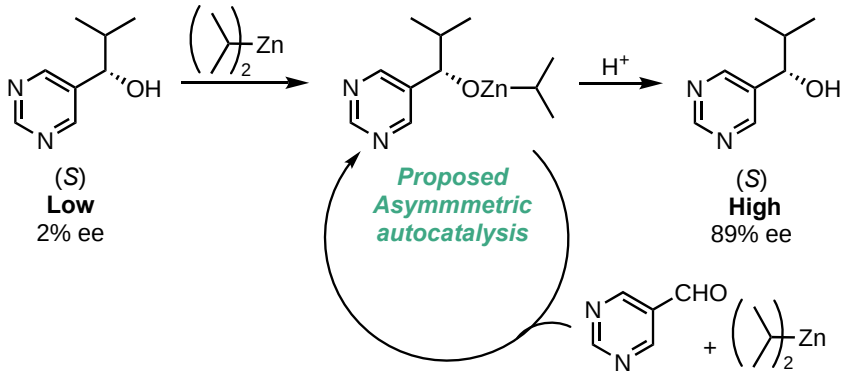
Asymmetric Autocatalysis:
The Soai reaction and investigation into the catalyst species

Samantha Grosslight
Sigman Group
June Synthesis Club



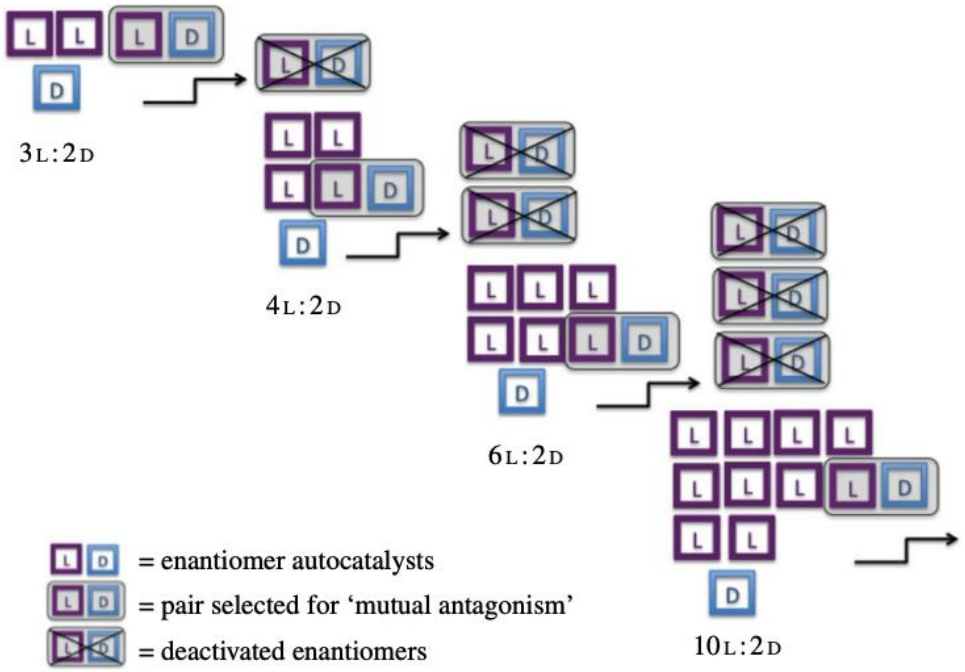
What is the Origin of Chirality ?

Models for the Origin of Chirality
Chiral Amnesia Model, Crystal Engineering Model, Frank Model, exc

Blackmond, D. G. *Phil. Trans. R. Soc. B.* **2011**, *366*, 28778

What is the Origin of Chirality ?

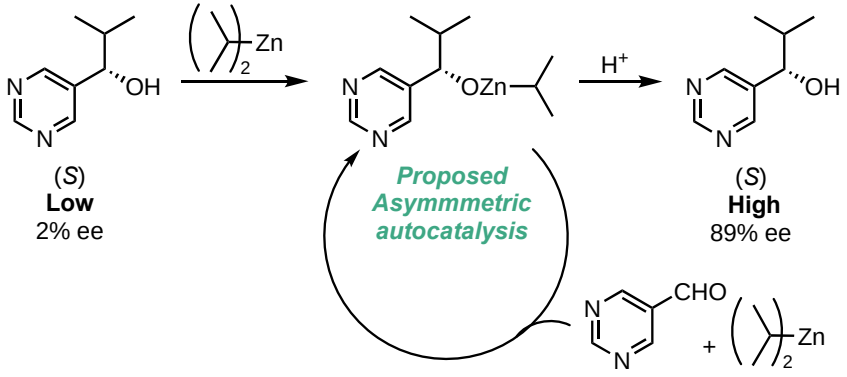
The Frank Model
Evolution of homochirality by autocatalysis and Mutal Antagonism

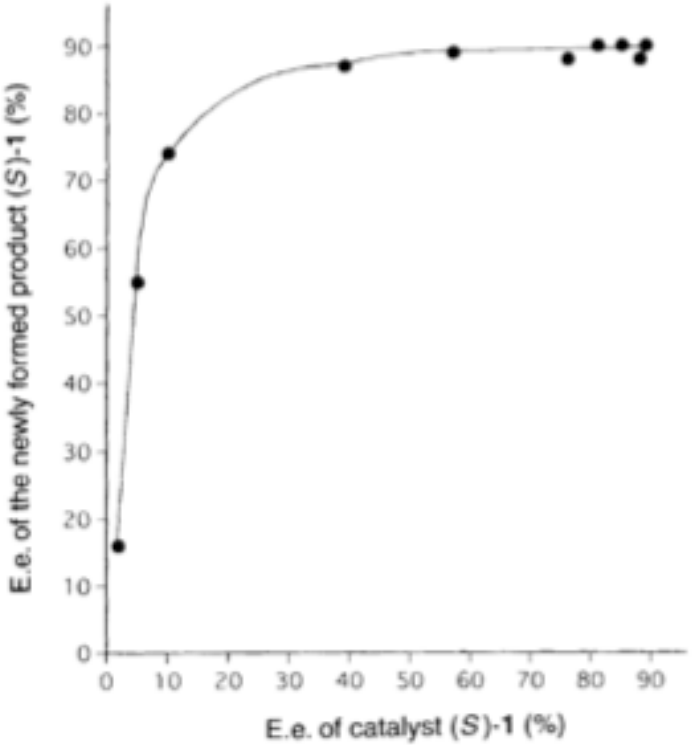


Blackmond, D. G. *Phil. Trans. R. Soc. B.* **2011**, *366*, 28778

The Soai Reaction

Experimental prof of the Frank Model



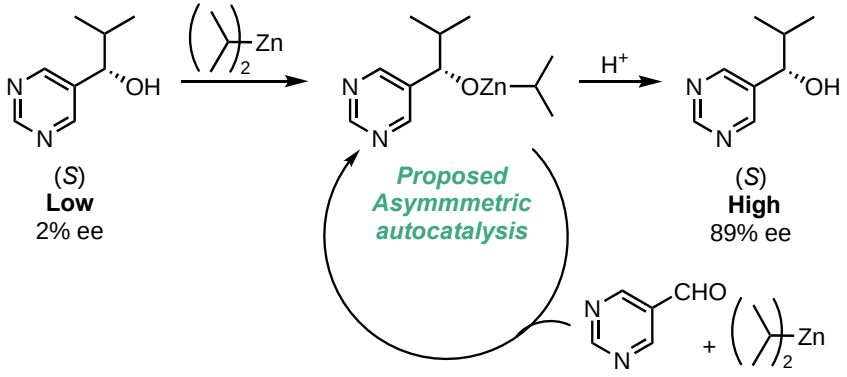


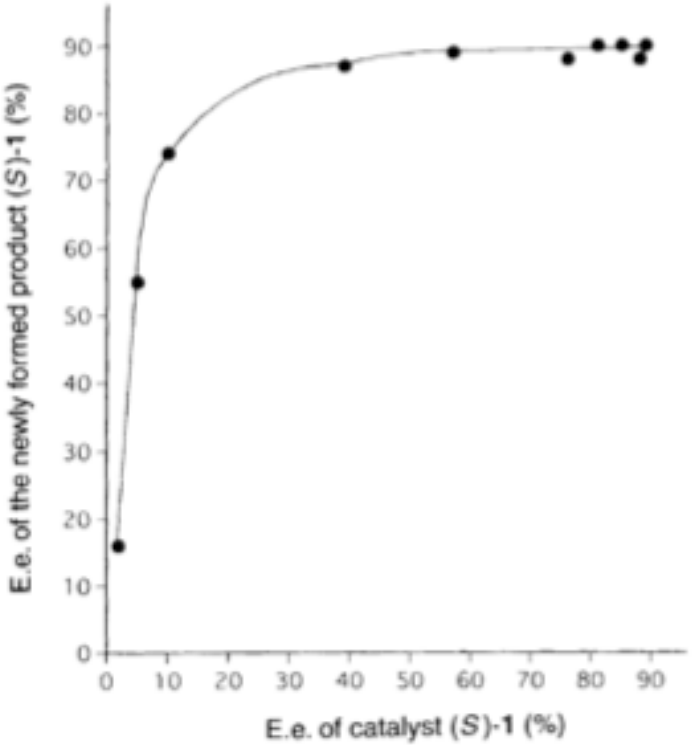
Blackmond, D. G. *Phil. Trans. R. Soc. B.* **2011**, *366*, 28778

Soai, K.; Shibata, T.; Morikoa, H.; Choji, K. Nature, 1995, 378, 767

The Soai Reaction

Experimental prof of the Frank Model





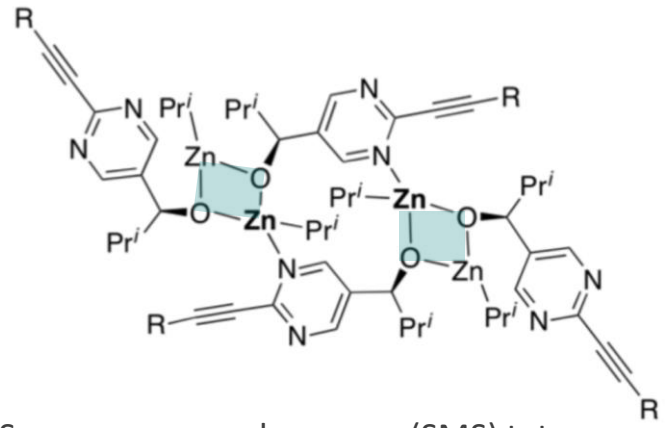
What is the structure of the Autocatalysis ?

Blackmond, D. G. *Phil. Trans. R. Soc. B.* **2011**, *366*, 28778

Soai, K.; Shibata, T.; Morikoa, H.; Choji, K. Nature, 1995, 378, 767

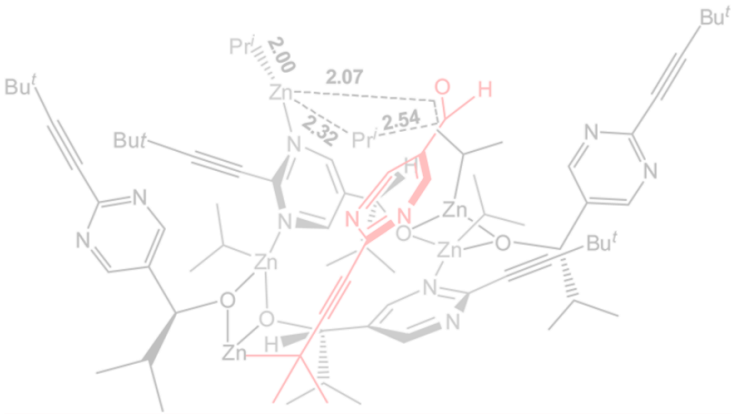
Background and Timeline: Asymmetric Autocatalytic behavior & Soai reaction

Brown & Blackmond - 2010

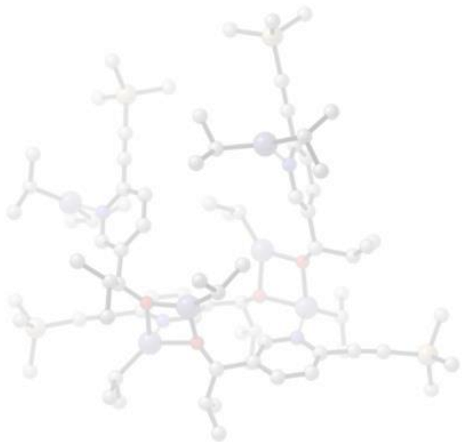


Square-macrocycle-square (SMS) tetramer

Gridnev - 2012

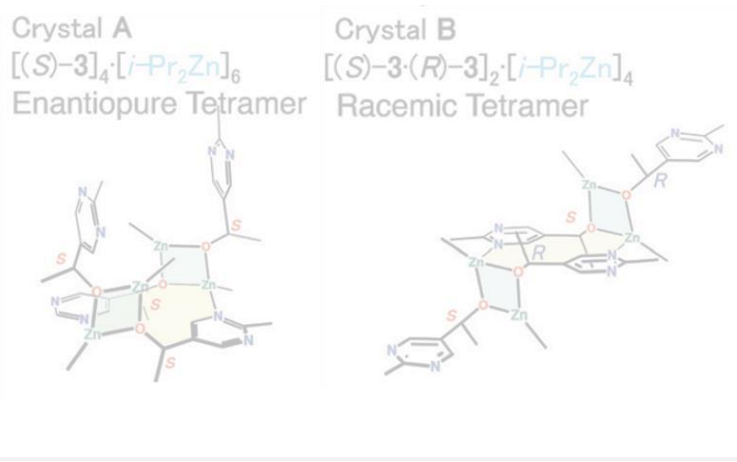


Houk & Denmark - 2020



Homochiral **PyII** tetramer, $G_{rel} = 2.1$

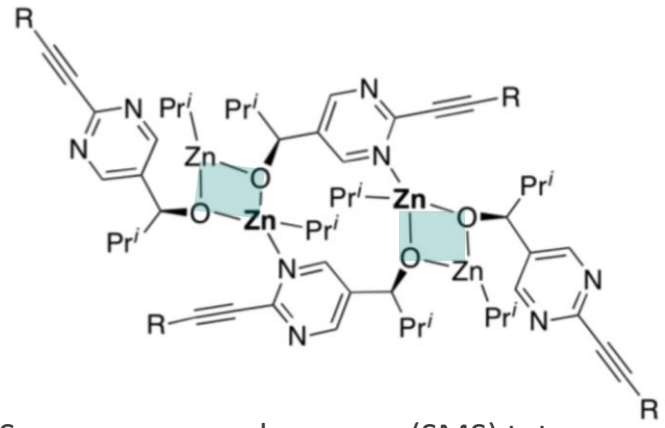
Soai - 2015



Quaranta, M.; Gehring, T.; Odell, B.; Brown. M. J.; Blackmond, D. G. JACS, 2010, 132, 15104.

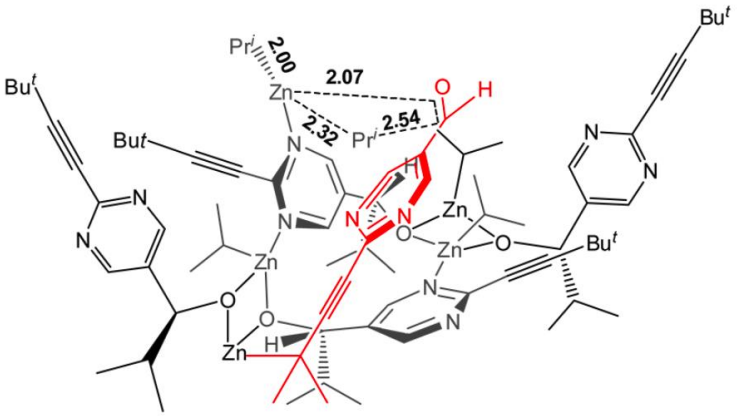
Background and Timeline: Asymmetric Autocatalytic behavior & Soai reaction

Brown & Blackmond - 2010

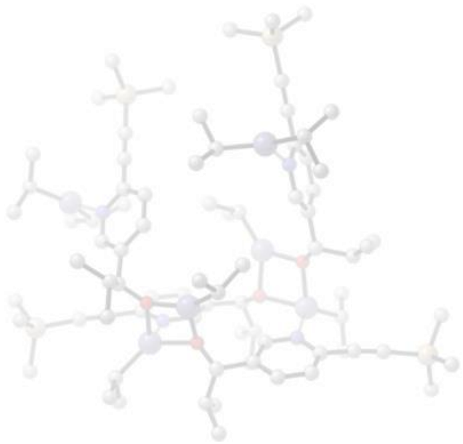


Square-macrocycle-square (SMS) tetramer

Gridnev - 2012

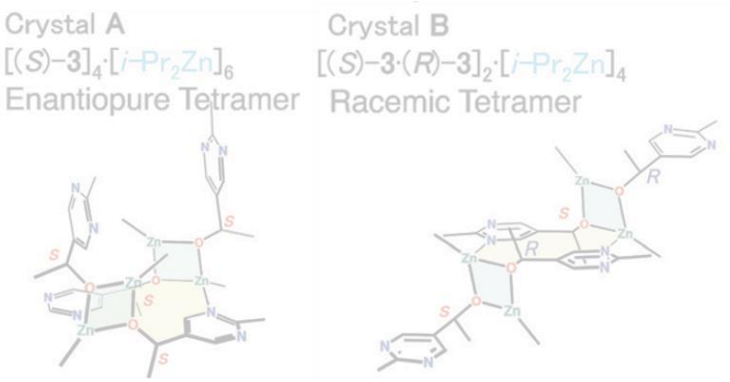


Houk & Denmark - 2020



Homochiral **PyII** tetramer, $G_{rel} = 2.1$

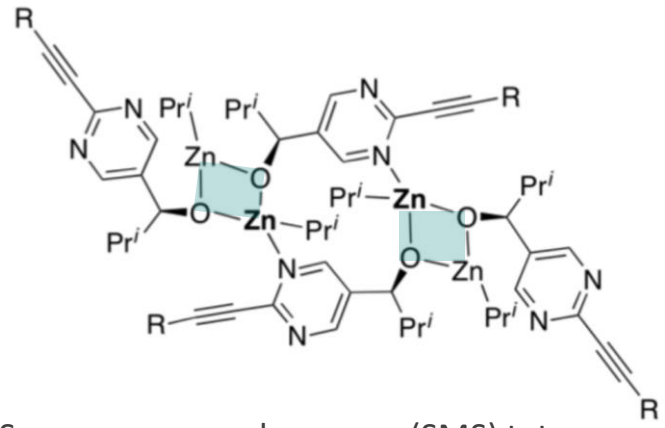
Soai - 2015



Gridnev. I. D.; Vorobiev, A. K. ACS. Catal. 2012, 2, 2137.

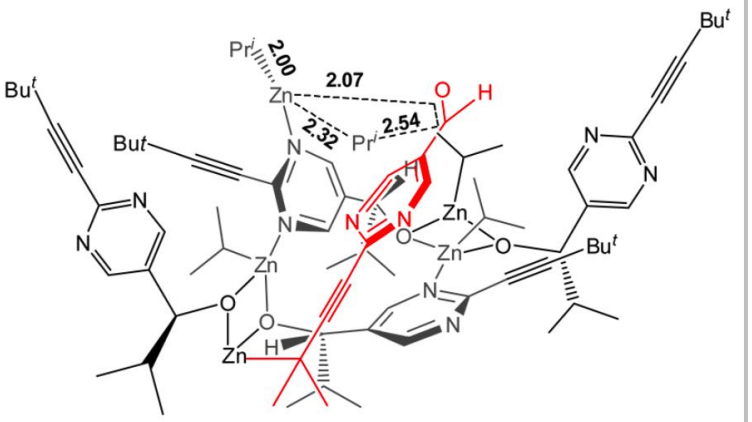
Background and Timeline: Asymmetric Autocatalytic behavior & Soai reaction

Brown & Blackmond - 2010

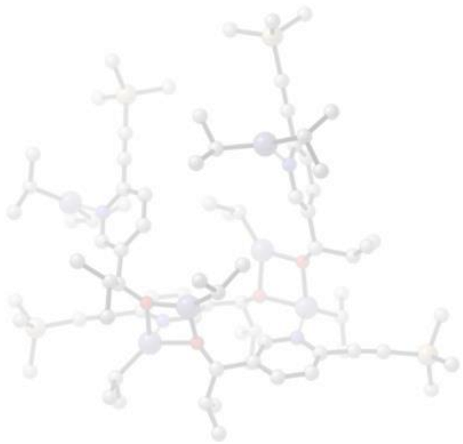


Square-macrocycle-square (SMS) tetramer

Gridnev - 2012

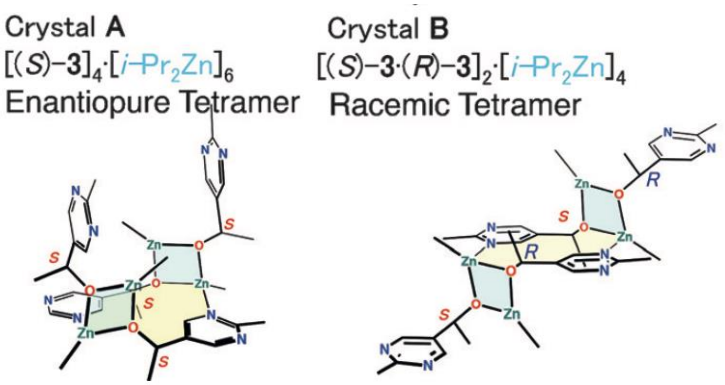


Houk & Denmark - 2020



Homochiral **PyII** tetramer, $G_{rel} = 2.1$

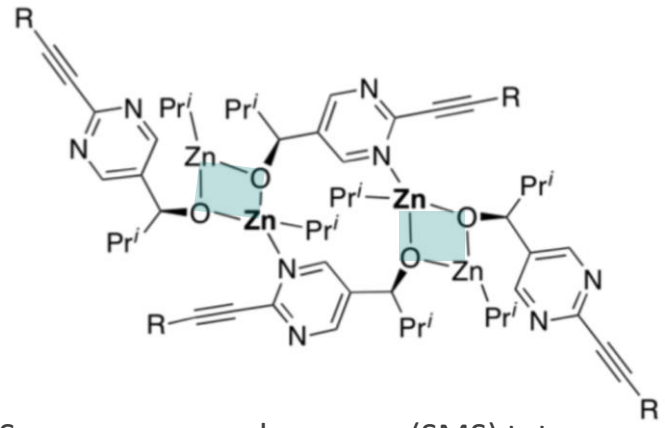
Soai - 2015



Matsumoto, A.; Abe, T.; hara, A.; Tobita, T.; Sasagawa, T.; Kawasaki, T.; Soai, K. Angew. Chem. Int. Ed. 2015, 54, 15218.

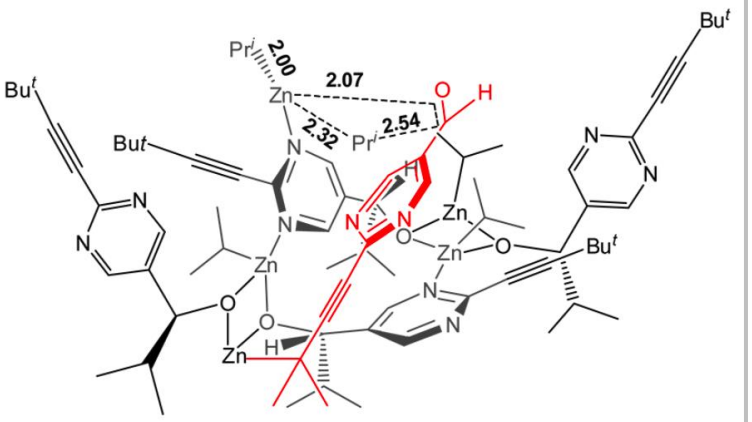
Background and Timeline: Asymmetric Autocatalytic behavior & Soai reaction

Brown & Blackmond - 2010

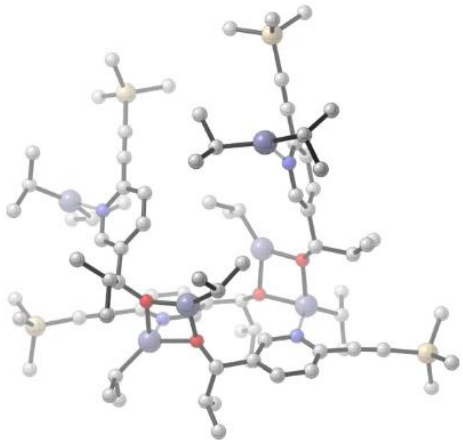


Square-macrocycle-square (SMS) tetramer

Gridnev - 2012

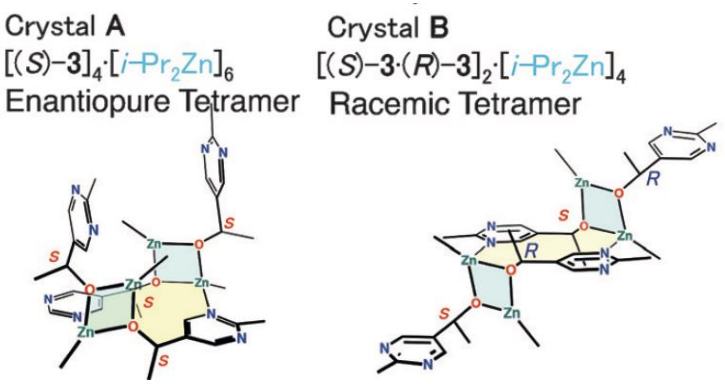


Houk & Denmark - 2020



Homochiral **PyII** tetramer, $G_{rel} = 2.1$

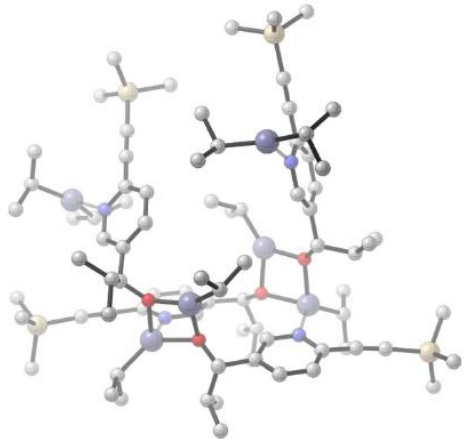
Soai - 2015



Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Background and Timeline: Asymmetric Autocatalytic behavior & Soai reaction

Houk & Denmark - 2020

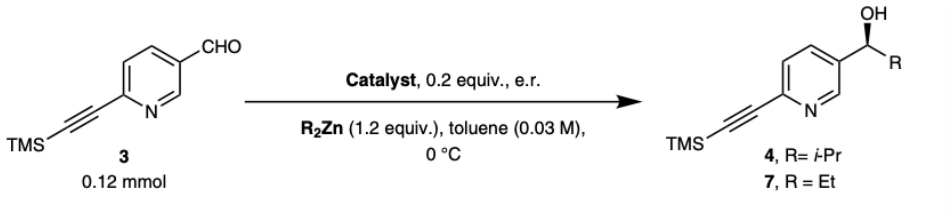


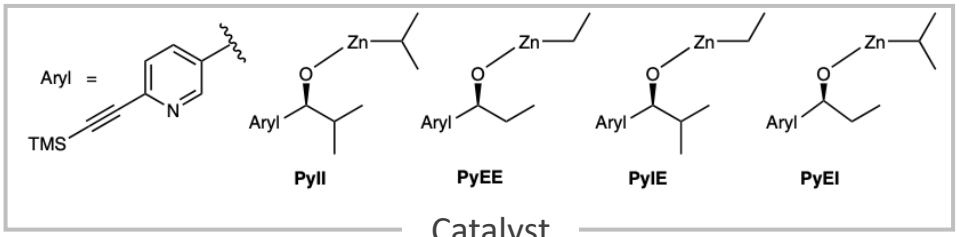
1) Substrate Dependence
How do substrate impact catalysis

2) Catalysis Structure
Computational Analysis

Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Substrate Specificity

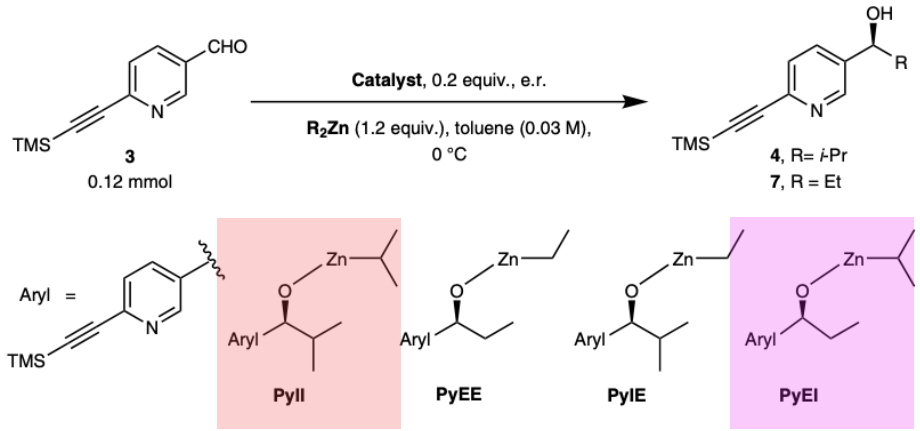




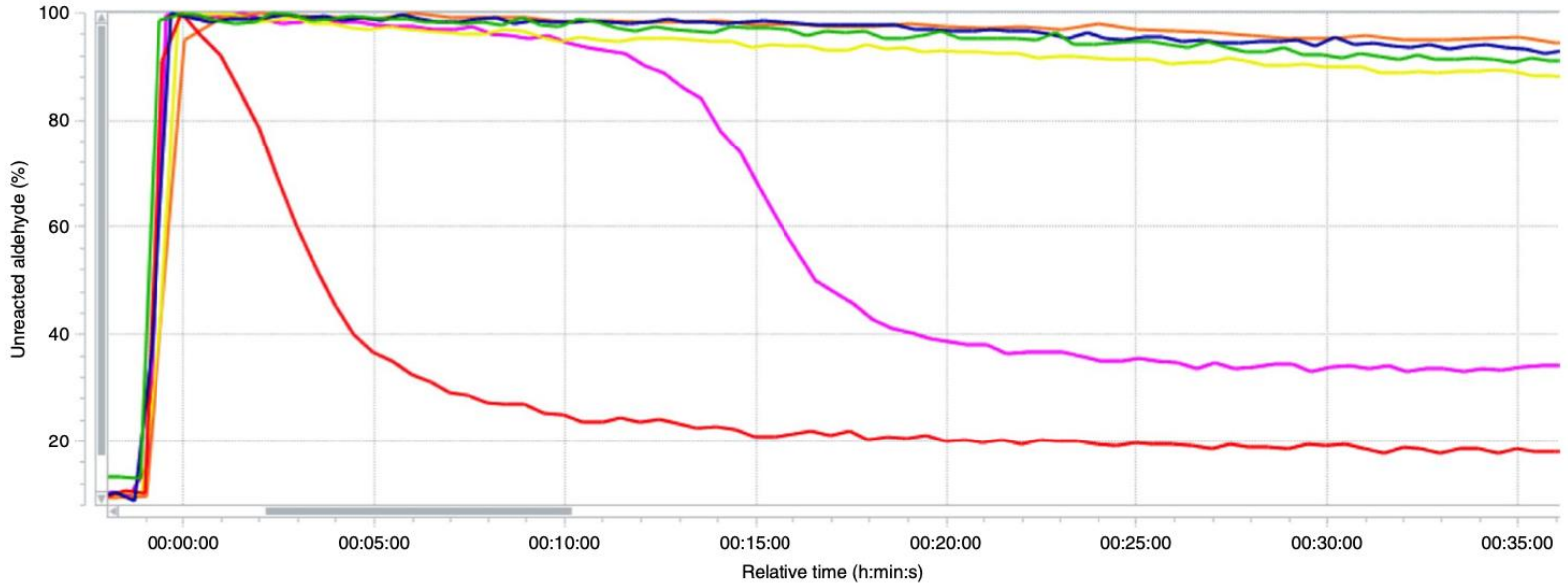
Pyridine also a competent substrate, traditionally used pyrimidine-5-carbaldehydes

Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Substrate Specificity



Entry	R	Catalyst	Key	Cat e.r.	Product e.r.[c]
1	*i*-Pr	None		–	–
2	*i*-Pr	PyII		62:38	92:8 (75)[d]
3	*i*-Pr	PyEI		70:30	98:2 (65)
4	Et	None		–	–
5	Et	PyEE		72:28	68:32 (15)[d]
6	Et	PyIE		70:30	74:26 (28)

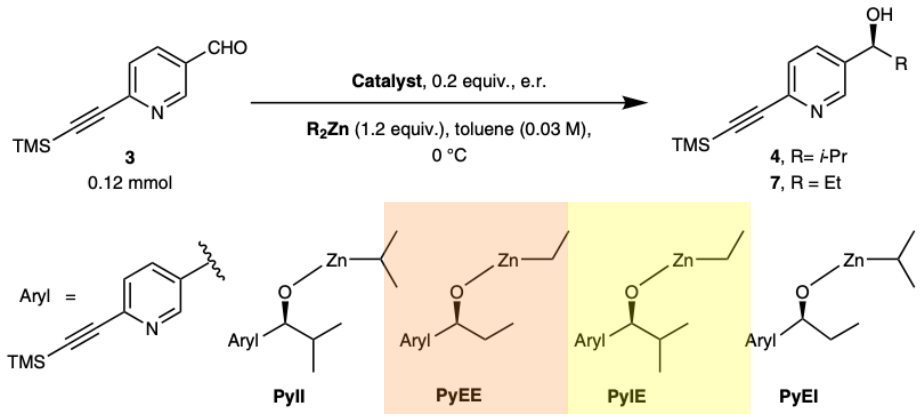


Pyridine also a competent substrate, traditionally used pyrimidine-5-carbaldehydes

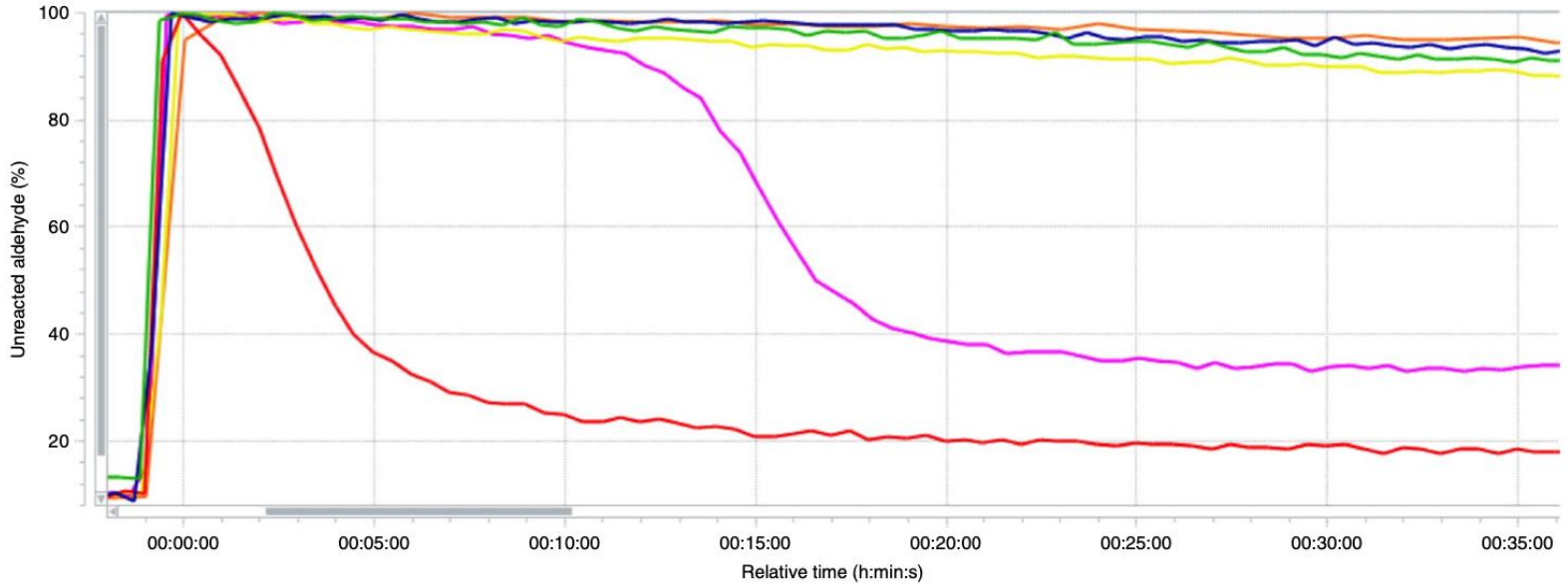
How are PyII PyEE PyIE PyEI structurally different in solution ?

Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Substrate Specificity



Entry	R	Catalyst	Key	Cat e.r.	Product e.r.[c]
1	*i*-Pr	None		–	–
2	*i*-Pr	PyII		62:38	92:8 (75)[d]
3	*i*-Pr	PyEI		70:30	98:2 (65)
4	Et	None		–	–
5	Et	PyEE		72:28	68:32 (15)[d]
6	Et	PyIE		70:30	74:26 (28)



Pyridine also a competent substrate, traditionally used pyrimidine-5-carbaldehydes

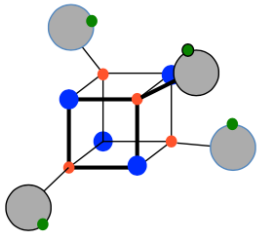
How are PyII PyEE PyIE PyEI structurally different in solution ?

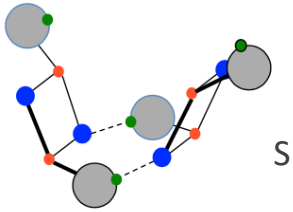
Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Solutions Species

SMS (square-macrocycle-square)

Cubic Tetramer





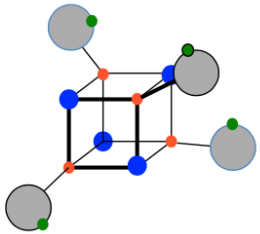
SMS Tetramer

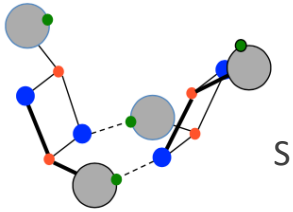
Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Solutions Species

SMS (square-macrocycle-square)

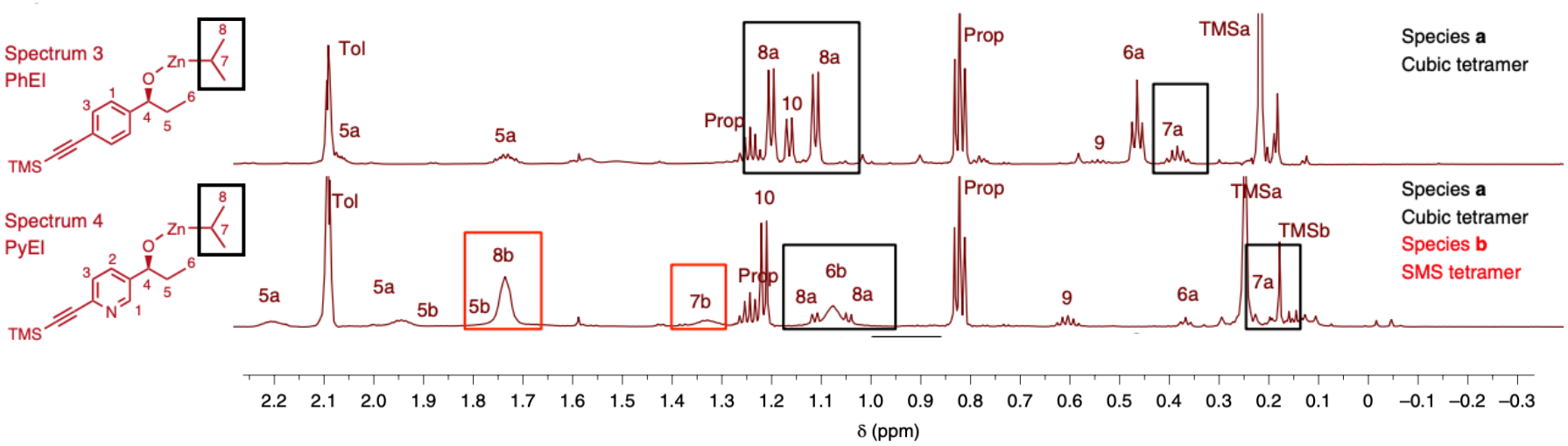
Cubic Tetramer





SMS Tetramer

Downfield shift of H8 and H7 + Peak broadening suggestive of SMS tetramer

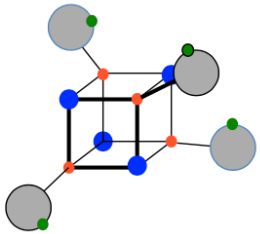


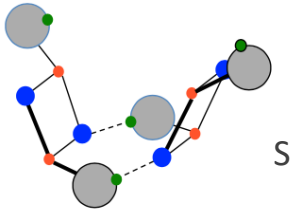
Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Solutions Species

SMS (square-macrocycle-square)

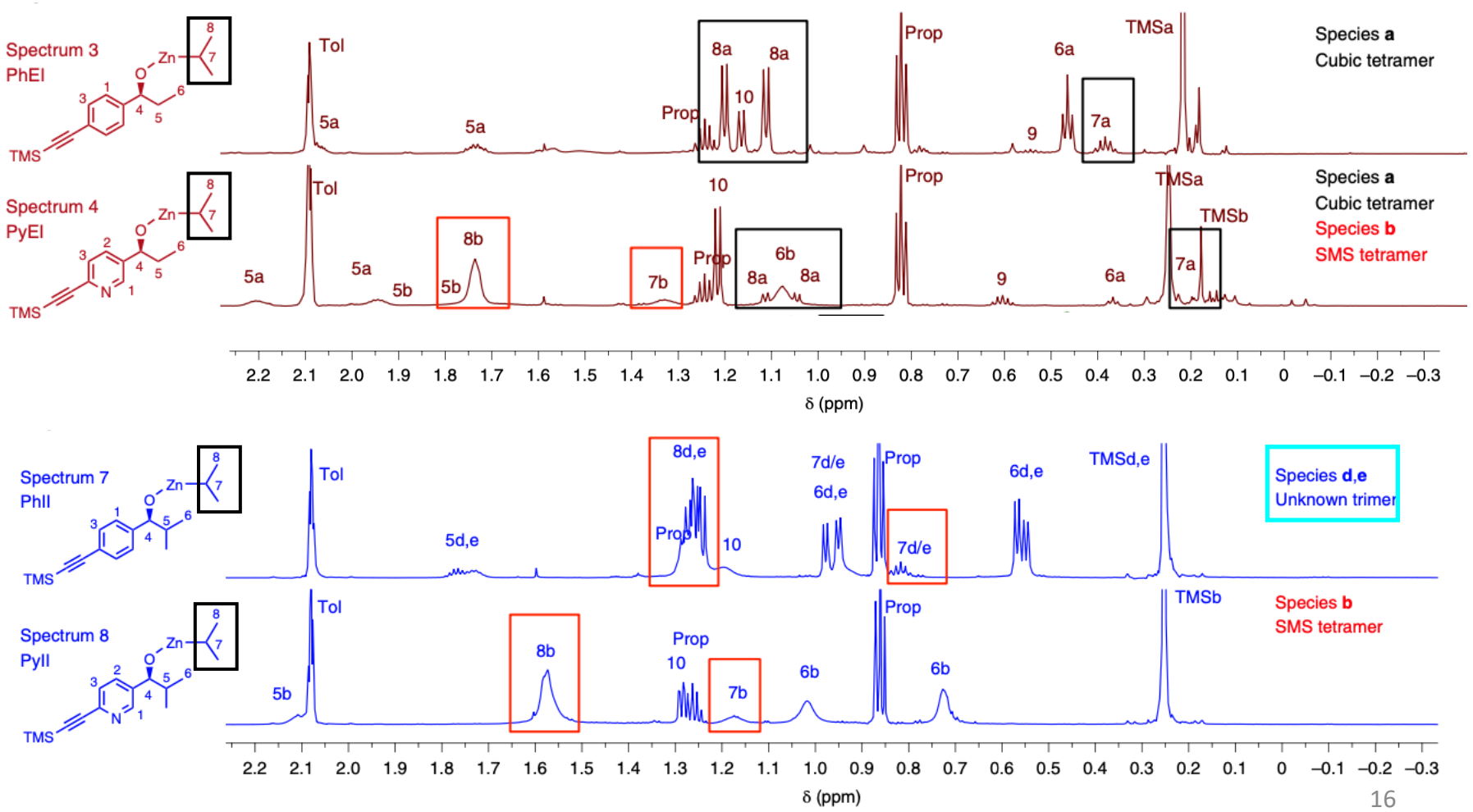
Cubic Tetramer





SMS Tetramer

Downfield shift of H8 and H7 + Peak broadening suggestive of SMS tetramer

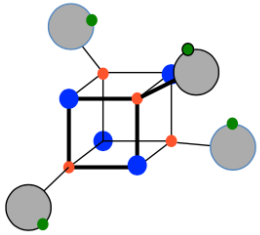


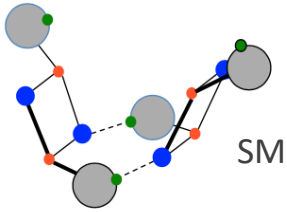
Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Solutions Species

SMS (square-macrocycle-square)

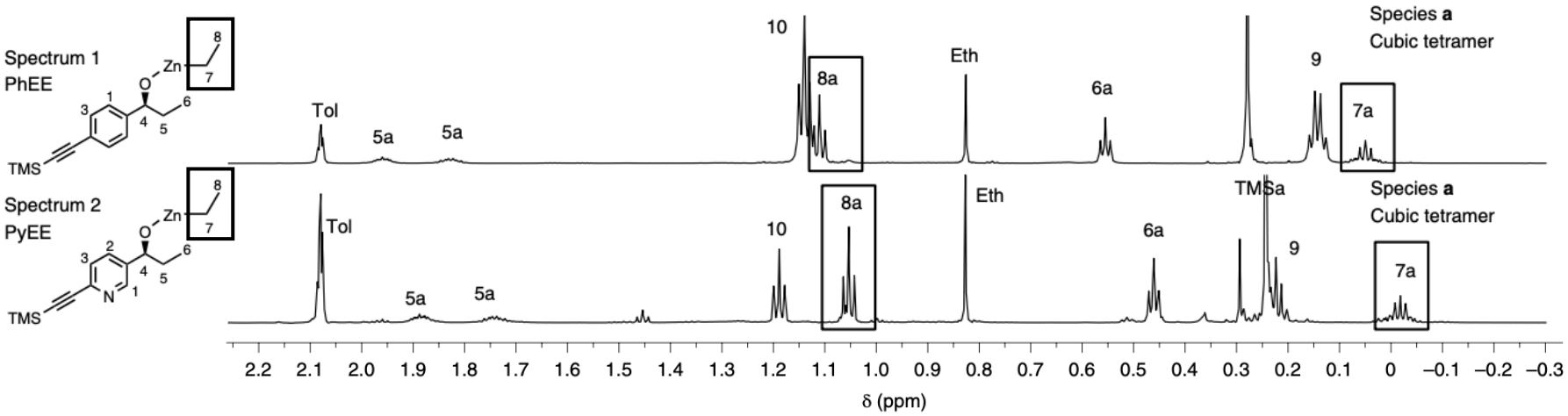
Cubic Tetramer





SMS Tetramer

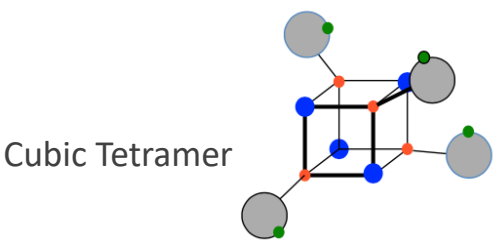
Downfield shift of H8 and H7 + Peak broadening suggestive of SMS tetramer



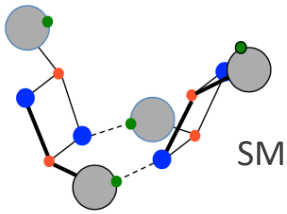
Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Solutions Species

SMS (square-macrocycle-square)

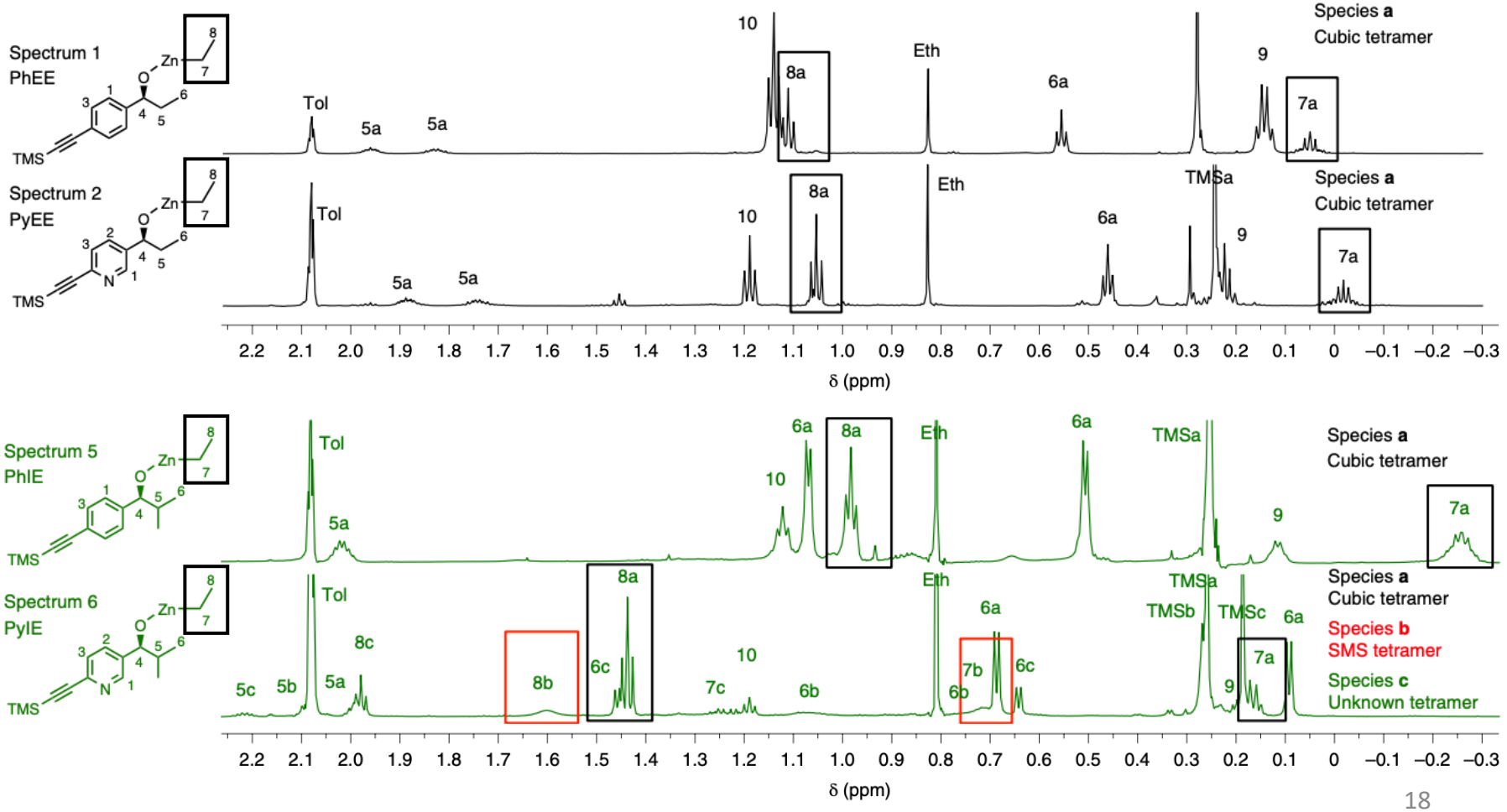


Cubic Tetramer



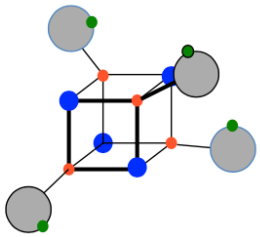
SMS Tetramer

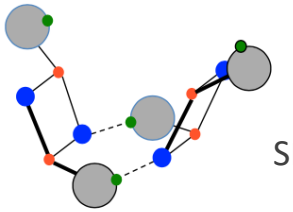
Downfield shift of H8 and H7 + Peak broadening suggestive of SMS tetramer



Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Solutions Species

Cubic Tetramer 

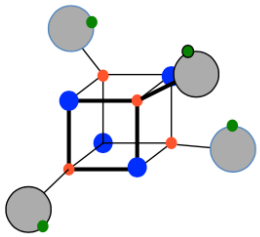
 SMS Tetramer

Cubic tetramer preferred 'organization'….however can be disrupted

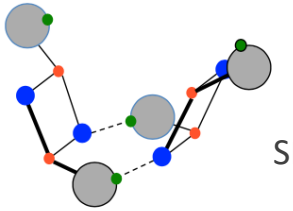
Disruption due to : Sterics (ethyl to isopropyl) & Pyridine N coordination

Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction :Pyridine disrupts the cube



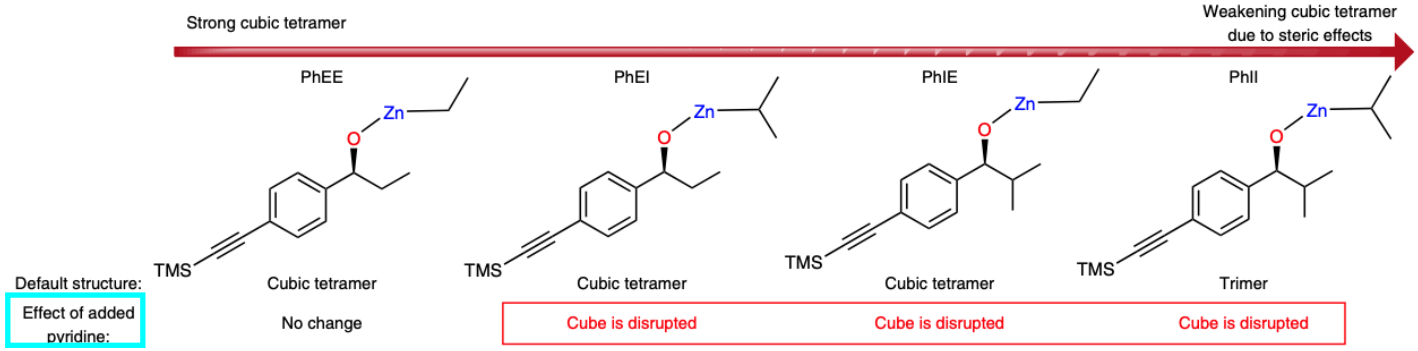
Cubic Tetramer

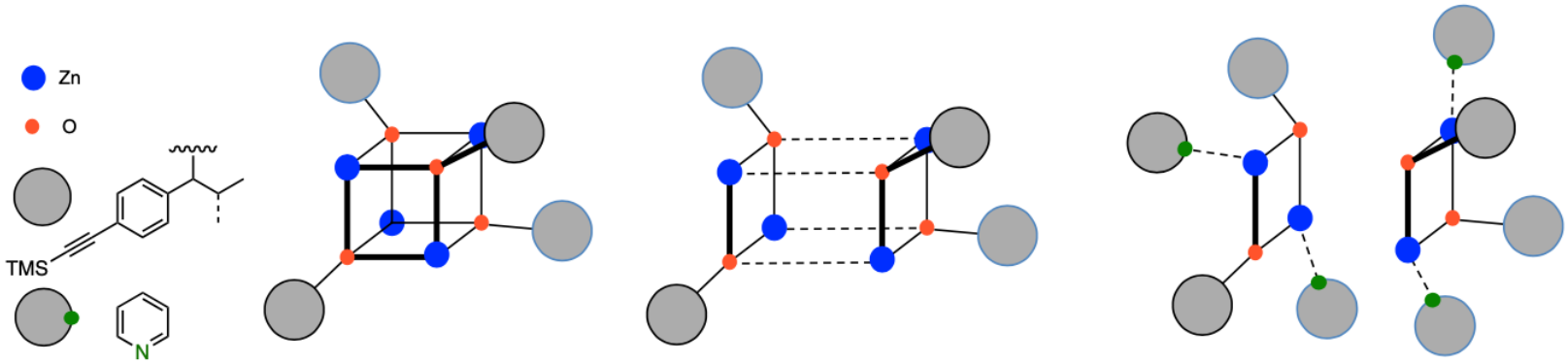


SMS Tetramer

Cubic tetramer preferred 'organization'….however can be disrupted

Disruption due to : Sterics (ethyl to isopropyl) & Pyridine N coordination

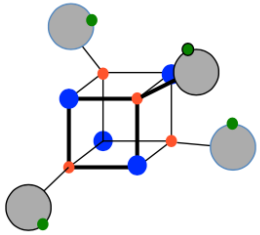


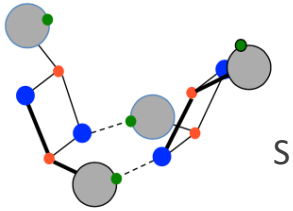


Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

SMS (square-macrocycle-square)

Cubic Tetramer

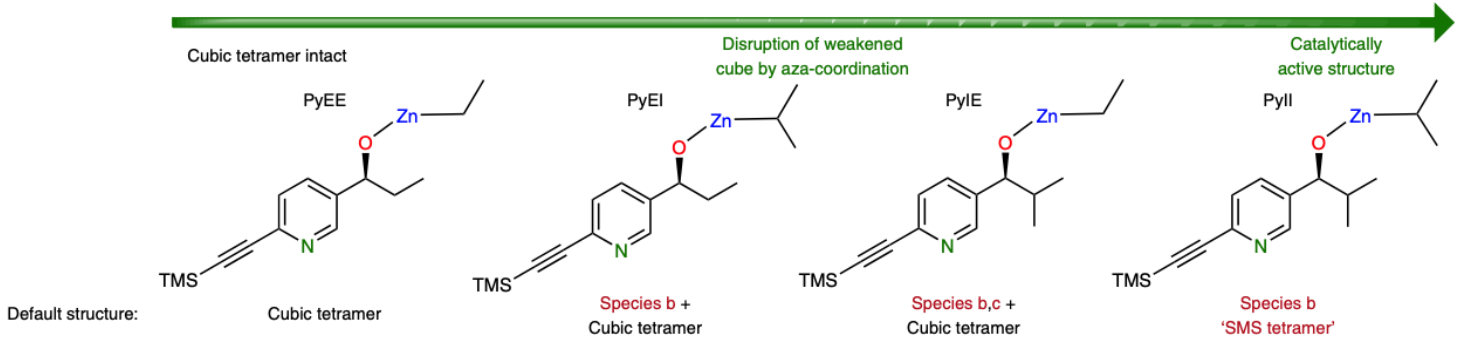


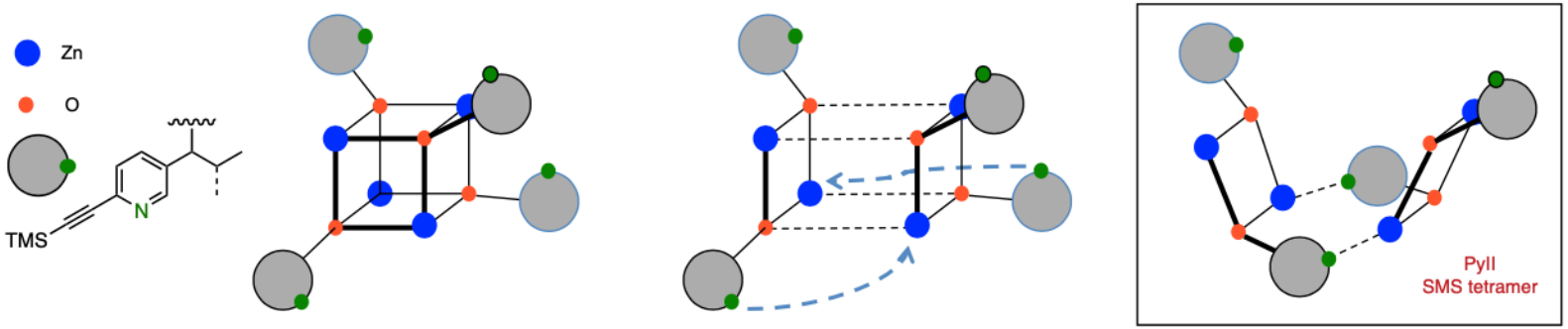


SMS Tetramer

Cubic tetramer preferred 'organization'….however can be disrupted

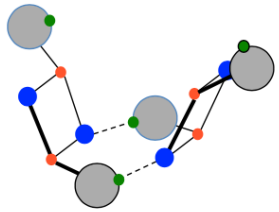
Disruption due to : Sterics (ethyl to isopropyl) & Pyridine N coordination



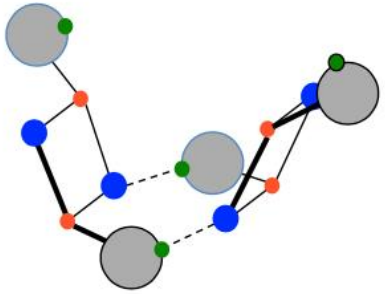


Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

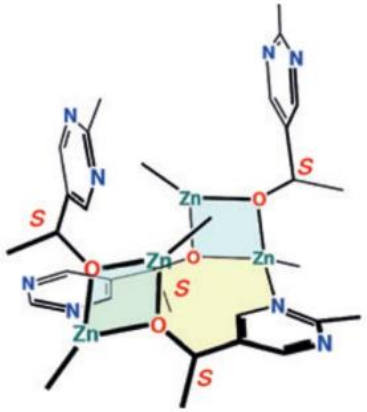
Soai Reaction : Agreement with Soai crystal structures



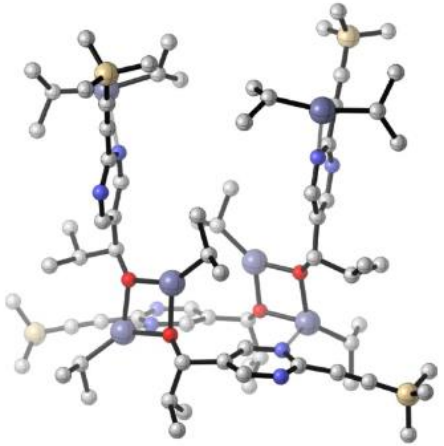
SMS tetramer agreement with Soai Crystal structure?



PyII SMS tetramer connectivity



Pyrimidine alkoxide crystal structure

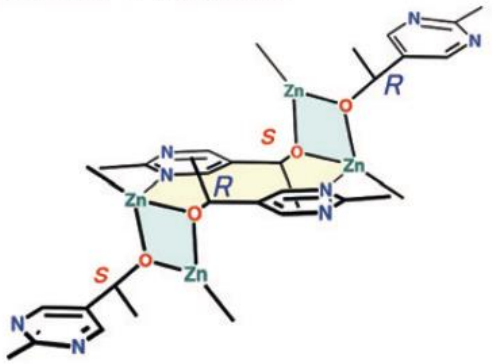


Predicted PyII SMS tetramer

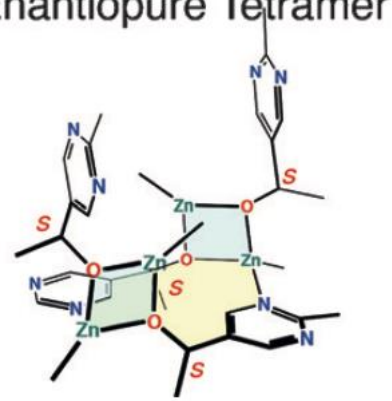
Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Agreement with Soai crystal structures

Crystal **B**
$[(S)\text{-}\mathbf{3}\cdot(R)\text{-}\mathbf{3}]_2\cdot[i\text{-}Pr_2Zn]_4$
Racemic Tetramer



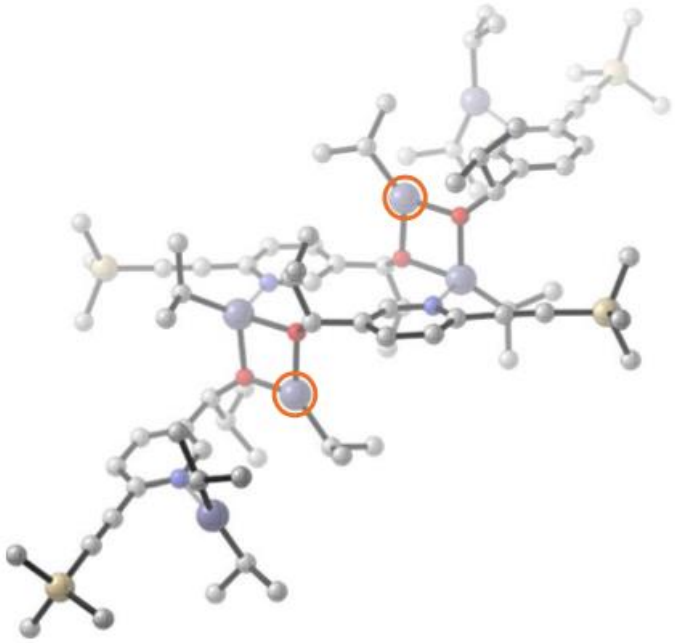
Crystal **A**
$[(S)\text{-}\mathbf{3}]_4\cdot[i\text{-}Pr_2Zn]_6$
Enantiopure Tetramer



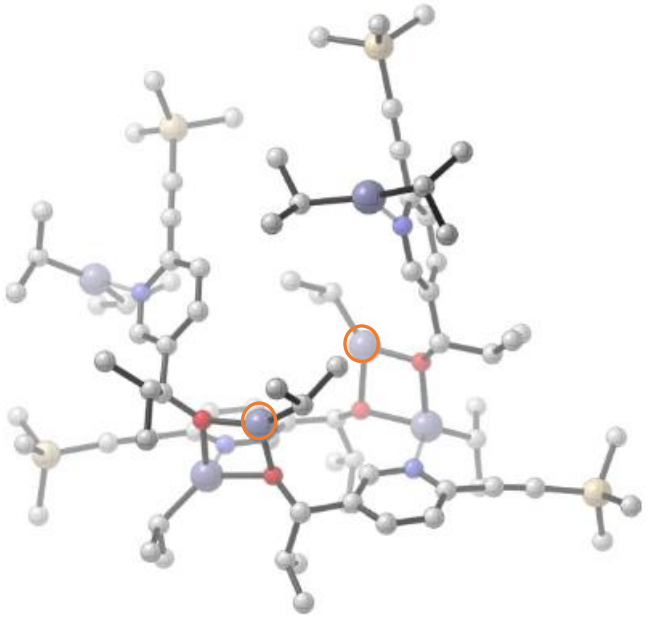
What is the difference between the enantiopure and racemic catalyst?
How does catalysis proceed?

Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Enantiopure vs Racemic



Heterochiral **PyII** tetramer,



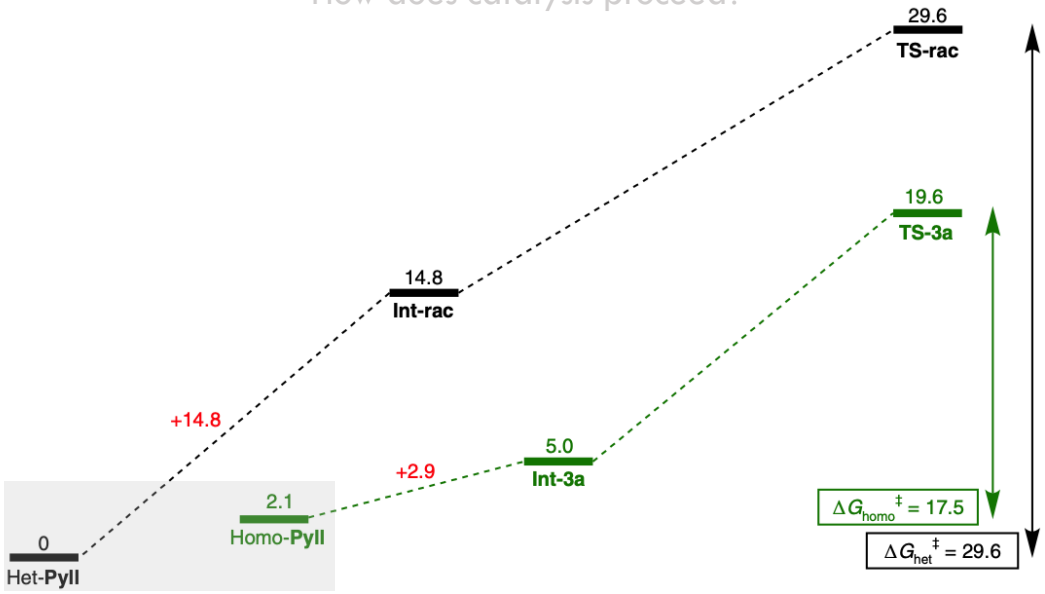
Homochiral **PyII** tetramer,

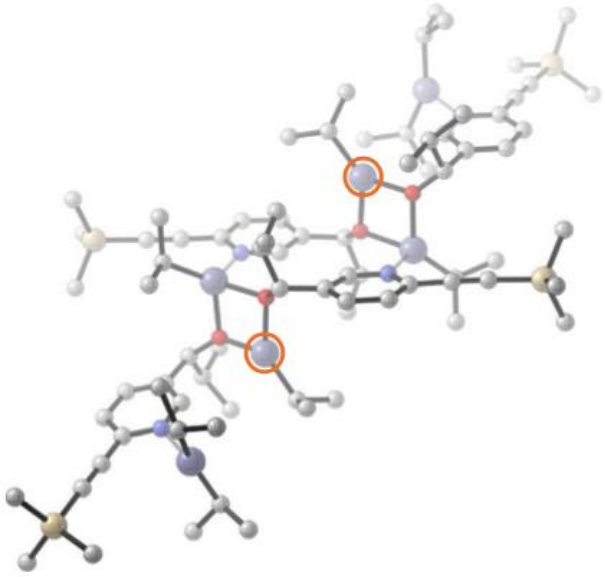
Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Non-linear effect

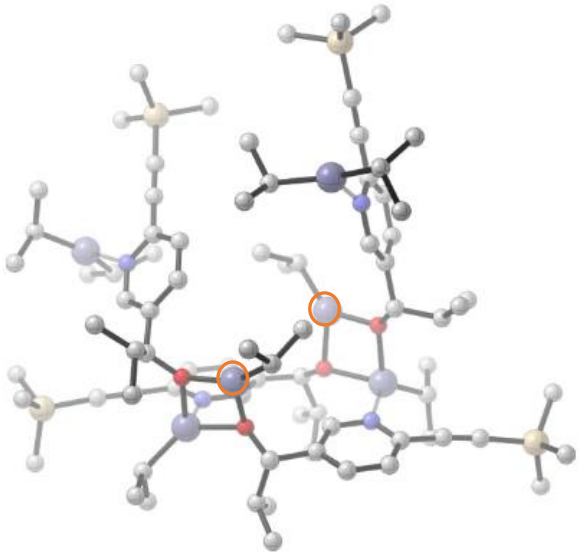
What is the difference between the enantiopure and racemic catalyst?

How does catalysis proceed?





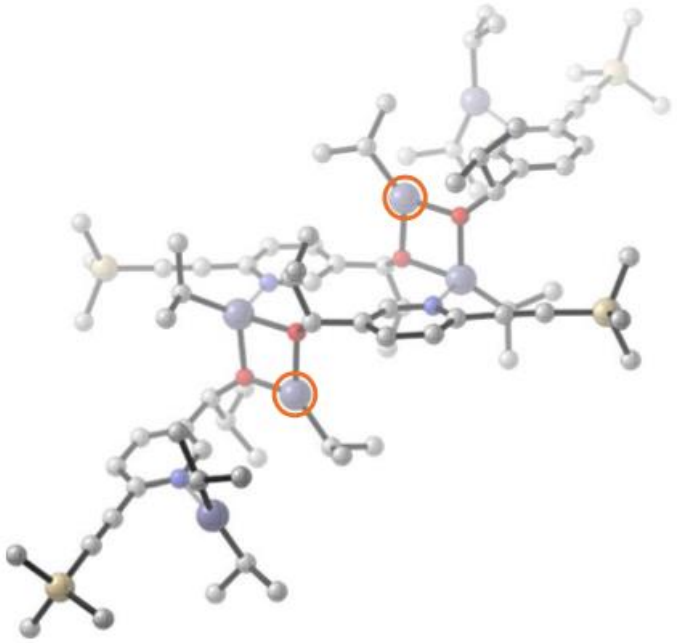
Heterochiral **PyII** tetramer, G_{rel} = 0



Homochiral **PyII** tetramer, G_{rel} = 2.1

Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

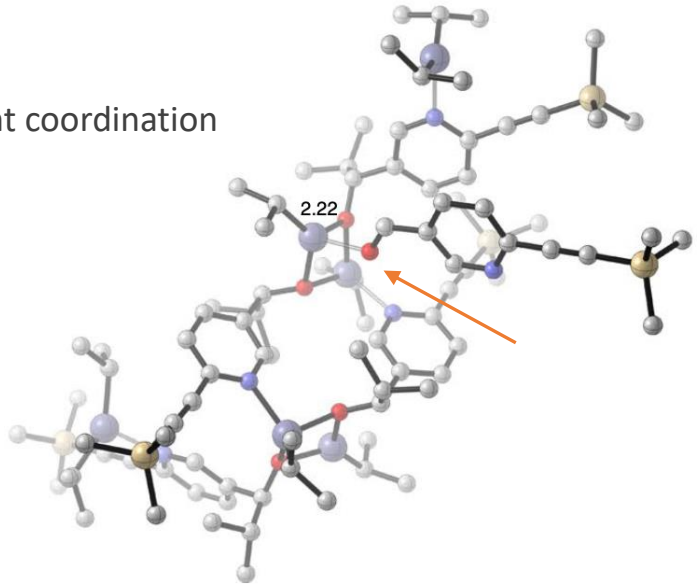
Soai Reaction : Racemic Binding Mode



Heterochiral **PyII** tetramer,

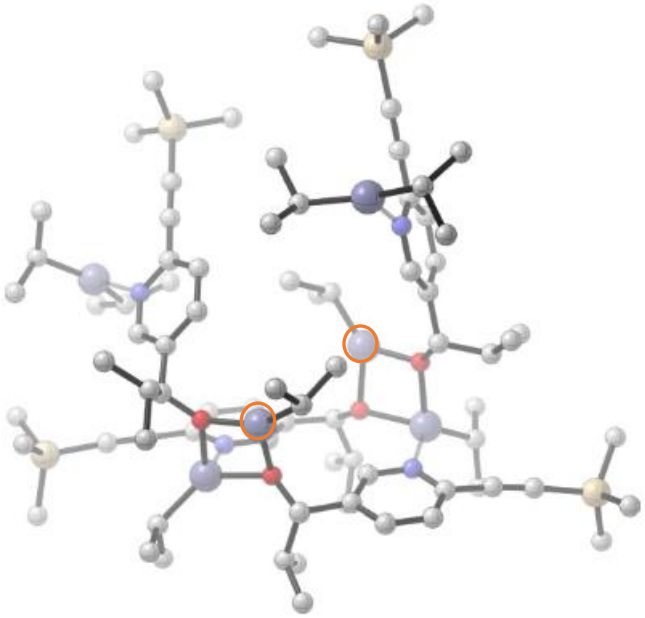
Substrate Binds

Single point coordination



Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Enantiopure Tetramer Binding

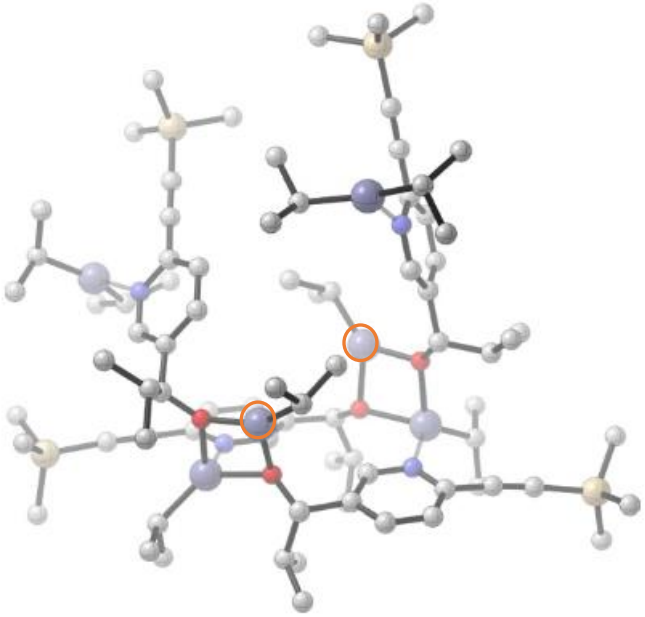


Homochiral **PyII** tetramer,

2 Modes of
Substrate Binding

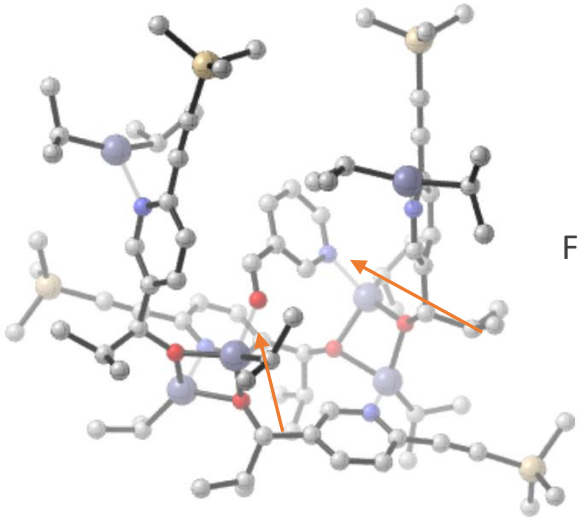
Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Enantiopure Tetramer Binding



Homochiral **PyII** tetramer,

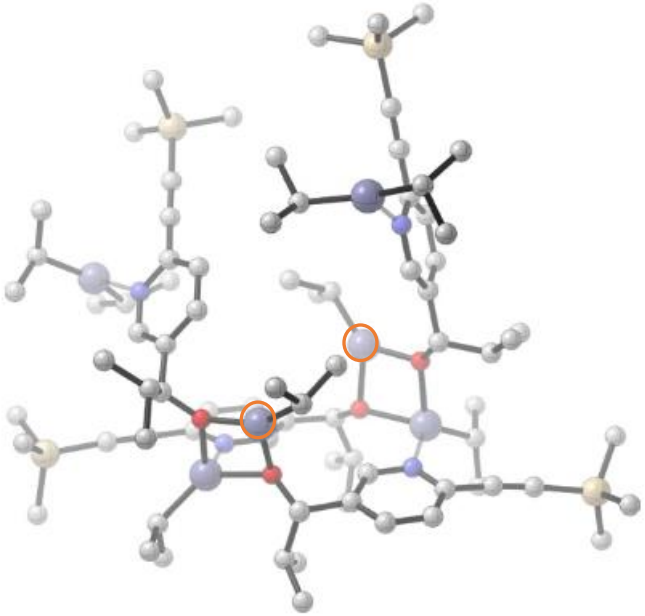
2 Modes of
Substrate Binding



Floor to Floor
$\Delta\Delta G=0$

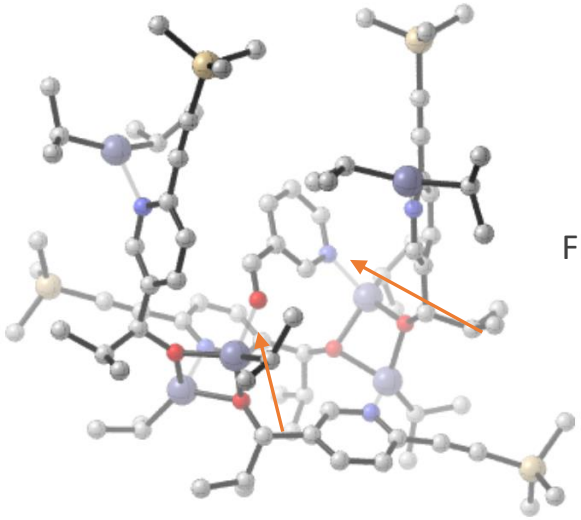
Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Enantiopure Tetramer Binding

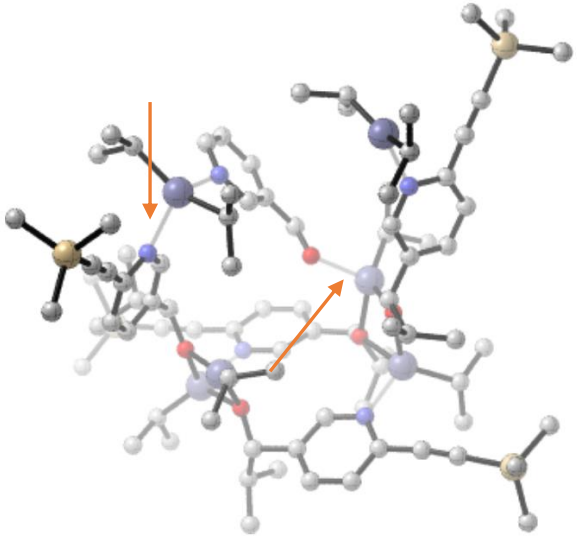


Homochiral **PyII** tetramer,

2 Modes of
Substrate Binding



Floor to Floor
$\Delta\Delta G=0$



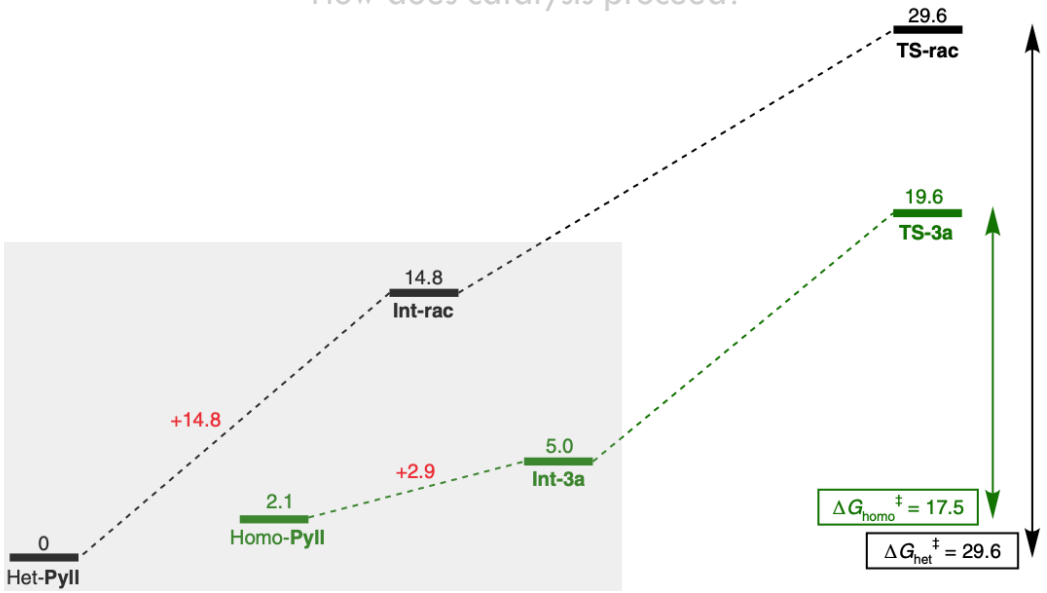
Floor to Arm
$\Delta\Delta G = 4.5$

Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

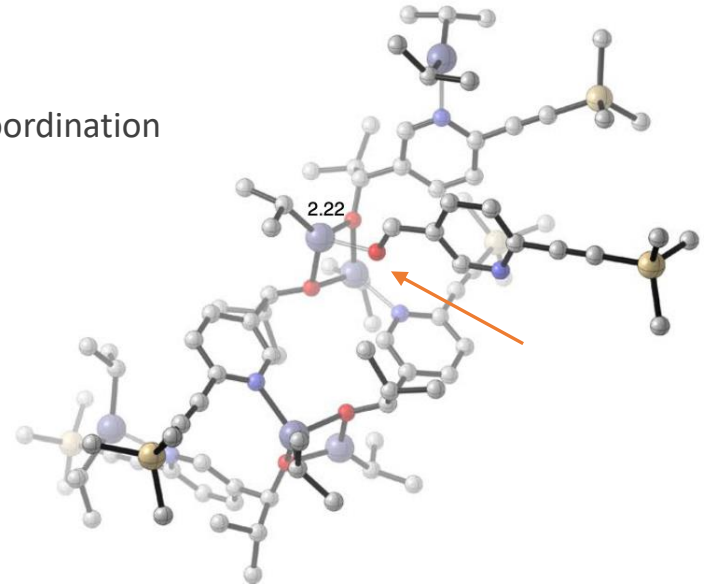
Soai Reaction : Enantiopure vs Racemic

What is the difference between the enantiopure and racemic catalyst?

How does catalysis proceed?

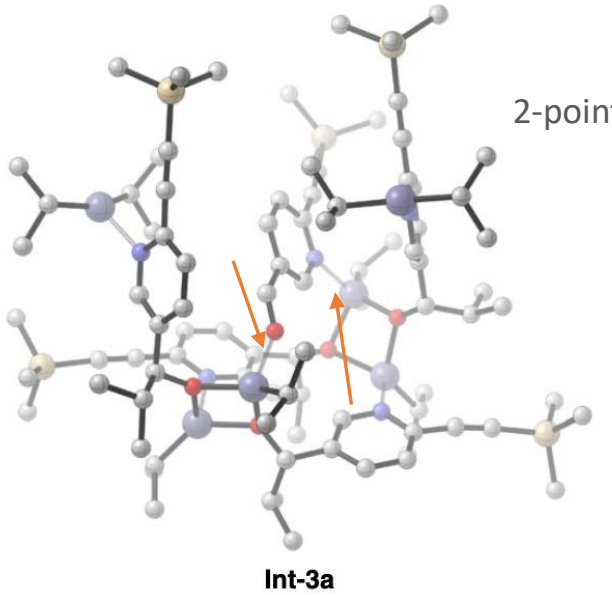


Single point coordination



Int-rac

2-point coordination



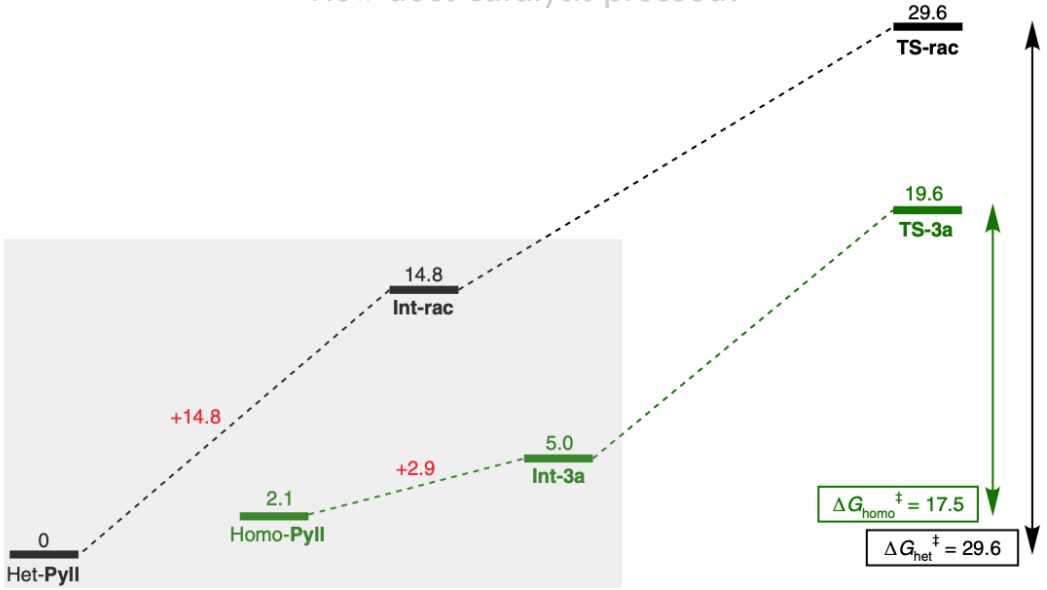
Int-3a

Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Enantiopure vs Racemic

What is the difference between the enantiopure and racemic catalyst?

How does catalysis proceed?



Heterochiral tetramer more favorable in solution, however, is kinetically incompetent

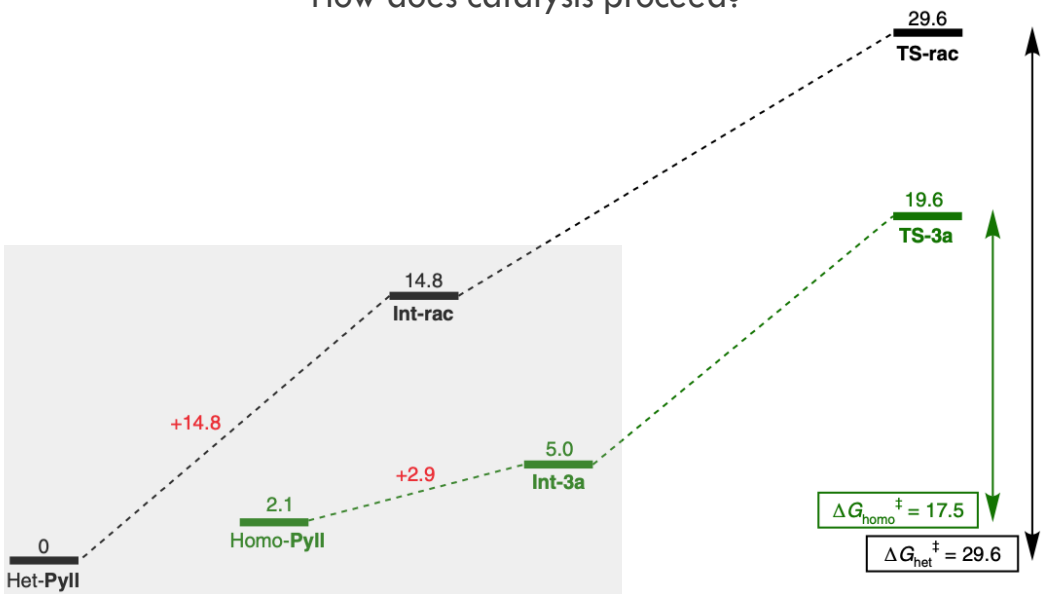
Catalytic incompetence due to aldehyde binding, not alkyl transfer

Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Selectivity ?

What is the difference between the enantiopure and racemic catalyst?

How does catalysis proceed?



Heterochiral tetramer more favorable in solution, however, is catalytically incompetent

Catalytic incompetence due to aldehyde binding, not alkyl transfer

Positive non-linear effect

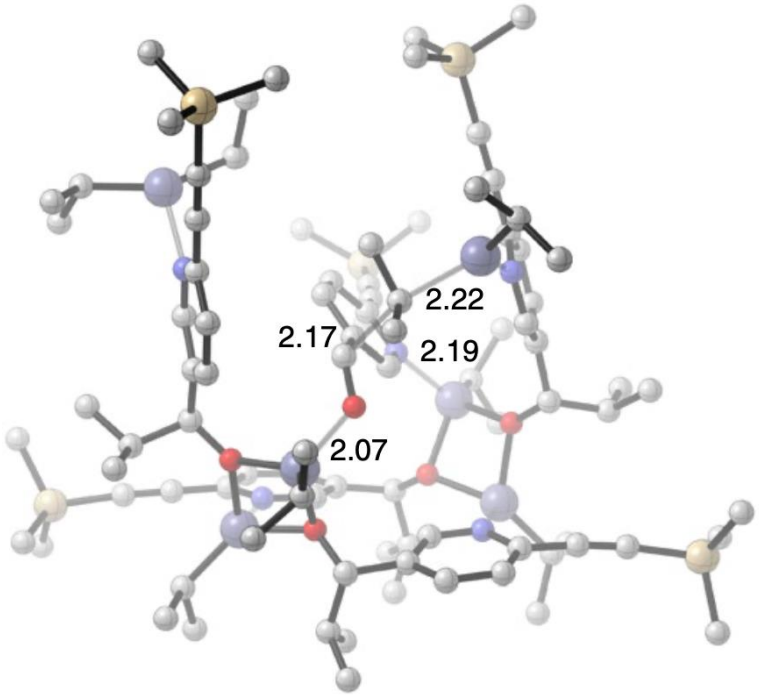
Production of enriched product results in the increase concentration of active catalyst species… what is controlling selectivity within the active catalyst?

Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

Soai Reaction : Source of selectivity

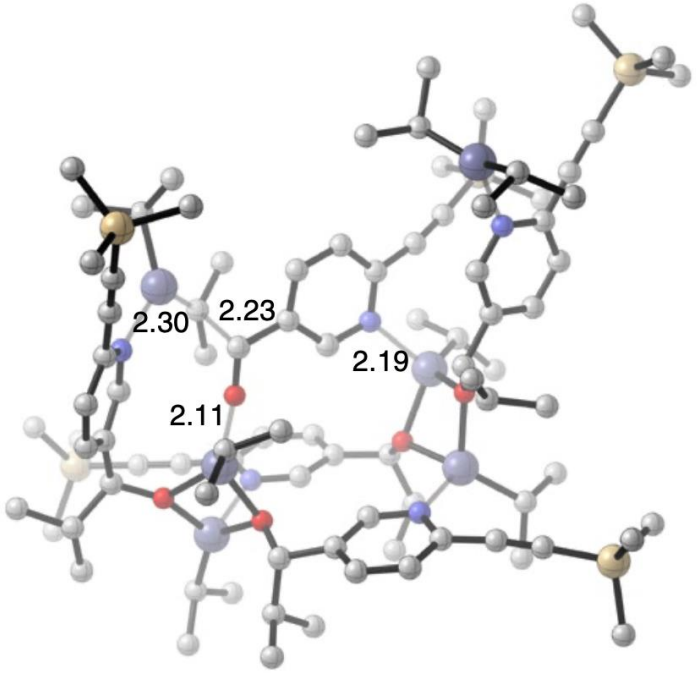
What is the difference between the enantiopure and racemic catalyst?

How does catalysis proceed?



TS-3a
$\Delta G^{\ddagger} = 14.6$

Si addition : Major enantiomer



TS-3b
$\Delta G^{\ddagger} = 19.0$
$\Delta\Delta G^{\ddagger} = 4.4$

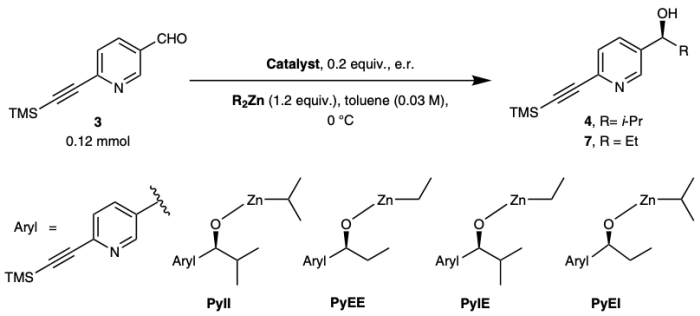
'Re' addition : Minor Enantiomer

Stereoselectivity due to the steric environment of the chiral tetramer

Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

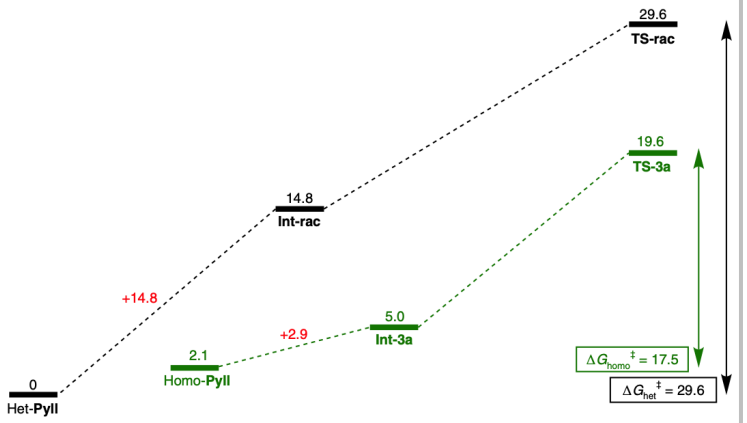
Soai Reaction : Conclusions

Substrate Scope



Substrate & catalyst dictate formation of active catalyst

Racemic vs Enatiopure



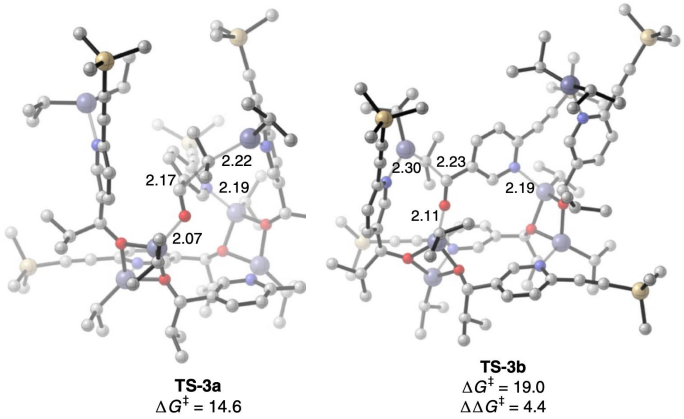
Racemic catalyst incompetent

Overall

Another way of thinking about catalysis

Not the typical Transition Metal species

Intermediates & Transition state



Steric environment influence stereoselectivity

Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. Nature Chem. 2020, 12, 412.

1953: The Frank Model

Proposed model for the origin of biological homochirality

$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} L$

$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} D$

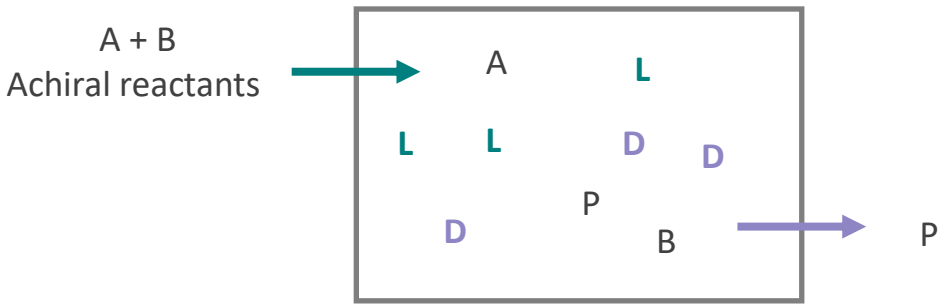
$A + B + L \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} 2L$

$A + B + D \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} 2D$

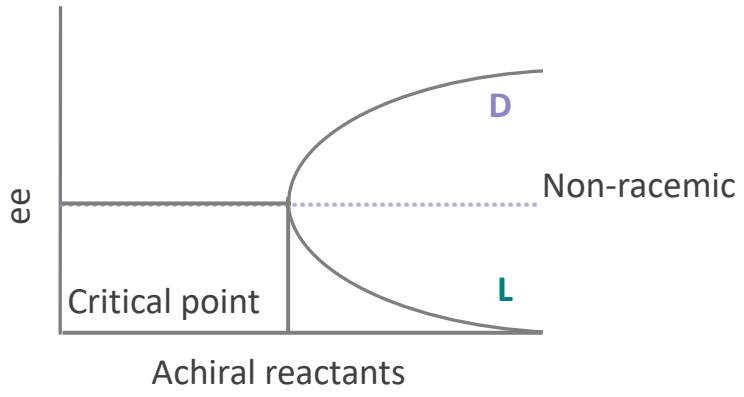
Autocatalytic
Chiral Reactions

$L + D \xrightarrow{k_3} P$

Open Flux reactor:
Non-equilibrium – Stationary state



Graphical Representation
Racemic & non-racemic



Background on asymmetric autocatalysis