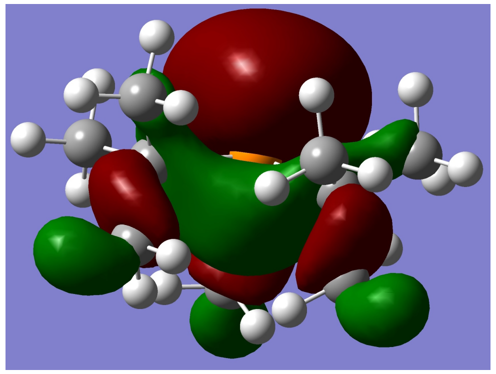




electrostatic potentials



molecular orbitals

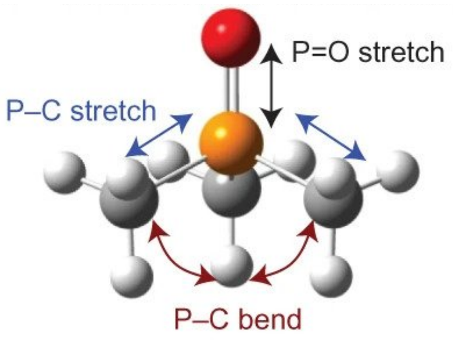


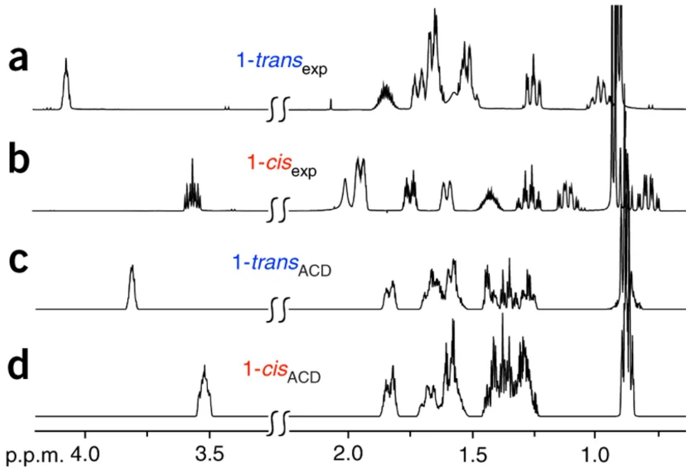
Understanding how molecules act

What can DFT do for us?

Molecular Properties

predicted spectral data





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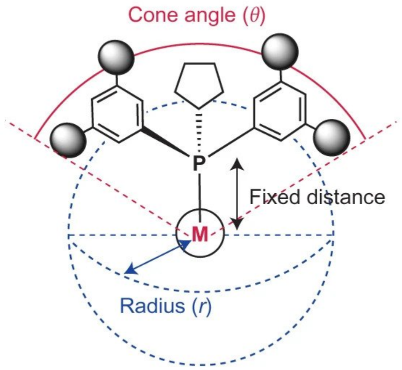

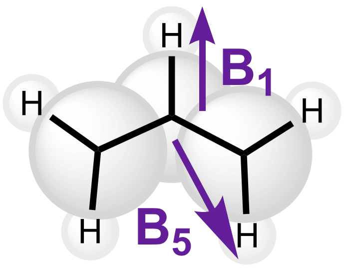

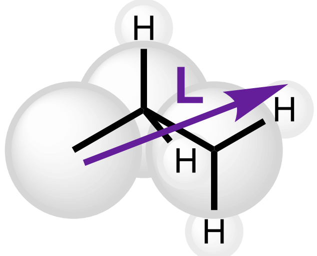

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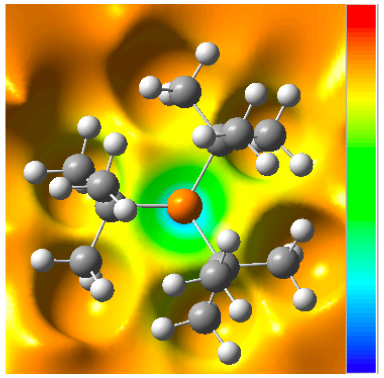
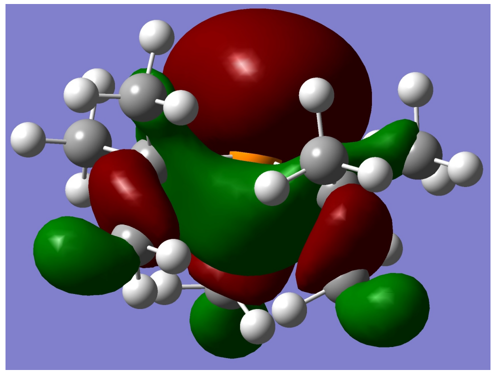


molecular orbitals



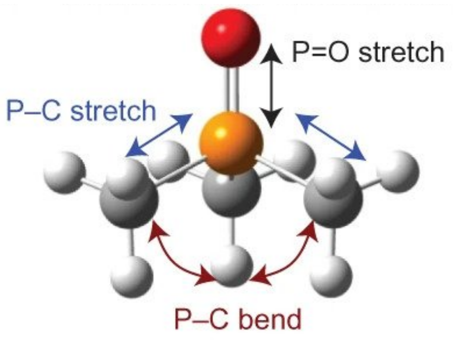
Mechanistic Insights

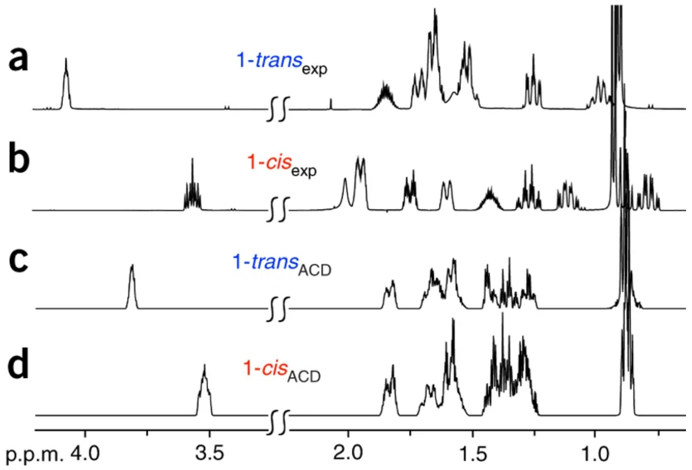
Understanding how molecules act

What can DFT do for us?

Molecular Properties

predicted spectral data





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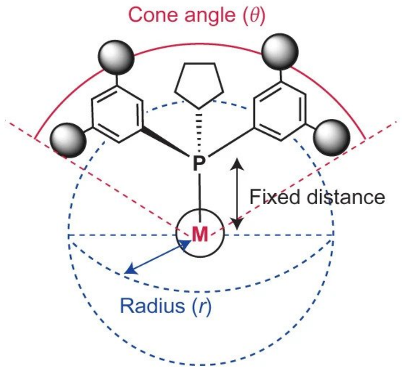

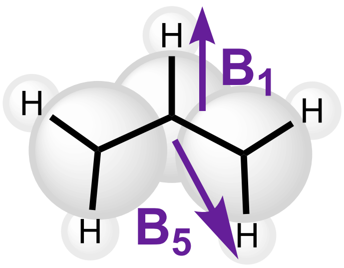

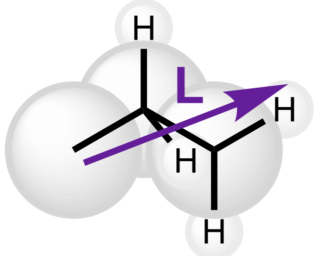

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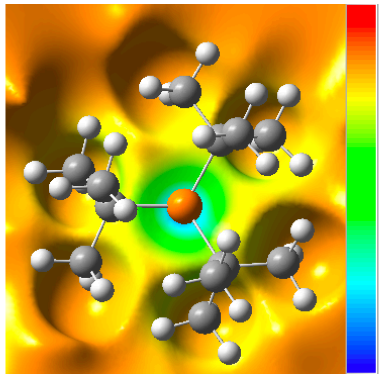
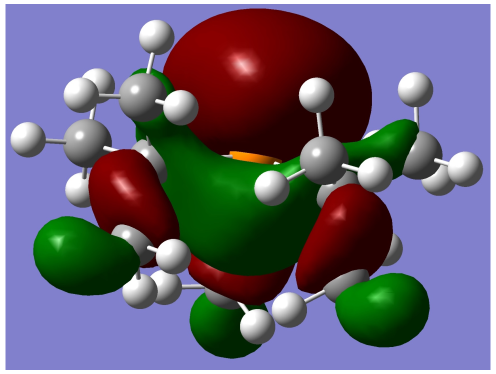
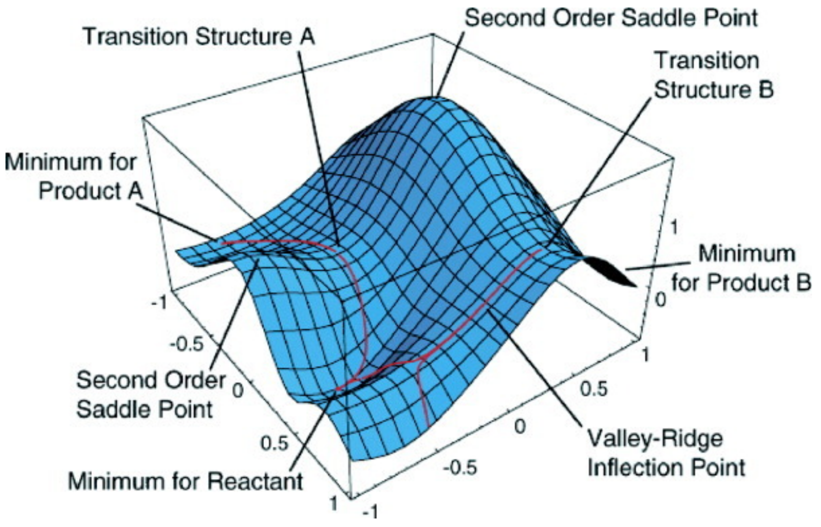


molecular orbitals



Mechanistic Insights

potential energy surfaces

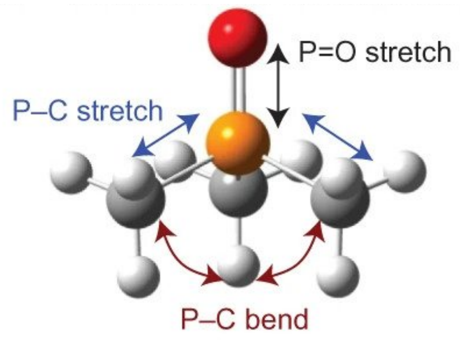


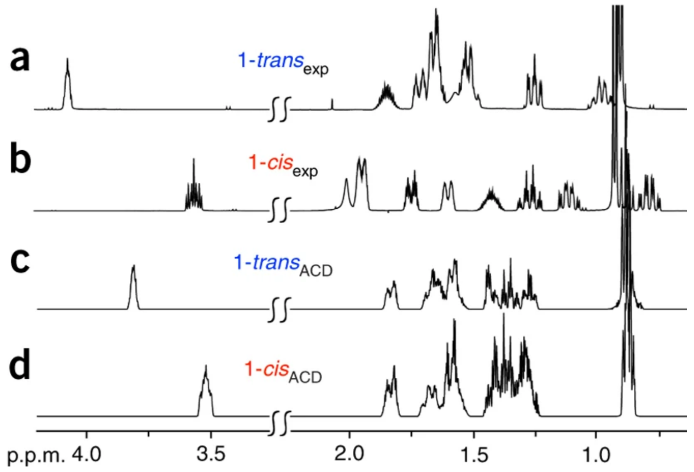
Understanding how molecules act

What can DFT do for us?

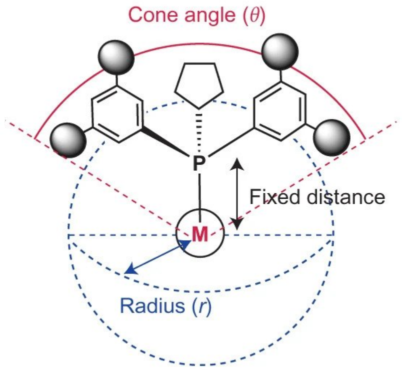
Molecular Properties

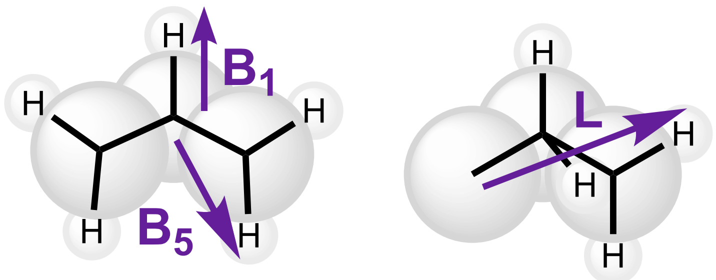
predicted spectral data





steric parameters





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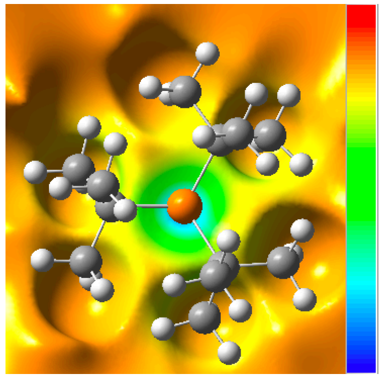

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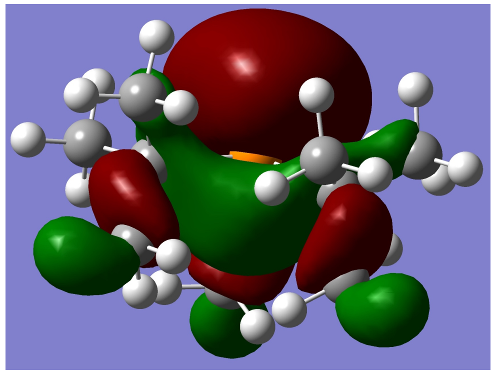
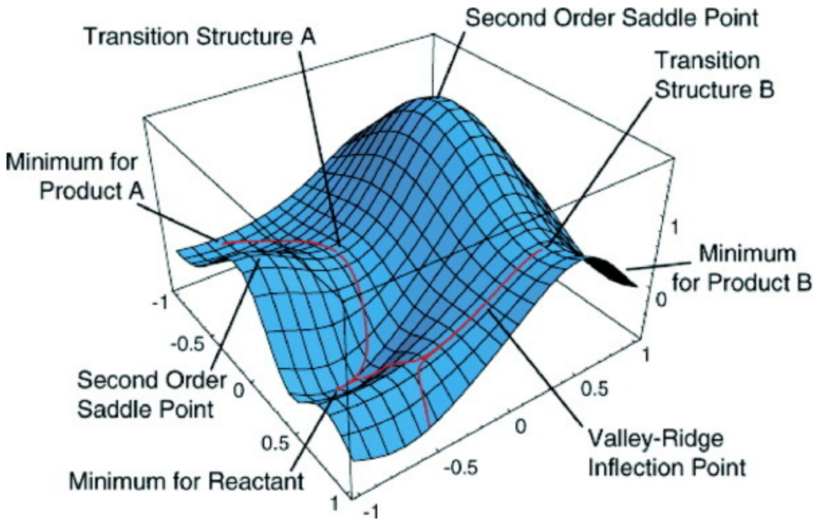
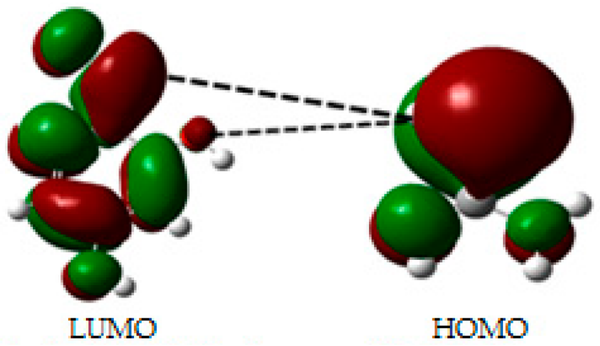


Mechanistic Insights

potential energy surfaces



orbital interactions

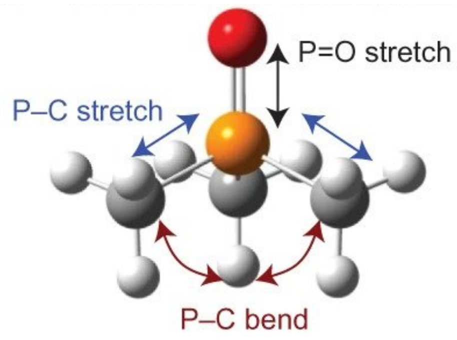


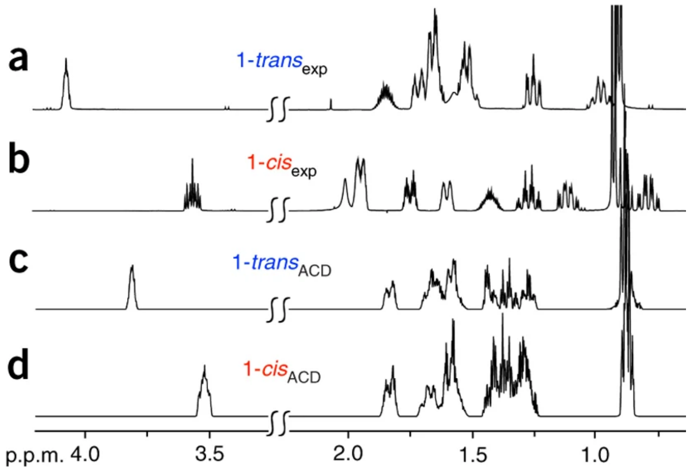
Understanding how molecules act

What can DFT do for us?

Molecular Properties

predicted spectral data





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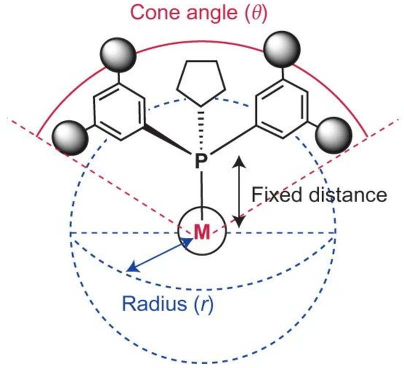
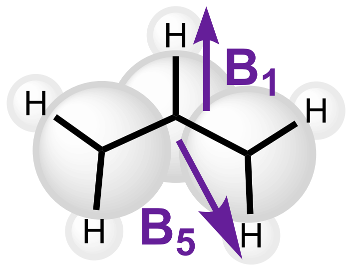
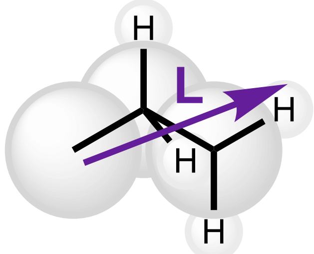
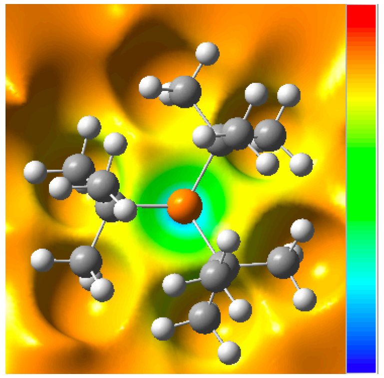


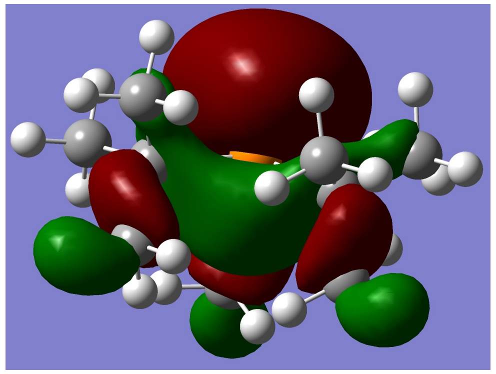




electrostatic potentials

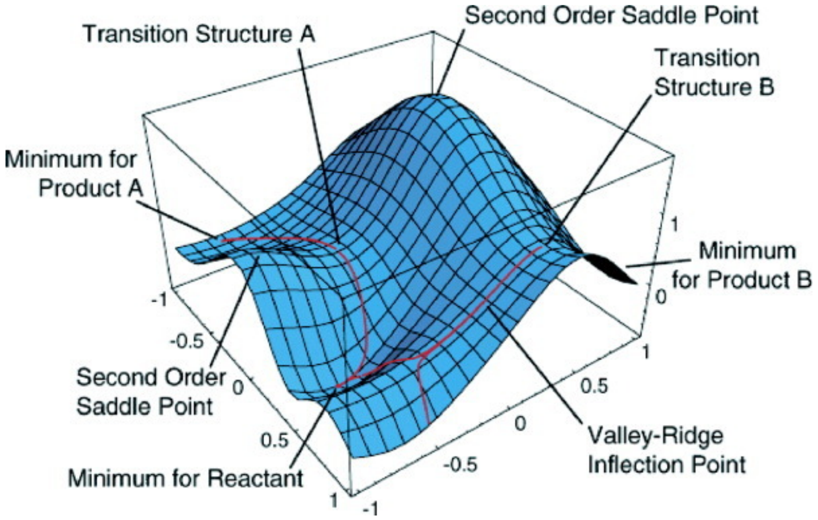


molecular orbitals

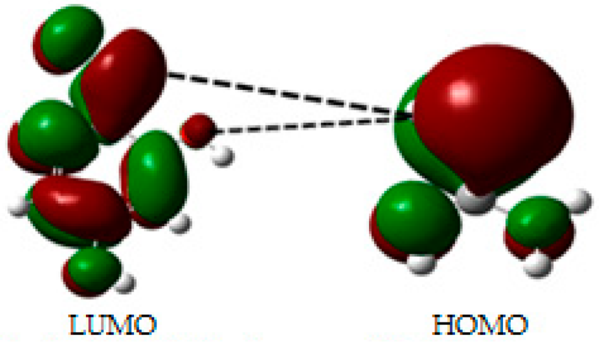


Mechanistic Insights

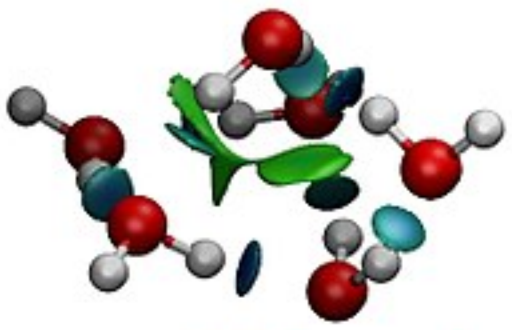
potential energy surfaces



orbital interactions



non-covalent interactions

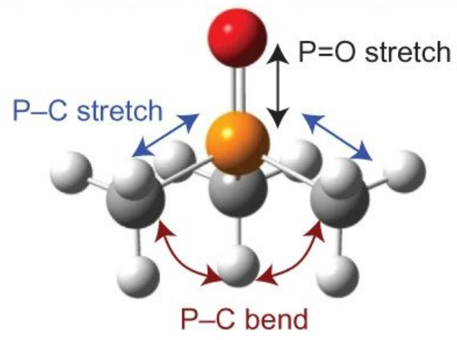


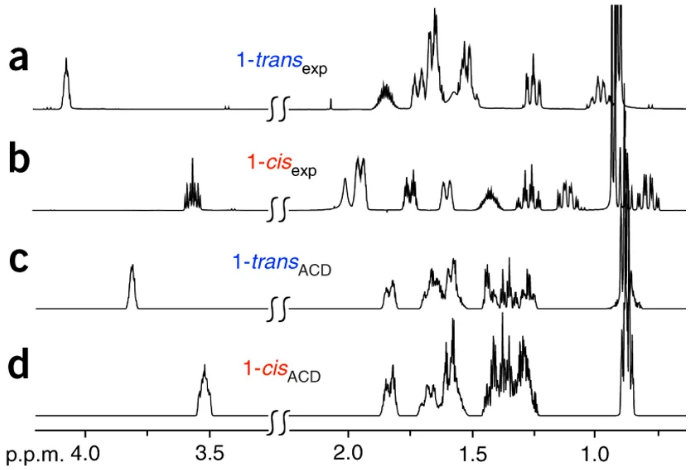
Understanding how molecules act

What can DFT do for us?

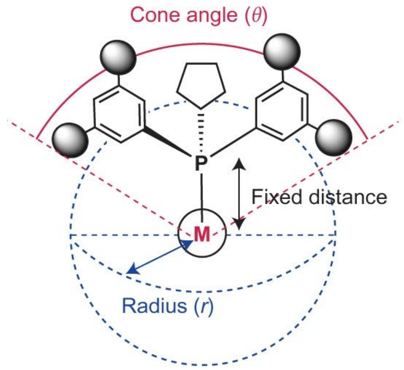
Molecular Properties

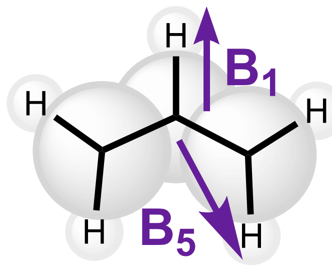
predicted spectral data

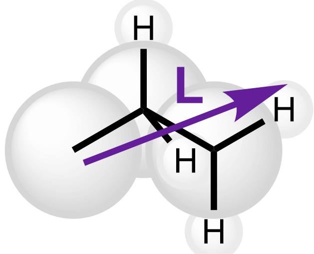




steric parameters







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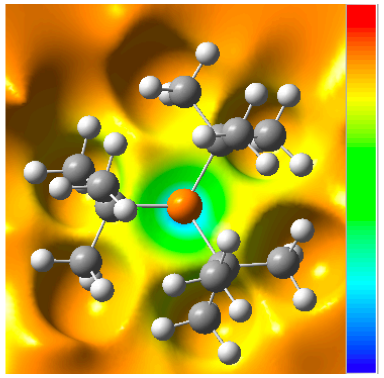

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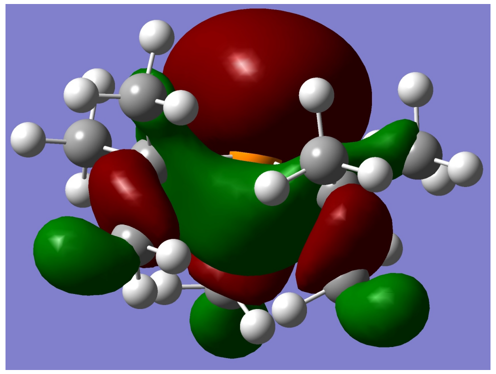

Mechanistic Insights

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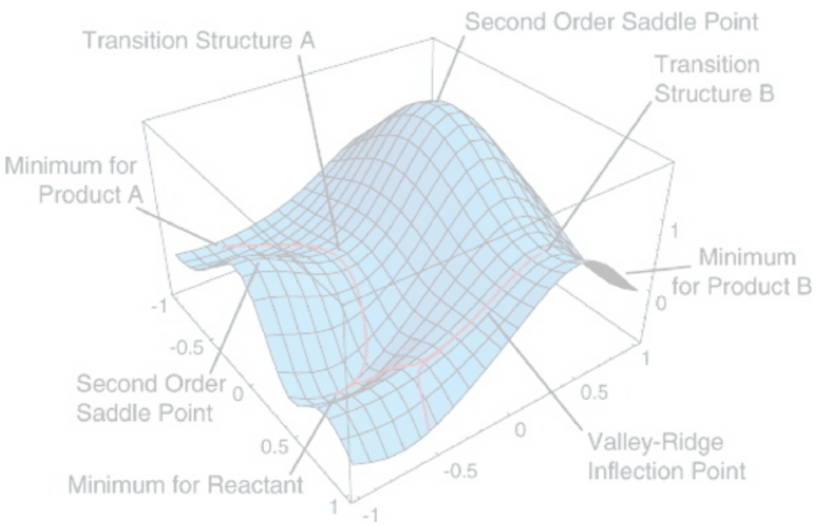

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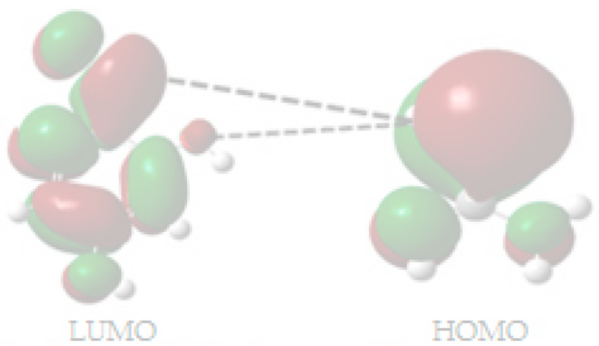

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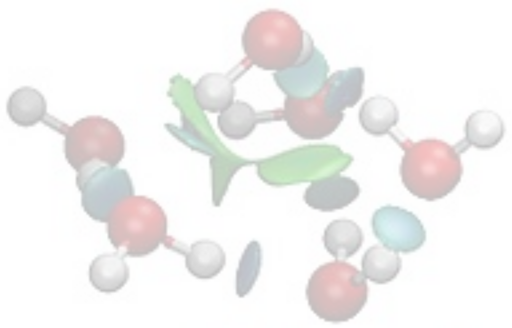
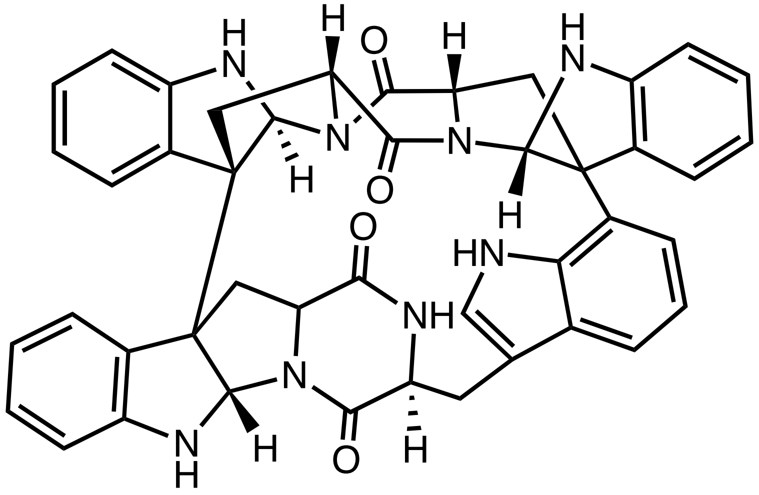


Understanding how molecules act

Predicting spectra

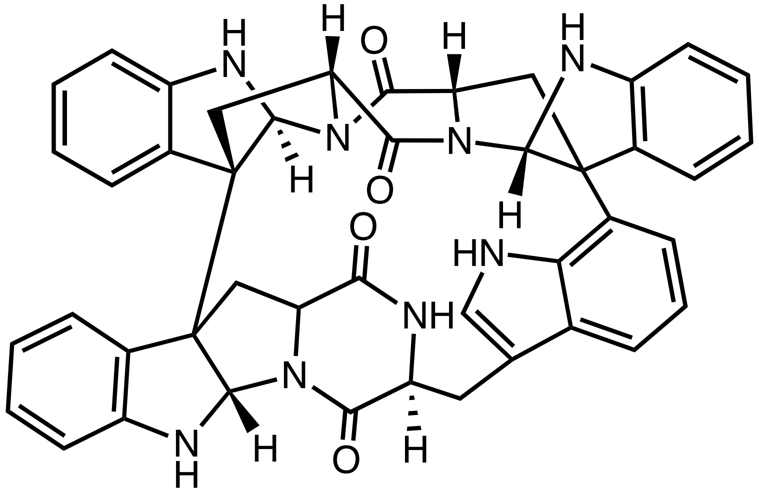


cyctetryptomycin A

Novitskiy, I. M.; Kutateladze, A. G. *J. Org. Chem.* **2022**, *87*, 4818-4828.

Understanding how molecules act

Predicting spectra



cyctetryptomycin A

what would the NMR spectra of cyctetryptomycin A look like?

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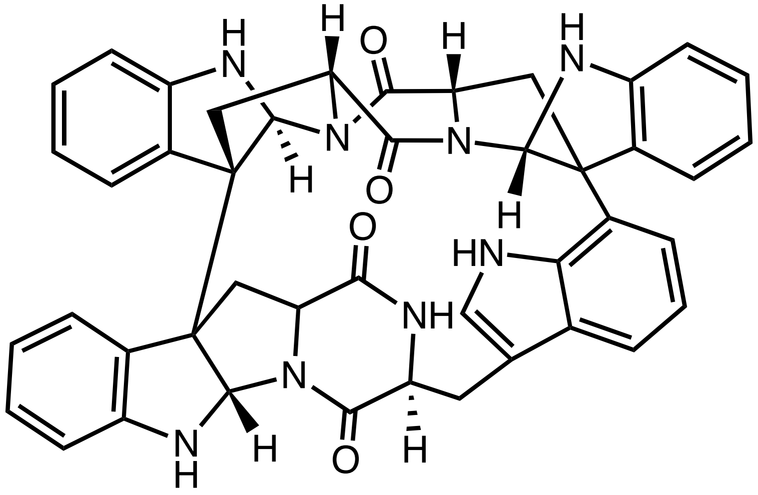
Understanding how molecules act

Predicting spectra



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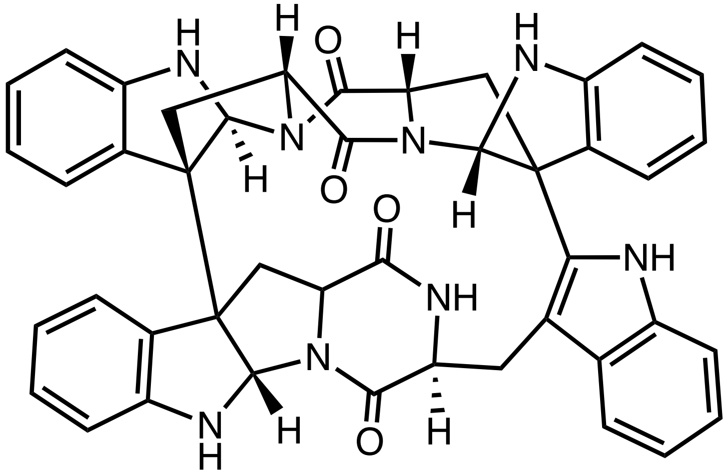

cyctetryptomycin A?

what would the NMR spectra of cyctetryptomycin A look like?

could you differentiate the spectra of cyctetryptomycin A and this isomer?

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Understanding how molecules act

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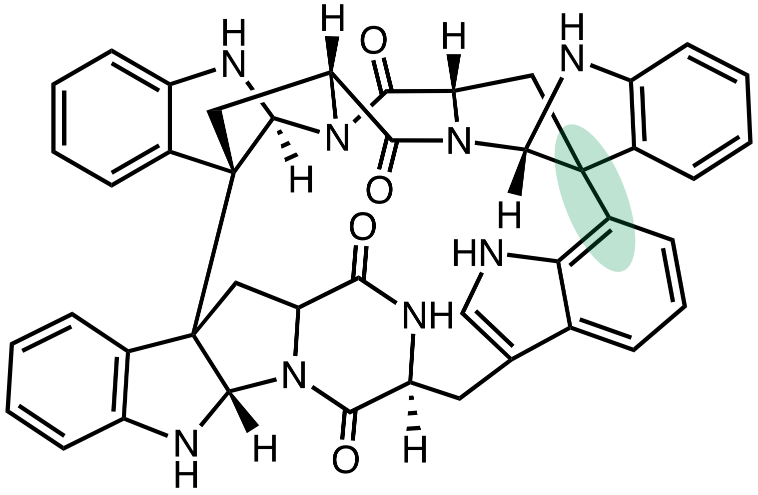

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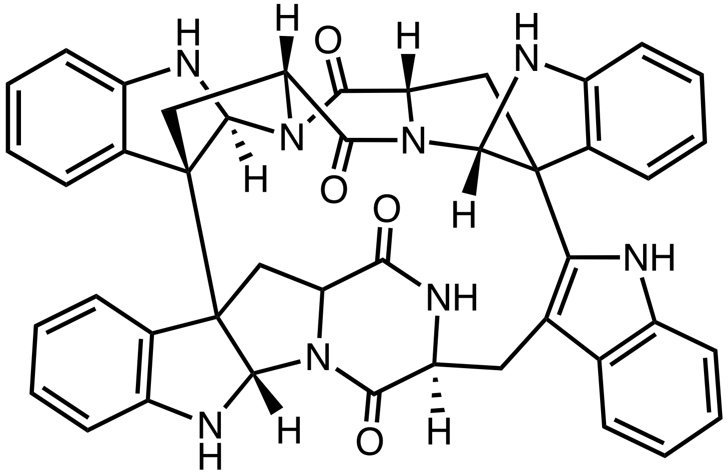

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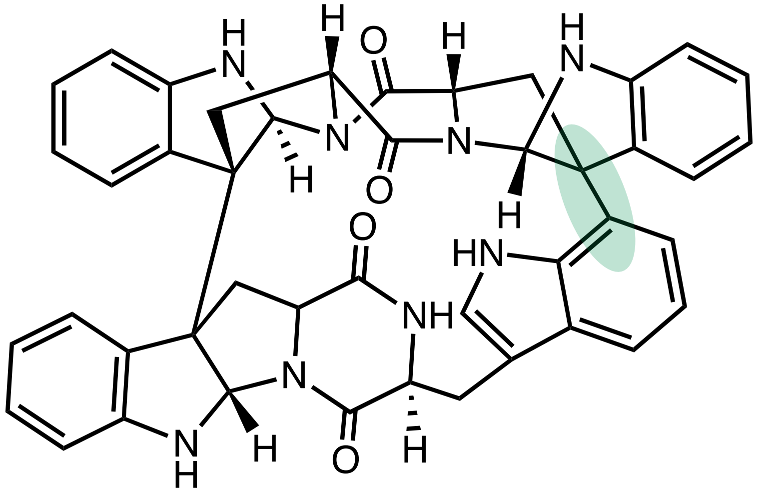
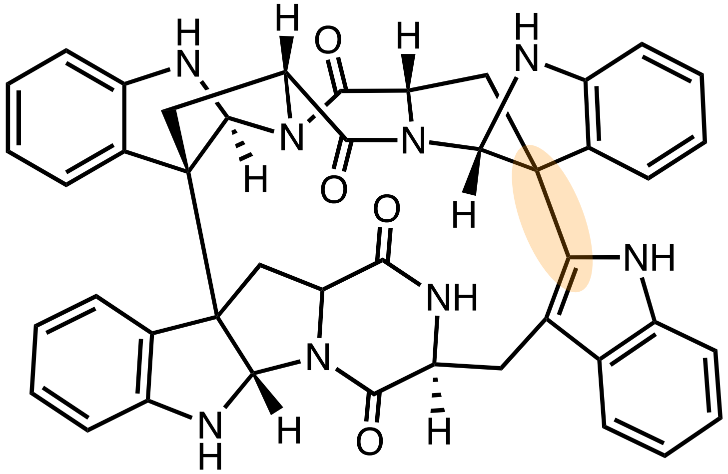
Understanding how molecules act

Predicting spectra



cyctetryptomycin A

what would the NMR spectra of cyctetryptomycin A look like?



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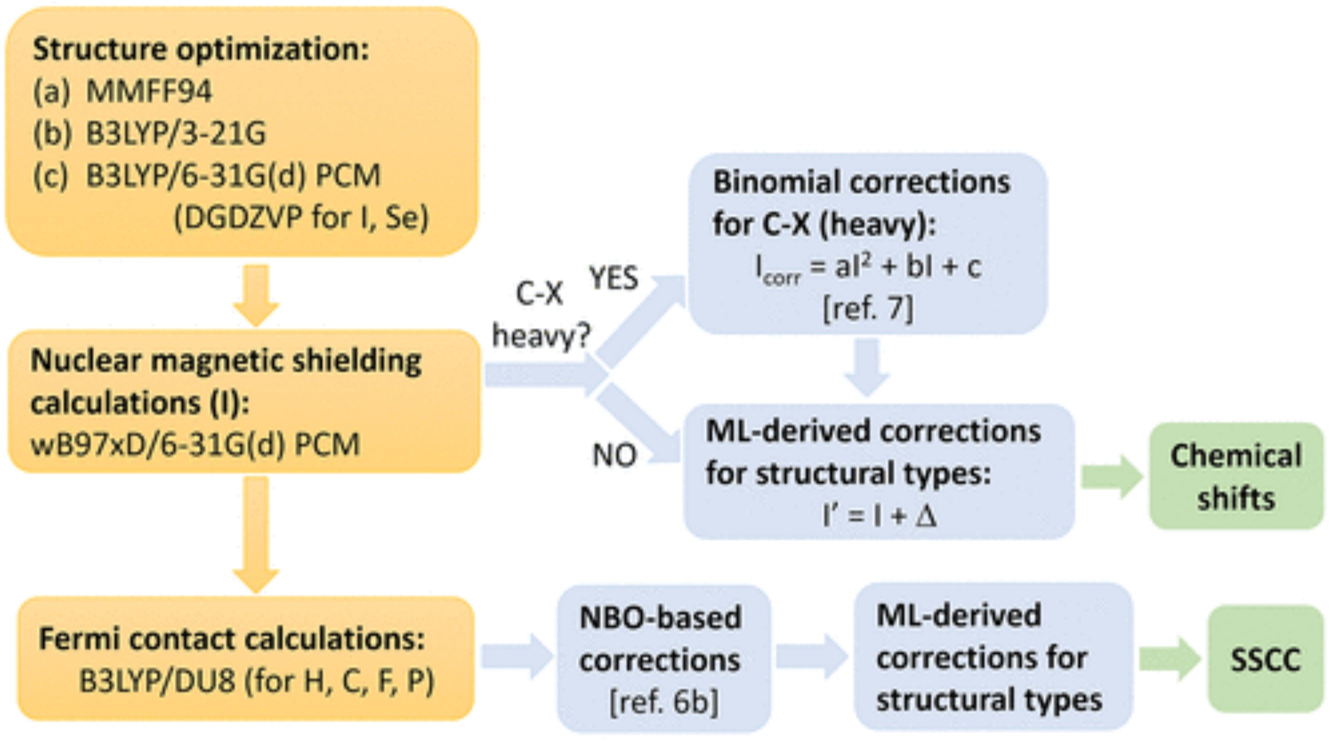
Understanding how molecules act

DU8ML - Machine-Learning Augmented DFT NMR Spectrum Prediction

DU8ML Workflow



Structure optimization:
(a) MMFF94
(b) B3LYP/3-21G
(c) B3LYP/6-31G(d) PCM
(DGDZVP for I, Se)

Nuclear magnetic shielding calculations (I):
wB97xD/6-31G(d) PCM

C-X heavy?

YES

Binomial corrections for C-X (heavy):
$I_{corr} = aI^2 + bI + c$
[ref. 7]

NO

ML-derived corrections for structural types:
$I' = I + \Delta$

Chemical shifts

Fermi contact calculations:
B3LYP/DU8 (for H, C, F, P)

NBO-based corrections
[ref. 6b]

ML-derived corrections for structural types

SSCC

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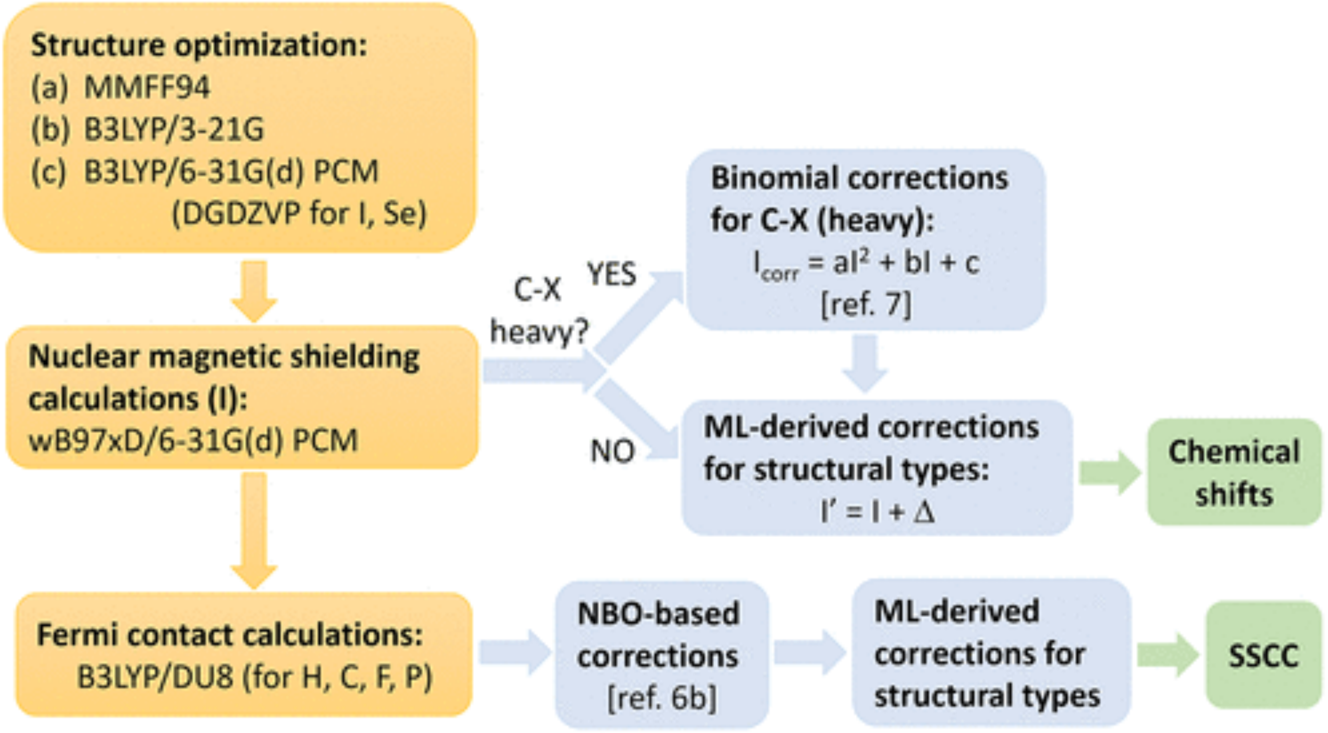

Applied to a set of 170 reported alkaloid structures, computations reveal a misassignment rate of 20%

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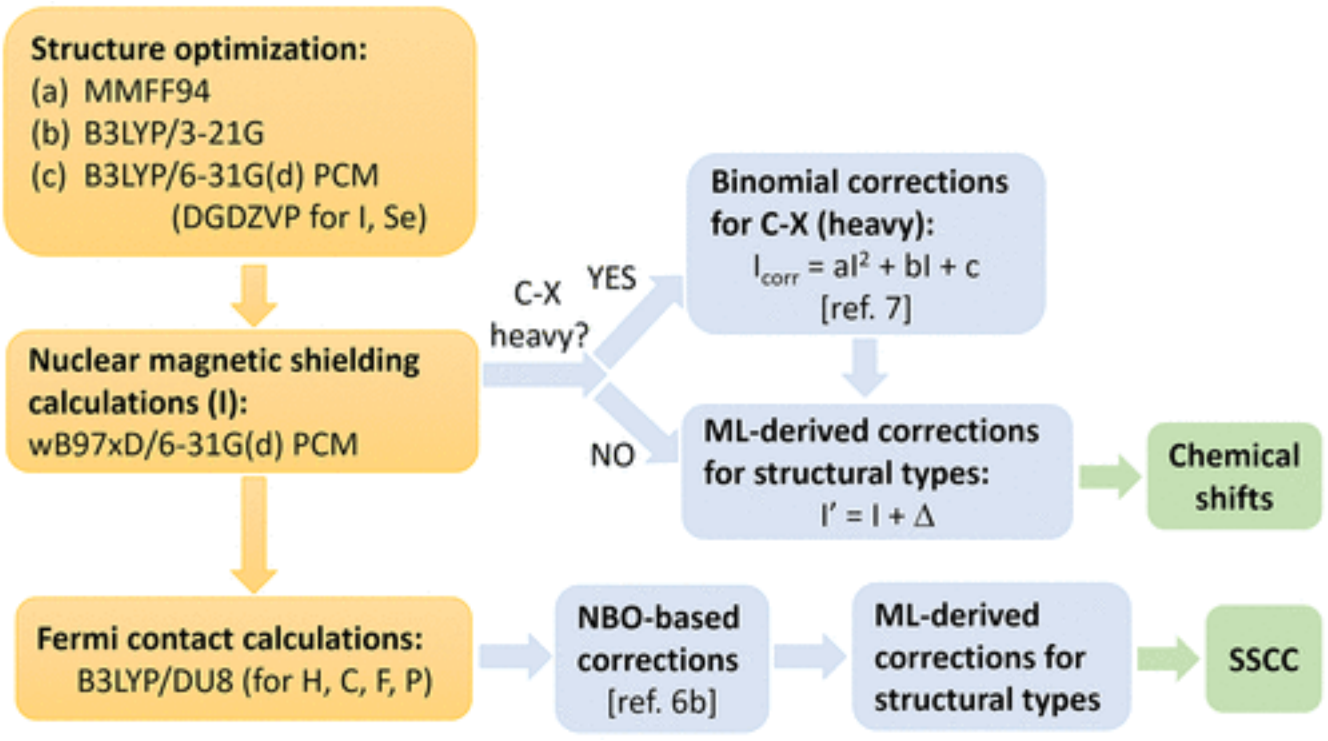

Applied to a set of 170 reported alkaloid structures, computations reveal a misassignment rate of 20%

DU8ML can identify errors in assignment and help us propose more reasonable alternatives

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Fixing incorrect constitutional isomers

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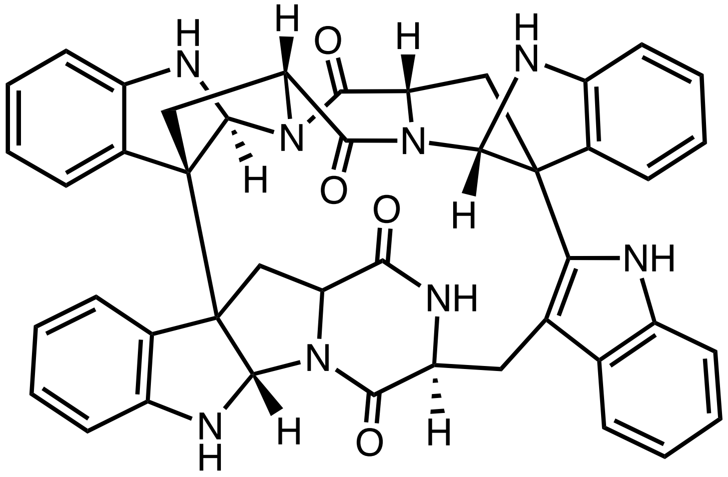

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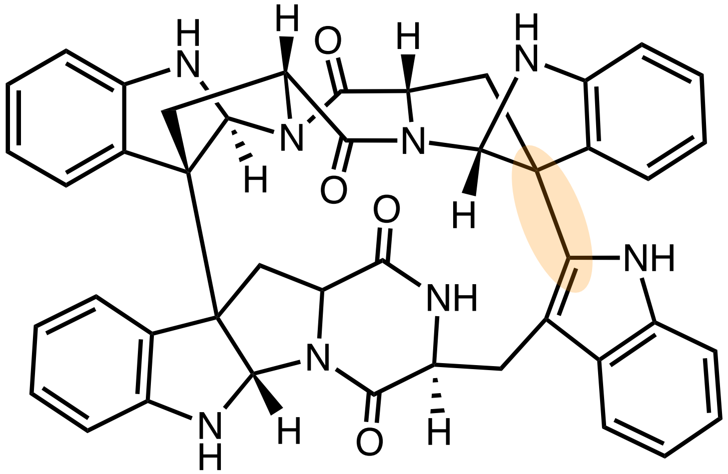

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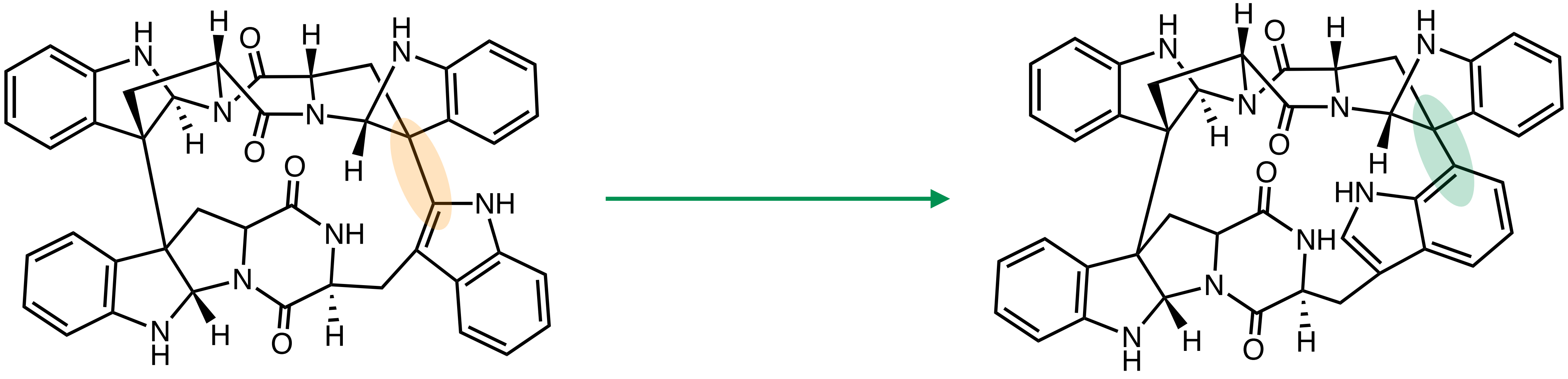

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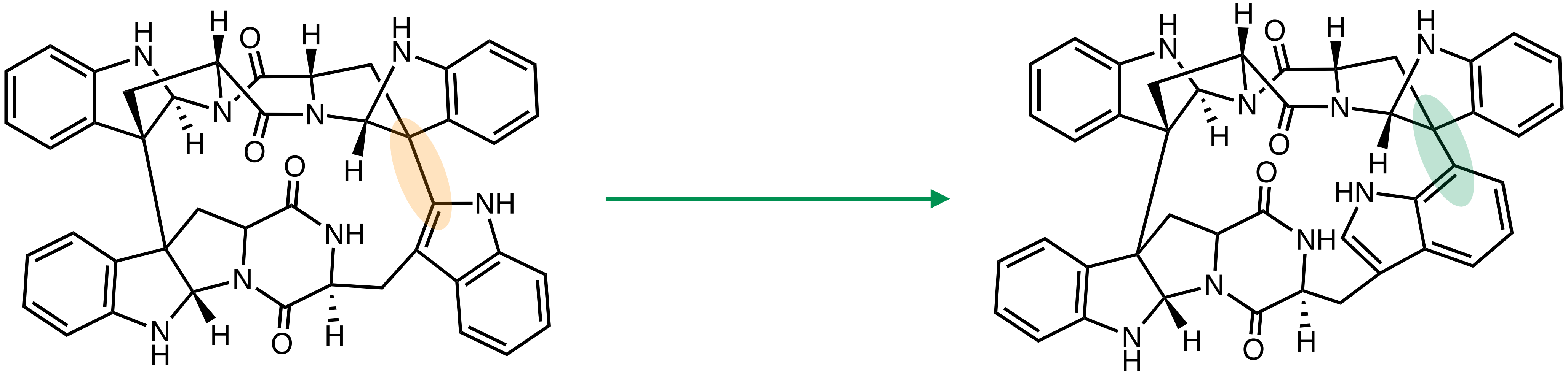

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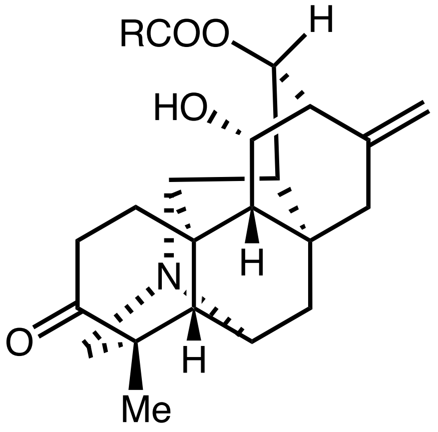

majusidine B?

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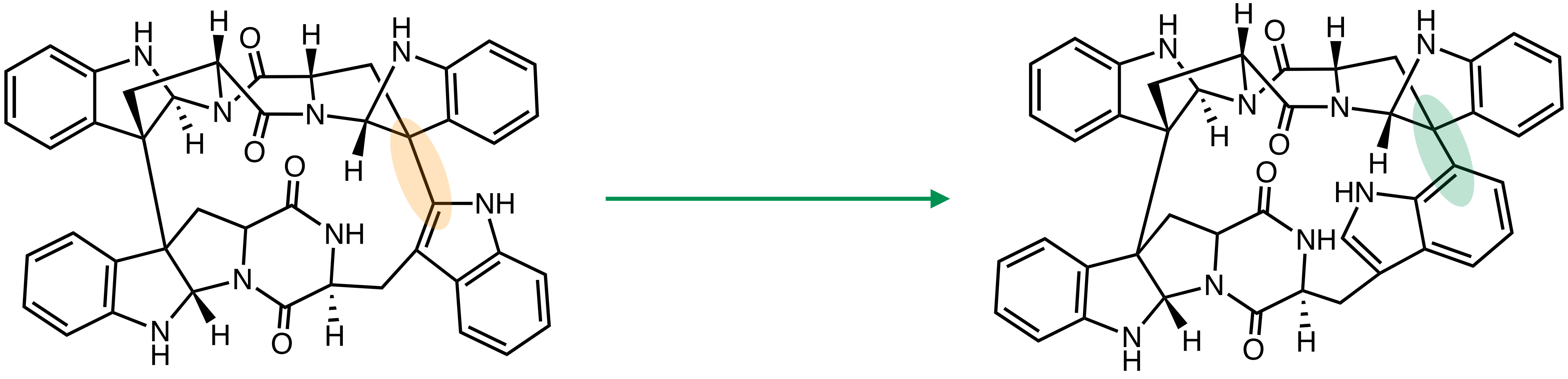

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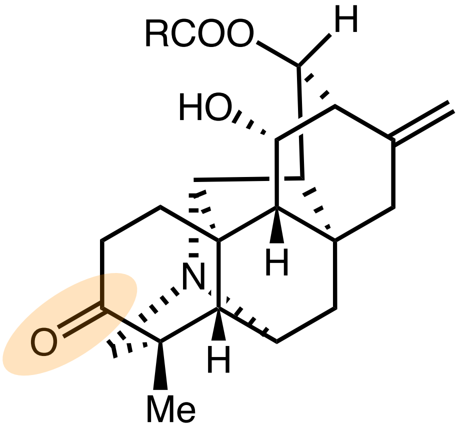

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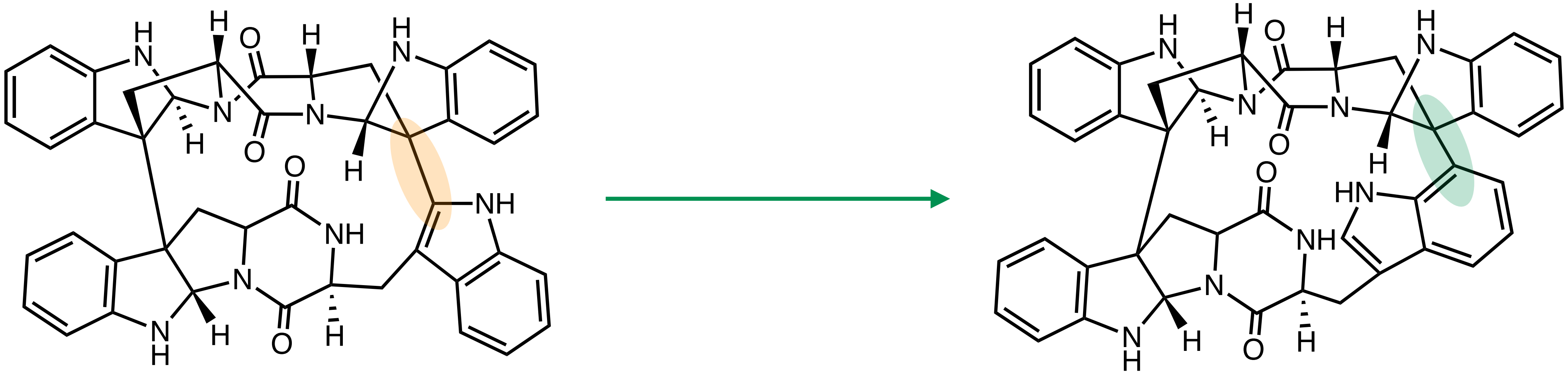

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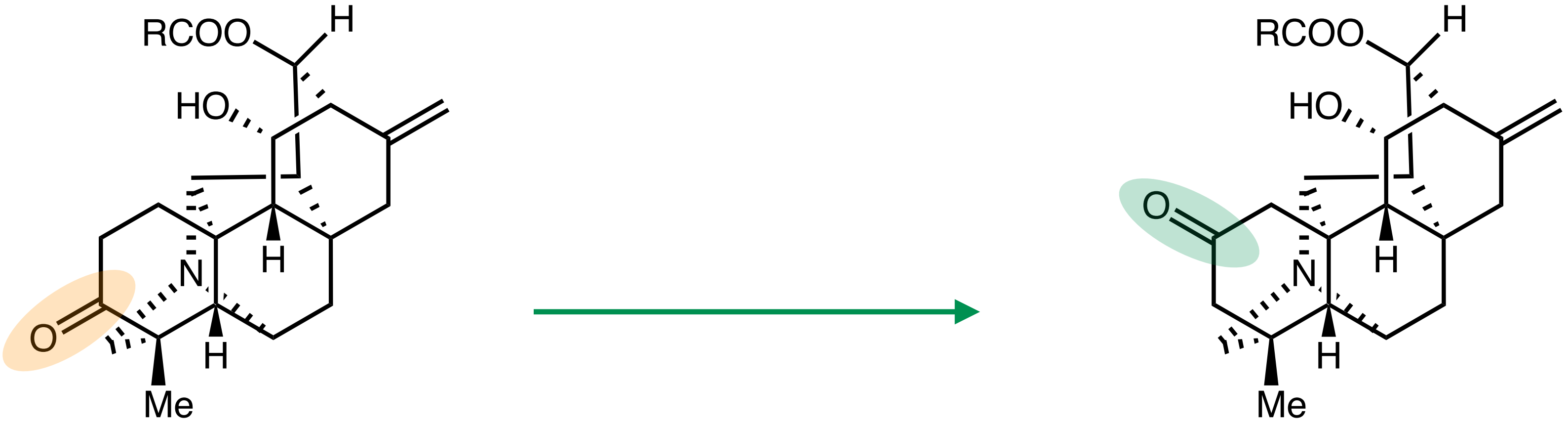

majusidine B?

2-oxo regioisomer

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Fixing incorrect stereoisomers

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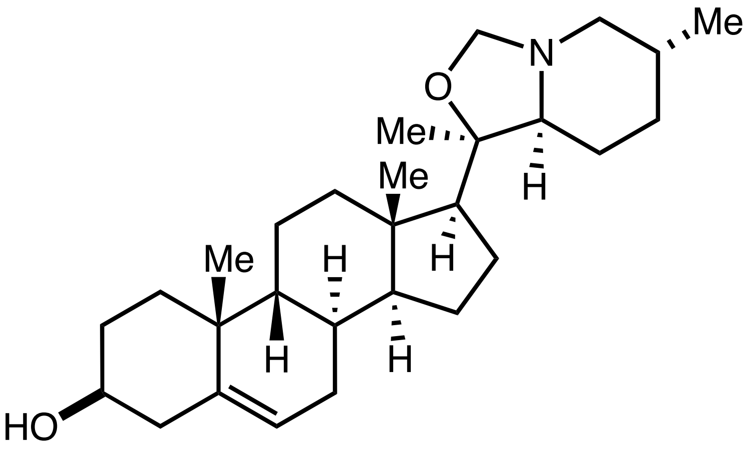

steroidal alkaloid from
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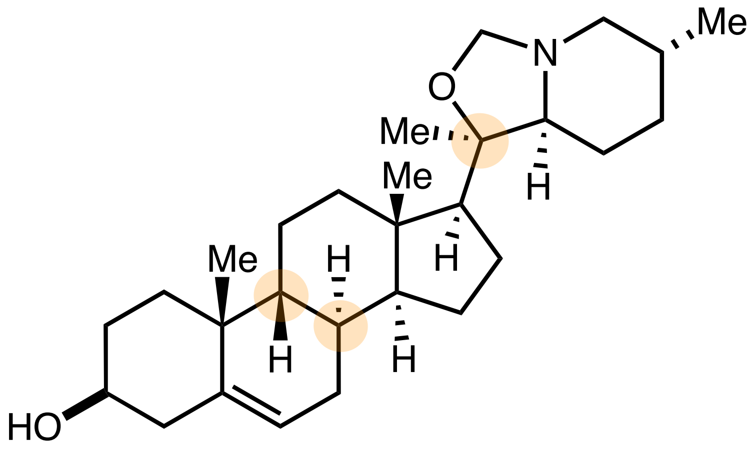

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8, 9, 20 epimer

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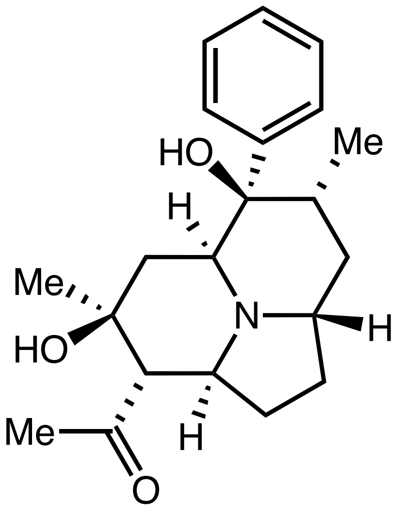

dendrocrepidine A?

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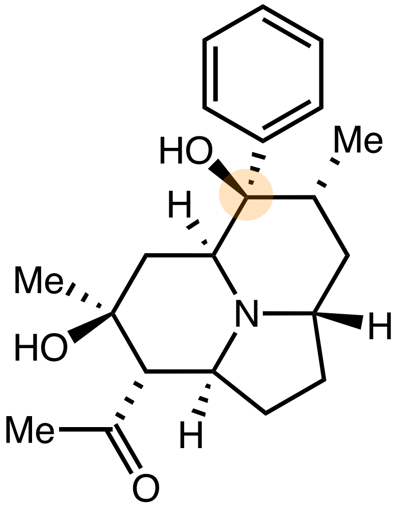

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6-epimer

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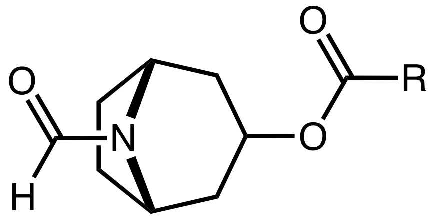

N-formyl-nortropane alkaloids?
(R = Me, Ph, Bn)

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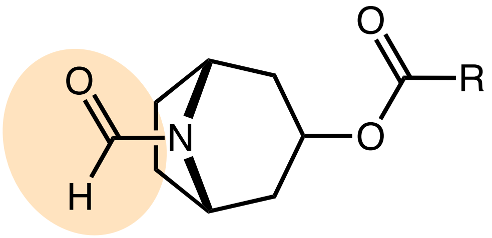

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N-thioformyl-nortropane alkaloids

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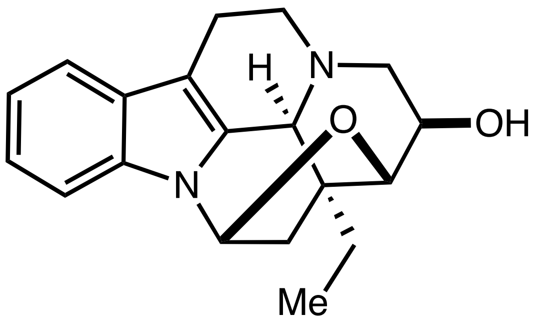

14β-hydroxymeloyunine?

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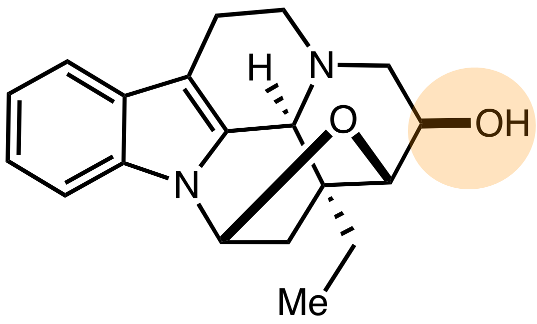

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14β-hydroxymeloyunine?

14α-chloromeloyunine

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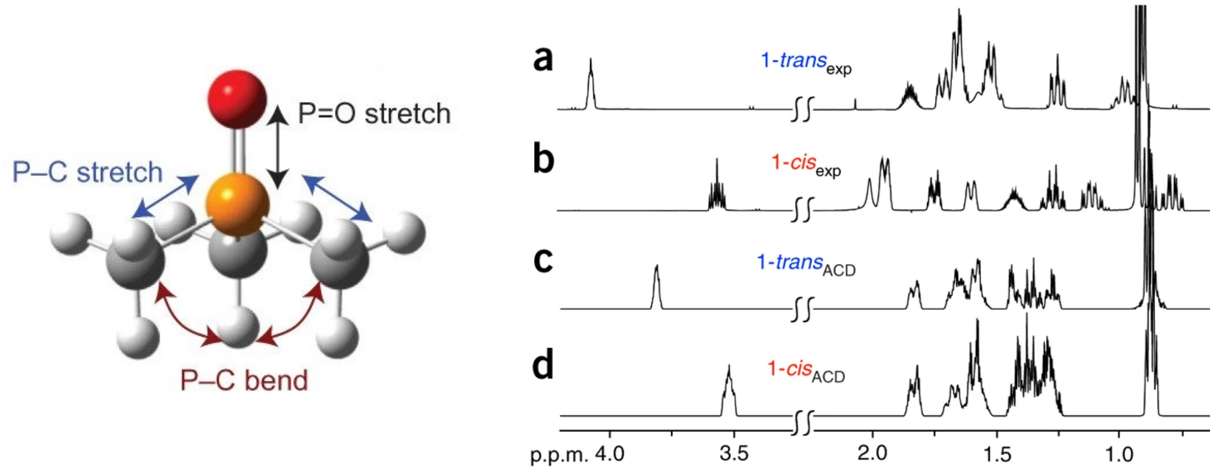
Understanding how molecules act

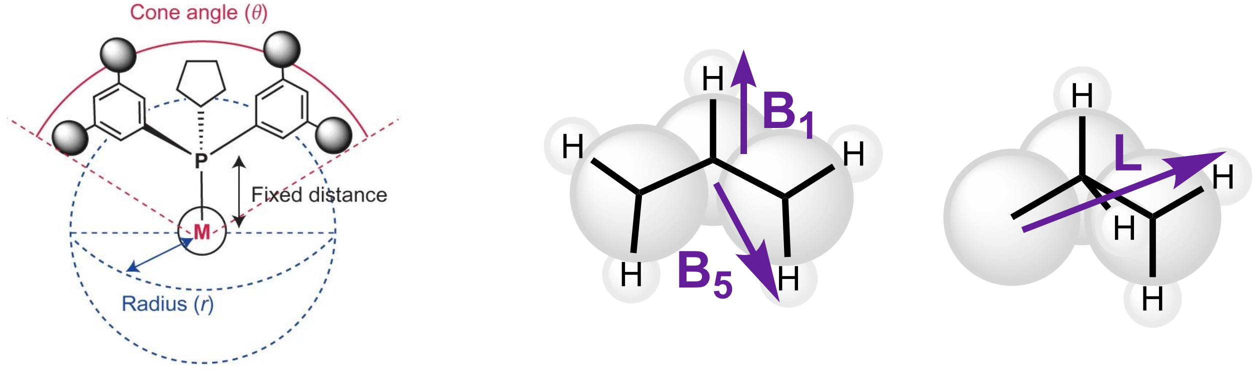
What can DFT do for us?

Molecular Properties

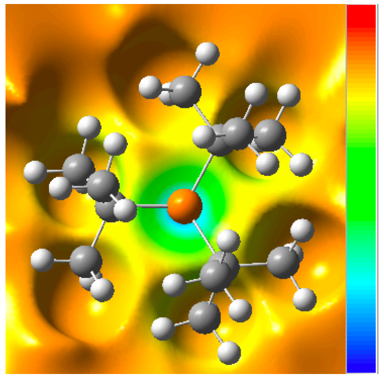
predicted spectral data



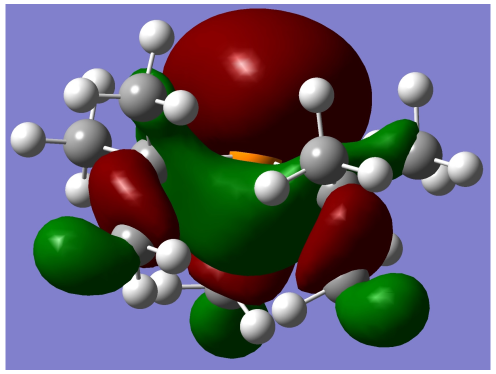
steric parameters



electrostatic potentials

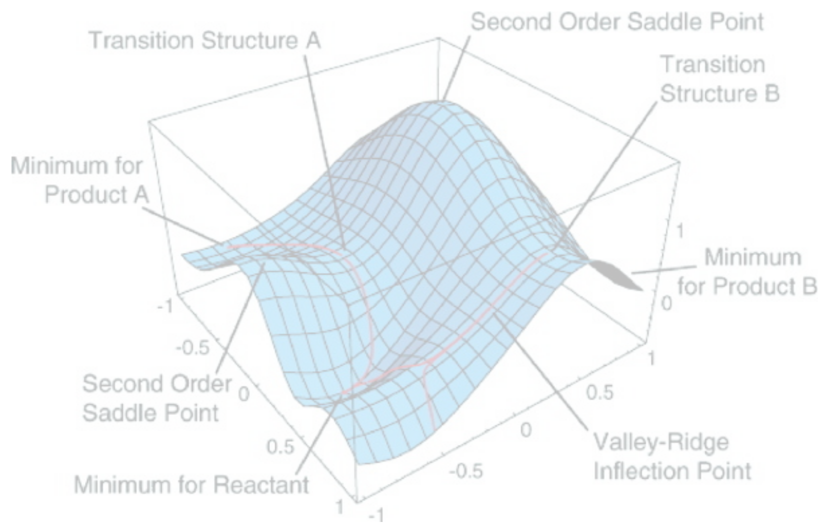


molecular orbitals

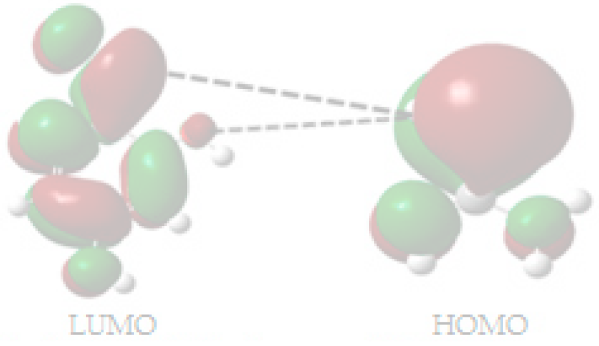


Mechanistic Insights

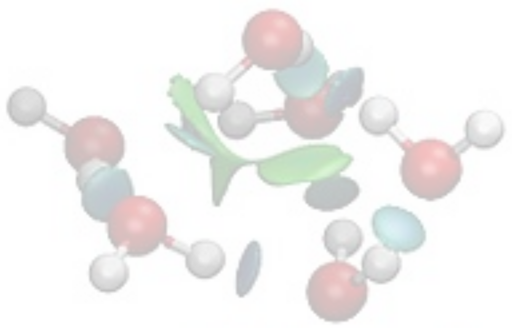
potential energy surfaces



orbital interactions



non-covalent interactions



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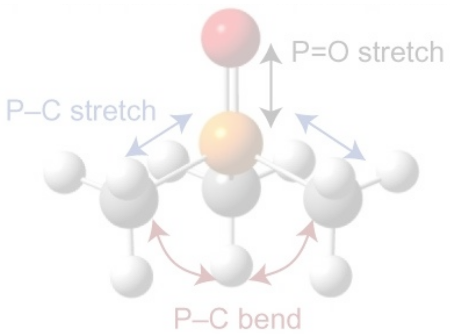

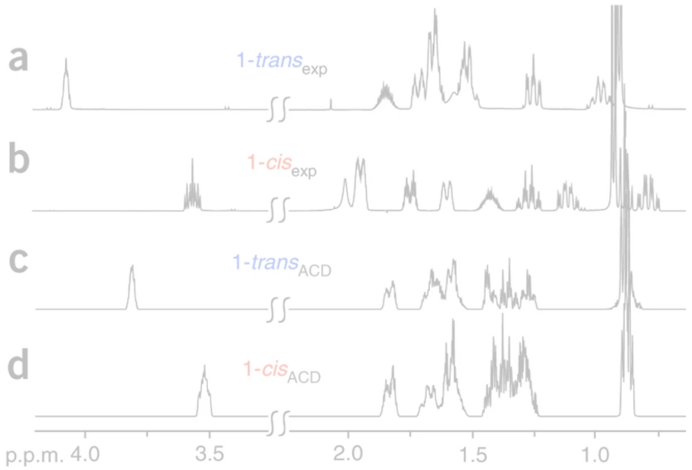

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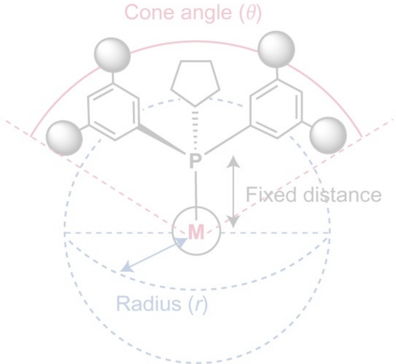
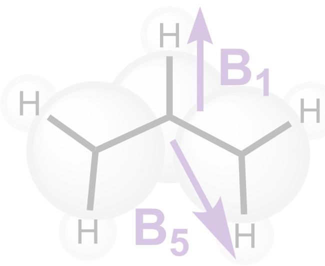
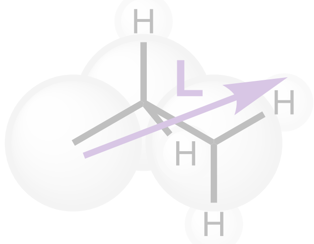
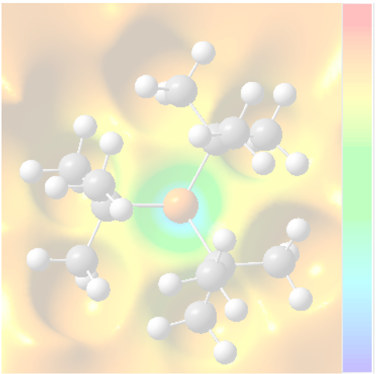






electrostatic potentials



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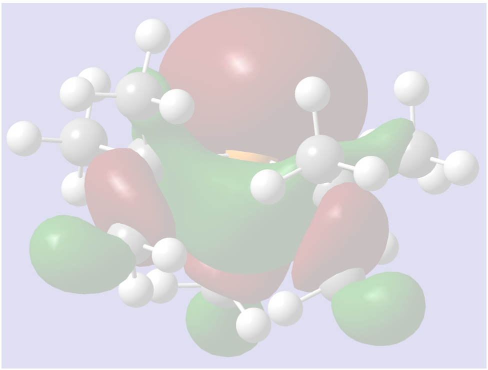

Mechanistic Insights

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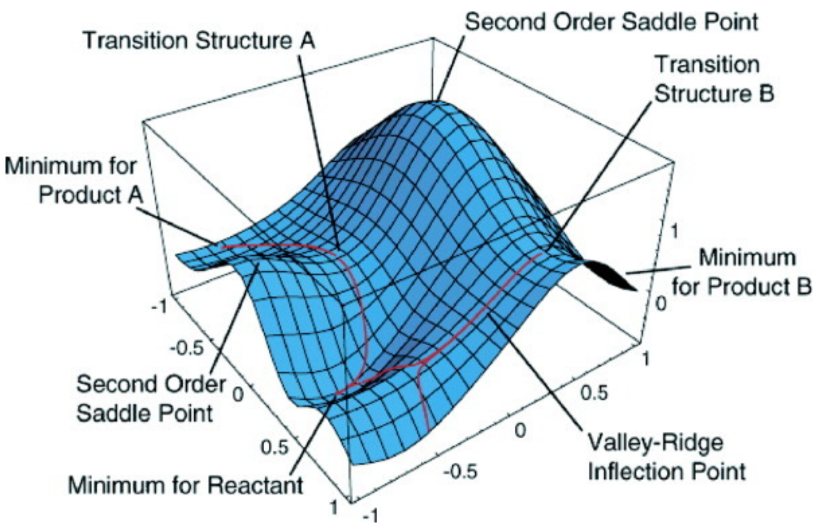

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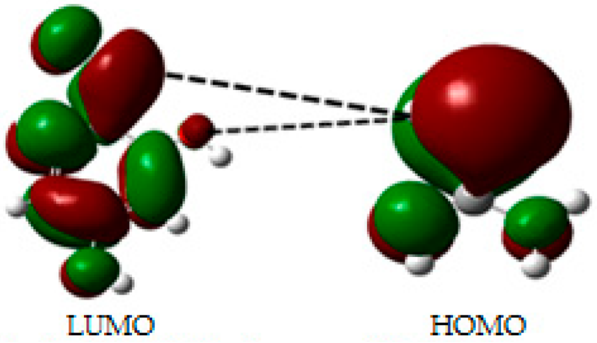

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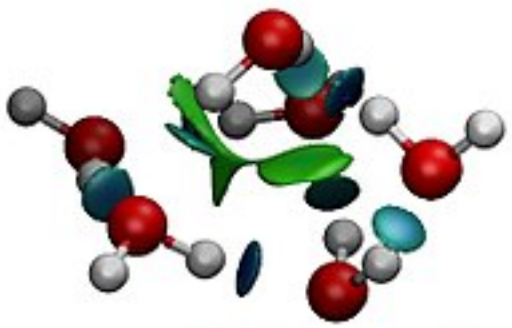
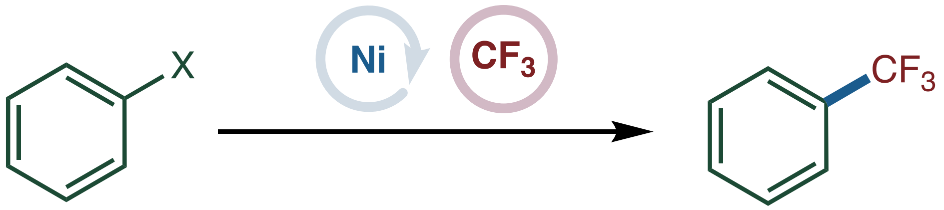


Understanding how molecules act

Mechanistic insights into trifluoromethylation of Ni(II)



Rigoulet, M.; Wellig, S.; Schoenebeck, F. *ACS. Catal.* **2024**, *14*, 7456-7462.

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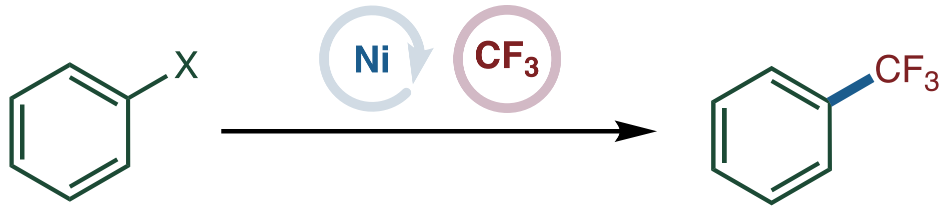

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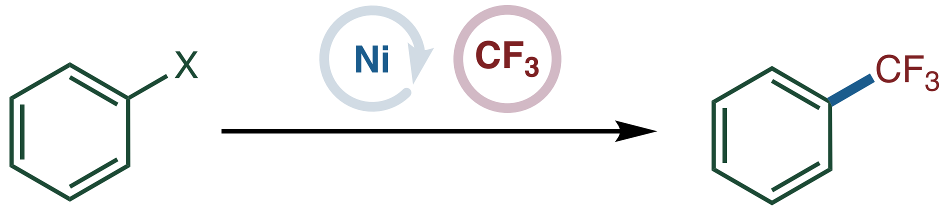

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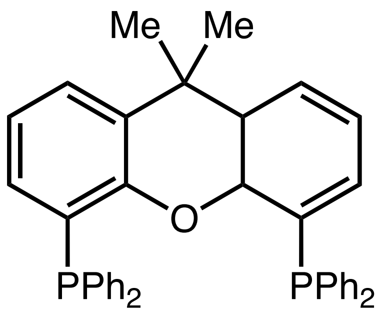

PPh_3

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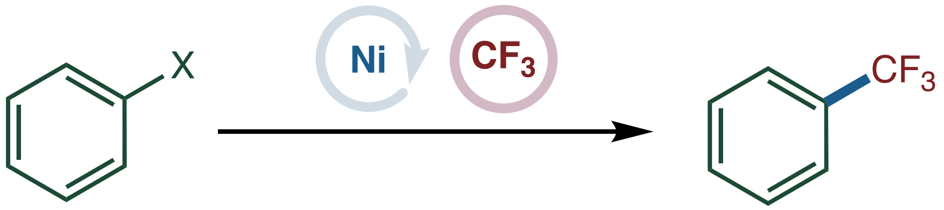

vs.

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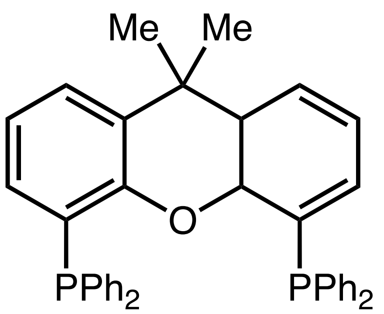

quantitative

PPh_3

quantitative

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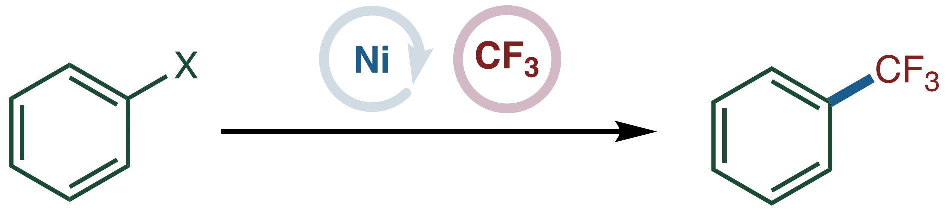
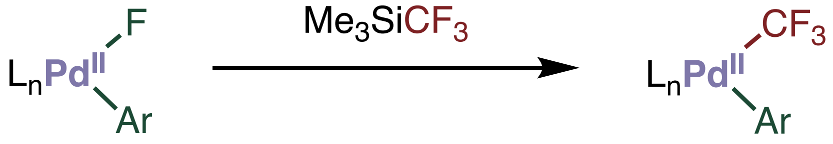
Mechanistic insights into trifluoromethylation of Ni(II)



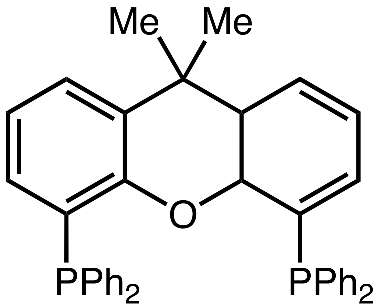


$$L_nPd^{II}(F)(Ar) \xrightarrow{Me_3SiCF_3} L_nPd^{II}(CF_3)(Ar)$$

vs.

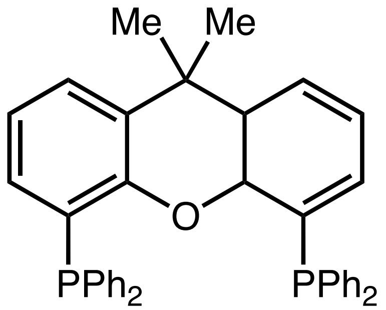
$$L_nNi^{II}(F)(Ar) \xrightarrow{Me_3SiCF_3} L_nNi^{II}(CF_3)(Ar)$$

L_n =



quantitative

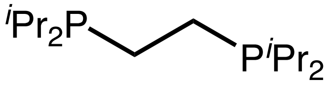
L_n =



PPh_3

quantitative

PCy_3



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Understanding how molecules act

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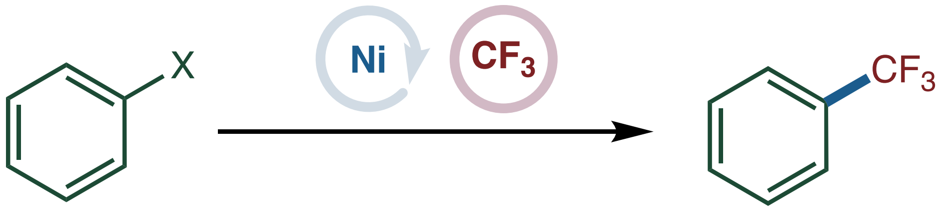
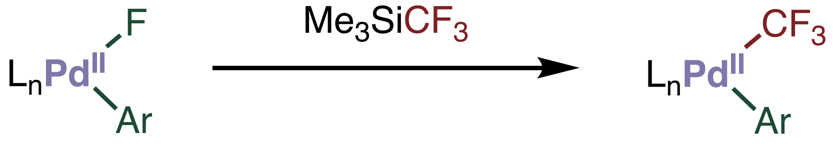
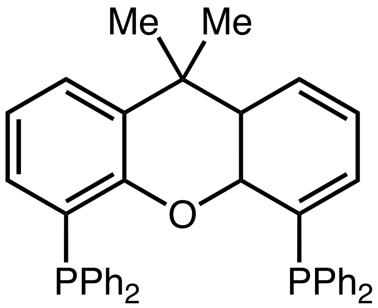




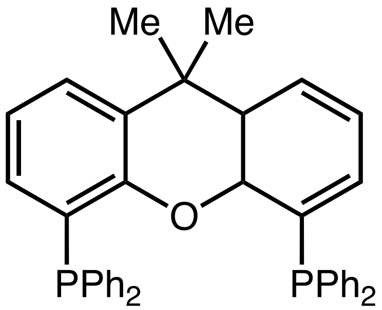
vs.

L_n =



quantitative

L_n =

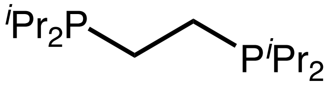


quantitative

PPh_3

quantitative

PCy_3



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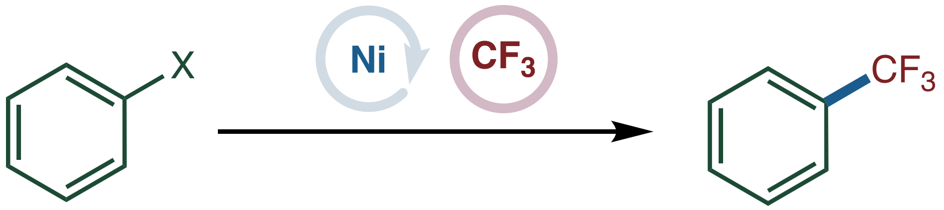
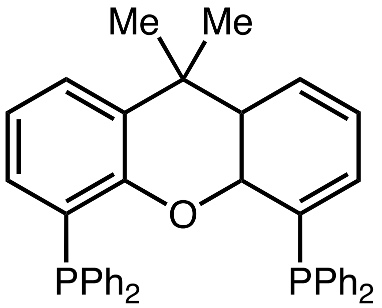


L_n =



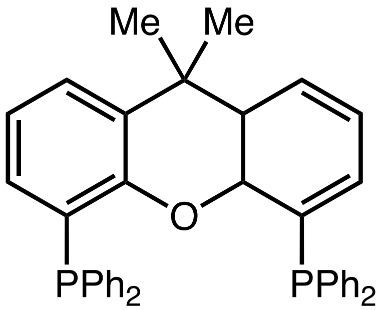
quantitative

PPh_3

quantitative

vs.

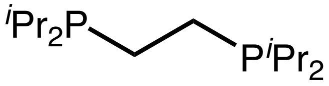
L_n =



quantitative

PCy_3

0% yield



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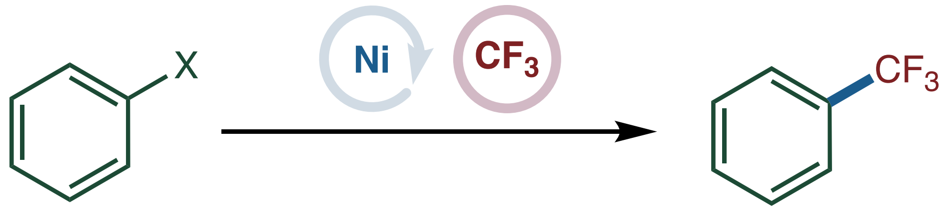

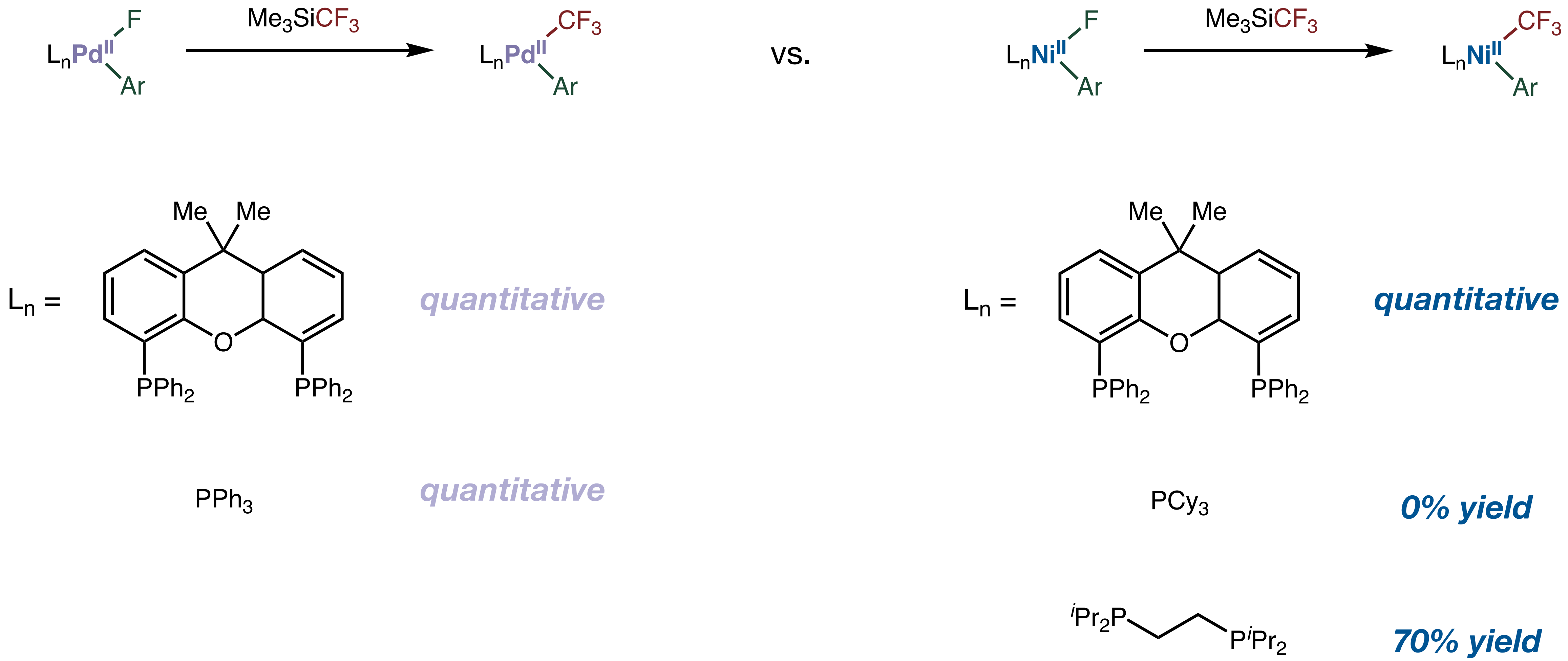

quantitative (L_n = Xantphos-type ligand, Pd)

quantitative (PPh_3, Pd)

quantitative (L_n = Xantphos-type ligand, Ni)

0% yield (PCy_3, Ni)

70% yield ($^iPr_2P$–CH$_2$CH$_2$–P^iPr_2, Ni)

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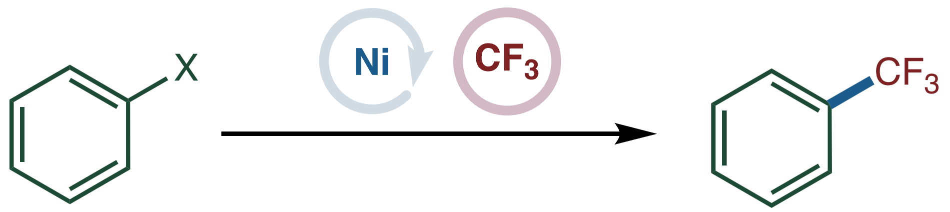
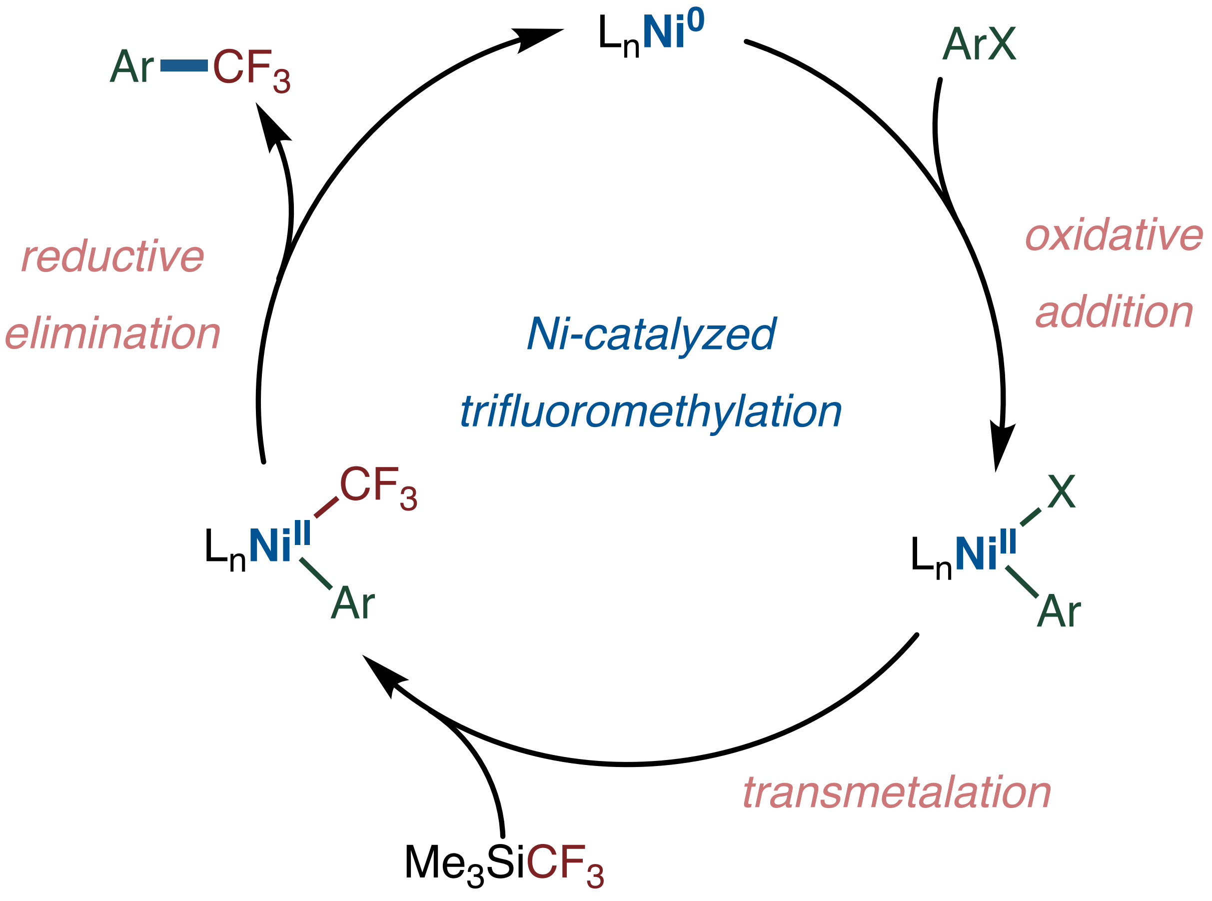
Mechanistic insights into trifluoromethylation of Ni(II)





L_nNi^0

ArX

oxidative addition

L_nNi^{II}(X)(Ar)

transmetalation

Me_3SiCF_3

L_nNi^{II}(CF_3)(Ar)

reductive elimination

Ar–CF_3

Ni-catalyzed trifluoromethylation

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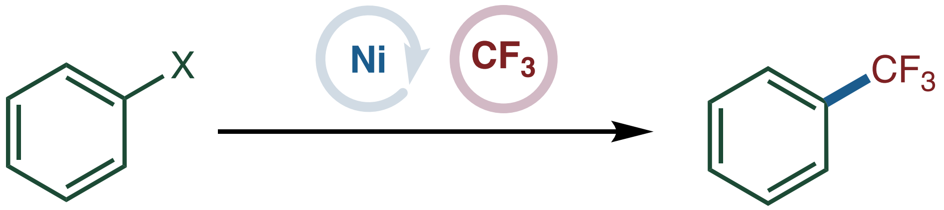
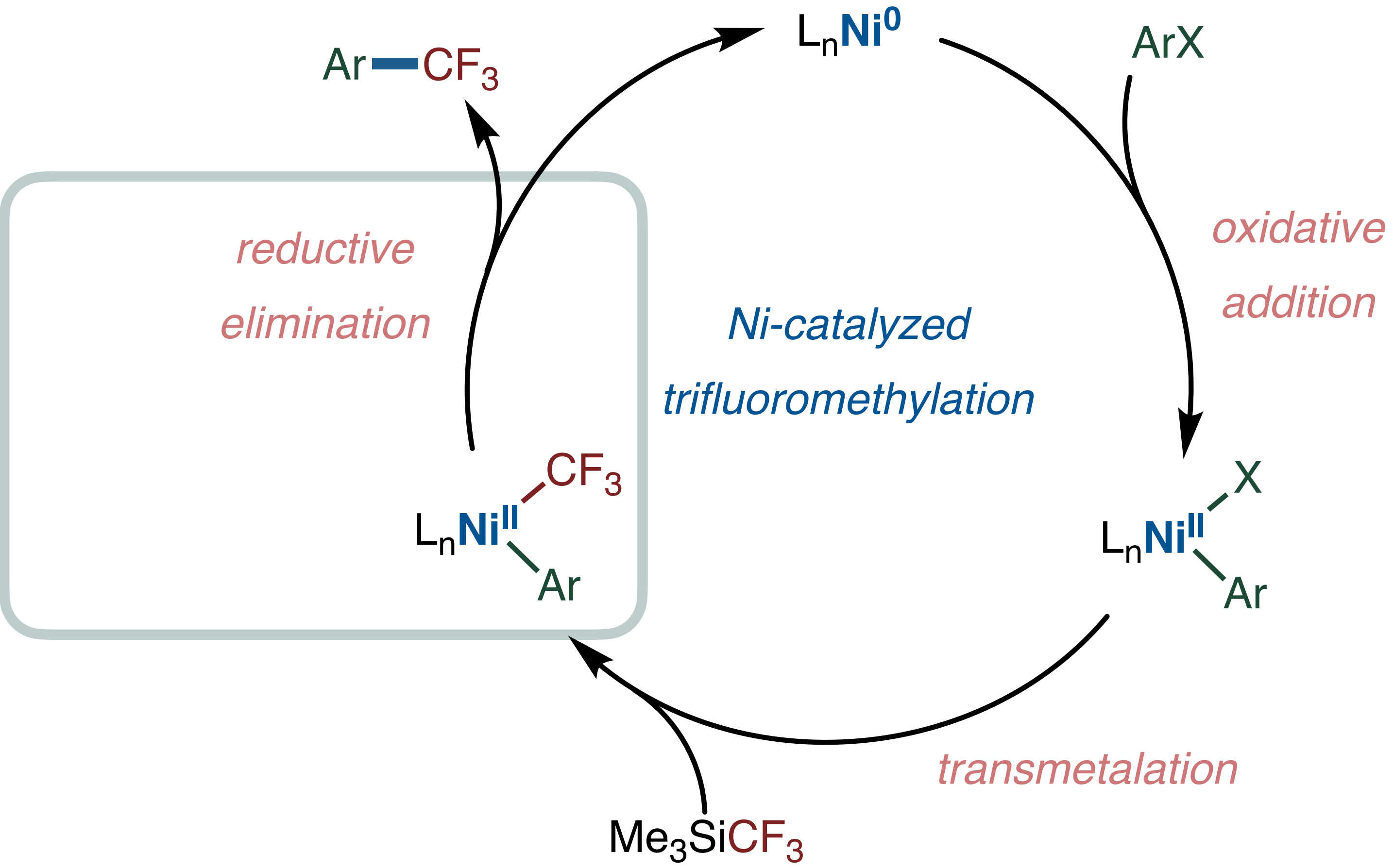
Mechanistic insights into trifluoromethylation of Ni(II)





L_nNi^0

ArX

oxidative addition

$L_nNi^{II}(X)(Ar)$

transmetalation

Me_3SiCF_3

$L_nNi^{II}(CF_3)(Ar)$

reductive elimination

Ar–CF_3

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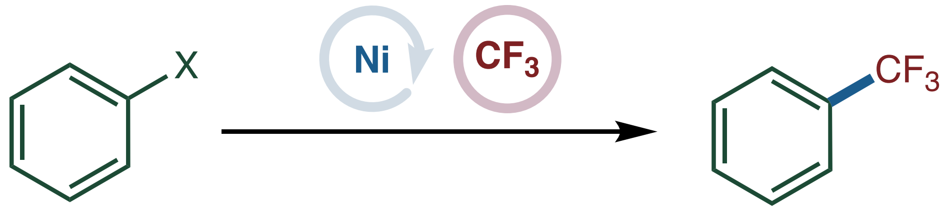

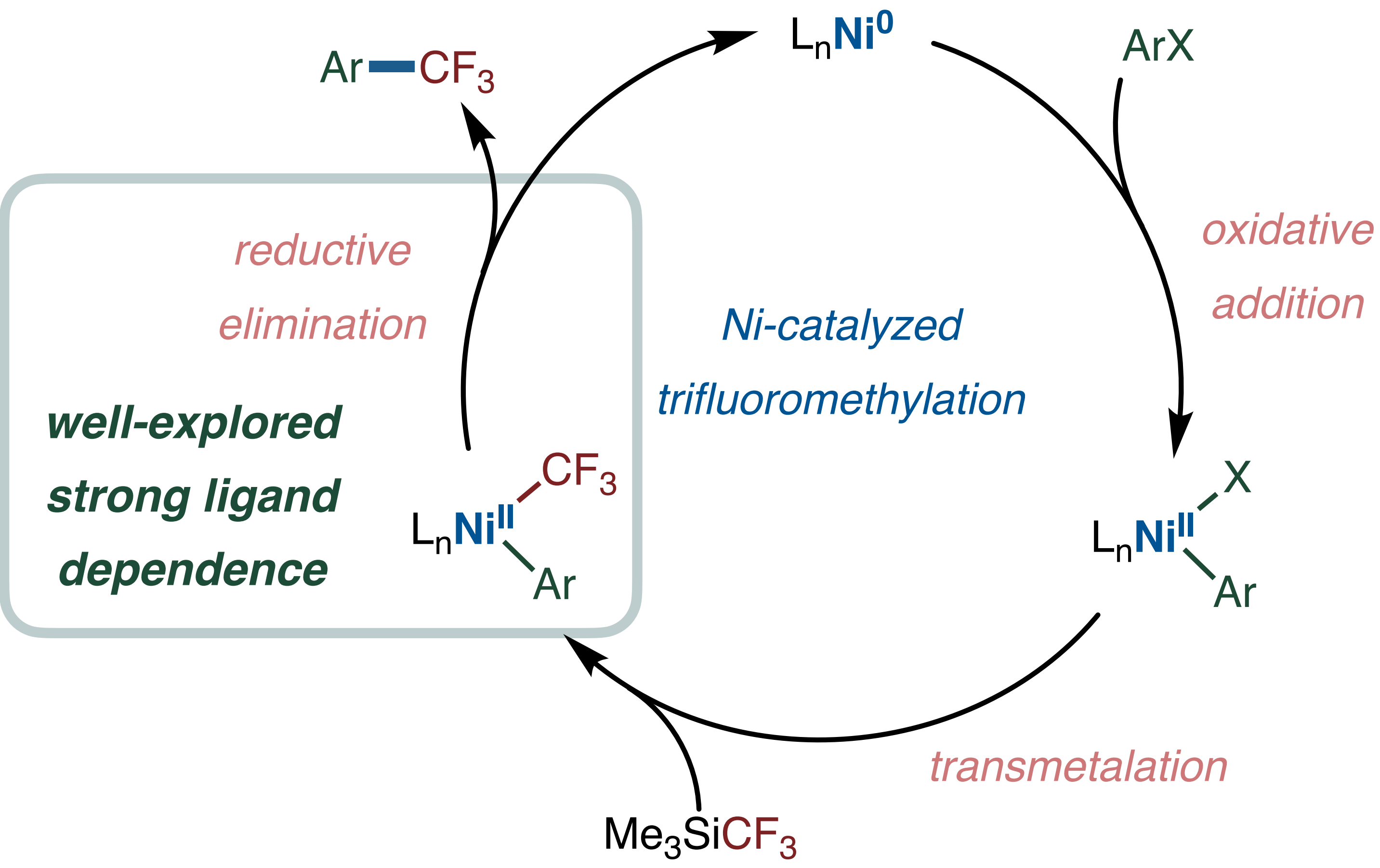

oxidative addition

transmetalation

reductive elimination

Ni-catalyzed trifluoromethylation

well-explored strong ligand dependence

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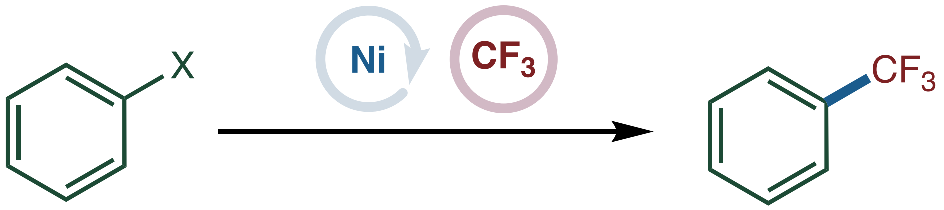
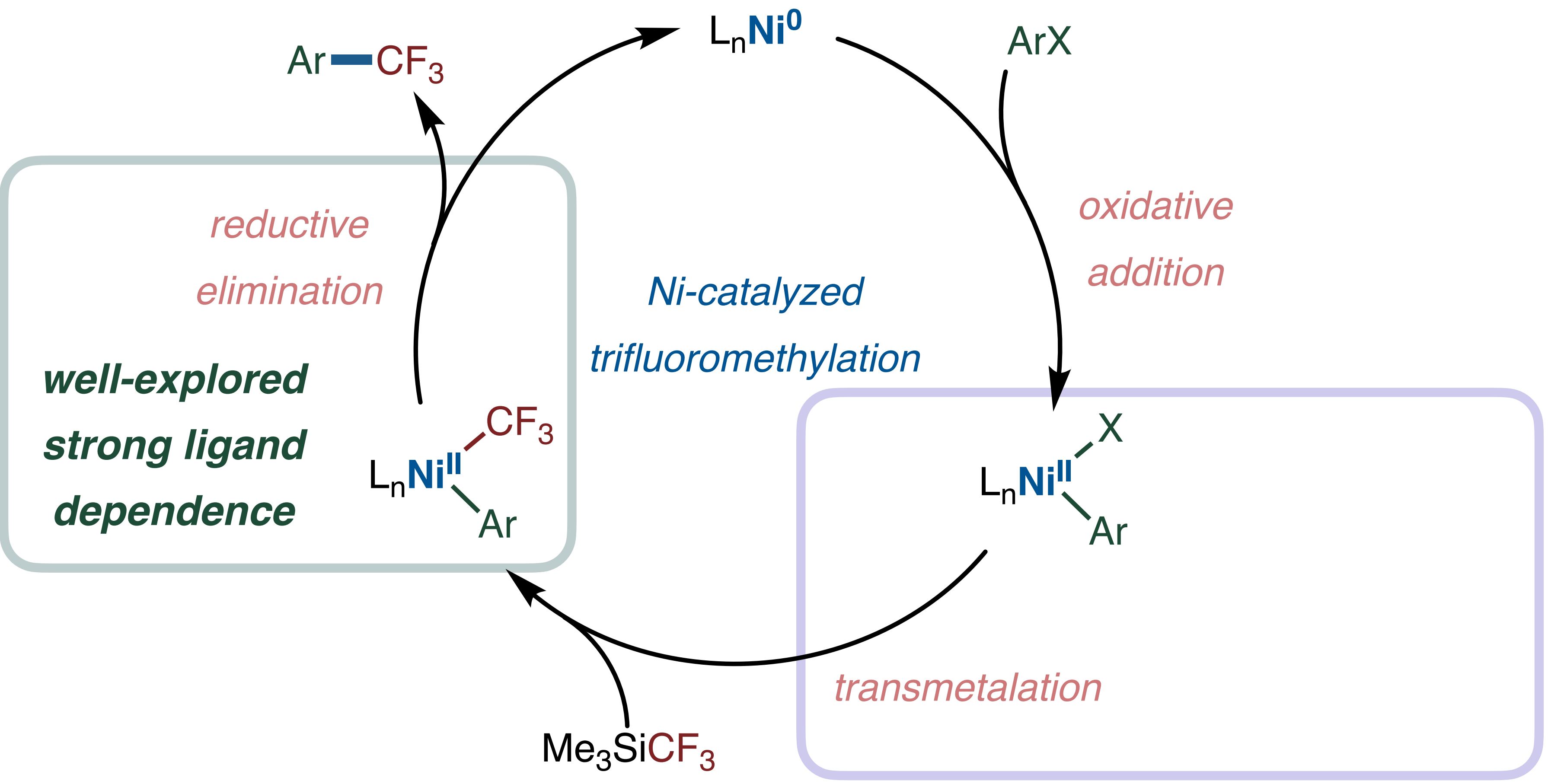
Mechanistic insights into trifluoromethylation of Ni(II)





L_nNi^0

ArX

oxidative

addition

$L_nNi^{II}(X)(Ar)$

transmetalation

Me_3SiCF_3

$L_nNi^{II}(CF_3)(Ar)$

reductive

elimination

$Ar-CF_3$

well-explored

strong ligand

dependence

Ni-catalyzed

trifluoromethylation

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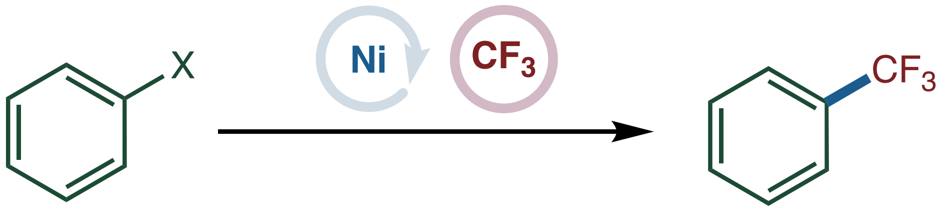
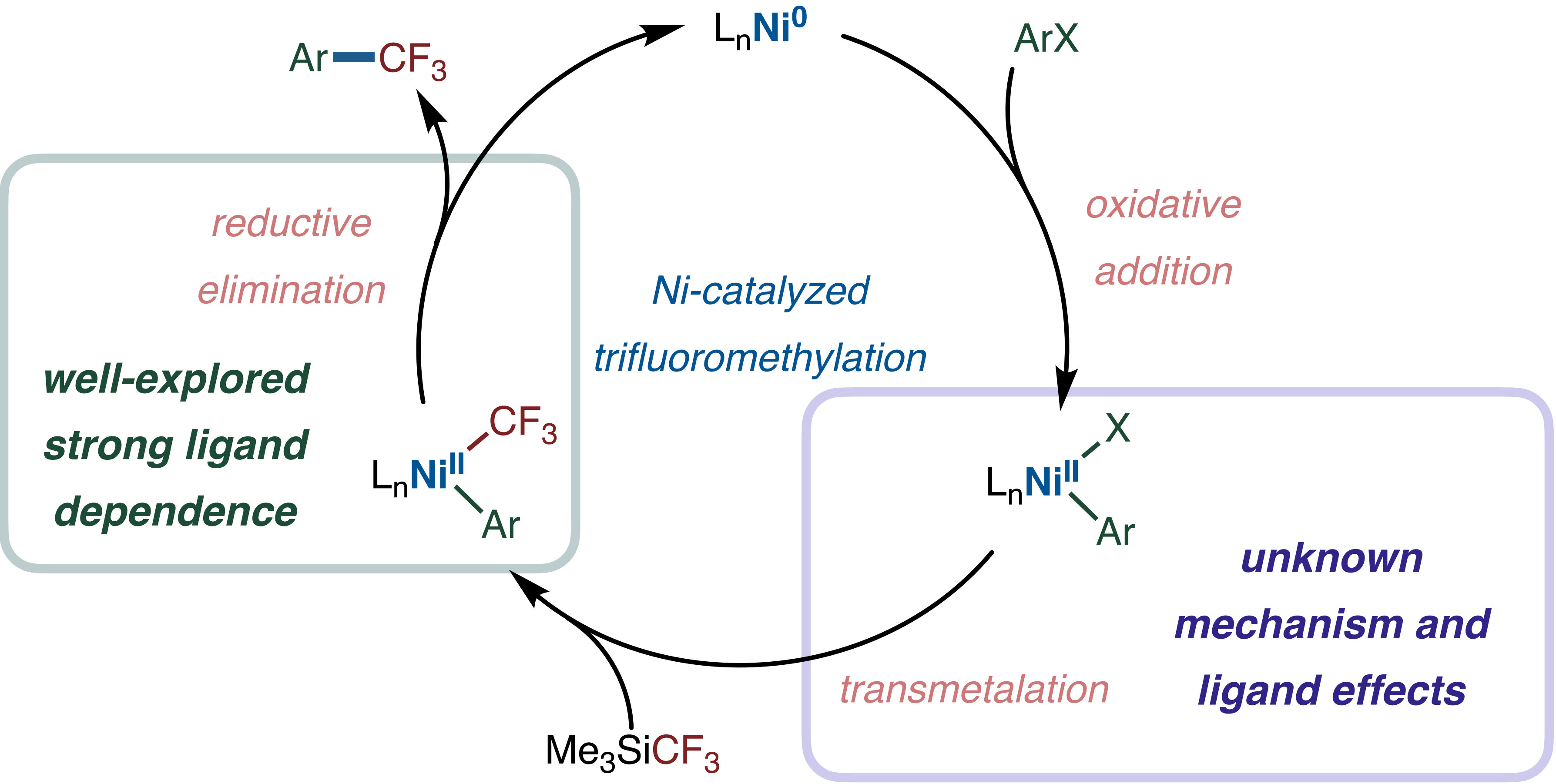
Understanding how molecules act

Mechanistic insights into trifluoromethylation of Ni(II)





oxidative addition

transmetalation

reductive elimination

Ni-catalyzed trifluoromethylation

well-explored strong ligand dependence

unknown mechanism and ligand effects

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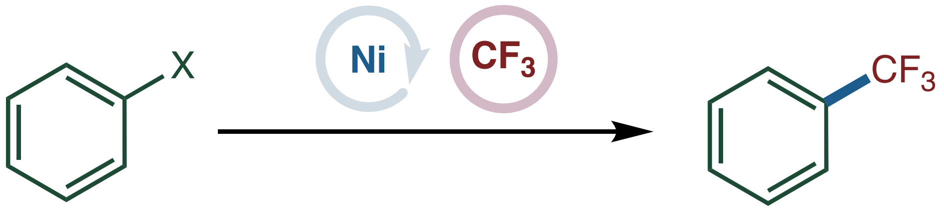
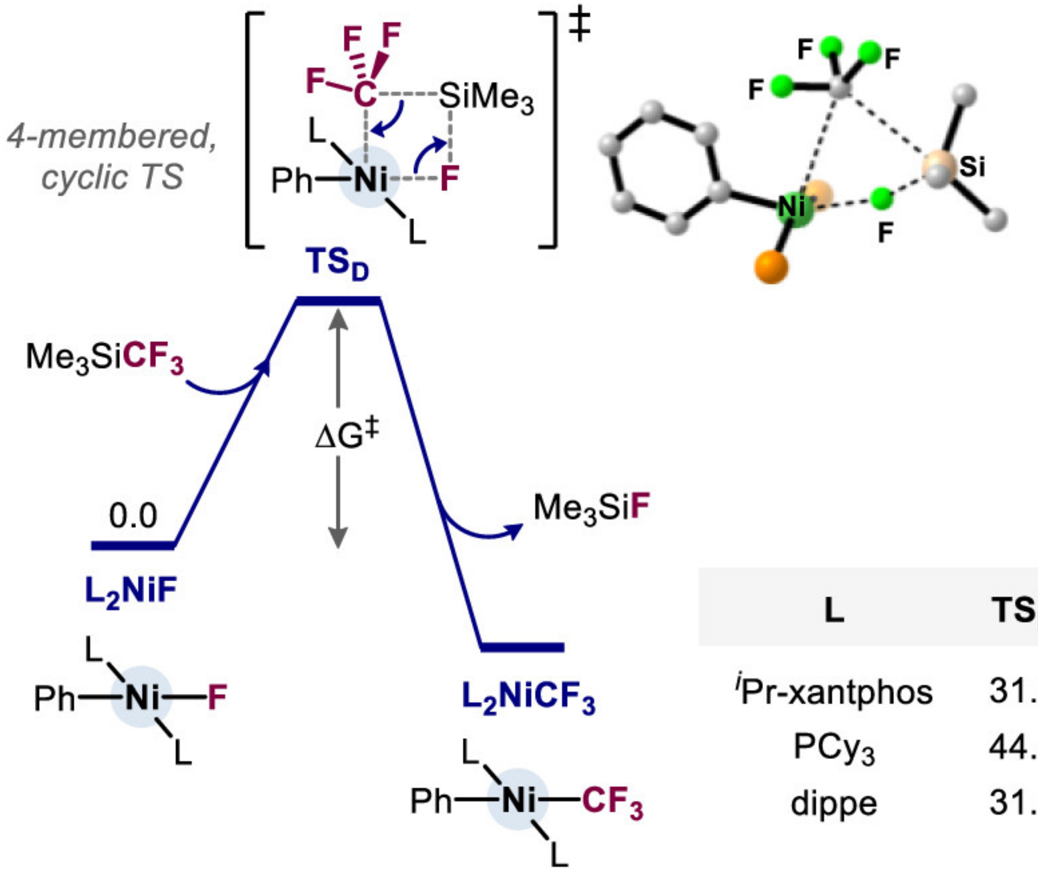
Understanding how molecules act

How does the transmetalation work?



A *Direct transmetalation*



L	TS_D
^{i}Pr-xantphos	31.6
PCy_3	44.0
dippe	31.2

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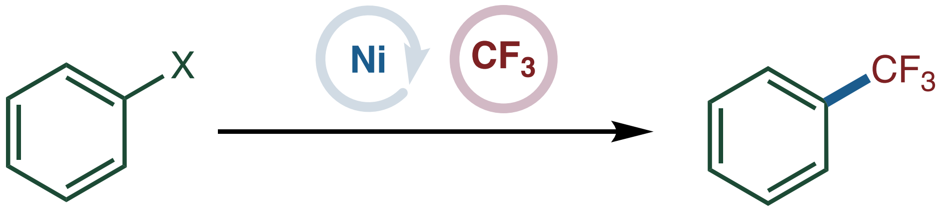
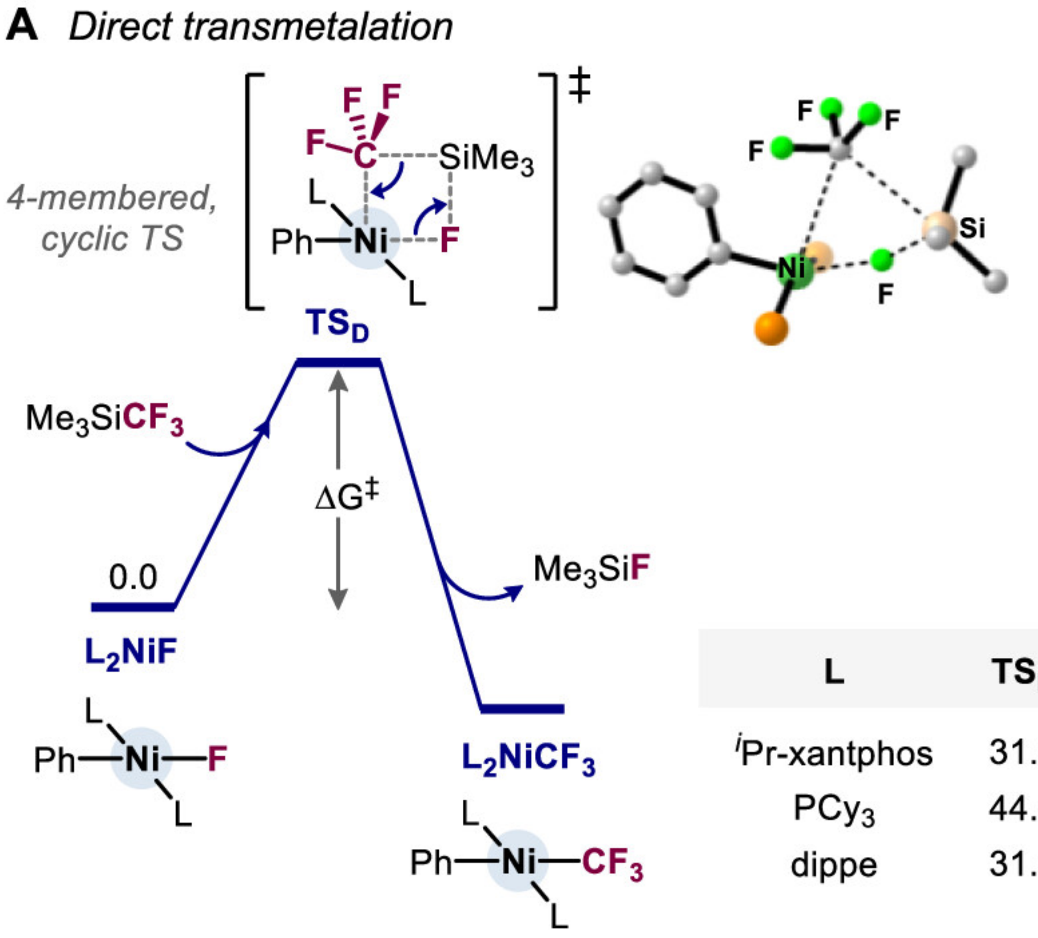
Understanding how molecules act

How does the transmetalation work?





L	TS_D
^{i}Pr-xantphos	31.6
PCy_3	44.0
dippe	31.2

not energetically feasible at room temperature

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Understanding how molecules act

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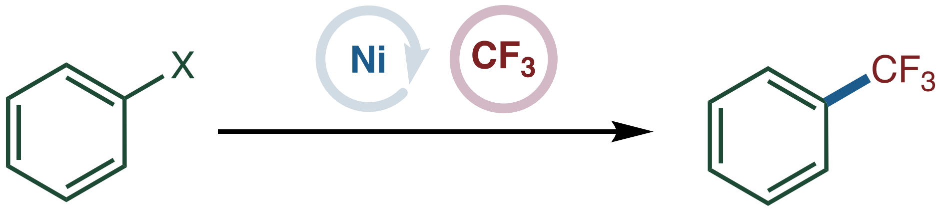
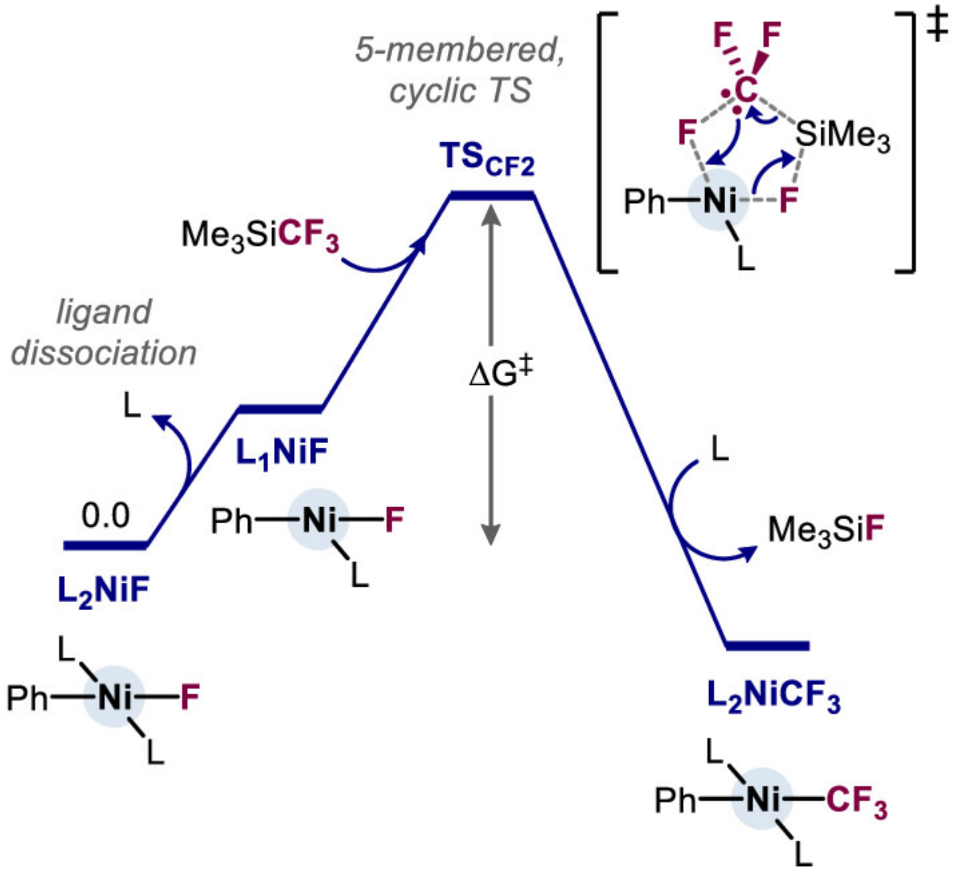
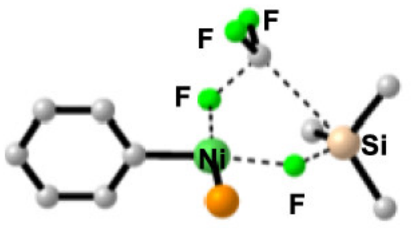


B *Transmetalation with CF_2 carbene generation*





L	L_1NiF	TS_{CF2}
^{i}Pr-xantphos	21.3	46.1
PCy_3	20.6	44.4
dippe	25.1	47.0

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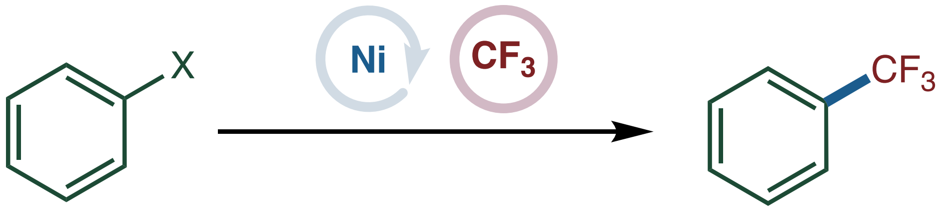
How does the transmetalation work?



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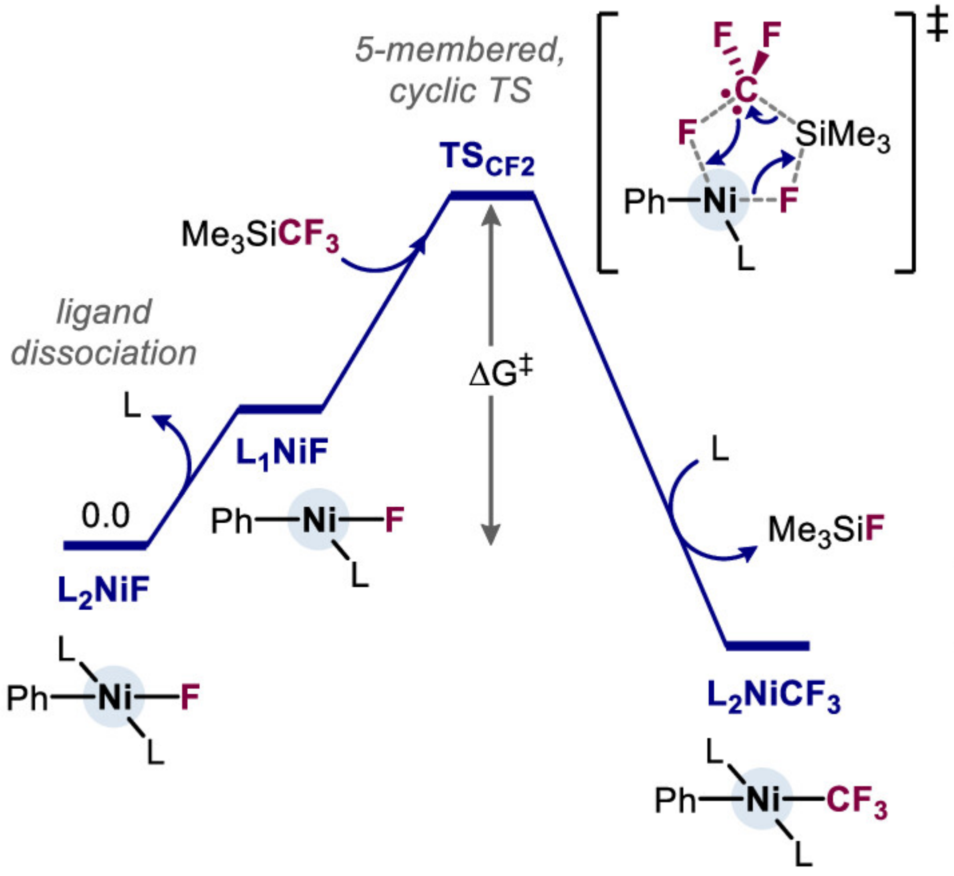

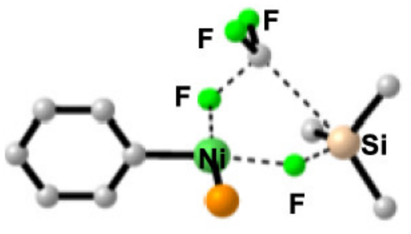

L	L_1NiF	TS_{CF2}
^{i}Pr-xantphos	21.3	46.1
PCy_3	20.6	44.4
dippe	25.1	47.0

ligand dissociation is always energetically disfavored

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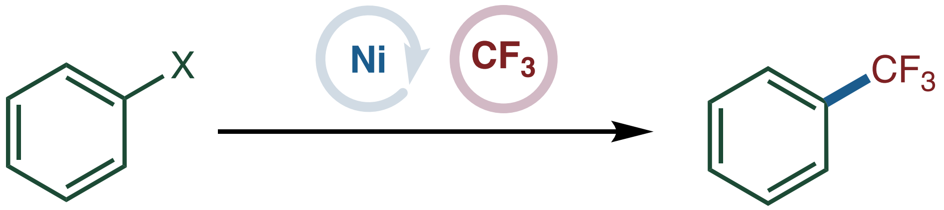
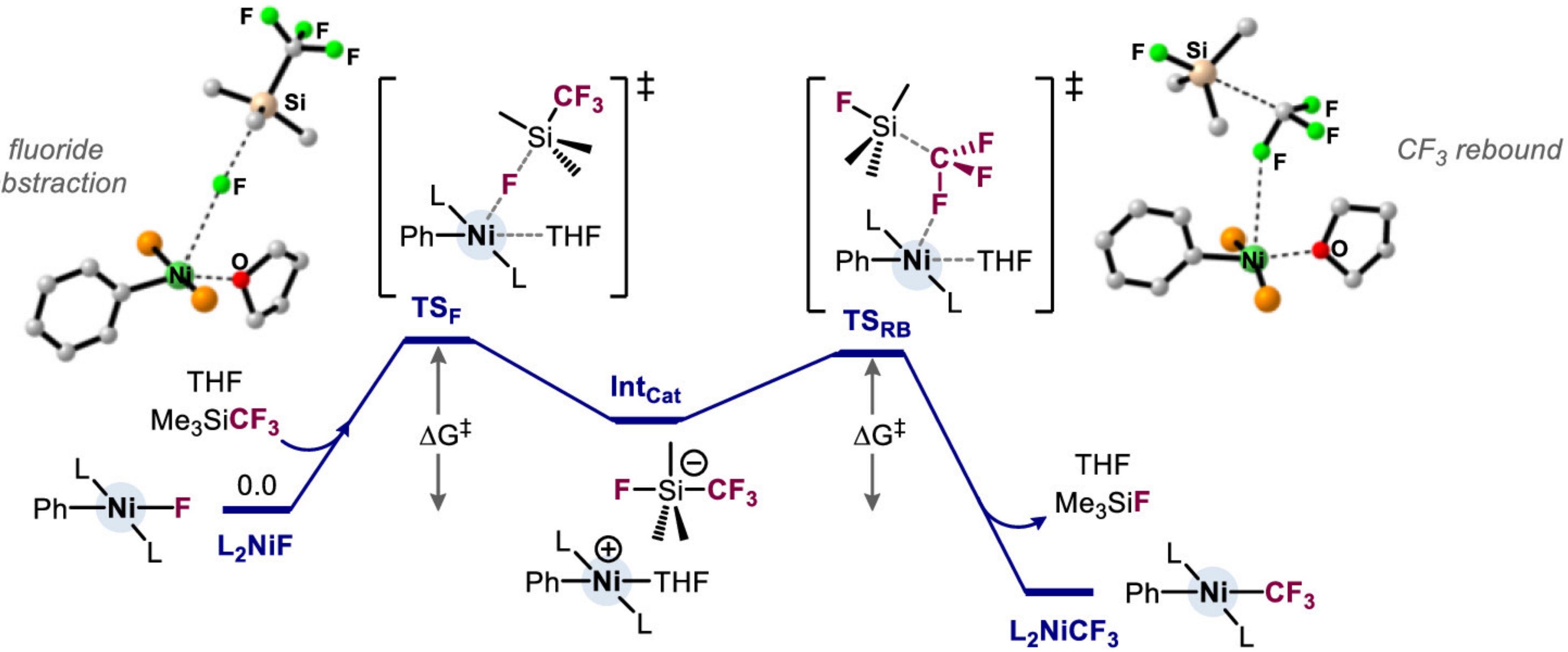
How does the transmetalation work?





C *Transmetalation via F abstraction, CF_3 release and rebound*

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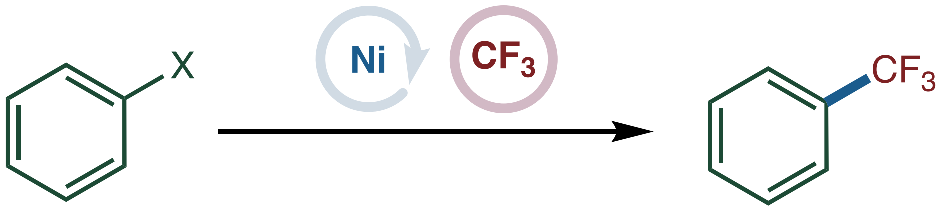
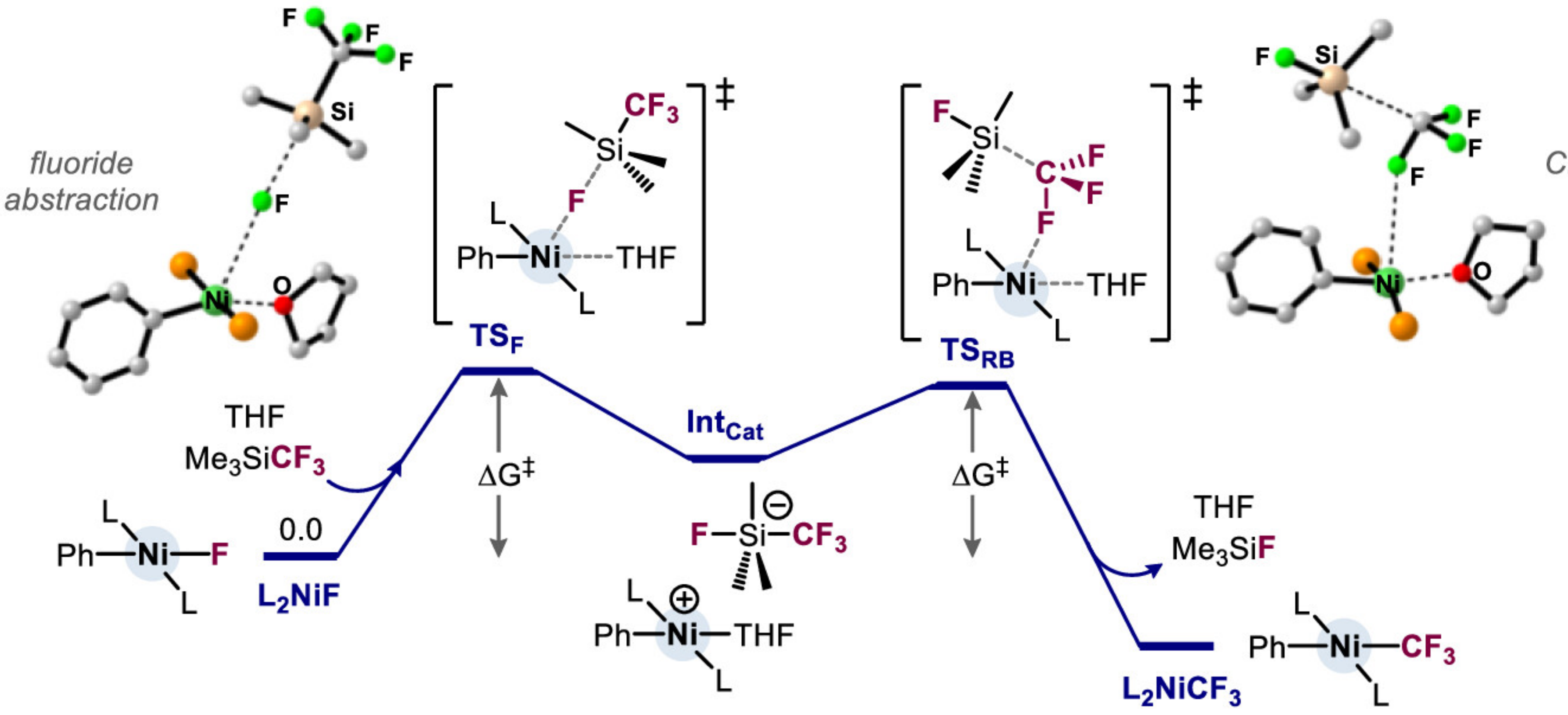
Understanding how molecules act

How does the transmetalation work?



C *Transmetalation via F abstraction, CF_3 release and rebound*



L	TS_F	TS_{RB}	
^{i}Pr-xantphos	22.1	21.8	✓
PCy_3	42.7	39.4	✗
dippe	20.1	24.9	✓

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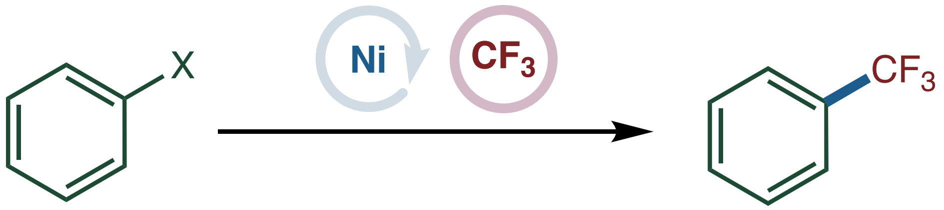
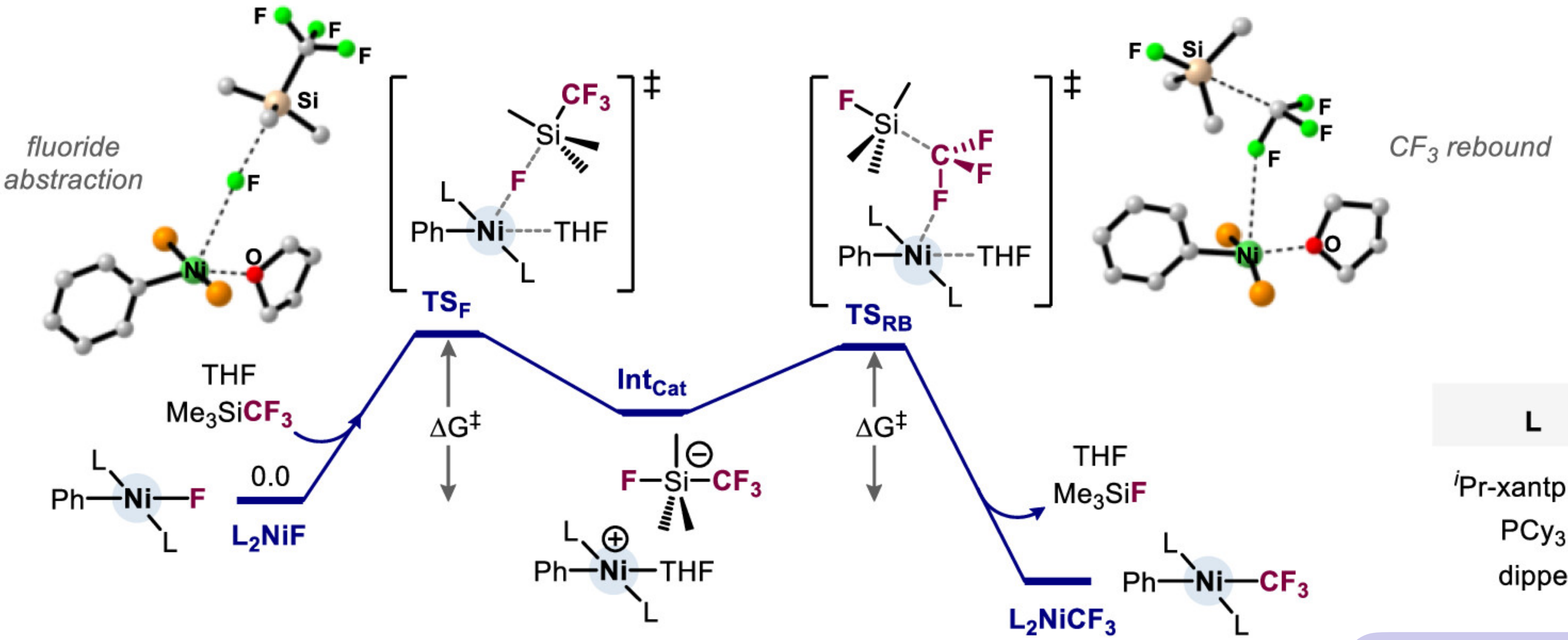
How does the transmetalation work?



C *Transmetalation via F abstraction, CF_3 release and rebound*



L	TS_F	TS_{RB}	
^{i}Pr-xantphos	22.1	21.8	✓
PCy_3	42.7	39.4	✗
dippe	20.1	24.9	✓

results align with experimental observations

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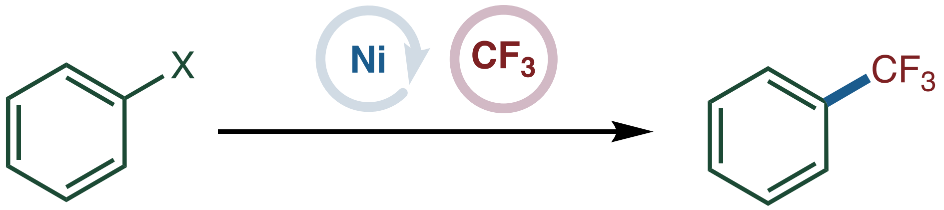
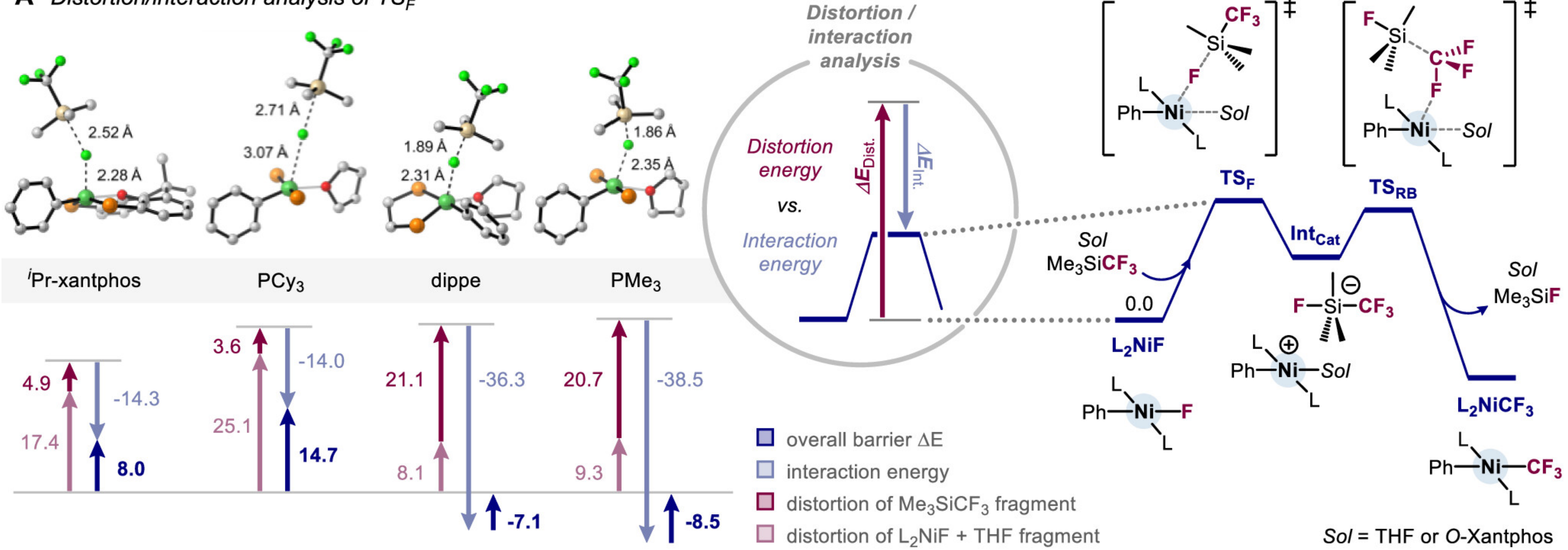
Computations guiding experiments



A *Distortion/interaction analysis of TS_F*



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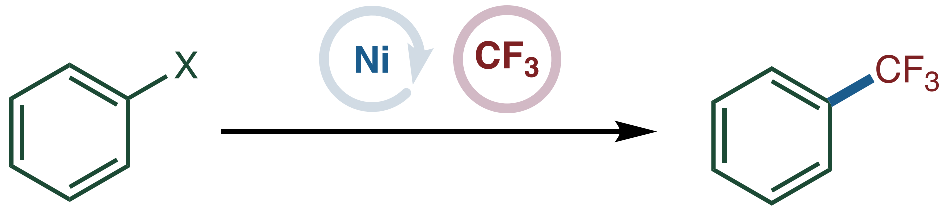

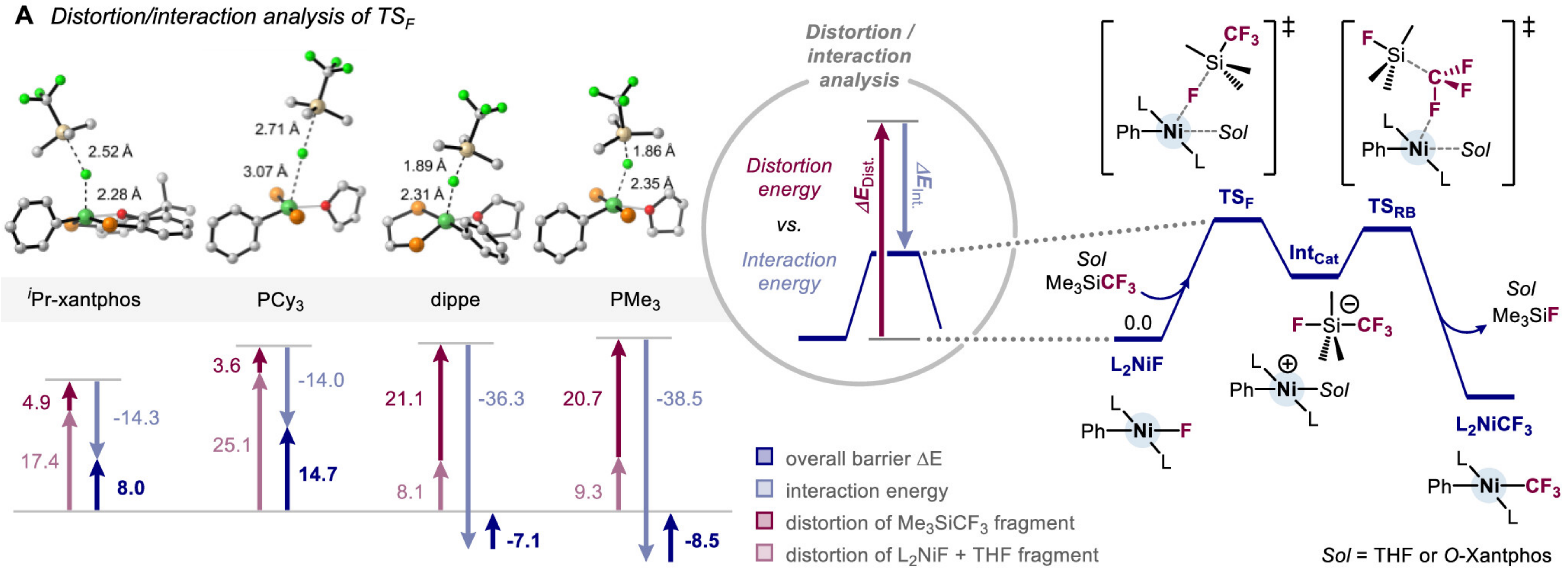

PMe_3 should be a viable ligand to enable transmetalation

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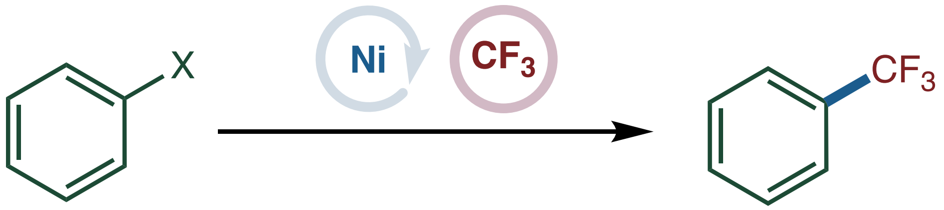
Understanding how molecules act

Computations guiding experiments



PMe_3 should be a viable ligand to enable transmetalation

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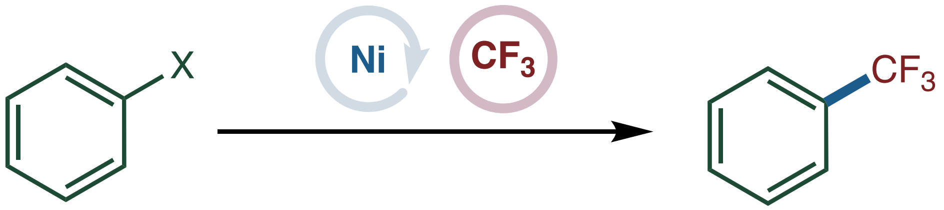
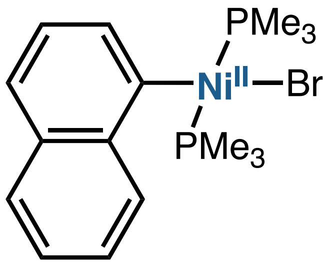
Understanding how molecules act

Computations guiding experiments



PMe₃ should be a viable ligand to enable transmetalation



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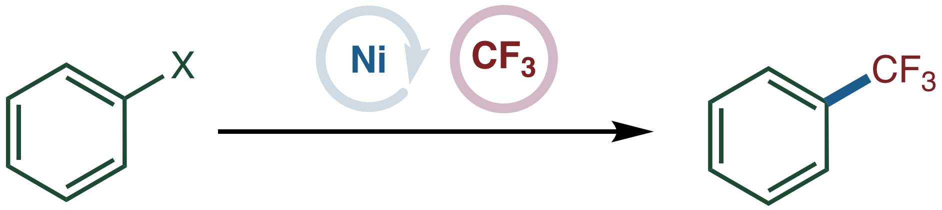
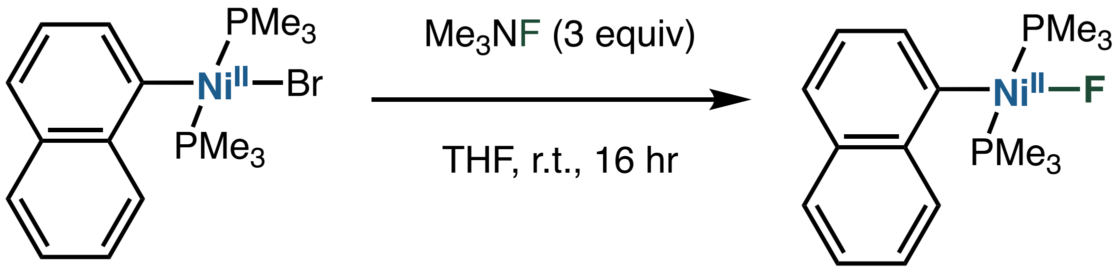
Computations guiding experiments



PMe_3 should be a viable ligand to enable transmetalation



Rigoulet, M.; Wellig, S.; Schoenebeck, F. *ACS. Catal.* **2024**, *14*, 7456-7462.

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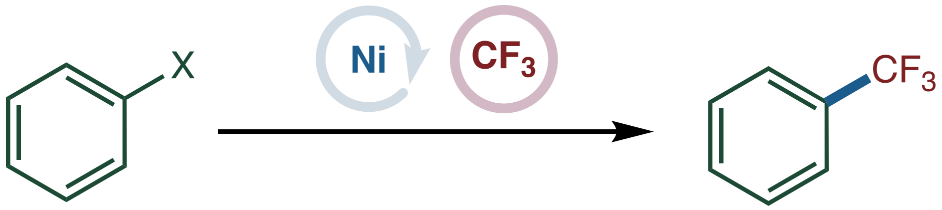
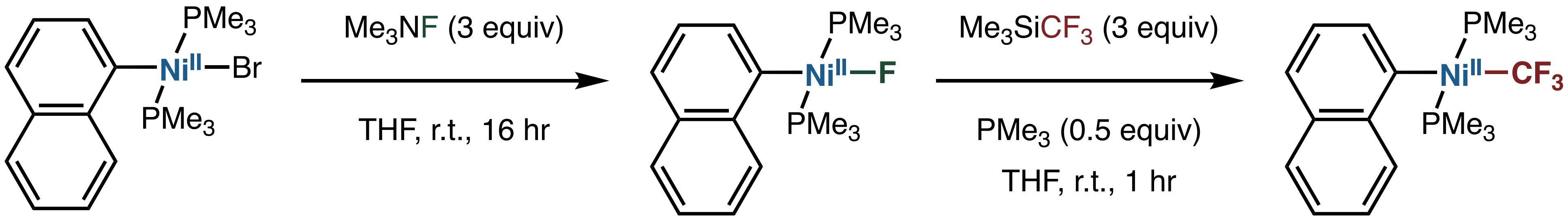
Computations guiding experiments



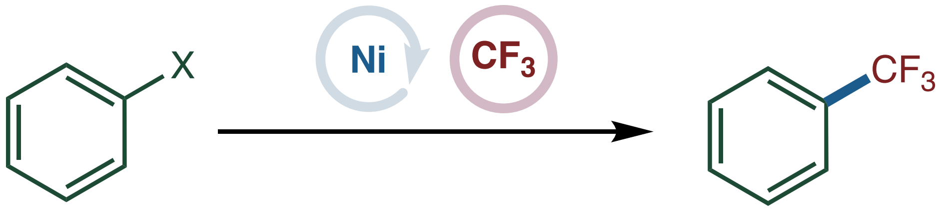
PMe$_3$ should be a viable ligand to enable transmetalation



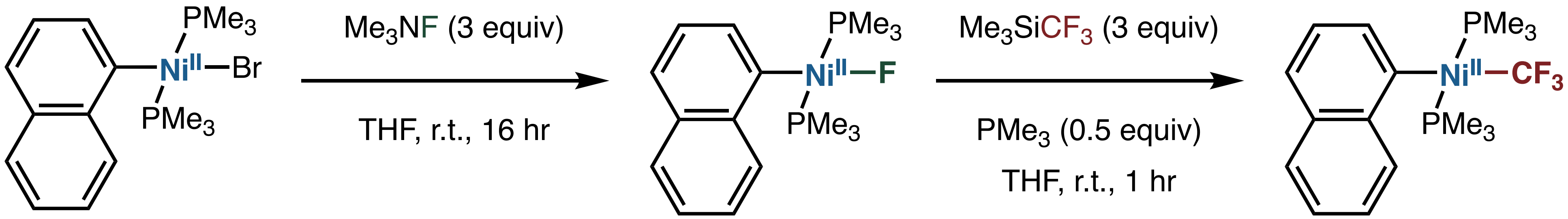
Rigoulet, M.; Wellig, S.; Schoenebeck, F. *ACS. Catal.* **2024**, *14*, 7456-7462.

Understanding how molecules act

Computations guiding experiments



PMe_3 should be a viable ligand to enable transmetalation



first Ni^{II}-CF_3 complex with monodentate chelating ligands

Rigoulet, M.; Wellig, S.; Schoenebeck, F. *ACS. Catal.* **2024**, *14*, 7456-7462.

Understanding how molecules act

Understanding how molecules act

What if DFT is not enough?

Understanding how molecules act

What if DFT is not enough?

DFT computations may not reflect observed experimental selectivities

Understanding how molecules act

What if DFT is not enough?

DFT computations may not reflect observed experimental selectivities

For very large systems, DFT calculations become very expensive

Understanding how molecules act

What if DFT is not enough?

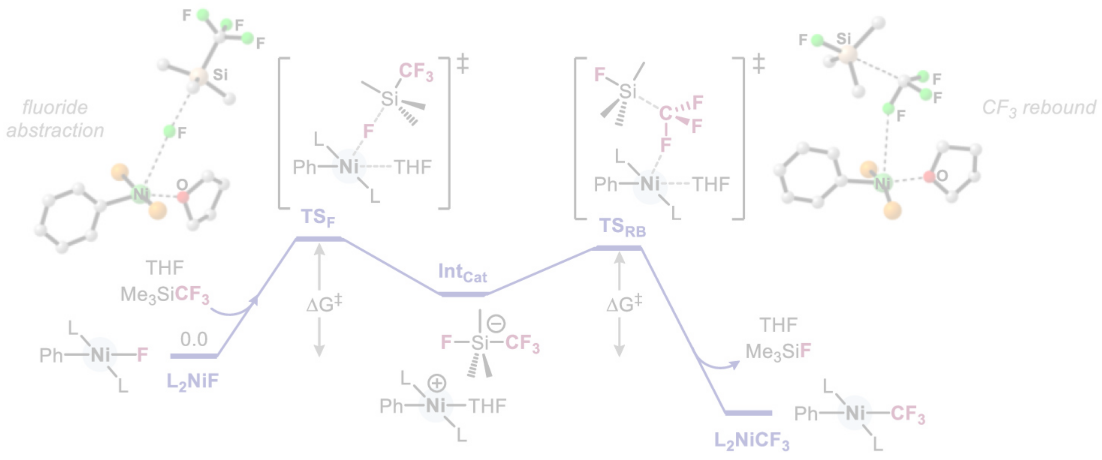
DFT computations may not reflect observed experimental selectivities

For very large systems, DFT calculations become very expensive

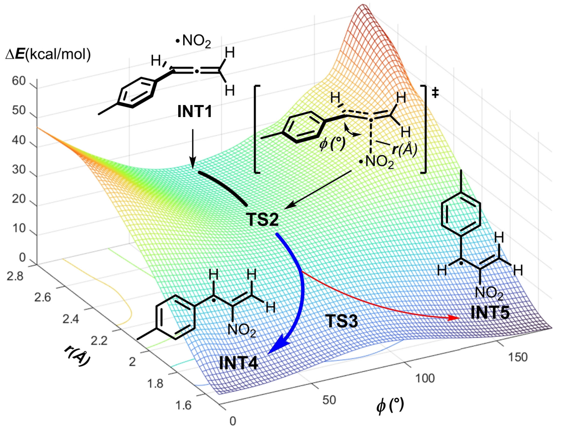
What can computational chemistry do for you?

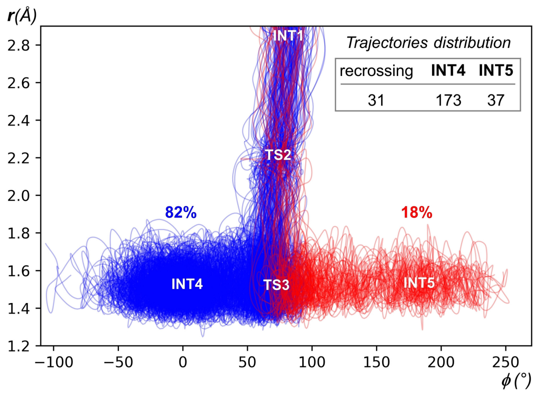
Understanding how molecules act

Density functional theory



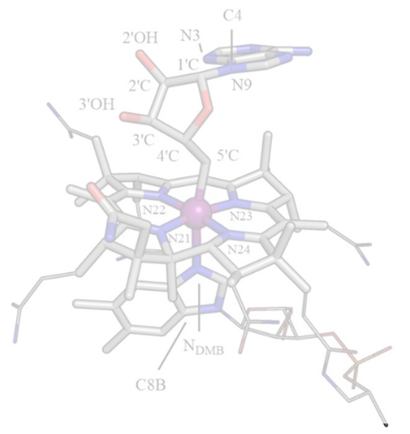
Dynamics Simulations

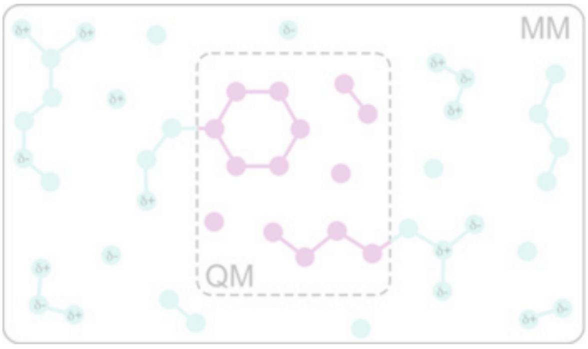




recrossing	INT4	INT5
31	173	37

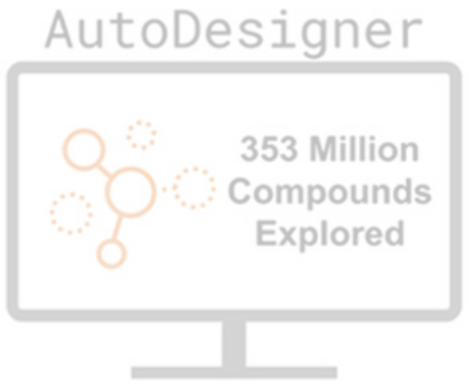
QM/MM

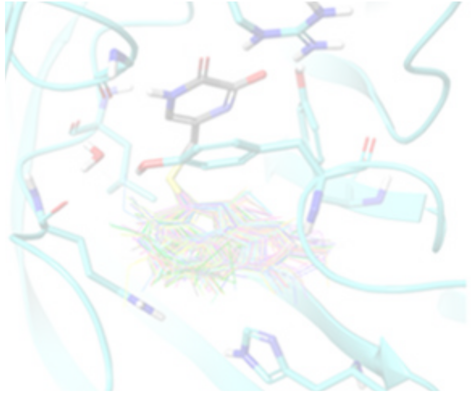




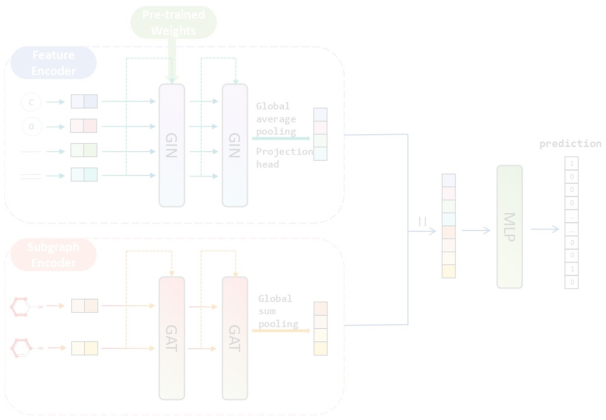
Predicting how molecules should act

Machine learning

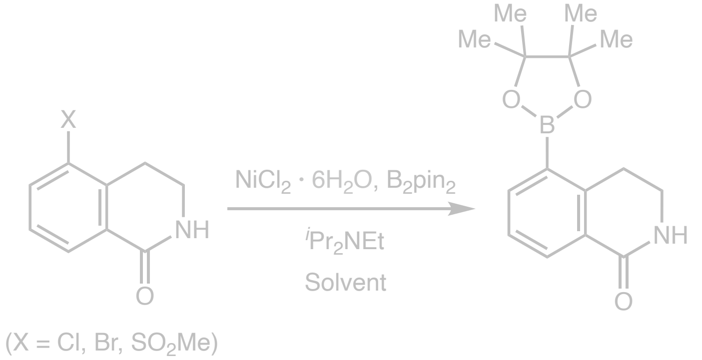


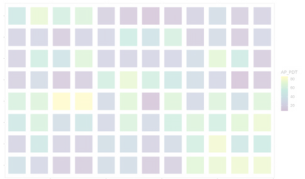


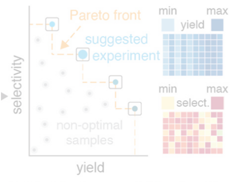
Neural networks



Data Science







Multi-objective acquisition function

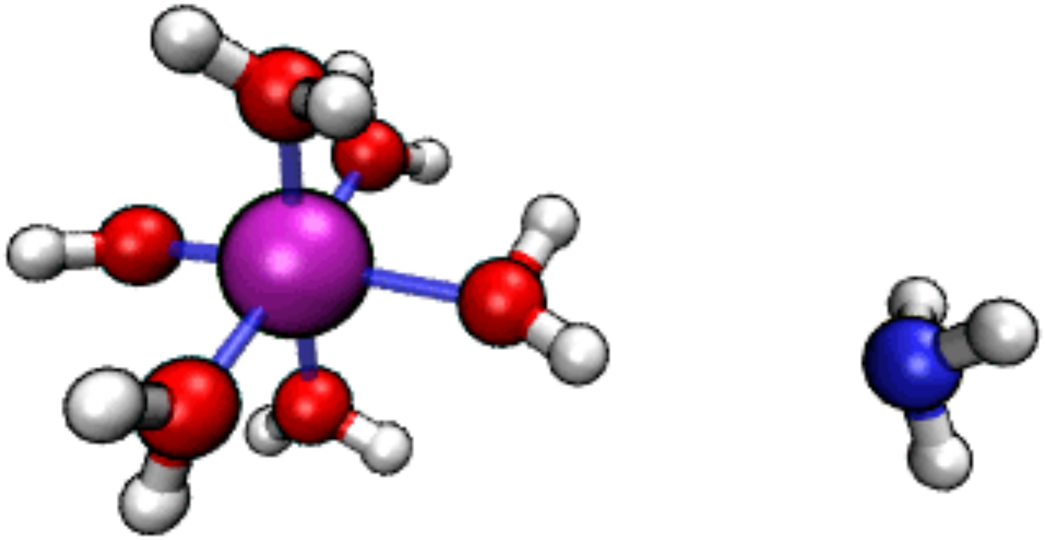
Understanding how molecules act

Molecular dynamics simulations

Understanding how molecules act

Molecular dynamics simulations

ab initio Molecular Dynamics (AIMD)



Understanding how molecules act

Molecular dynamics simulations

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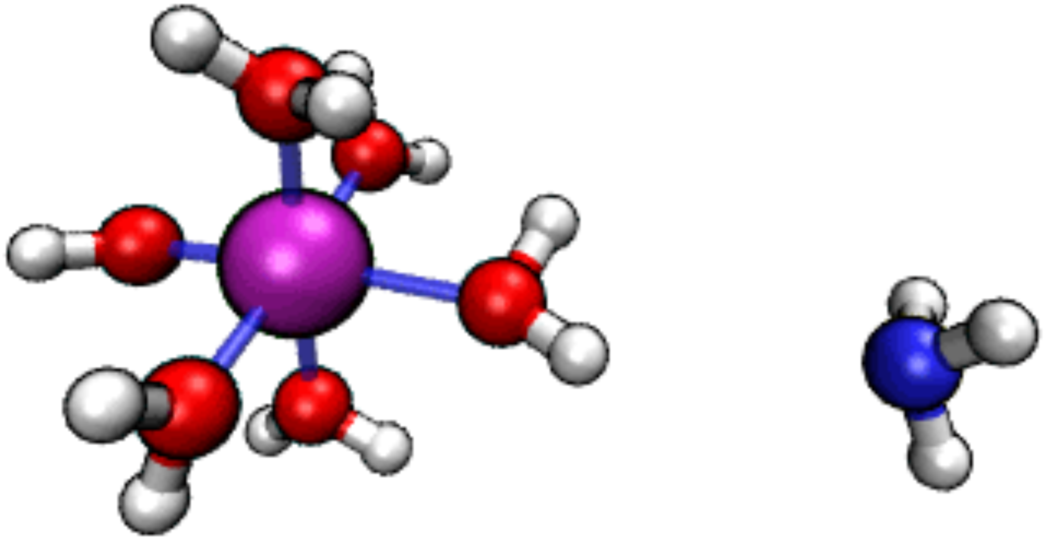
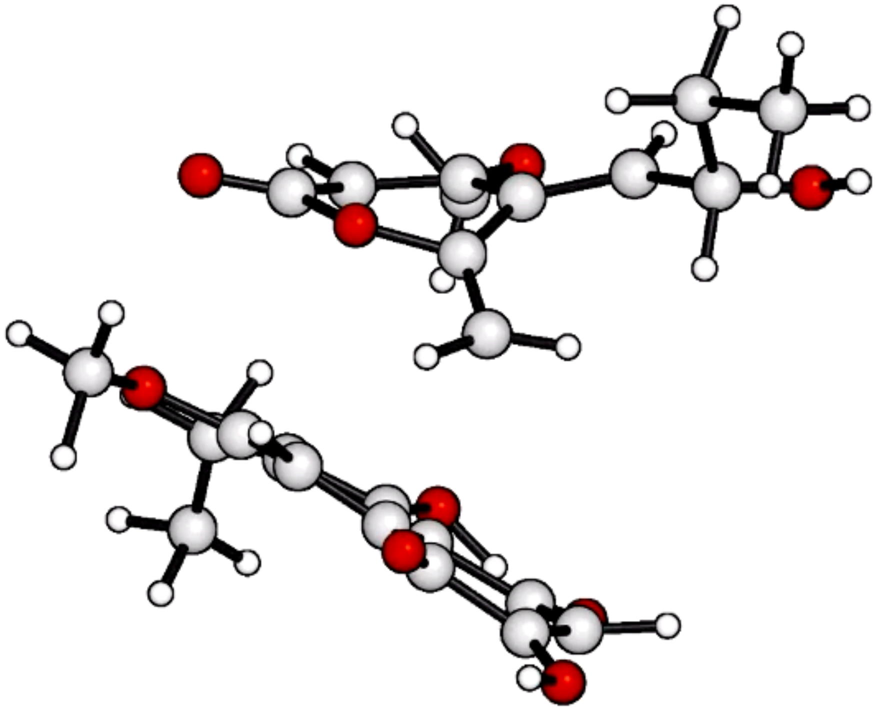


Dynamic Trajectories



Understanding how molecules act

Molecular dynamics simulations

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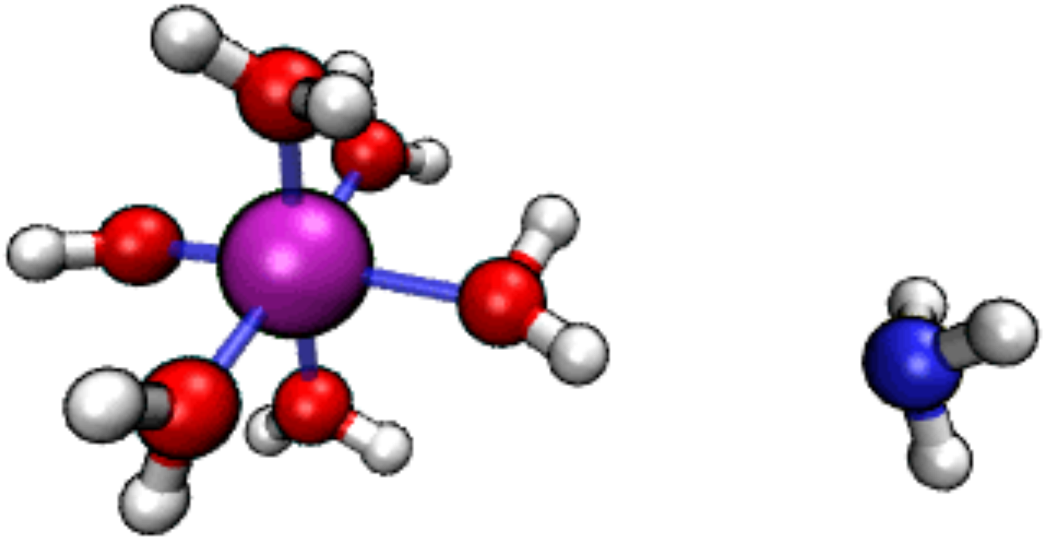

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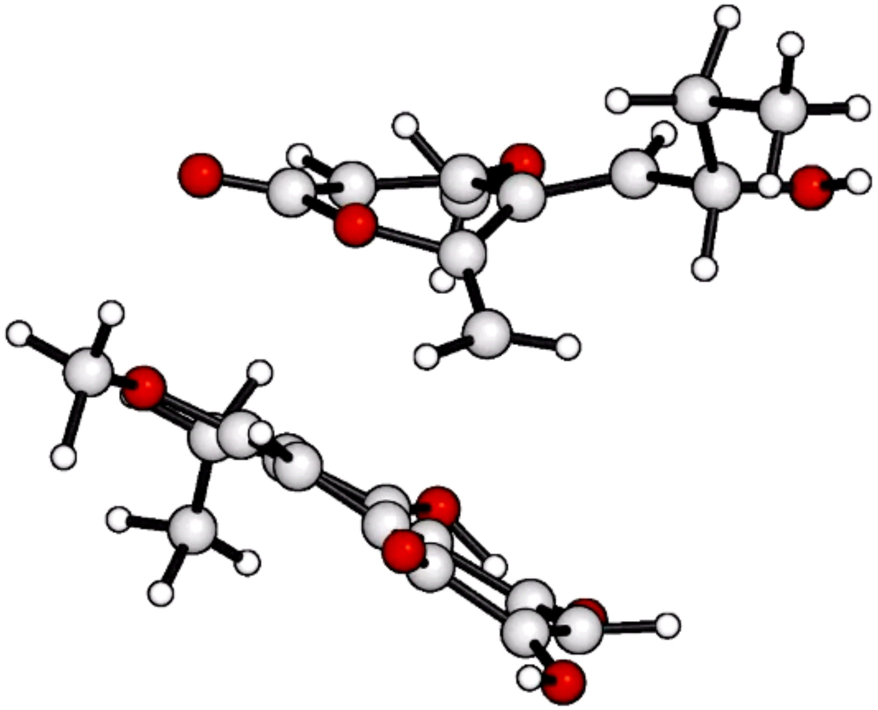

apply energy to all atoms in the system

Understanding how molecules act

Molecular dynamics simulations

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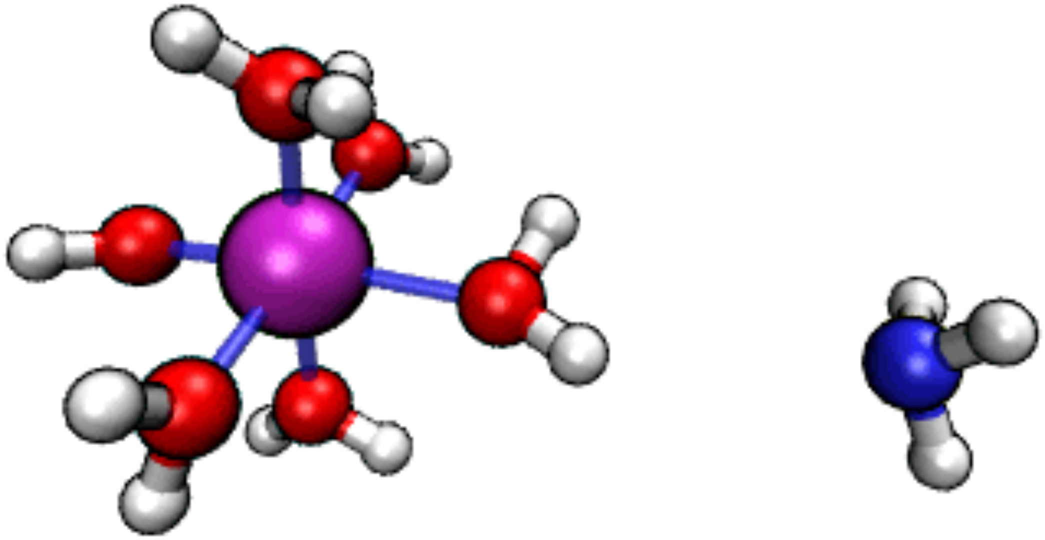

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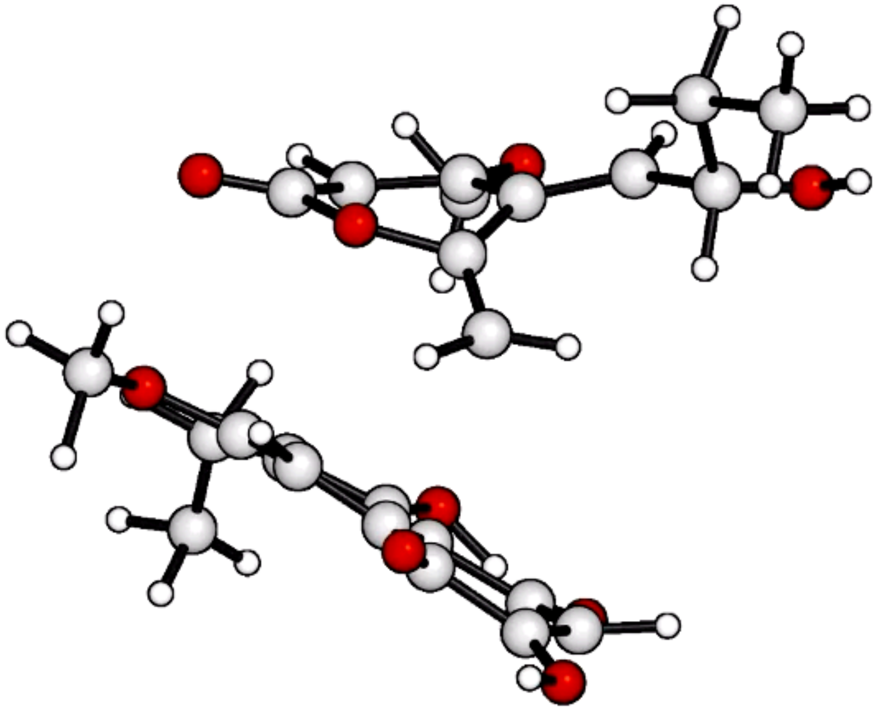

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Understanding how molecules act

Molecular dynamics simulations

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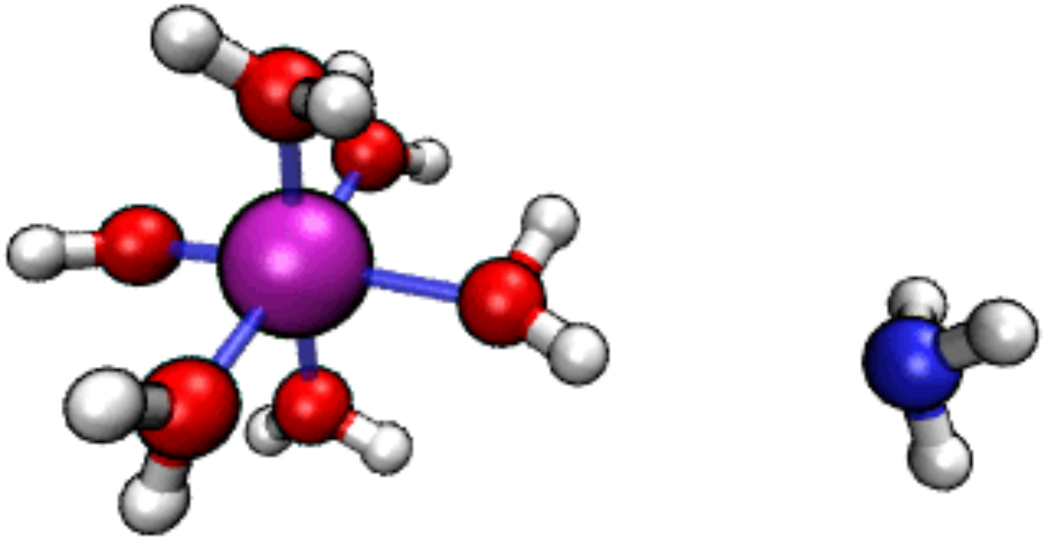

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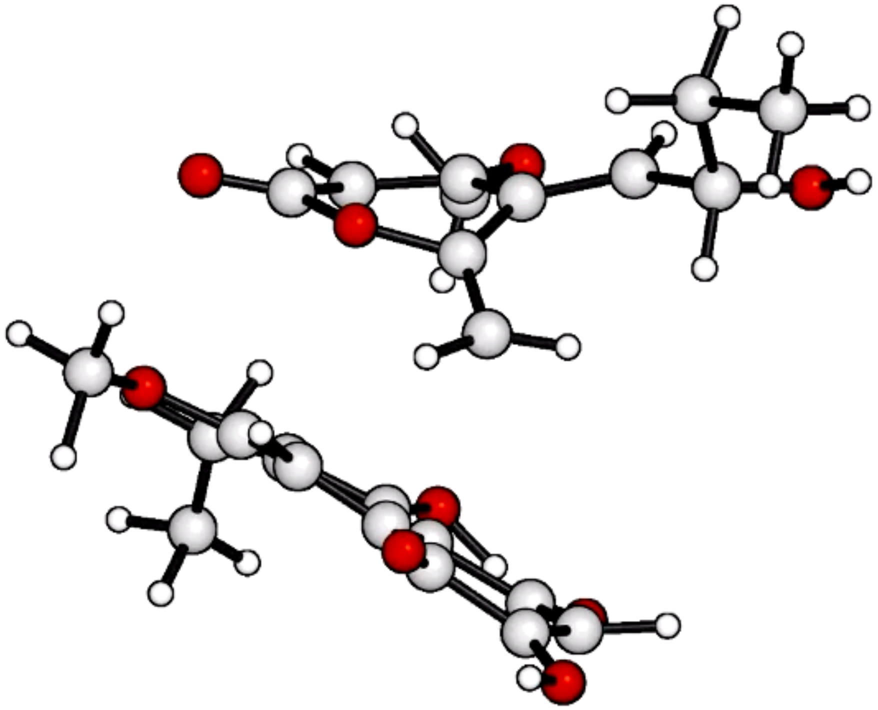


apply energy to all atoms in the system → ***run calculations to see how atoms interact and the system evolves over time***

Understanding how molecules act

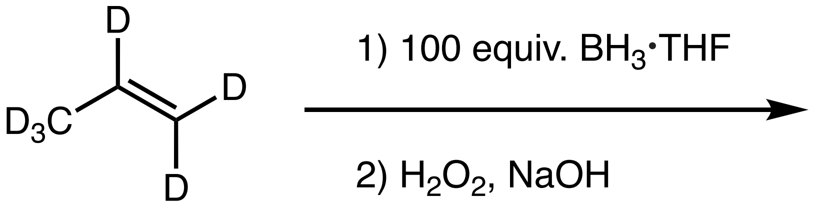
When DFT goes wrong?

Oyola, Y.; Singleton, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 3130-3131.

Understanding how molecules act

When DFT goes wrong?

What are the products of this hydroboration-oxidation reaction?



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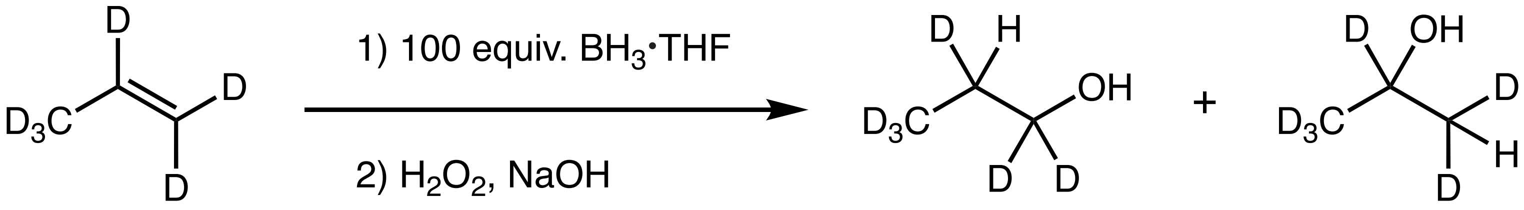

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Understanding how molecules act

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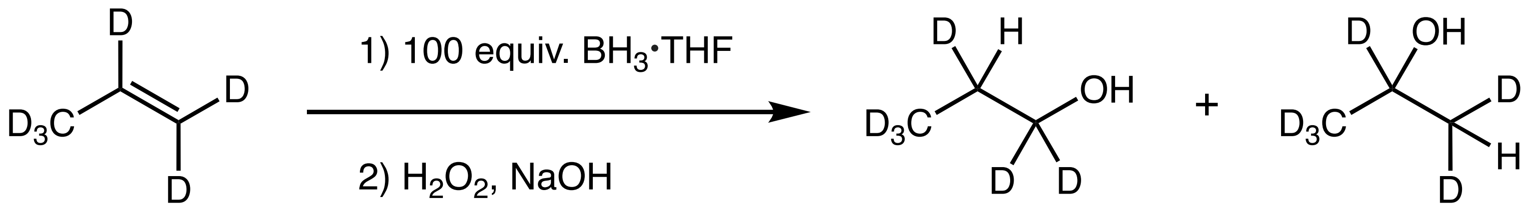

Predicted ratio (by DFT) 99 : 1

Oyola, Y.; Singleton, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 3130-3131.

Understanding how molecules act

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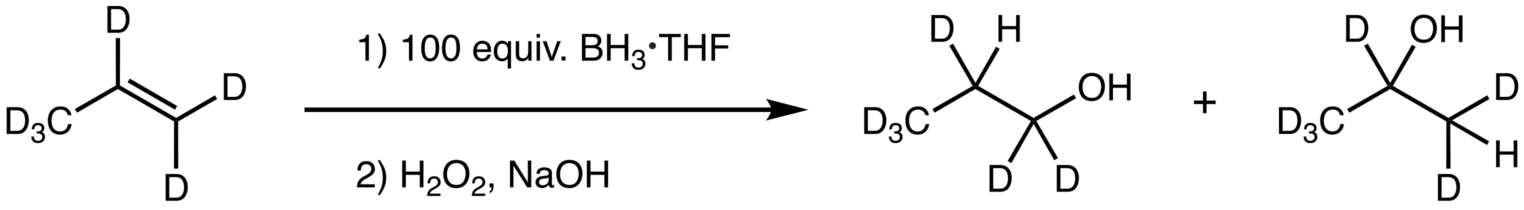

Predicted ratio (by DFT)	99	:	1
Observed experimental ratio	90	:	10

Oyola, Y.; Singleton, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 3130-3131.

Understanding how molecules act

When DFT goes wrong?

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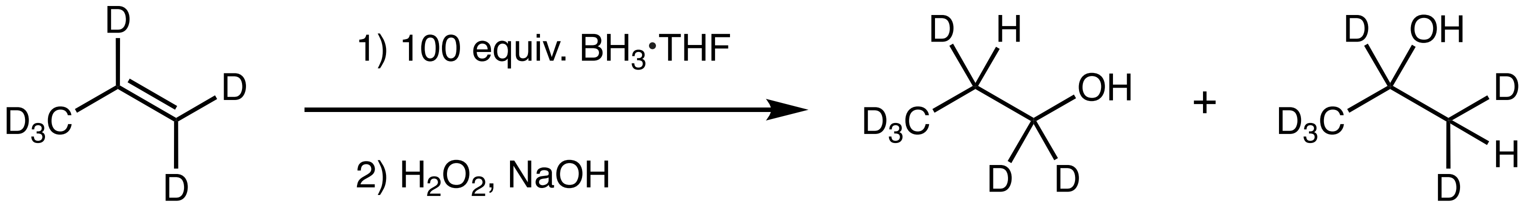

Predicted ratio (by DFT) 99 : 1

Observed experimental ratio 90 : 10

What is the cause of this discrepancy?

Oyola, Y.; Singleton, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 3130-3131.

Understanding how molecules act

Dynamic trajectories

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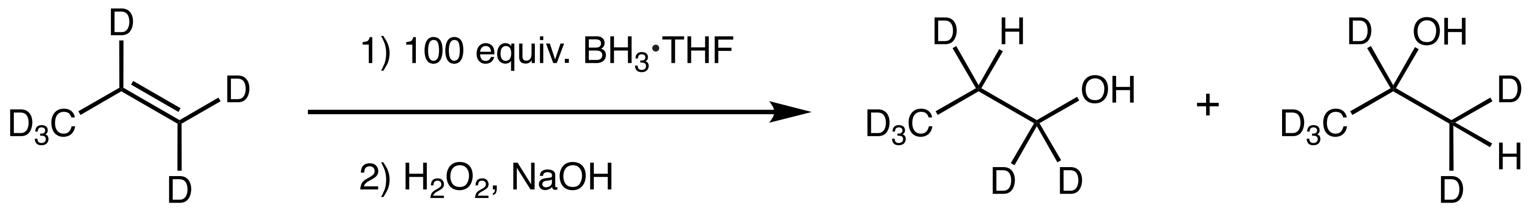

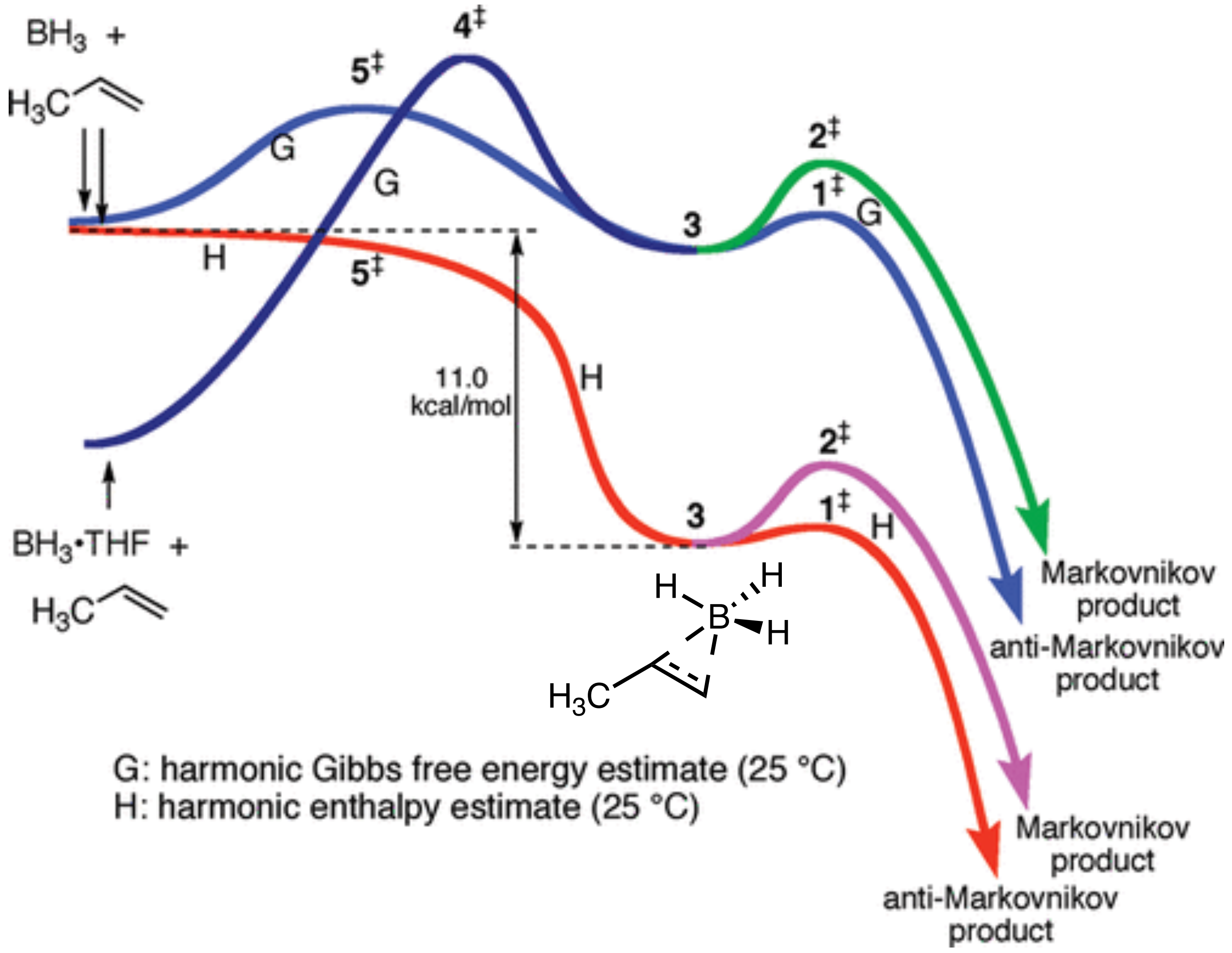

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Understanding how molecules act

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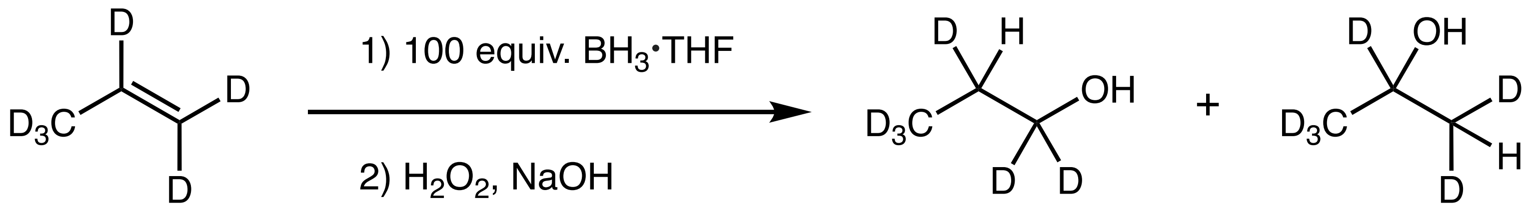

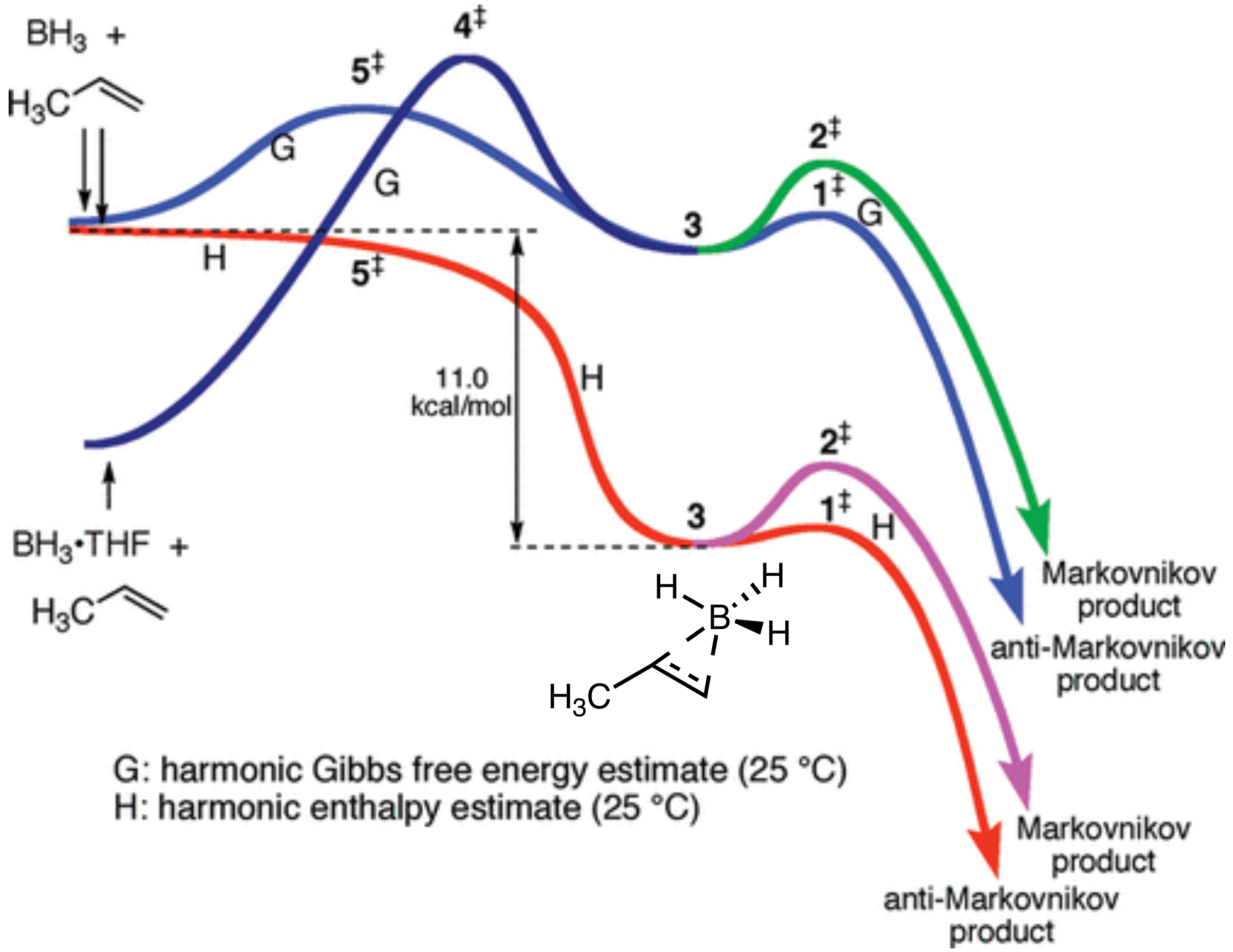

G: harmonic Gibbs free energy estimate (25 °C)
H: harmonic enthalpy estimate (25 °C)

Starting from 3, the TS barriers dictate selectivity (~1% of trajectories lead to markovnikov product), which <u>does not</u> match experiments

Oyola, Y.; Singleton, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 3130-3131.

Understanding how molecules act

Dynamic trajectories

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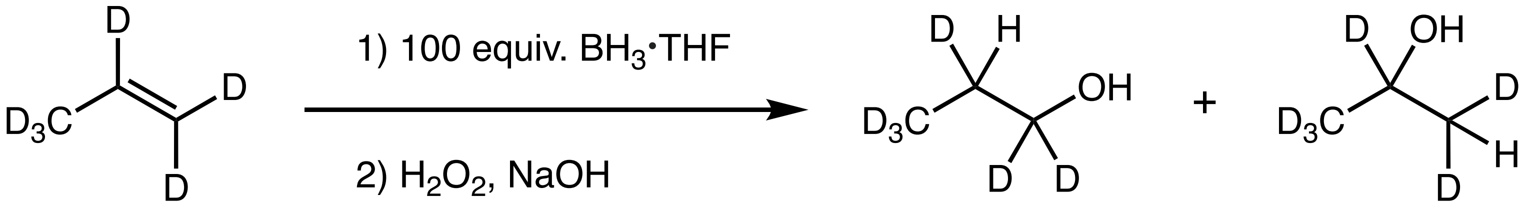
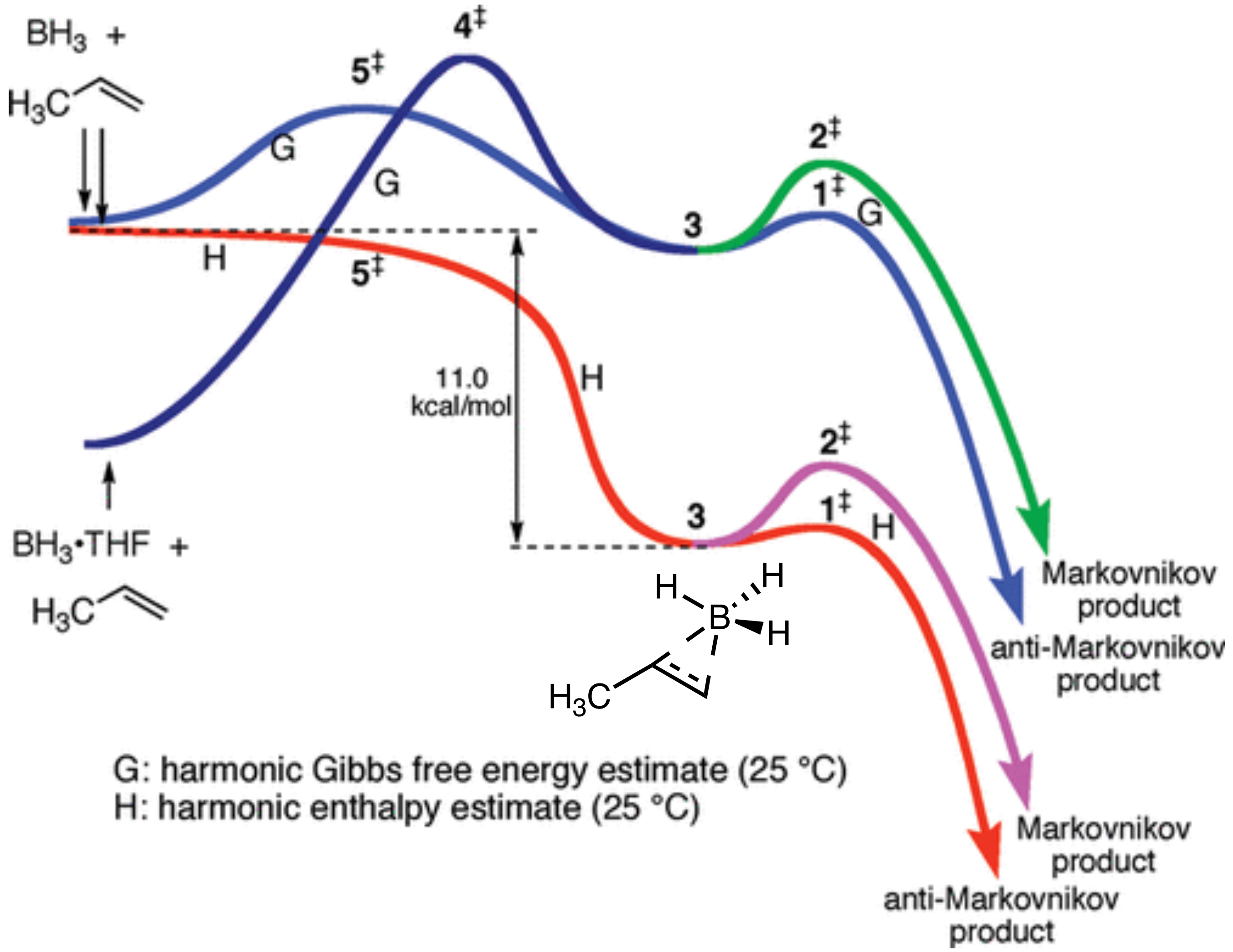


1) 100 equiv. $BH_3 \cdot THF$

2) H_2O_2, NaOH



G: harmonic Gibbs free energy estimate (25 °C)
H: harmonic enthalpy estimate (25 °C)

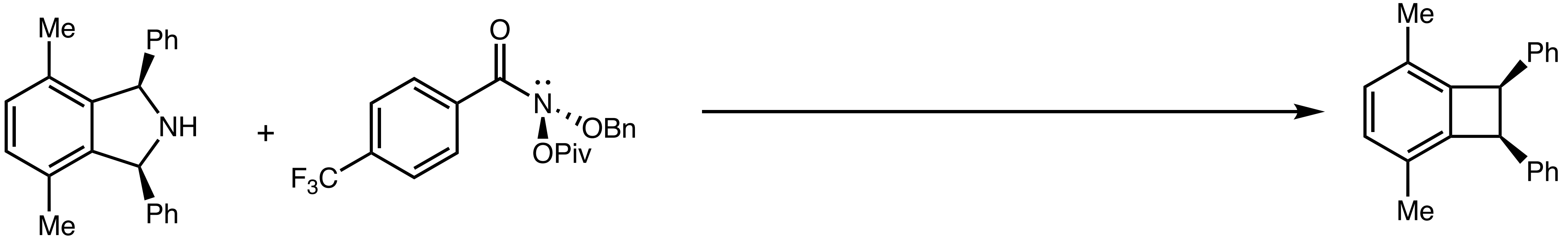
Starting from 3, the TS barriers dictate selectivity (~1% of trajectories lead to markovnikov product), which <u>does not</u> match experiments

Starting from before 3, the distribution of trajectories matches experiments (~10% of trajectories lead to markovnikov product)

Oyola, Y.; Singleton, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 3130-3131.

Understanding how molecules act

Dynamic effects in nitrogen deletion of tetrahydroisoquinolines

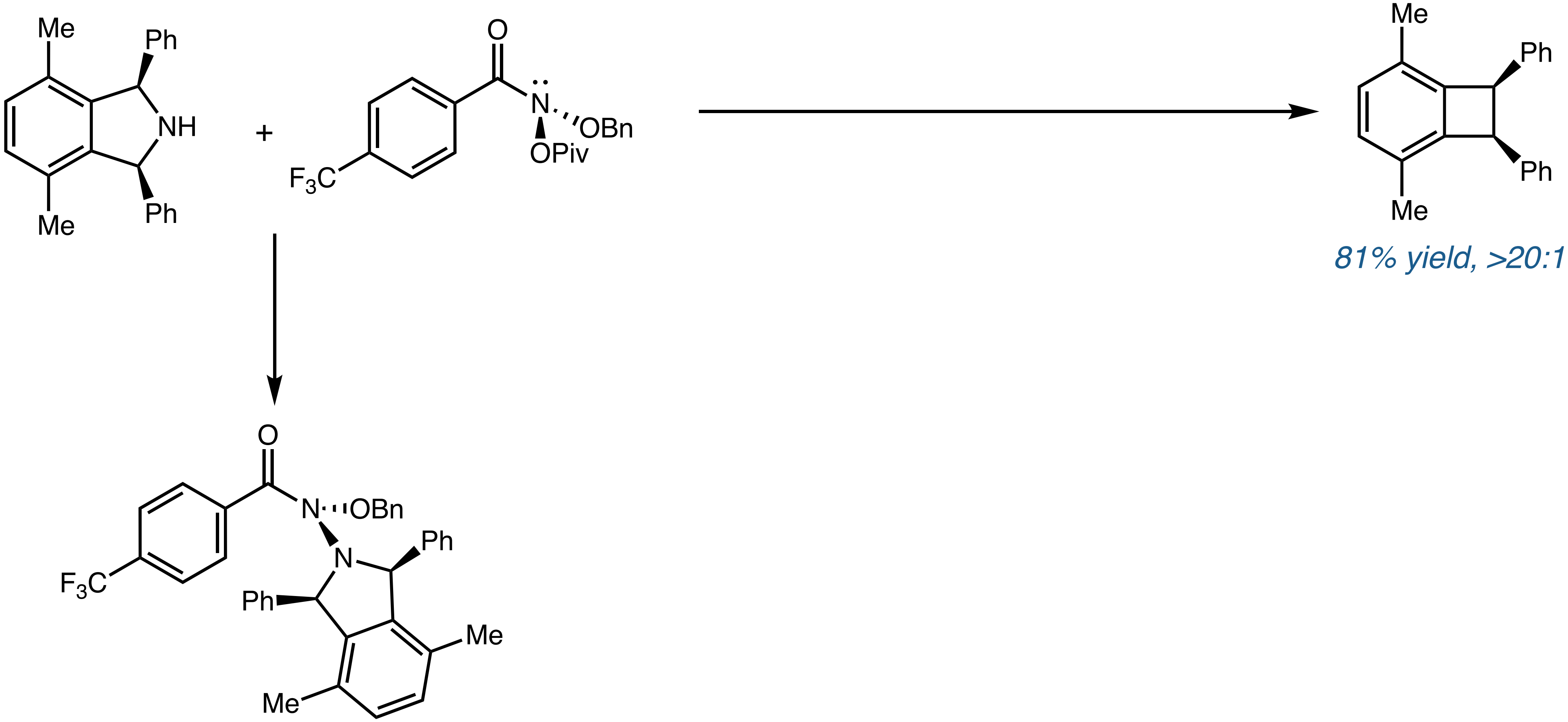


81% yield, >20:1 dr

Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

Understanding how molecules act

Dynamic effects in nitrogen deletion of tetrahydroisoquinolines



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Understanding how molecules act

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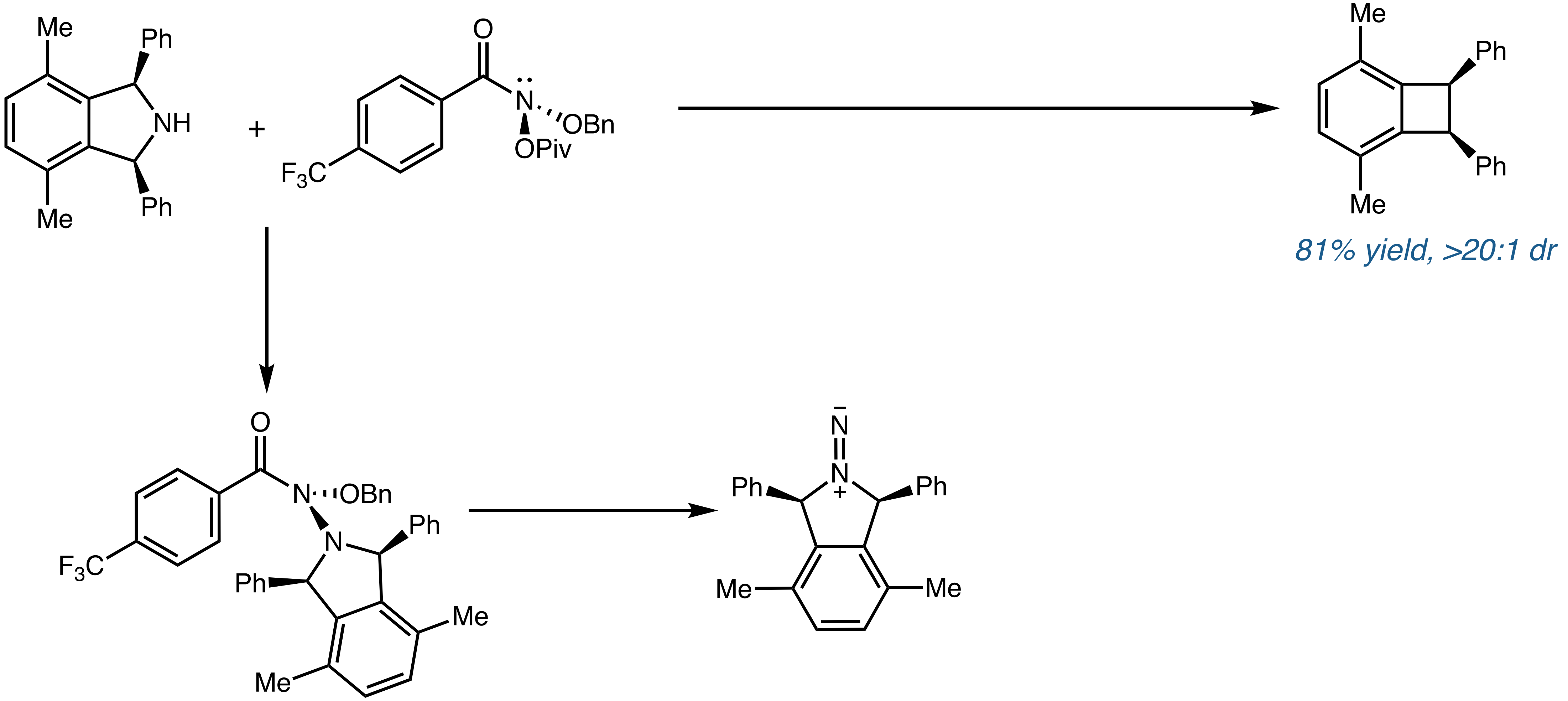

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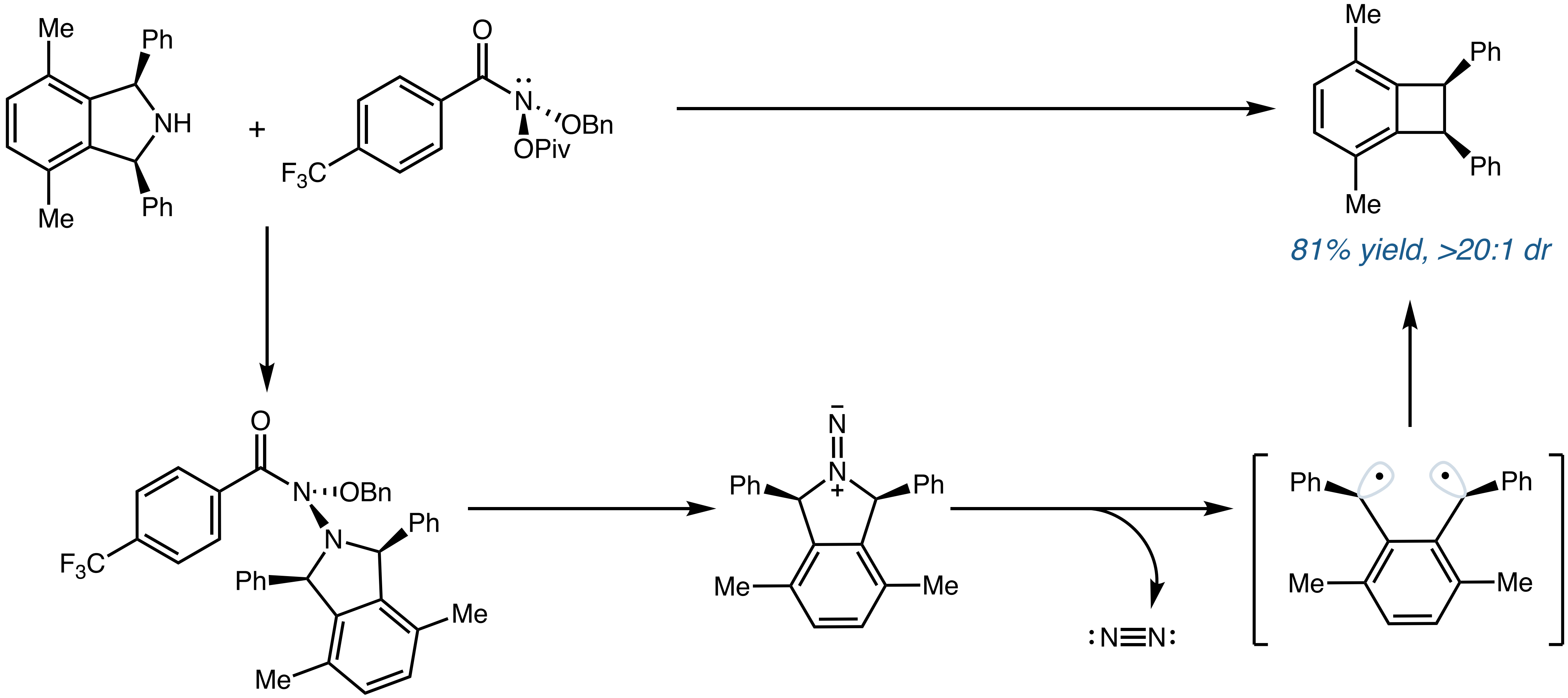

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Understanding how molecules act

Unusual observations

Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

Understanding how molecules act

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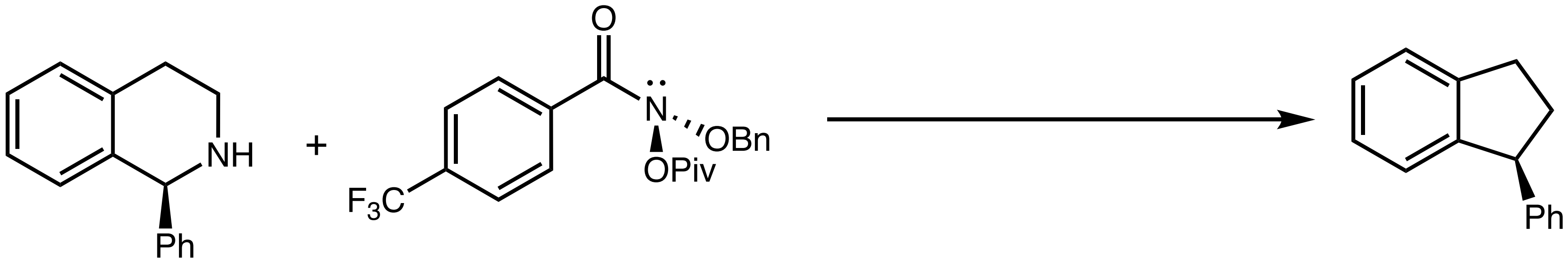

56% yield, 31.2 : 68.8 er

Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

Understanding how molecules act

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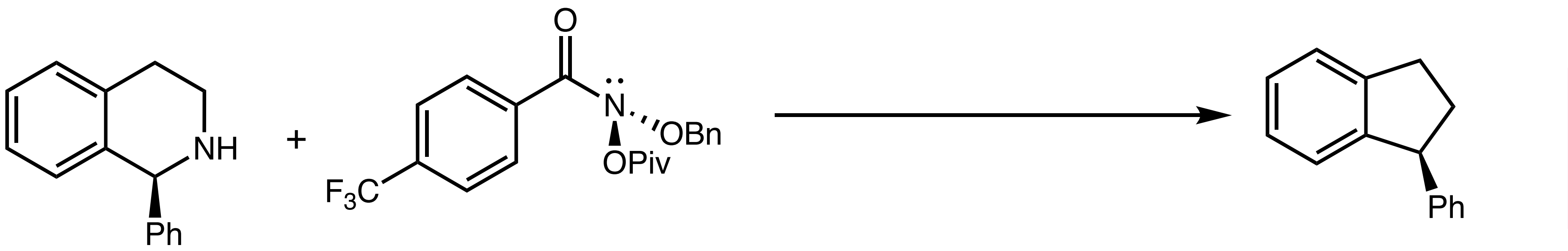

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Why is there erosion of enantiopurity in the product?

Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

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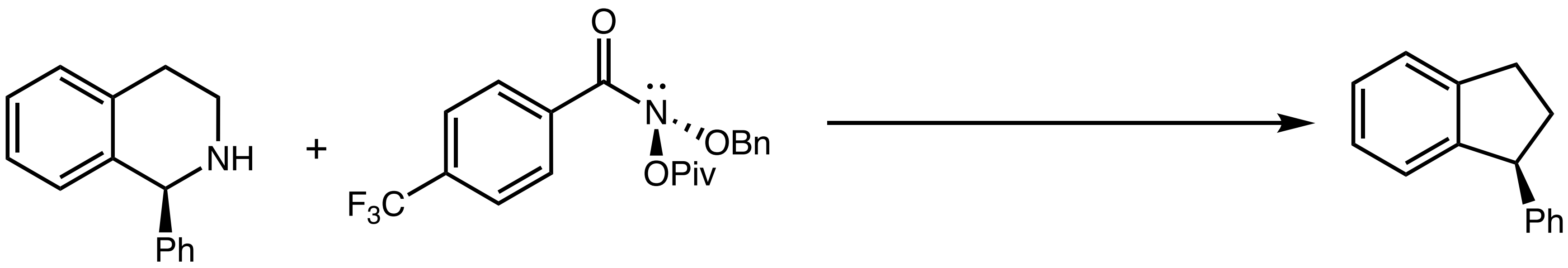

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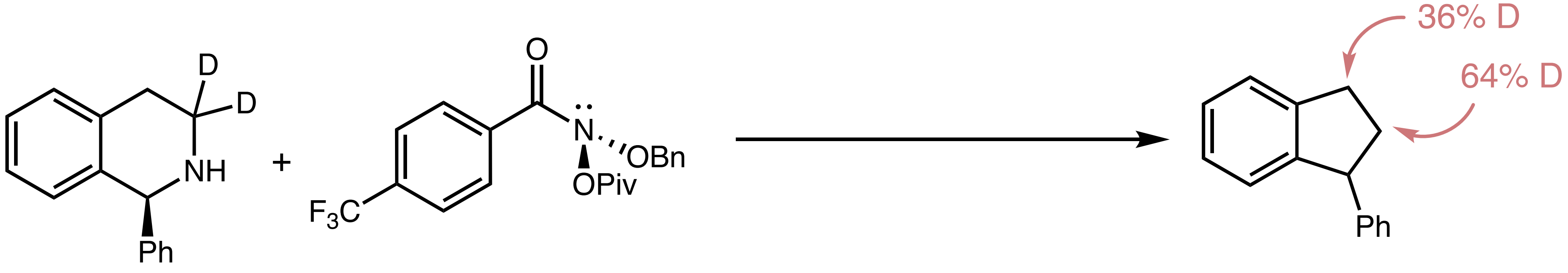

48% yield

Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

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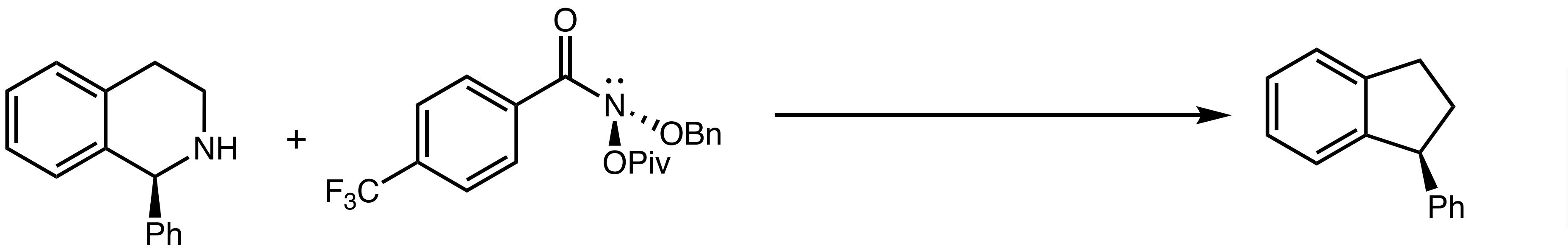

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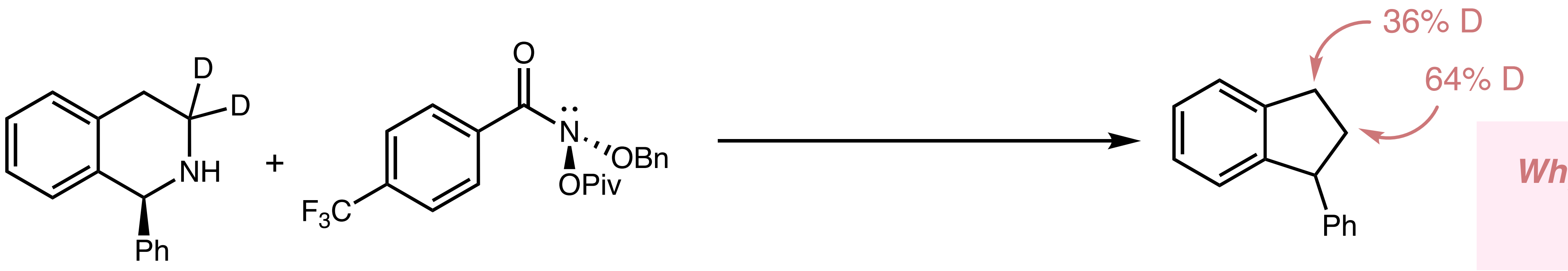

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Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

Understanding how molecules act

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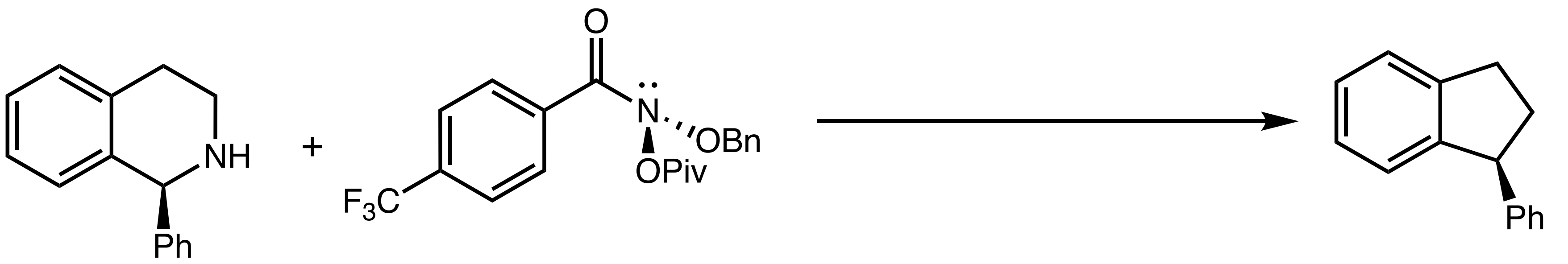

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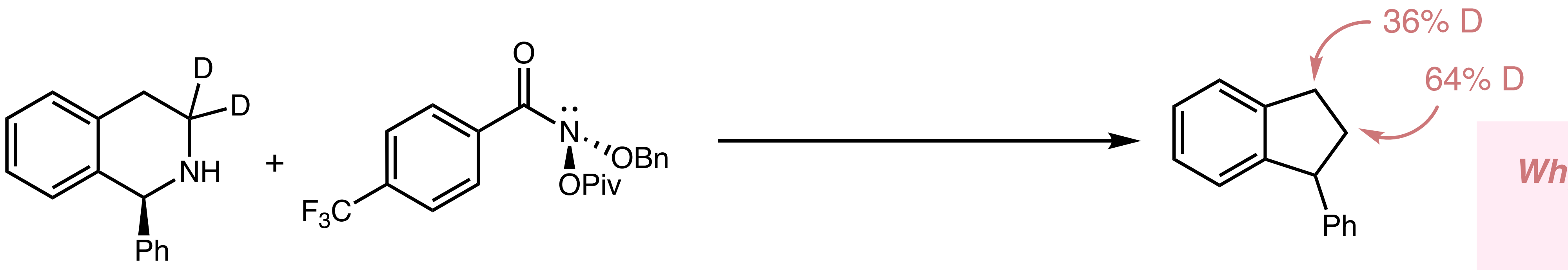

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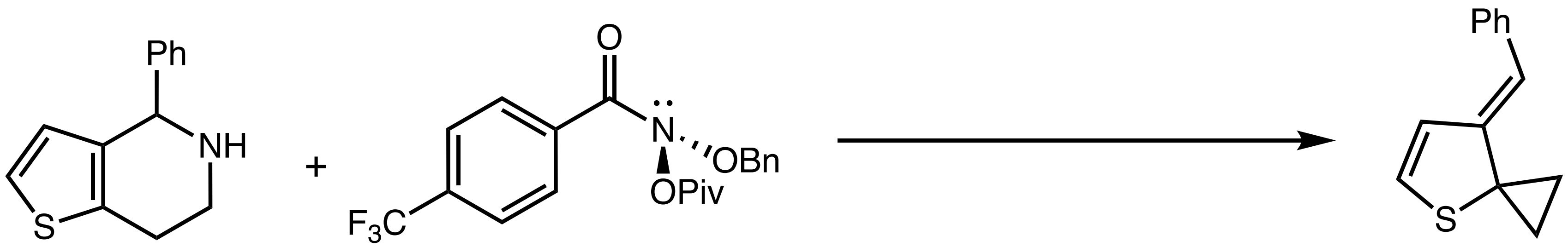

64% yield

Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

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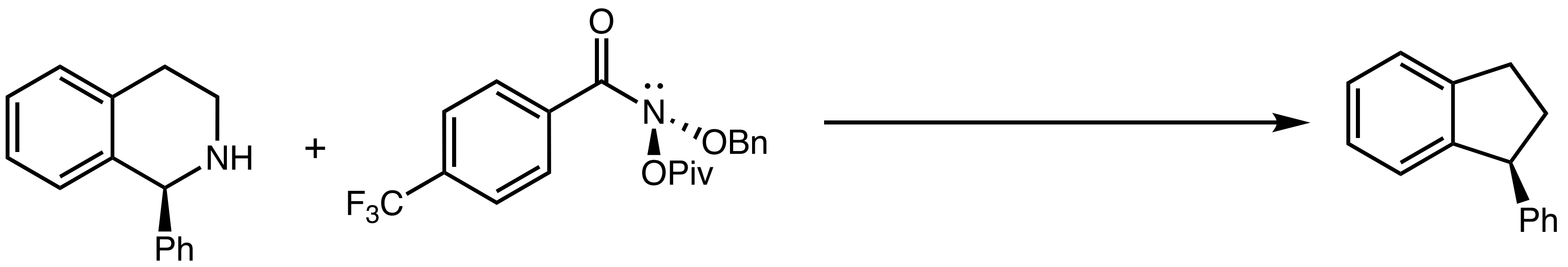

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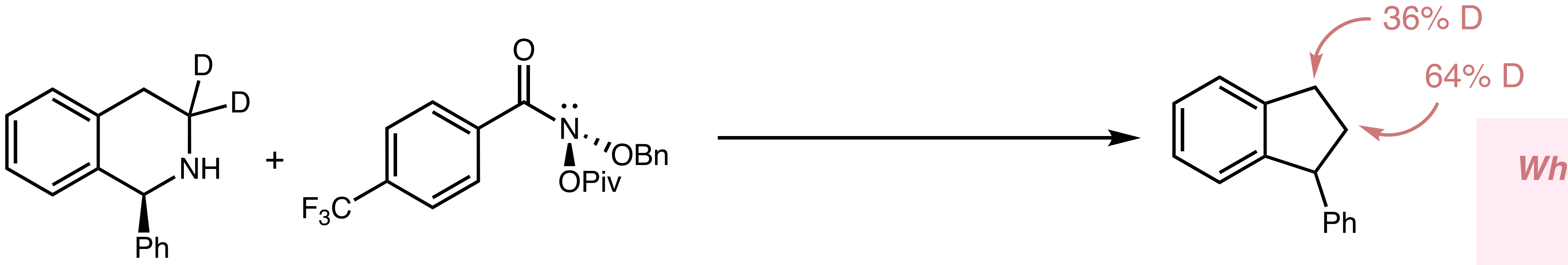

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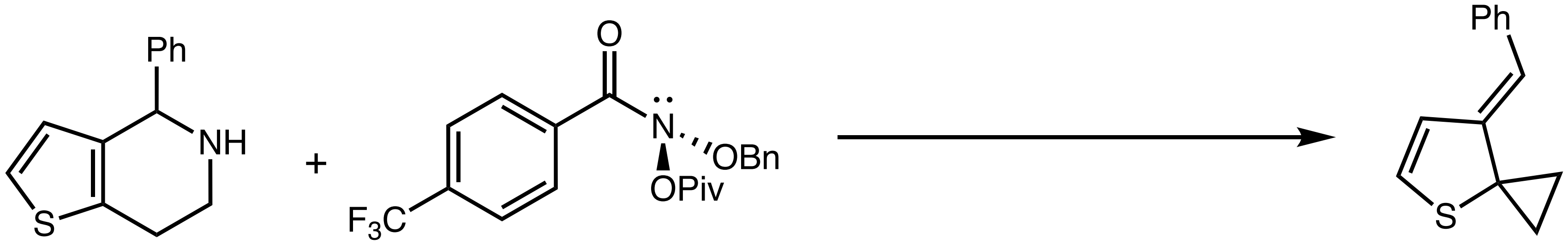


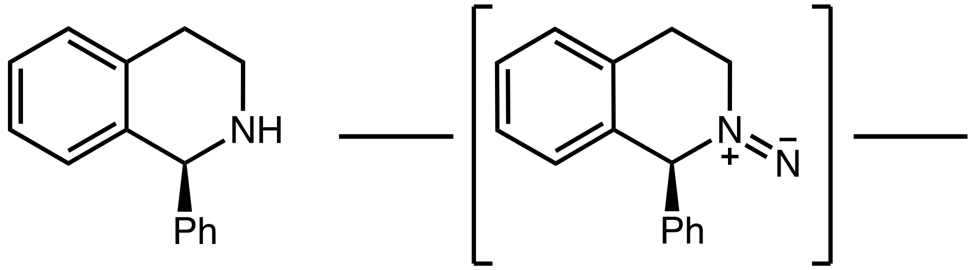
64% yield

What is the origin of this dearomatized product?

Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

Understanding how molecules act

Potential mechanisms



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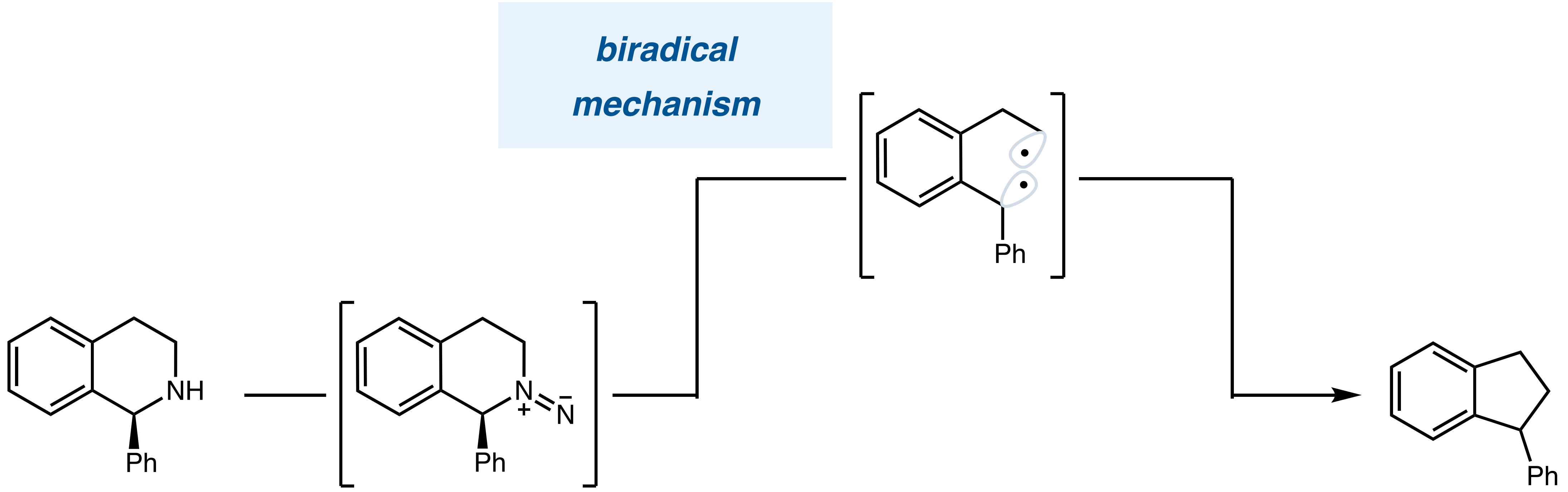
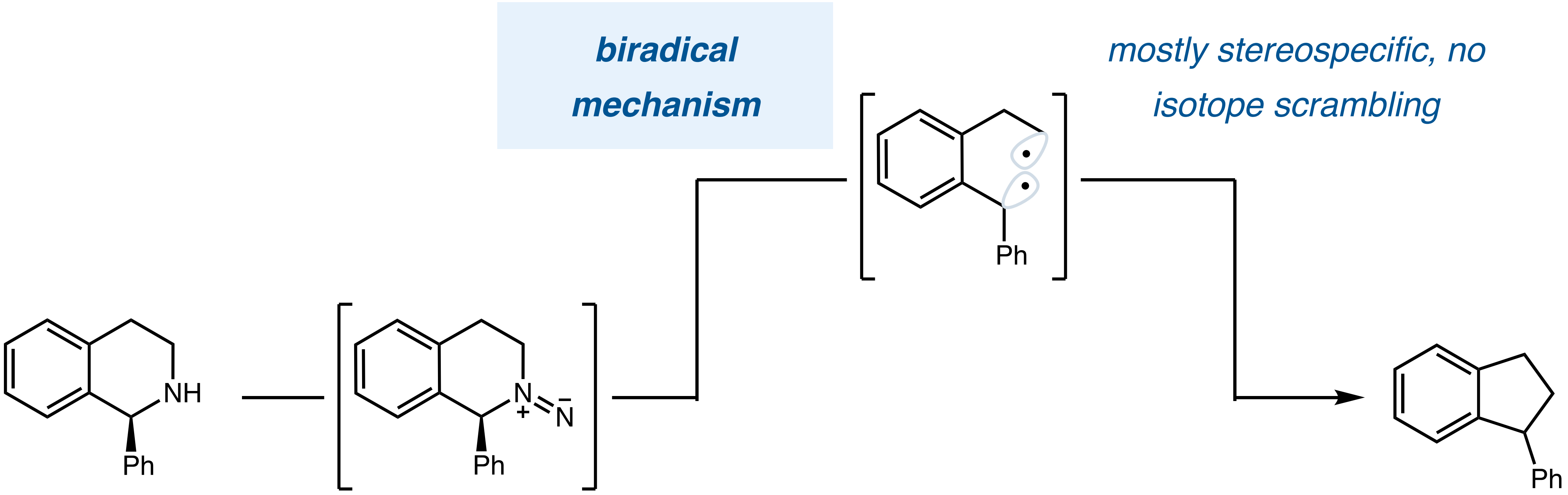


biradical mechanism

Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

Understanding how molecules act

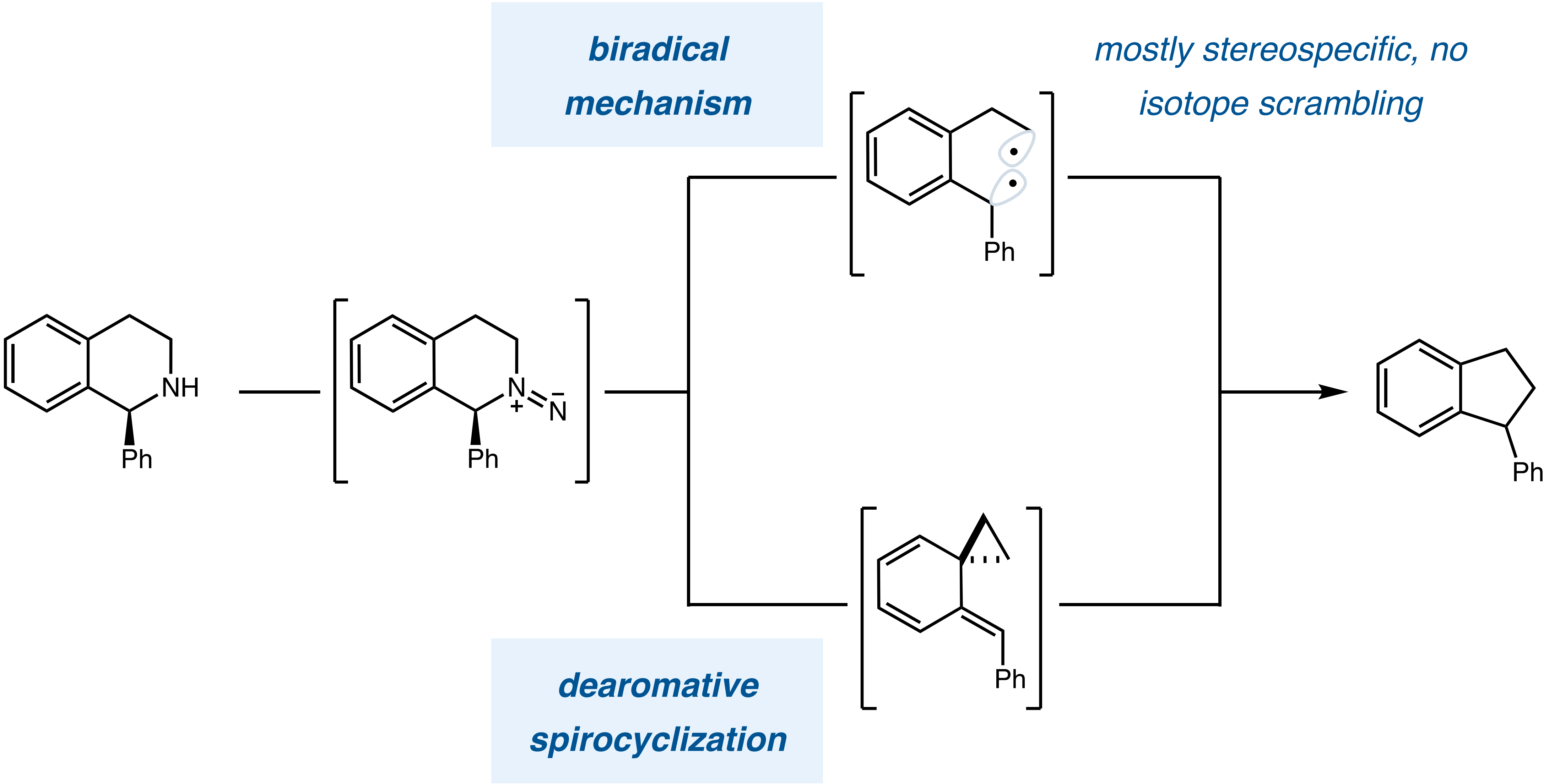
Potential mechanisms



Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

Understanding how molecules act

Potential mechanisms



biradical mechanism

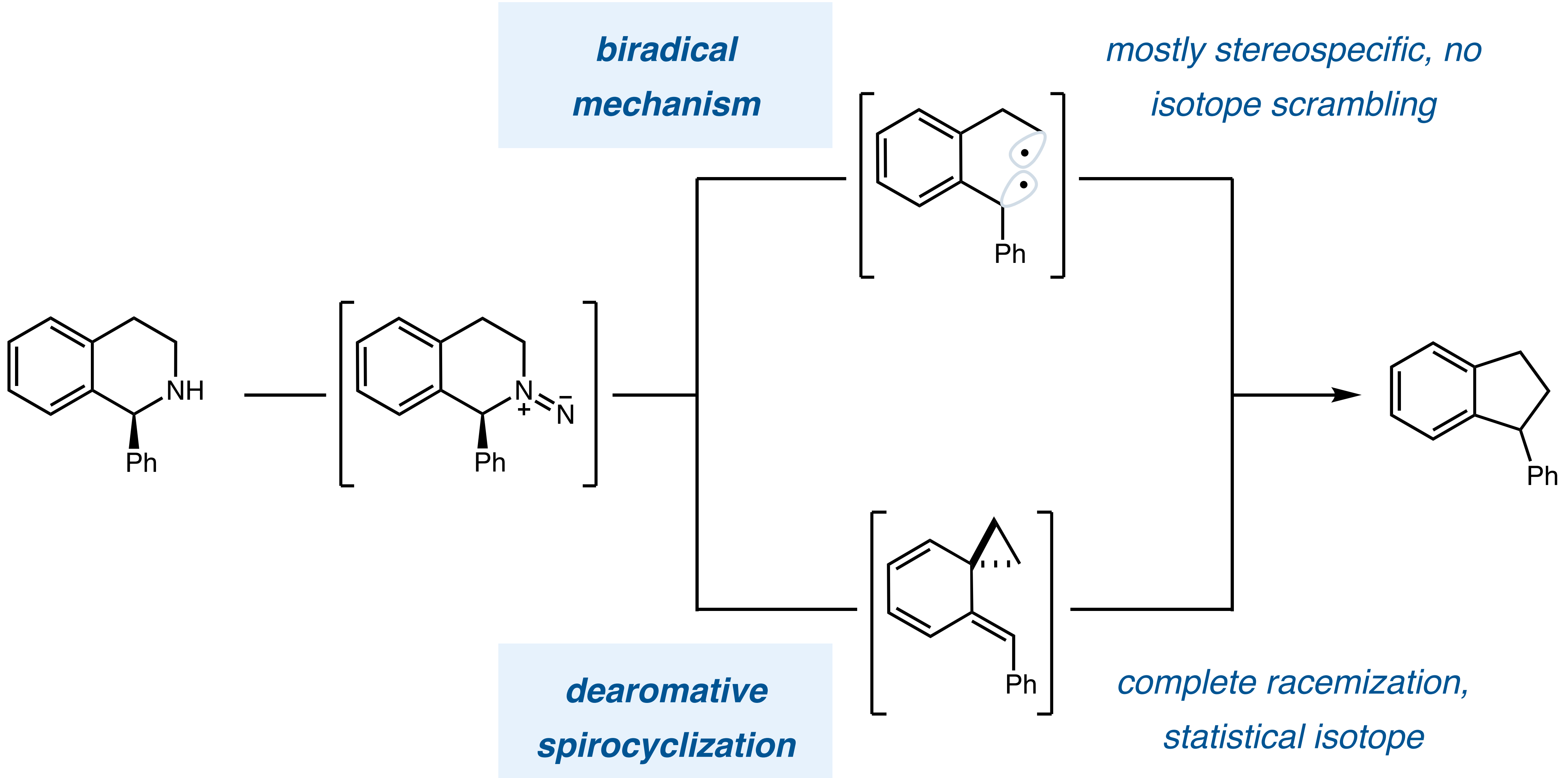
mostly stereospecific, no isotope scrambling

dearomative spirocyclization

Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

Understanding how molecules act

Potential mechanisms



biradical mechanism

mostly stereospecific, no isotope scrambling

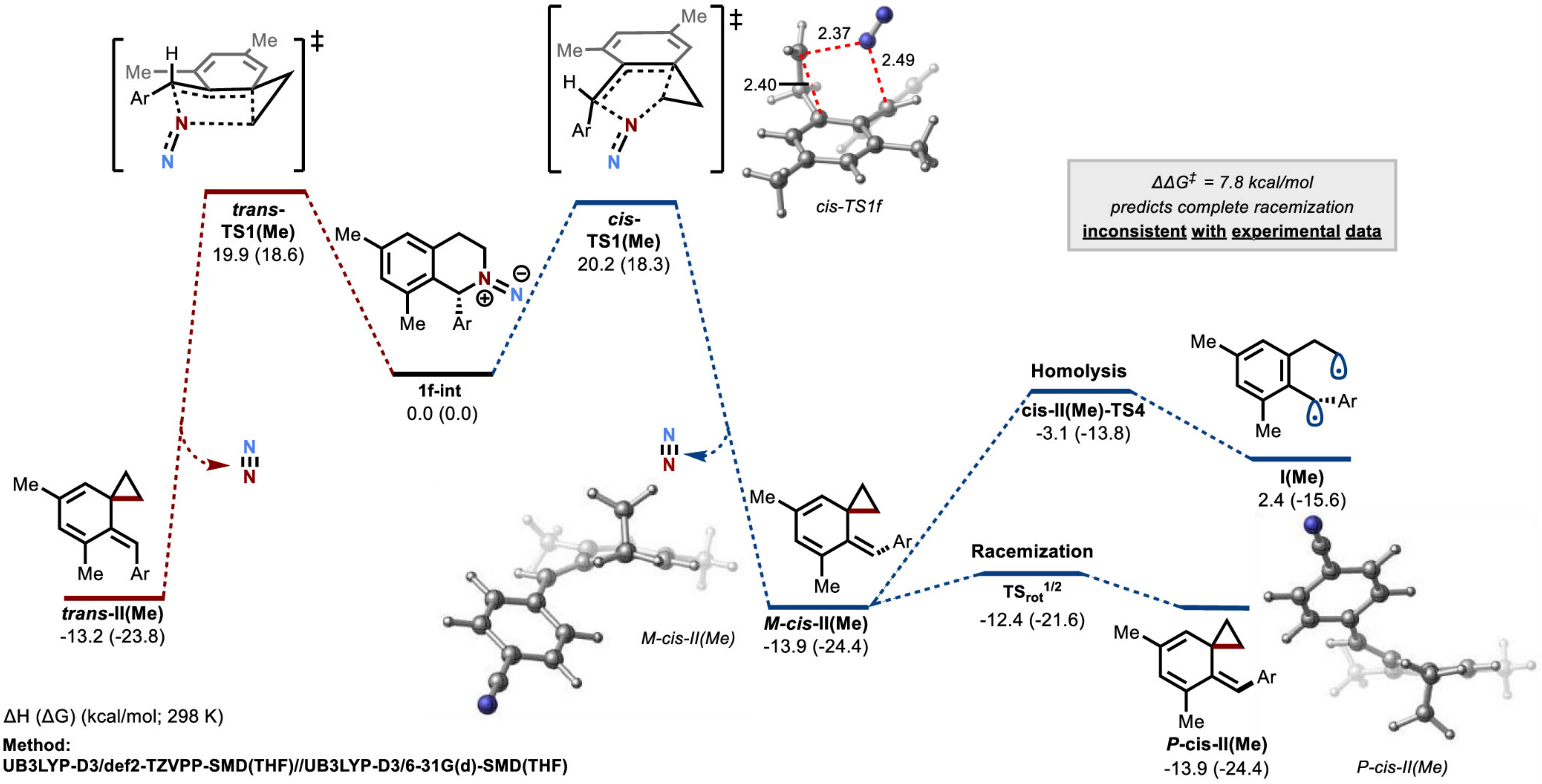
dearomative spirocyclization

complete racemization, statistical isotope scrambling

Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

Understanding how molecules act

Static DFT does not match observations



ΔΔG‡ = 7.8 kcal/mol
predicts complete racemization
inconsistent with experimental data

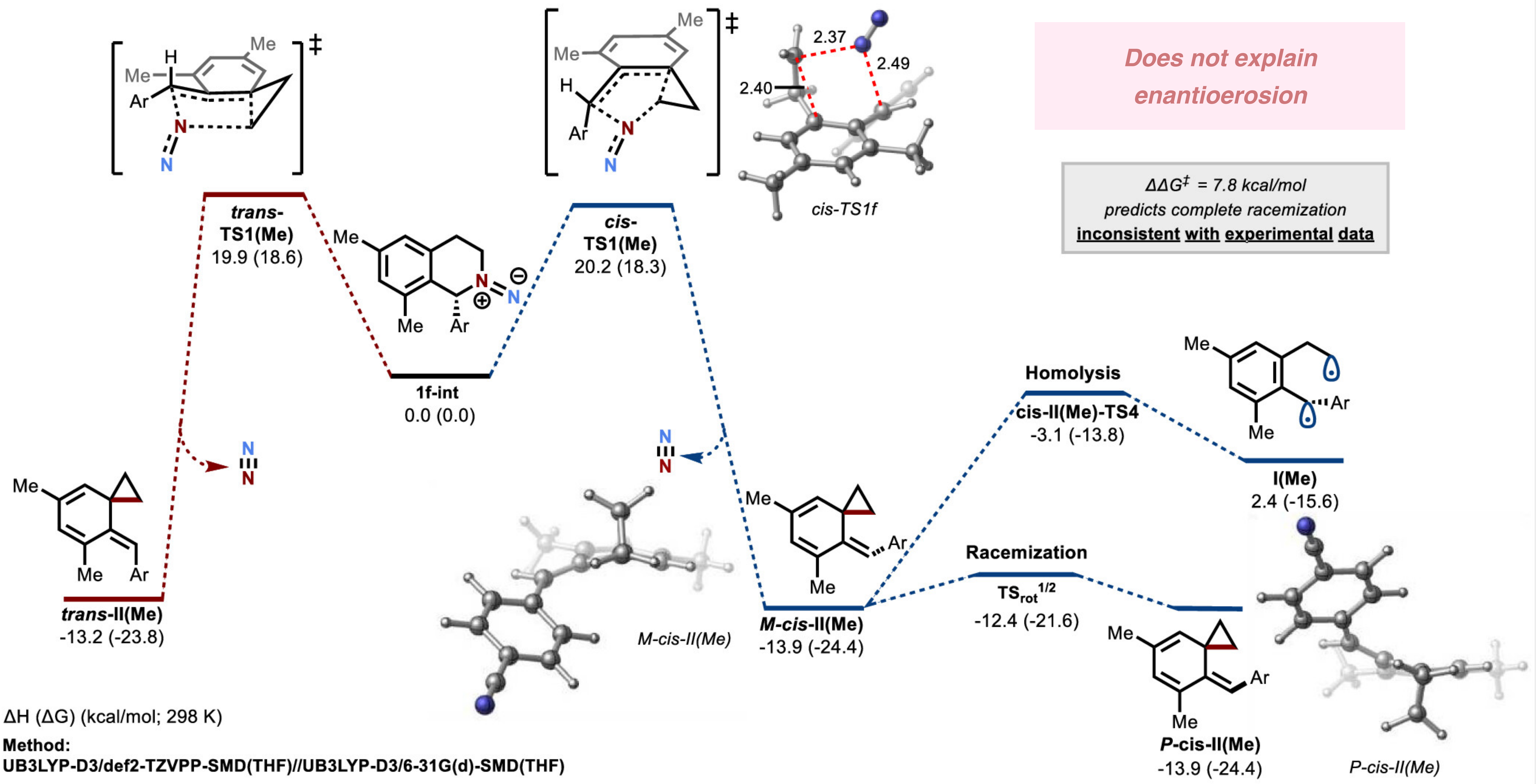
ΔH (ΔG) (kcal/mol; 298 K)

Method:
UB3LYP-D3/def2-TZVPP-SMD(THF)//UB3LYP-D3/6-31G(d)-SMD(THF)

Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

Understanding how molecules act

Static DFT does not match observations



Does not explain enantioerosion

$\Delta\Delta G^{\ddagger}$ = 7.8 kcal/mol
predicts complete racemization
inconsistent with experimental data

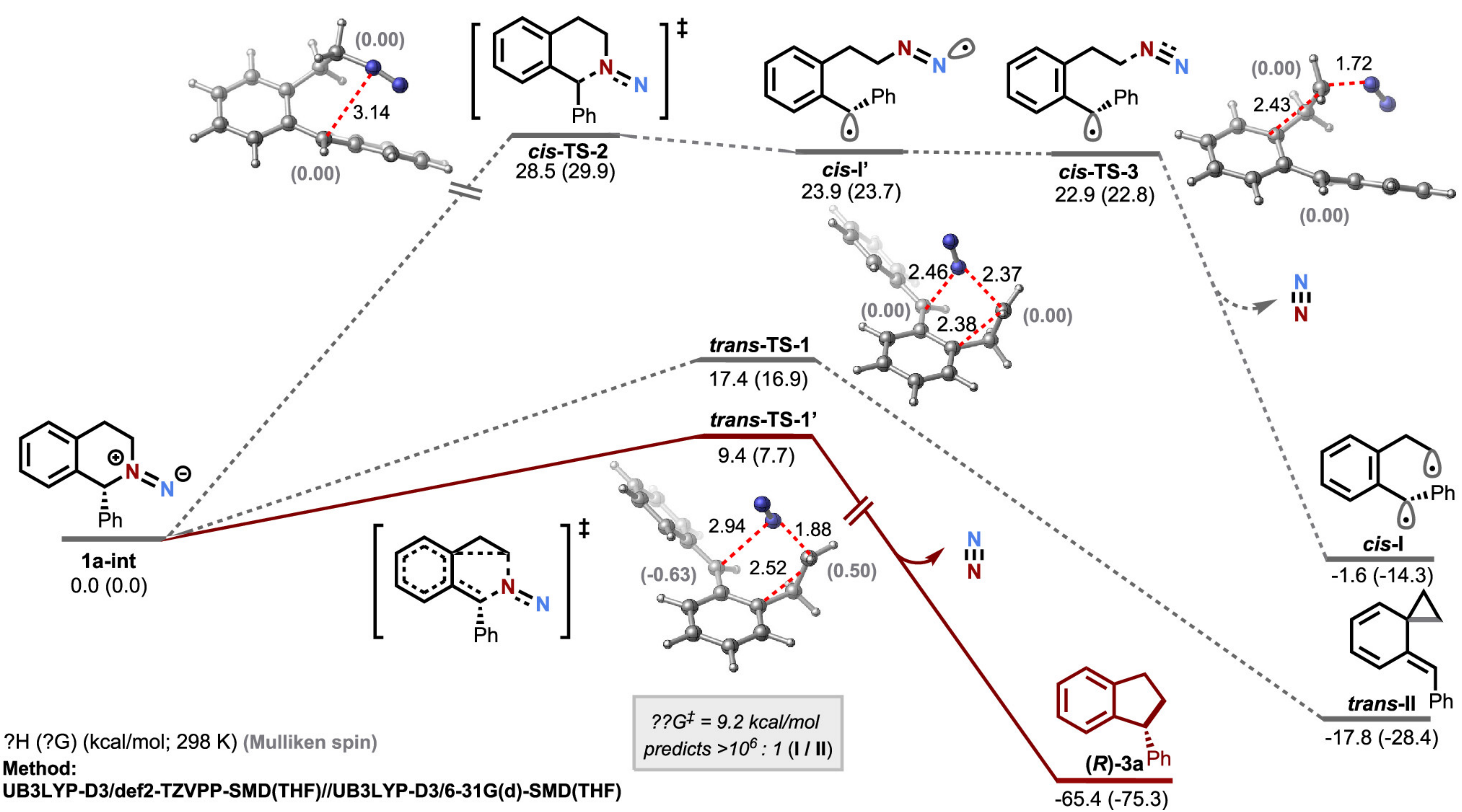
ΔH (ΔG) (kcal/mol; 298 K)

Method:
UB3LYP-D3/def2-TZVPP-SMD(THF)//UB3LYP-D3/6-31G(d)-SMD(THF)

Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

Understanding how molecules act

Static DFT does not match observations



*??G‡ = 9.2 kcal/mol predicts >10^6 : 1 (**I / II**)*

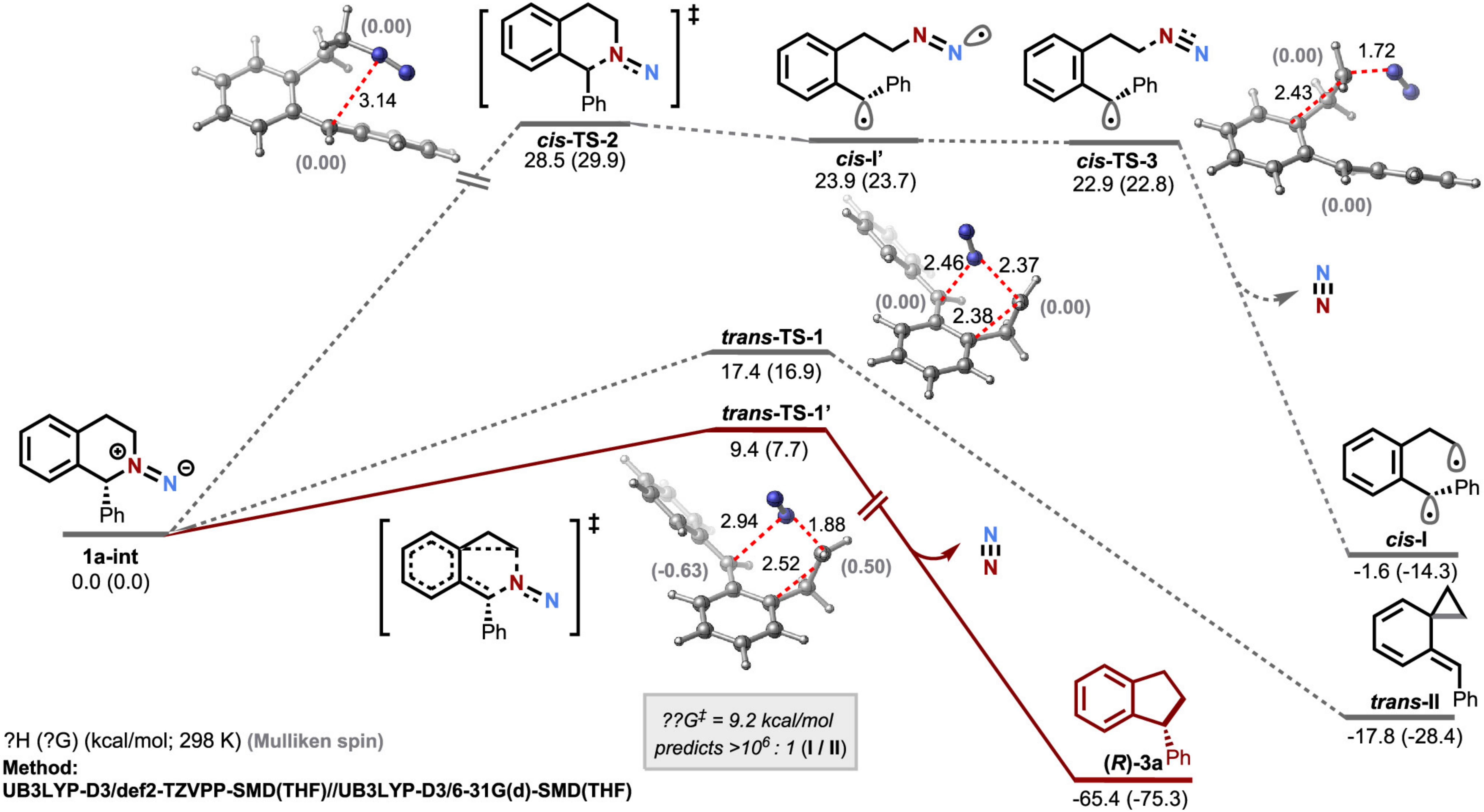
?H (?G) (kcal/mol; 298 K) **(Mulliken spin)**

Method:
UB3LYP-D3/def2-TZVPP-SMD(THF)//UB3LYP-D3/6-31G(d)-SMD(THF)

Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

Understanding how molecules act

Static DFT does not match observations



??G‡ = 9.2 kcal/mol predicts >10^6 : 1 (**I / II**)

?H (?G) (kcal/mol; 298 K) **(Mulliken spin)**

Method:
UB3LYP-D3/def2-TZVPP-SMD(THF)//UB3LYP-D3/6-31G(d)-SMD(THF)

Does not align with isotope scrambling or enantioerosion

Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

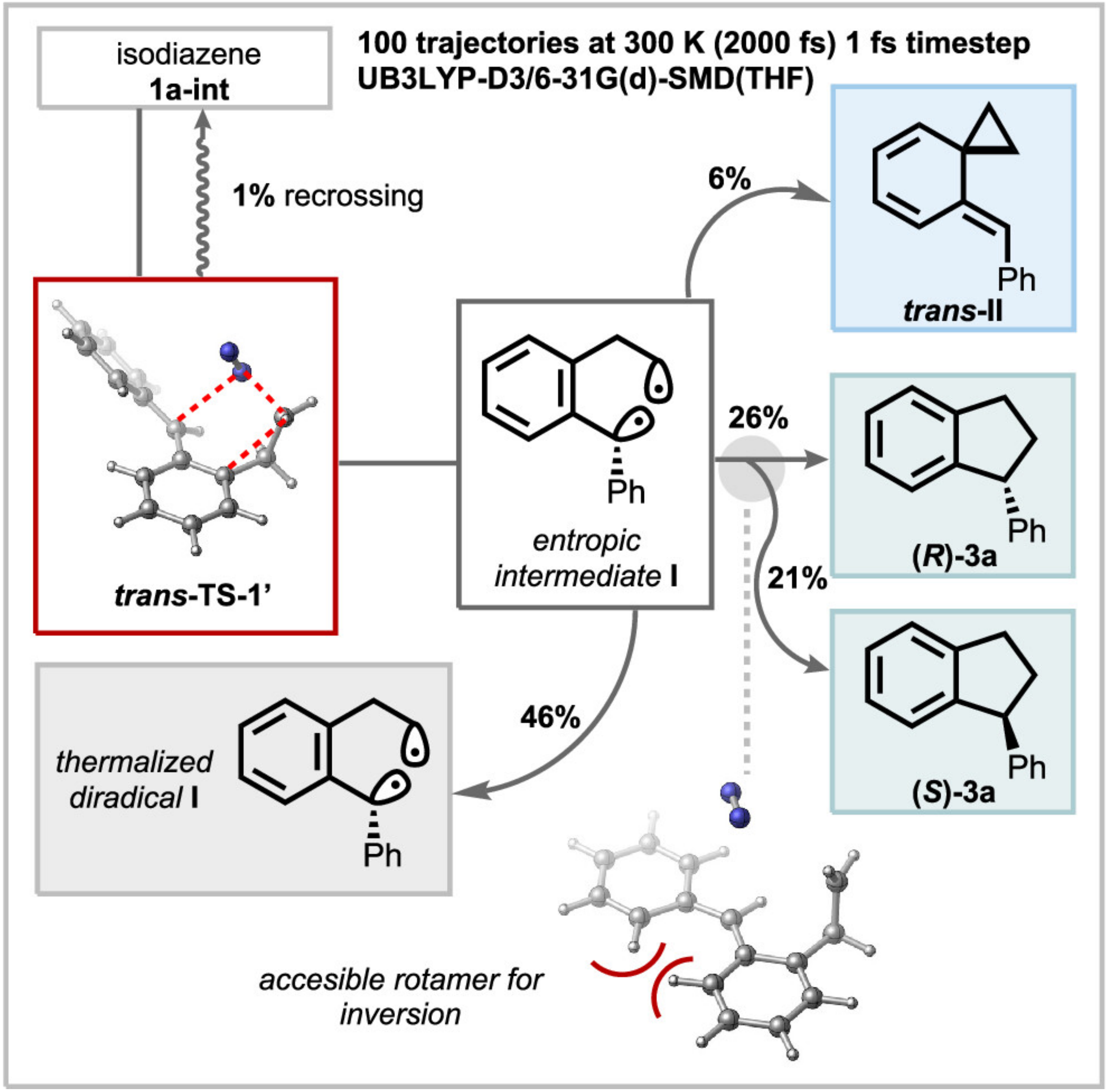
Understanding how molecules act

Can dynamics simulations help?

Masson-Makdassi, J.; Lalisse, R. F.; Yuan, M.; Dherange, B. D.; Gutierrez, O.; Levin, M. D. *J. Am. Chem. Soc.* **2024**, *146*, 17719-17727.

Understanding how molecules act

Can dynamics simulations help?



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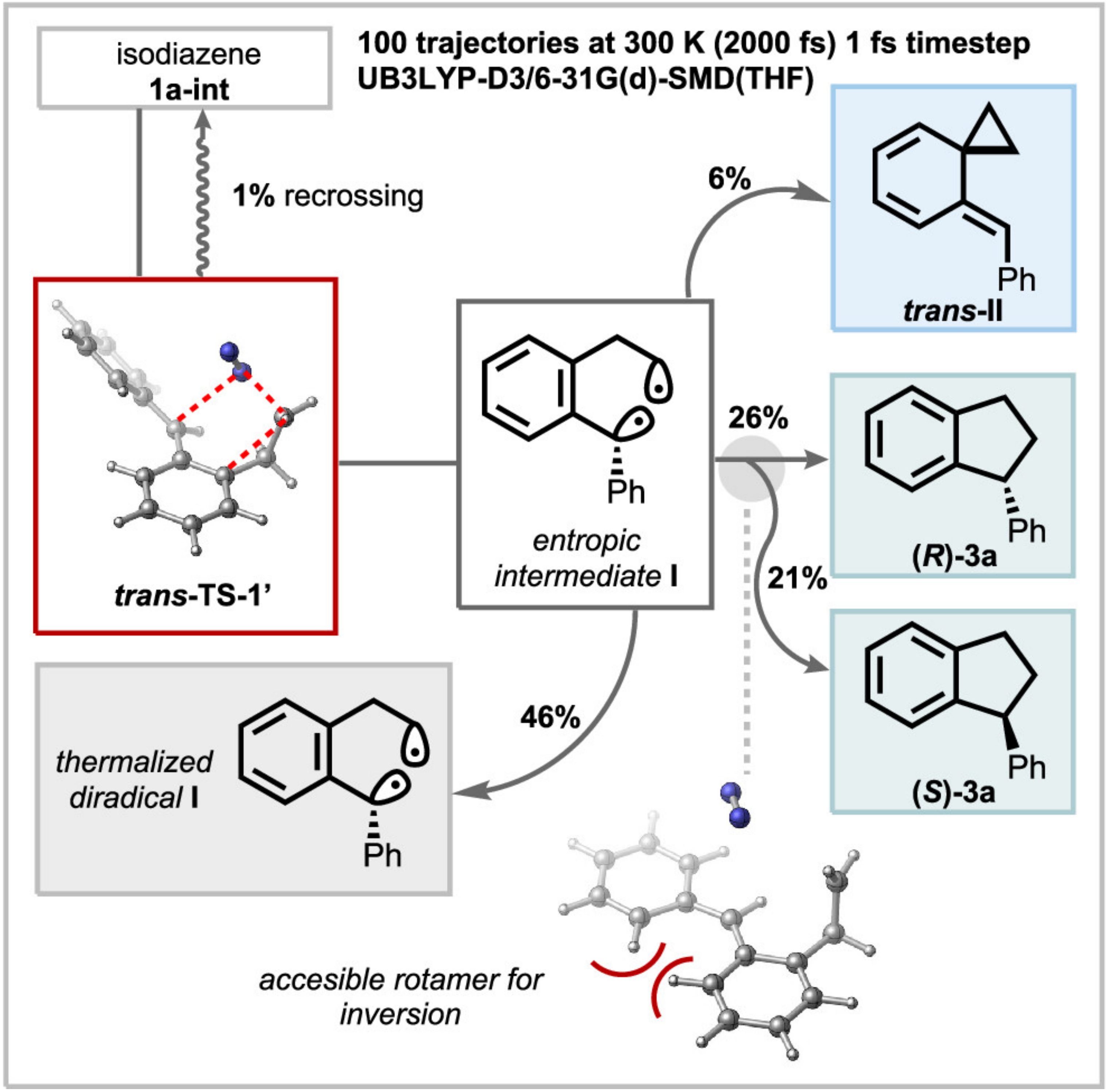
Understanding how molecules act

Can dynamics simulations help?



Dynamics simulations better explain observed enantioerosion and isotope scrambling

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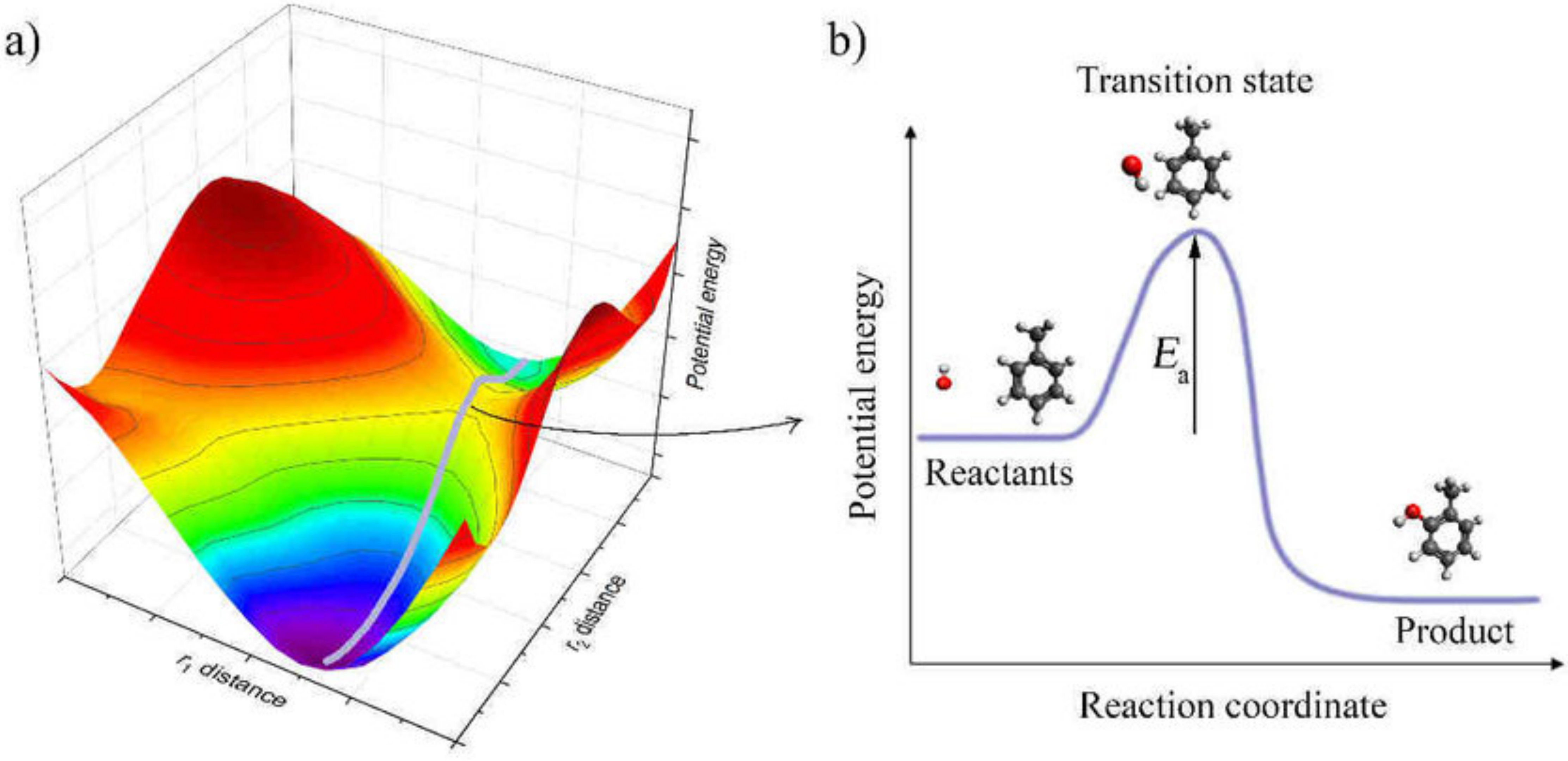
Understanding how molecules act

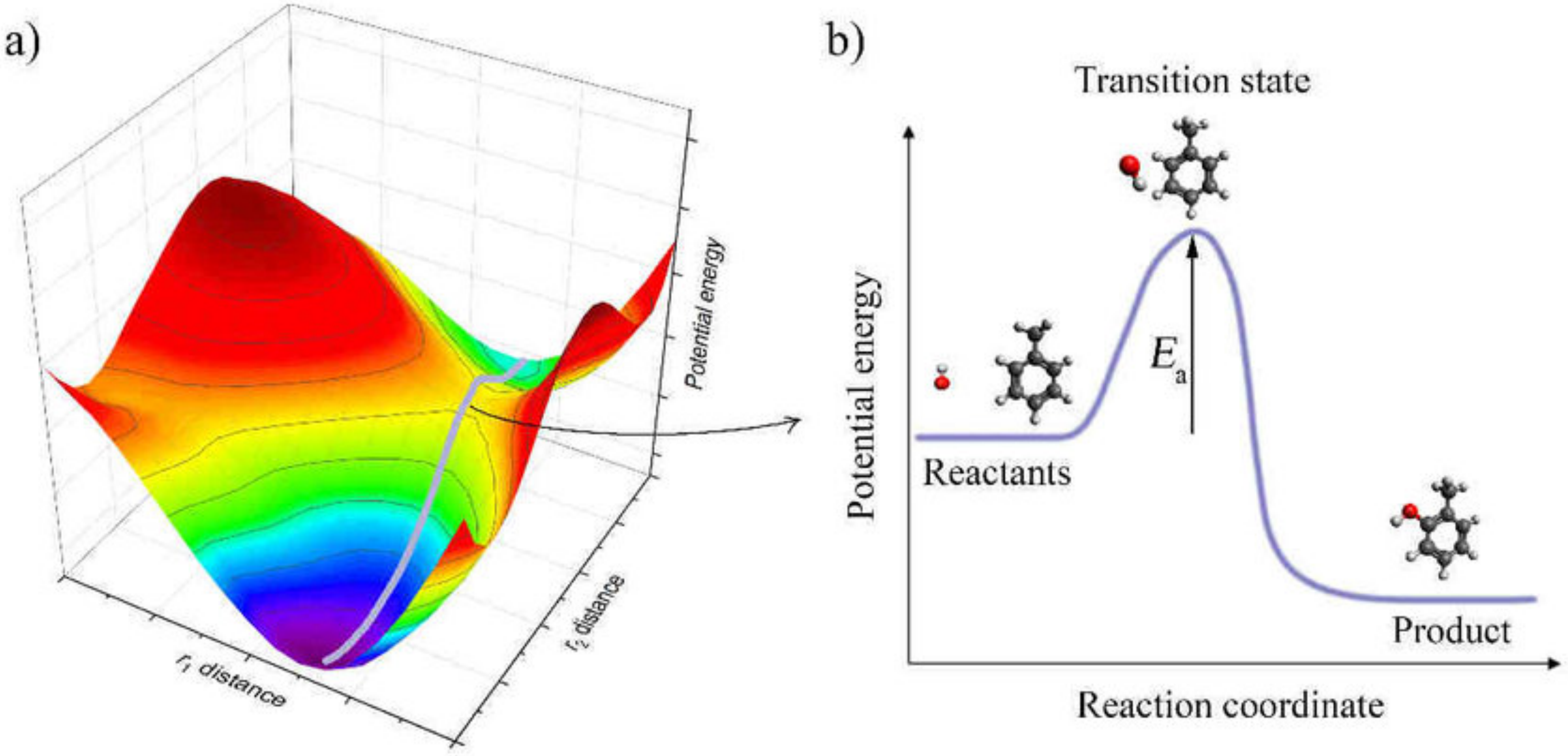
Typical potential energy surfaces



Wacławek, S. *Ecol. Chem. Eng. S.* **2021**, *28*, 11-28.

Understanding how molecules act

Typical potential energy surfaces

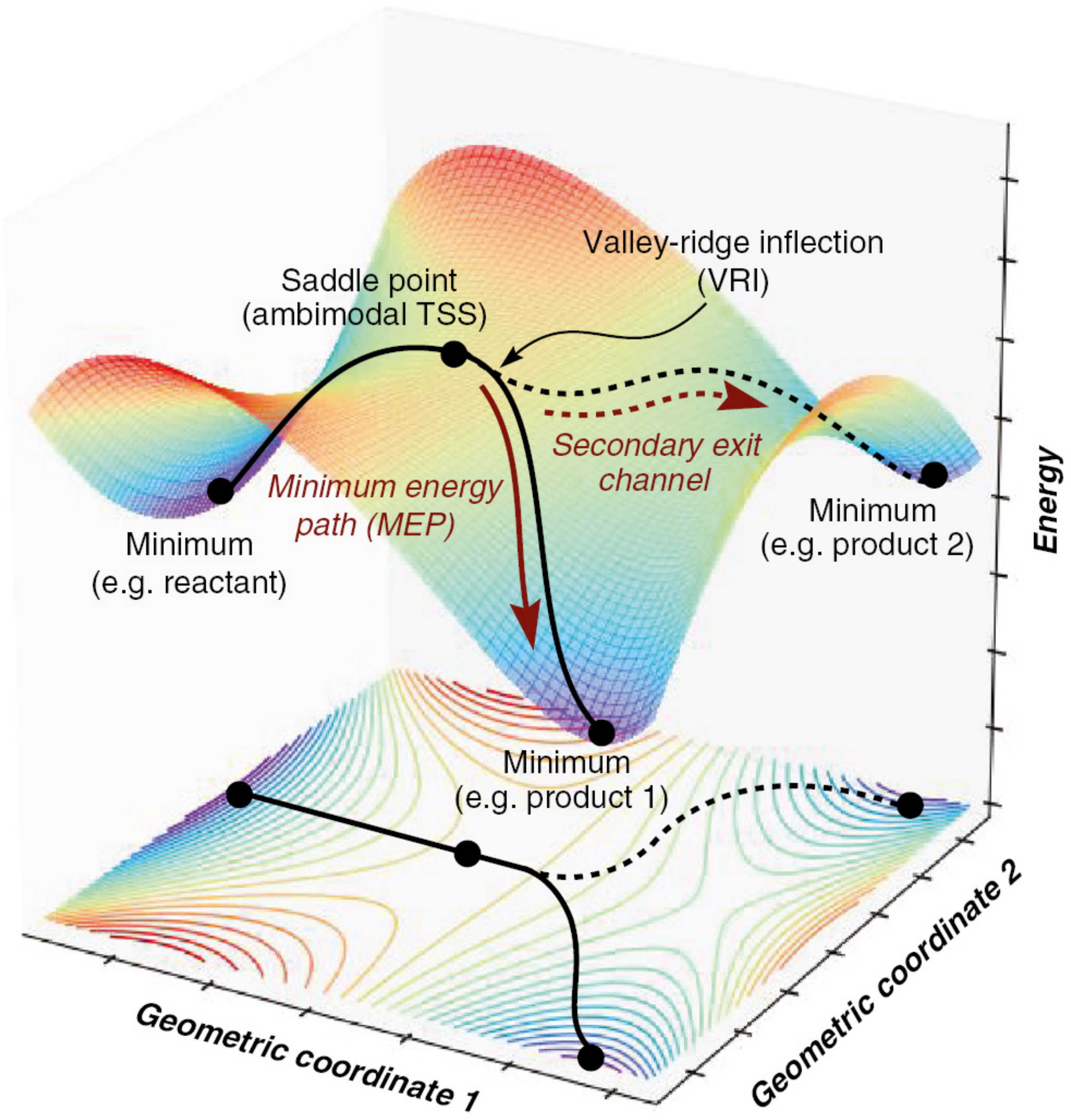


What if a transition state could lead to two different products?

Wacławek, S. *Ecol. Chem. Eng. S.* **2021**, *28*, 11-28.

Understanding how molecules act

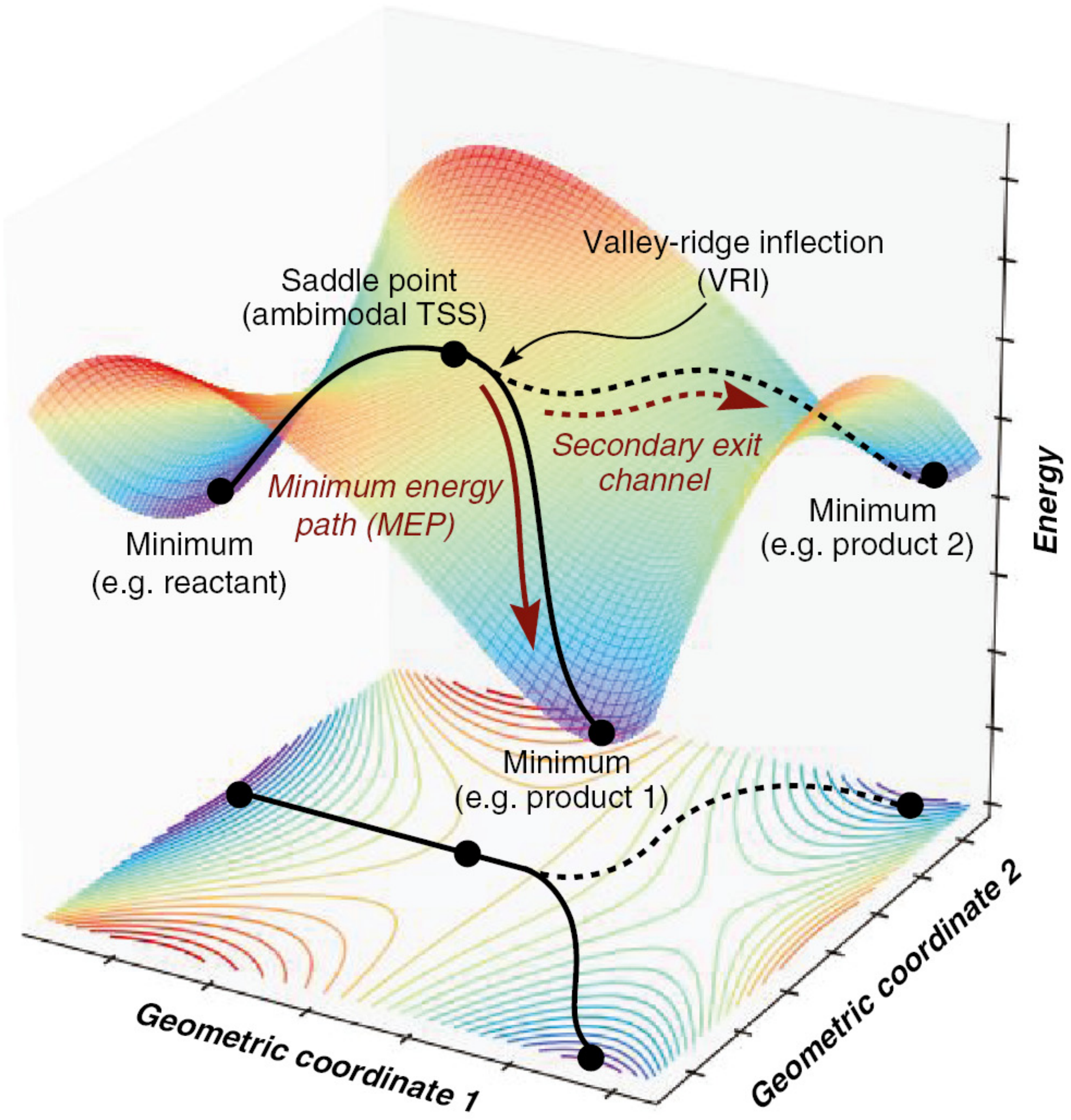
Post-transition state bifurcations



Hare, S.; Tantillo, D. J. *Pure Appl. Chem.* **2017**, *89*, 679-698.

Understanding how molecules act

Post-transition state bifurcations



When you have a PTSB, you no longer necessarily follow the lowest energy pathway (i.e. the intrinsic reaction coordinate)

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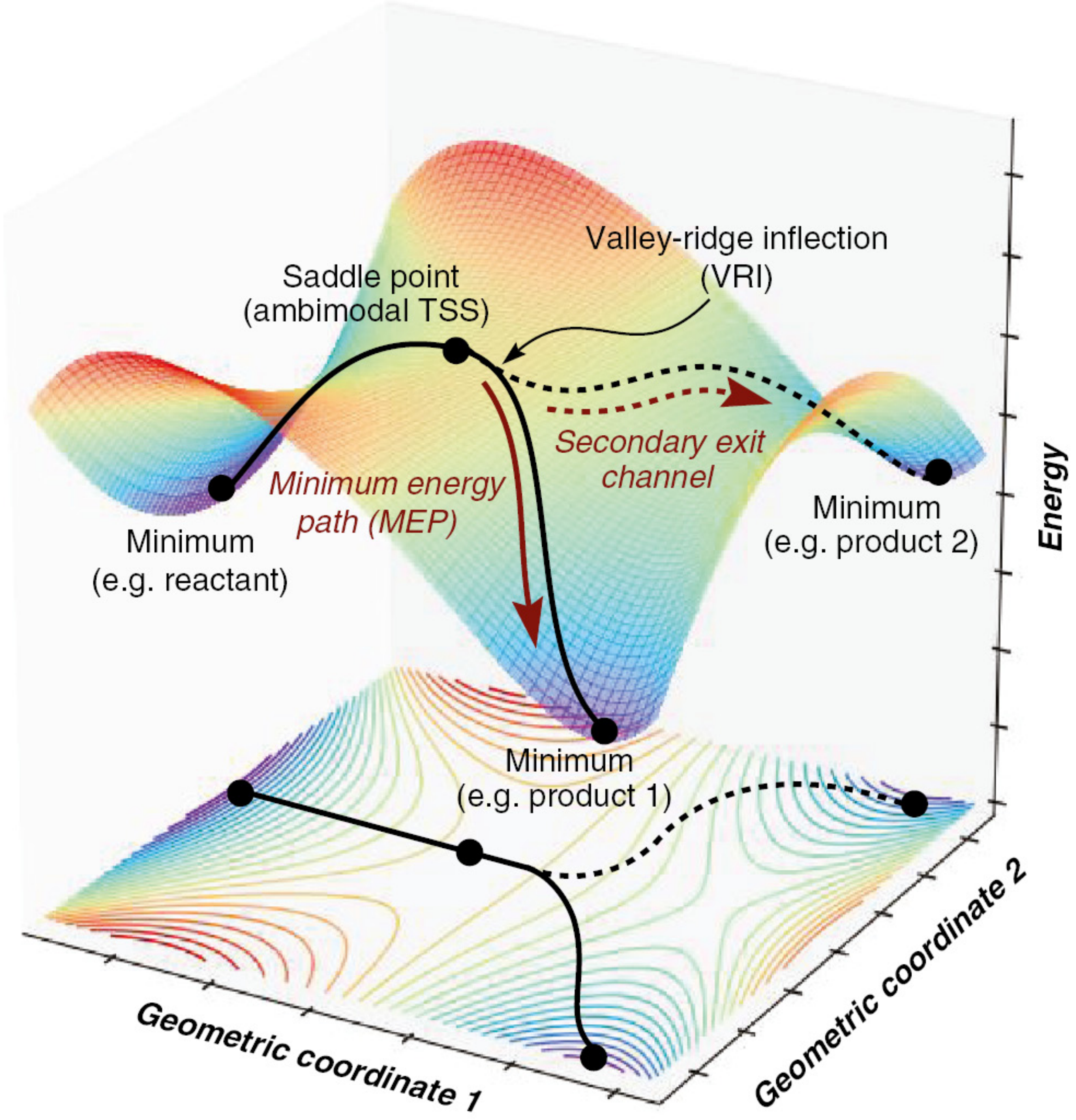
Understanding how molecules act

Post-transition state bifurcations



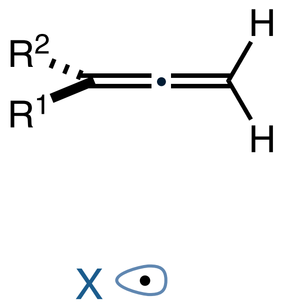
When you have a PTSB, you no longer necessarily follow the lowest energy pathway (i.e. the intrinsic reaction coordinate)

Dynamics simulations can model non-IRC behavior and predict experimental outcomes

Hare, S.; Tantillo, D. J. *Pure Appl. Chem.* **2017**, *89*, 679-698.

Understanding how molecules act

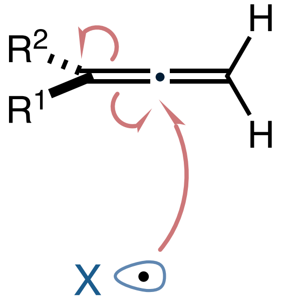
PTSB in radical addition to allenes



Wu, R.-K.; Zhang, S.-Q.; Hong, X. *Chem. Eur. J.* **2024**, *30*, e202403316.

Understanding how molecules act

PTSB in radical addition to allenes



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Understanding how molecules act

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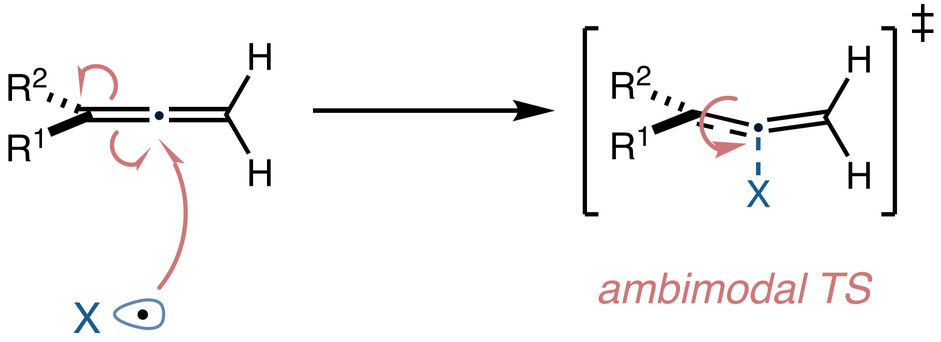

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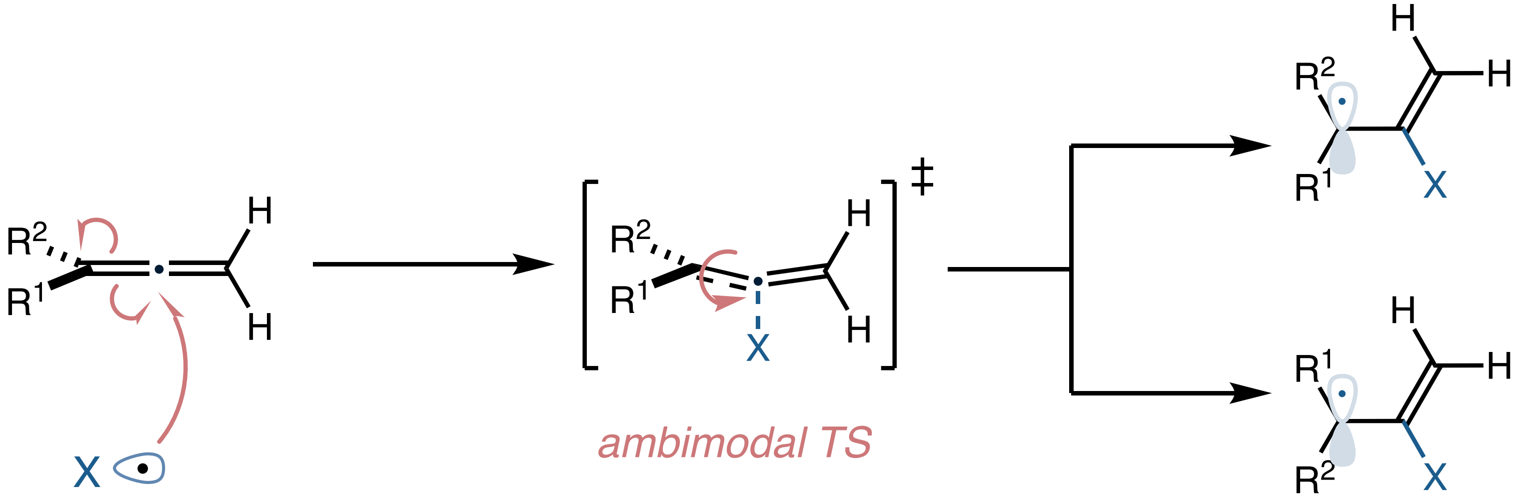
Understanding how molecules act

PTSB in radical addition to allenes



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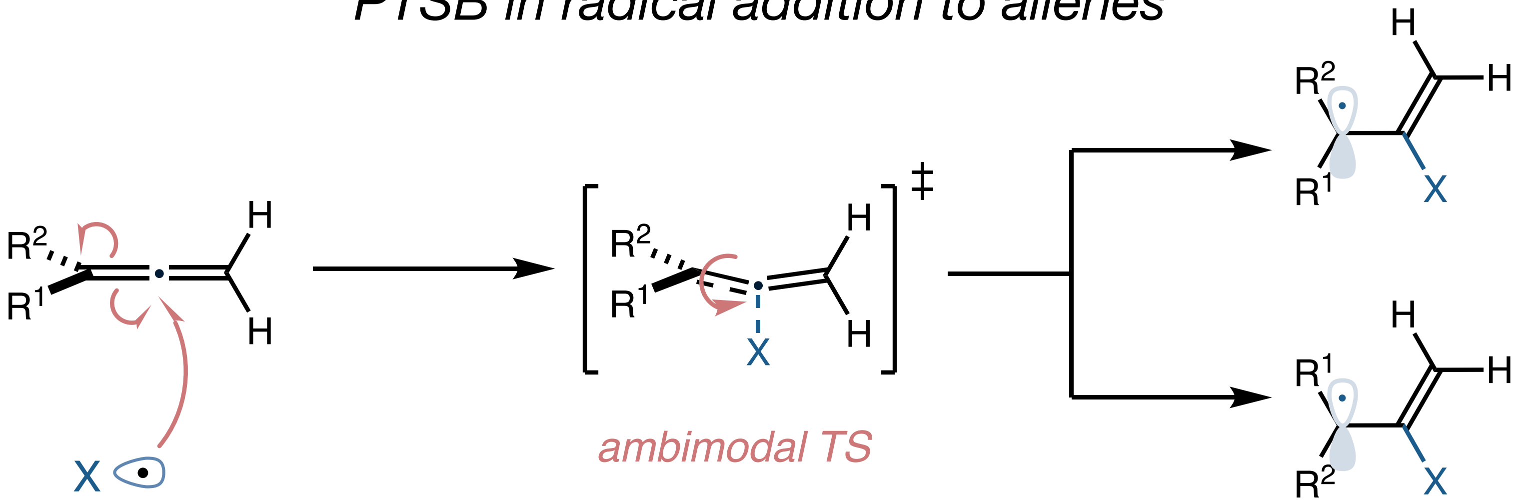
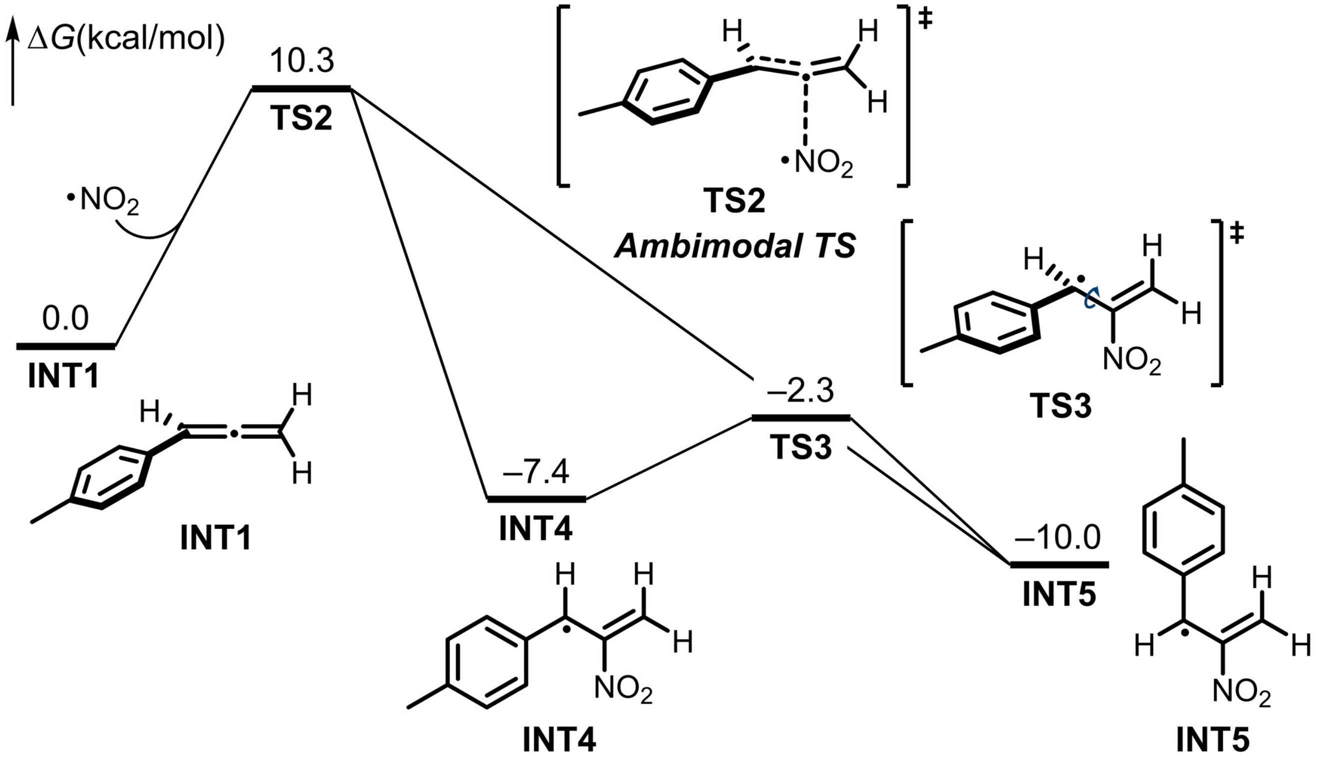
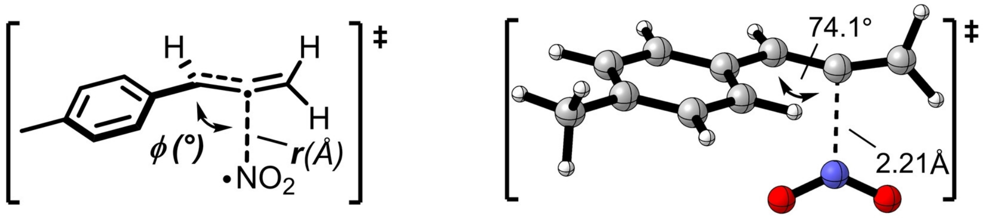
Understanding how molecules act

PTSB in radical addition to allenes





One transition state



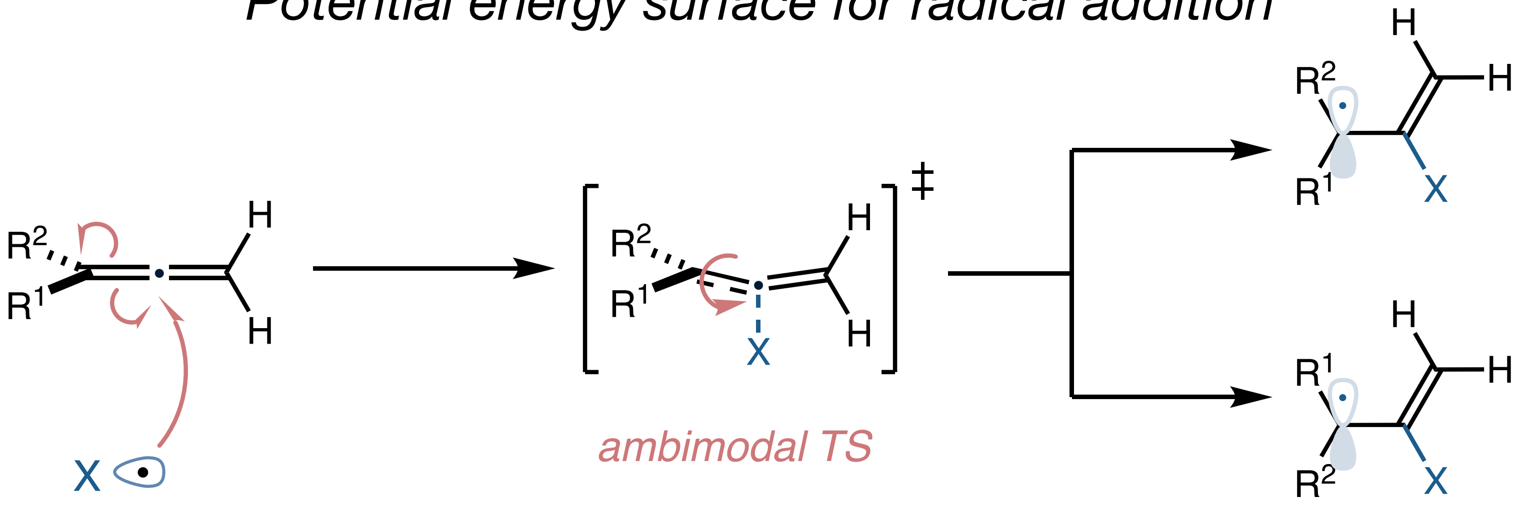
TS2

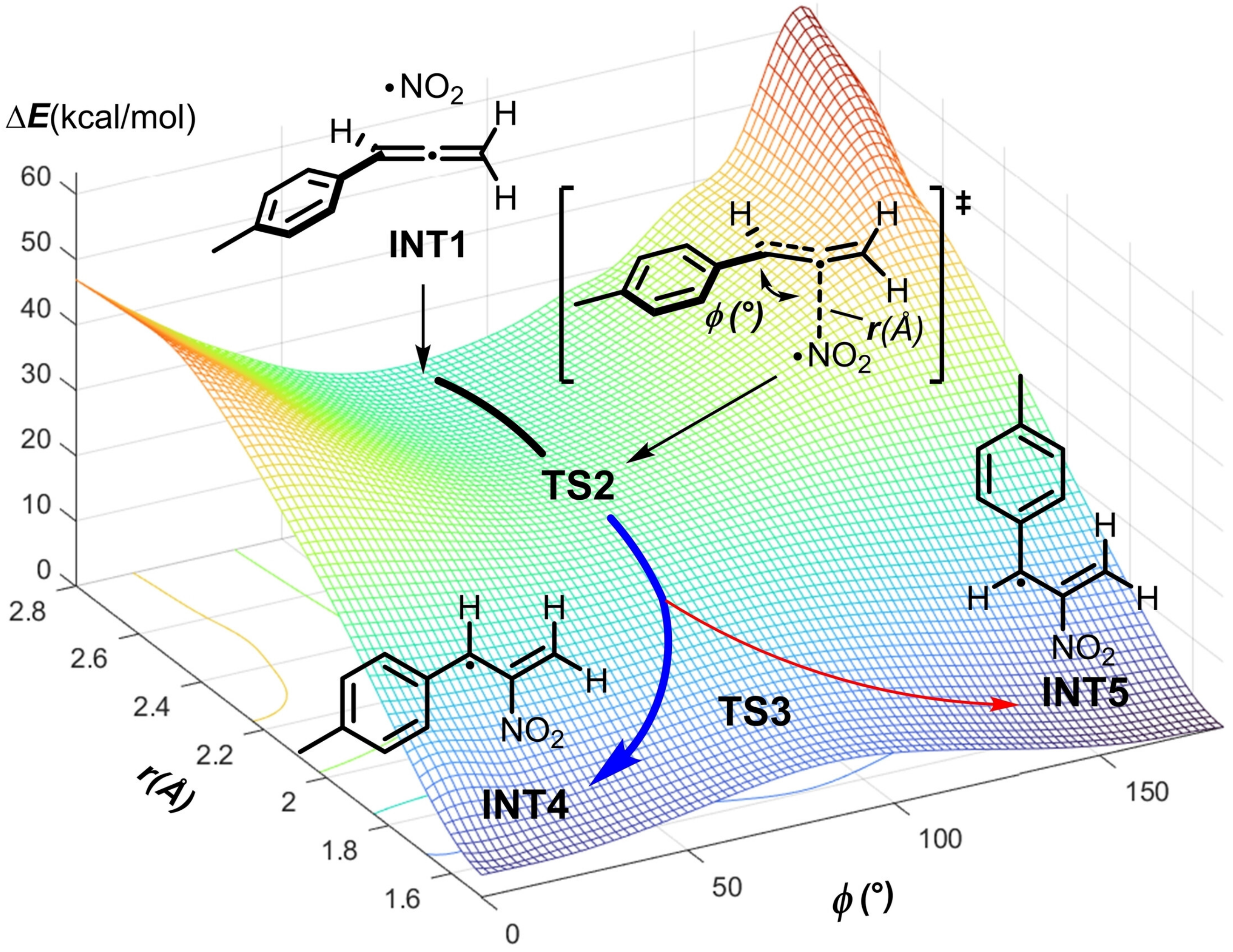
Wu, R.-K.; Zhang, S.-Q.; Hong, X. *Chem. Eur. J.* **2024**, *30*, e202403316.

B3LYP-D3(BJ)/def2-TZVP-SMD(dioxane) //
B3LYP-D3(BJ)/def2-SVP-SMD(dioxane)
level of theory

Understanding how molecules act

Potential energy surface for radical addition





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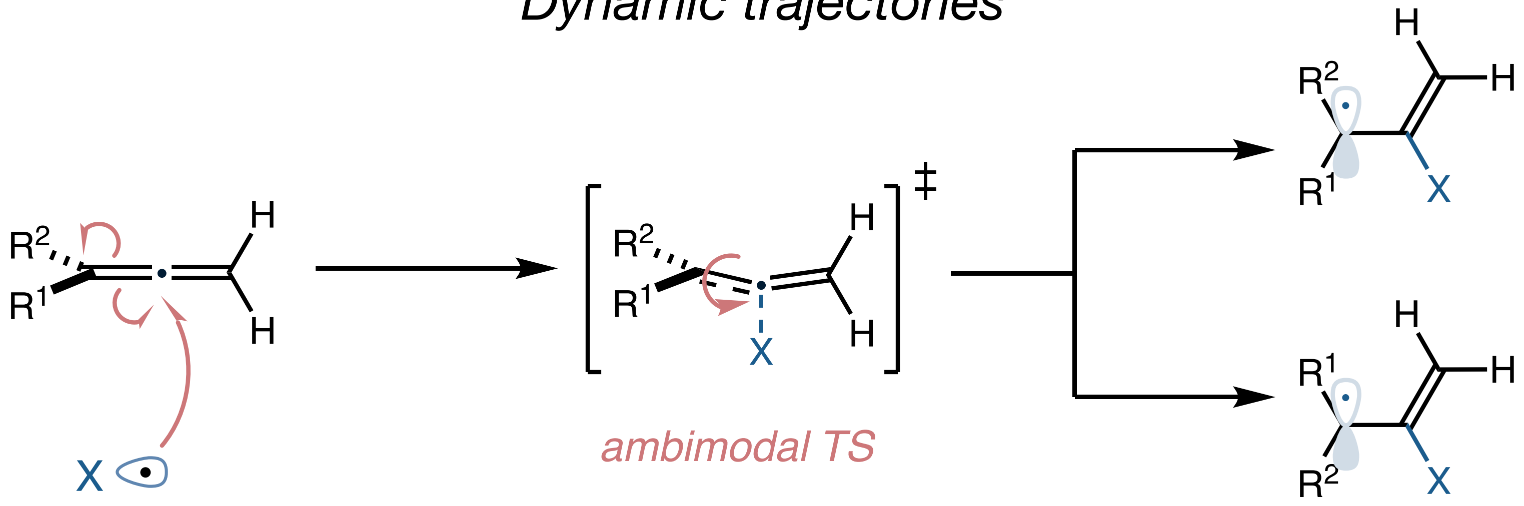
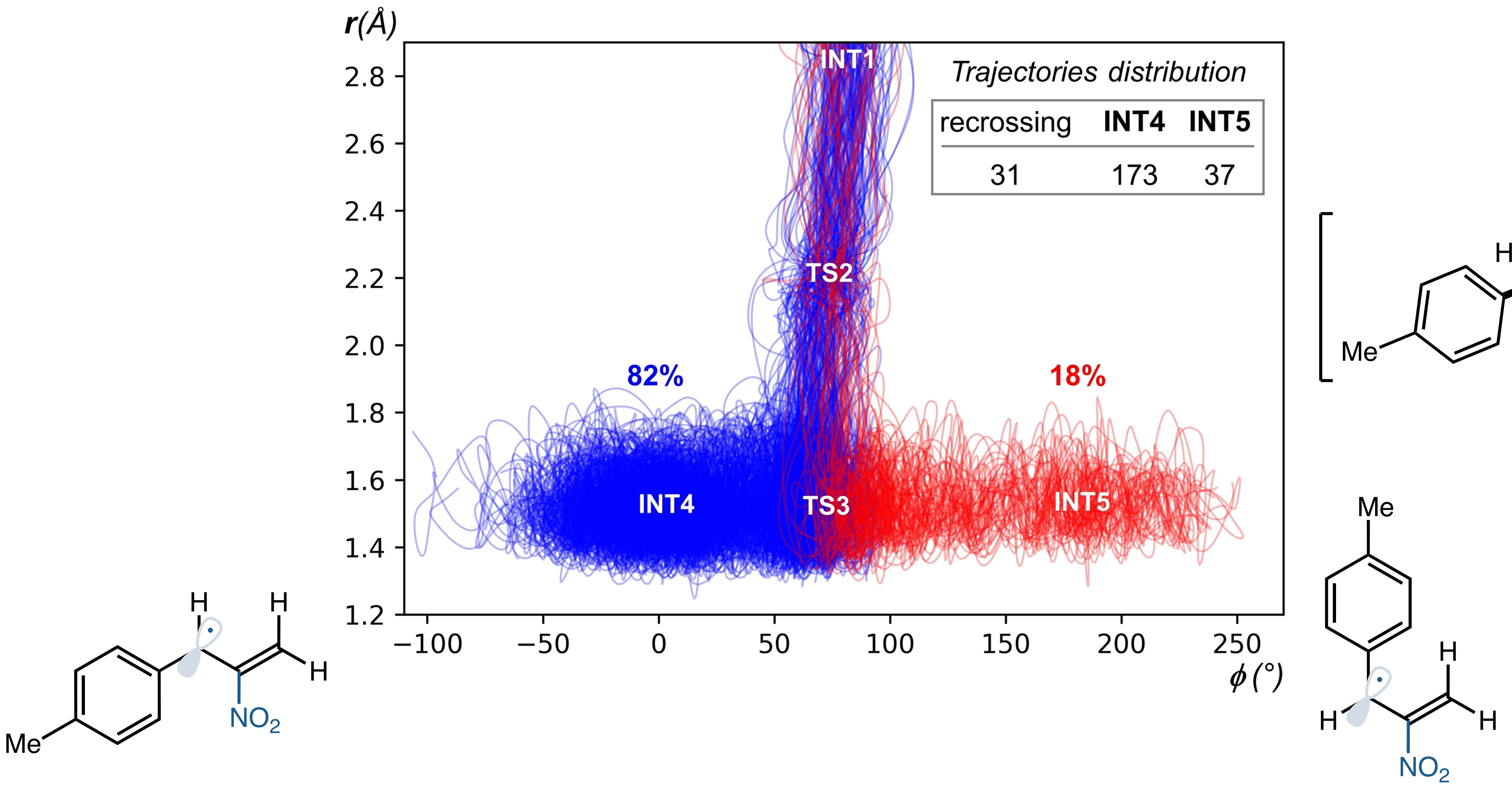
B3LYP-D3(BJ)/def2-TZVP-SMD(dioxane) //
B3LYP-D3(BJ)/def2-SVP-SMD(dioxane)
level of theory

Understanding how molecules act

Dynamic trajectories





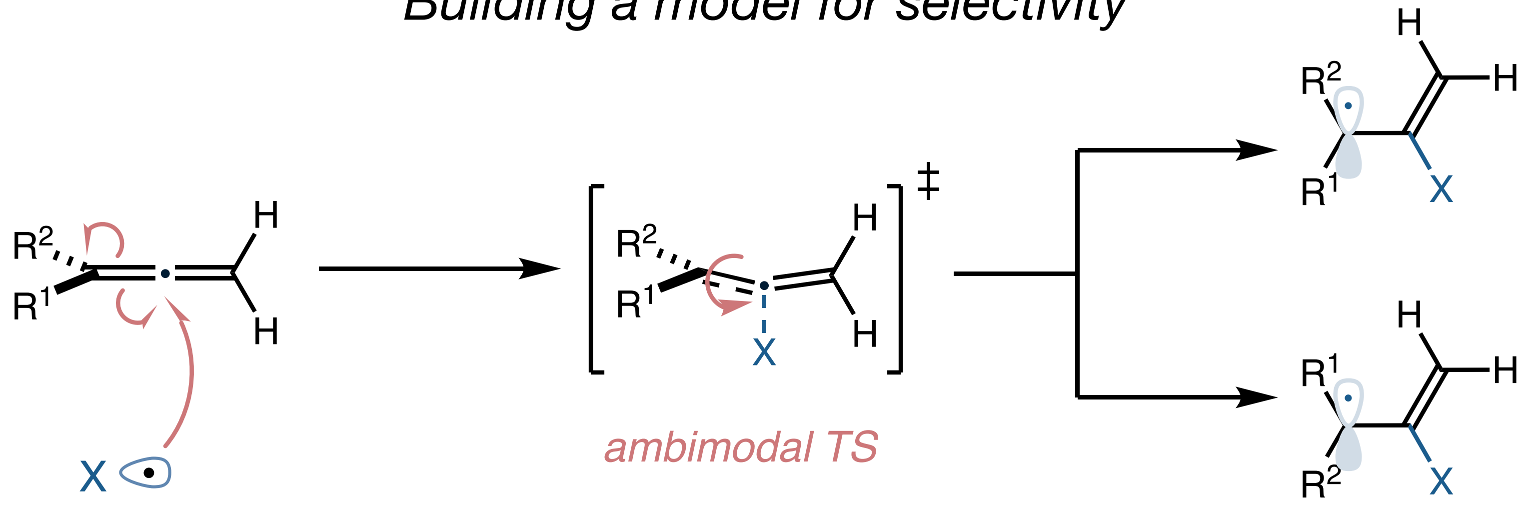
Trajectories distribution

recrossing	**INT4**	**INT5**
31	173	37

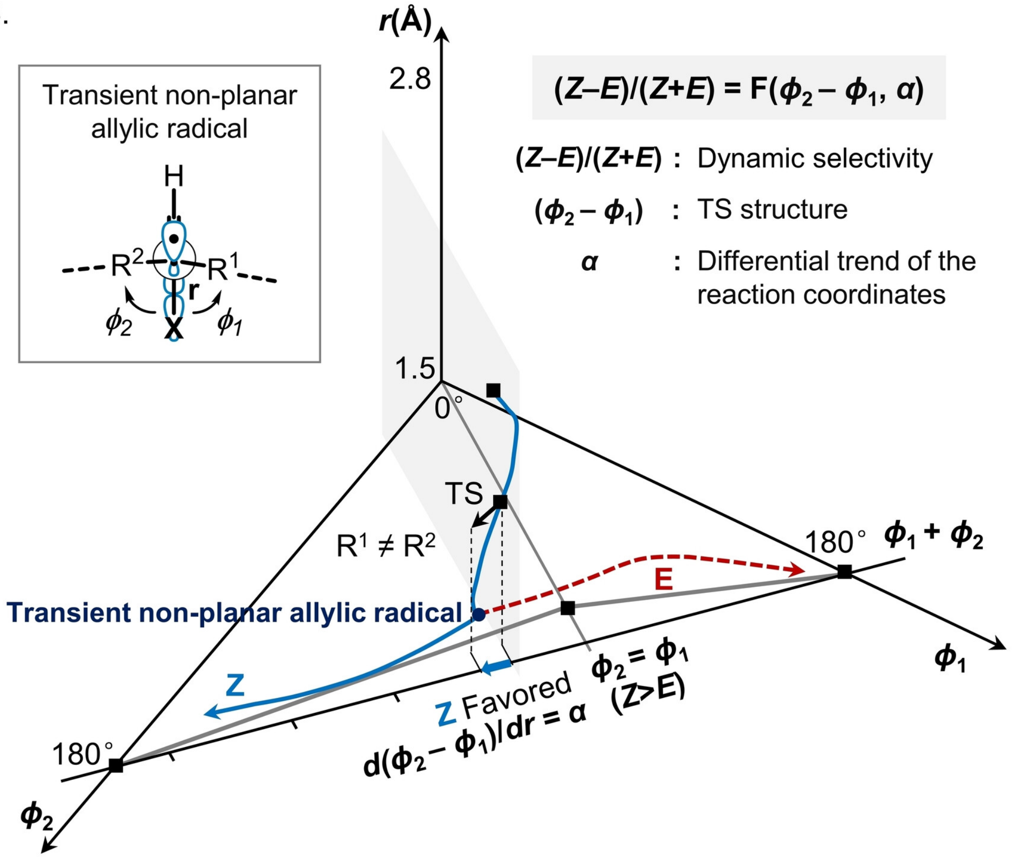
Wu, R.-K.; Zhang, S.-Q.; Hong, X. *Chem. Eur. J.* **2024**, *30*, e202403316.

Understanding how molecules act

Building a model for selectivity



B.



$(Z–E)/(Z+E) = F(\phi_2 – \phi_1, \alpha)$

$(Z–E)/(Z+E)$: Dynamic selectivity

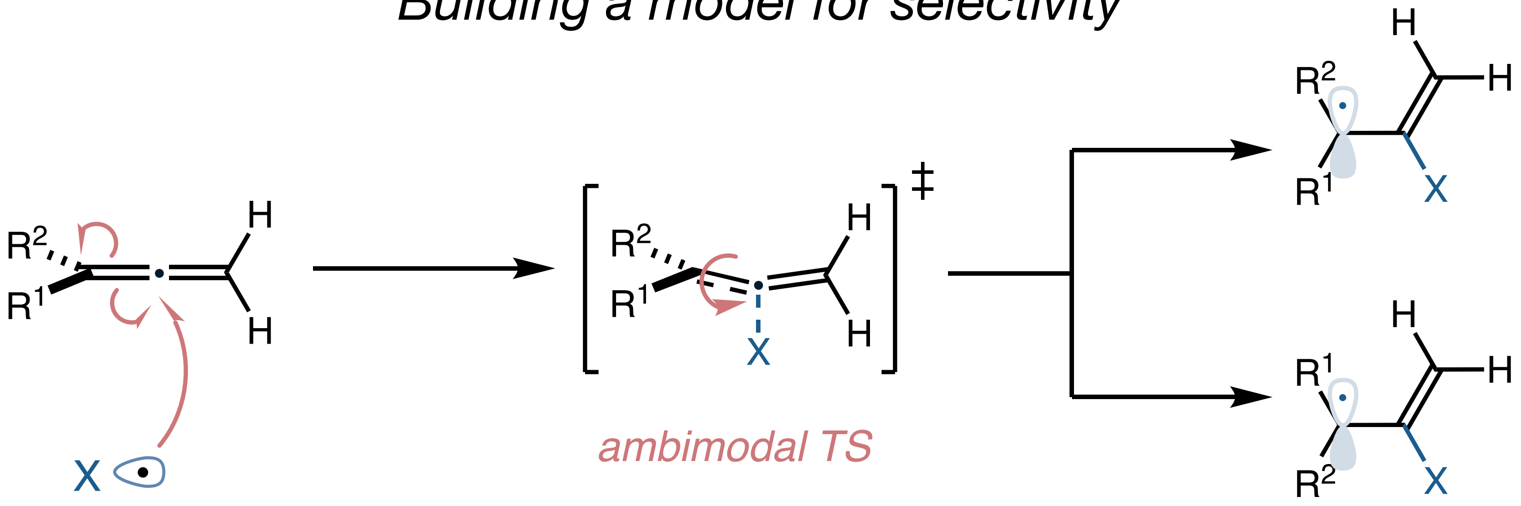
$(\phi_2 – \phi_1)$: TS structure

α : Differential trend of the reaction coordinates

Wu, R.-K.; Zhang, S.-Q.; Hong, X. *Chem. Eur. J.* **2024**, *30*, e202403316.

Understanding how molecules act

Building a model for selectivity



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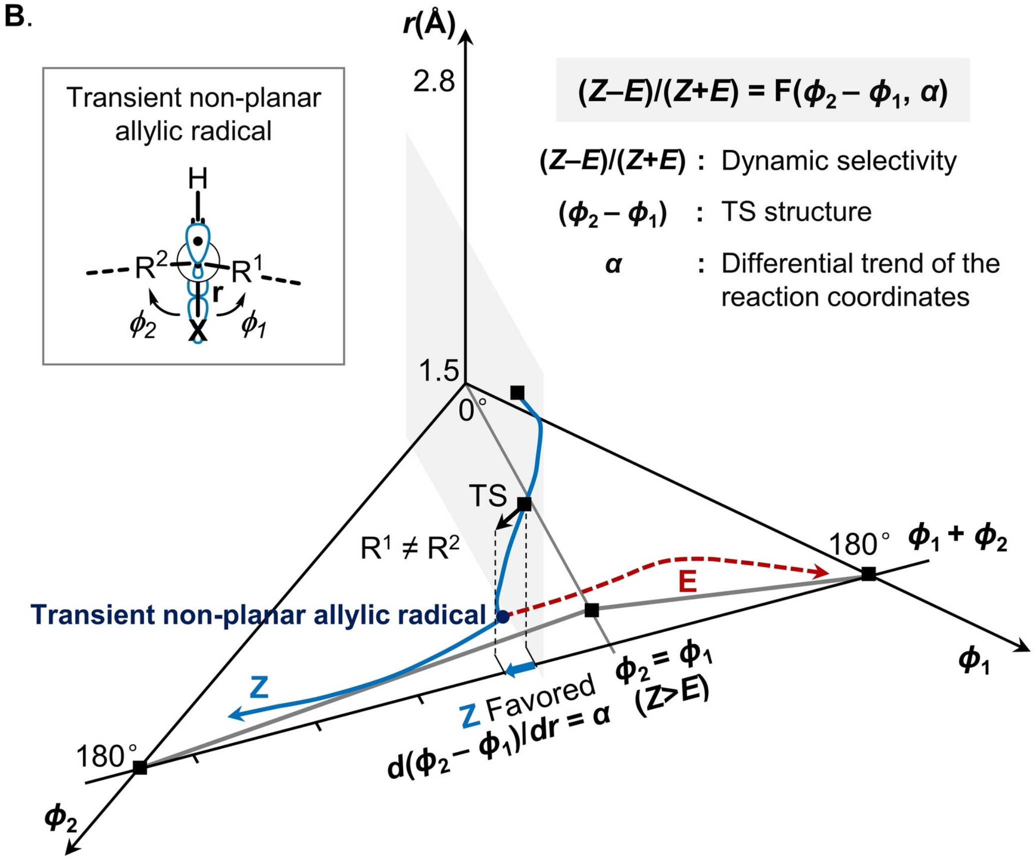

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selectivity can be modeled by properties of transition state structure

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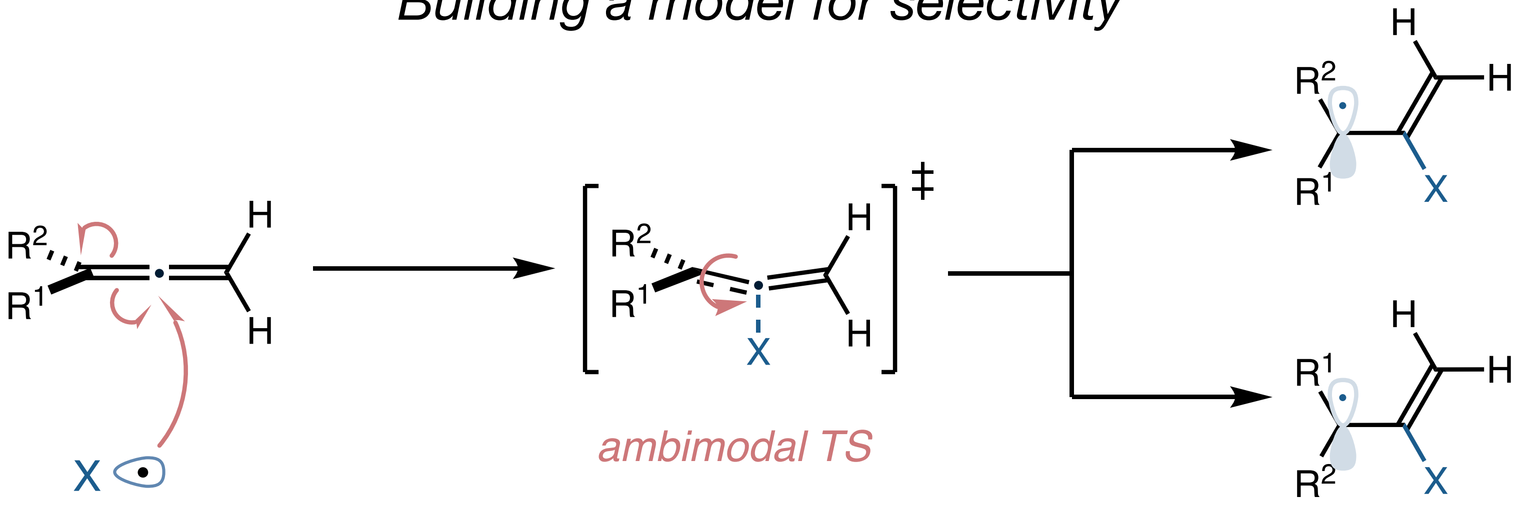
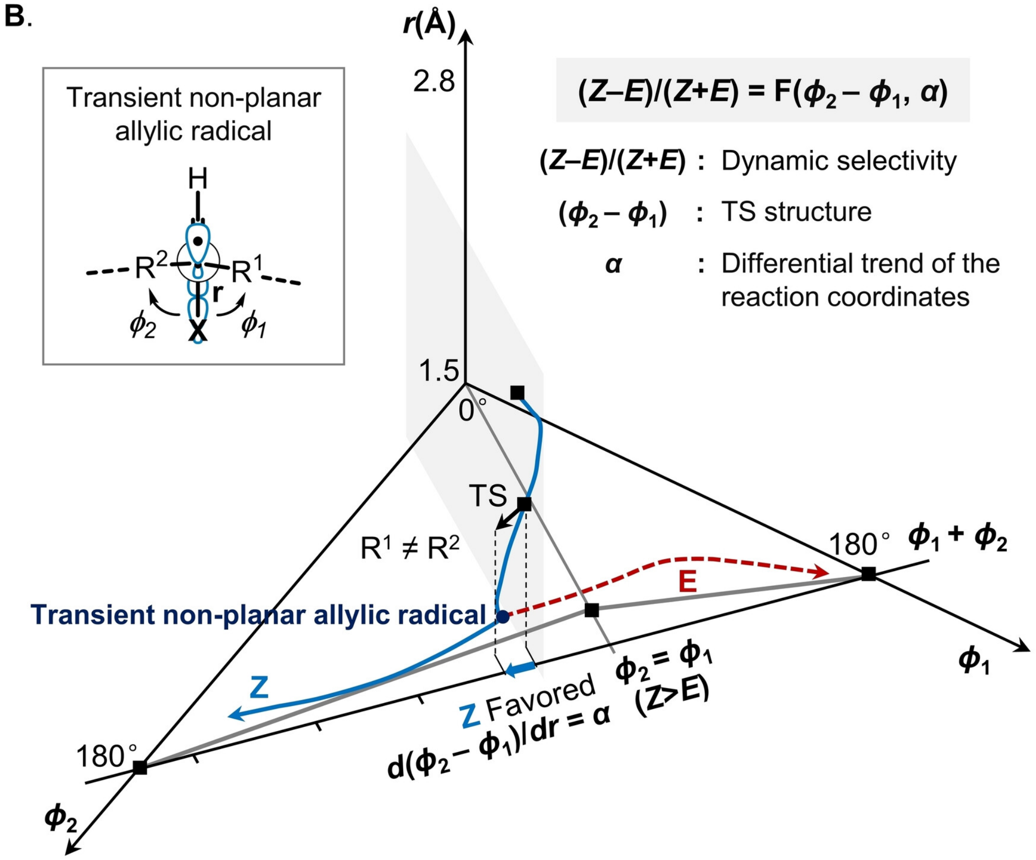
Understanding how molecules act

Building a model for selectivity





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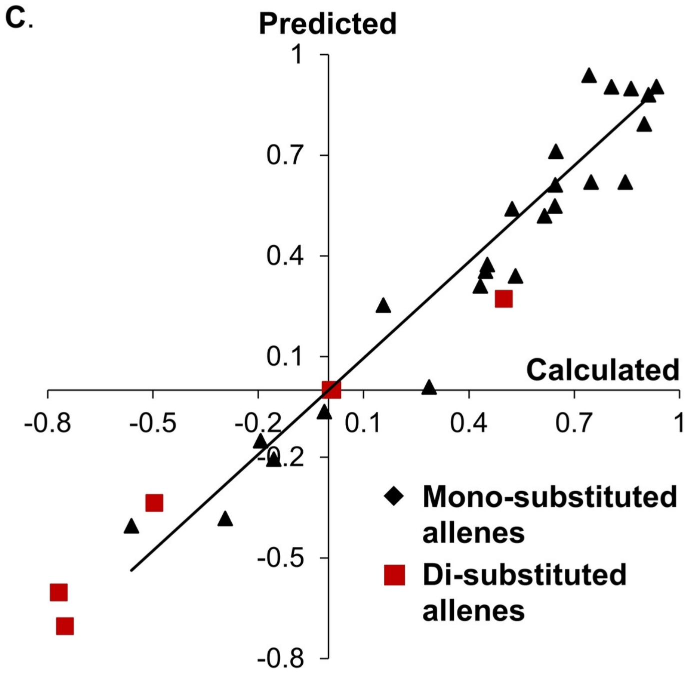


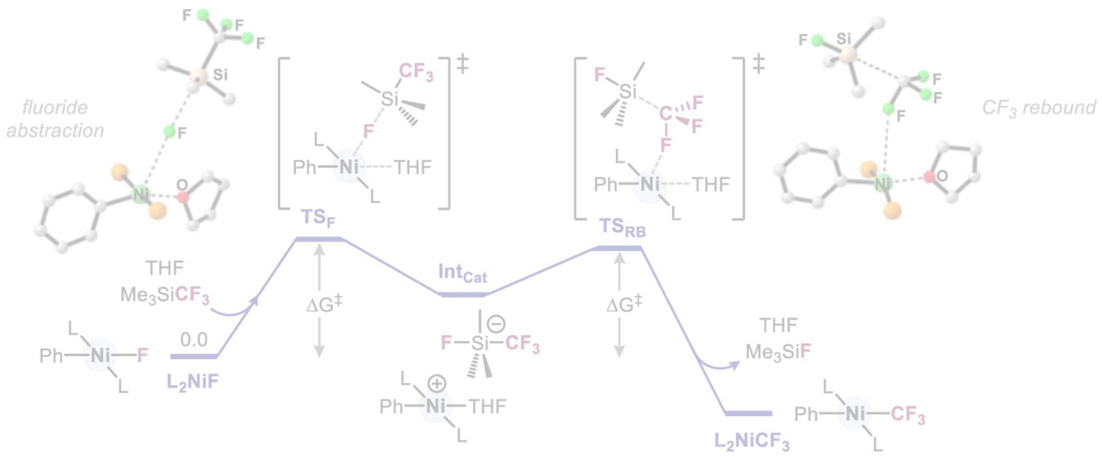
$(Z–E)/(Z+E) = 0.0170(\phi_2 - \phi_1) + 0.0201\alpha$
$R^2 = 0.956$

Wu, R.-K.; Zhang, S.-Q.; Hong, X. *Chem. Eur. J.* **2024**, *30*, e202403316.

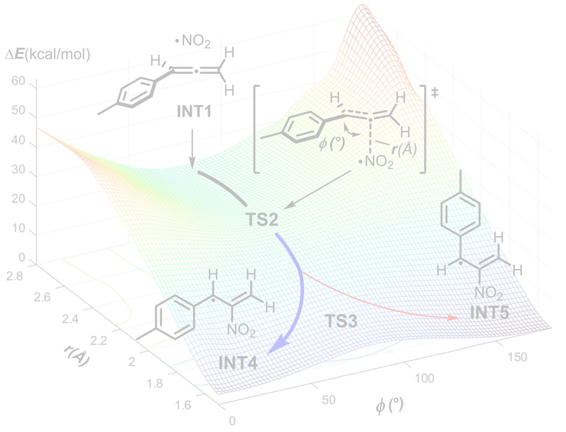
What can computational chemistry do for you?

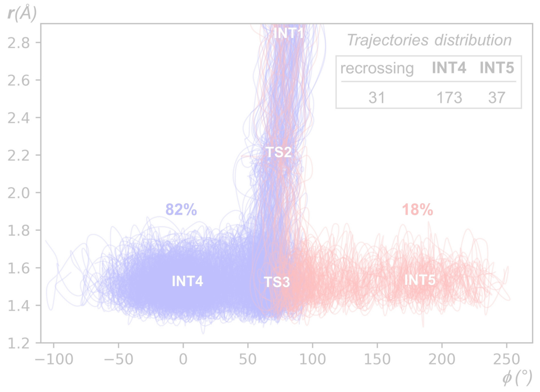
Understanding how molecules act

Density functional theory

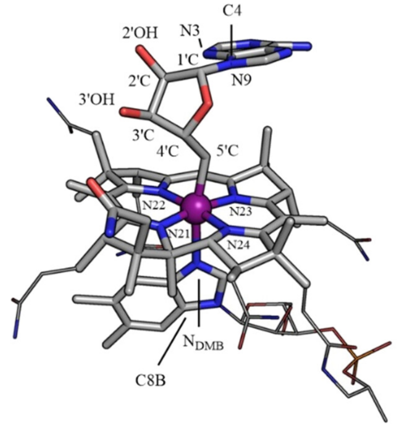


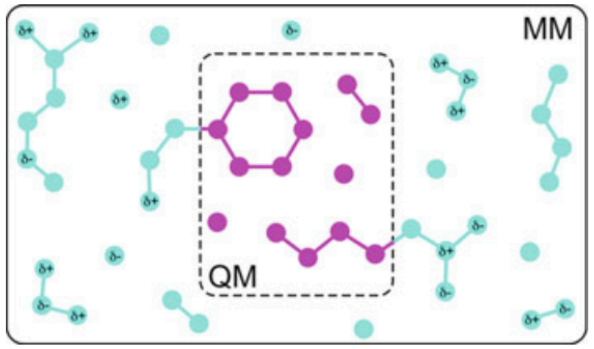
Dynamics Simulations





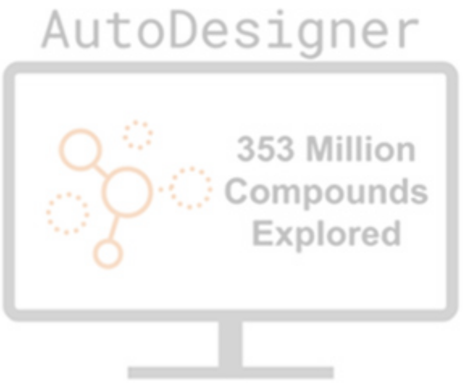
QM/MM

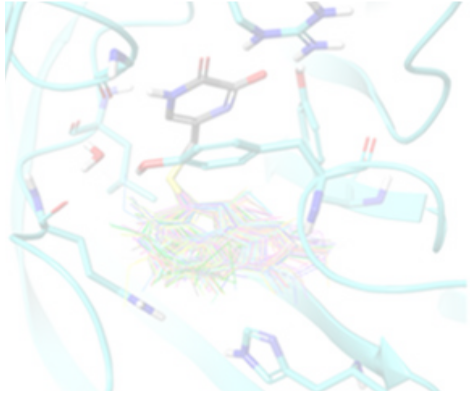




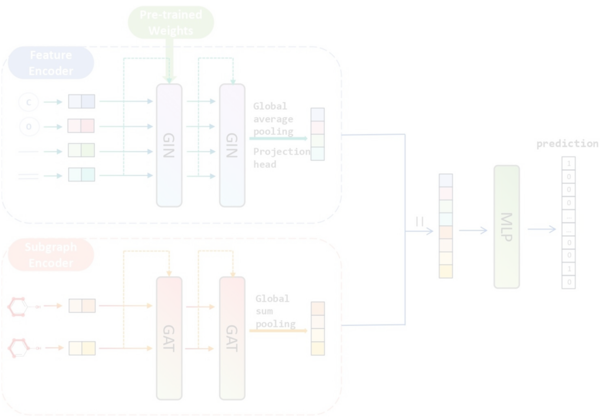
Predicting how molecules should act

Machine learning

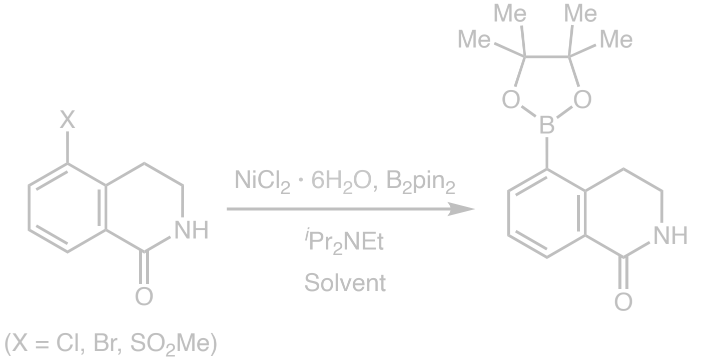


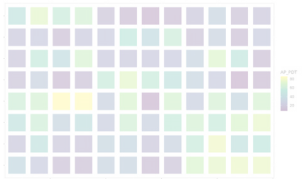


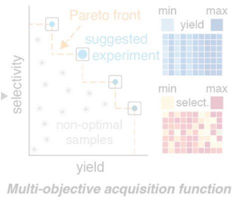
Neural networks



Data Science







Understanding how molecules act

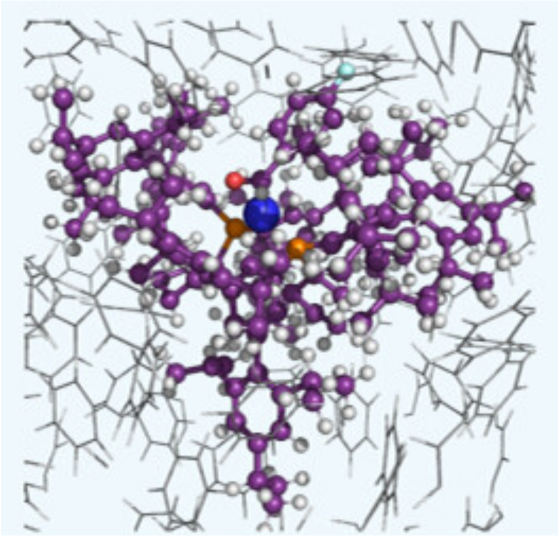
What if DFT is not enough?

DFT computations may not reflect observed experimental selectivities

For very large systems, DFT calculations become very expensive

Understanding how molecules act

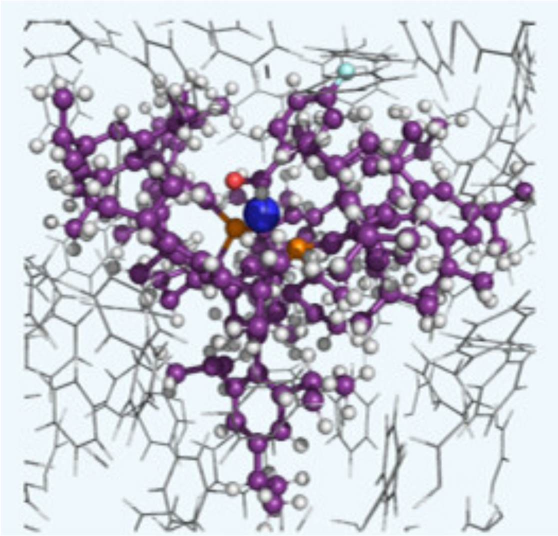
Quantum Mechanics/Molecular Mechanics Simulations (QM/MM)

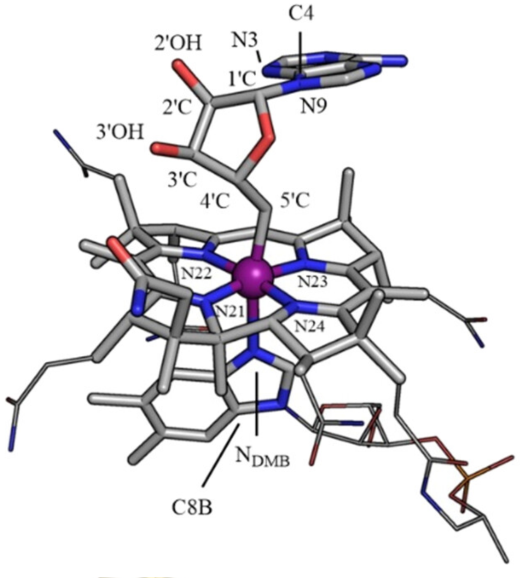


Pultar, F.; Thürlemann, M.; Gordiy, I.; Doloszeski, E.; Riniker, S. *J. Am. Chem. Soc.* **2025**, *147*, 6835-6856.
Elmendorf, L. D.; Hall, R. L.; Costa, F. G.; Escalante-Semerena, J. C.; Brunold, T. C. *J. Am. Chem. Soc.* **2025**, *147*, 2380-2392.
Li, C.; Kin-Lic Chan, G. *J. Chem. Theory Comput.* **2025**, *21*, 803-816.
Broenhof, G. *Methods Mol. Biol.* **2013**, *924*, 43-66.

Understanding how molecules act

Quantum Mechanics/Molecular Mechanics Simulations (QM/MM)





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Understanding how molecules act

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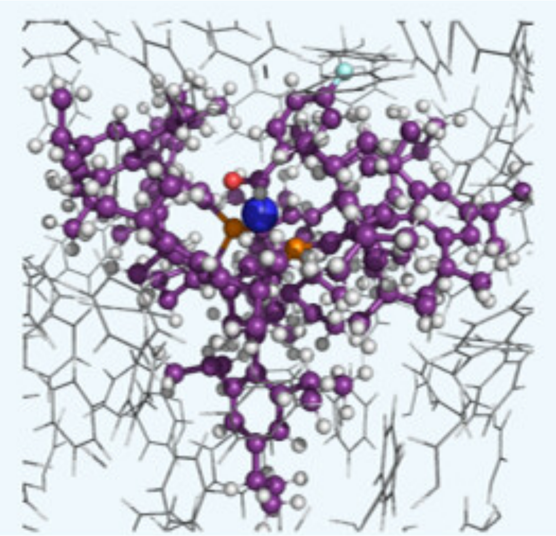

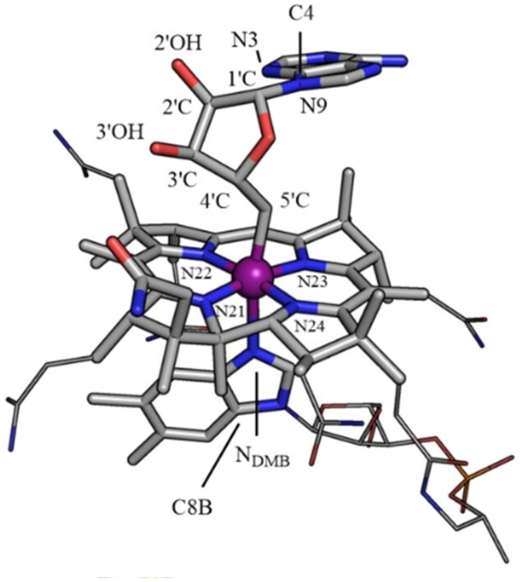

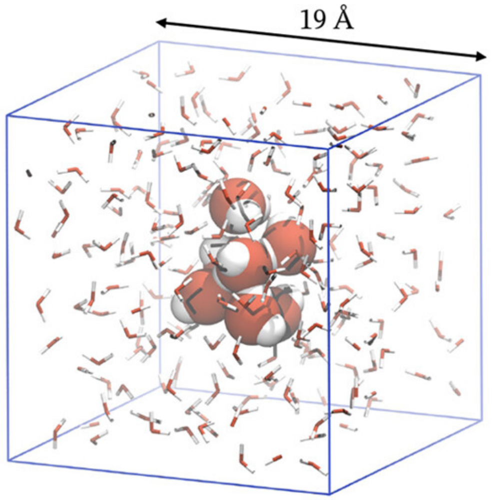

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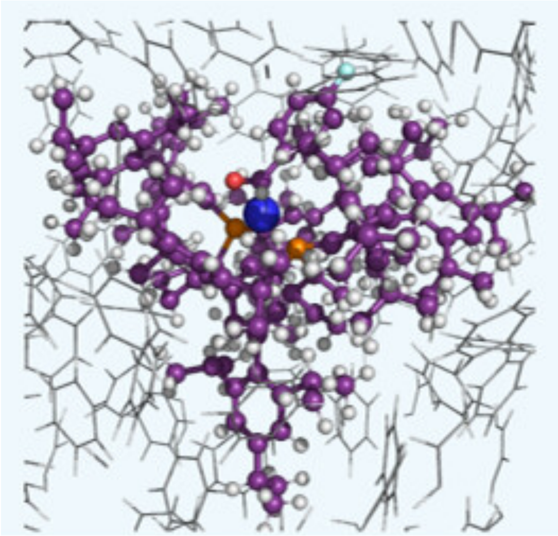
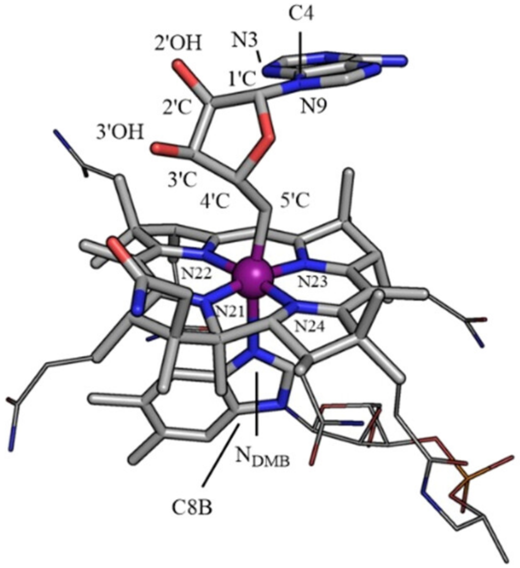
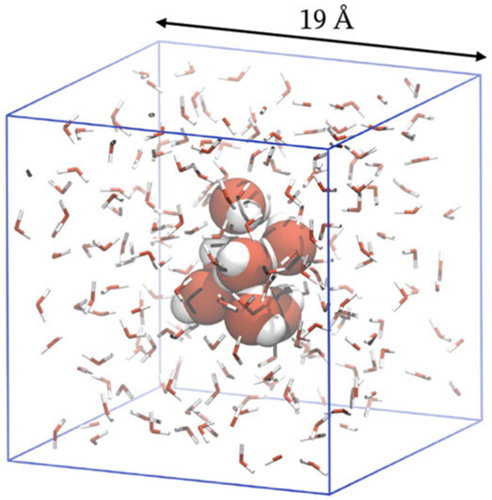
Li, C.; Kin-Lic Chan, G. *J. Chem. Theory Comput.* **2025**, *21*, 803-816.
Broenhof, G. *Methods Mol. Biol.* **2013**, *924*, 43-66.

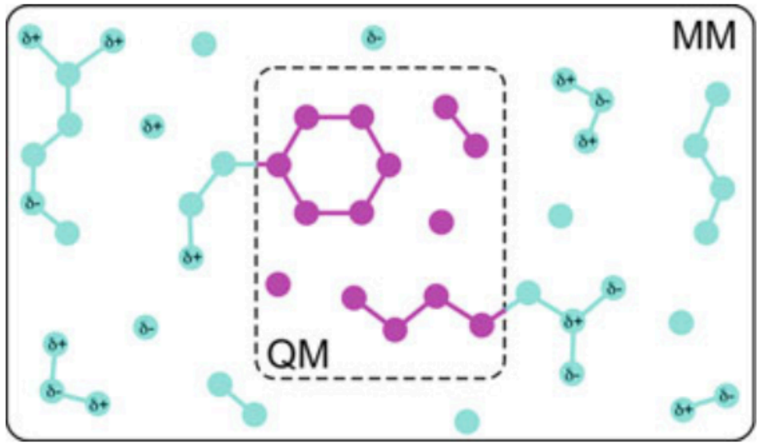
Understanding how molecules act

Quantum Mechanics/Molecular Mechanics Simulations (QM/MM)









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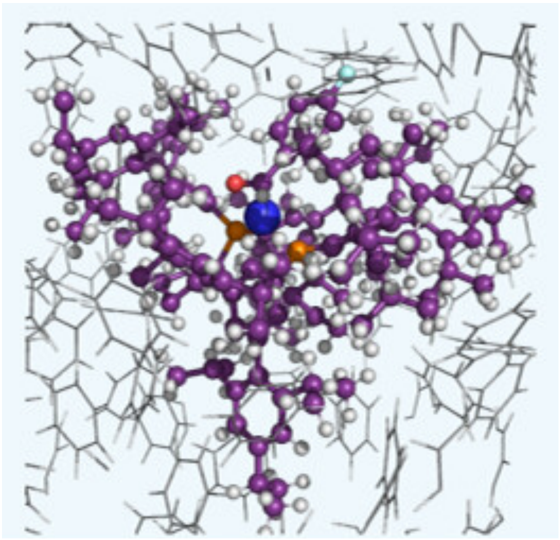

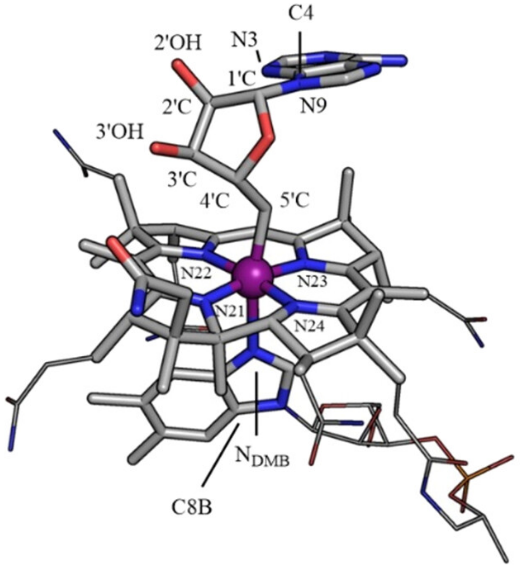

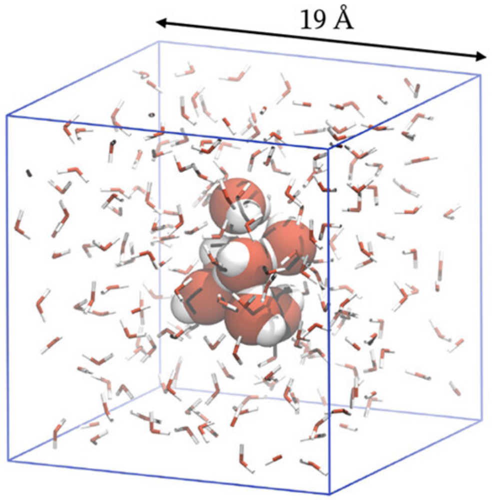

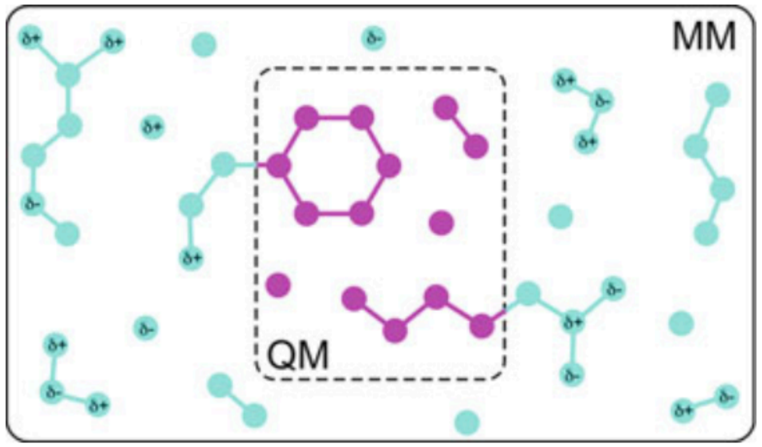

The Nobel Prize in Chemistry 2013

Martin Karplus
Harvard

Michael Levitt
Stanford

Arieh Warshel
USC

"for the development of multiscale models for complex chemical systems"

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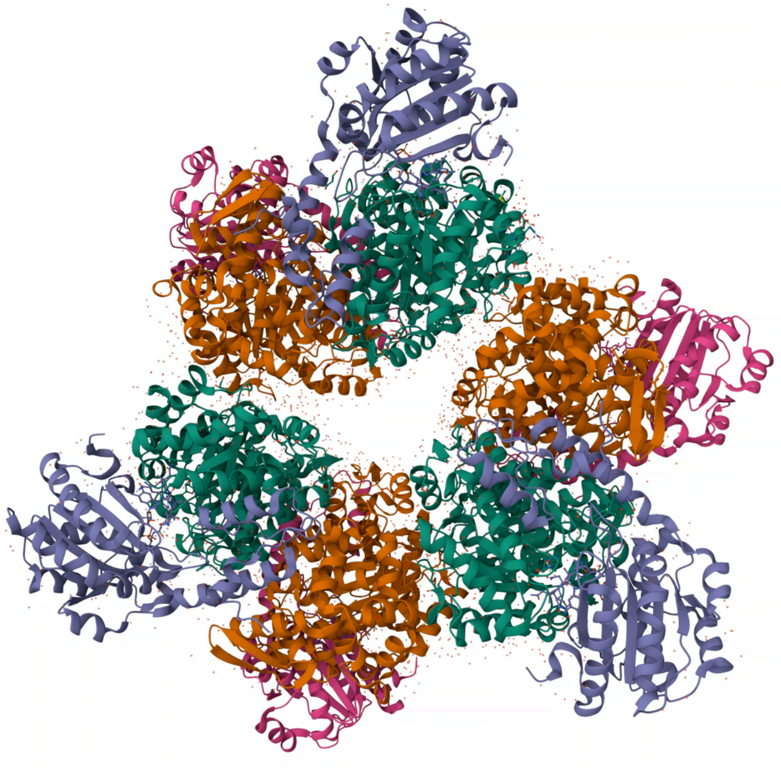
Understanding how molecules act

QM/MM for understanding Co—C bond homolysis in Ethanolamine Ammonia-Lyase



AdoCbl/EAL
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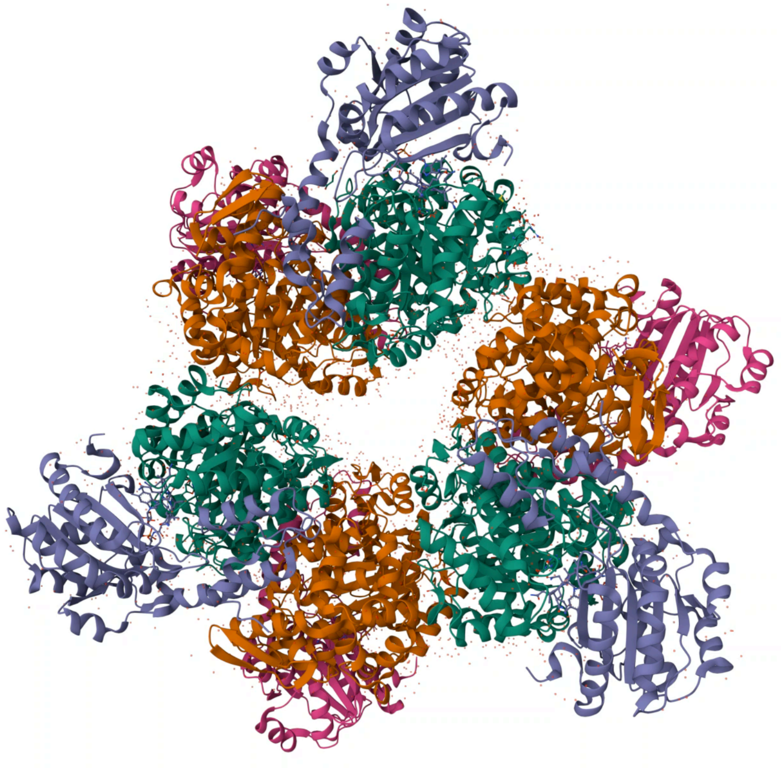

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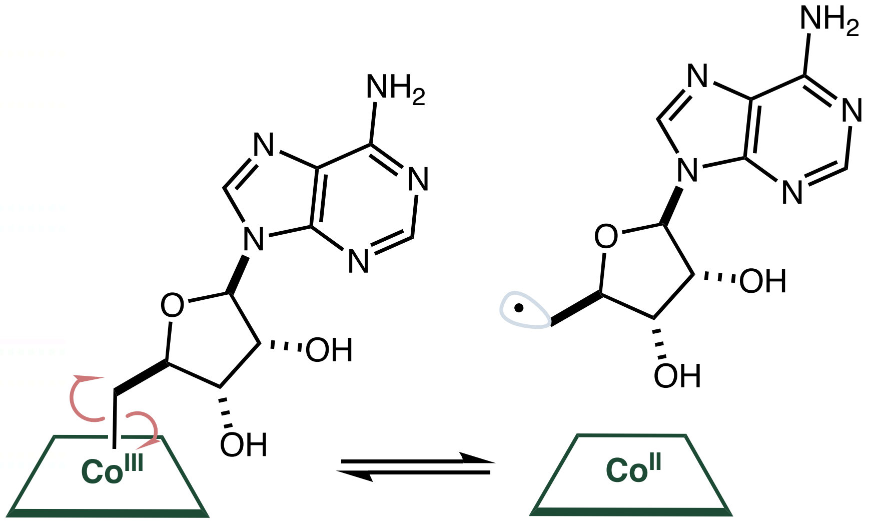

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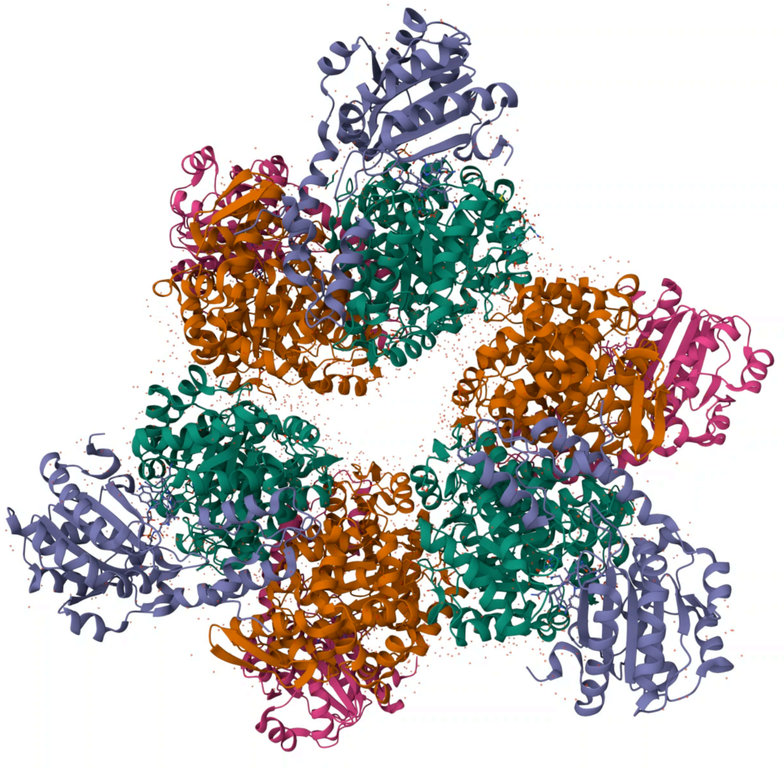

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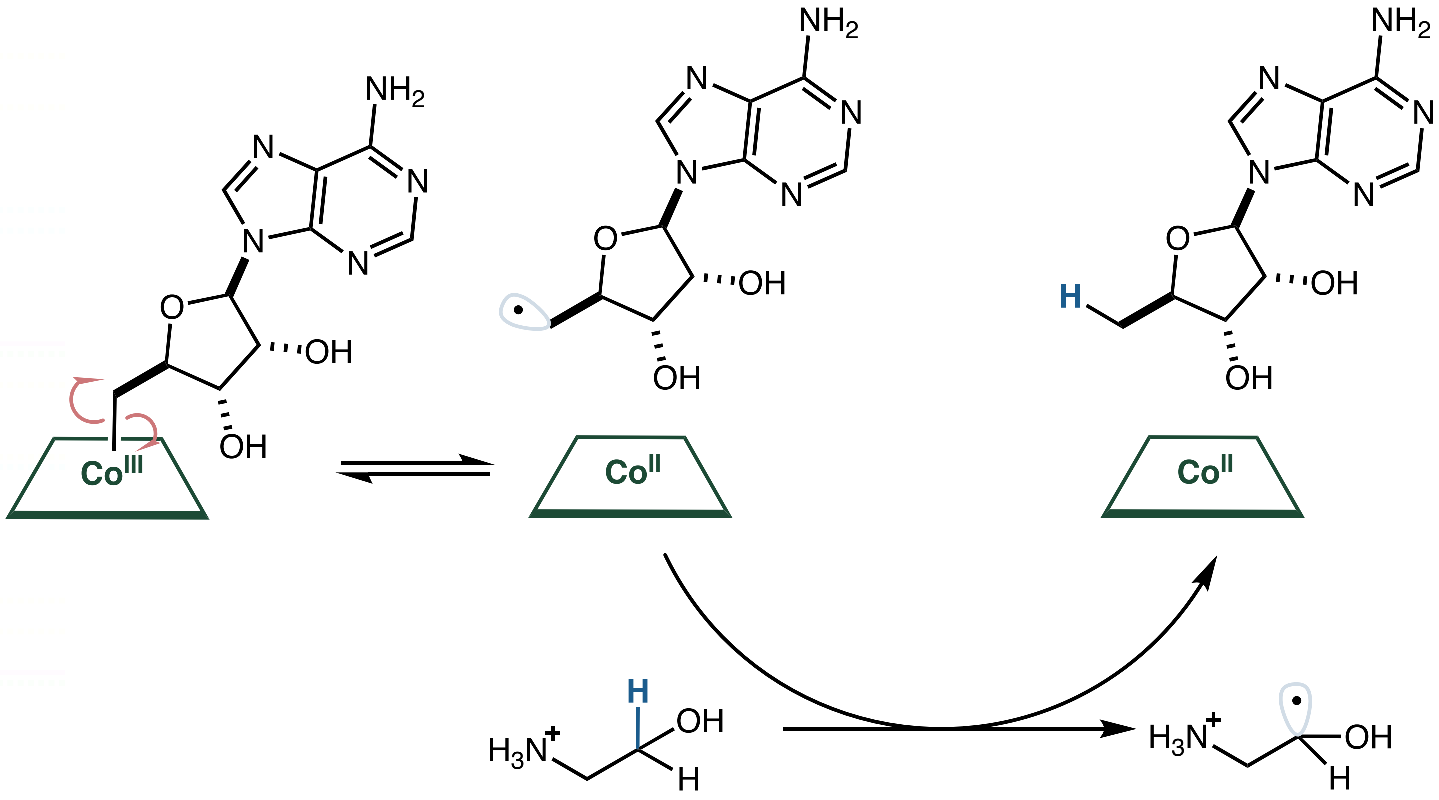

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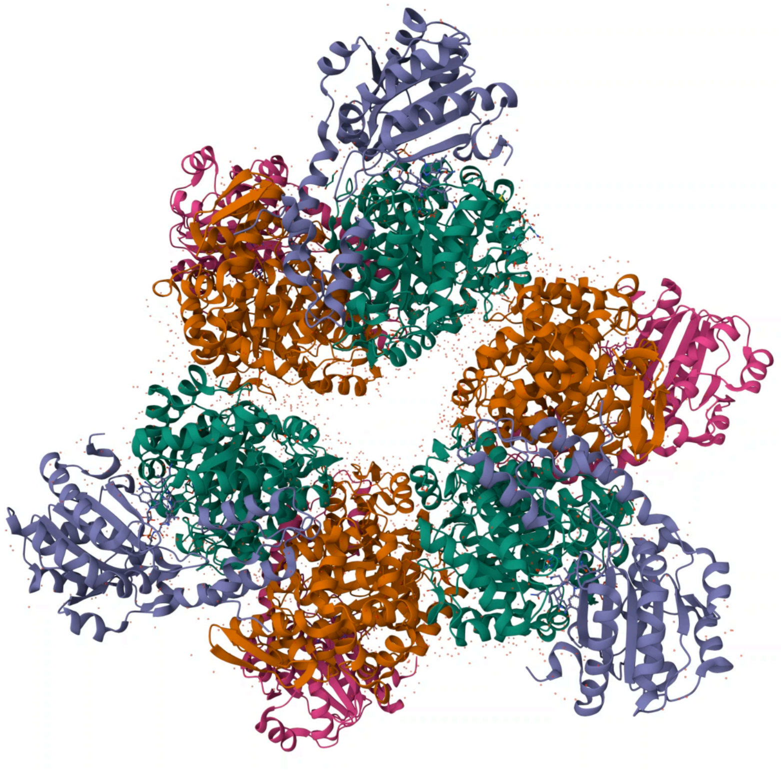

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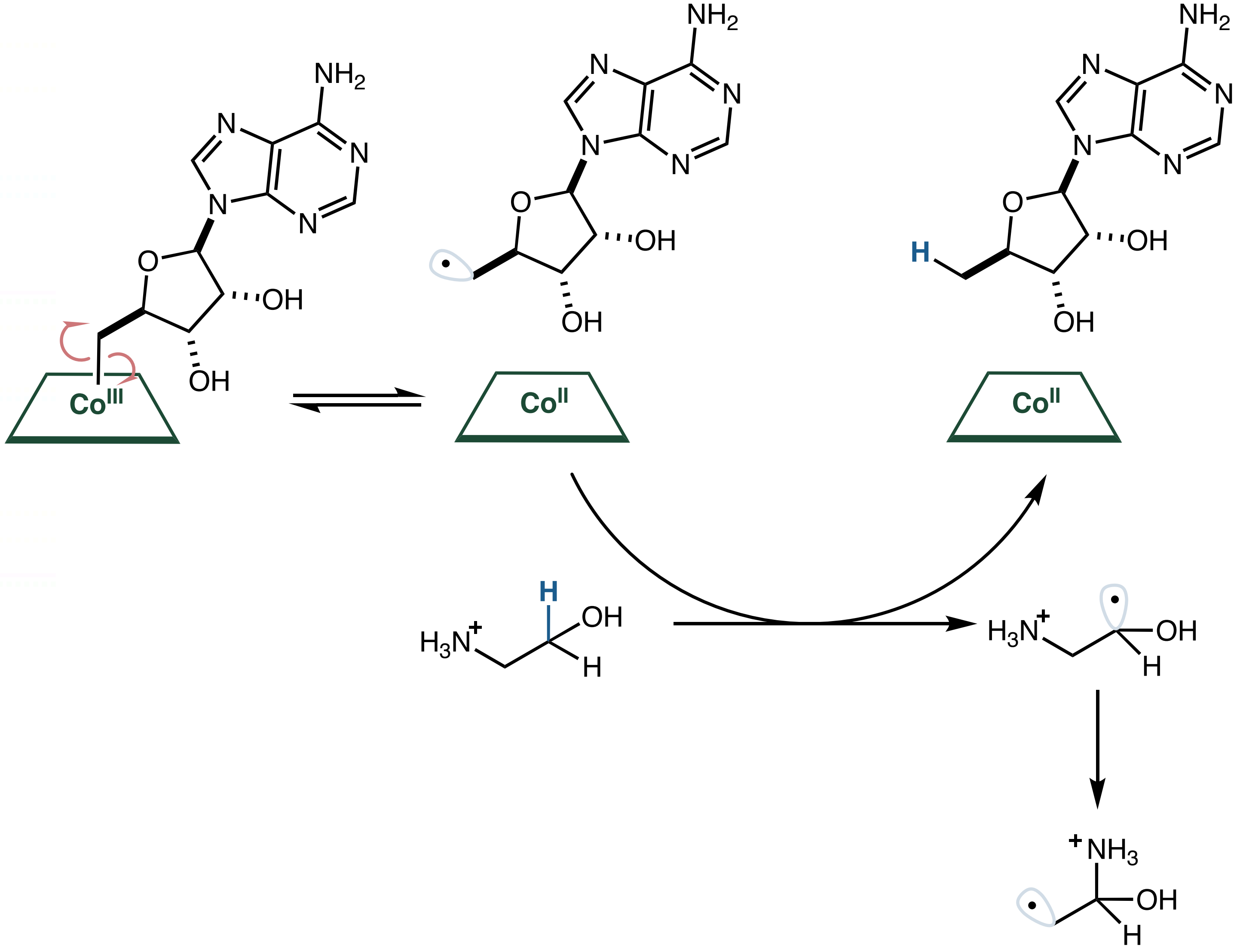

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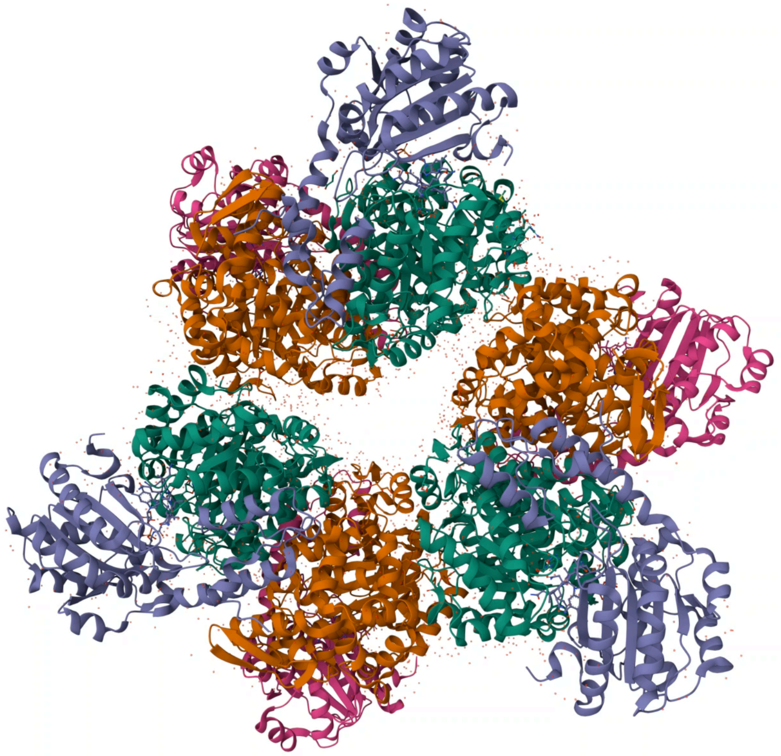

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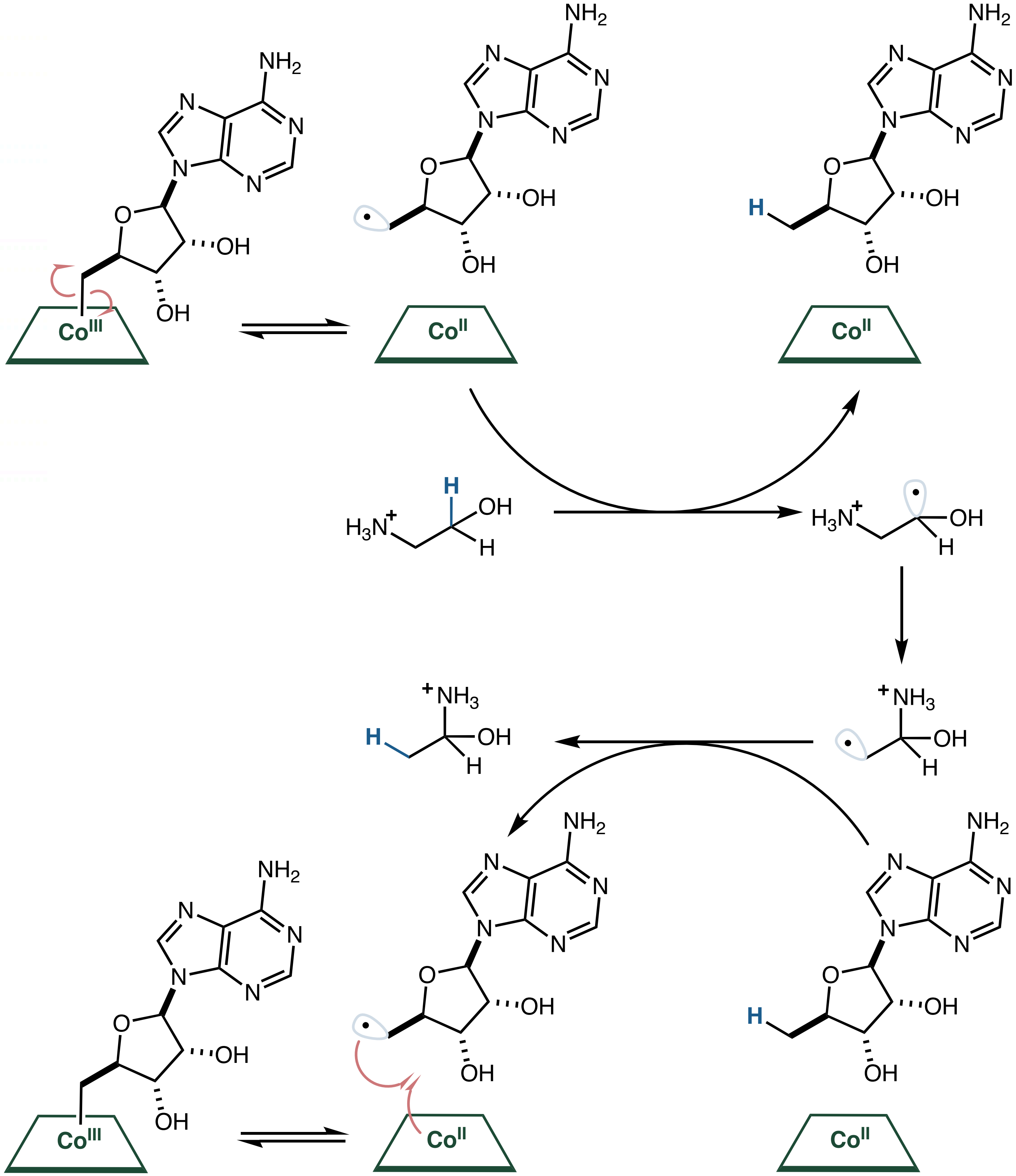

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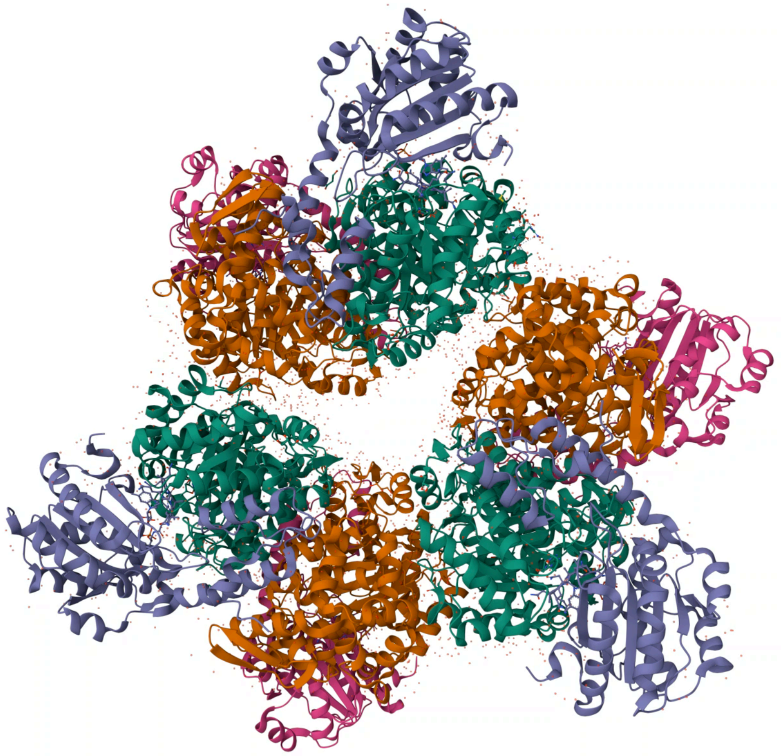

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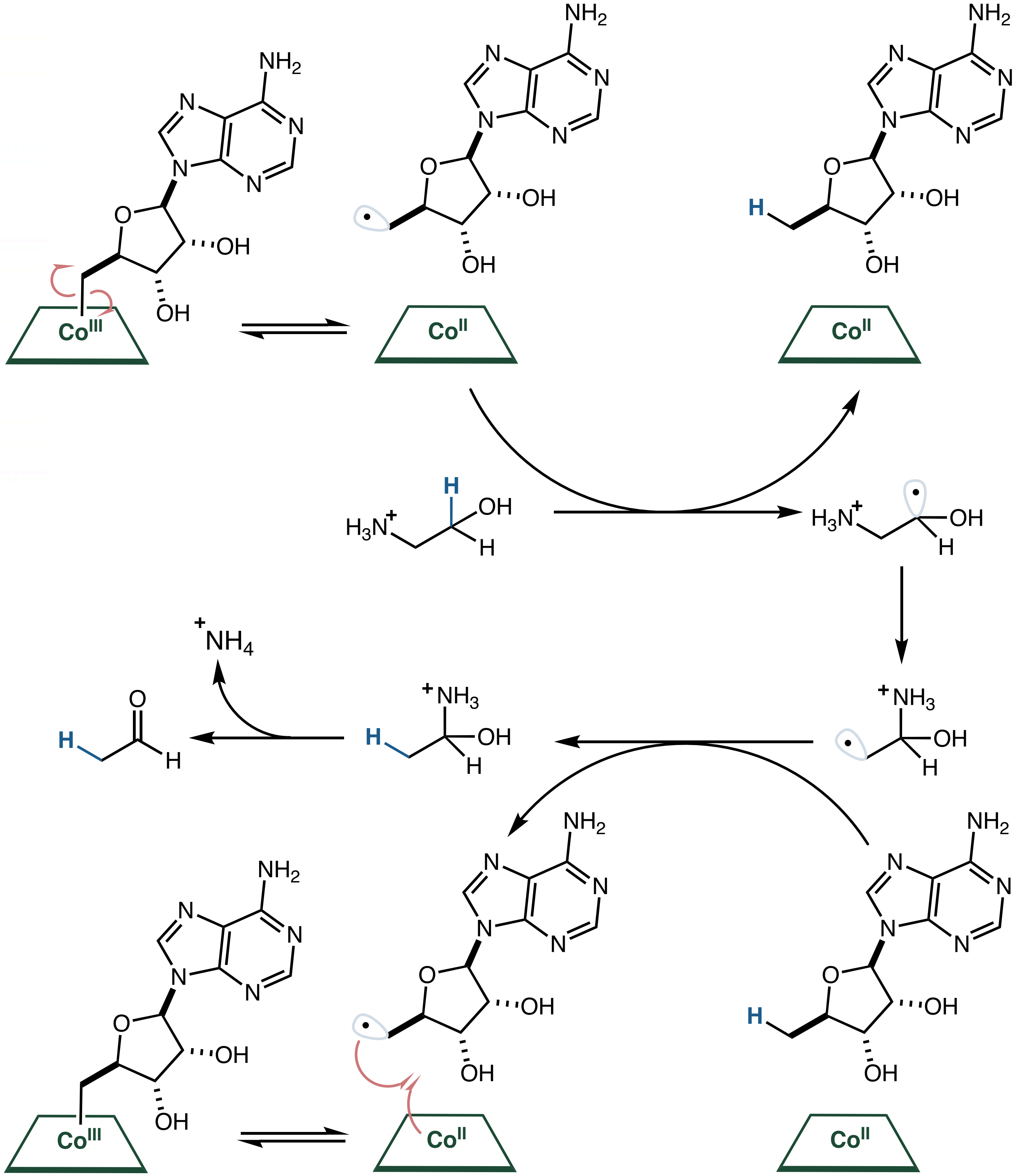

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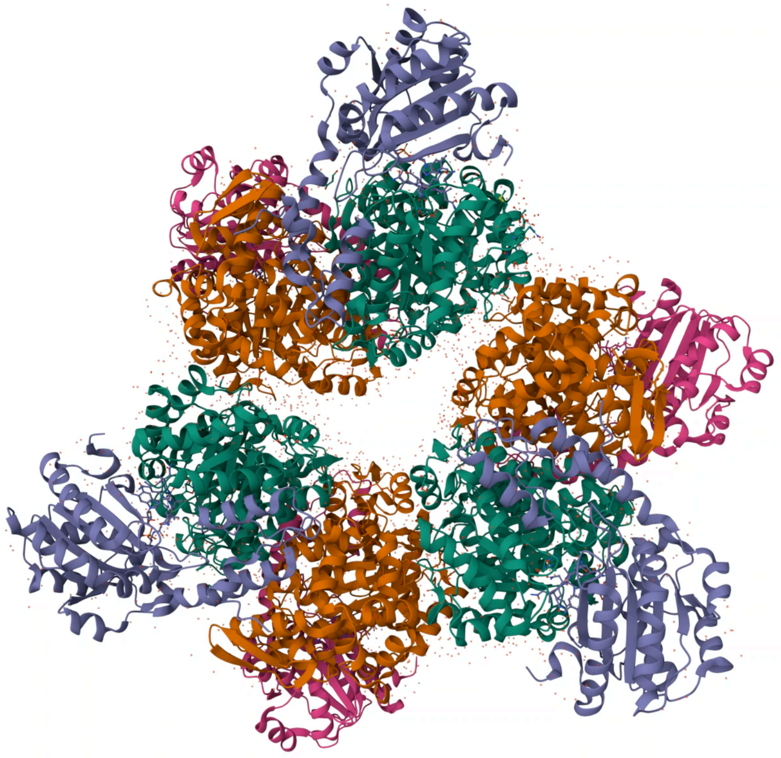

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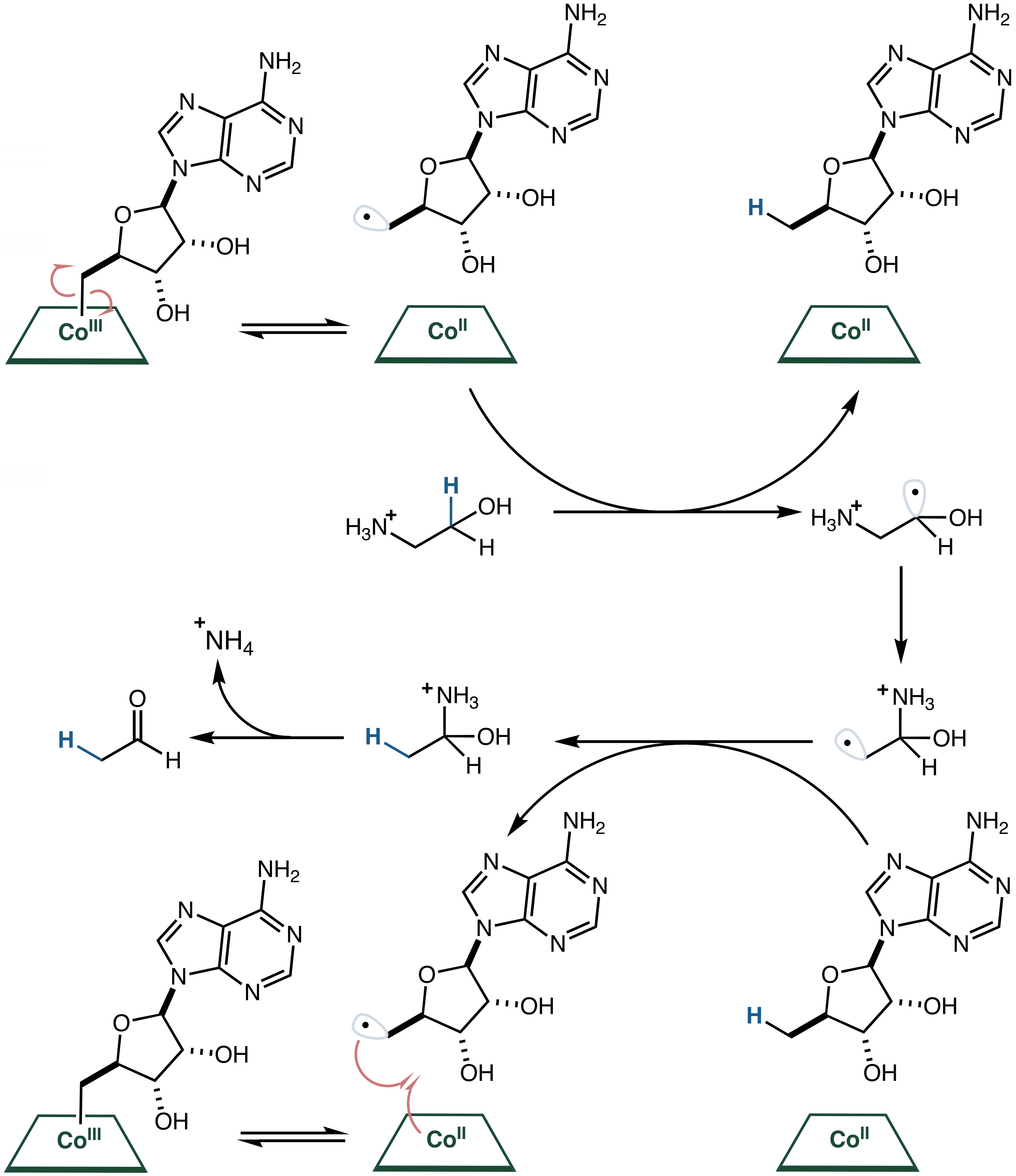

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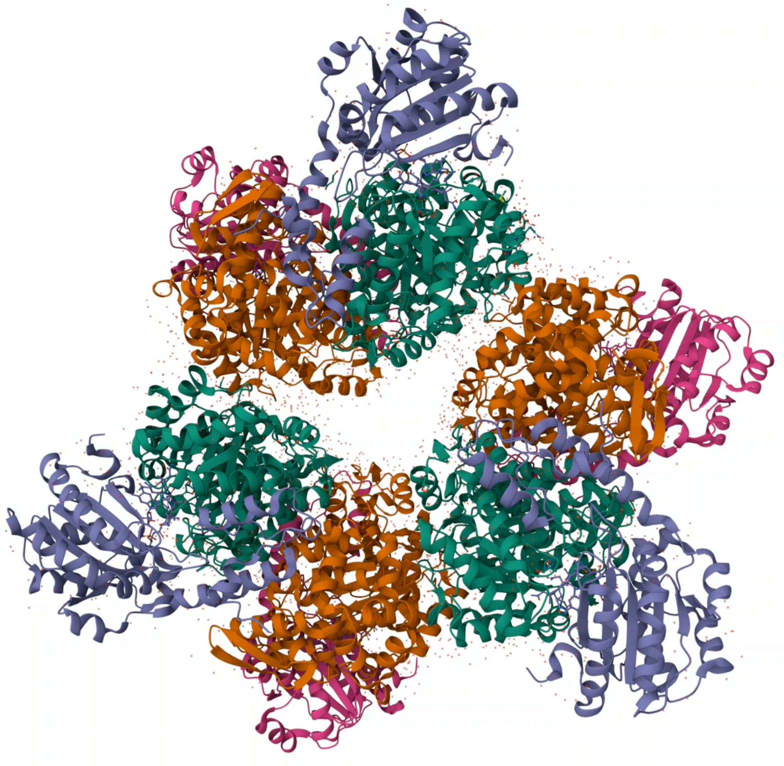

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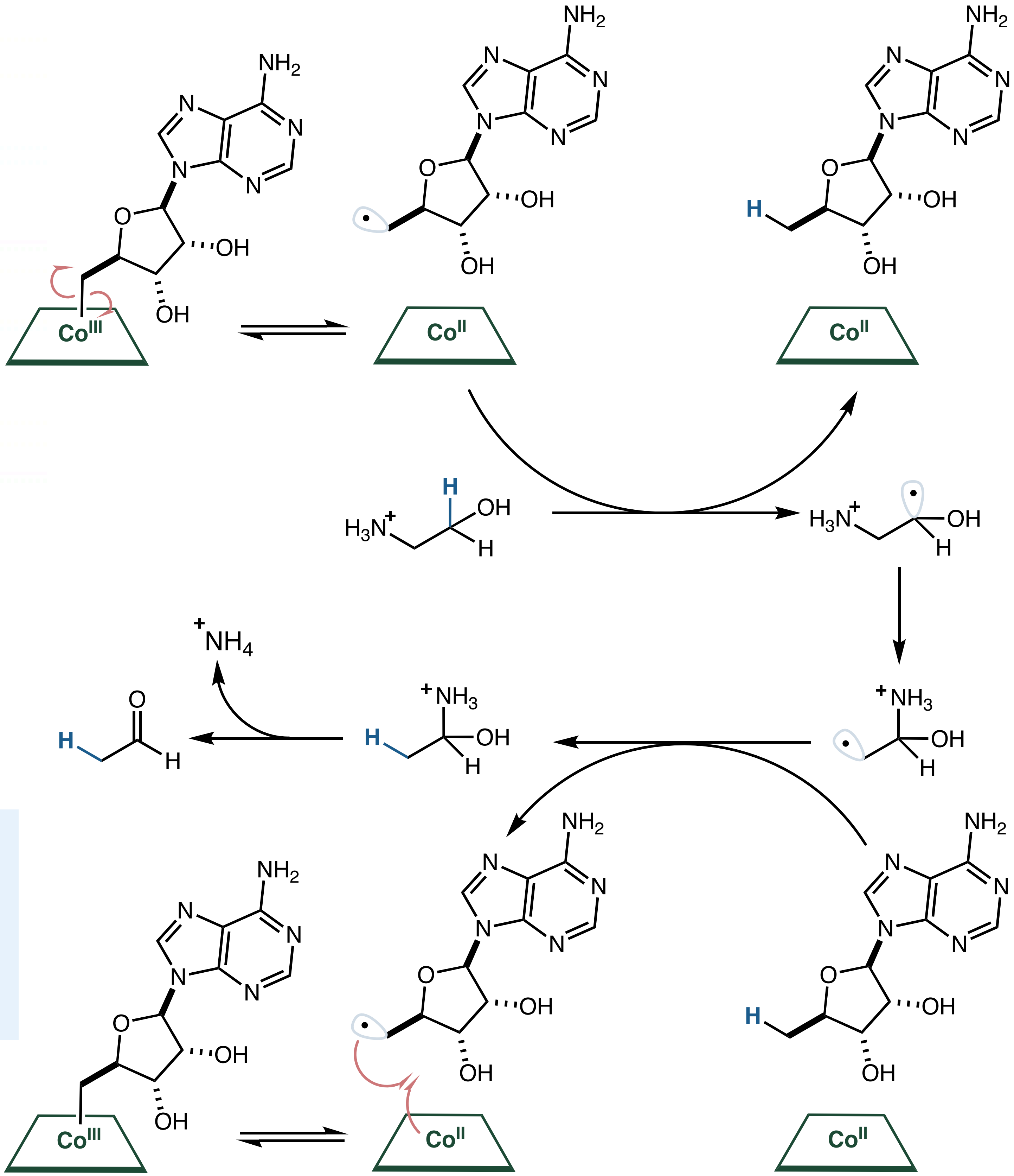

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Understanding how molecules act

Confirming QM/MM methodology

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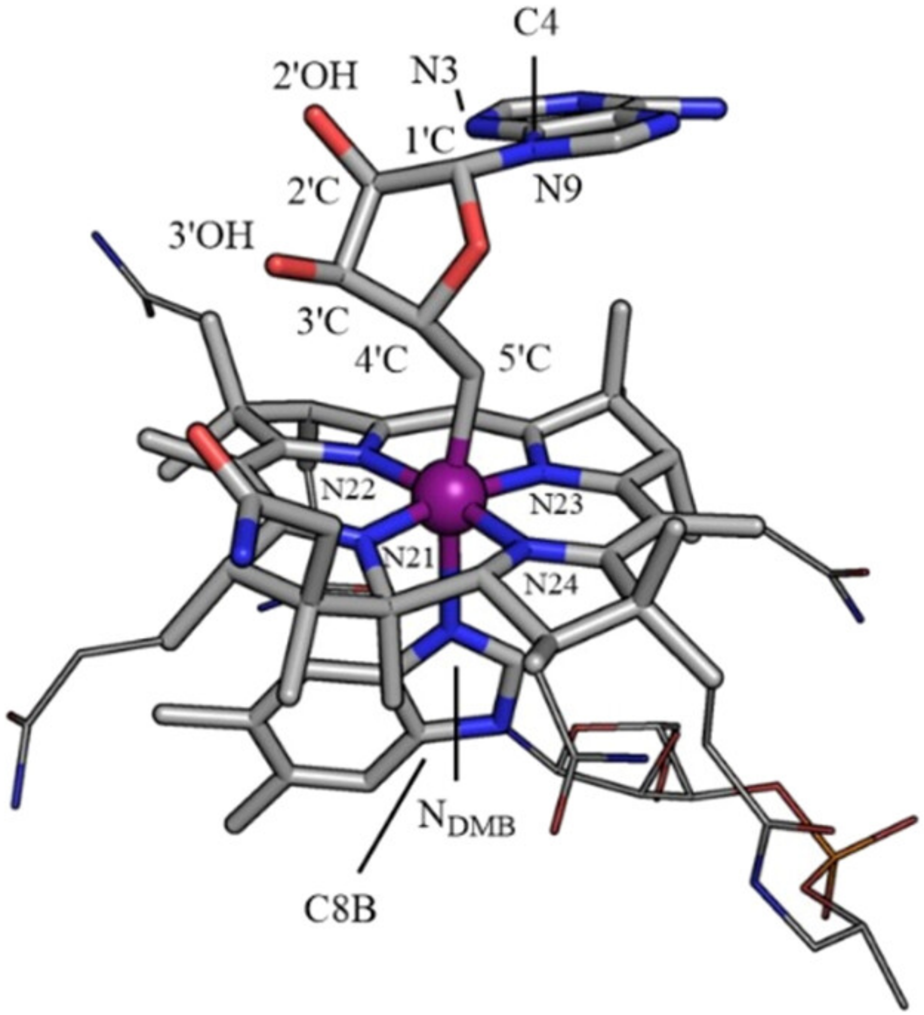

AdoCbl

(QM region shown as thick stick,
MM region shown as thin sticks)

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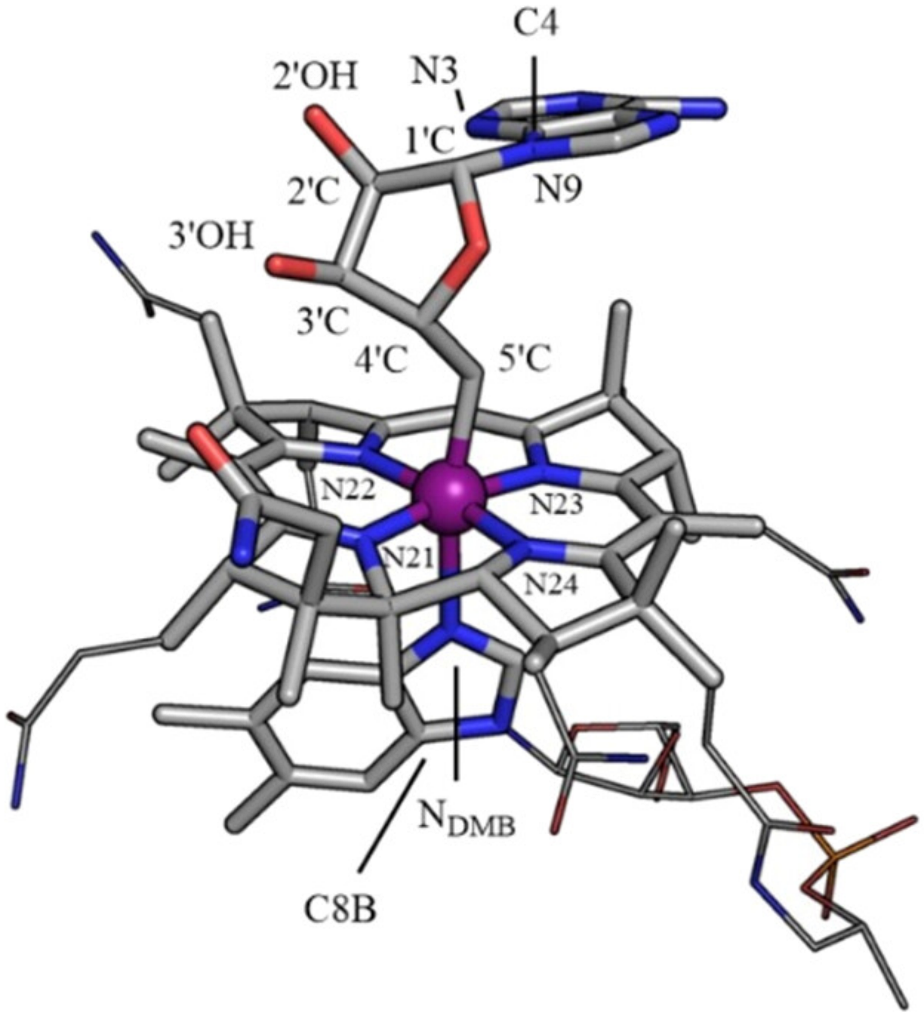

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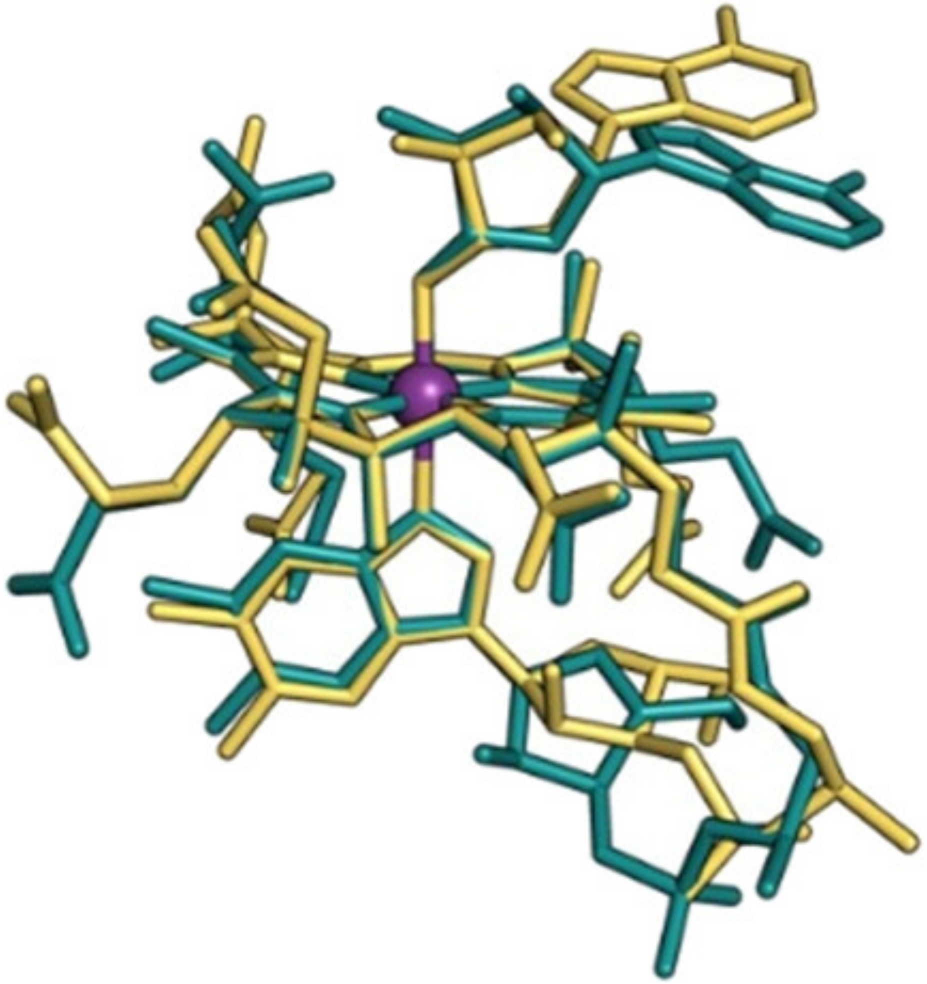

AdoCbl crystal structure (yellow)
vs. Solvated AdoCbl (green)

Elmendorf, L. D.; Hall, R. L.; Costa, F. G.; Escalante-Semerena, J. C.; Brunold, T. C. *J. Am. Chem. Soc.* **2025**, *147*, 2380-2392.

Understanding how molecules act

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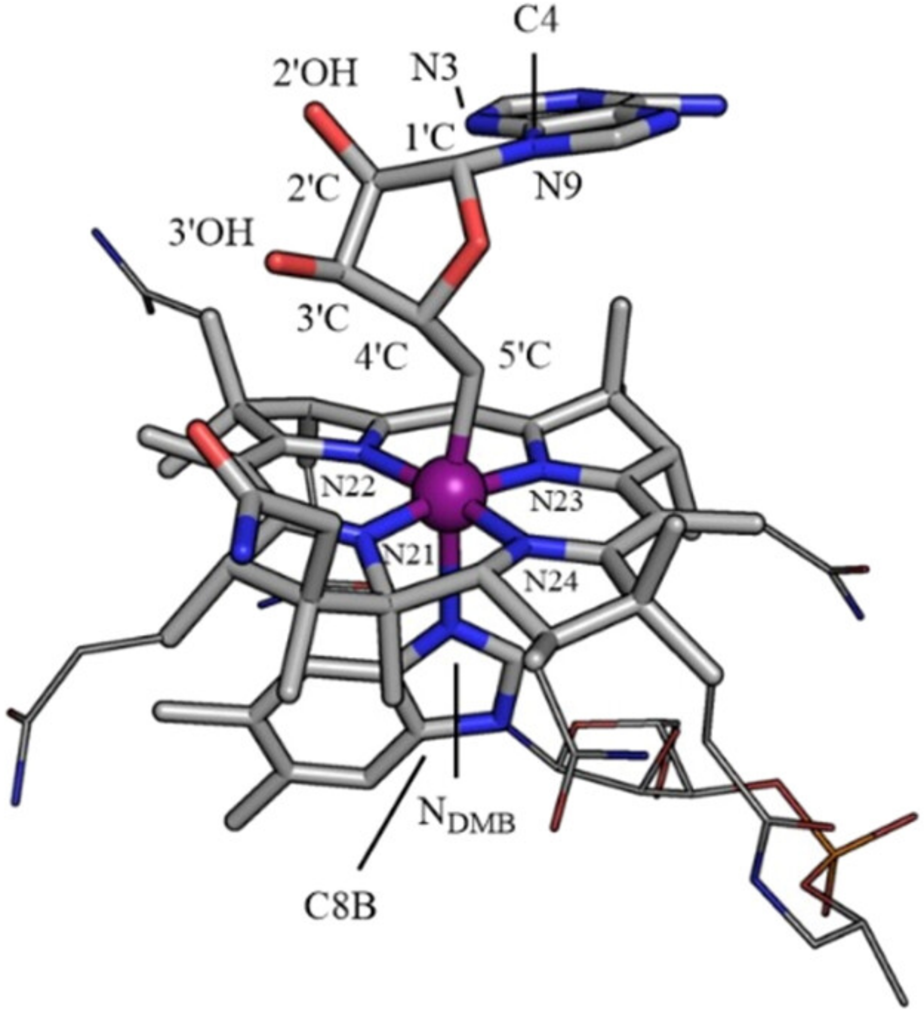

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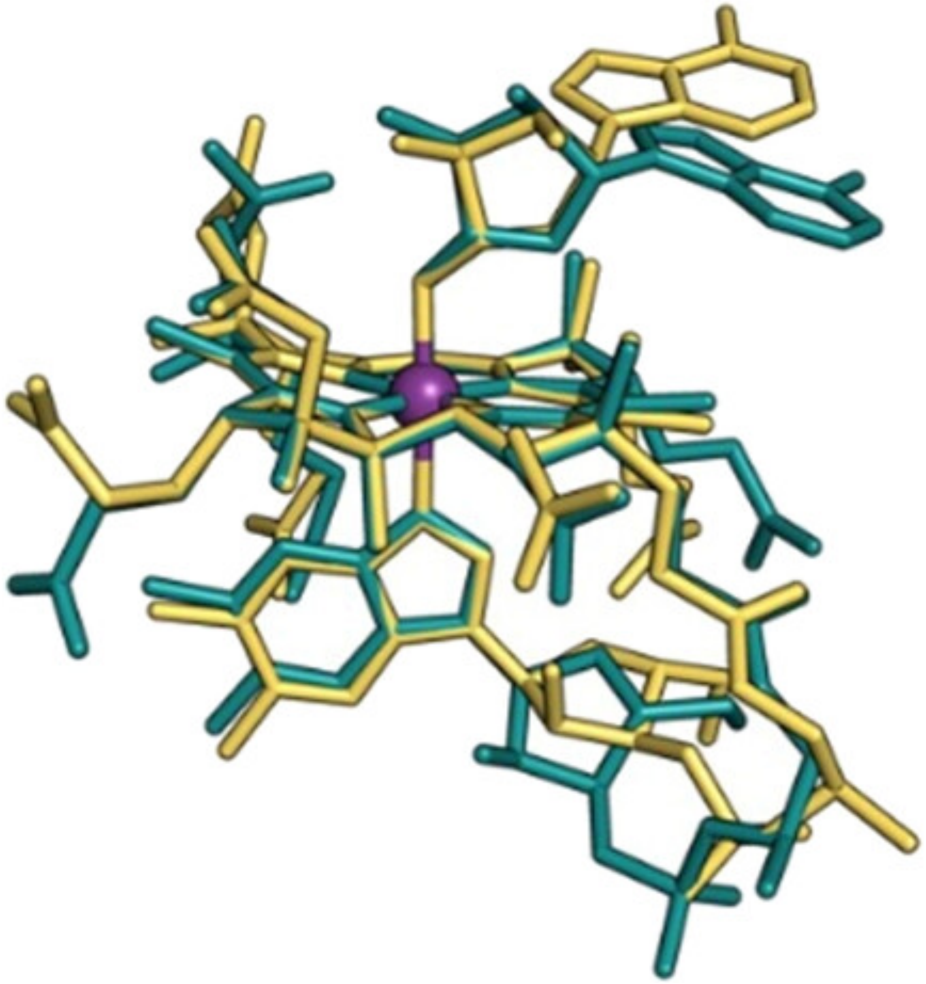

AdoCbl crystal structure (yellow) vs. Solvated AdoCbl (green)

Good agreement between crystal structure and solvated QM/MM structure

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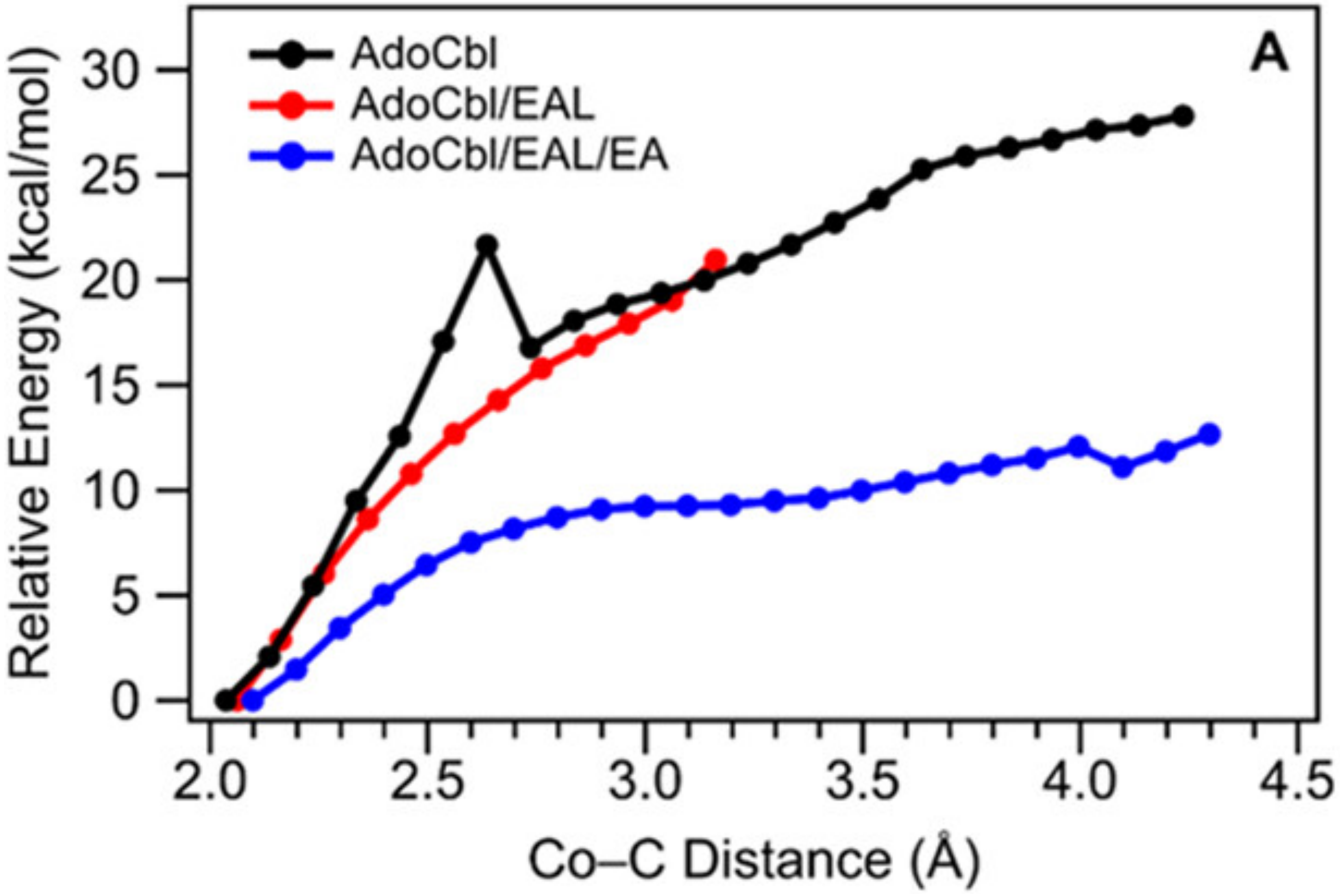
Understanding how molecules act

Scanning Co—C bond length for different complexes



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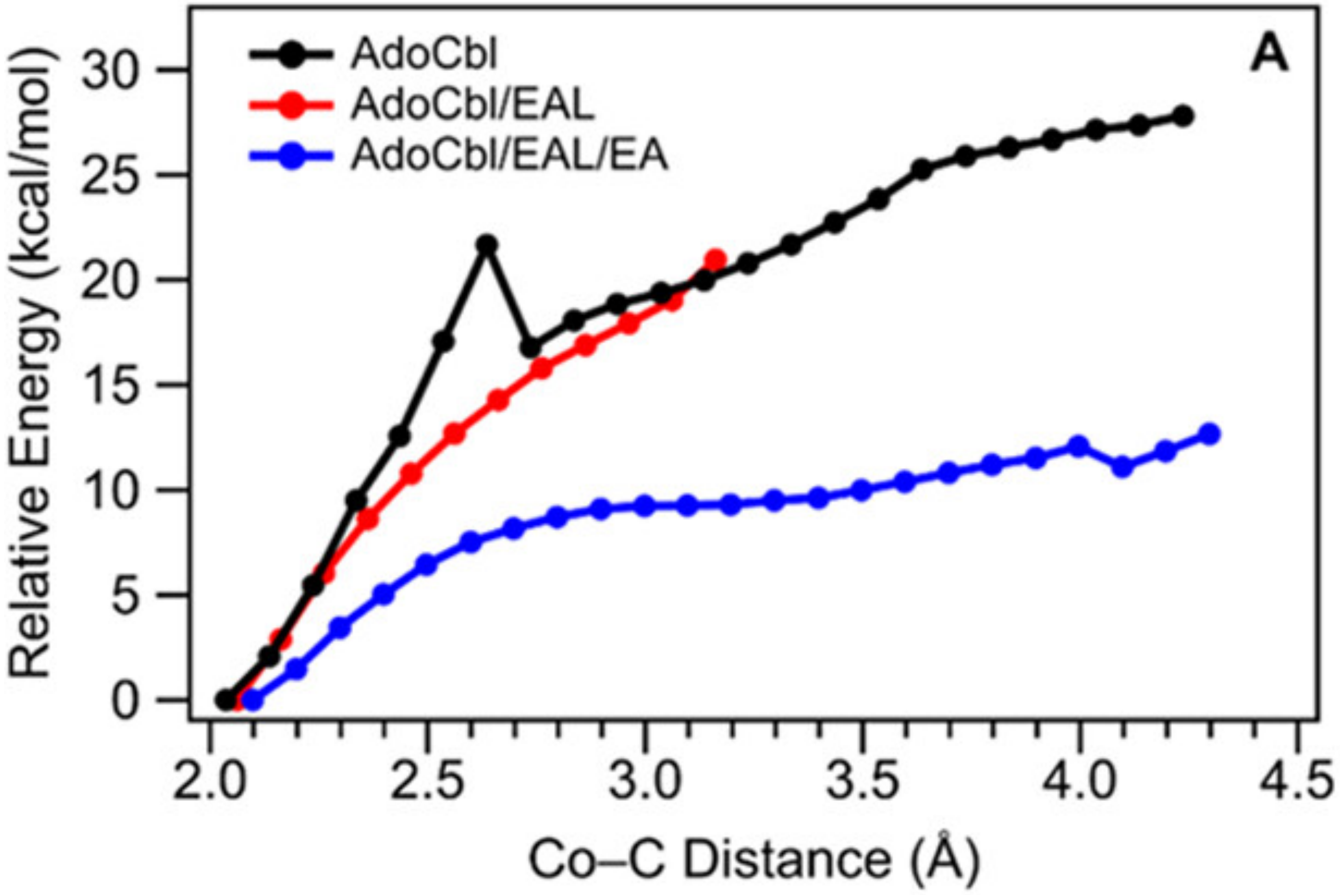

Significant decrease in energy of Co—C bond elongation with substrate present

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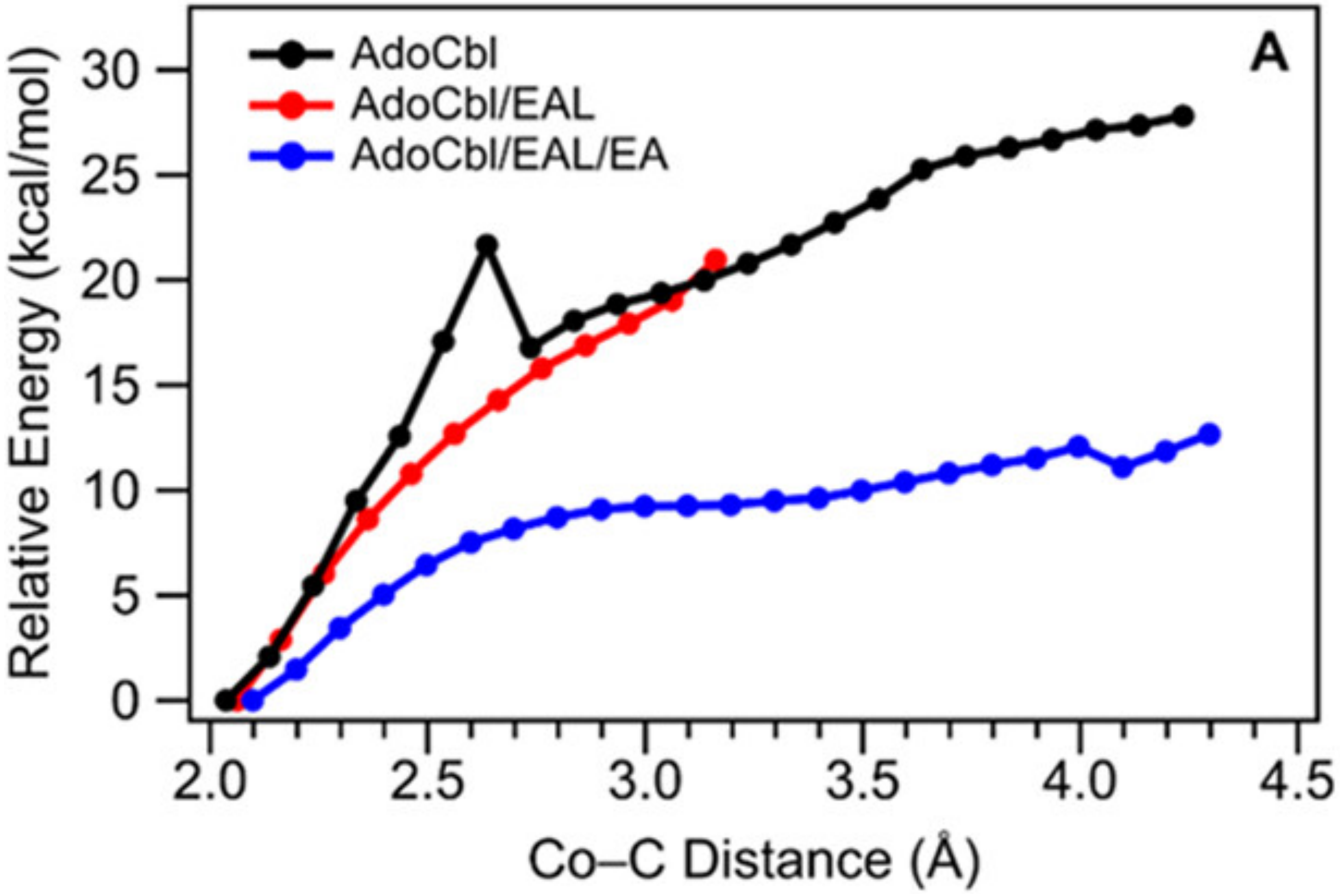

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Energy decrease is only seen with substrate present

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Understanding how molecules act

Substrate-induced active site changes

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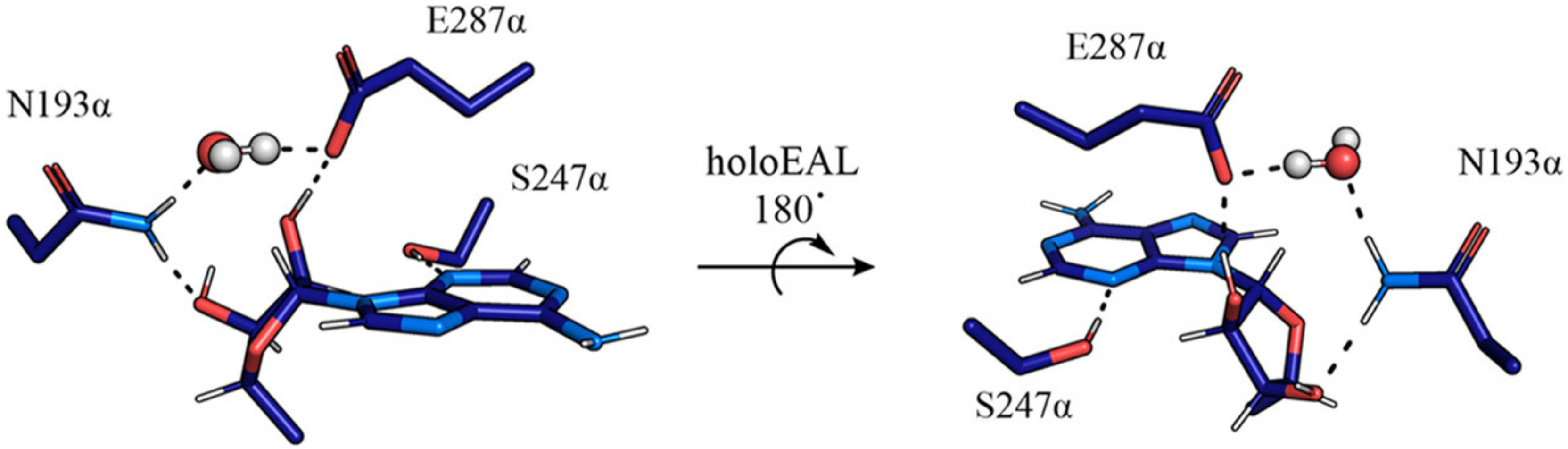

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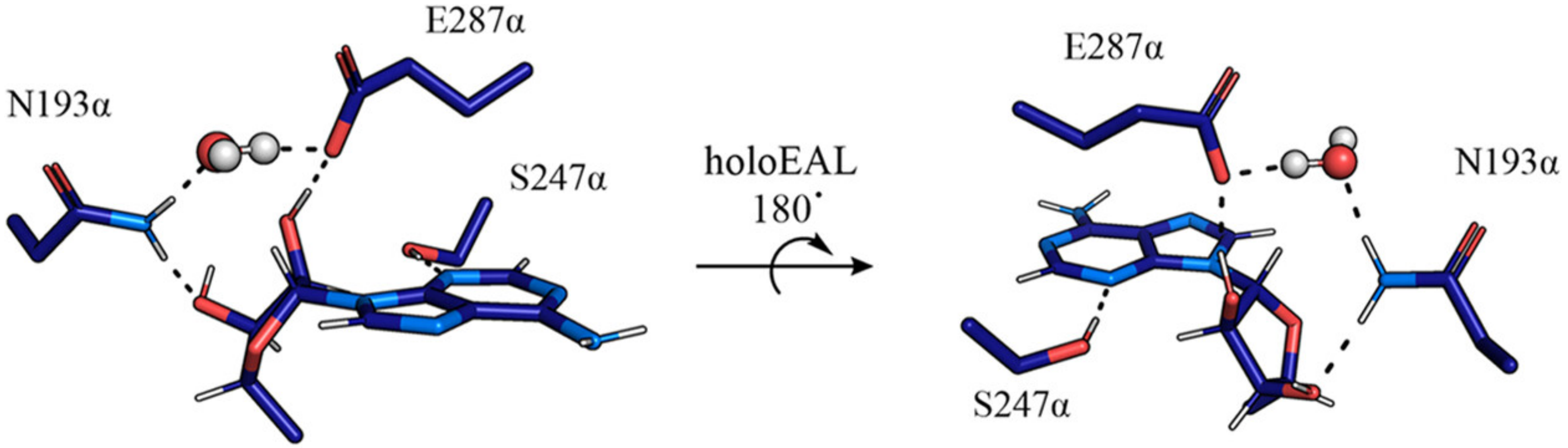

Without substrate

Three hydrogen-bonding interactions between active site residues —prevents Ado· from rotating freely

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Understanding how molecules act

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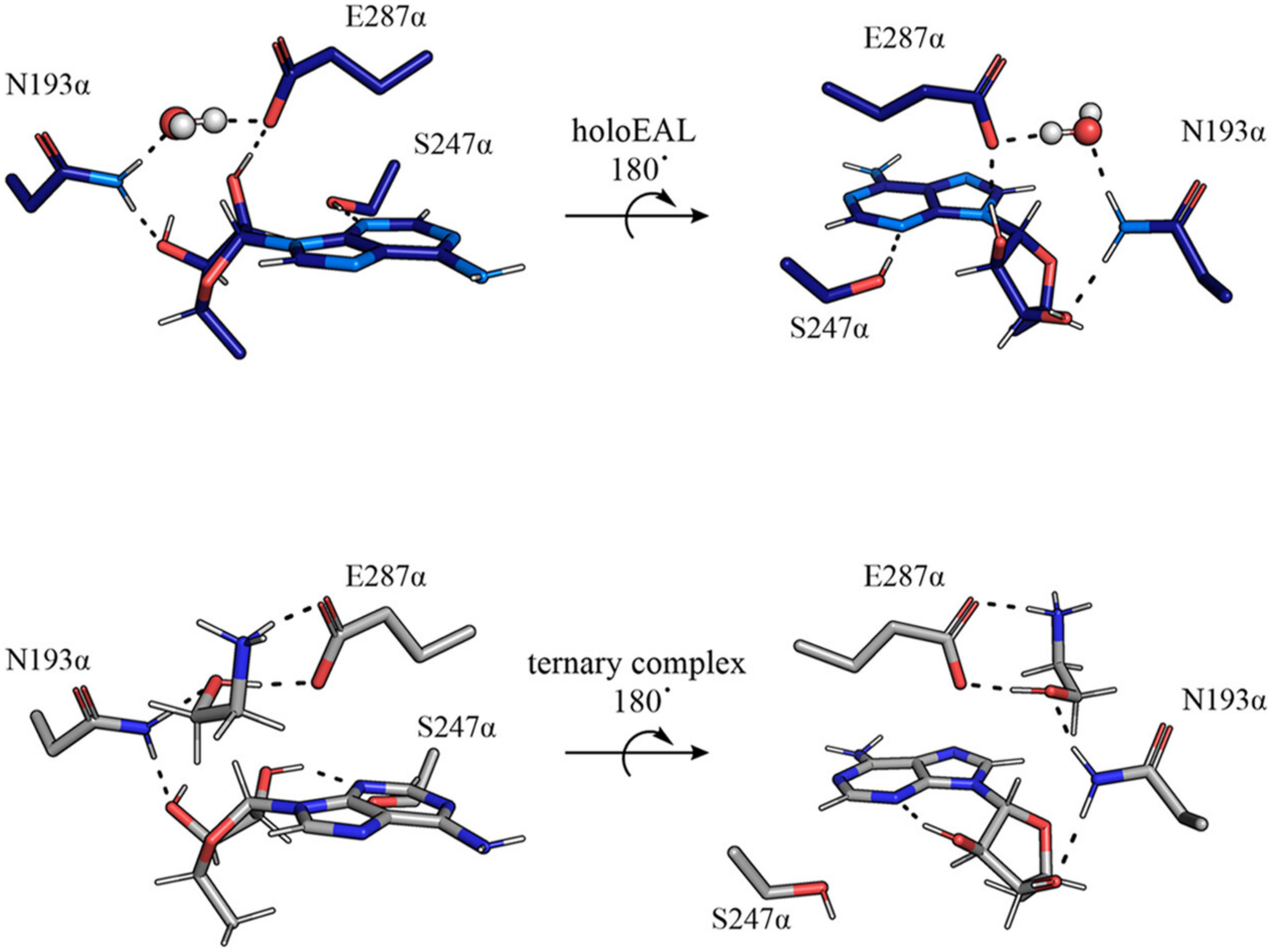

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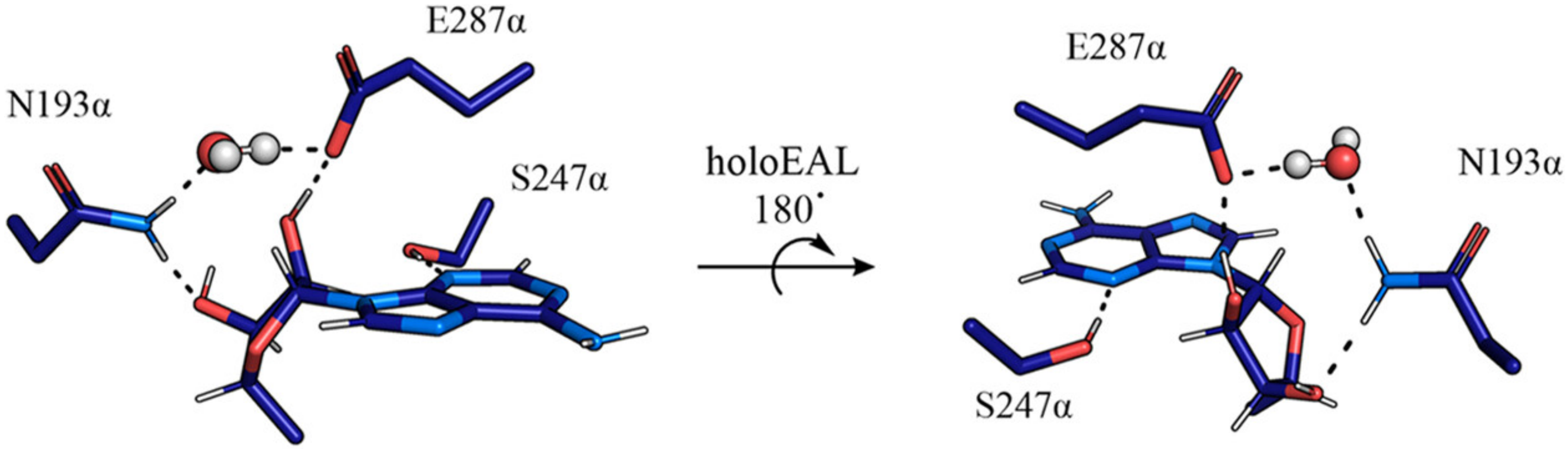

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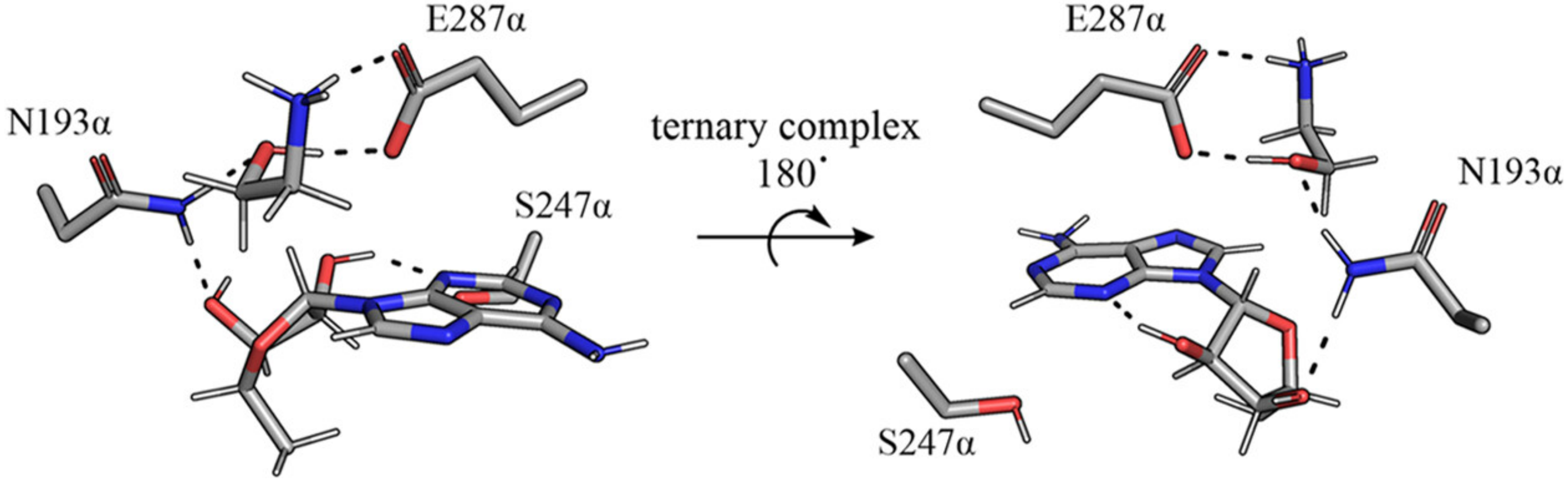

With substrate:

Only one hydrogen-bonding interaction between active site residues — frees Ado· up to rotate

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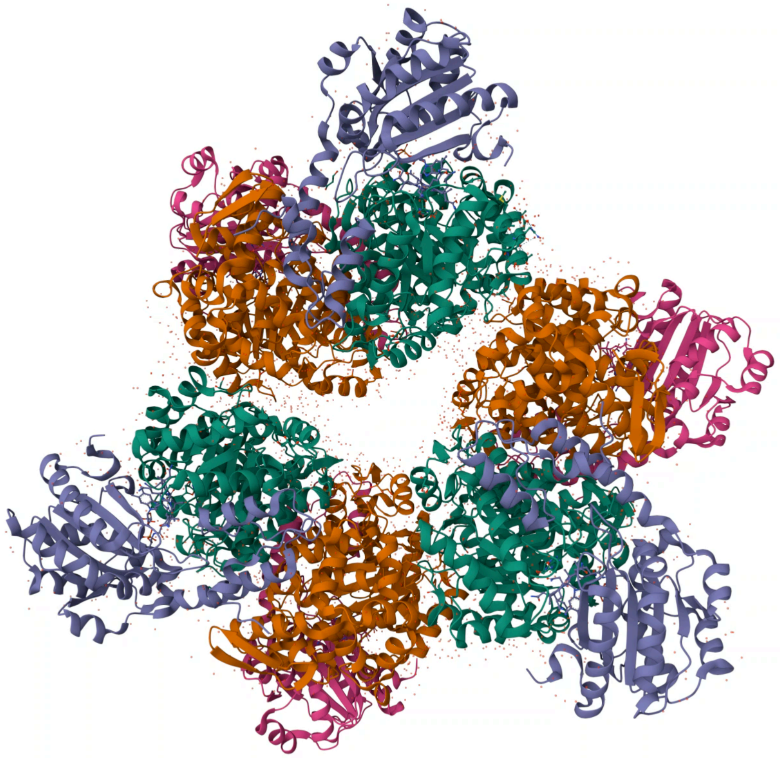
Understanding how molecules act

QM/MM for understanding Co-C bond homolysis in Ethanolamine Ammonia-Lyase



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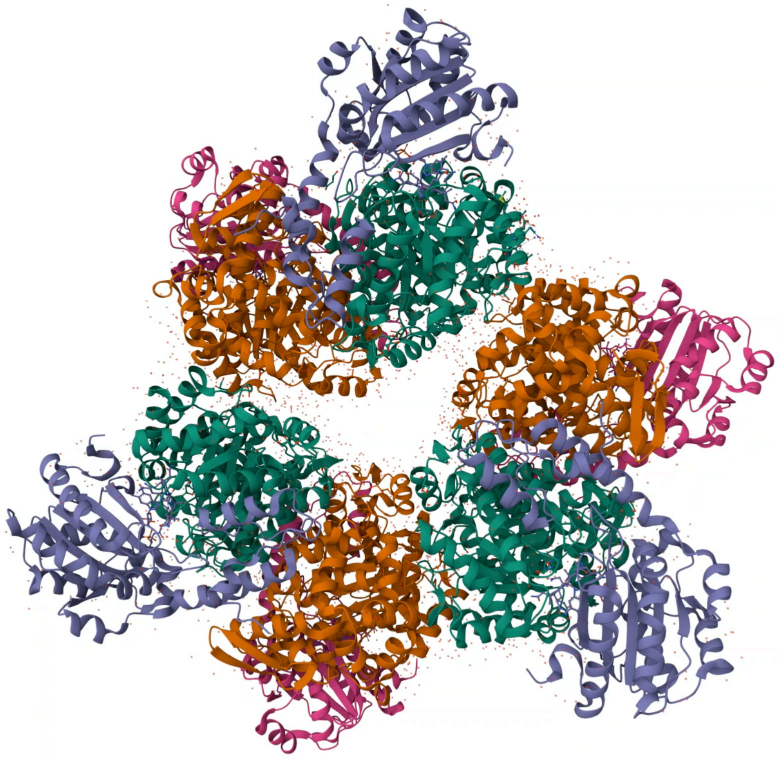

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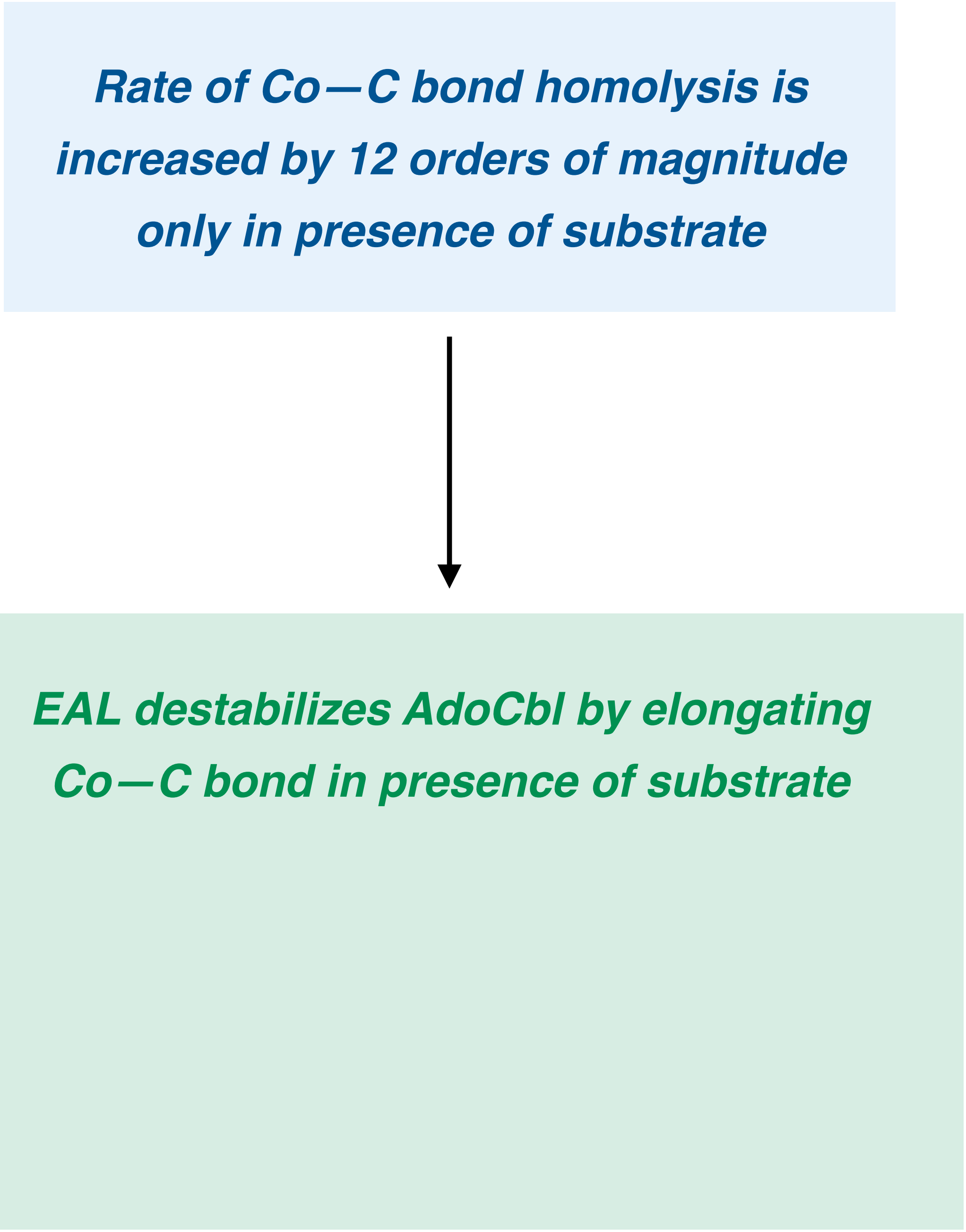

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EAL destabilizes AdoCbl by elongating Co—C bond in presence of substrate

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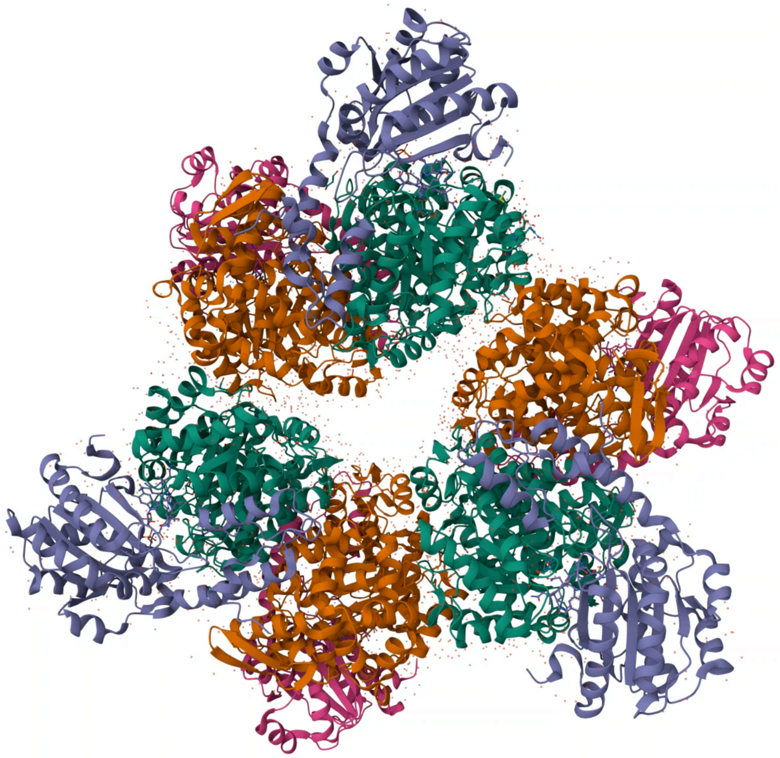

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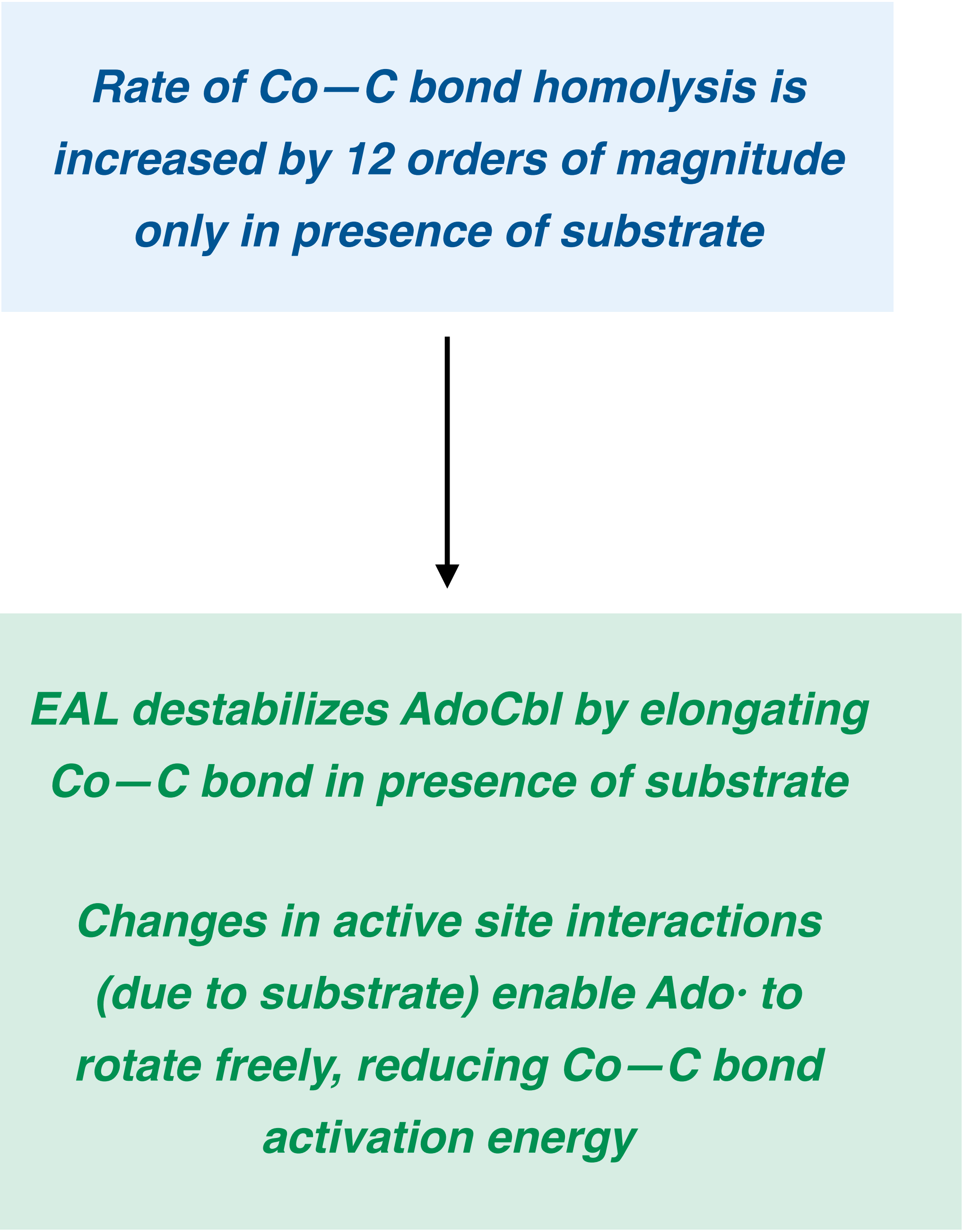

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EAL destabilizes AdoCbl by elongating Co—C bond in presence of substrate

Changes in active site interactions (due to substrate) enable Ado· to rotate freely, reducing Co—C bond activation energy

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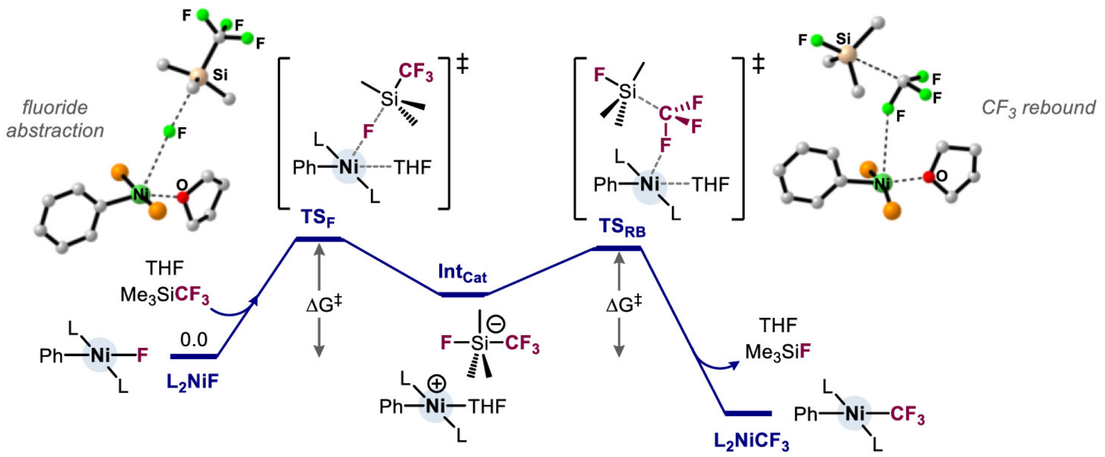
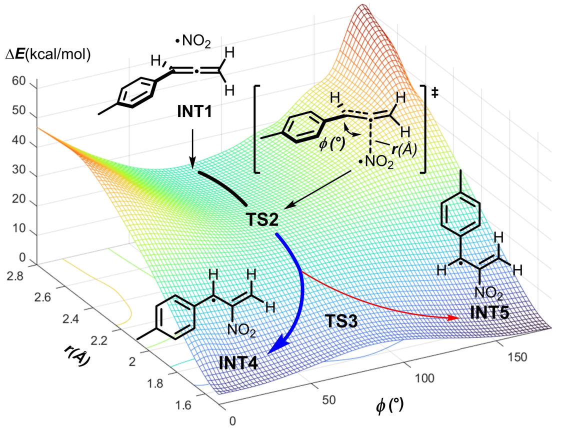
What can computational chemistry do for you?

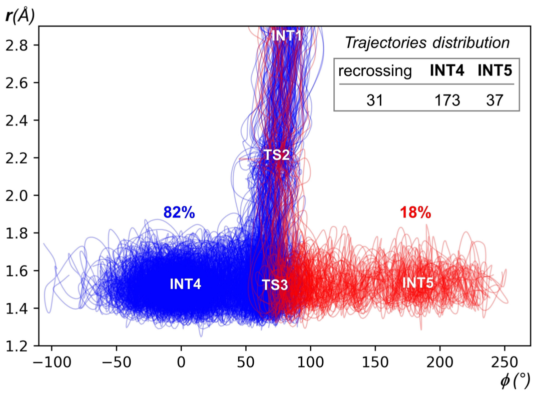
Understanding how molecules act

Density functional theory



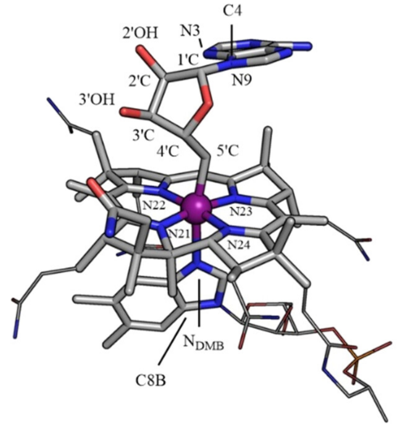
Dynamics Simulations

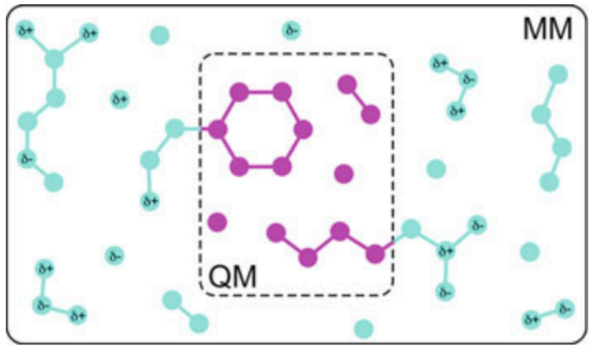




recrossing	INT4	INT5
31	173	37

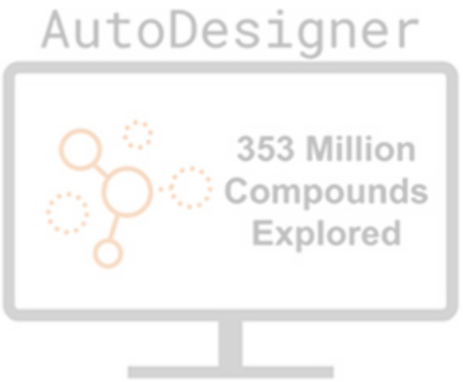
QM/MM

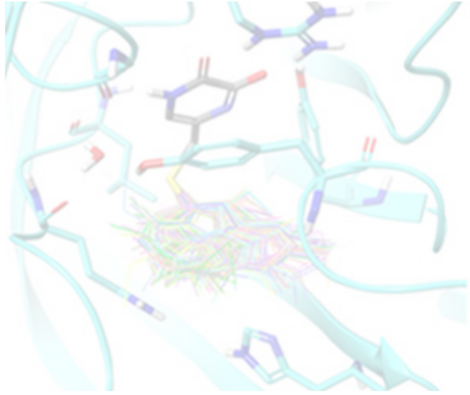




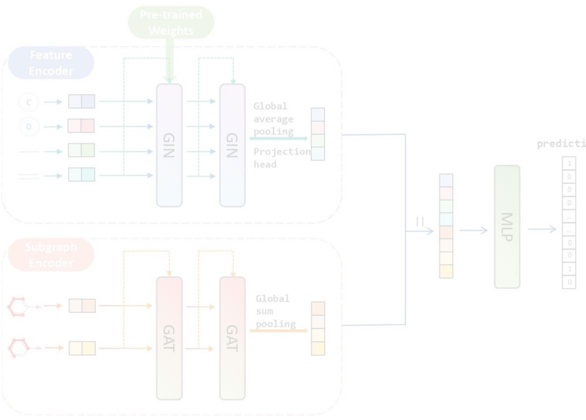
Predicting how molecules should act

Machine learning

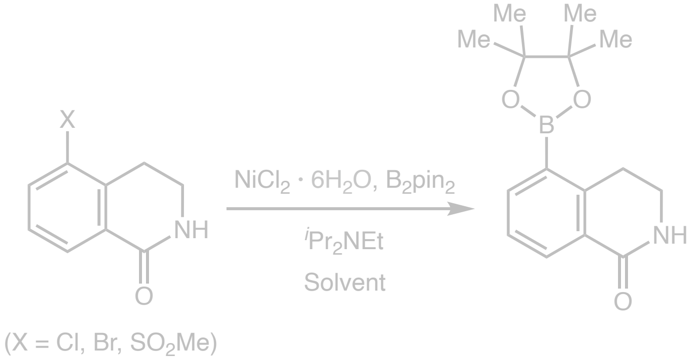


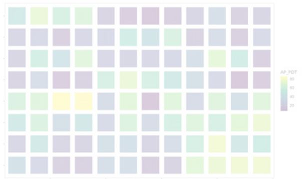


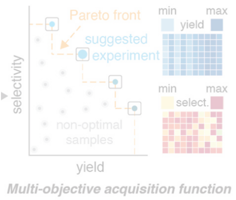
Neural networks



Data Science





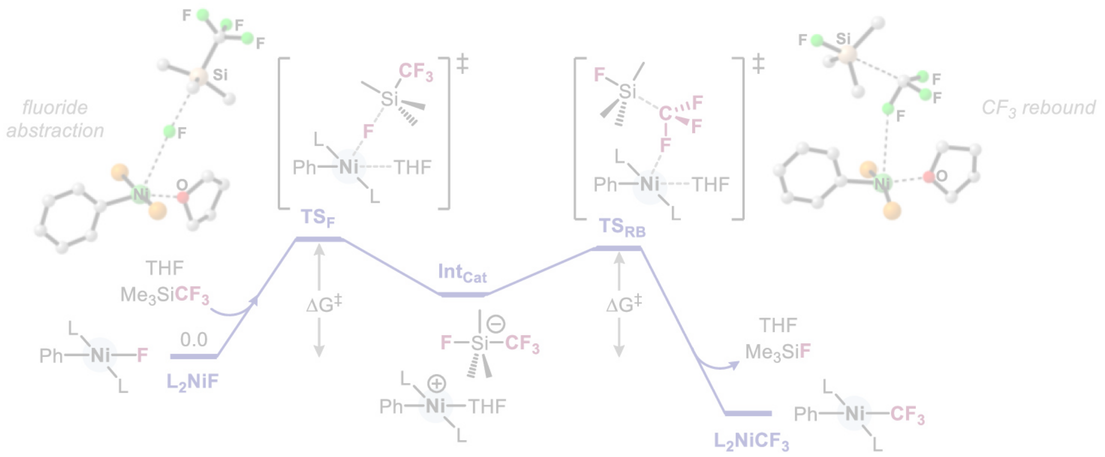


Multi-objective acquisition function

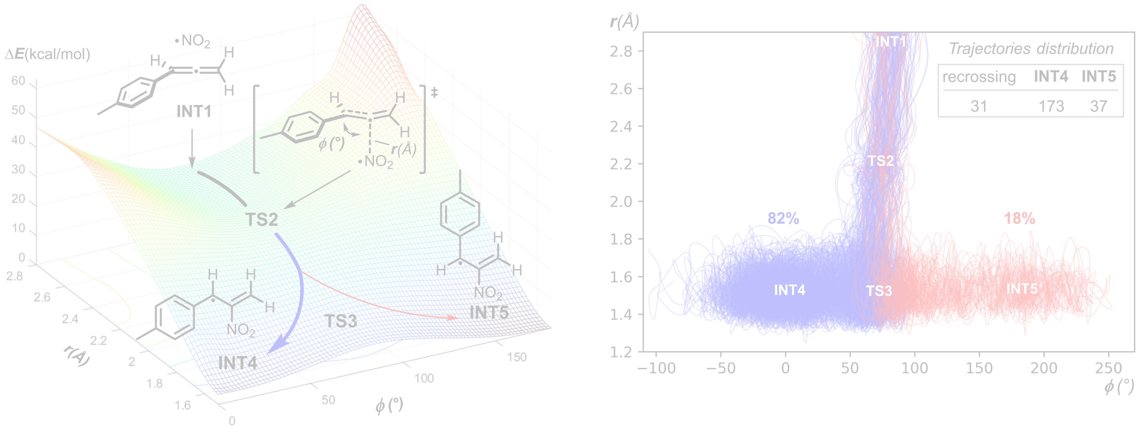
What can computational chemistry do for you?

Understanding how molecules act

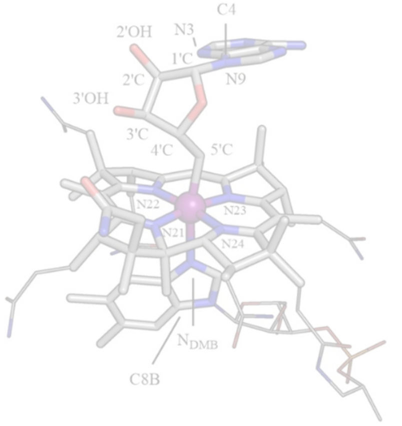
Density functional theory

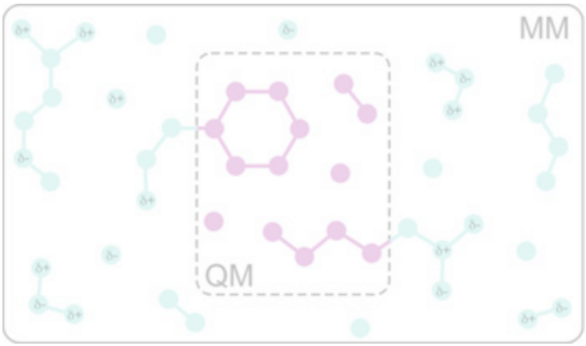


Dynamics Simulations



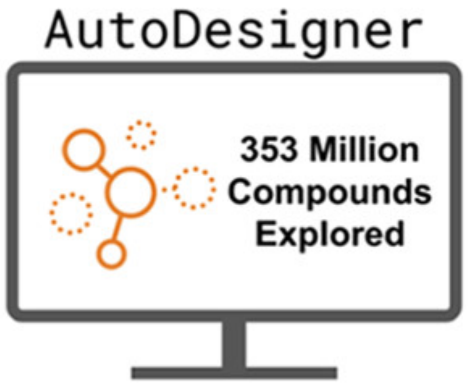
QM/MM

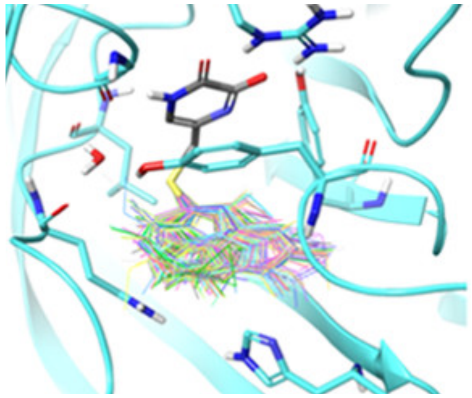




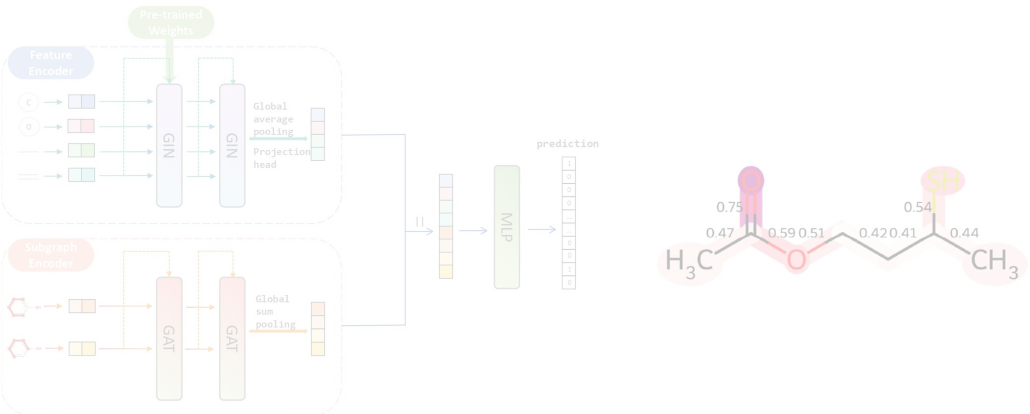
Predicting how molecules should act

Machine learning

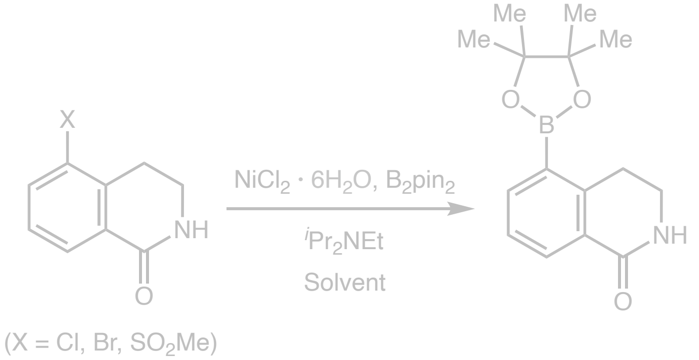


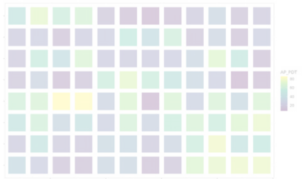


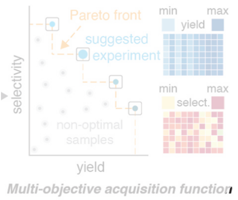
Neural networks



Data Science

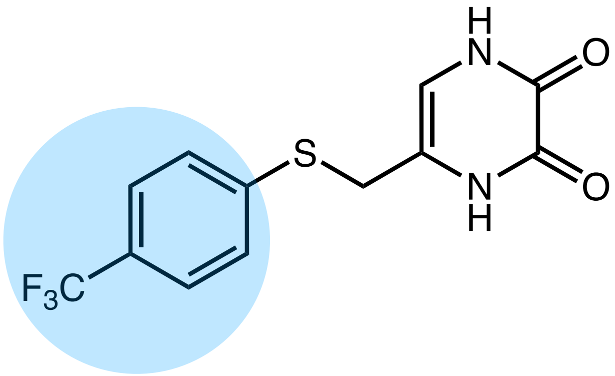






Predicting how molecules should act

De novo design algorithm for lead optimization — AutoDesigner



Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

Predicting how molecules should act

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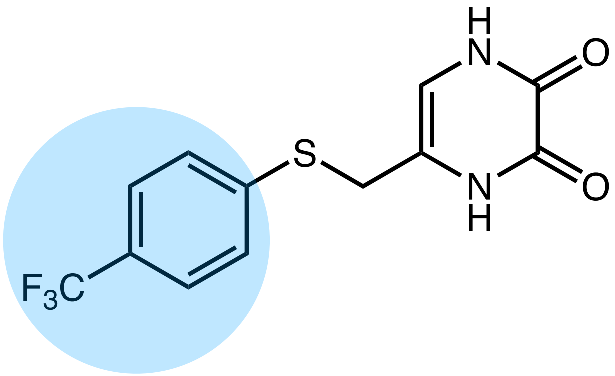

want to rapidly optimize lead compounds while adhering to project specific criteria

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Predicting how molecules should act

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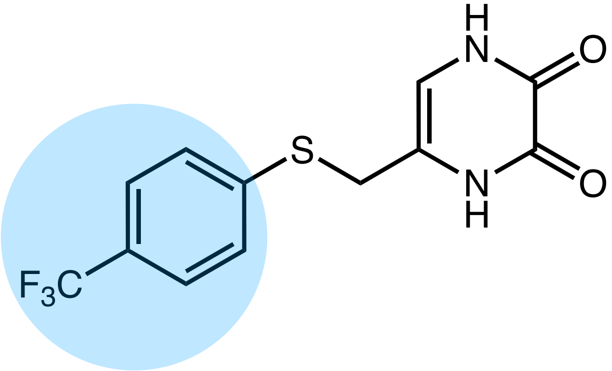

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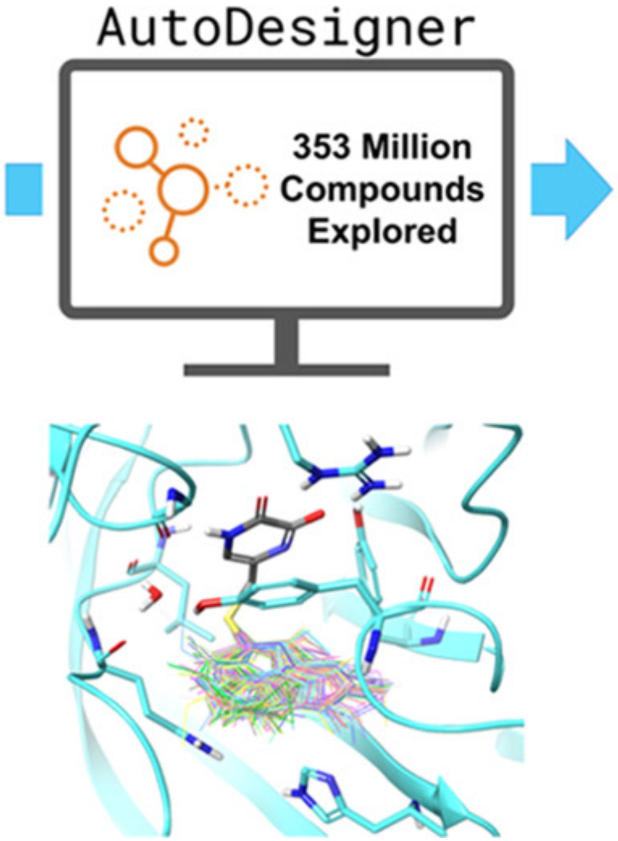

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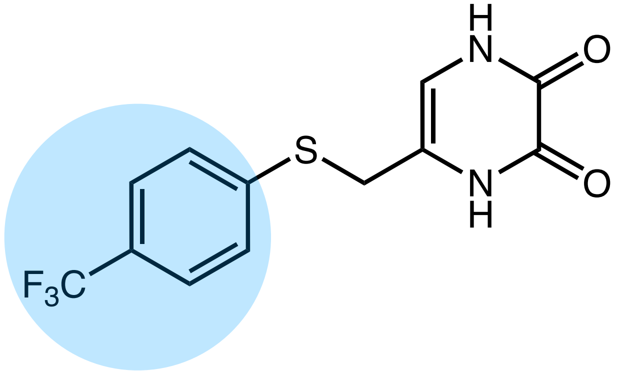
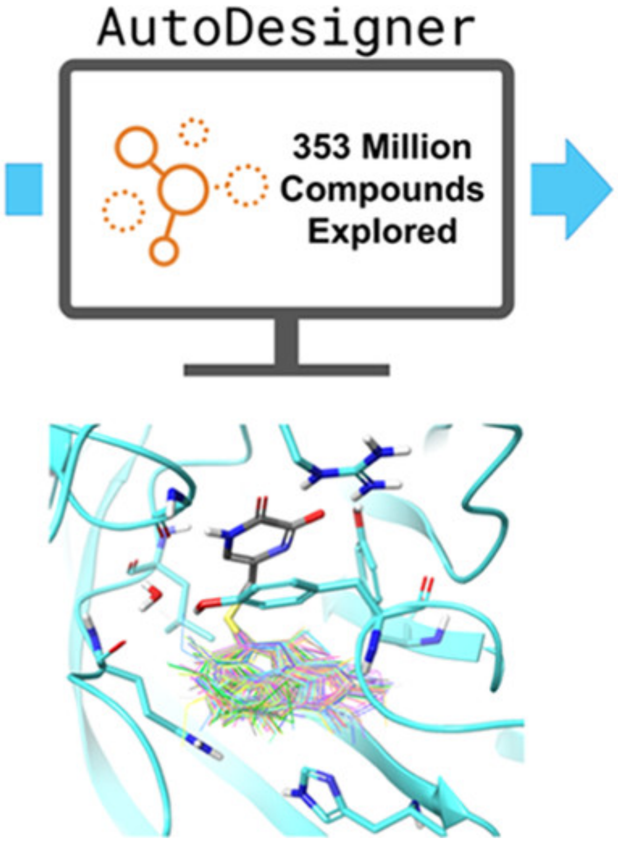
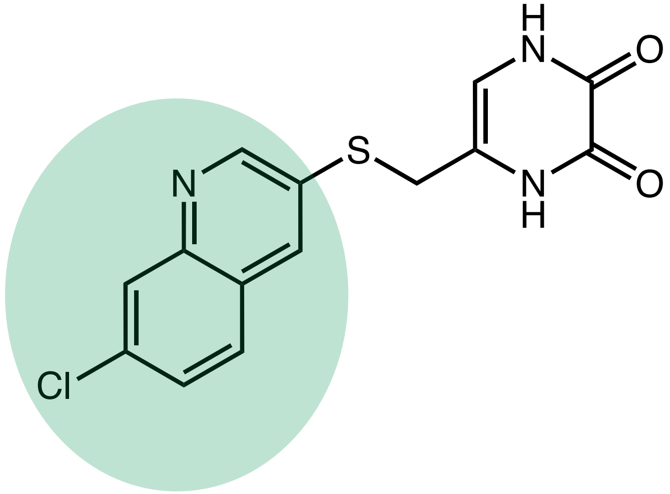
Predicting how molecules should act

De novo design algorithm for lead optimization — AutoDesigner



want to rapidly optimize lead compounds while adhering to project specific criteria



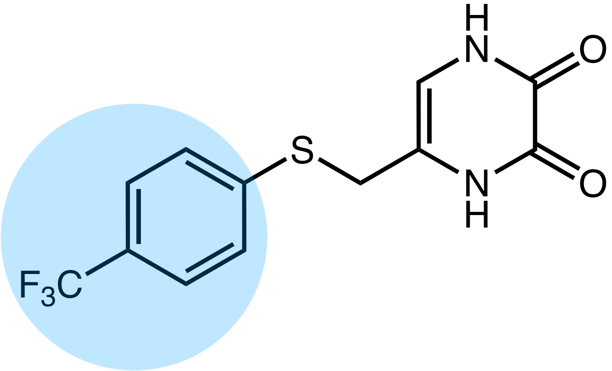


optimized lead compound

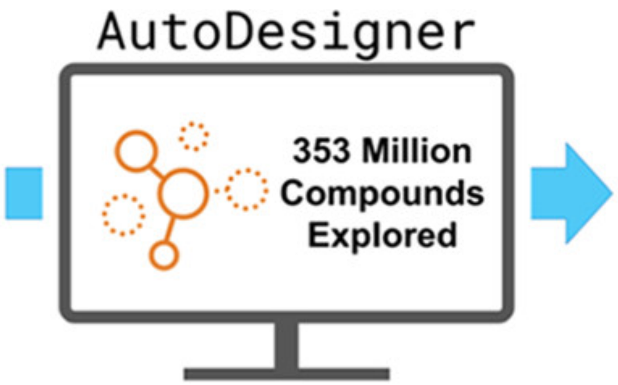
Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

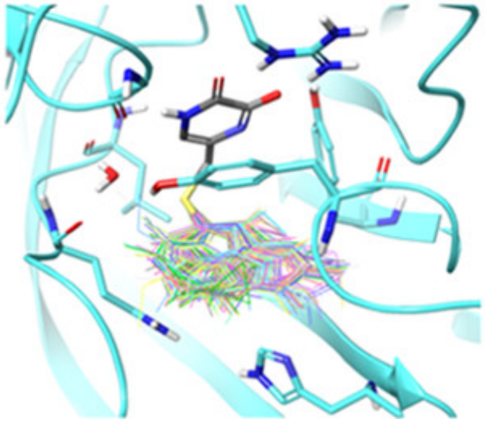
Predicting how molecules should act

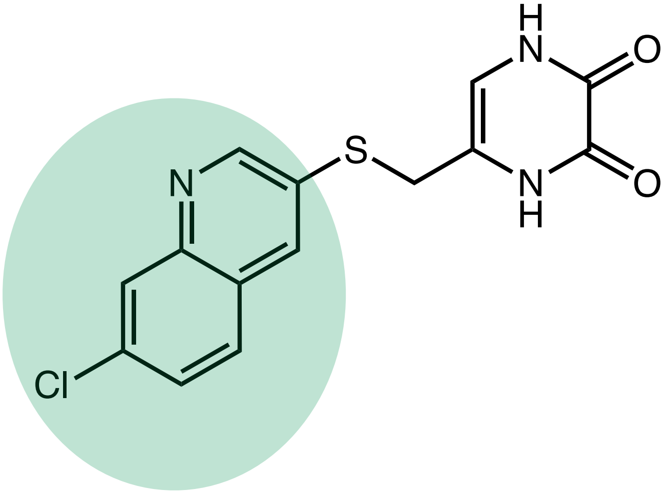
De novo design algorithm for lead optimization — AutoDesigner



want to rapidly optimize lead compounds while adhering to project specific criteria







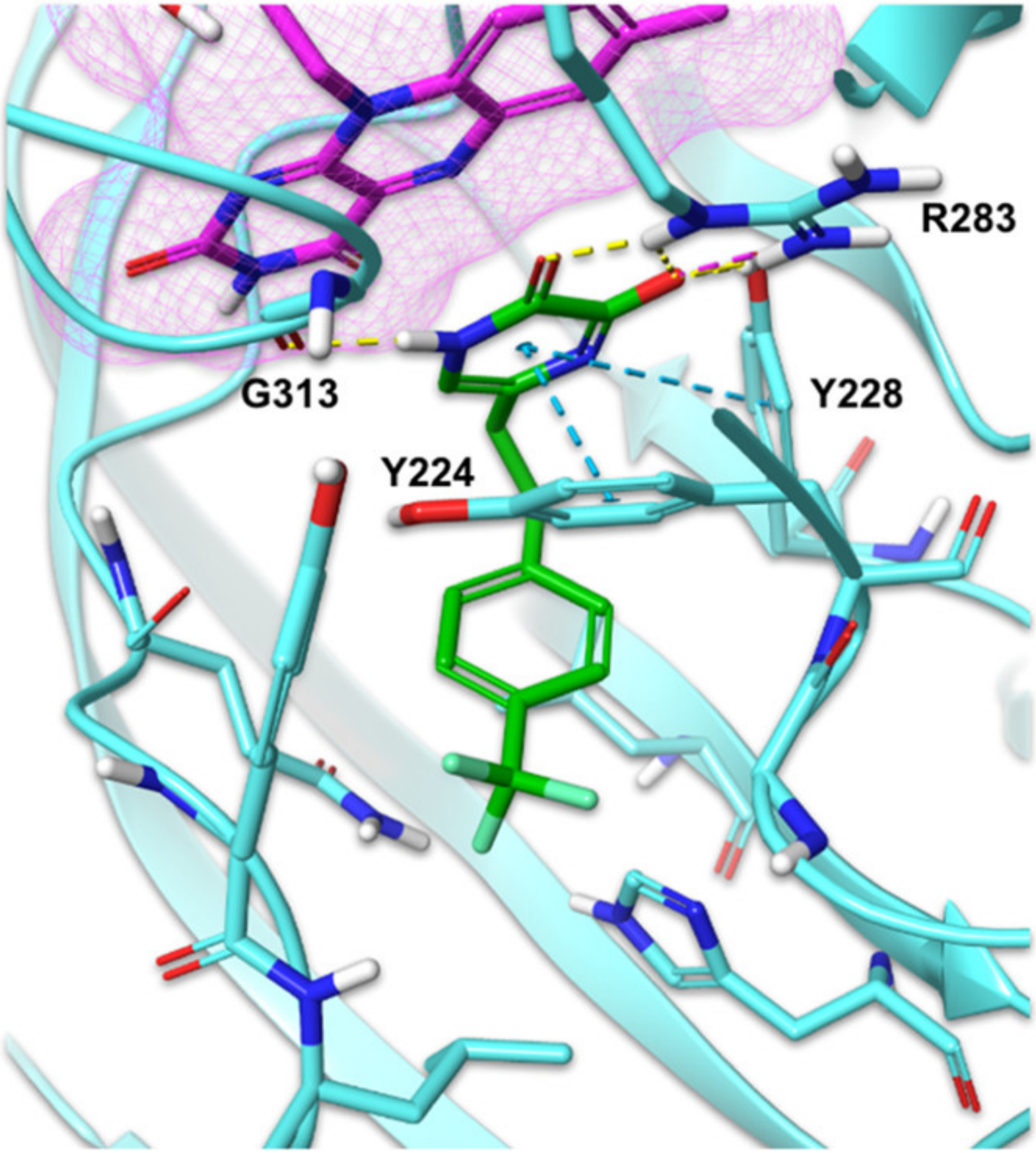
optimized lead compound

`pIC50`	✅
`Novelty`	✅
`LLE`	✅
`CNS MPO`	✅
`Exp. Clearance`	✅
`Exp. Kpuu`	✅

Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

Predicting how molecules should act

ᴅ-*amino acid oxidase (DAO) inhibition*



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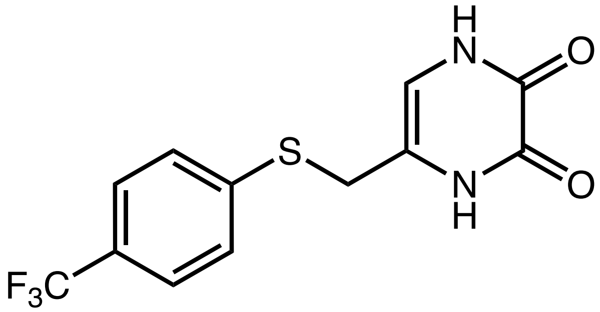
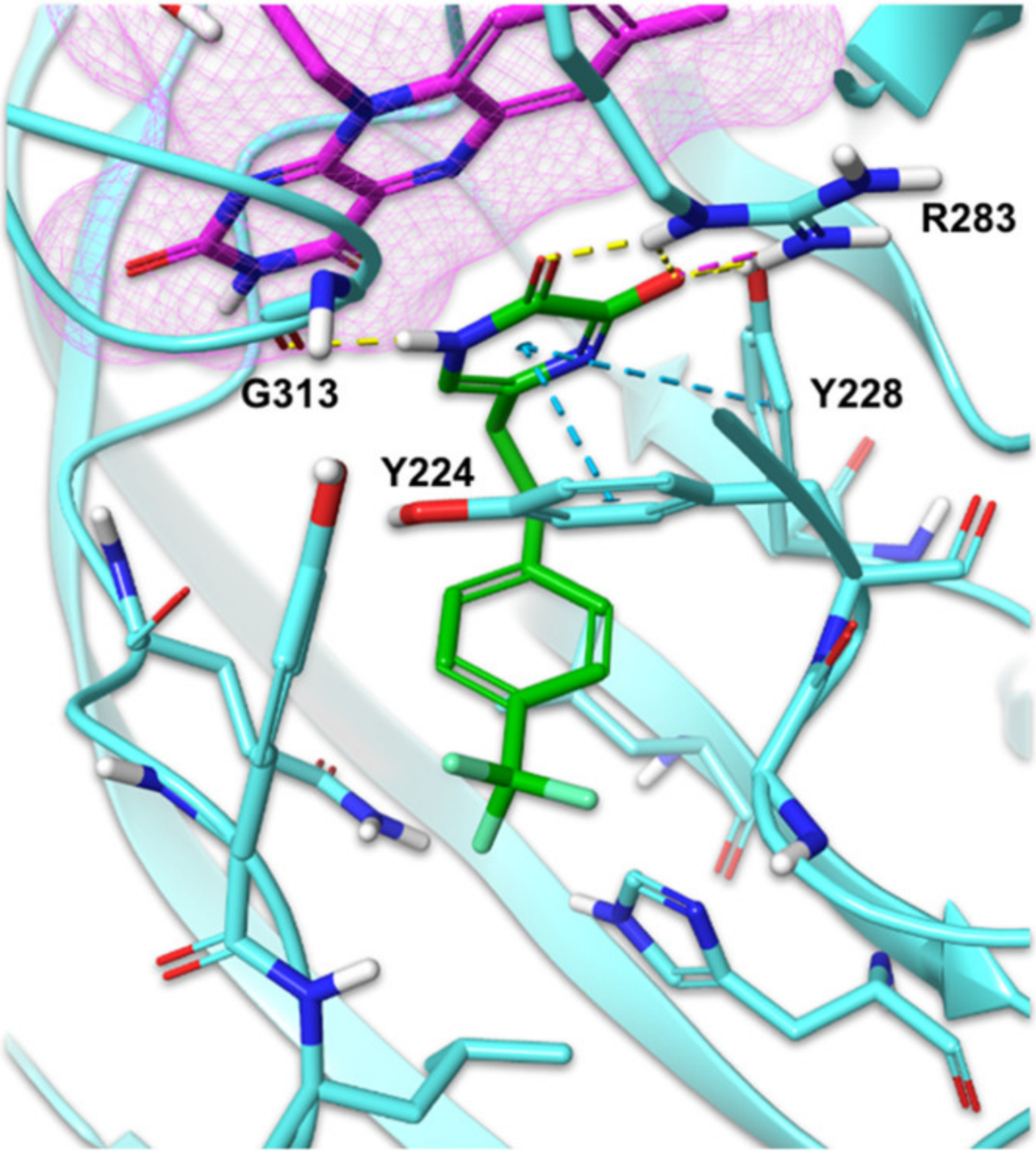
Predicting how molecules should act

D-amino acid oxidase (DAO) inhibition



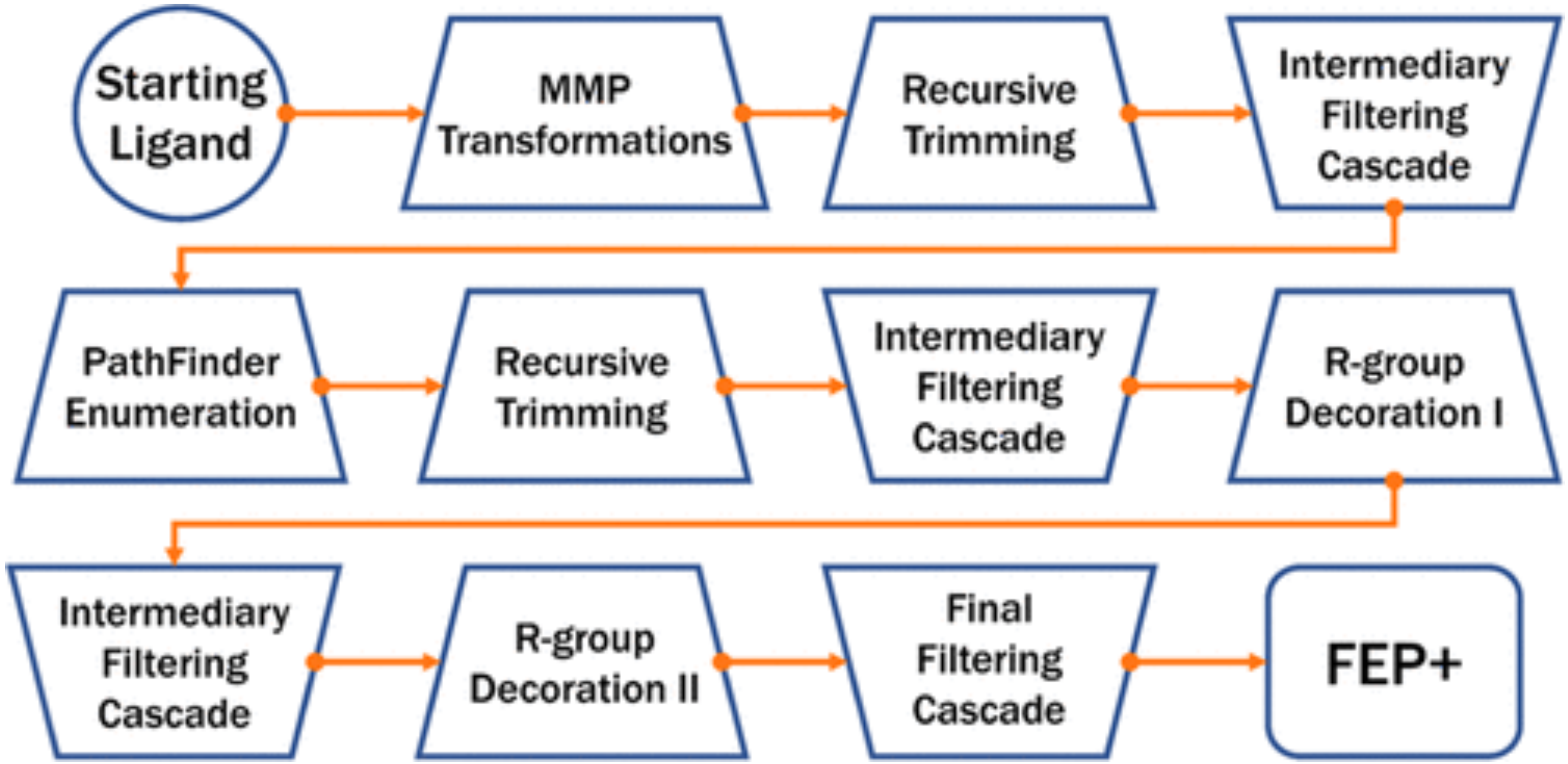
potential treatment for schizophrenia



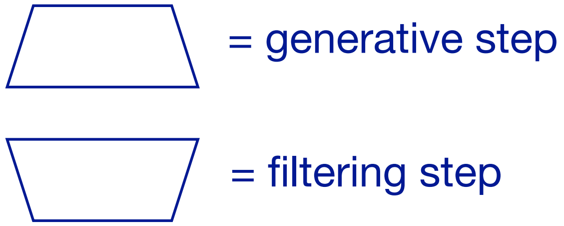
Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

Predicting how molecules should act

Overview of AutoDesigner algorithm



Starting Ligand → MMP Transformations → Recursive Trimming → Intermediary Filtering Cascade → PathFinder Enumeration → Recursive Trimming → Intermediary Filtering Cascade → R-group Decoration I → Intermediary Filtering Cascade → R-group Decoration II → Final Filtering Cascade → FEP+



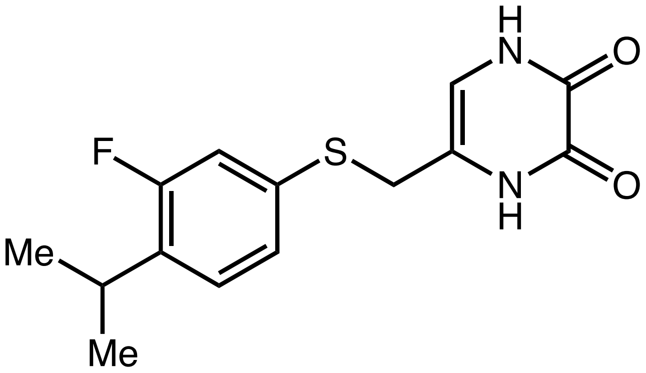
= generative step

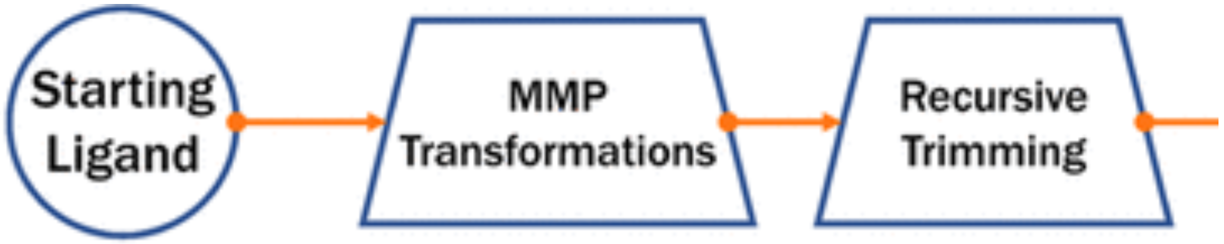
= filtering step

Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

Predicting how molecules should act

MMP and Recursive trimming





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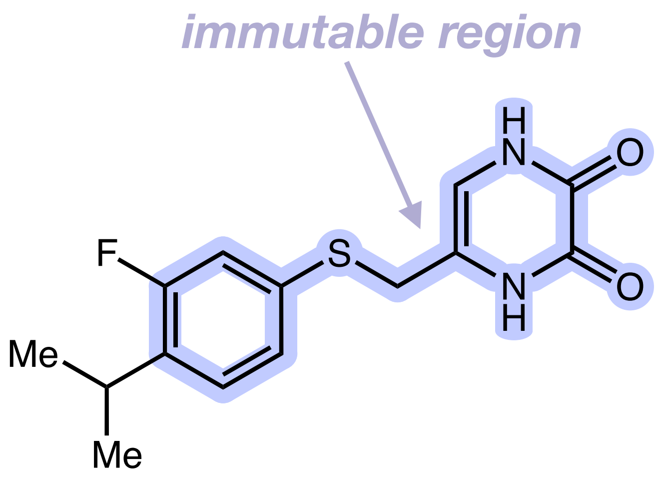
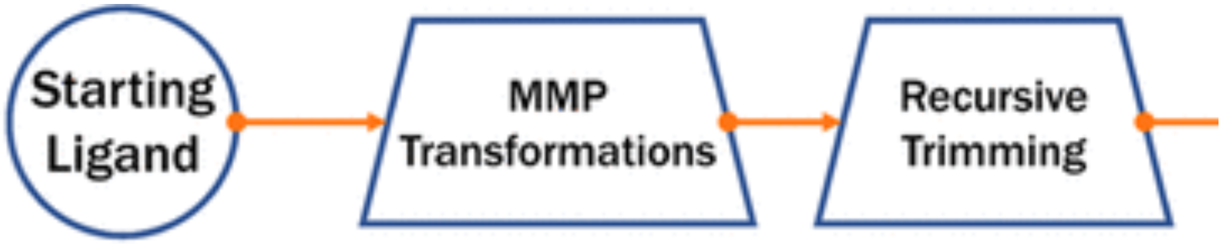
Predicting how molecules should act

MMP and Recursive trimming




Starting Ligand

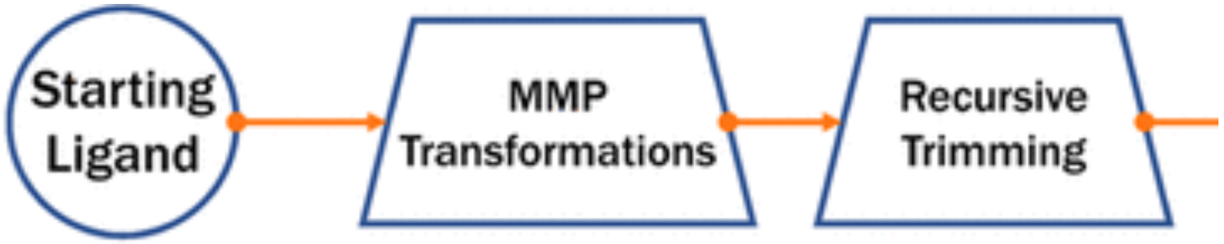
MMP Transformations

Recursive Trimming

Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

Predicting how molecules should act

MMP and Recursive trimming

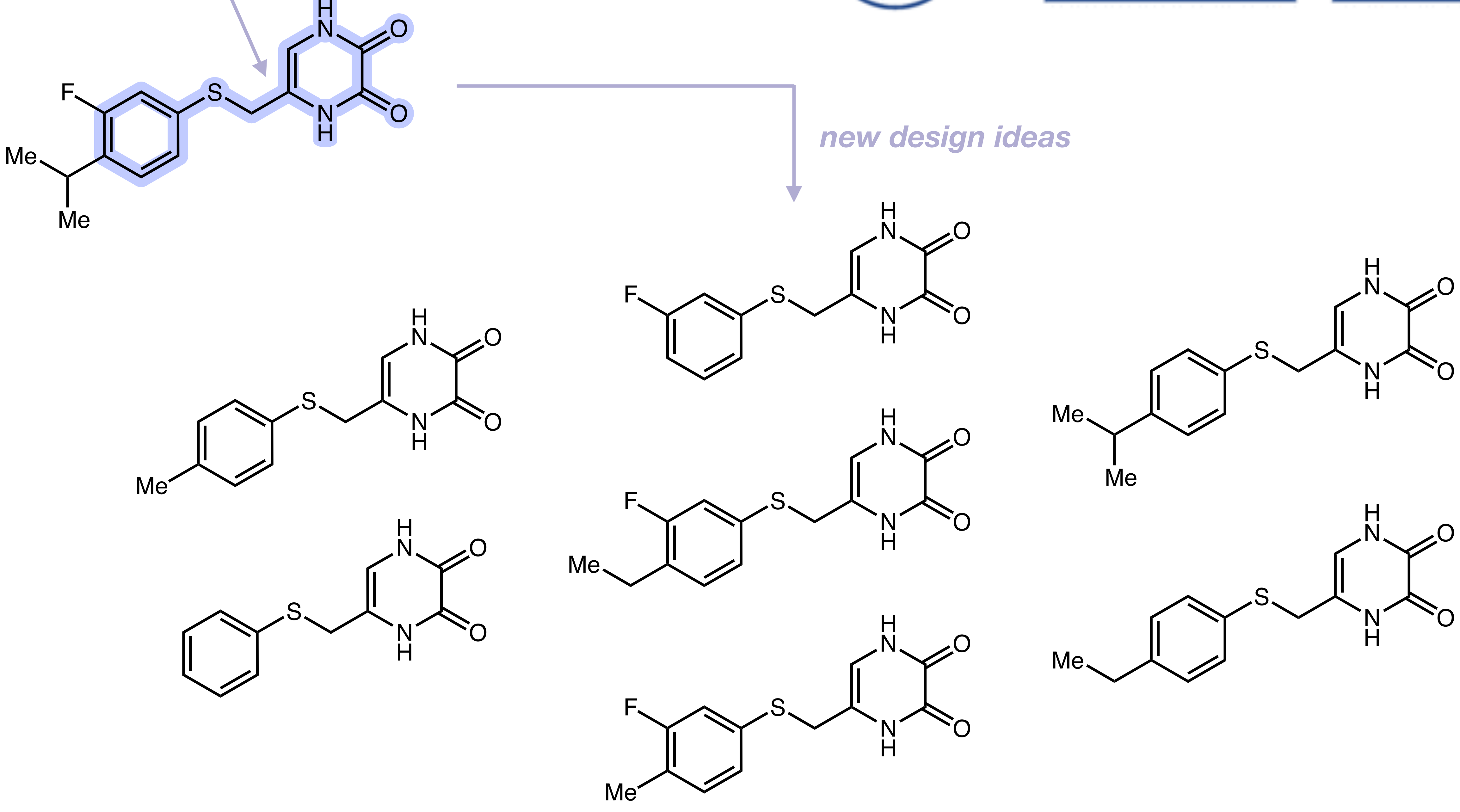


Starting Ligand

MMP Transformations

Recursive Trimming

immutable region



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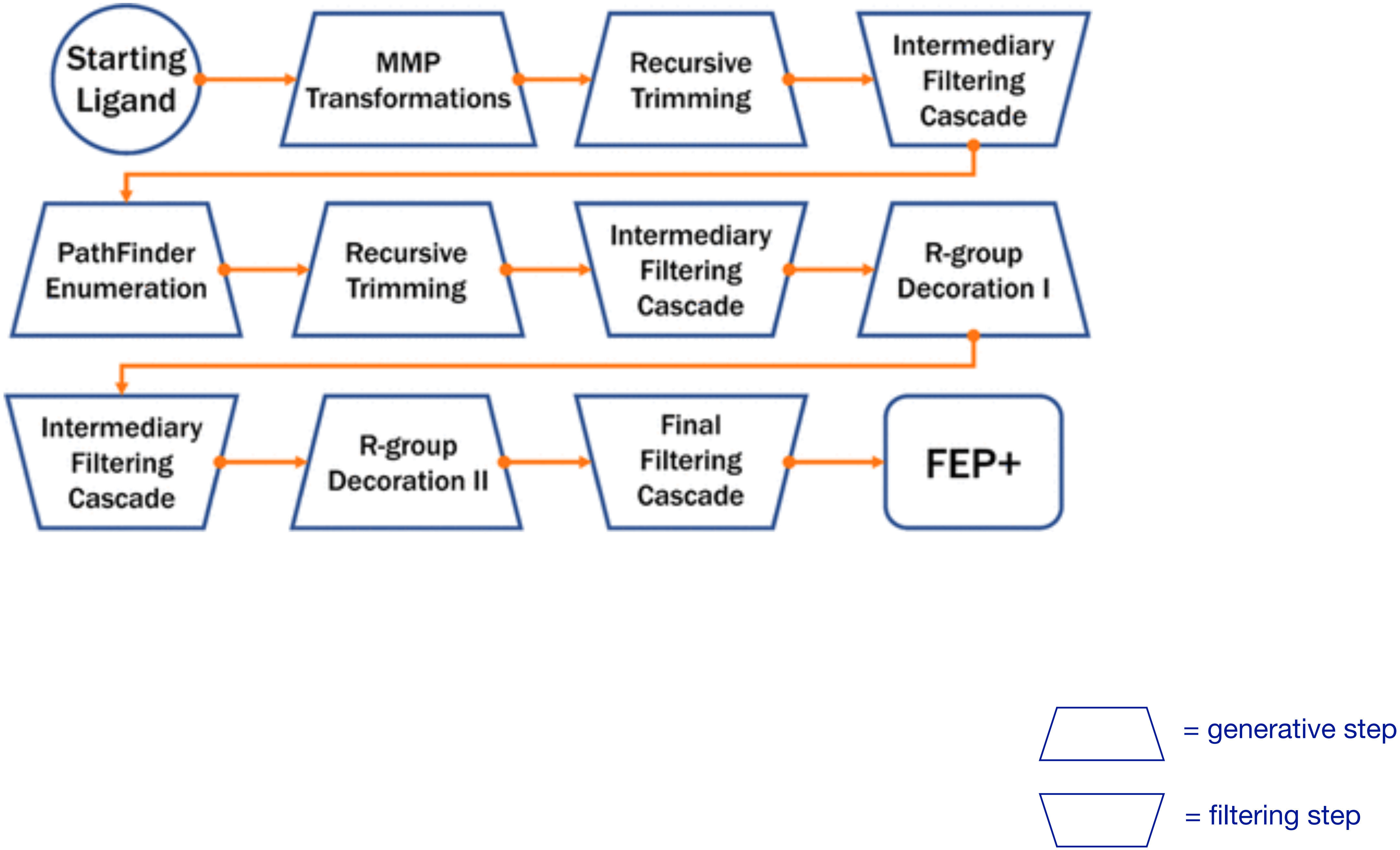
Predicting how molecules should act

Overview of AutoDesigner algorithm



Starting Ligand

MMP Transformations

Recursive Trimming

Intermediary Filtering Cascade

PathFinder Enumeration

Recursive Trimming

Intermediary Filtering Cascade

R-group Decoration I

Intermediary Filtering Cascade

R-group Decoration II

Final Filtering Cascade

FEP+

= generative step

= filtering step

Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

Predicting how molecules should act

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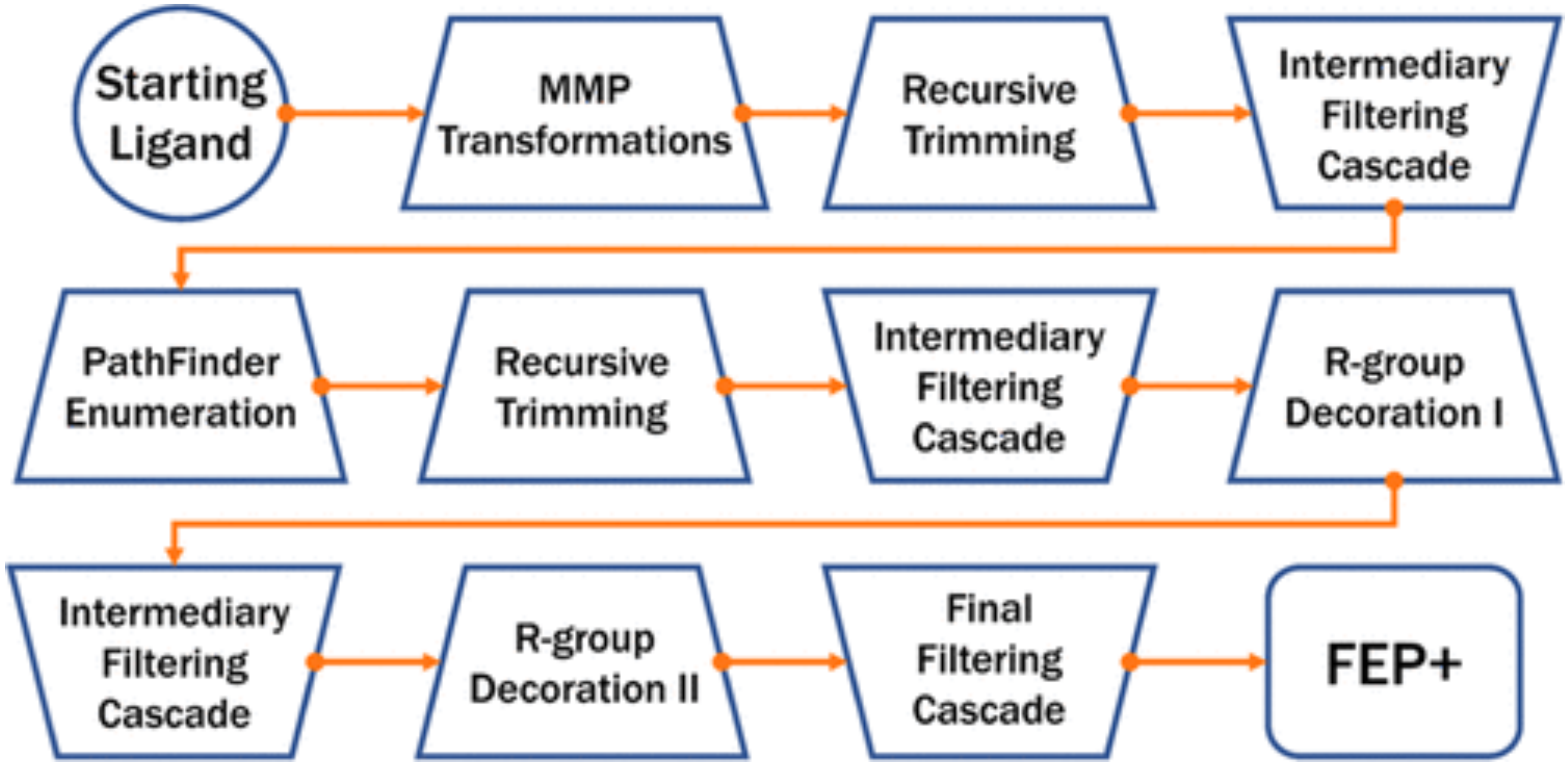
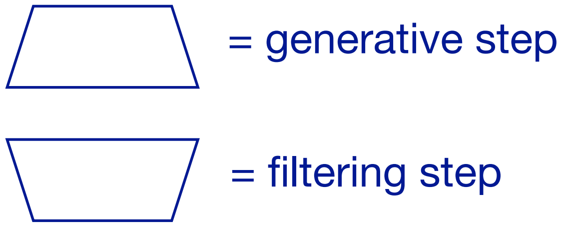


perform retrosynthetic analysis and adjust non-immutable region



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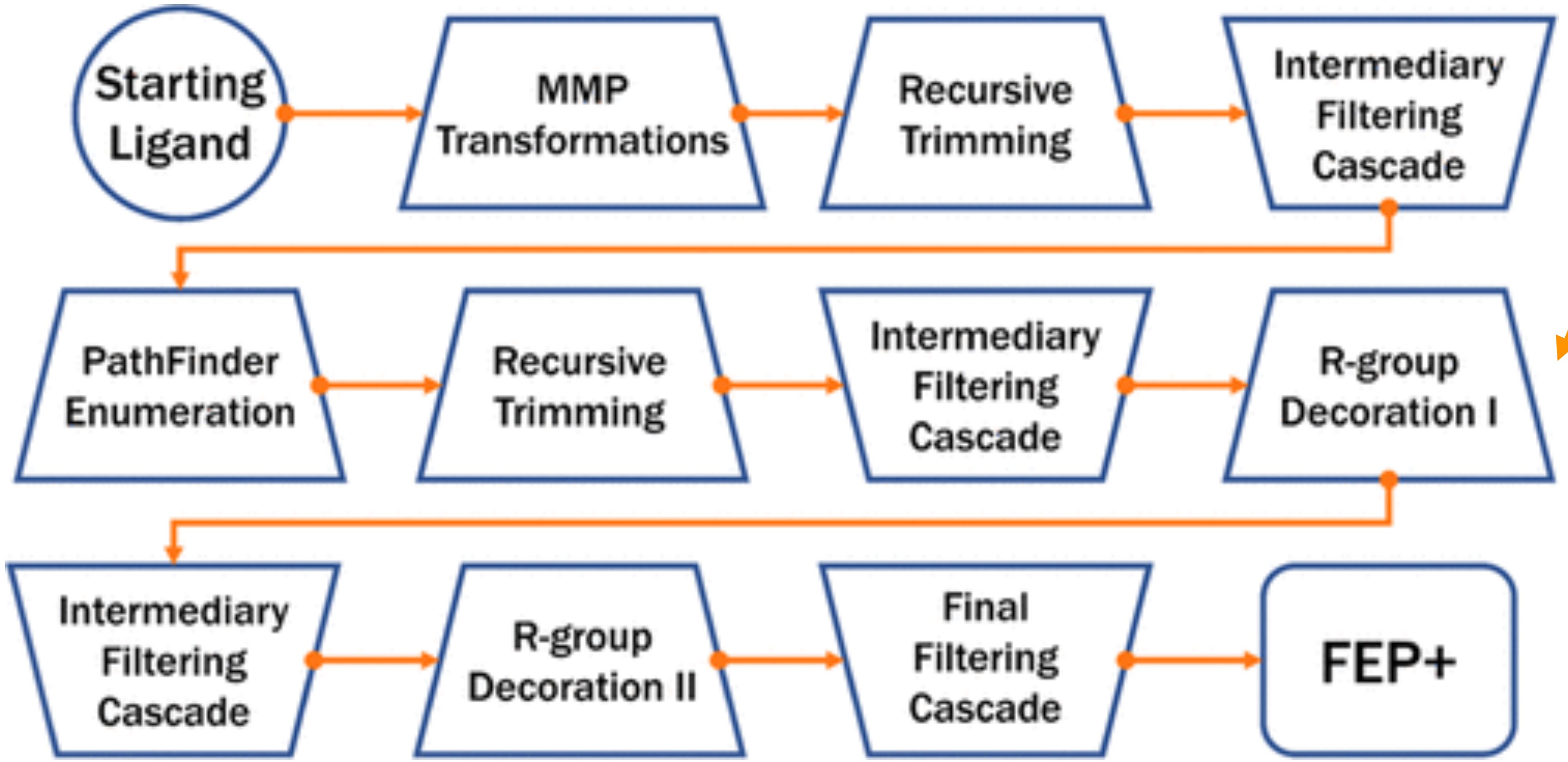
Predicting how molecules should act

Overview of AutoDesigner algorithm

decorate ligands with R-groups to broaden chemical space


Starting Ligand

MMP Transformations

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Final Filtering Cascade

FEP+

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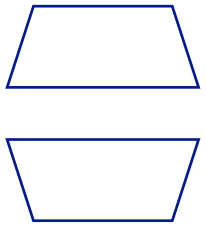
= generative step

= filtering step

Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

Predicting how molecules should act

Filtering stages

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Predicting how molecules should act

Filtering stages

- *Fewer filters, allows some potentially undesirable ligands through*
- *Aims for higher efficiency*

Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

Predicting how molecules should act

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Predicting how molecules should act

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Predicting how molecules should act

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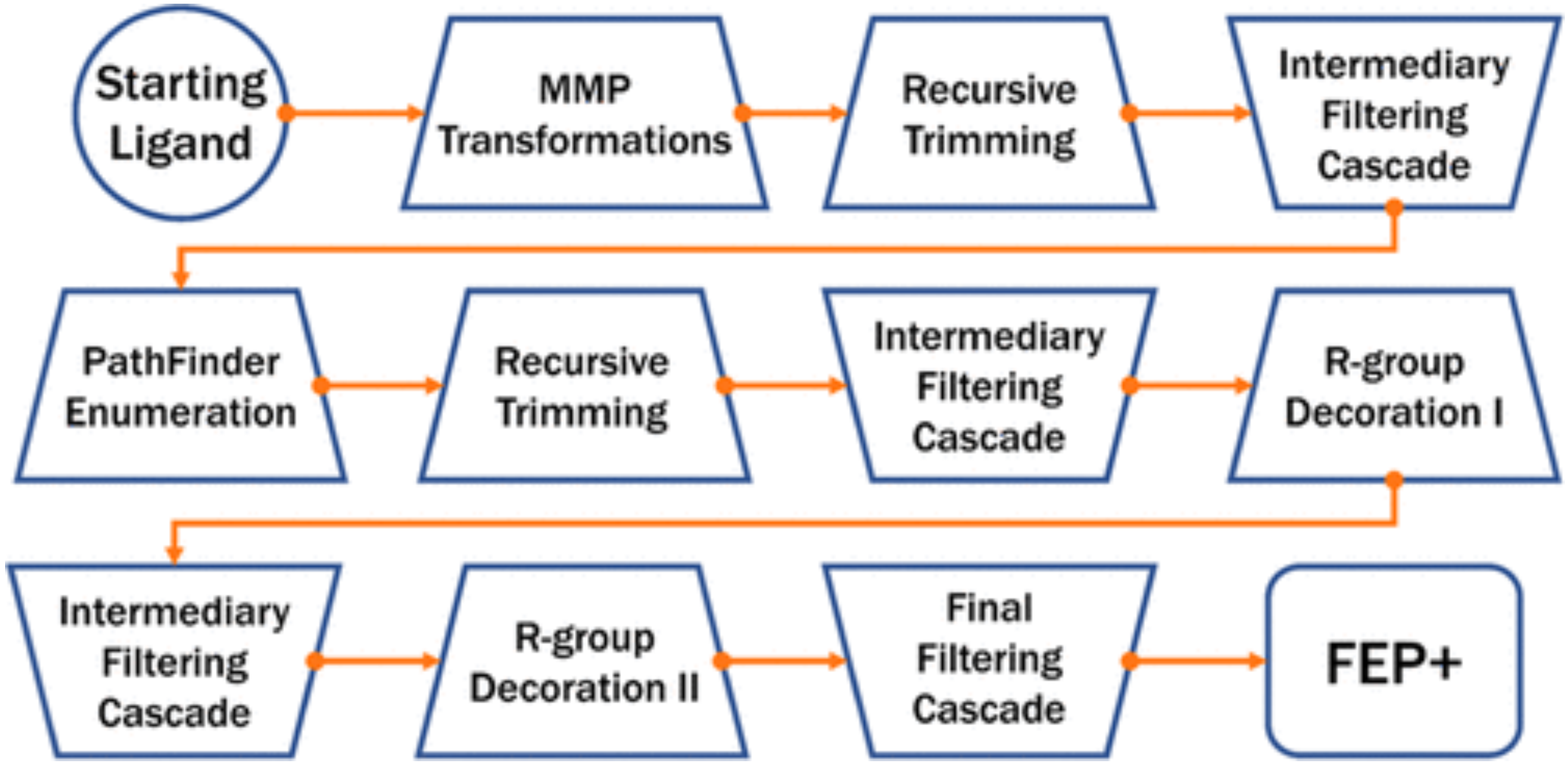
- *Complexity filter screens out compounds that would be too challenging to synthesize*
- *Human intervention to see if compounds need to be manually removed (became less necessary with more runs)*
- *Set of optional filters that can be adjusted based on project requirements*

Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

Predicting how molecules should act

Overview of AutoDesigner algorithm



Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

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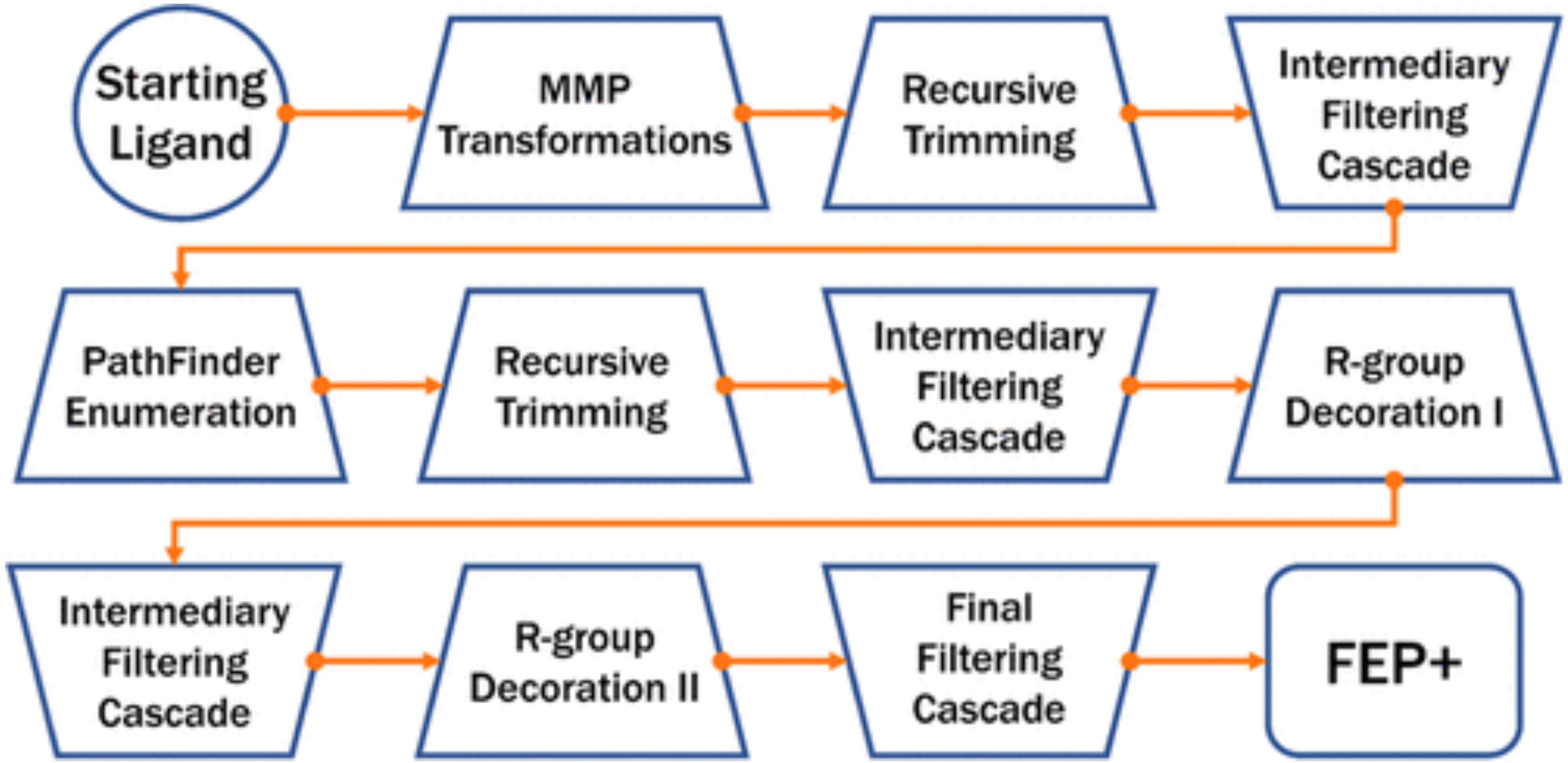
3 ligands to start



Starting Ligand

MMP Transformations

Recursive Trimming

Intermediary Filtering Cascade

PathFinder Enumeration

Recursive Trimming

Intermediary Filtering Cascade

R-group Decoration I

Intermediary Filtering Cascade

R-group Decoration II

Final Filtering Cascade

FEP+

Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

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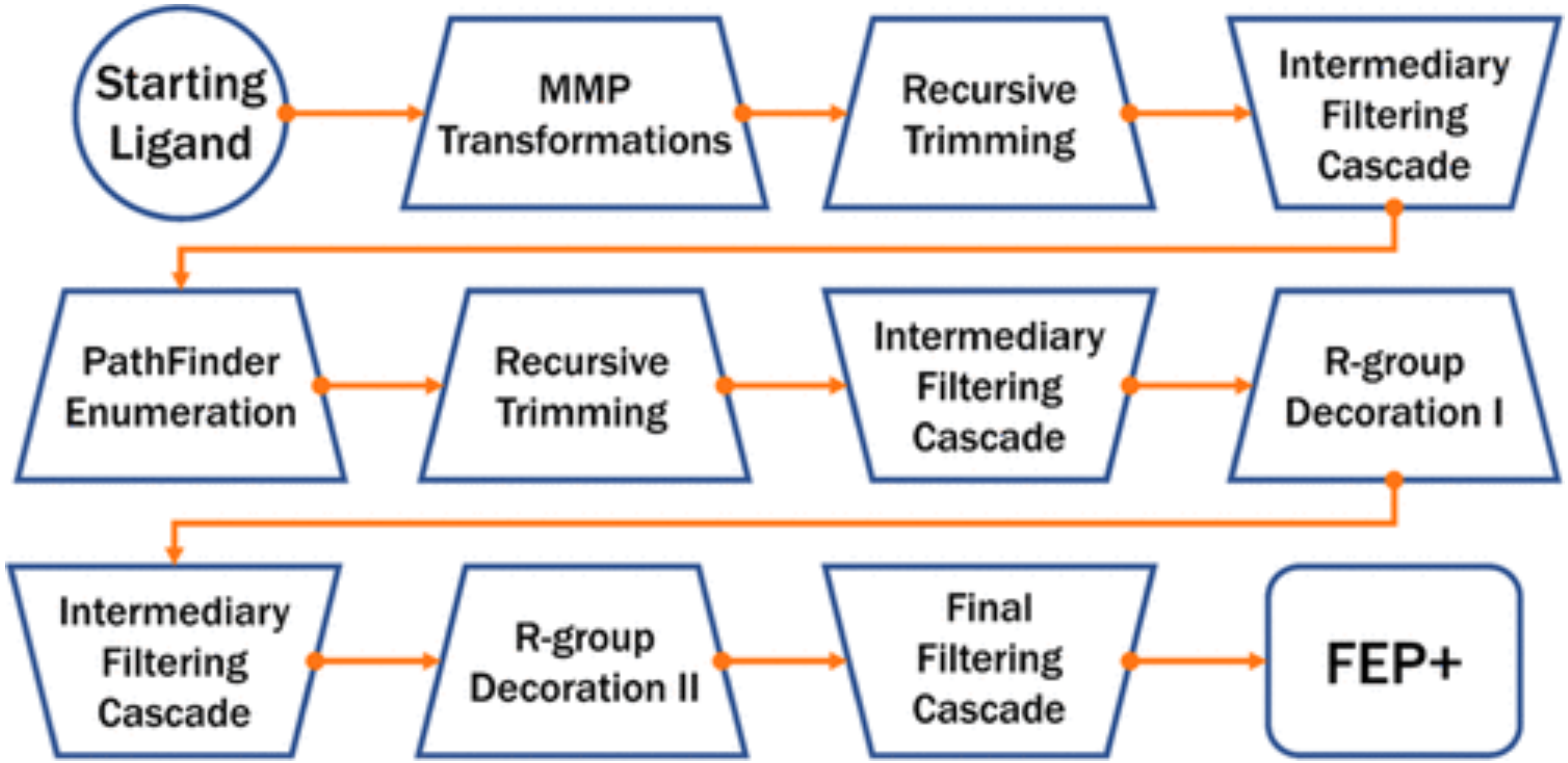

over 1 billion ligands explored in 24-48 hours

Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

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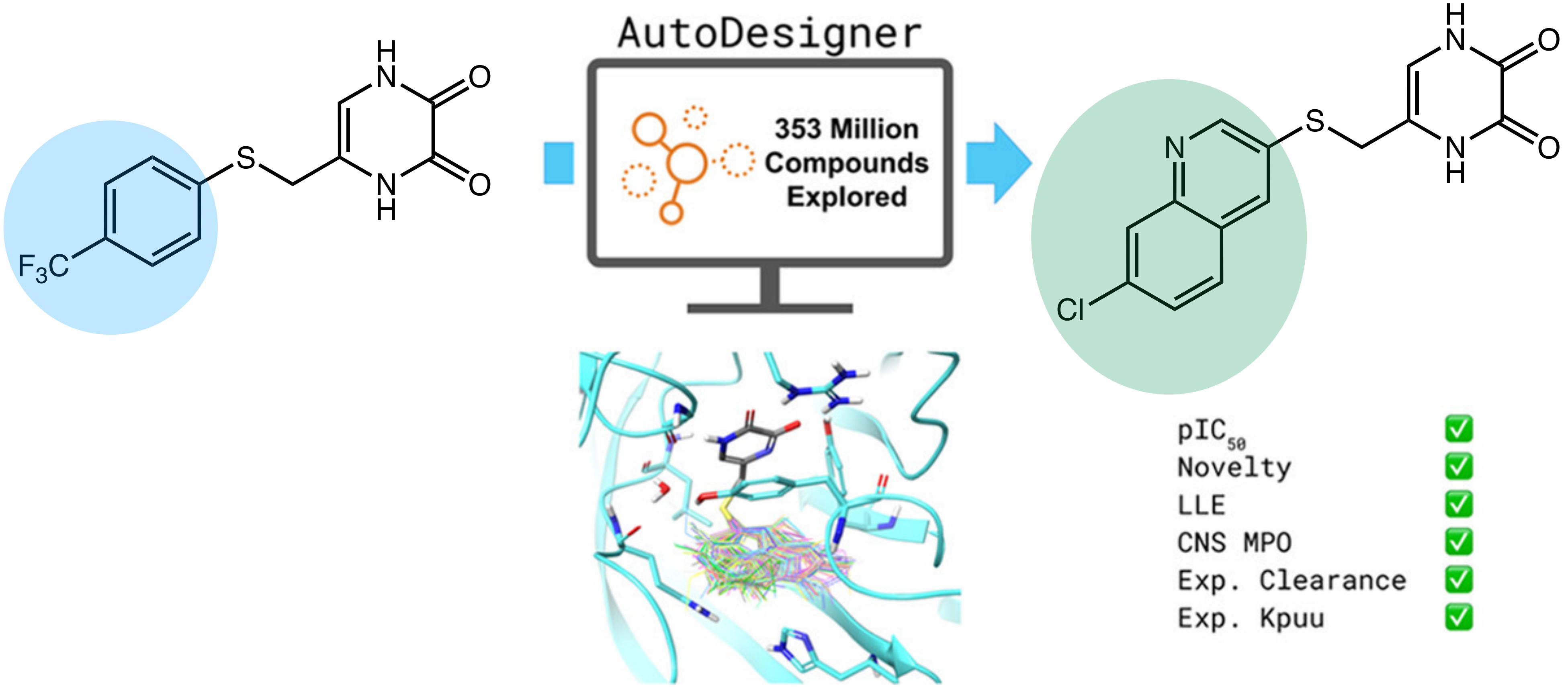
Results of AutoDesigner algorithm



pIC_{50}	✅
Novelty	✅
LLE	✅
CNS MPO	✅
Exp. Clearance	✅
Exp. Kpuu	✅

synthetically tractable and potent, while meeting desired criteria

Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

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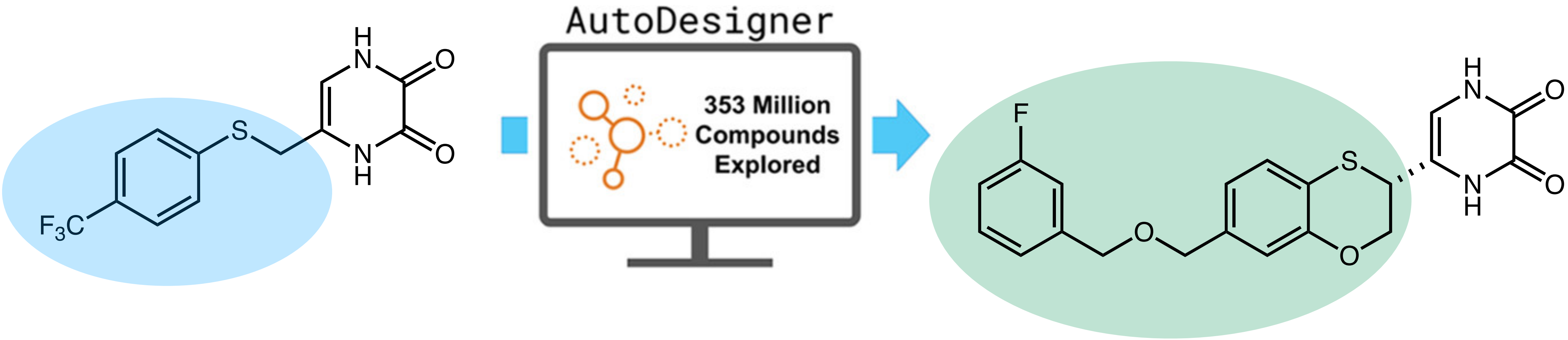

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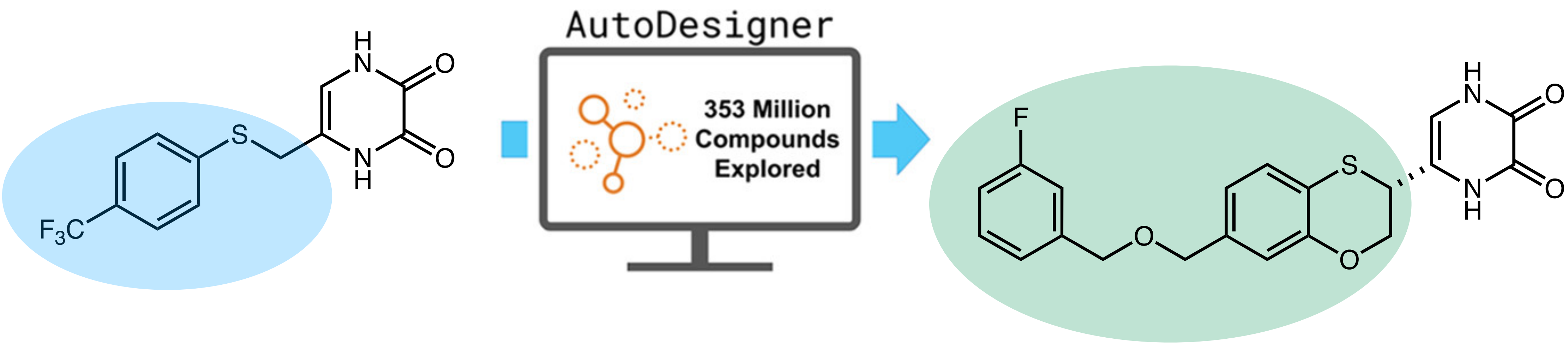
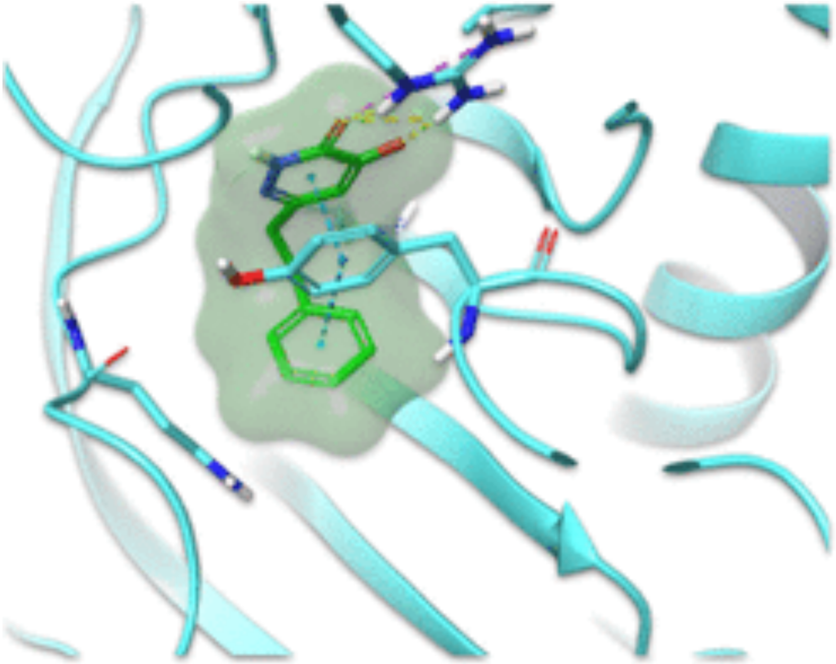
Predicting how molecules should act

Results of AutoDesigner algorithm



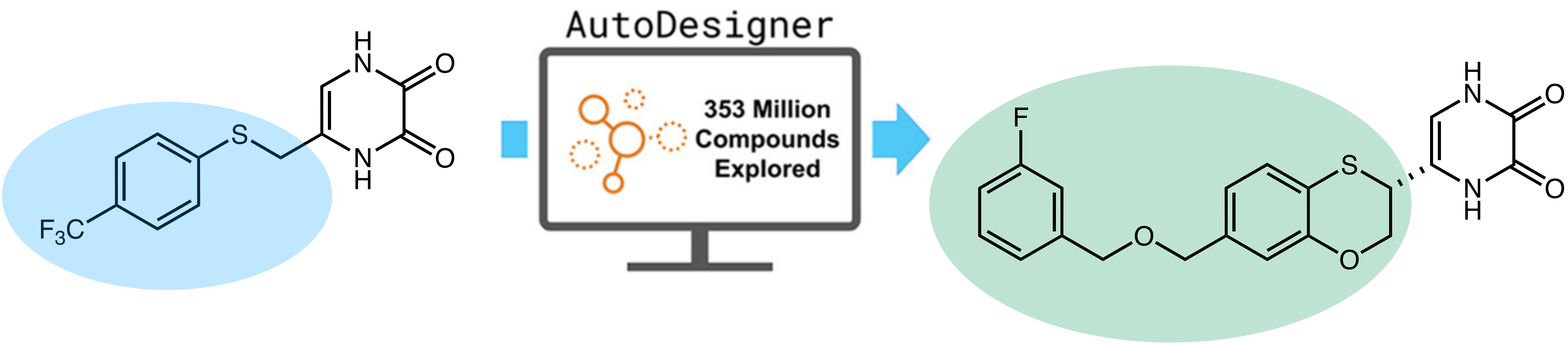


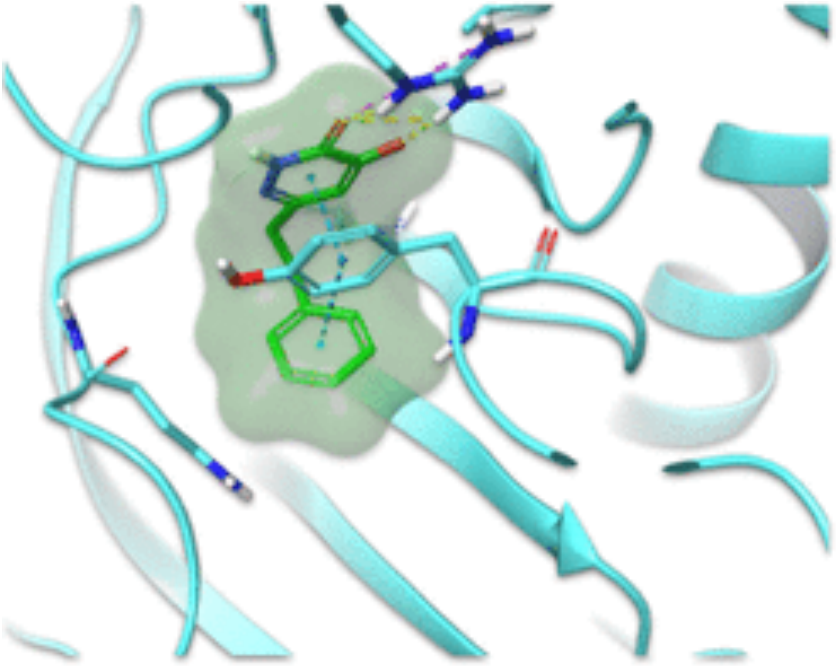
previously disclosed crystallized inhibitor

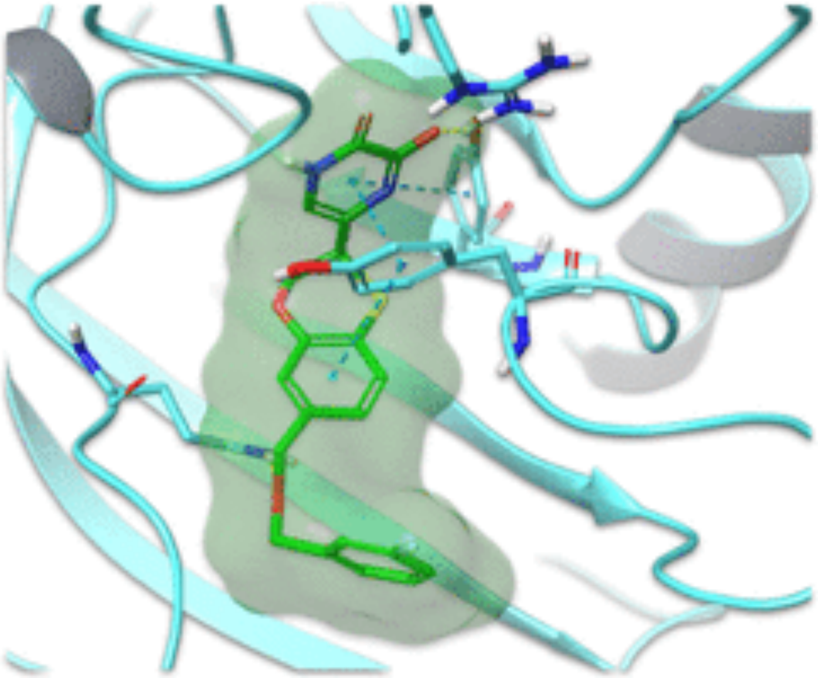
Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

Predicting how molecules should act

Results of AutoDesigner algorithm







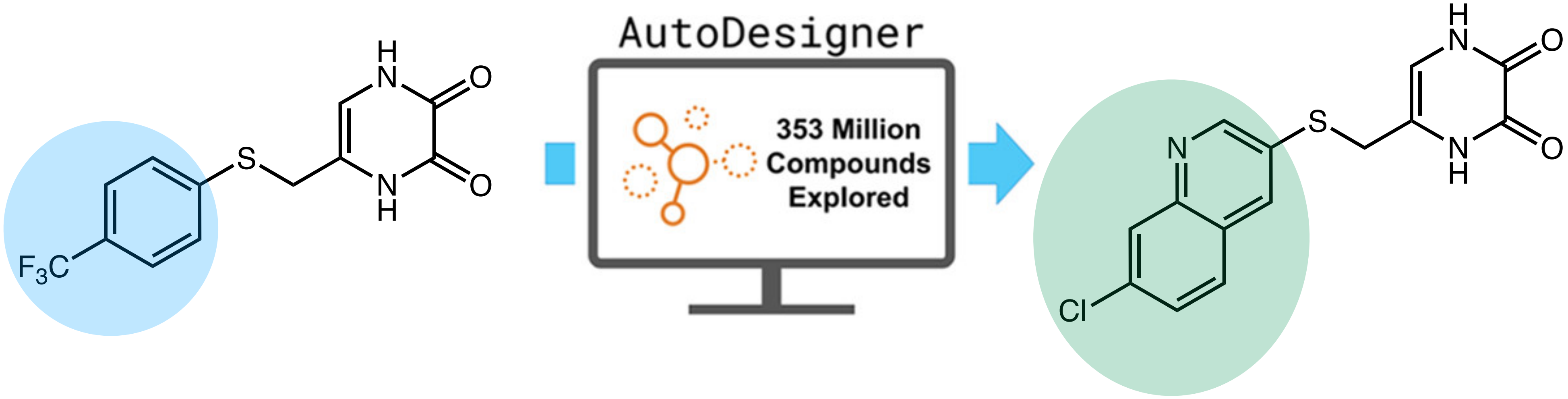
previously disclosed crystallized inhibitor

New DAO inhibitor explores novel subpocket not previously reported

Bos, P. H.; Houang, E. M.; Ranalli, F.; Leffler, A. E.; Boyles, N. A.; Eyrich, V. A.; Luria, Y.; Katz, D.; Tang, H.; Abel, R.; Bhat, S. *J. Chem. Inf. Model.* **2022**, *62*, 1905-1915.

Predicting how molecules should act

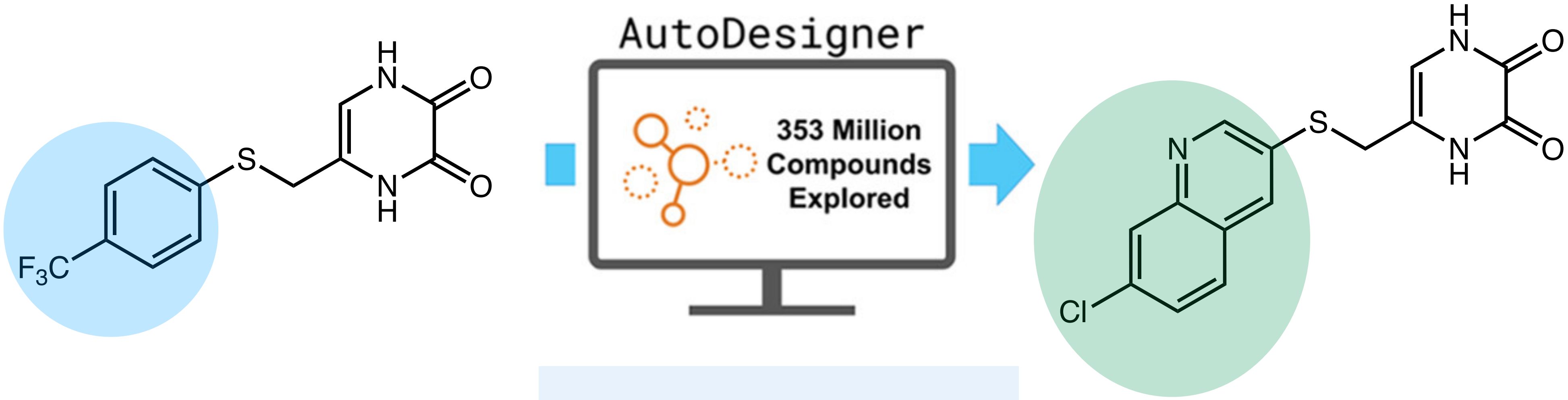
Further application of AutoDesigner algorithm



Bos, P. H. et al. *J. Chem. Inf. Model.* **2024**, *64*, 7513–7524.

Predicting how molecules should act

Further application of AutoDesigner algorithm

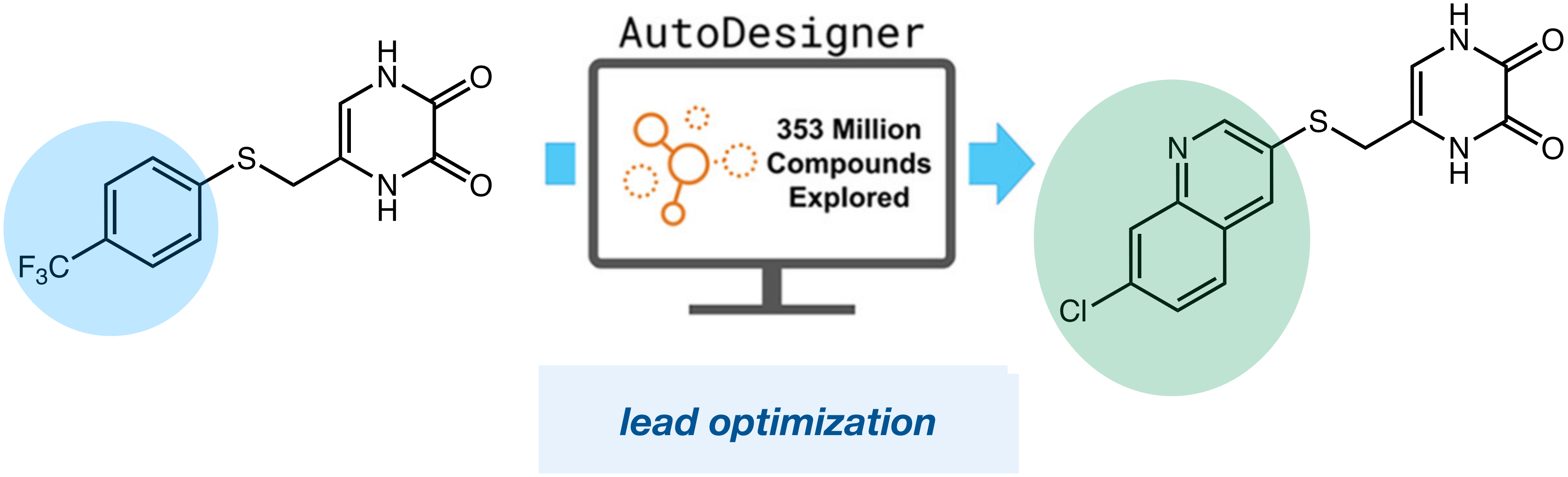


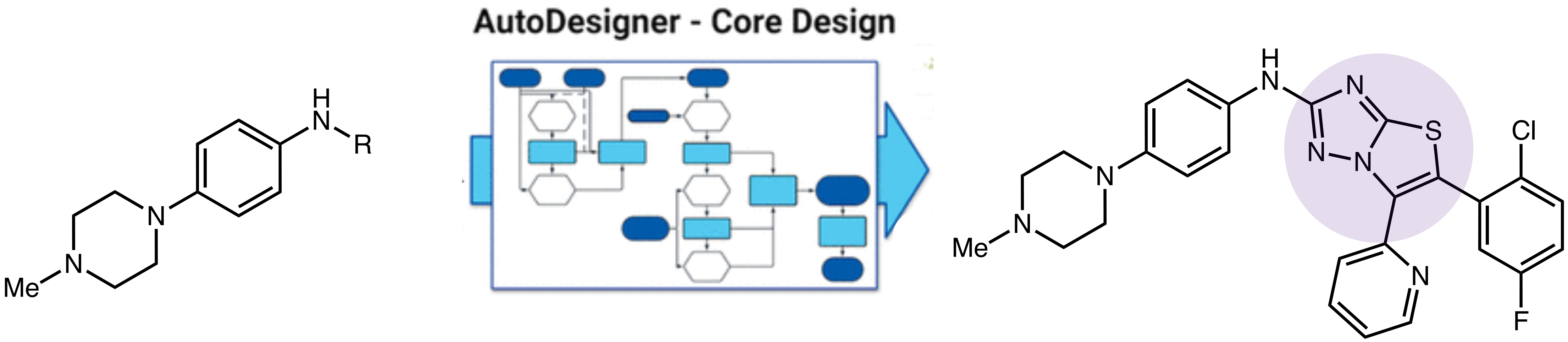
lead optimization

Bos, P. H. et al. *J. Chem. Inf. Model.* **2024**, *64*, 7513–7524.

Predicting how molecules should act

Further application of AutoDesigner algorithm





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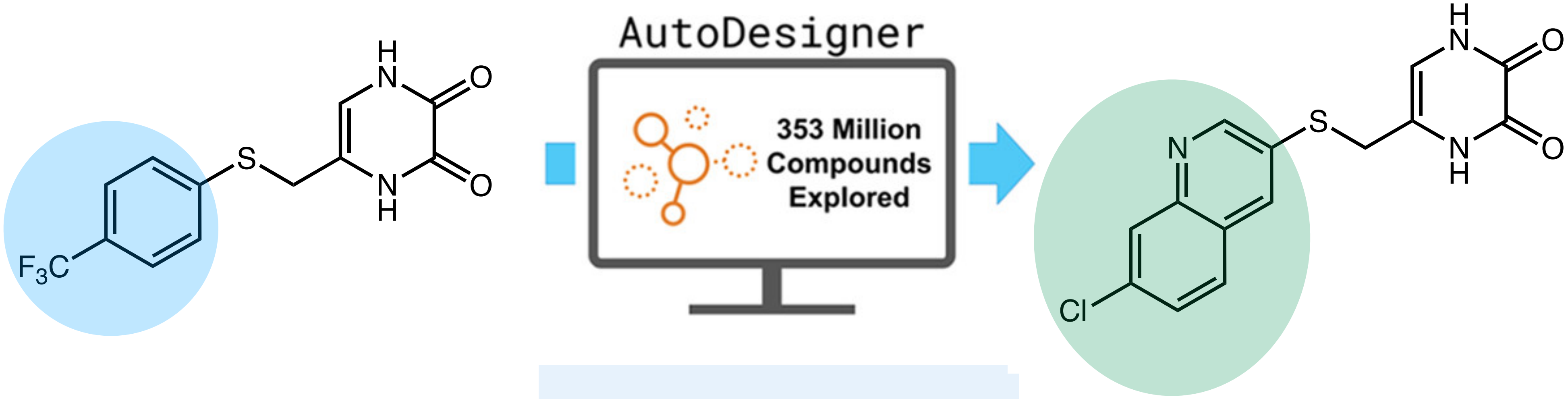
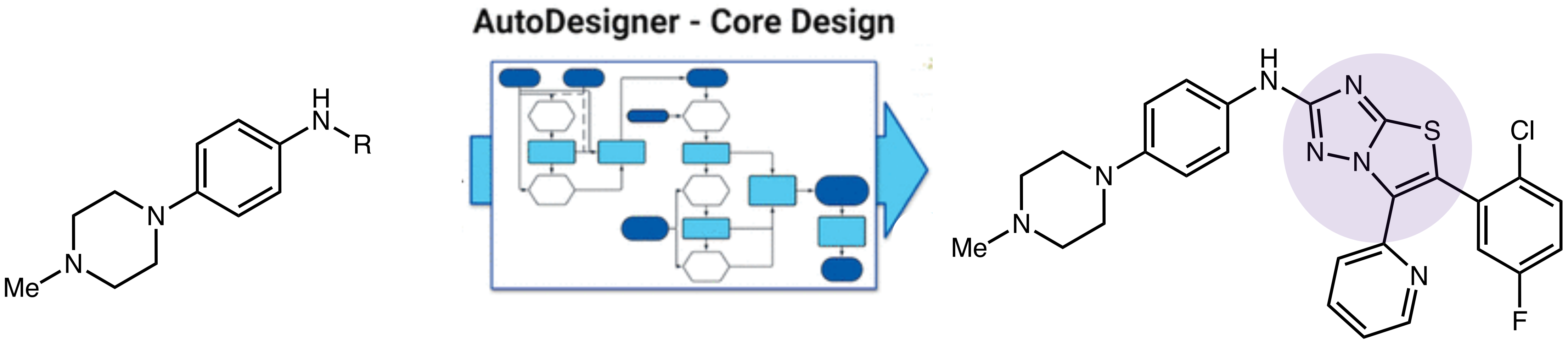
Predicting how molecules should act

Further application of AutoDesigner algorithm



lead optimization



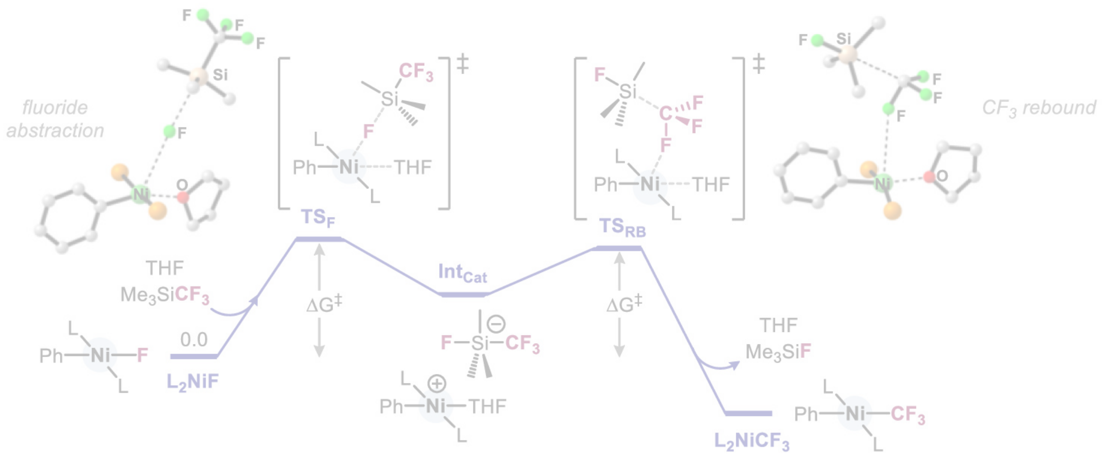
scaffold design

Bos, P. H. et al. *J. Chem. Inf. Model.* **2024**, *64*, 7513–7524.

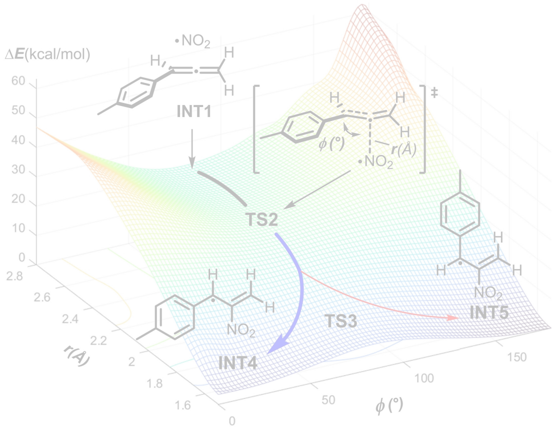
What can computational chemistry do for you?

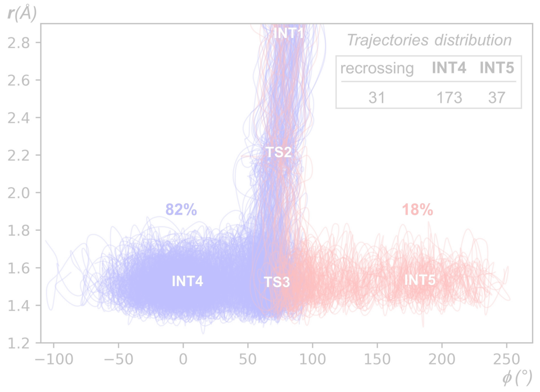
Understanding how molecules act

Density functional theory

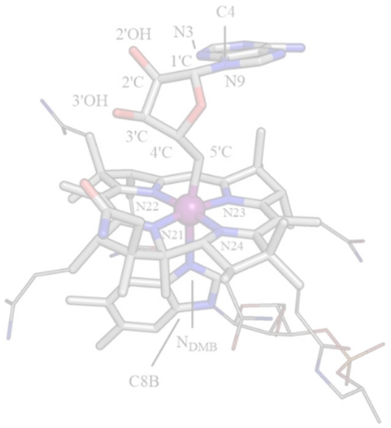


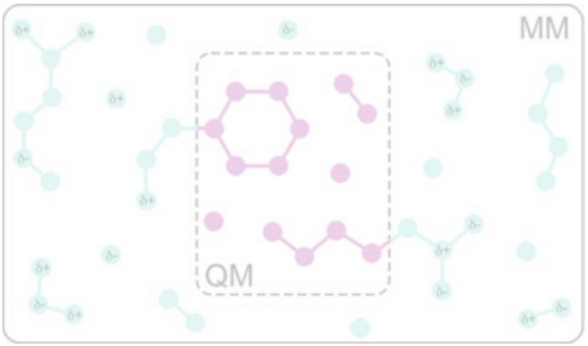
Dynamics Simulations





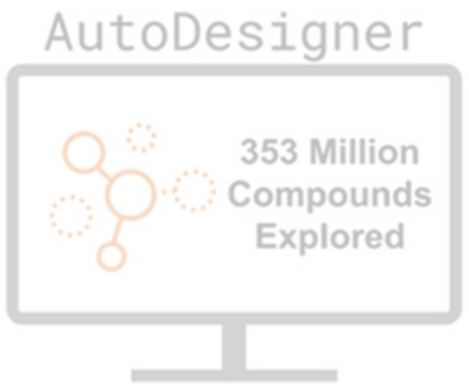
QM/MM

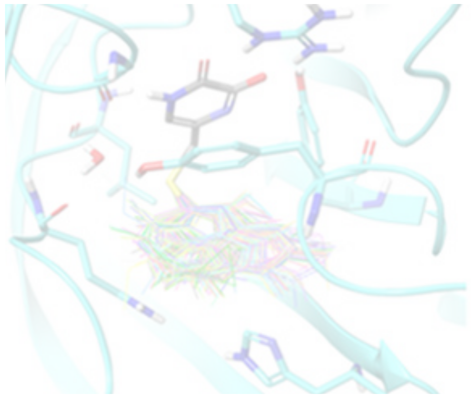




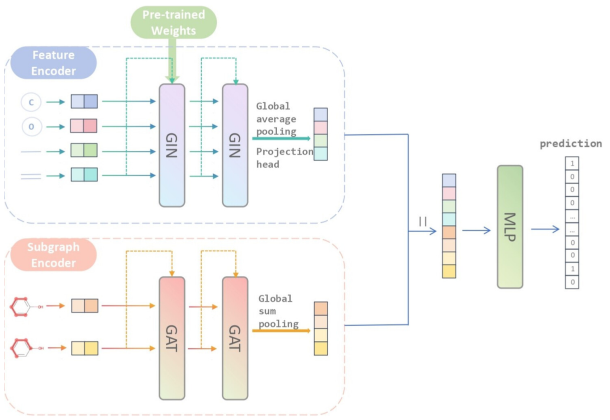
Predicting how molecules should act

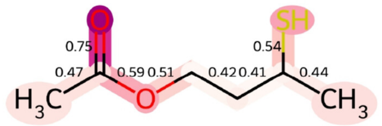
Machine learning



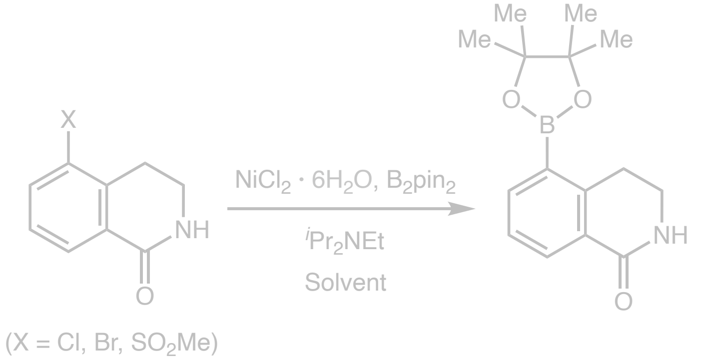


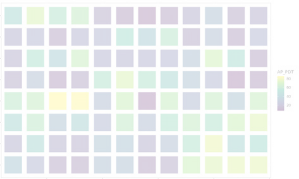
Neural networks

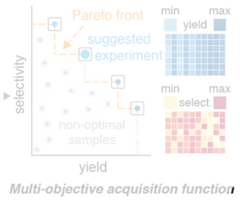




Data Science





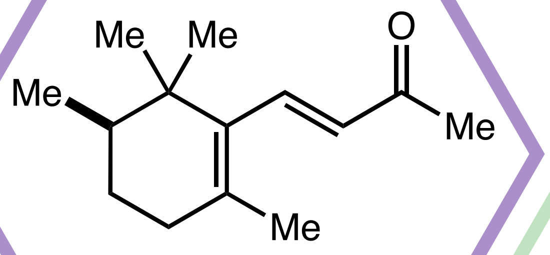


Predicting how molecules should act

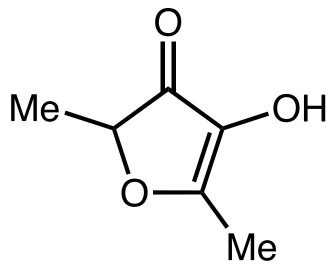
Neural networks for predicting molecular odors

Predicting how molecules should act

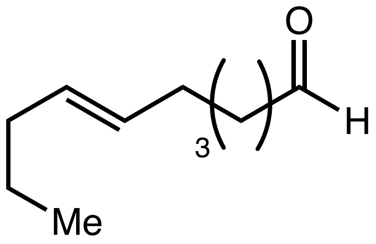
Neural networks for predicting molecular odors



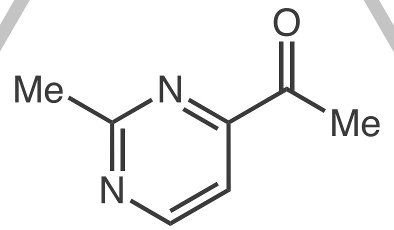
β-irone
(violet)



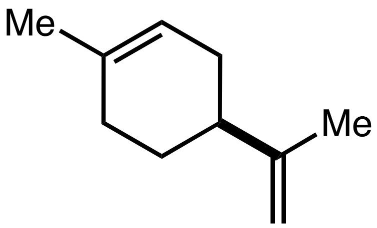
furaneol
(strawberry)



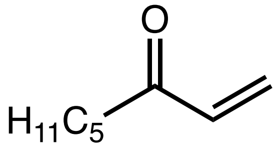
***(E)*-dec-6-enal**
(cucumber)



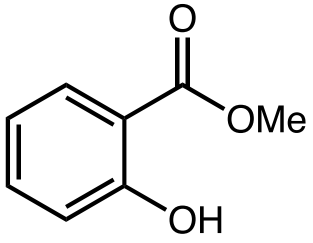
4-acetyl-2-methyl pyrimidine
(burnt)



limonene
(orange)



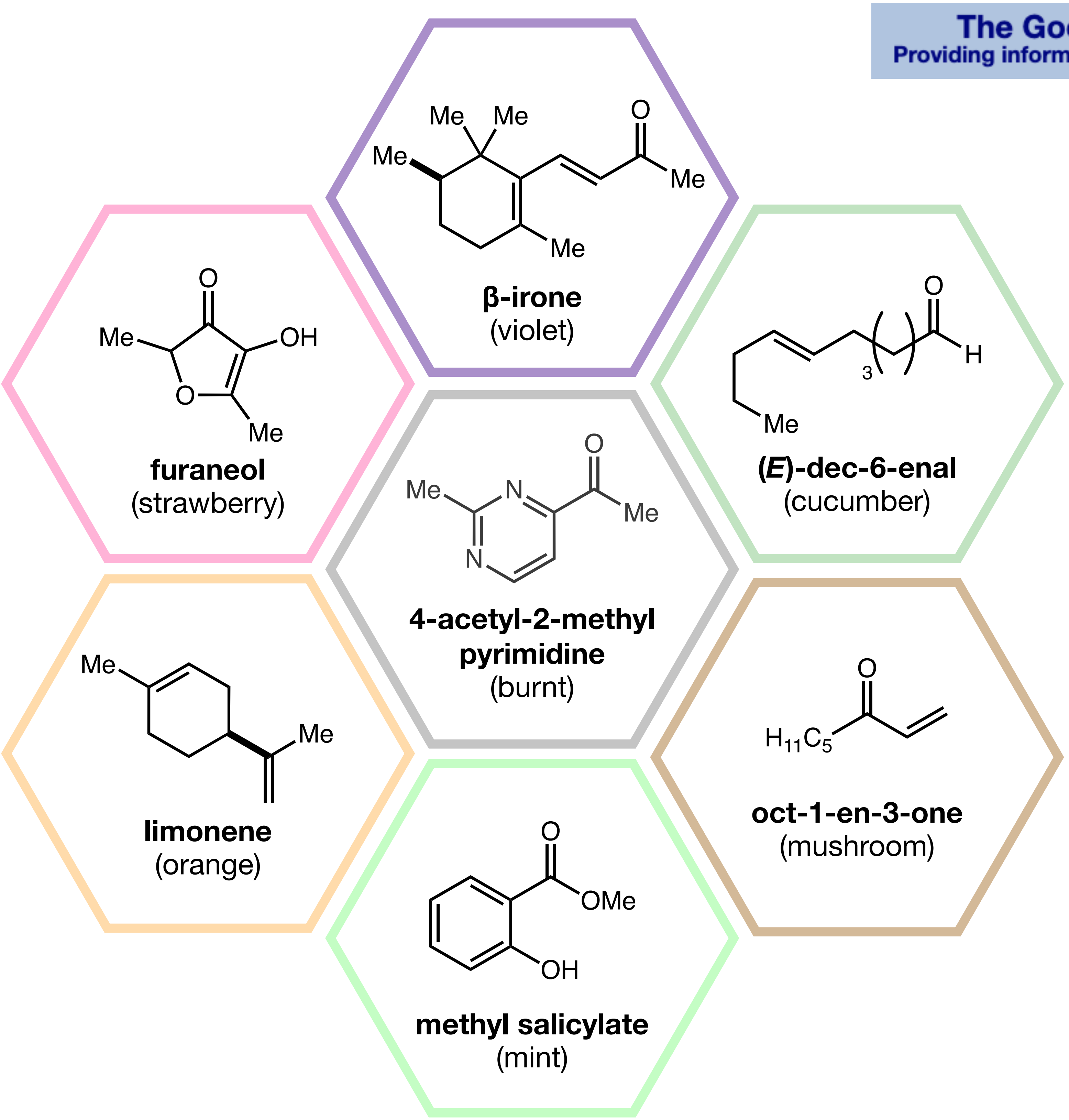
oct-1-en-3-one
(mushroom)



methyl salicylate
(mint)

Predicting how molecules should act

Neural networks for predicting molecular odors



β-irone
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furaneol
(strawberry)

***(E)*-dec-6-enal**
(cucumber)

4-acetyl-2-methyl pyrimidine
(burnt)

limonene
(orange)

oct-1-en-3-one
(mushroom)

methyl salicylate
(mint)

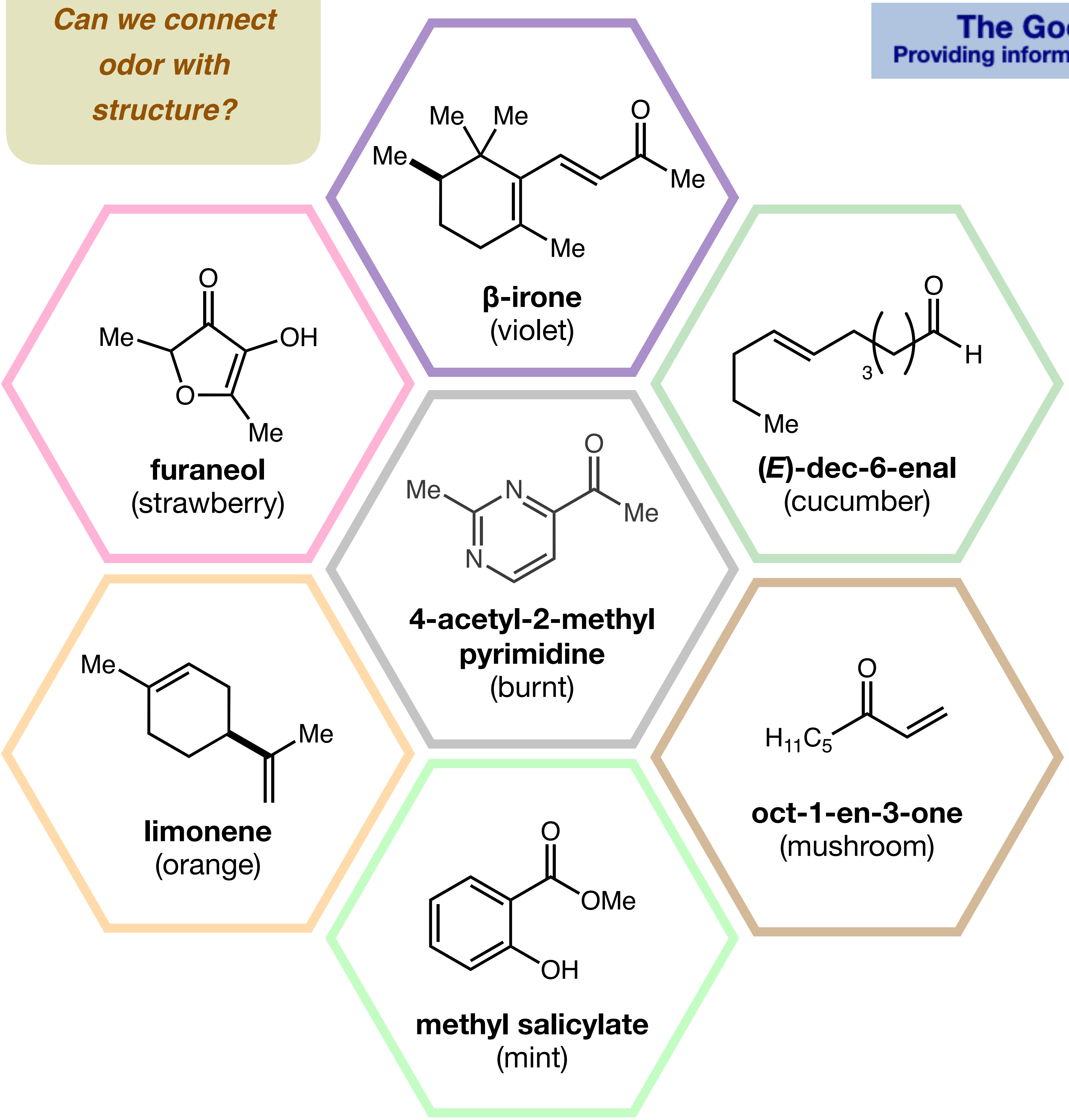
The Good Scents Company Information System
Providing information for the Flavor, Fragrance, Food and Cosmetic industries.

alcoholic
aldehydic
alliaceous
almond
amber
animal
anisic
apple
apricot
aromatic
balsamic
banana
beefy
bergamot
berry
bitter
black currant
brandy
burnt
buttery
cabbage
camphoreous
caramellic
cedar
celery
chamomile
cheesy
cherry
chocolate
cinnamon
citrus
clean
clove
cocoa
coconut
coffee
cognac
cooked
cooling
cortex
coumarinic
creamy
cucumber
dairy
dry
earthy
ethereal
fatty
fermented
fishy
floral
fresh
fruit skin
fruity
garlic
gassy
geranium
grape
grapefruit
grassy
green
hawthorn
hay
hazelnut
herbal
honey
hyacinth
jasmin
juicy
ketonic
lactonic
lavender
leafy
leathery
lemon
lily
malty
meaty
medicinal
melon
metallic
milky
mint
muguet
mushroom
musk
musty
natural
nutty
odorless
oily
onion
orange
orangeflower
orris
ozone
peach
pear
phenolic
pine
pineapple
plum
popcorn
potato
powdery
pungent
radish
raspberry
ripe
roasted
rose
rummy
sandalwood
savory
sharp
smoky
soapy
solvent
sour
spicy
strawberry
sulfurous
sweaty
sweet
tea
terpenic
tobacco
tomato
tropical
vanilla
vegetable
vetiver
violet
warm
waxy
weedy
winey
woody

Predicting how molecules should act

Neural networks for predicting molecular odors

Can we connect odor with structure?



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(violet)

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chamomile
cheesy
cherry
chocolate
cinnamon
citrus
clean
clove
cocoa
coconut
coffee
cognac
cooked
cooling
cortex
coumarinic
creamy
cucumber
dairy
dry
earthy
ethereal
fatty
fermented
fishy
floral
fresh
fruit skin
fruity
garlic
gassy
geranium
grape
grapefruit
grassy
green
hawthorn
hay
hazelnut
herbal
honey
hyacinth
jasmin
juicy
ketonic
lactonic
lavender
leafy
leathery
lemon
lily
malty
meaty
medicinal
melon
metallic
milky
mint
muguet
mushroom
musk
musty
natural
nutty
odorless
oily
onion
orange
orangeflower
orris
ozone
peach
pear
phenolic
pine
pineapple
plum
popcorn
potato
powdery
pungent
radish
raspberry
ripe
roasted
rose
rummy
sandalwood
savory
sharp
smoky
soapy
solvent
sour
spicy
strawberry
sulfurous
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tobacco
tomato
tropical
vanilla
vegetable
vetiver
violet
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weedy
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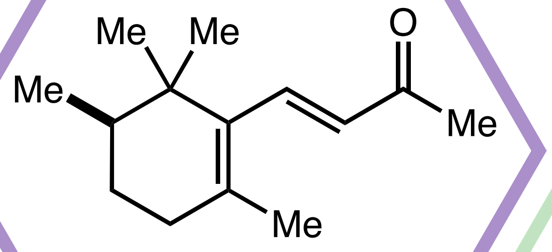
Jiang, Y.; Xie, X.; Yang, Y.; Liu, Y.; Gong,, K.; Li, T. *J. Comp. Chem.* **2025**, *46*, e70069.

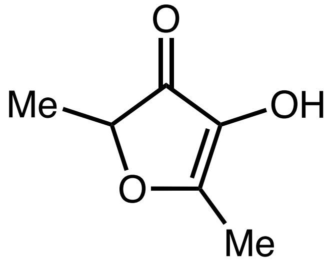
Predicting how molecules should act

Neural networks for predicting molecular odors

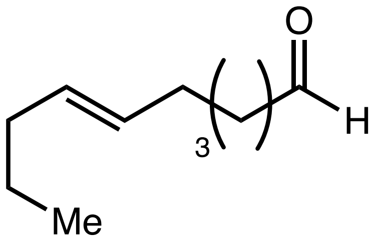
Can we connect odor with structure?



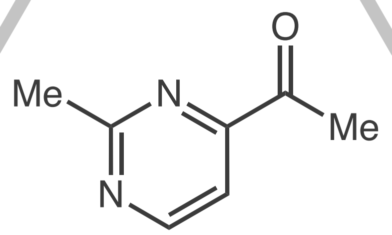
β-irone
(violet)



furaneol
(strawberry)



(*E*)-dec-6-enal
(cucumber)



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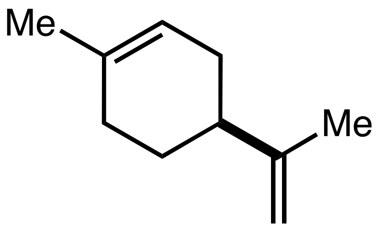
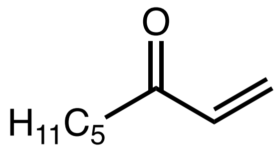
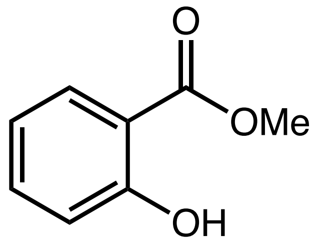


limonene
(orange)



oct-1-en-3-one
(mushroom)



methyl salicylate
(mint)

Can we predict odor given structure?

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brandy
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buttery
cabbage
camphoreous
caramellic
cedar
celery
chamomile
cheesy
cherry
chocolate
cinnamon
citrus
clean
clove
cocoa
coconut
coffee
cognac
cooked
cooling
cortex
coumarinic
creamy
cucumber
dairy
dry
earthy

ethereal
fatty
fermented
fishy
floral
fresh
fruit skin
fruity
garlic
gassy
geranium
grape
grapefruit
grassy
green
hawthorn
hay
hazelnut
herbal
honey
hyacinth
jasmin
juicy
ketonic
lactonic
lavender
leafy
leathery
lemon
lily
malty
meaty
medicinal
melon
metallic
milky
mint
muguet
mushroom
musk
musty
natural
nutty
odorless
oily
onion

orange
orangeflower
orris
ozone
peach
pear
phenolic
pine
pineapple
plum
popcorn
potato
powdery
pungent
radish
raspberry
ripe
roasted
rose
rummy
sandalwood
savory
sharp
smoky
soapy
solvent
sour
spicy
strawberry
sulfurous
sweaty
sweet
tea
terpenic
tobacco
tomato
tropical
vanilla
vegetable
vetiver
violet
warm
waxy
weedy
winey
woody

Jiang, Y.; Xie, X.; Yang, Y.; Liu, Y.; Gong,, K.; Li, T. *J. Comp. Chem.* **2025**, *46*, e70069.

Predicting how molecules should act

Basics of neural networks

How Do Neural Network Systems Work? computerhistory.org/blog/how-do-neural-network-systems-work/

Predicting how molecules should act

Basics of neural networks

FIG. 1 — Organization of a biological brain. (Red areas indicate active cells, responding to the letter X.)

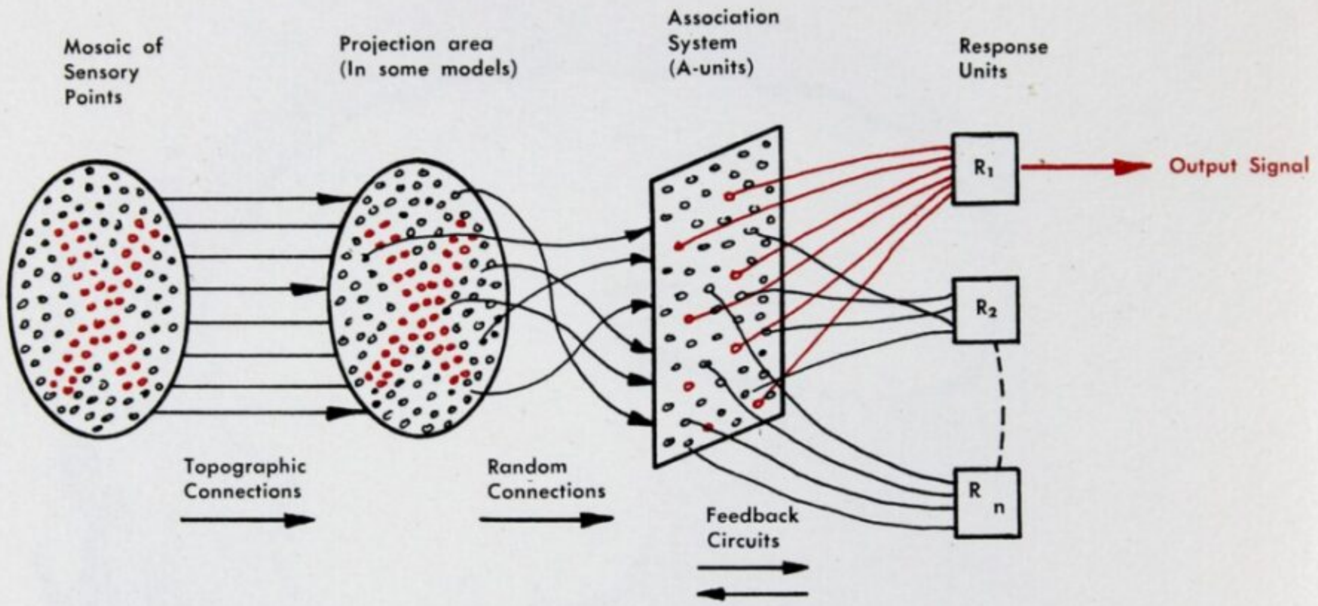

FIG. 2 — Organization of a perceptron.

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Predicting how molecules should act

Basics of neural networks

FIG. 1 — Organization of a biological brain. (Red areas indicate active cells, responding to the letter X.)

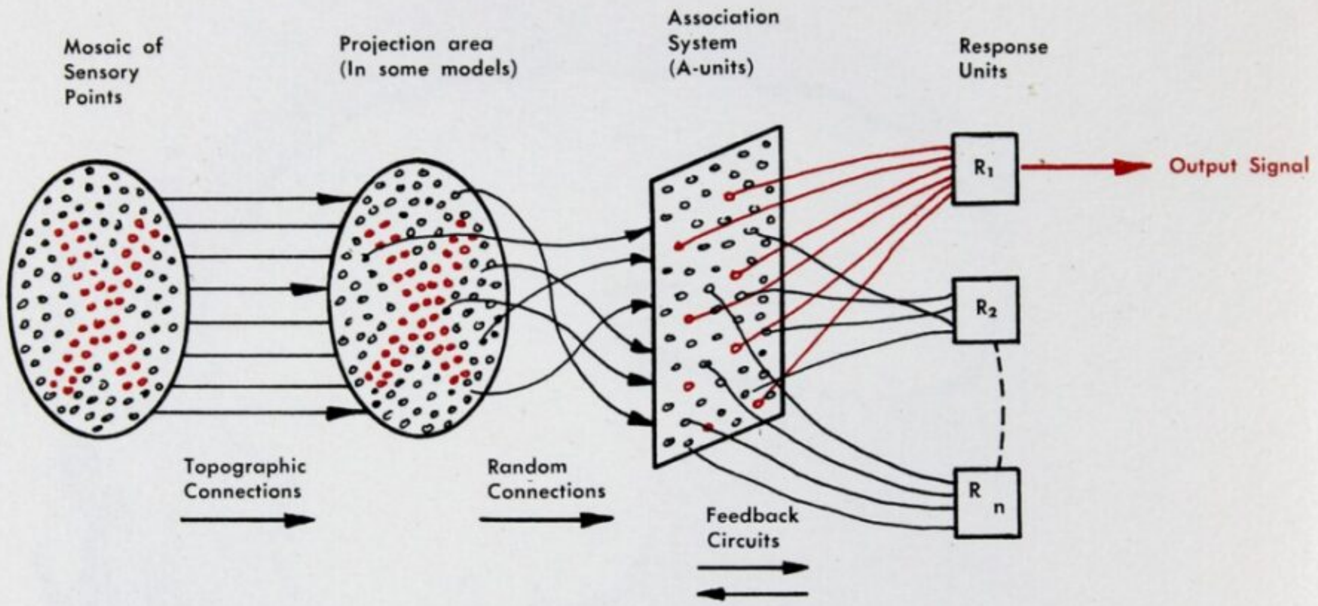
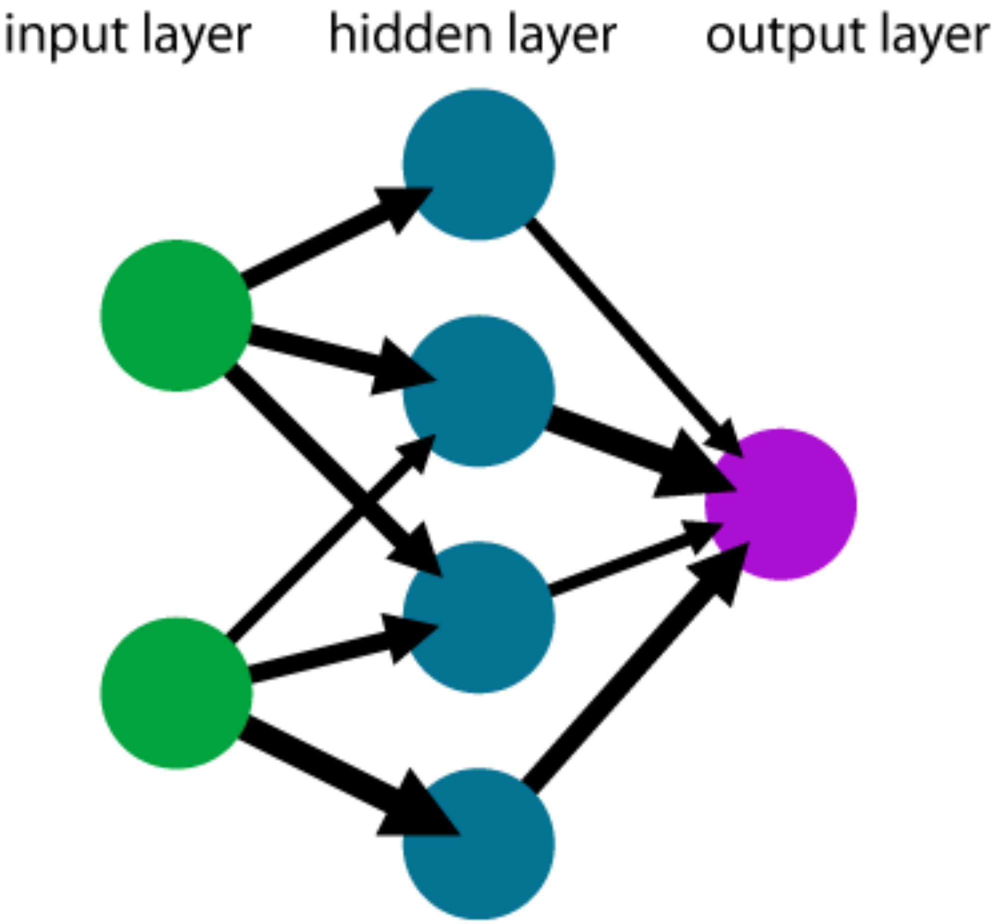


FIG. 2 — Organization of a perceptron.

A simple neural network



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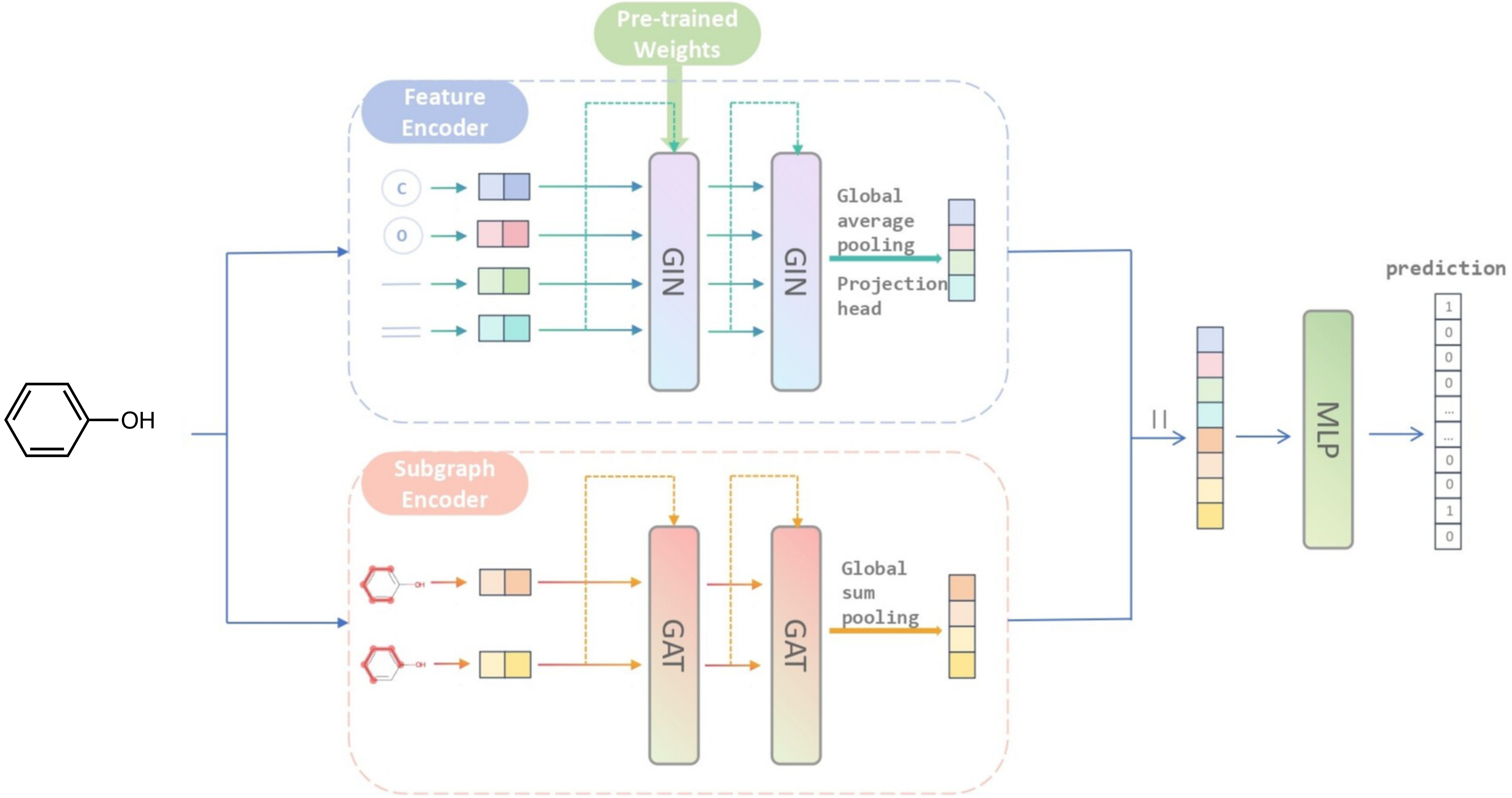
Predicting how molecules should act

Workflow for ScentGraphX



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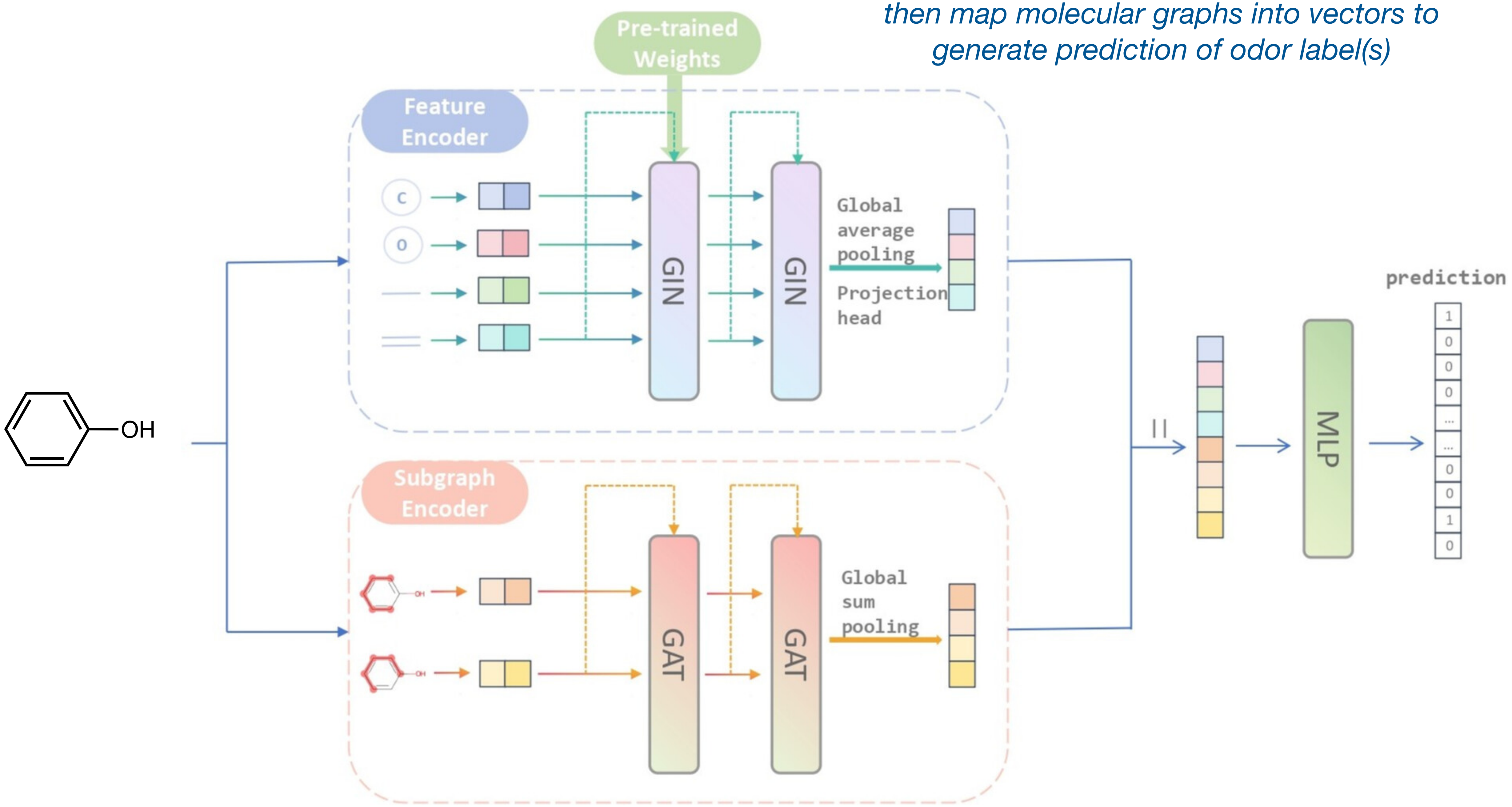
Predicting how molecules should act

Workflow for ScentGraphX

Feature encoder: *Convert structures to graphs, then map molecular graphs into vectors to generate prediction of odor label(s)*



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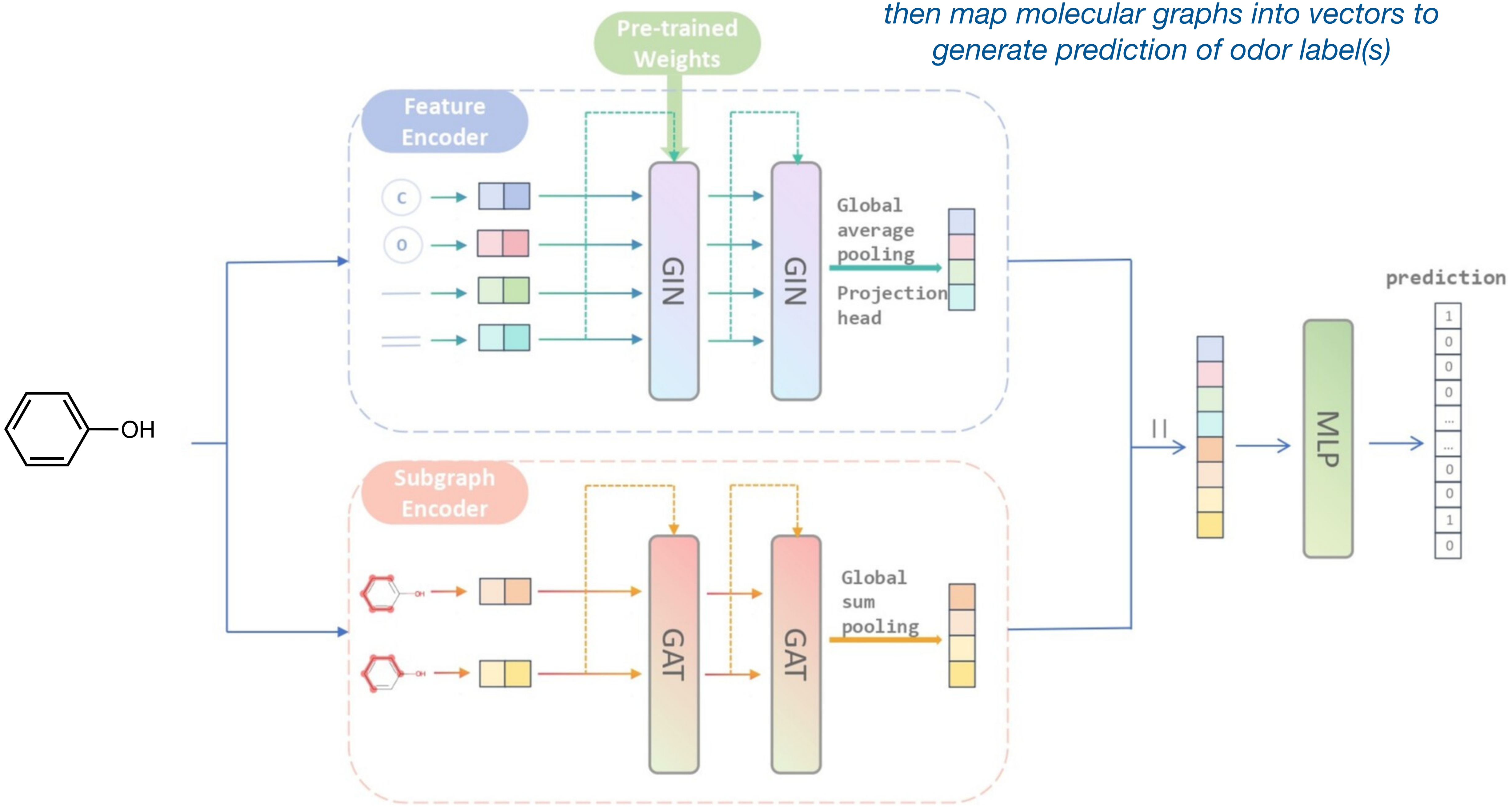
Predicting how molecules should act

Workflow for ScentGraphX



***Feature encoder:** Convert structures to graphs, then map molecular graphs into vectors to generate prediction of odor label(s)*

***Subgraph Encoder:** Provides model with more features based on substructures to improve prediction of odor label(s)*

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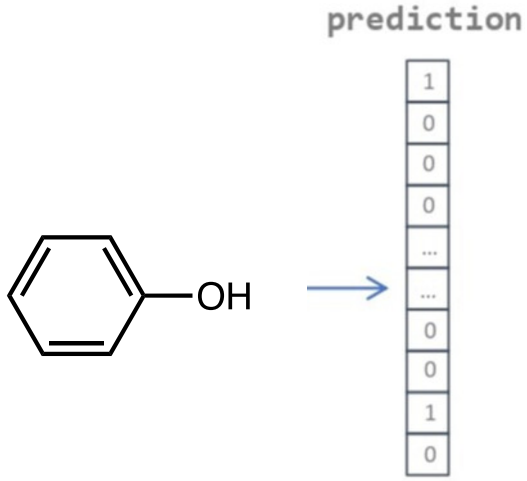
Predicting how molecules should act

Predicting odors with ScentGraphX



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Predicting how molecules should act

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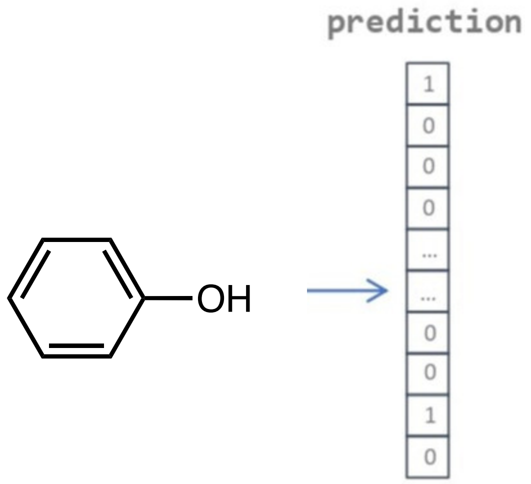

Predictions are tested for…

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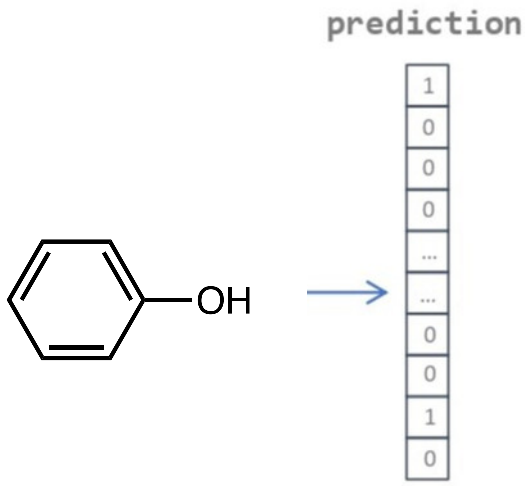

Predictions are tested for…

✓ ***Precision*** *— How often are positive predictions correct?*

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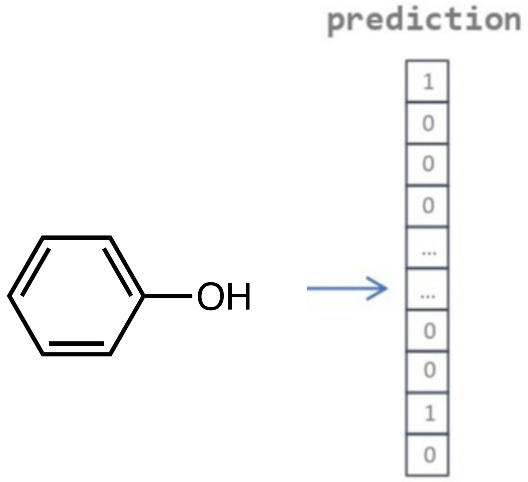

Predictions are tested for…

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✓ ***Recall*** *— How good is the model at finding positive results?*

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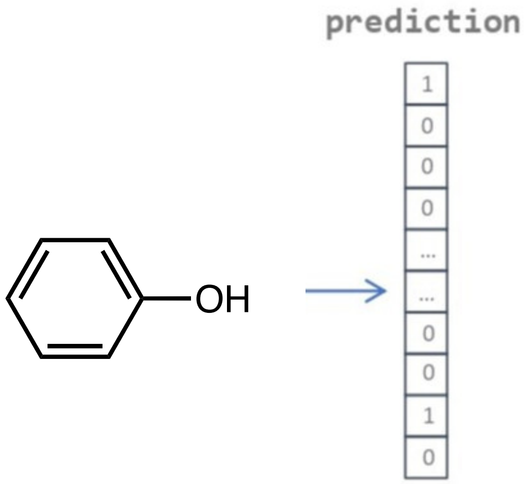
Predicting how molecules should act

Predicting odors with ScentGraphX



Predictions are tested for…

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✓ ***Recall*** *— How good is the model at finding positive results?*

✓ ***F1 score*** *— Combination of precision and recall*

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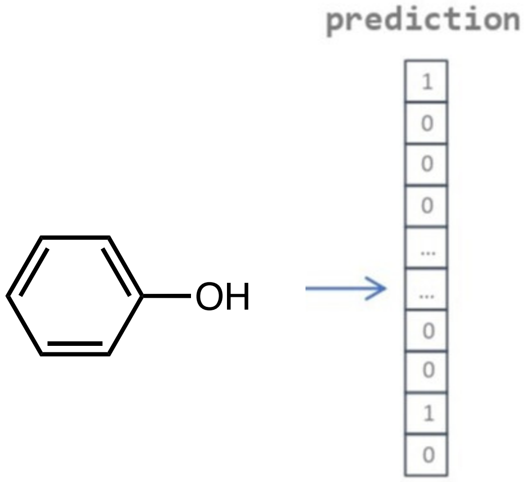
Predicting how molecules should act

Predicting odors with ScentGraphX



Predictions are tested for…

- ✓ ***Precision*** *— How often are positive predictions correct?*
- ✓ ***Recall*** *— How good is the model at finding positive results?*
- ✓ ***F1 score*** *— Combination of precision and recall*
- ✓ ***AUCROC*** *— Probability that the model, if given a randomly chosen positive and negative example, will rank the positive higher than the negative*

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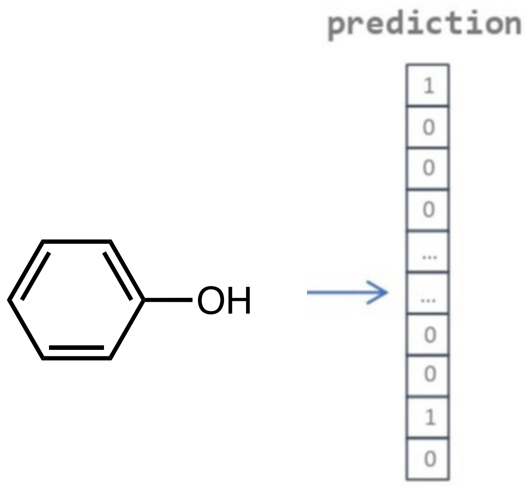
Predicting how molecules should act

Predicting odors with ScentGraphX



Predictions are tested for…

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Given 4967 molecules (each with multiple odor labels), ScentGraphX has improved performance on all 4 metrics over previous models.

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Predicting how molecules should act

Interpretability of ScentGraphX results

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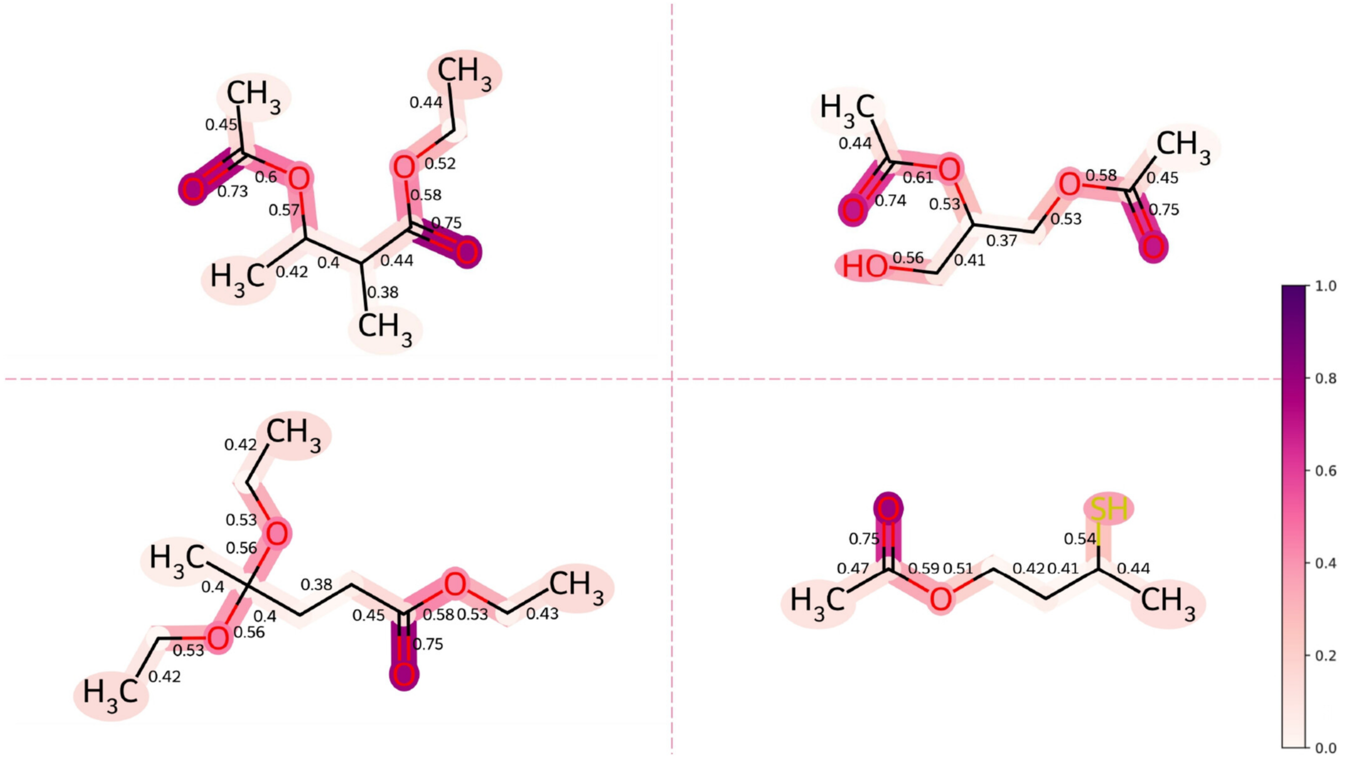

Contribution to “fruity” scent

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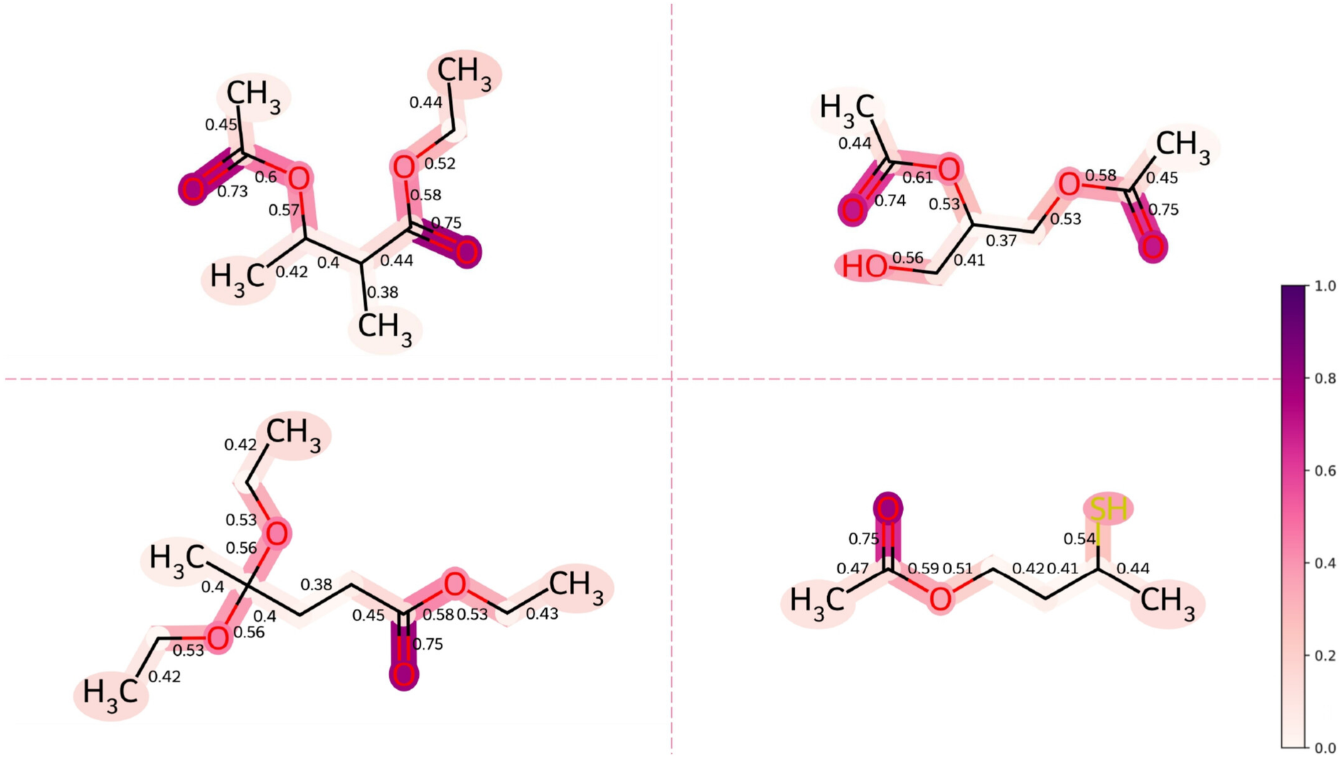
Predicting how molecules should act

Interpretability of ScentGraphX results



Contribution to
“fruity” scent

Subgraph encoding provides unique insight into the effects of functional groups on scents

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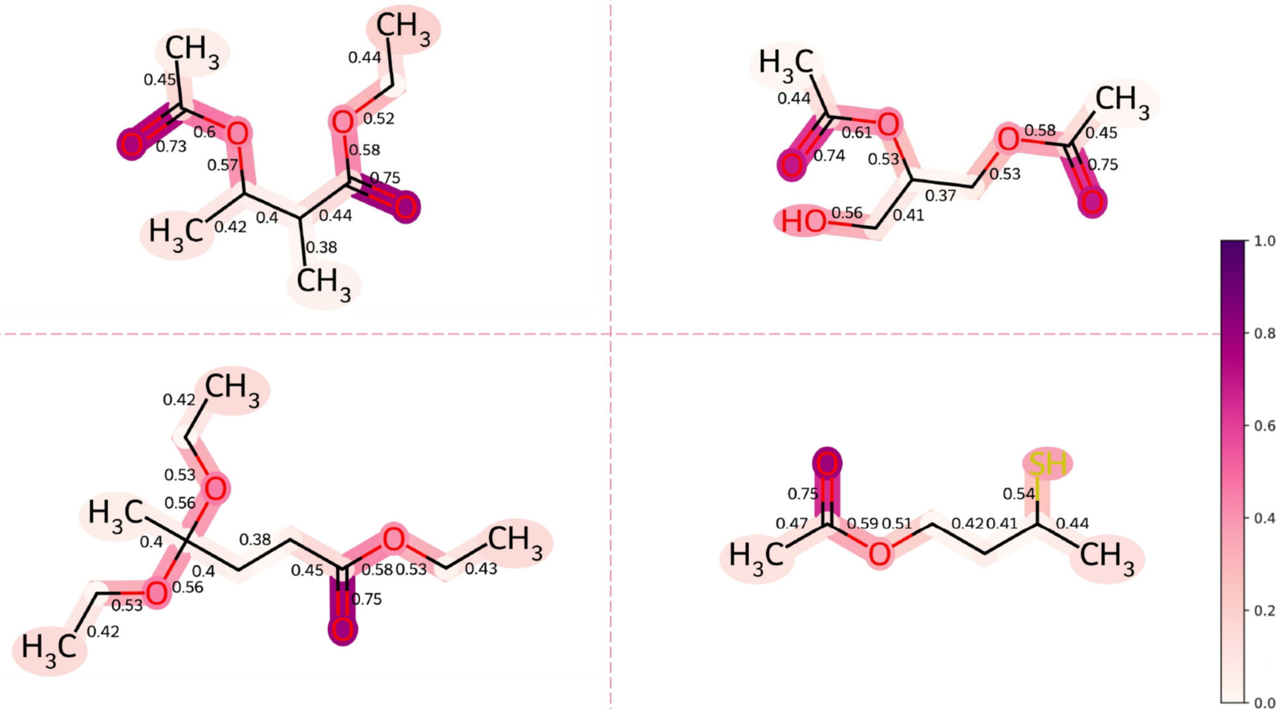

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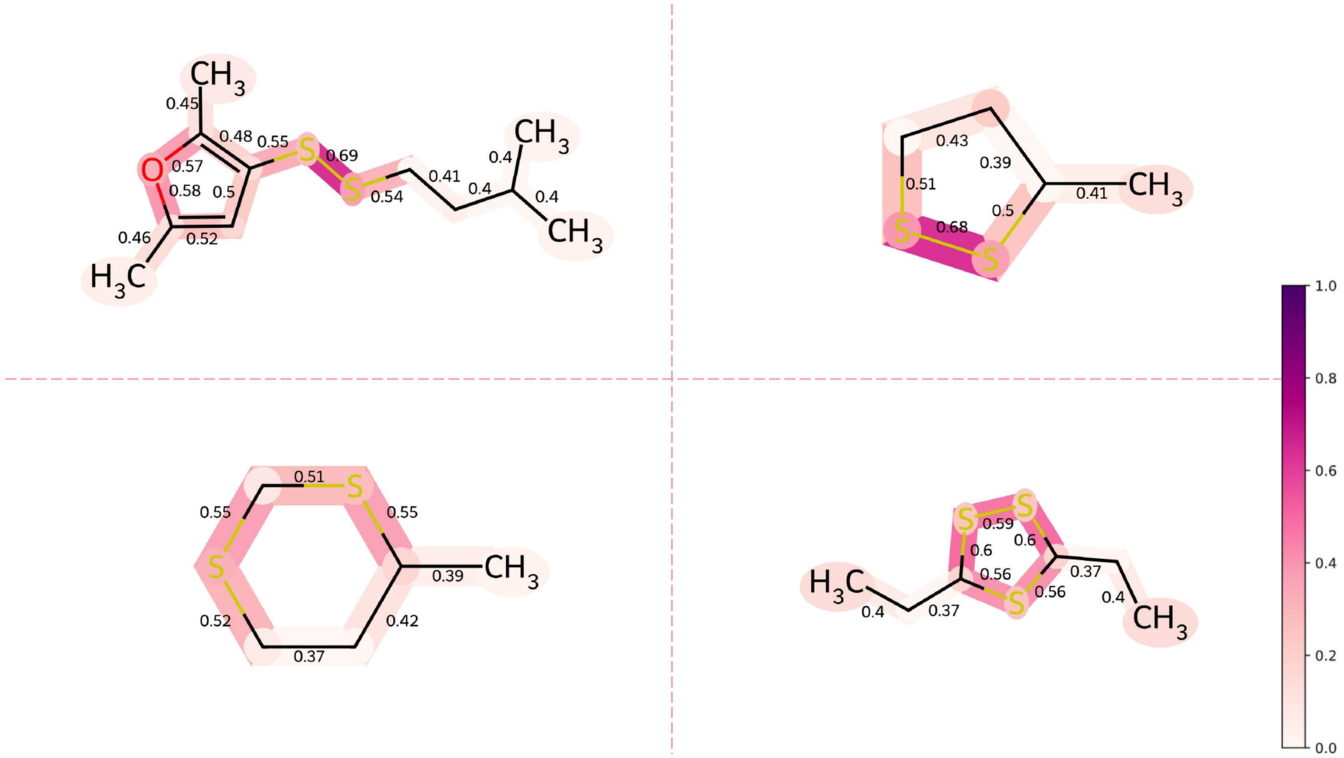

Contribution to “sulfurous” scent

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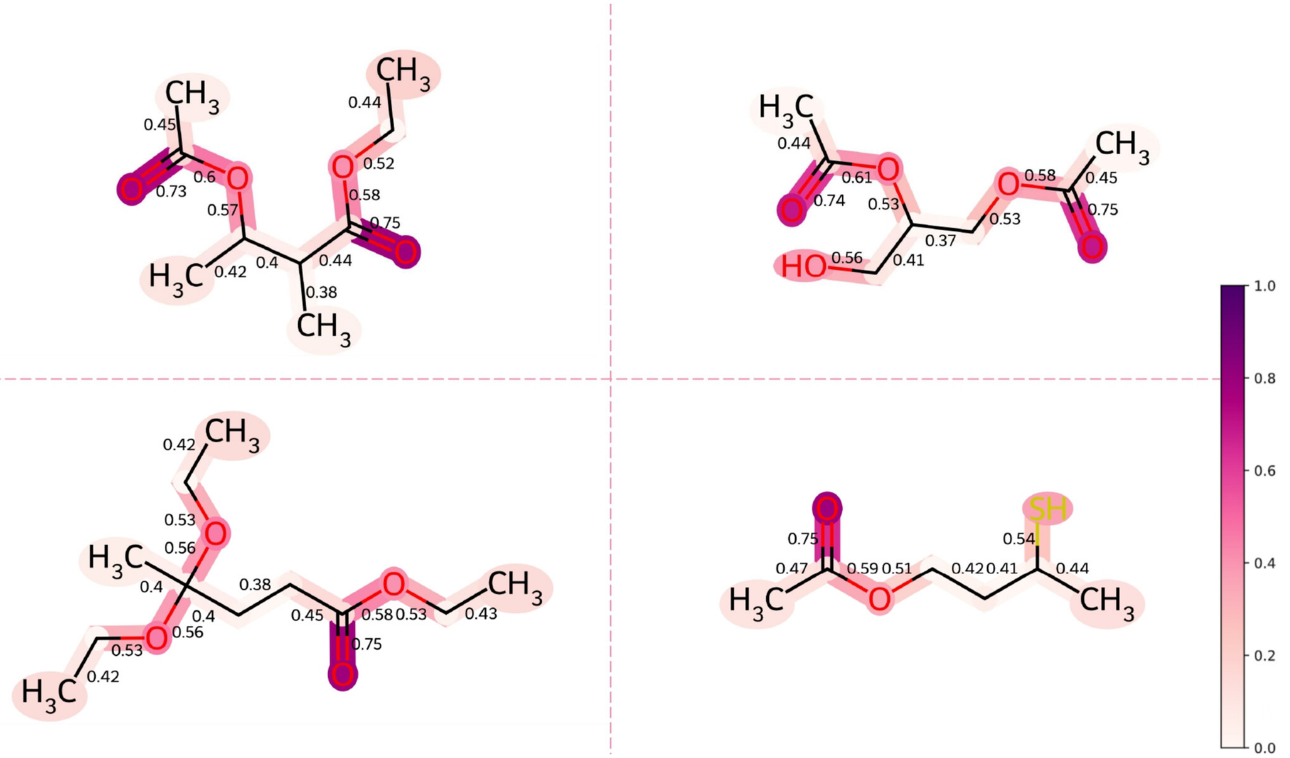
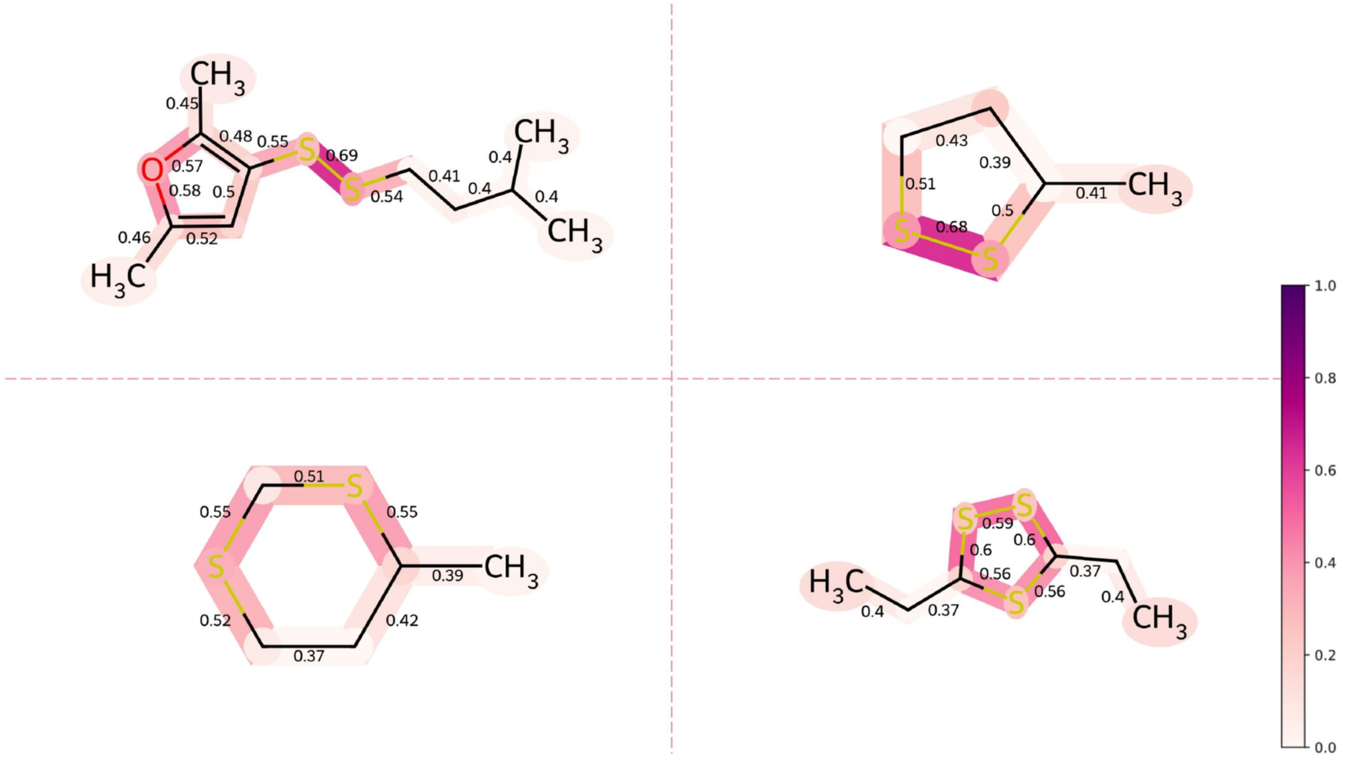
Interpretability of ScentGraphX results



Contribution to "fruity" scent

Subgraph encoding provides unique insight into the effects of functional groups on scents

ScentGraphX learned to identify functional groups that have the strongest effects on scent



Contribution to "sulfurous" scent

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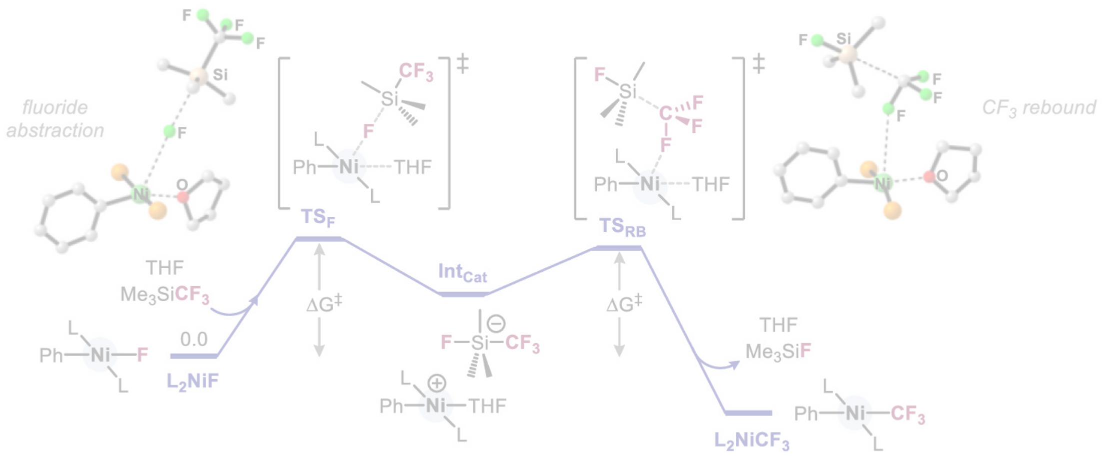
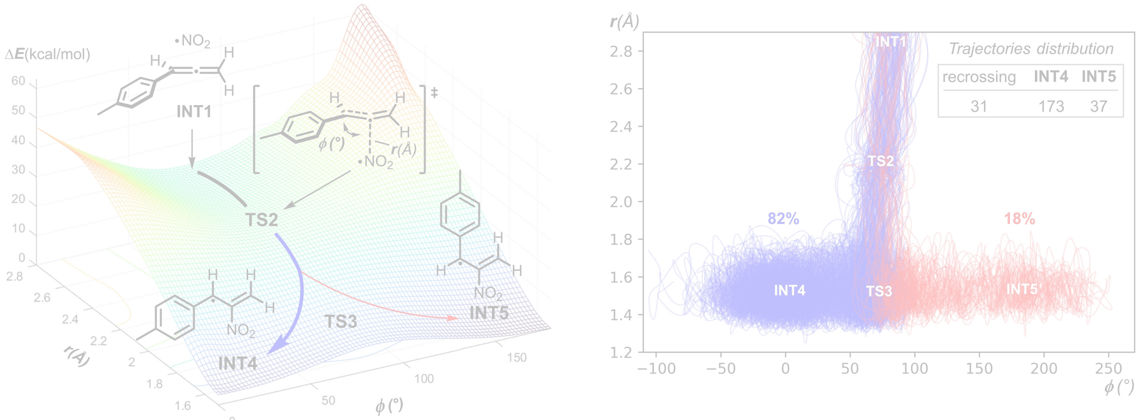
What can computational chemistry do for you?

Understanding how molecules act

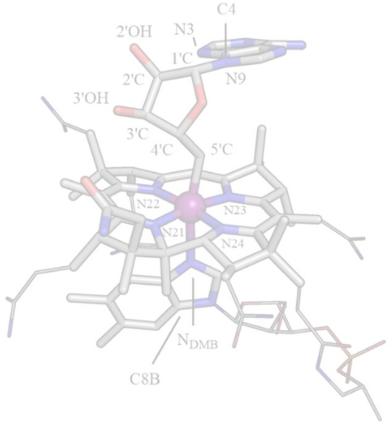
Density functional theory

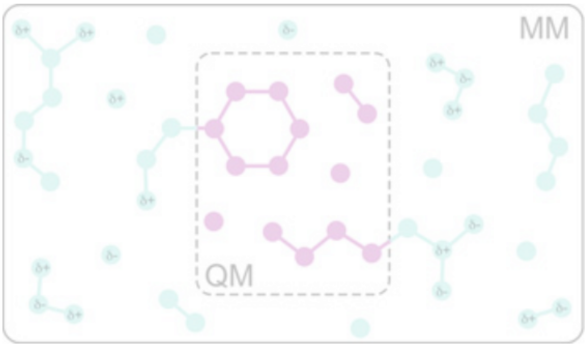


Dynamics Simulations



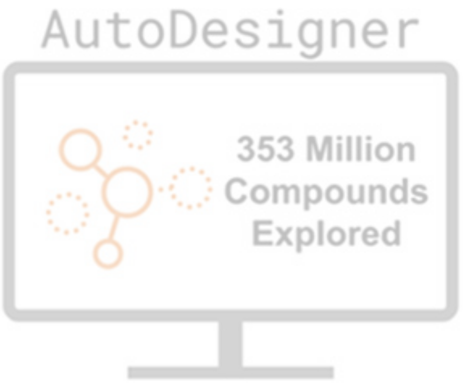
QM/MM

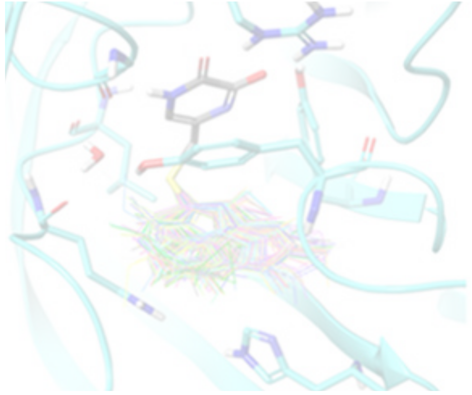




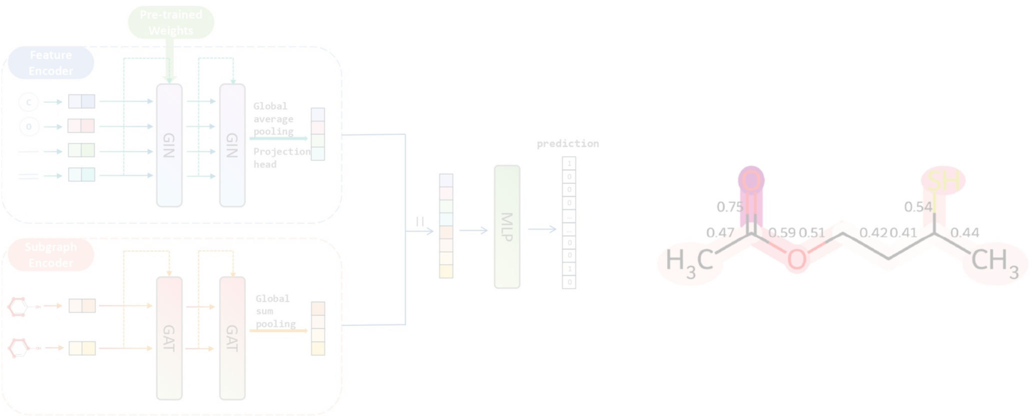
Predicting how molecules should act

Machine learning

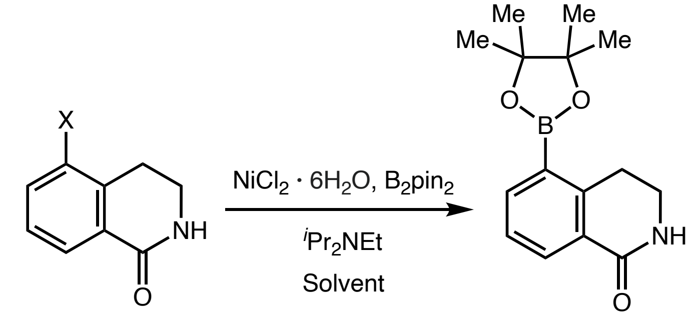




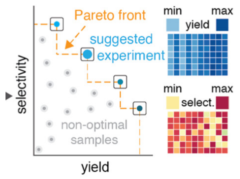
Neural networks



Data Science



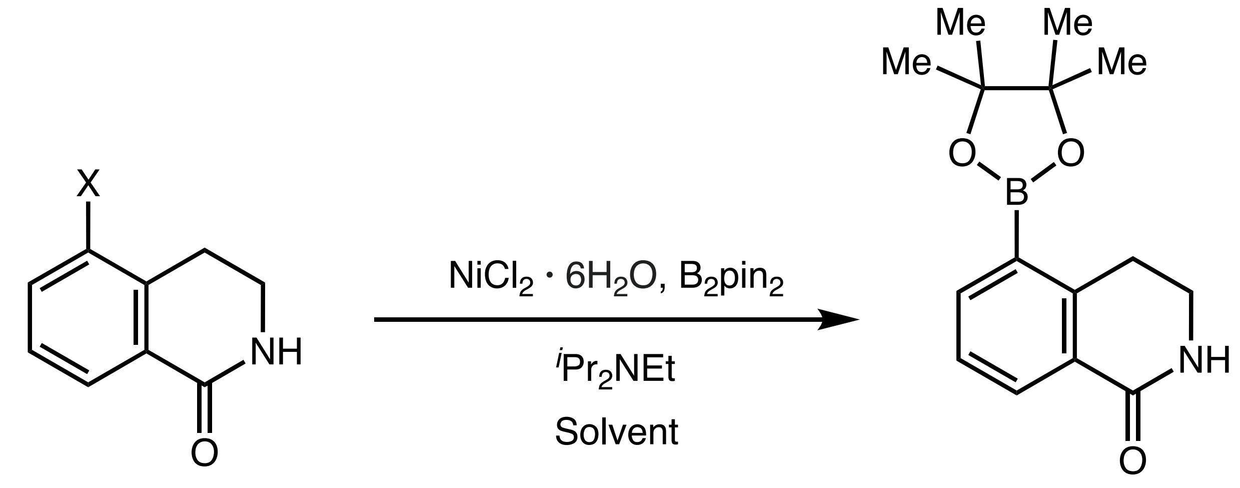
(X = Cl, Br, SO$_2$Me)



Multi-objective acquisition function

Predicting how molecules should act

Development of sustainable catalytic processes with data science



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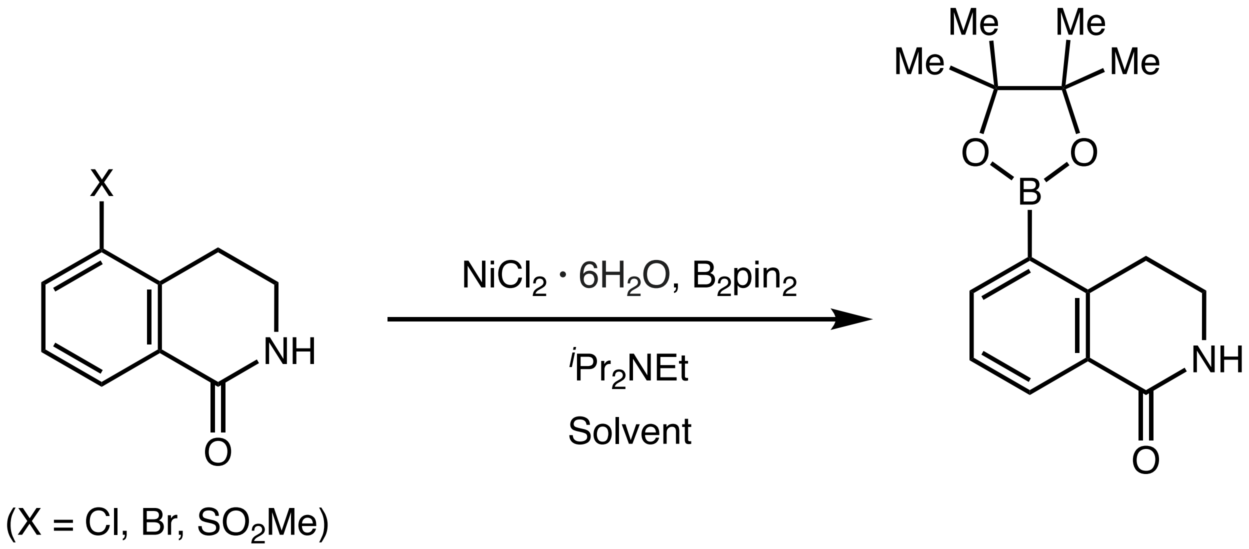
Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.

Predicting how molecules should act

Development of sustainable catalytic processes with data science



Can data science approaches be used to rapidly develop and optimize a reaction?

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Development of sustainable catalytic processes with data science

workflow for accelerating catalysis optimization with data-science

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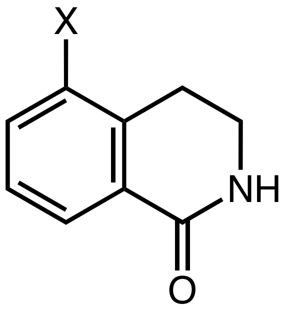

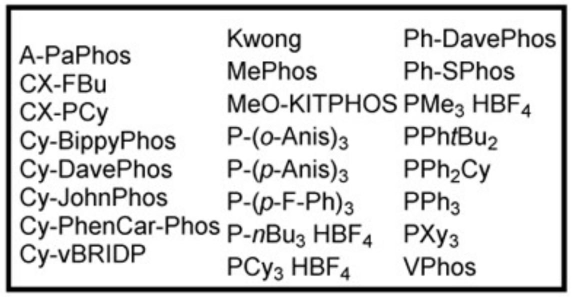
A-PaPhos
CX-FBu
CX-PCy
Cy-BippyPhos
Cy-DavePhos
Cy-JohnPhos
Cy-PhenCar-Phos
Cy-vBRIDP

Kwong
MePhos
MeO-KITPHOS
P-(*o*-Anis)$_3$
P-(*p*-Anis)$_3$
P-(*p*-F-Ph)$_3$
P-*n*Bu$_3$ HBF$_4$
PCy$_3$ HBF$_4$

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Ph-SPhos
PMe$_3$ HBF$_4$
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PPh$_2$Cy
PPh$_3$
PXy$_3$
VPhos

ligand library

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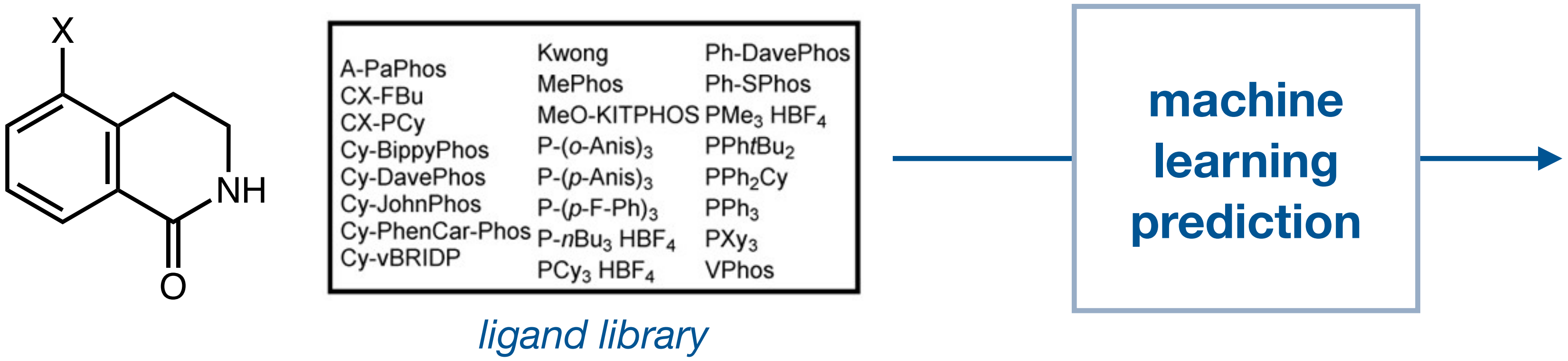

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machine learning prediction

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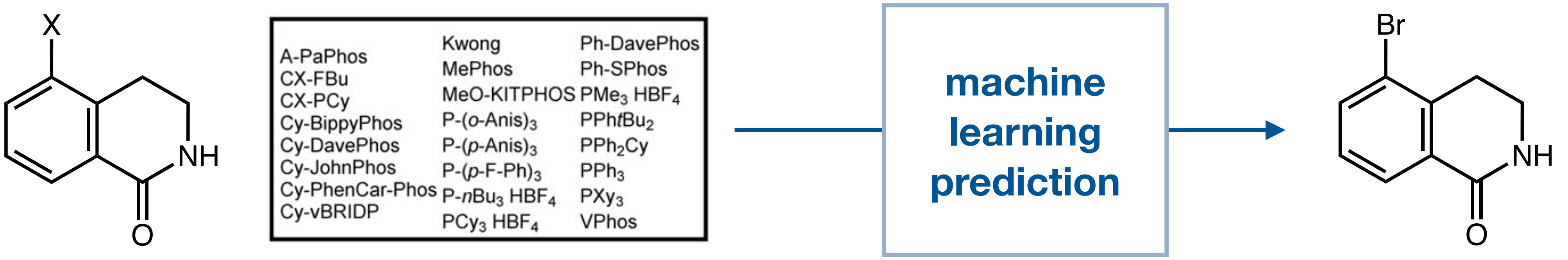
Predicting how molecules should act

Development of sustainable catalytic processes with data science



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machine learning prediction

top substrate candidate

workflow for accelerating catalysis optimization with data-science

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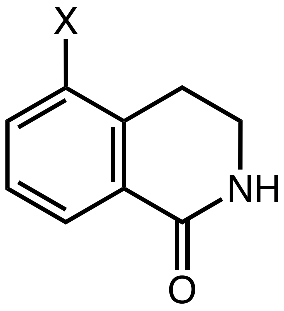
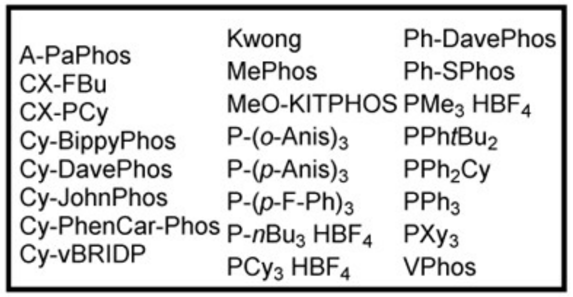
Predicting how molecules should act

Development of sustainable catalytic processes with data science

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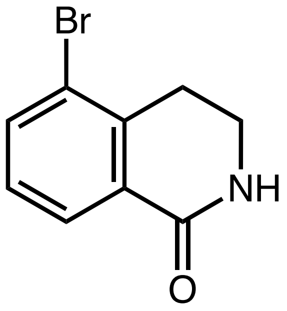
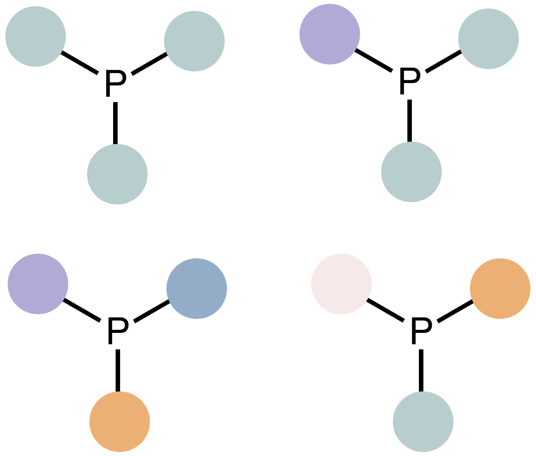
machine learning prediction



top substrate candidate



top ligand candidates

workflow for accelerating catalysis optimization with data-science

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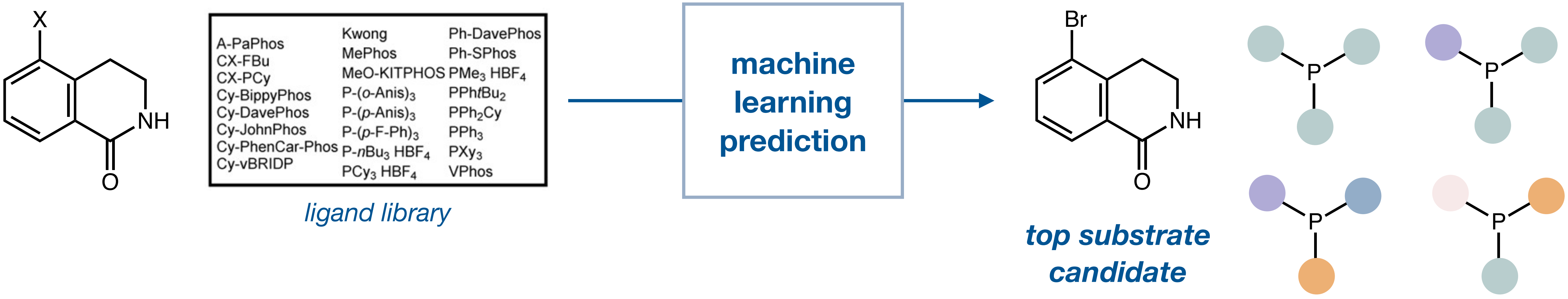
Development of sustainable catalytic processes with data science



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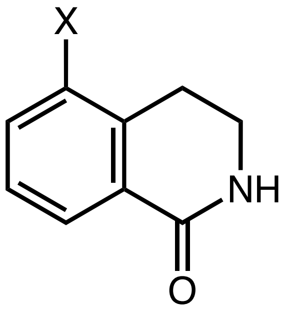
Predicting how molecules should act

Development of sustainable catalytic processes with data science



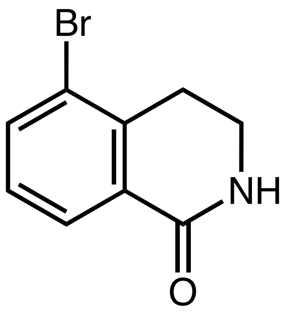
A-PaPhos
CX-FBu
CX-PCy
Cy-BippyPhos
Cy-DavePhos
Cy-JohnPhos
Cy-PhenCar-Phos
Cy-vBRIDP

Kwong
MePhos
MeO-KITPHOS
P-(*o*-Anis)$_3$
P-(*p*-Anis)$_3$
P-(*p*-F-Ph)$_3$
P-*n*Bu$_3$ HBF$_4$
PCy$_3$ HBF$_4$

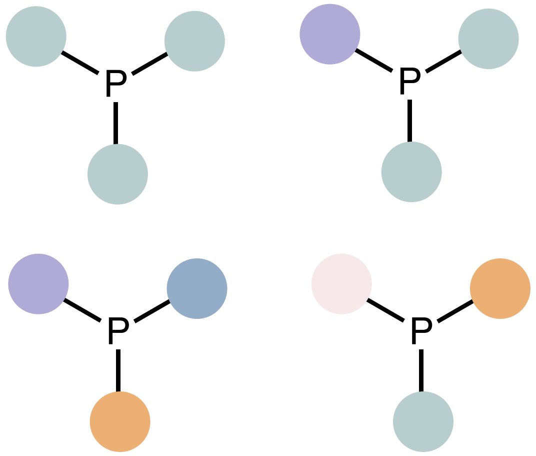
Ph-DavePhos
Ph-SPhos
PMe$_3$ HBF$_4$
PPh*t*Bu$_2$
PPh$_2$Cy
PPh$_3$
PXy$_3$
VPhos

ligand library

machine learning prediction



top substrate candidate



top ligand candidates

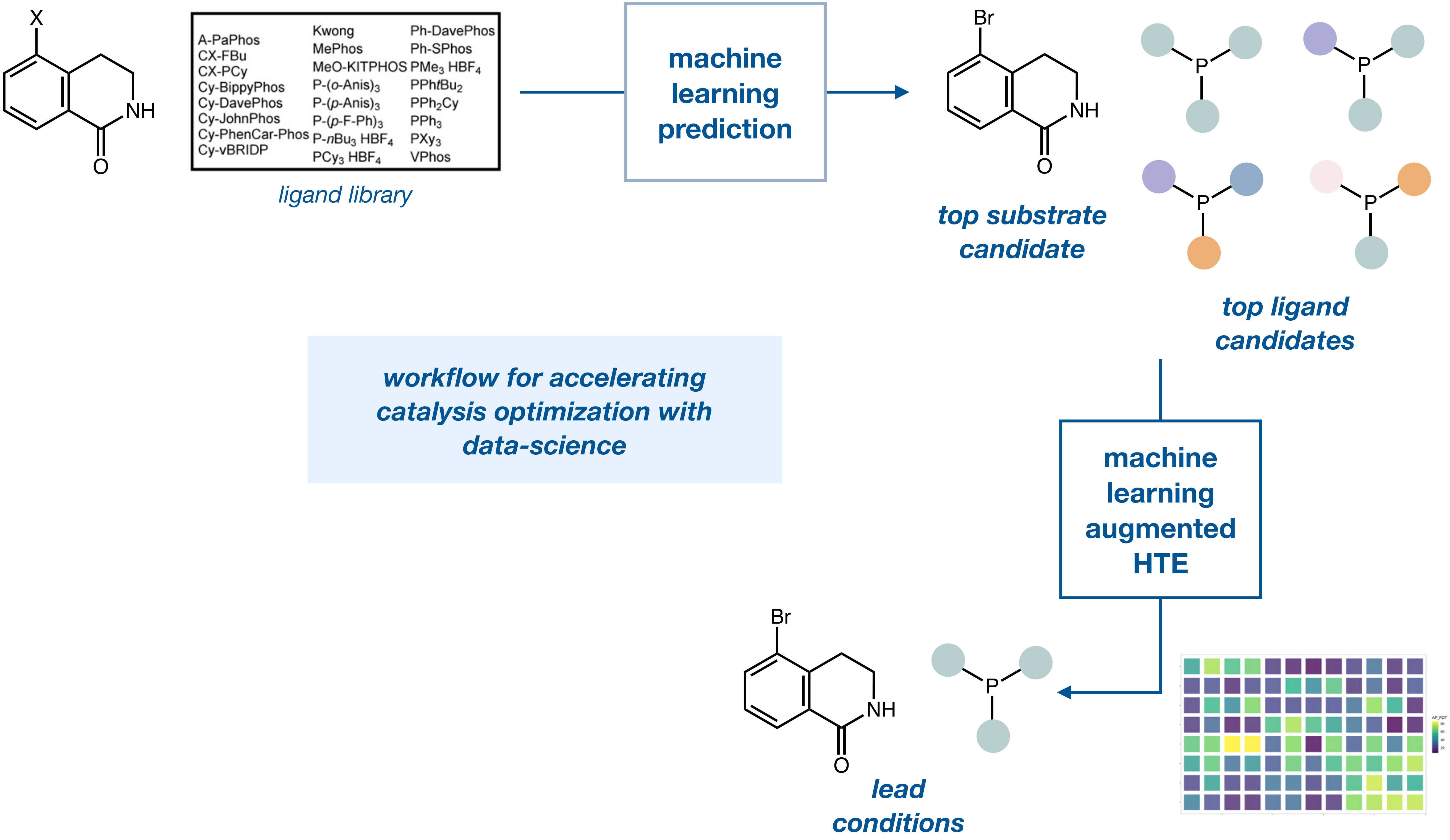
workflow for accelerating catalysis optimization with data-science

machine learning augmented HTE

Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.

Predicting how molecules should act

Development of sustainable catalytic processes with data science



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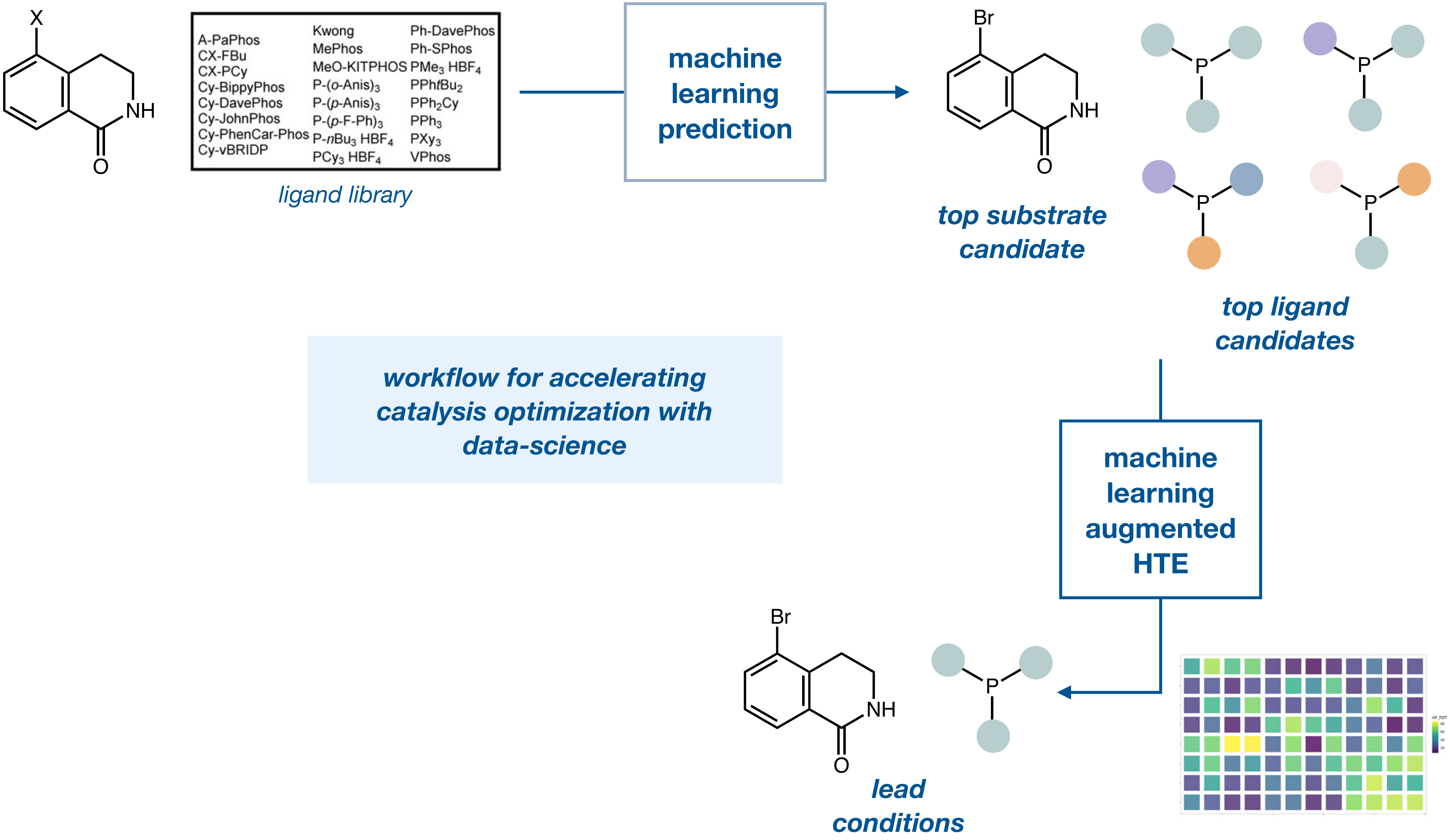
Predicting how molecules should act

Development of sustainable catalytic processes with data science



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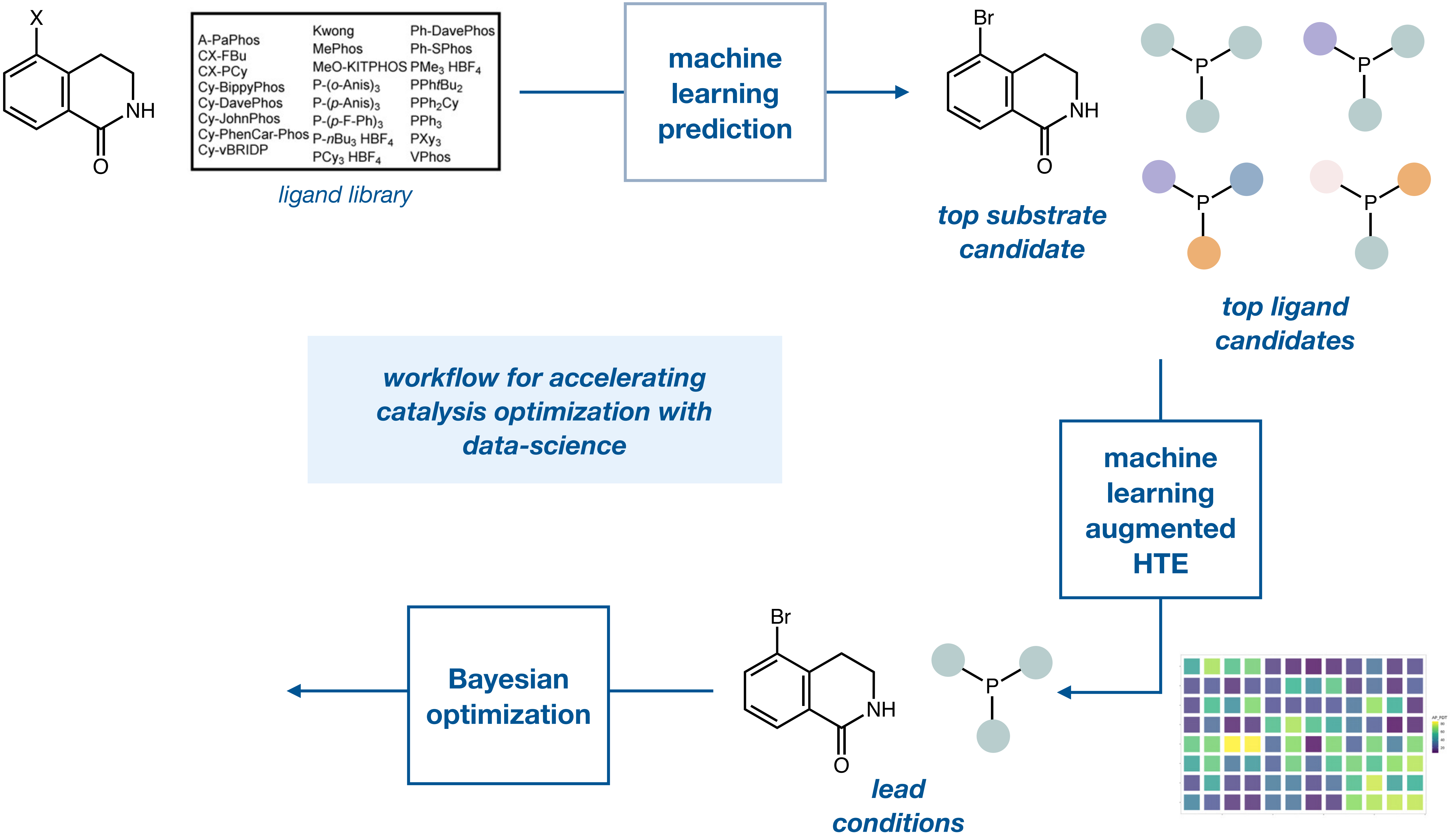
Predicting how molecules should act

Development of sustainable catalytic processes with data science



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ligand library

machine learning prediction

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workflow for accelerating catalysis optimization with data-science

machine learning augmented HTE

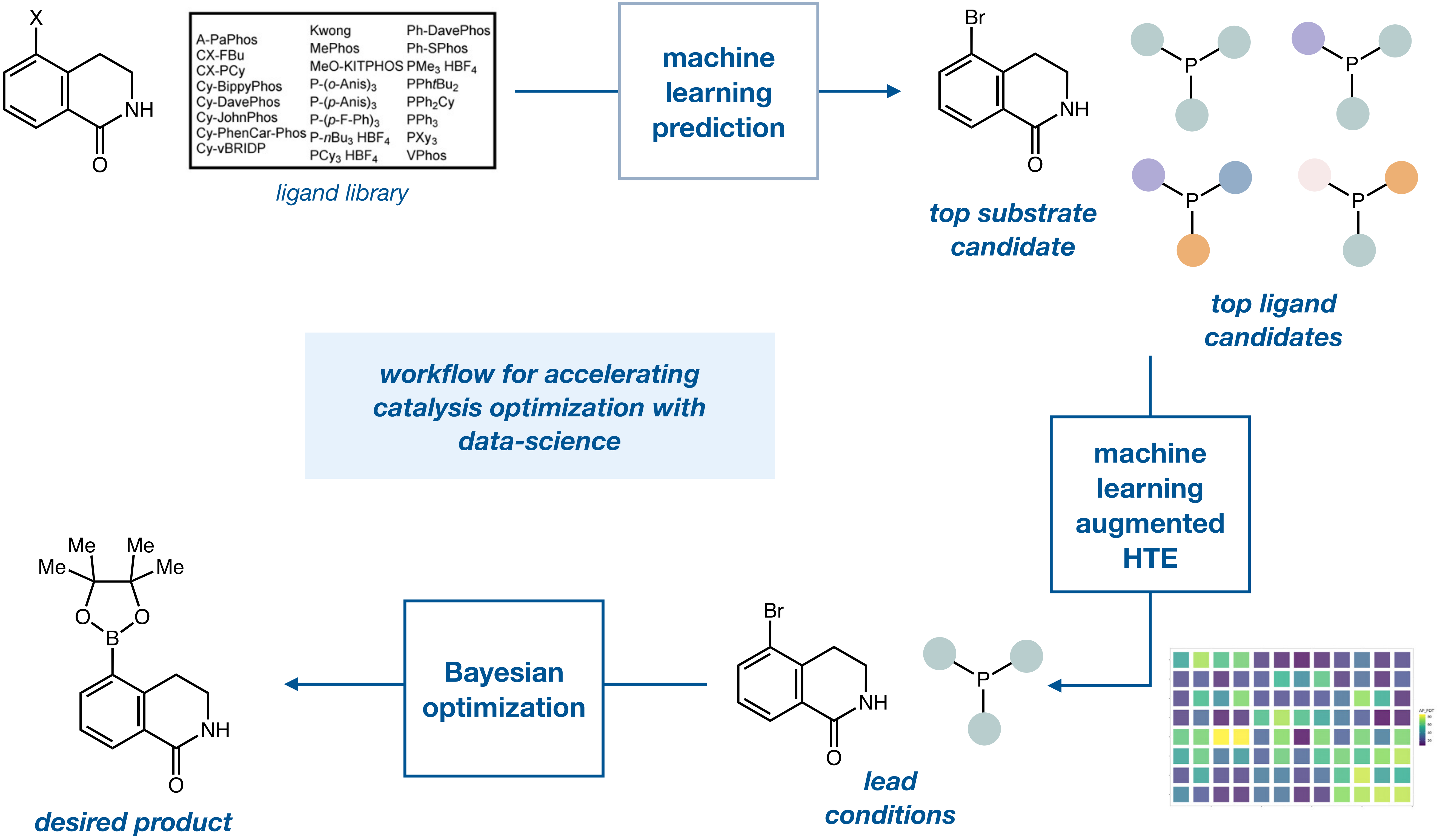
lead conditions

Bayesian optimization

Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.

Predicting how molecules should act

Development of sustainable catalytic processes with data science



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ligand library

machine learning prediction

top substrate candidate

top ligand candidates

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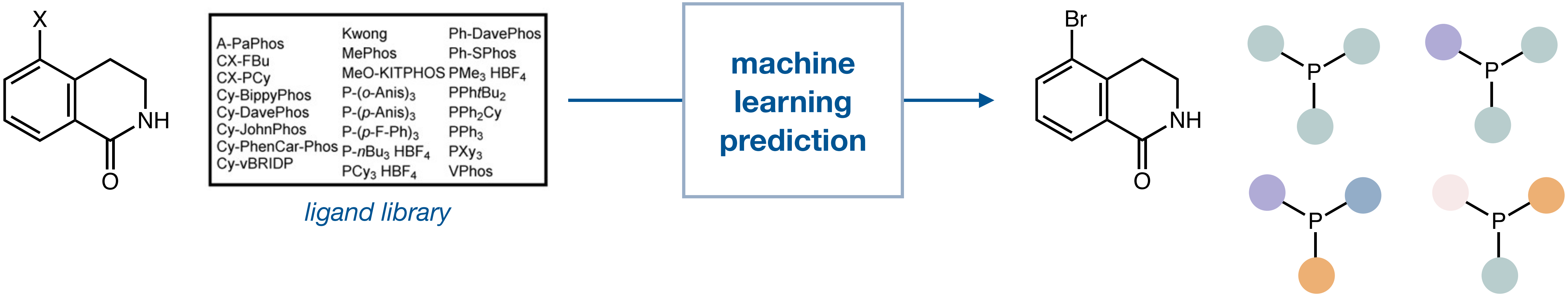
Bayesian optimization

desired product

Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.

Predicting how molecules should act

Machine learning prediction for substrate and ligand candidates



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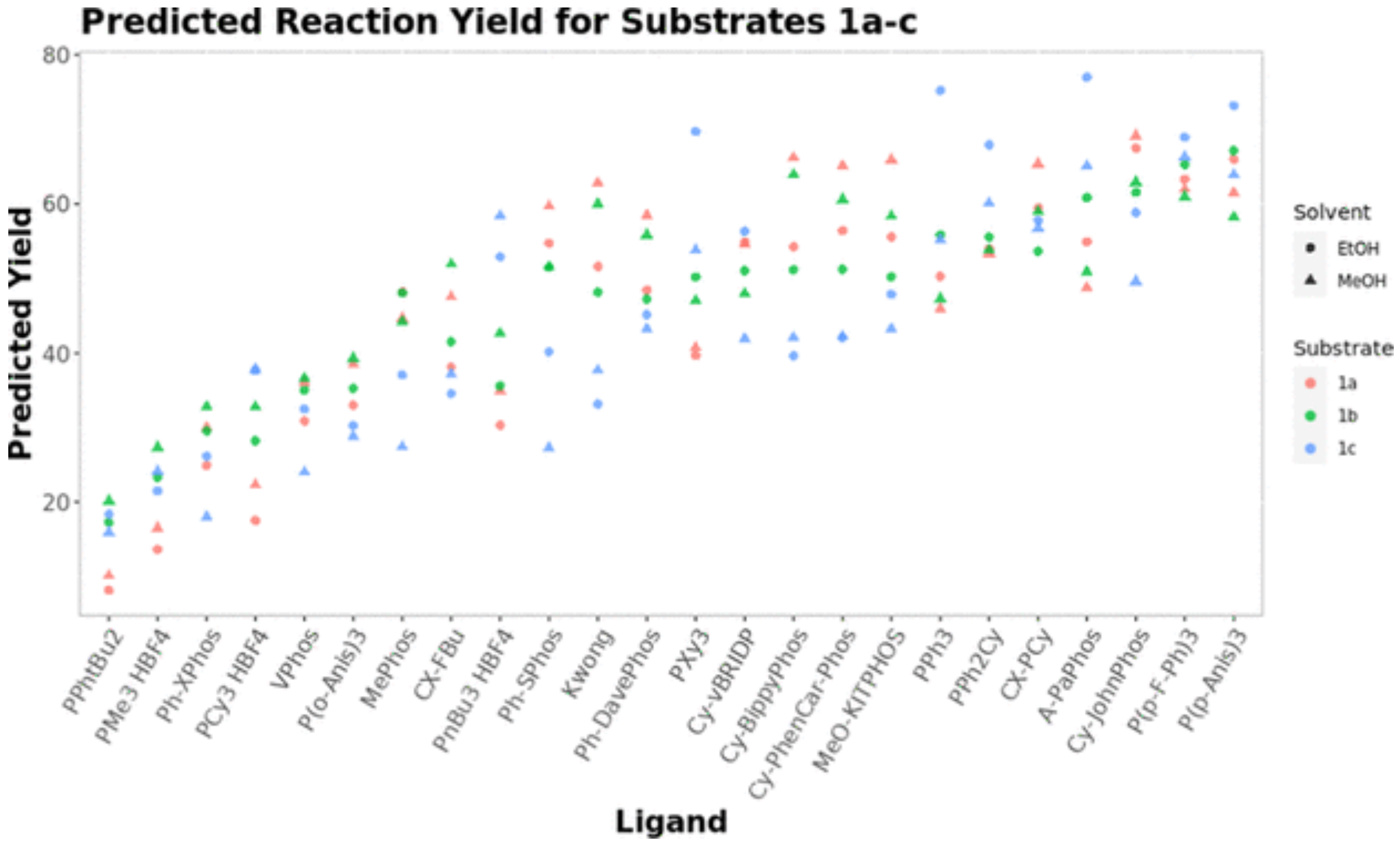
ligand library

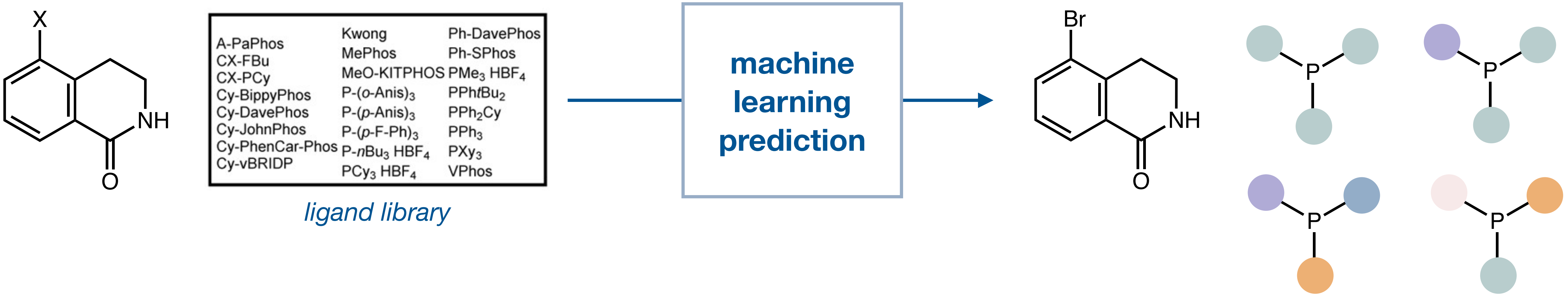
machine learning prediction



Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.

Predicting how molecules should act

Machine learning prediction for substrate and ligand candidates



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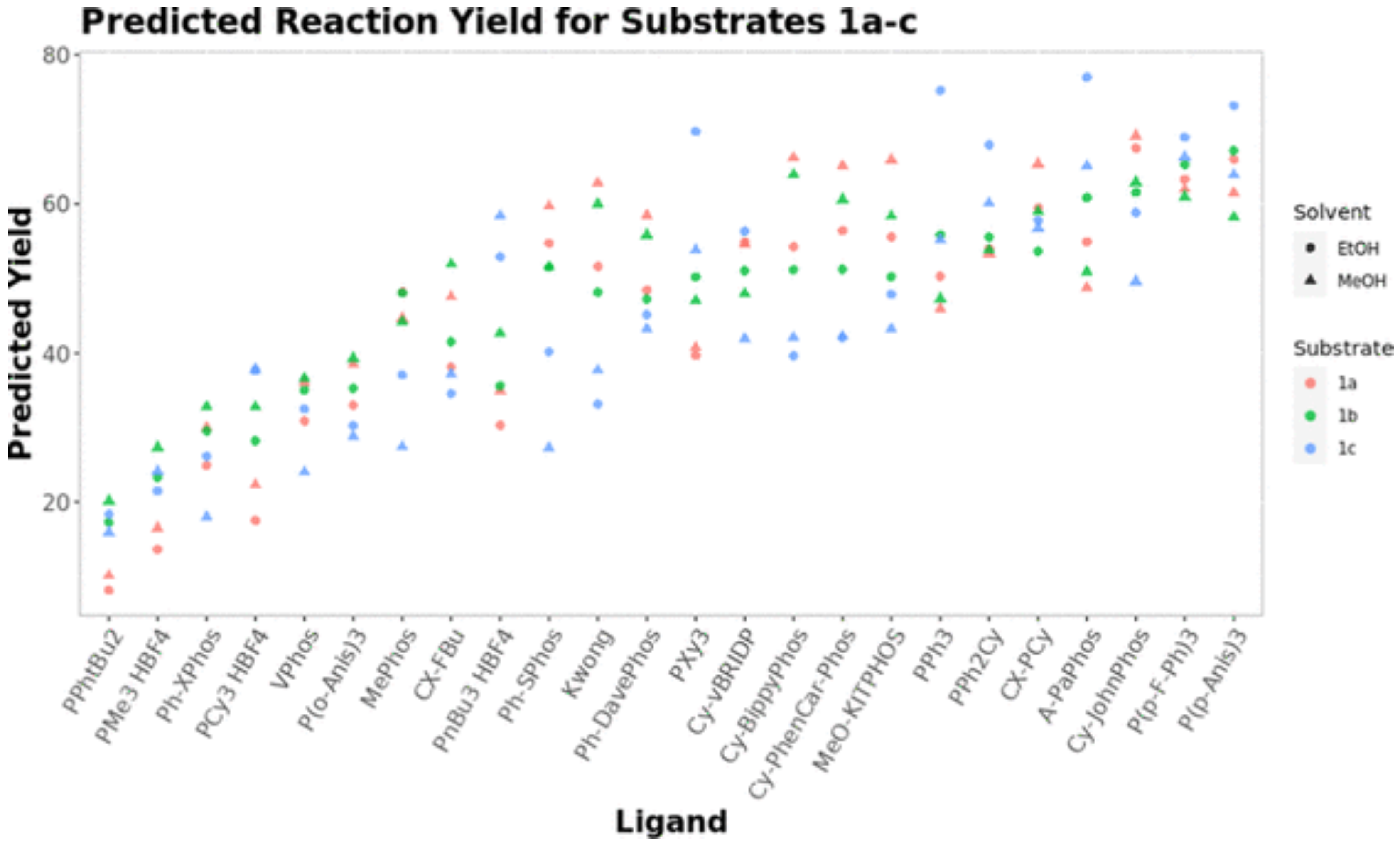
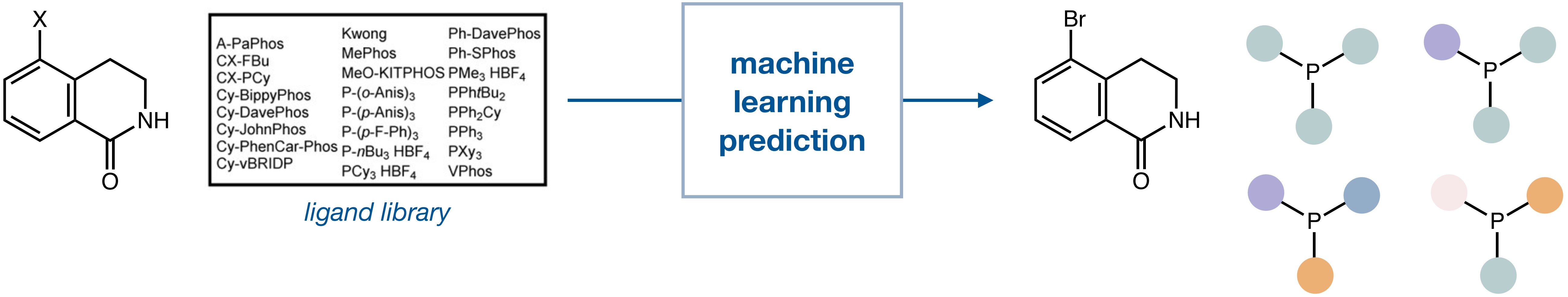

Predicted Reaction Yield for Substrates 1a-c

Key takeaways from ML prediction:

Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.

Predicting how molecules should act

Machine learning prediction for substrate and ligand candidates



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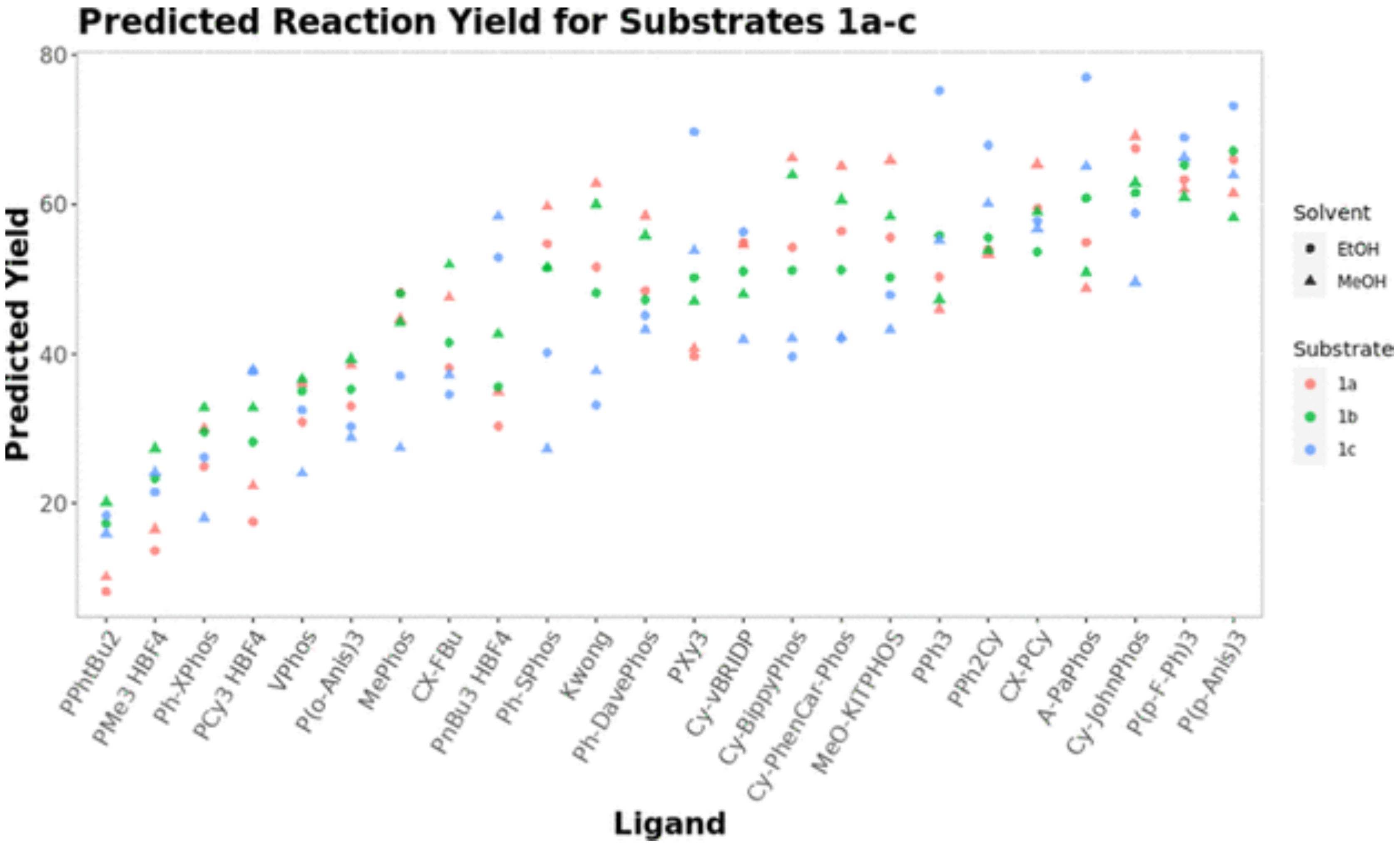


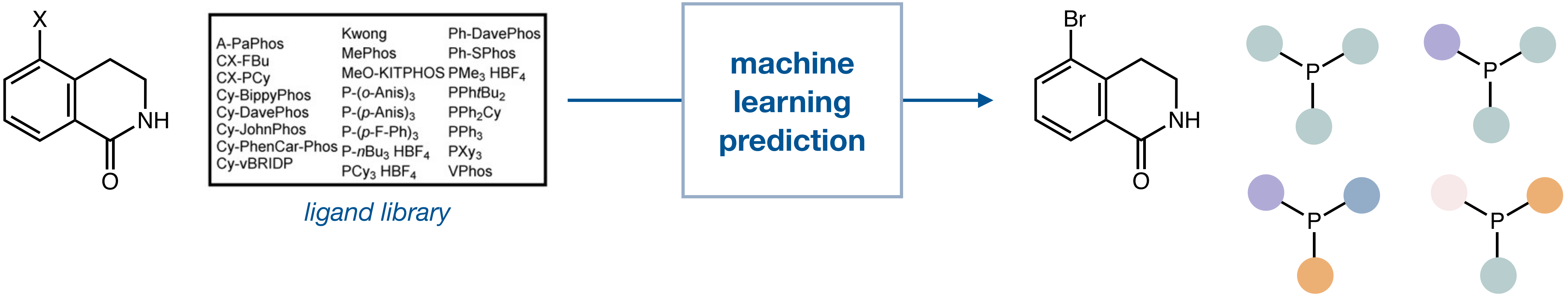
Key takeaways from ML prediction:

- *Little difference in performance based on leaving group*

Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.

Predicting how molecules should act

Machine learning prediction for substrate and ligand candidates



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ligand library

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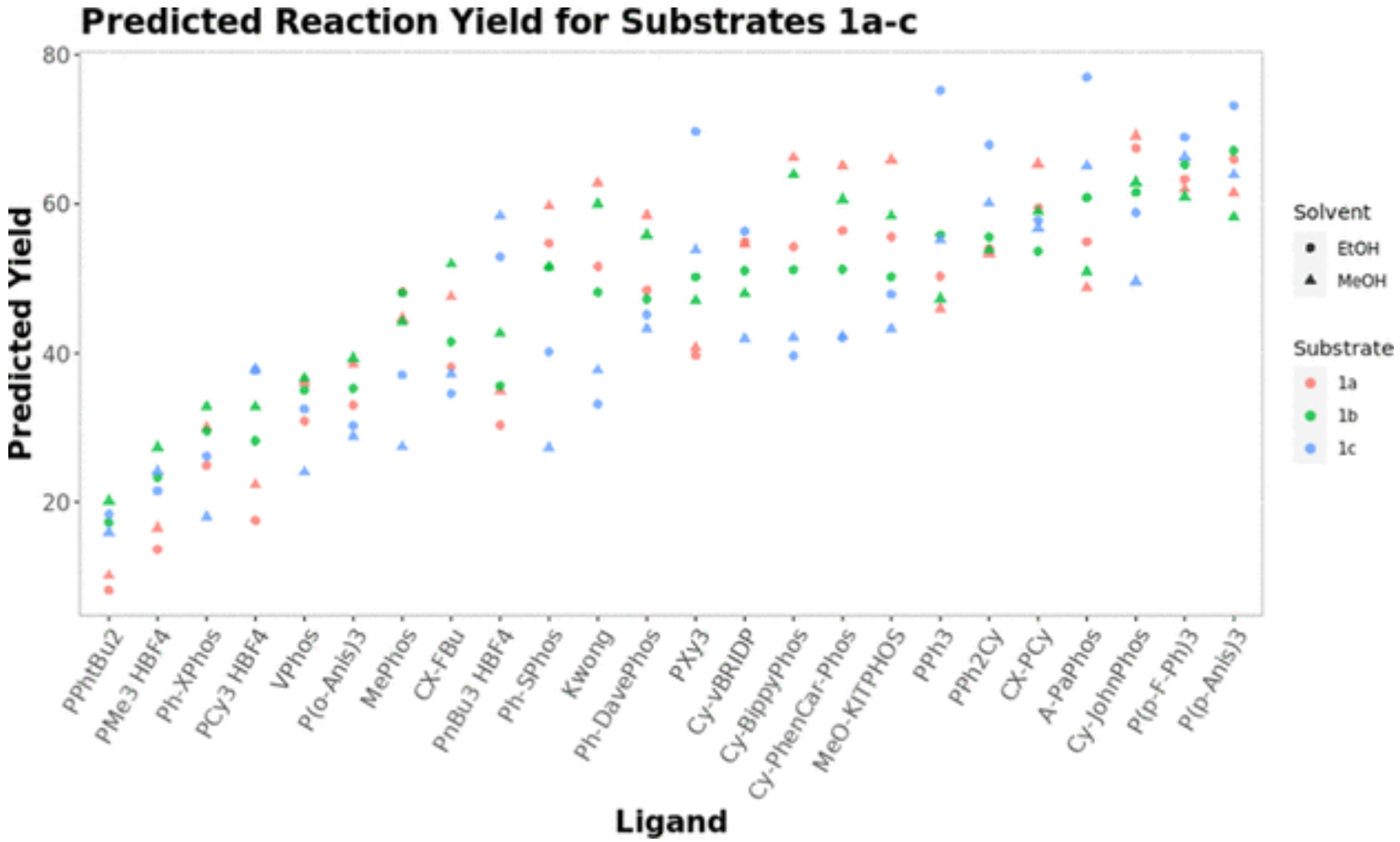


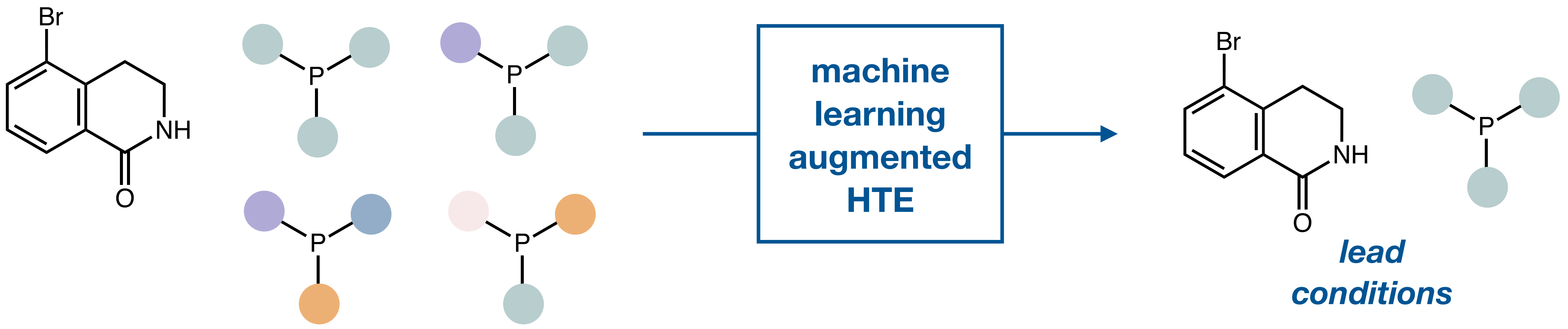
Key takeaways from ML prediction:

- *Little difference in performance based on leaving group*
- *Top five ligands were in line with previously successful ligands in nickel-catalyzed borylations*

Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.

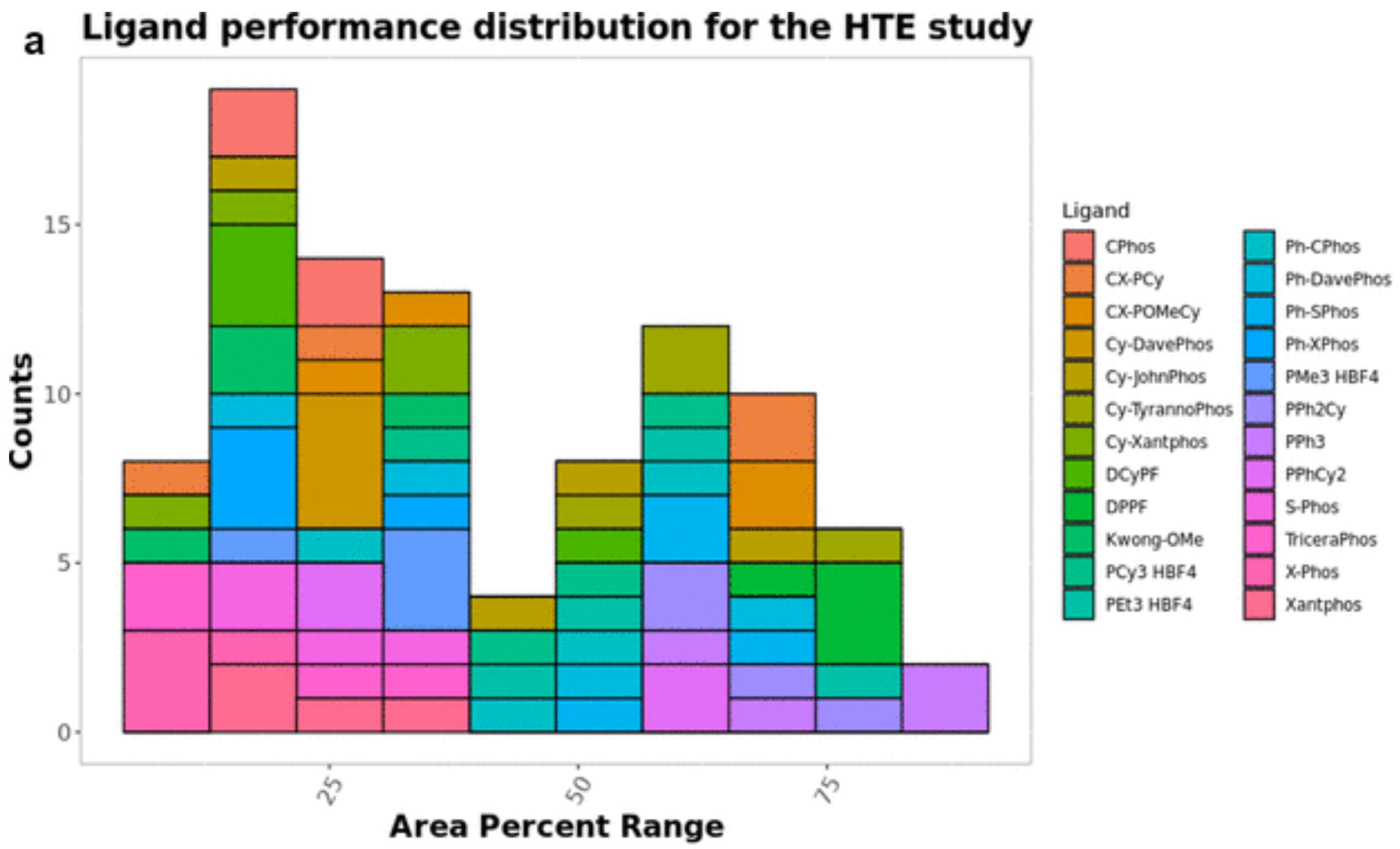
Predicting how molecules should act

Machine learning augmented HTE for lead conditions



machine learning augmented HTE

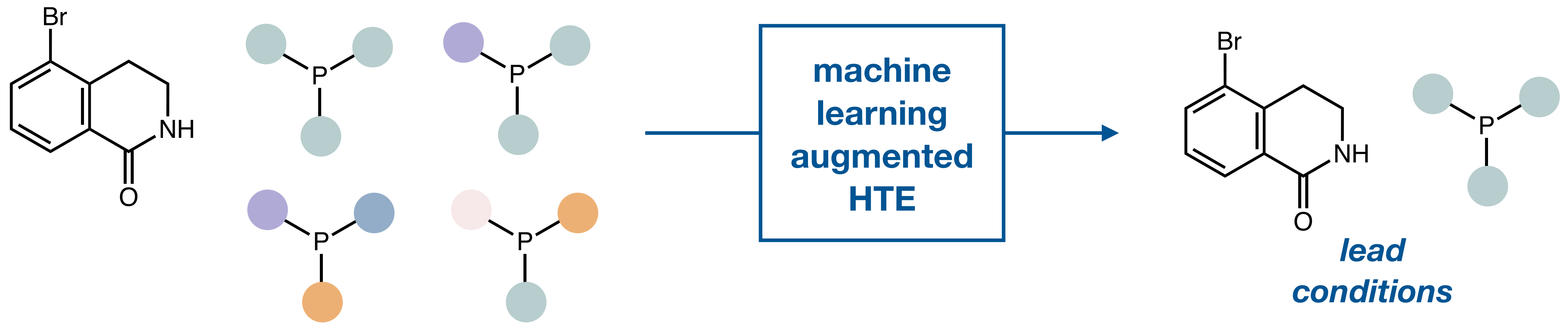
lead conditions



Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.

Predicting how molecules should act

Machine learning augmented HTE for lead conditions



machine learning augmented HTE

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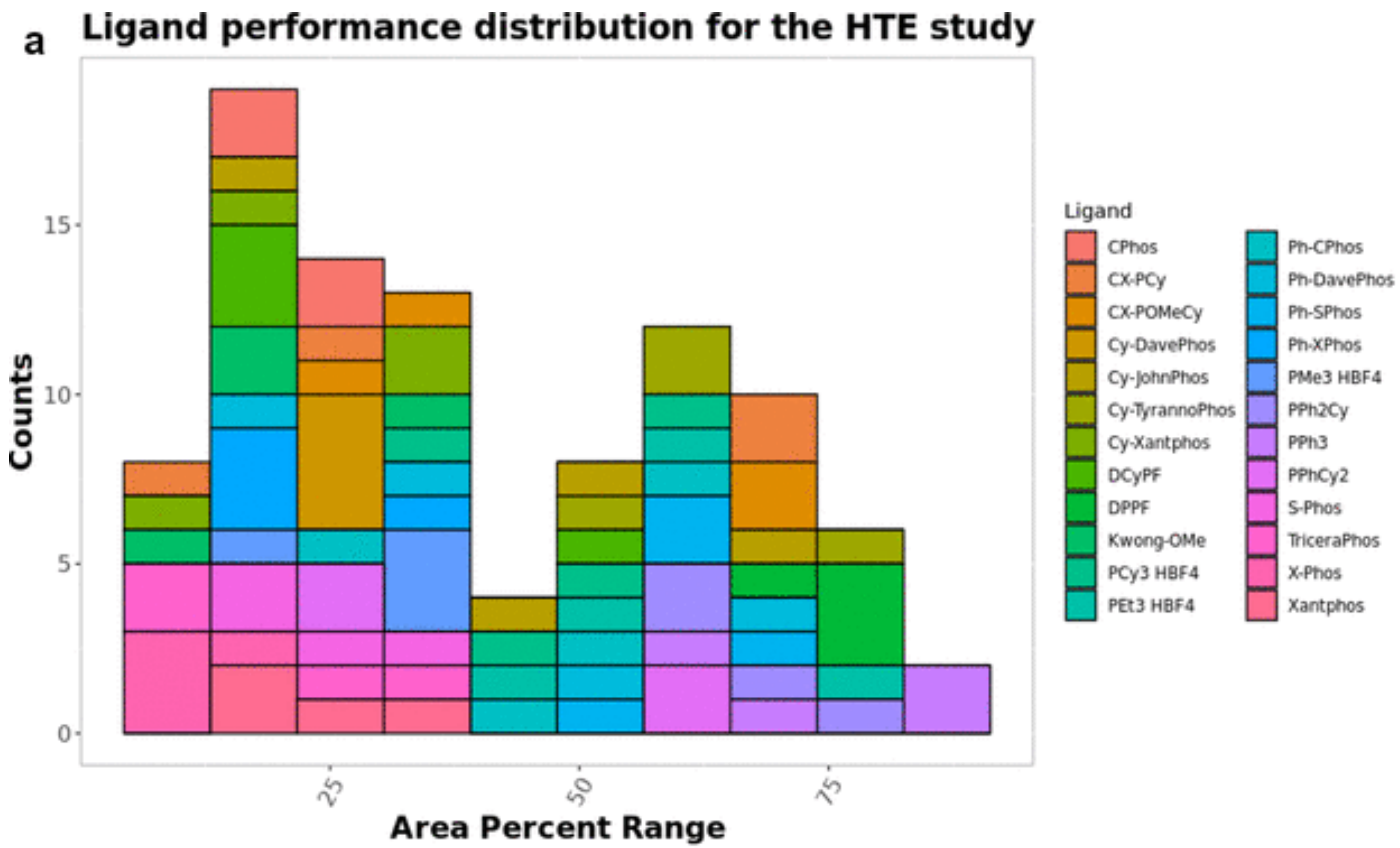


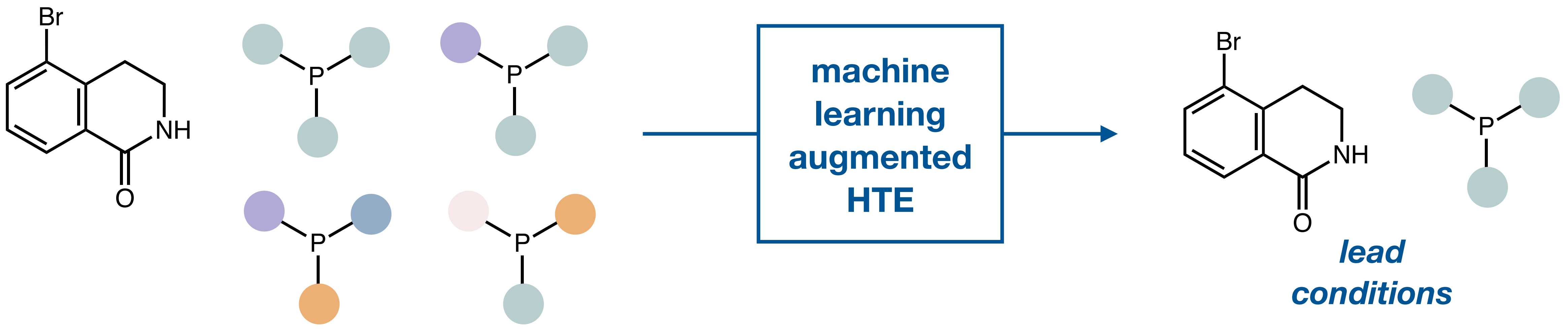
Optimal Ligands:

DPPF, **PPh_3**, PPh_2Cy,
Ph-SPhos, Cy-Tyrannophos

Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.

Predicting how molecules should act

Machine learning augmented HTE for lead conditions



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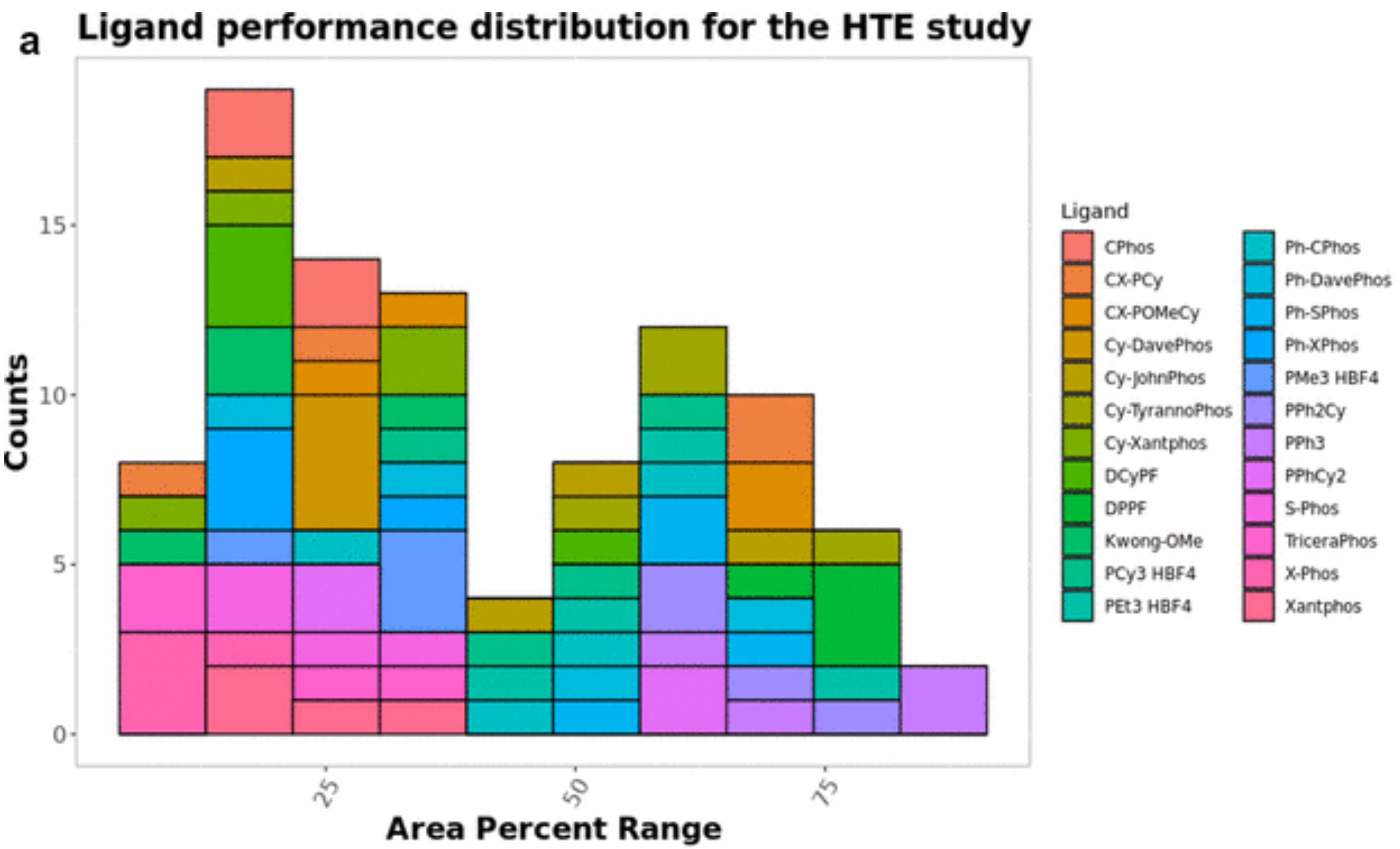

Optimal Ligands:

DPPF, **PPh_3**, PPh_2Cy,
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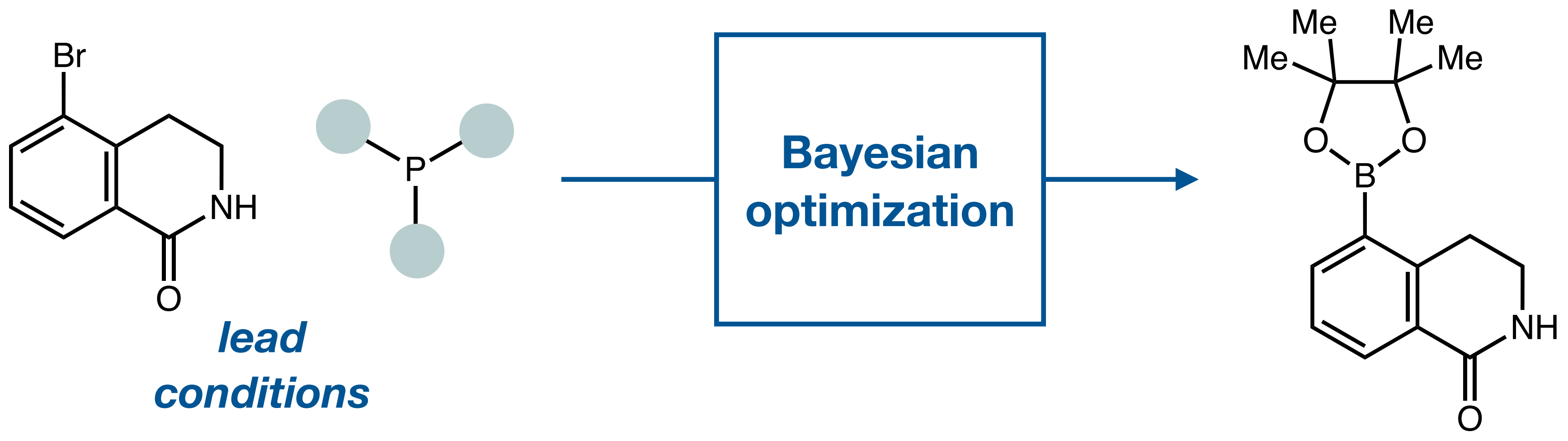
Optimal Solvent:

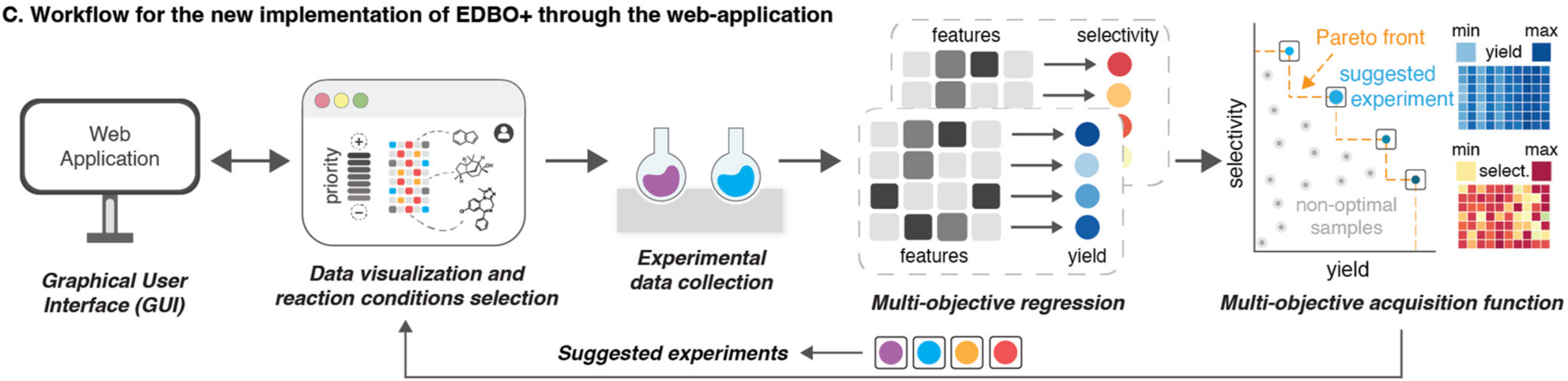
MeOH

Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.

Predicting how molecules should act

Bayesian optimization for ideal reaction conditions

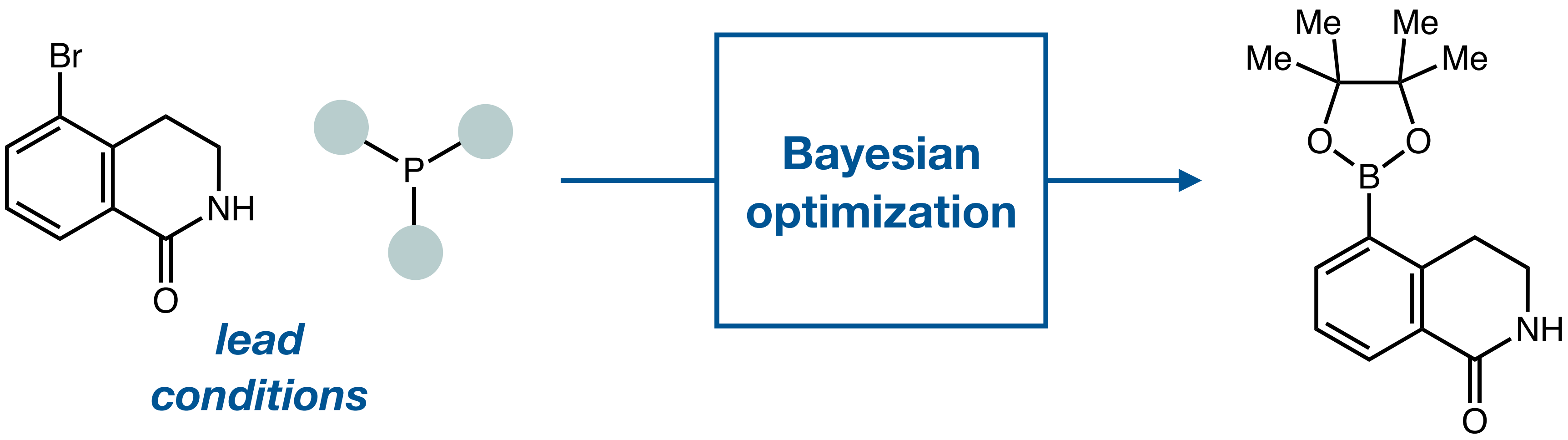



C. Workflow for the new implementation of EDBO+ through the web-application

Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.
Torres, J. A. G.; Lau, S. H.; Anchuri, P.; Stevens, J. M.; Tabora, J. E.; Li, J.; Borovika, A.; Adams, R. P.; Doyle, A. G. J. Am. Chem. Soc. 2022, 144, 19999–20007.

Predicting how molecules should act

Bayesian optimization for ideal reaction conditions



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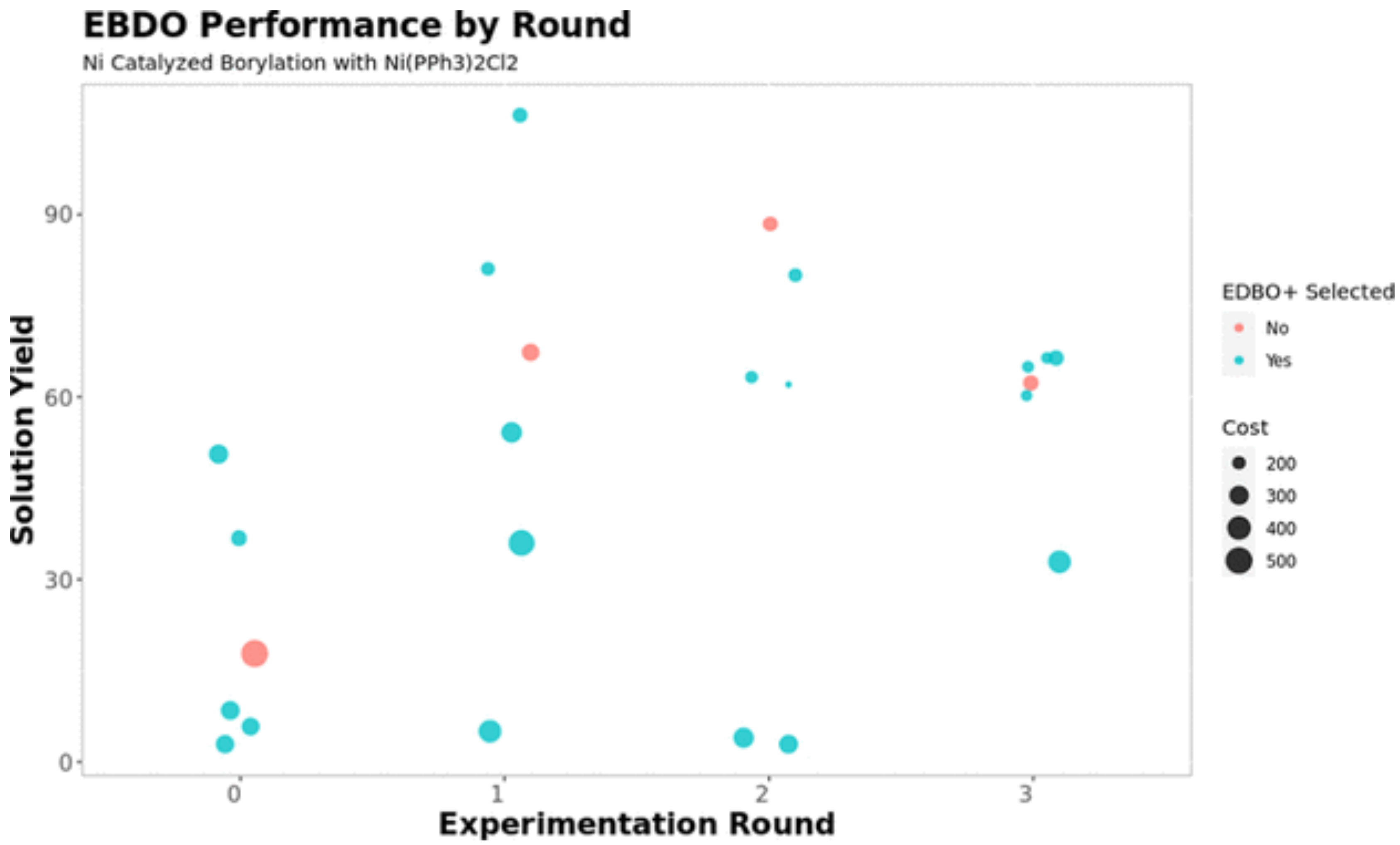

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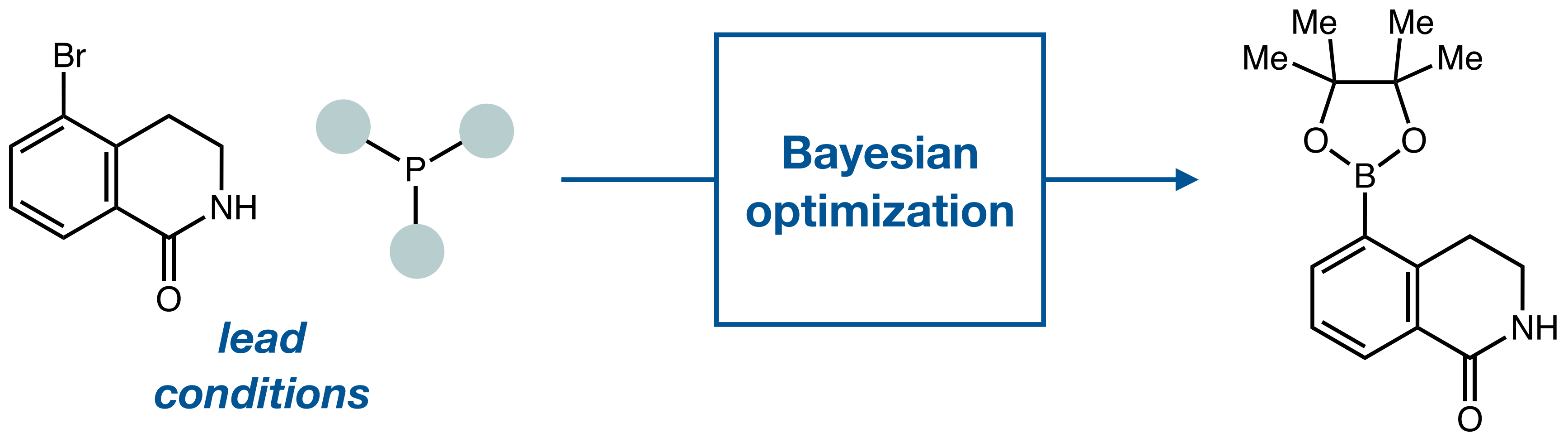

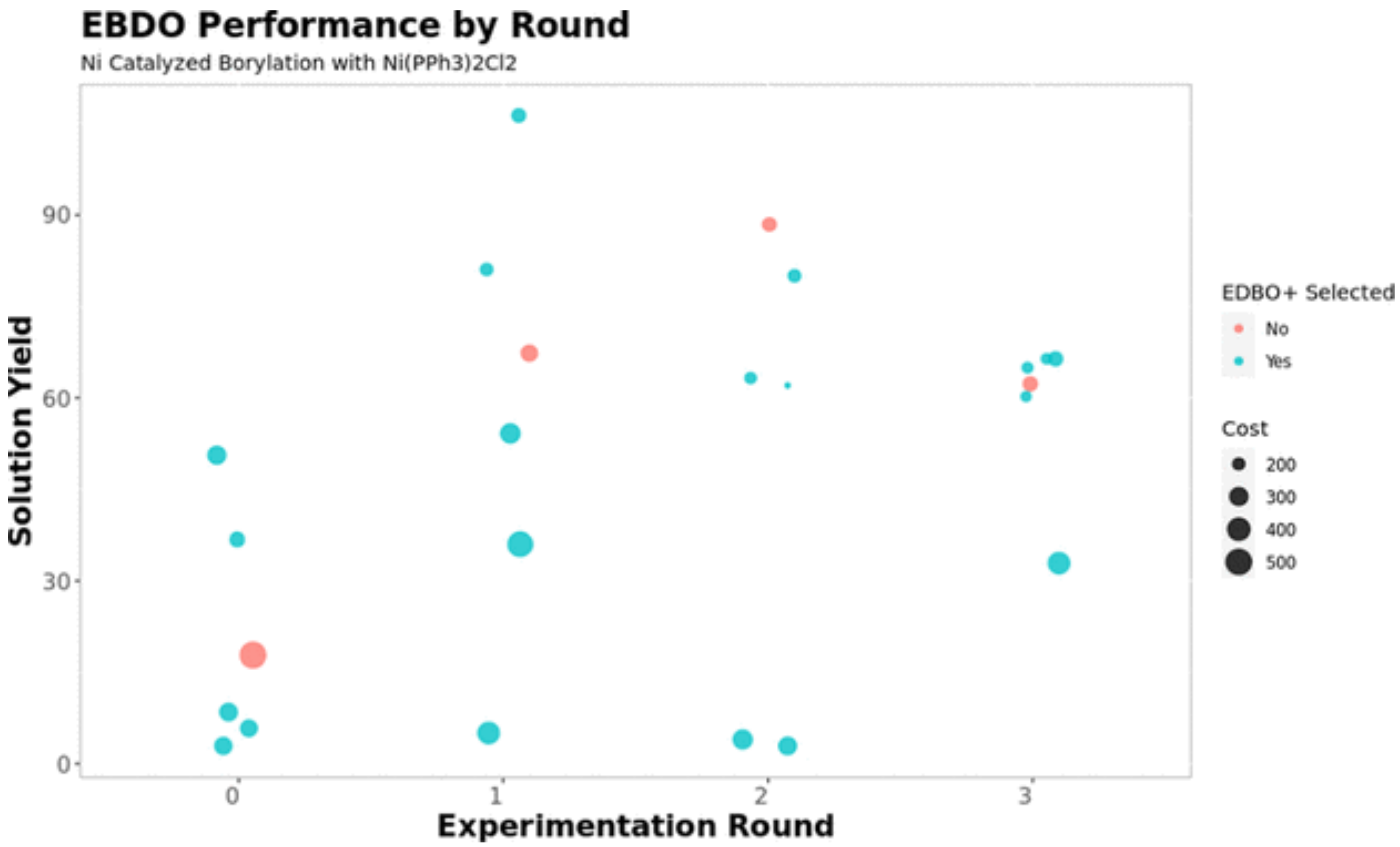

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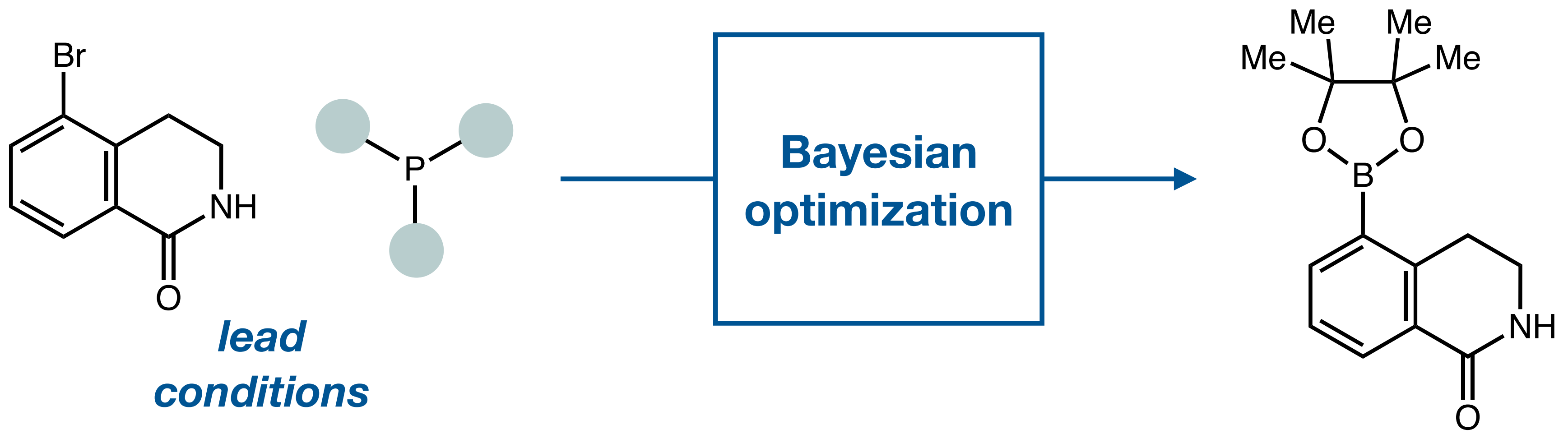

lead conditions

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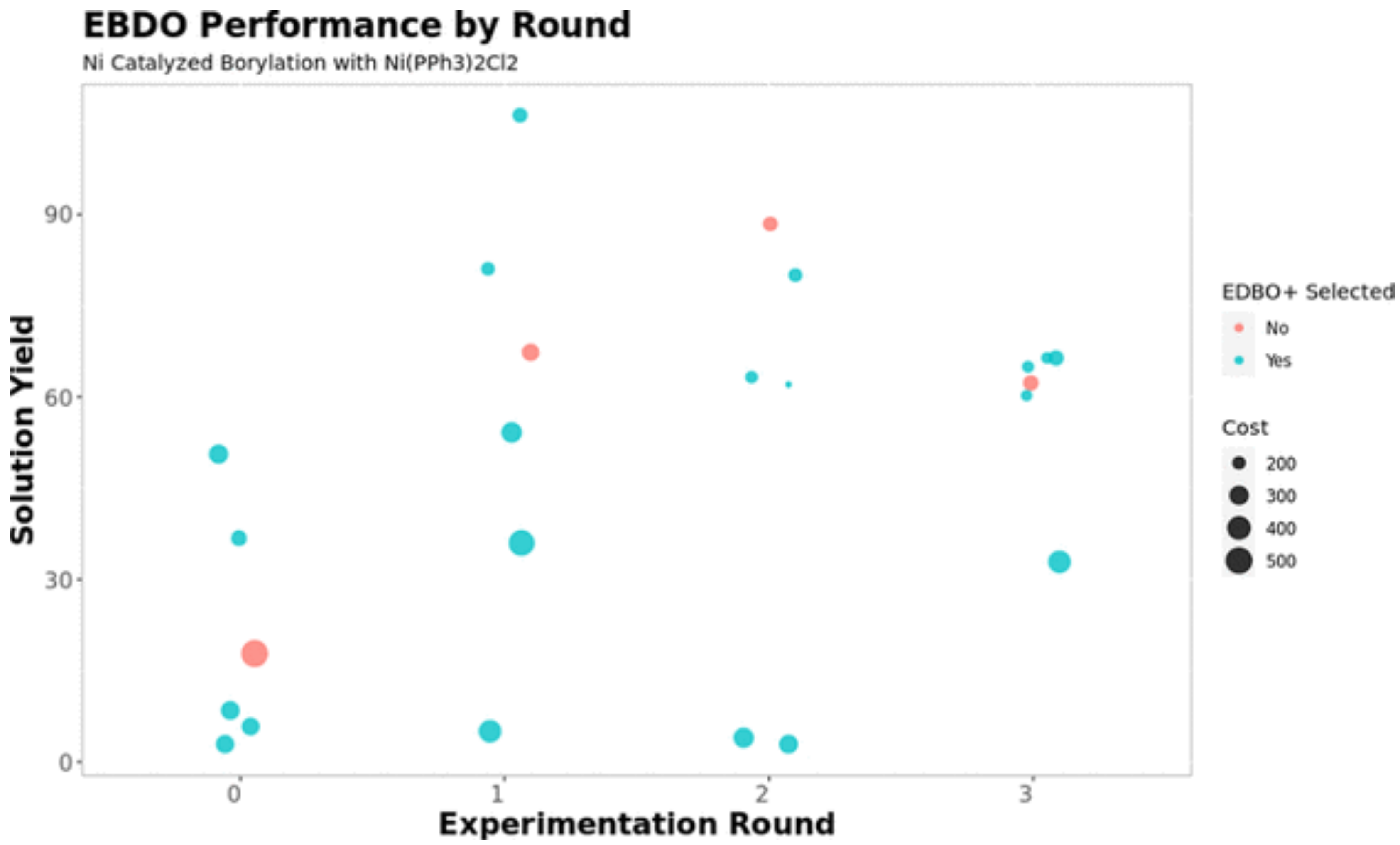

Optimal Conditions:

$(PPh_3)_2NiCl_2$ (2.5 mol%)
B_2pin_2 (1.75 equiv)
DIPEA (3.0 equiv)
MeOH/MIBK (40:60, 0.3 M)

Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.

Predicting how molecules should act

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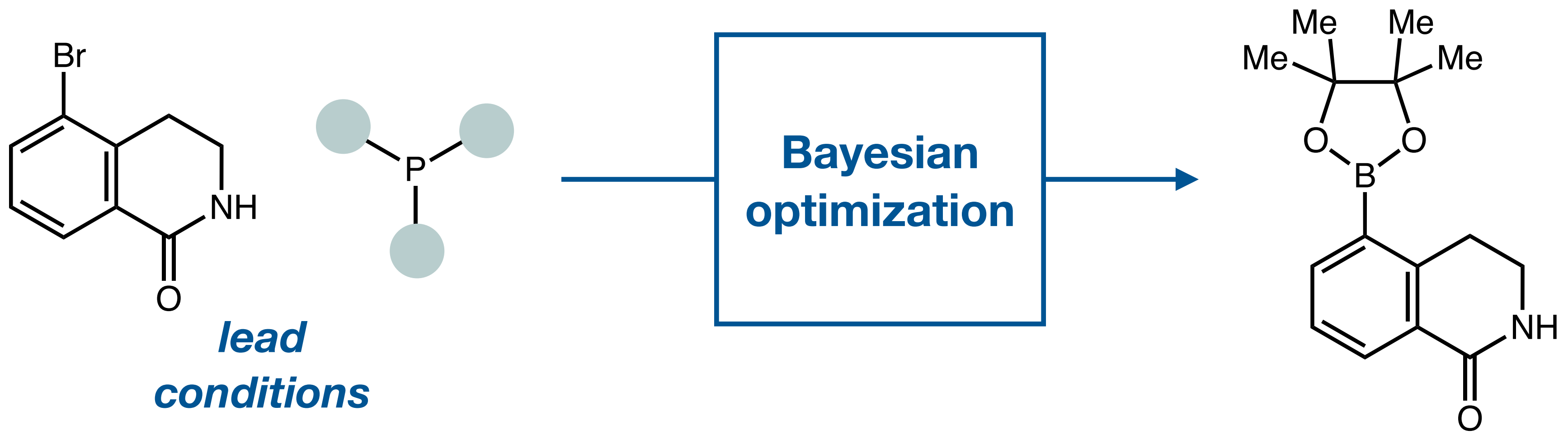

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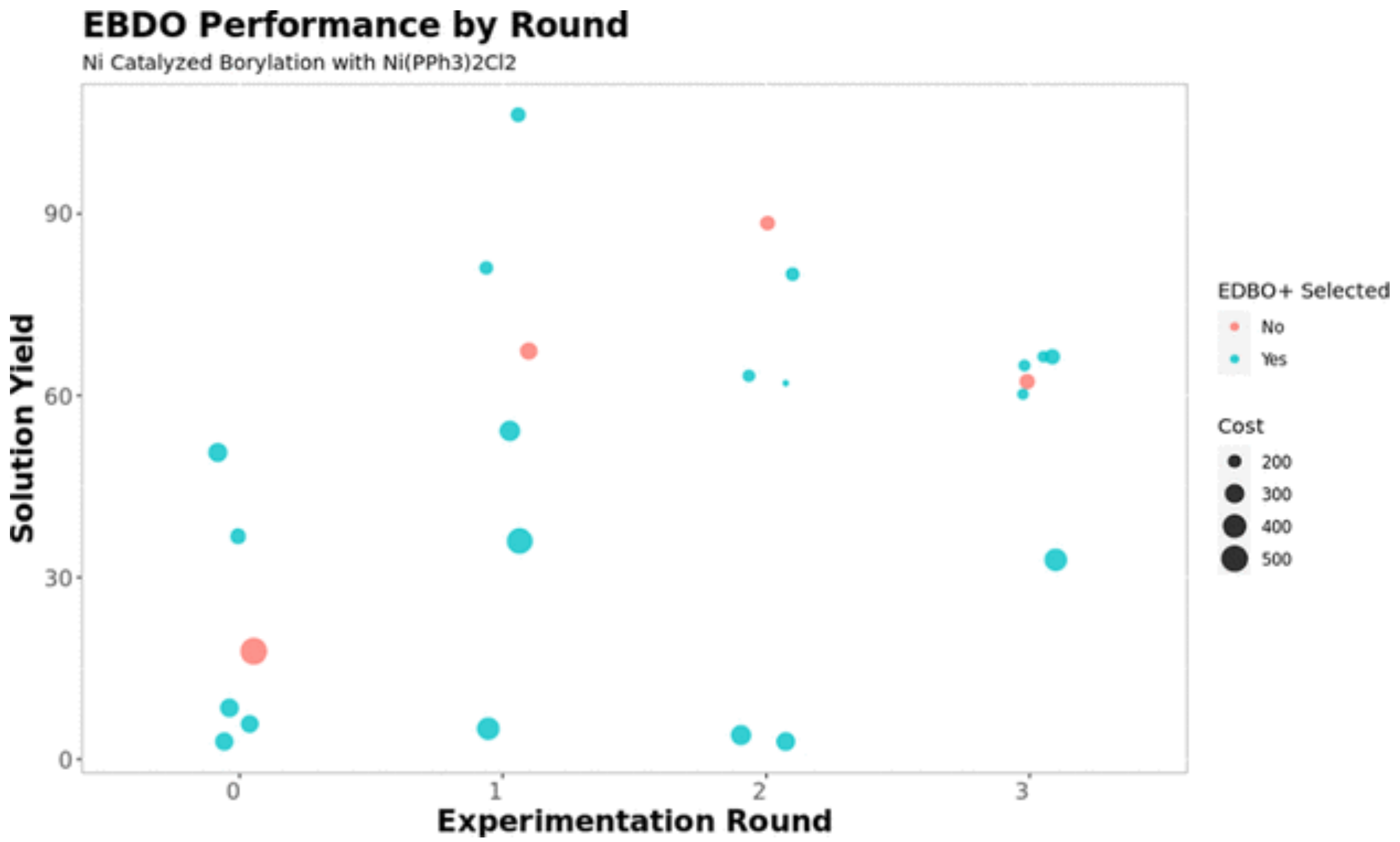

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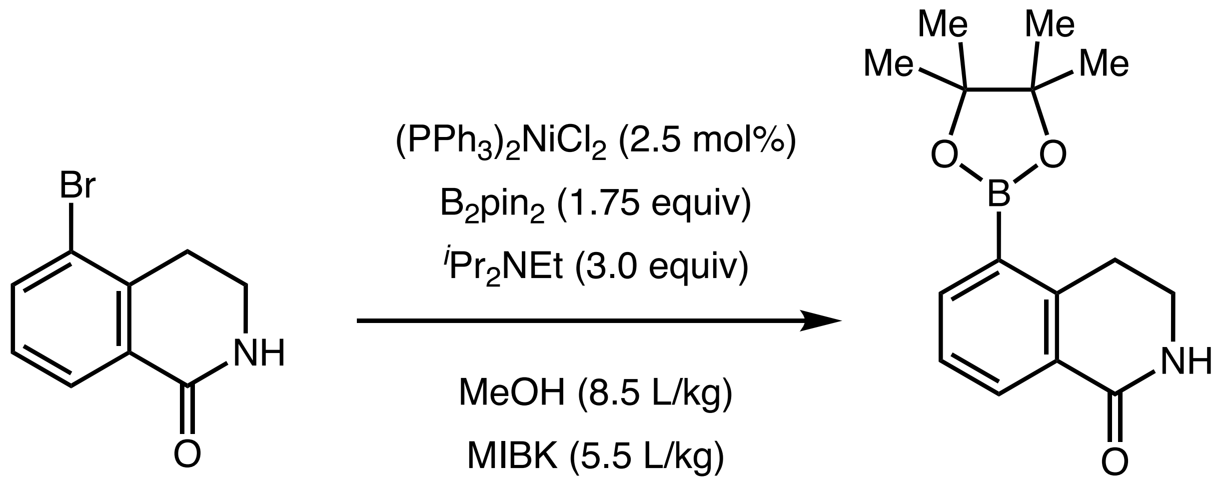
EDBO+ algorithm beats scientist predictions

Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.

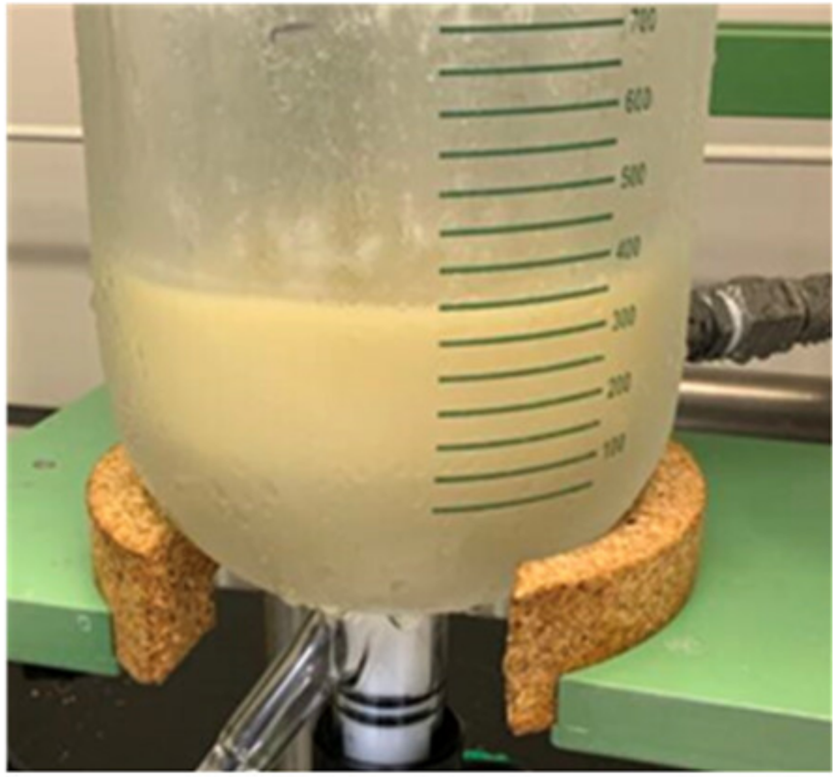
Predicting how molecules should act

Development of sustainable catalytic processes with data science



40 g scale
100% conversion
83.5% isolated yield

Crystallization Slurry



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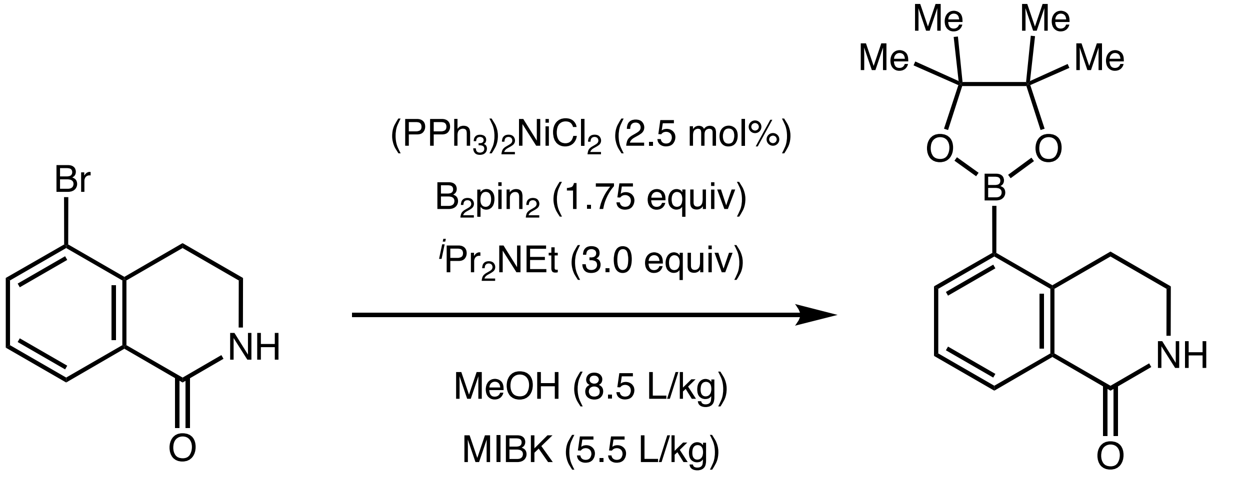
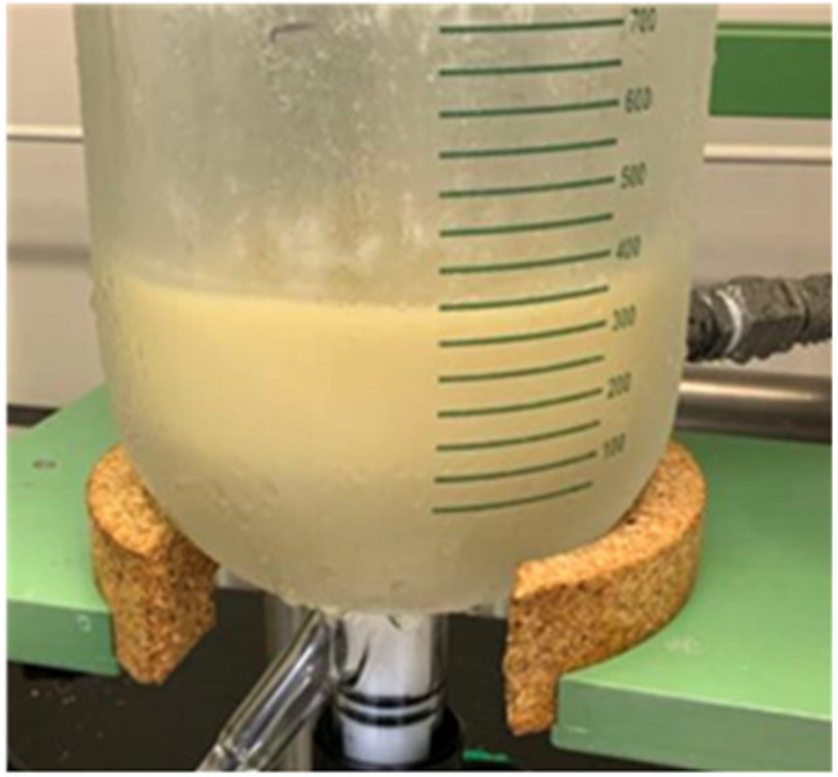


$(PPh_3)_2NiCl_2$ (2.5 mol%)
B_2pin_2 (1.75 equiv)
$^{i}Pr_2NEt$ (3.0 equiv)

MeOH (8.5 L/kg)
MIBK (5.5 L/kg)
5 °C, 18 hr

40 g scale
100% conversion
83.5% isolated yield

Crystallization Slurry



only 120 experiments (~1 week)
required for optimized conditions
(including 96 by HTE)

Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.

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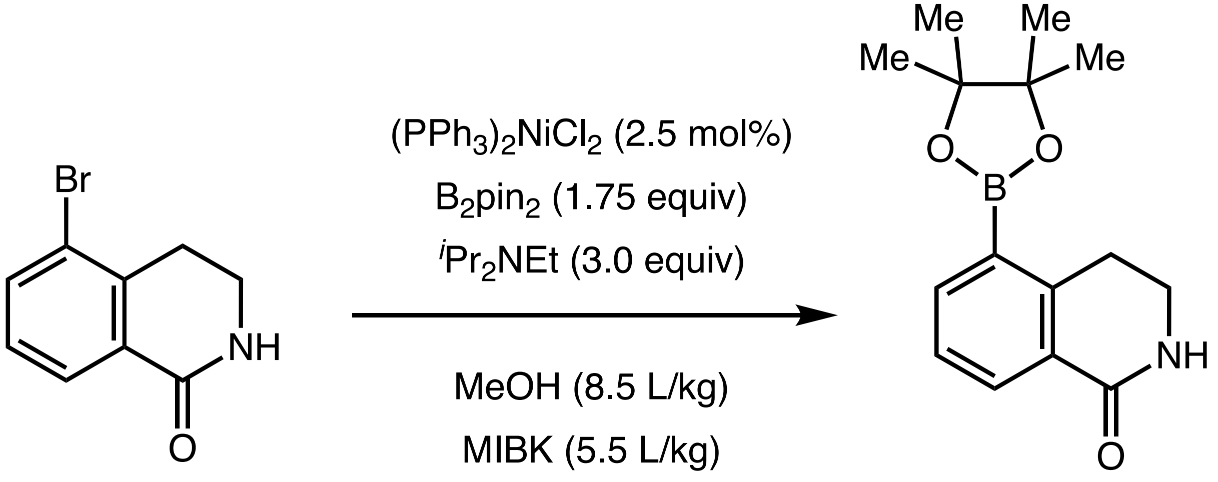

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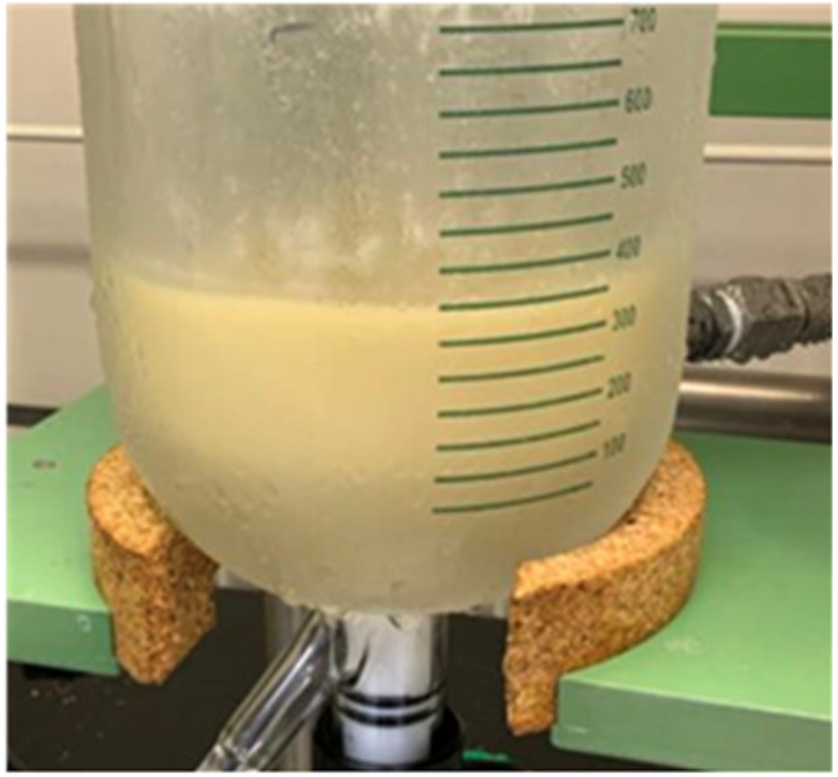
5 ^{o}C, 18 hr

40 g scale

100% conversion

83.5% isolated yield

Crystallization Slurry



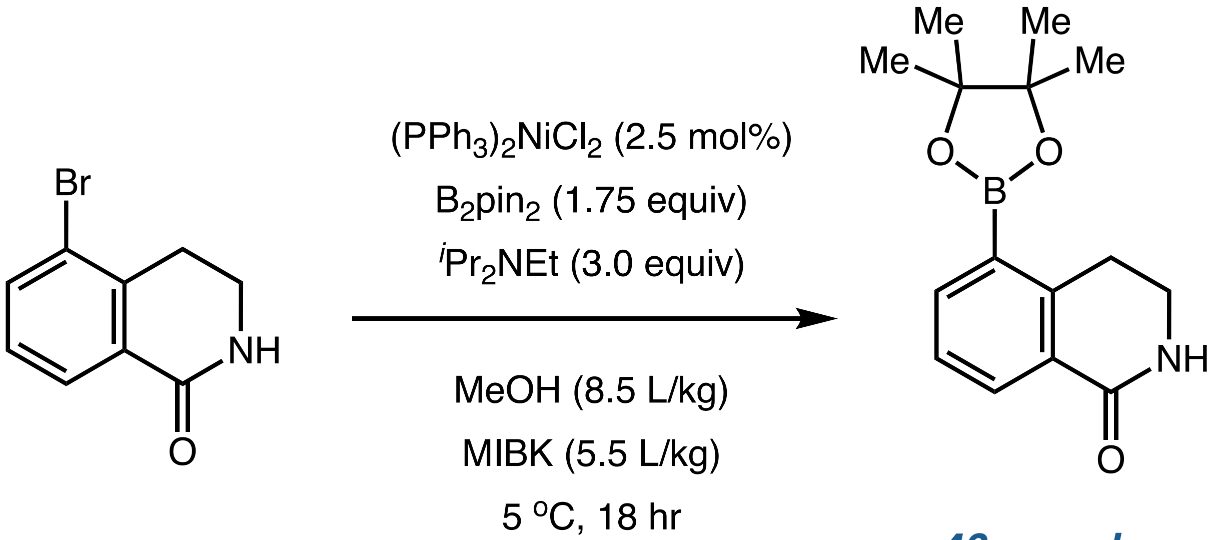
Data Science/HTE Approach…

only 120 experiments (~1 week)
required for optimized conditions
(including 96 by HTE)

Stevens, J. M.; Ganley, J. M.; Goldfogel, M. J.; Furman, A.; Wisniewski, S. R. *Org. Process. Res. Dev.* **2025**, *29*, 189-199.

Predicting how molecules should act

Development of sustainable catalytic processes with data science

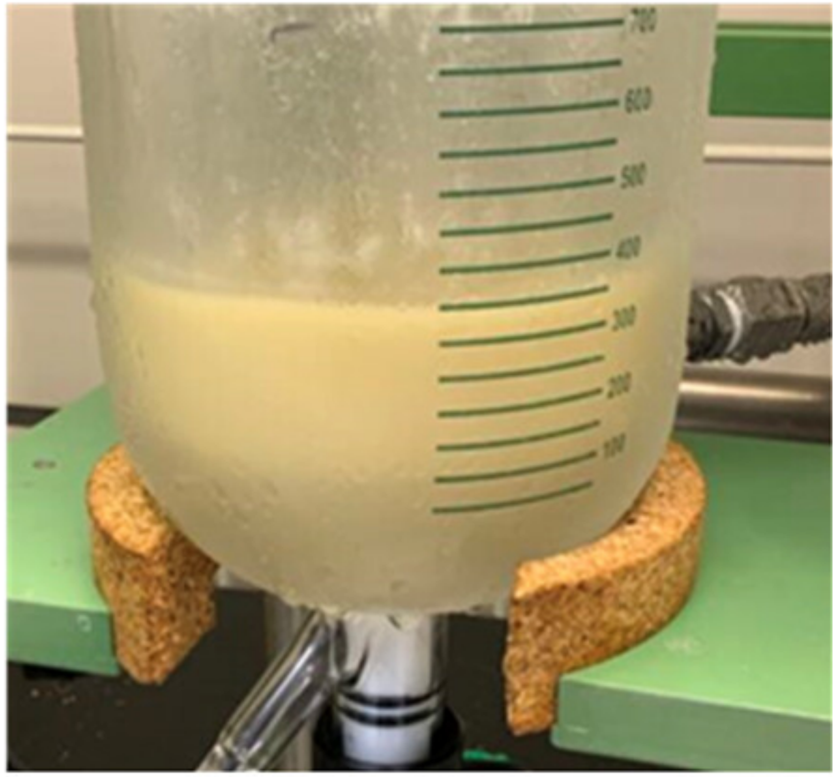


$(PPh_3)_2NiCl_2$ (2.5 mol%)
B_2pin_2 (1.75 equiv)
${}^{i}Pr_2NEt$ (3.0 equiv)

MeOH (8.5 L/kg)
MIBK (5.5 L/kg)
5 °C, 18 hr

40 g scale
100% conversion
83.5% isolated yield

Crystallization Slurry



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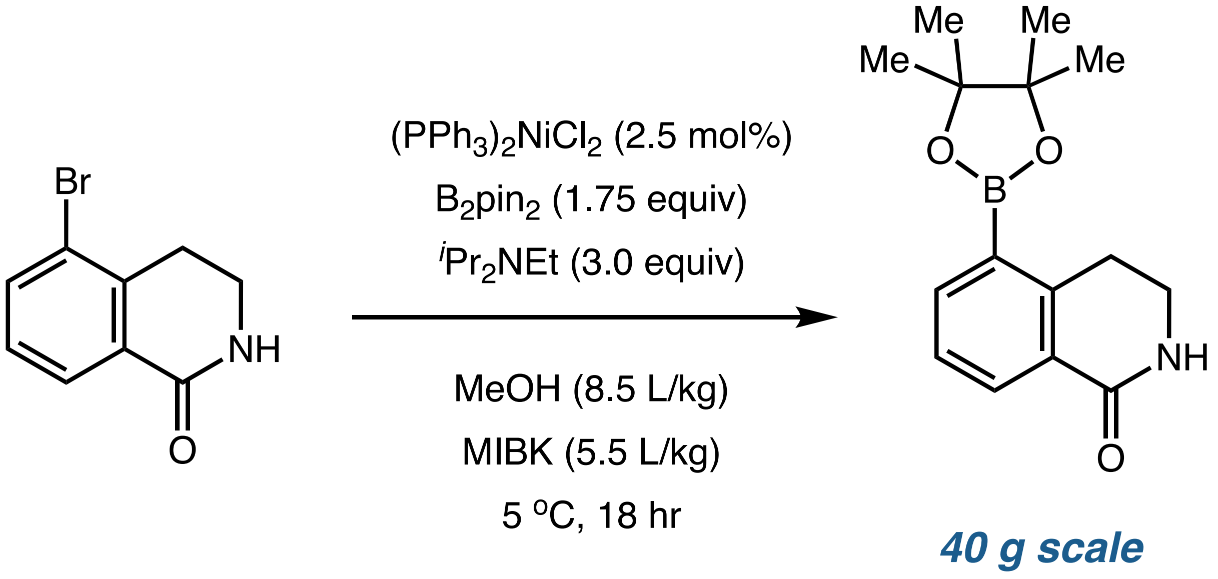

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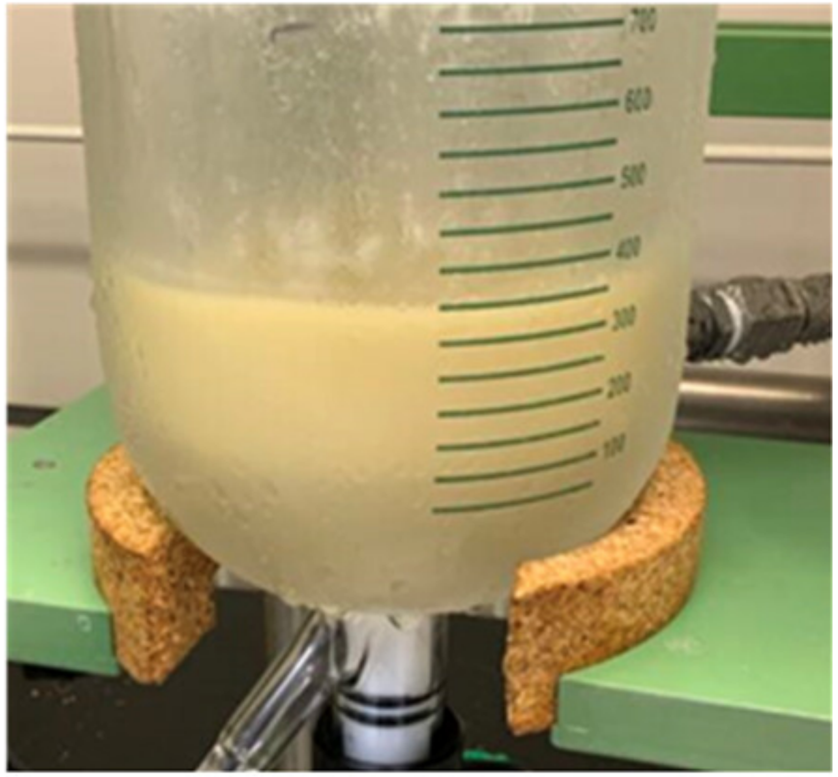

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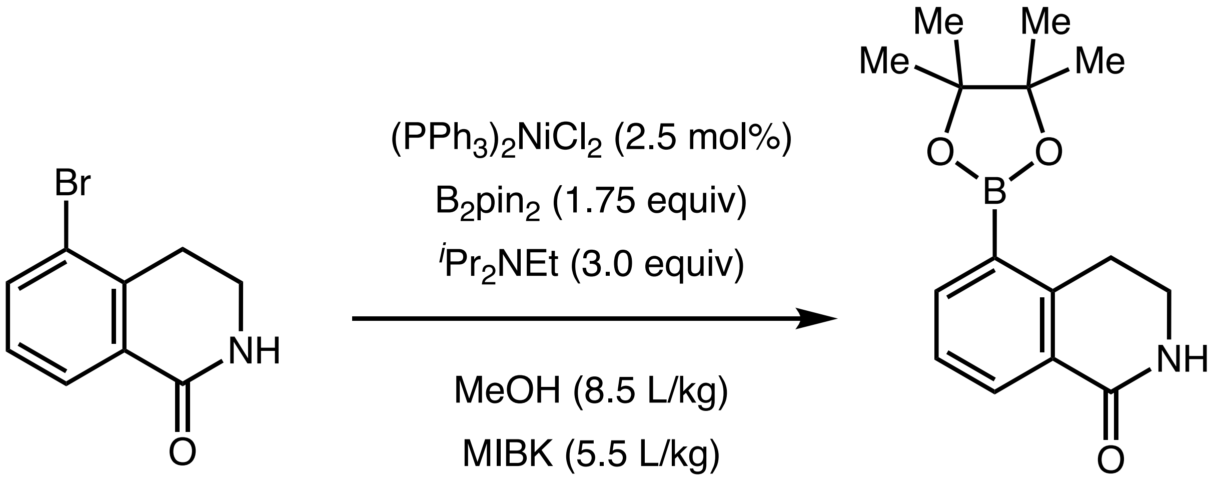
Predicting how molecules should act

Development of sustainable catalytic processes with data science



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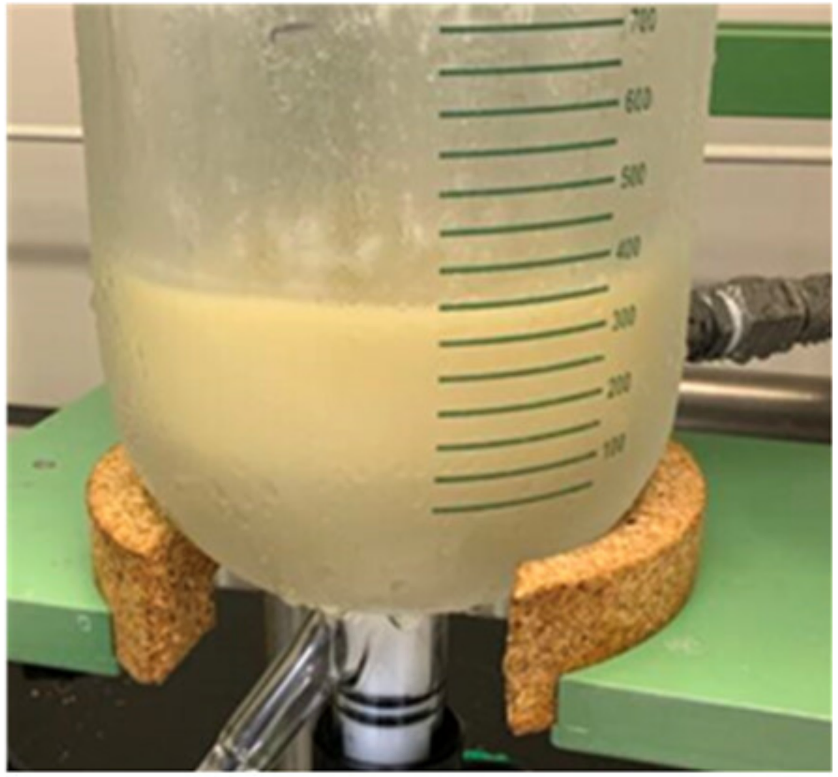

only 120 experiments (~1 week) required for optimized conditions (including 96 by HTE)

Data Science/HTE Approach…

✓ Provides yield and cost predictions for the targeted chemical space

✓ Mitigates unnecessary experimentation

✓ Informs downstream process development decisions

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Why would you use computational chemistry?

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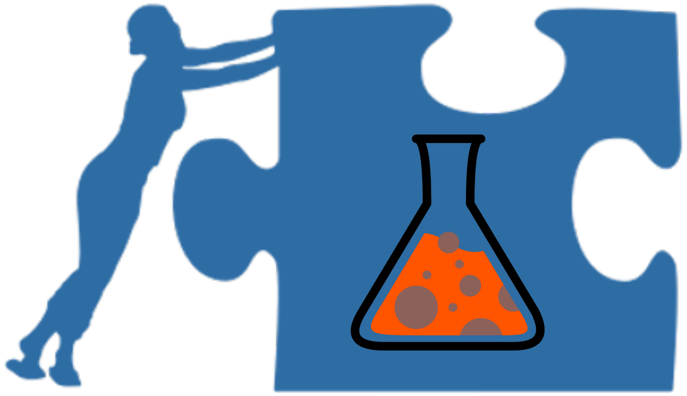

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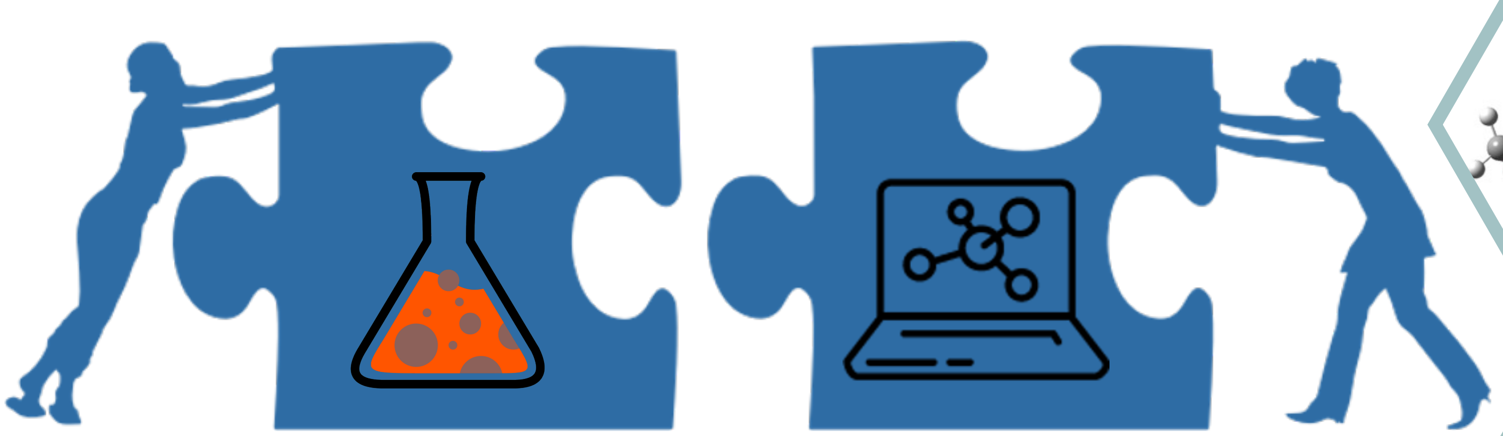

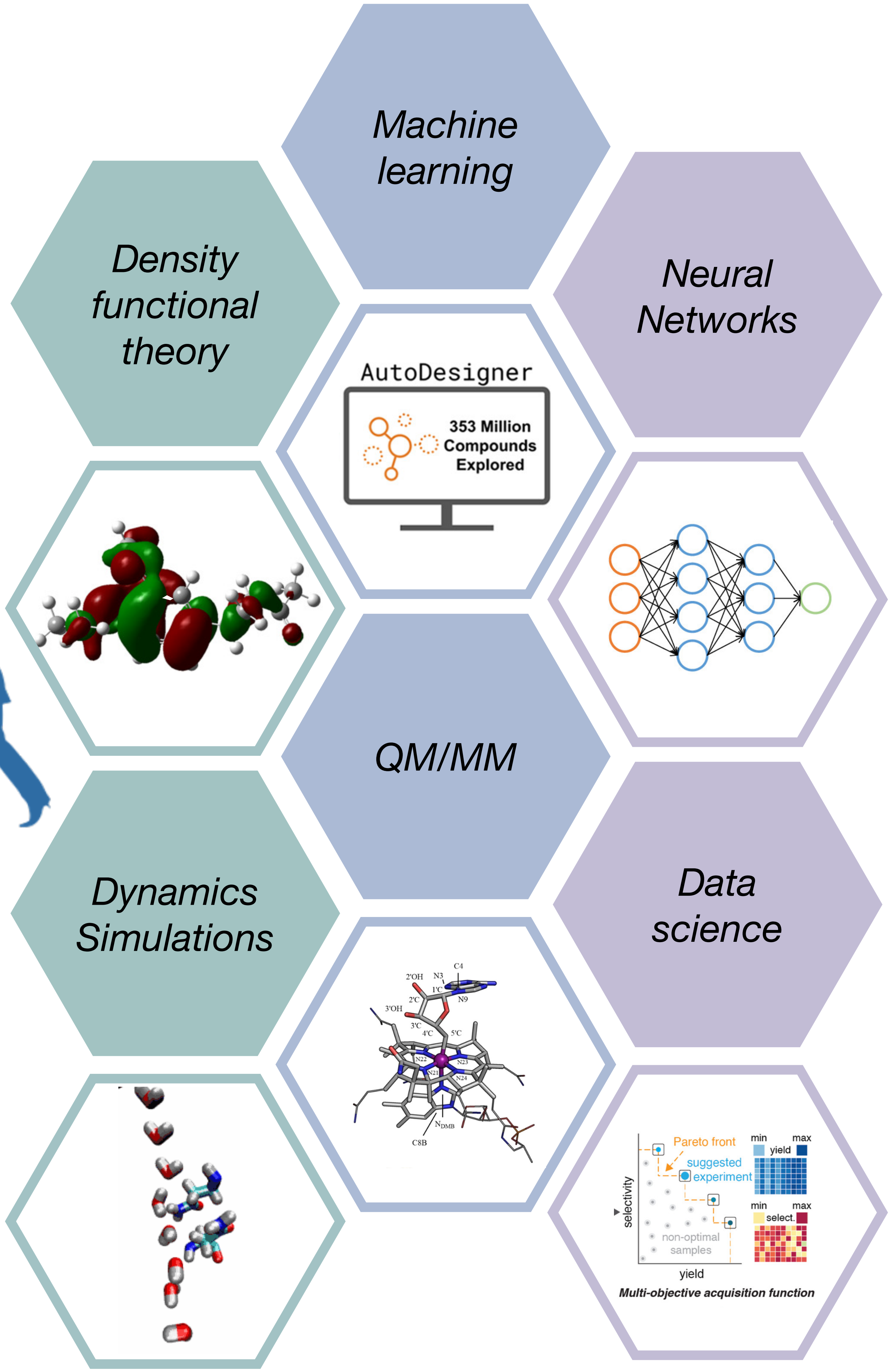

Machine learning

Density functional theory

Neural Networks

QM/MM

Dynamics Simulations

Data science

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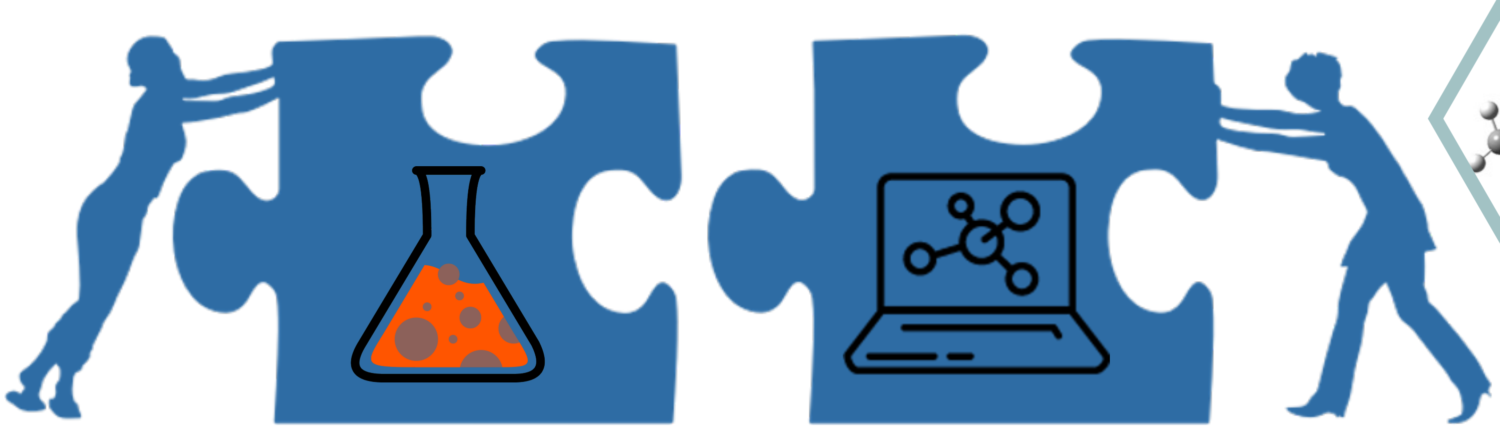
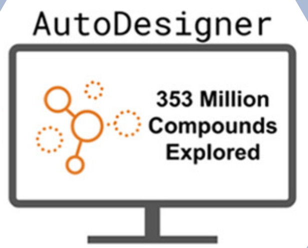


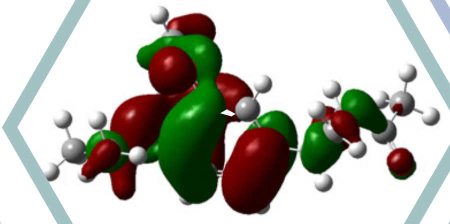
Questions?

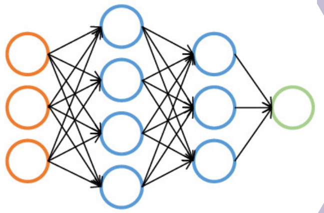
Machine learning

Density functional theory

Neural Networks







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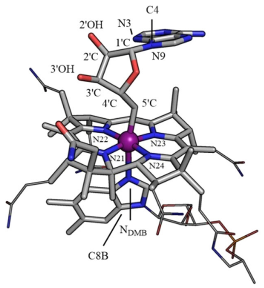

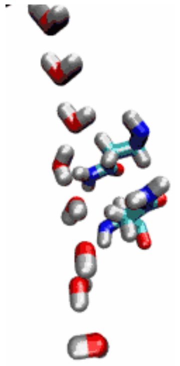

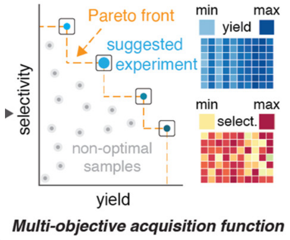

Multi-objective acquisition function