Stereodivergent Catalysis

Aragorn Laverny

SED Group Meeting

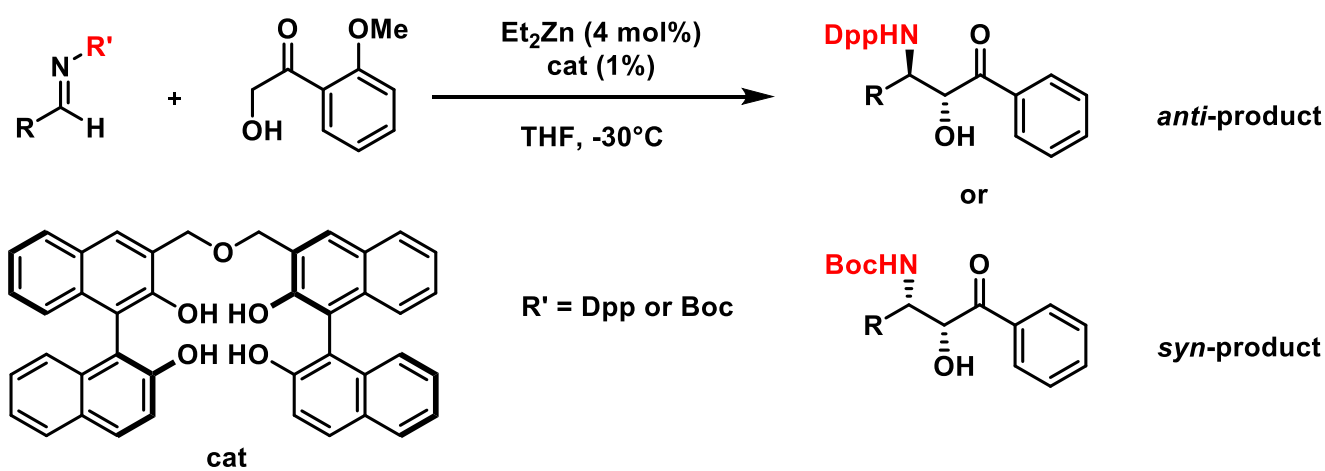
July 31 2018

Stereodivergent Catalysis

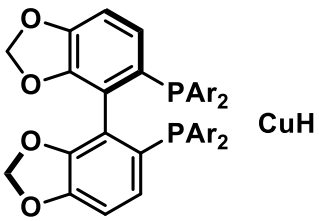
”In the context of asymmetric synthesis, a stereodivergent process is one that allows access to **any** given stereoisomer of a product with **multiple stereocenters** from the **same set** of starting materials. […]

Transformation that are rendered stereodivergent through **structural modification** of the substrate have been termed **pseudo-divergent**.”

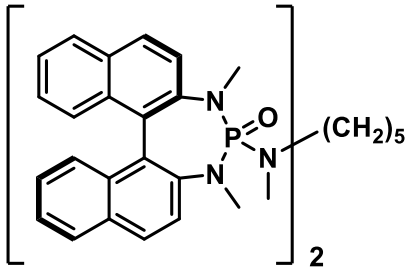
-Erick Carreira

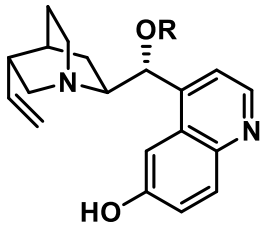


J. Am. Chem. Soc. **2017,** *139*, 5627–5639.

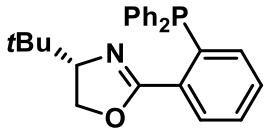


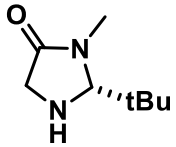
Pseudo-divergent catalysis



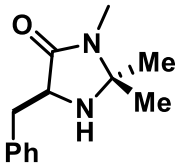


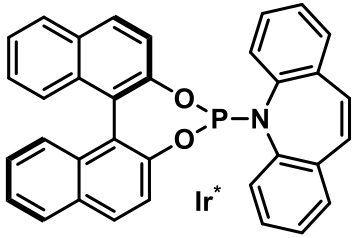
Ad-hoc modifications



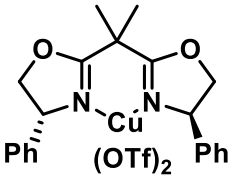


Cascade catalysis





Dual catalysis



History of Stereodivergence

Denmark

Pseudo-divergent Catalysis

Cascade Catalysis

MacMillan

Buchwald

2000 2005 2015

Divergent Catalysis

Deng

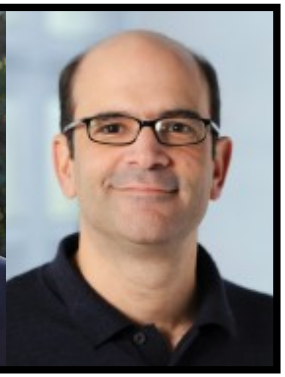
Dual Catalysis

Jørgensen

Jacobsen

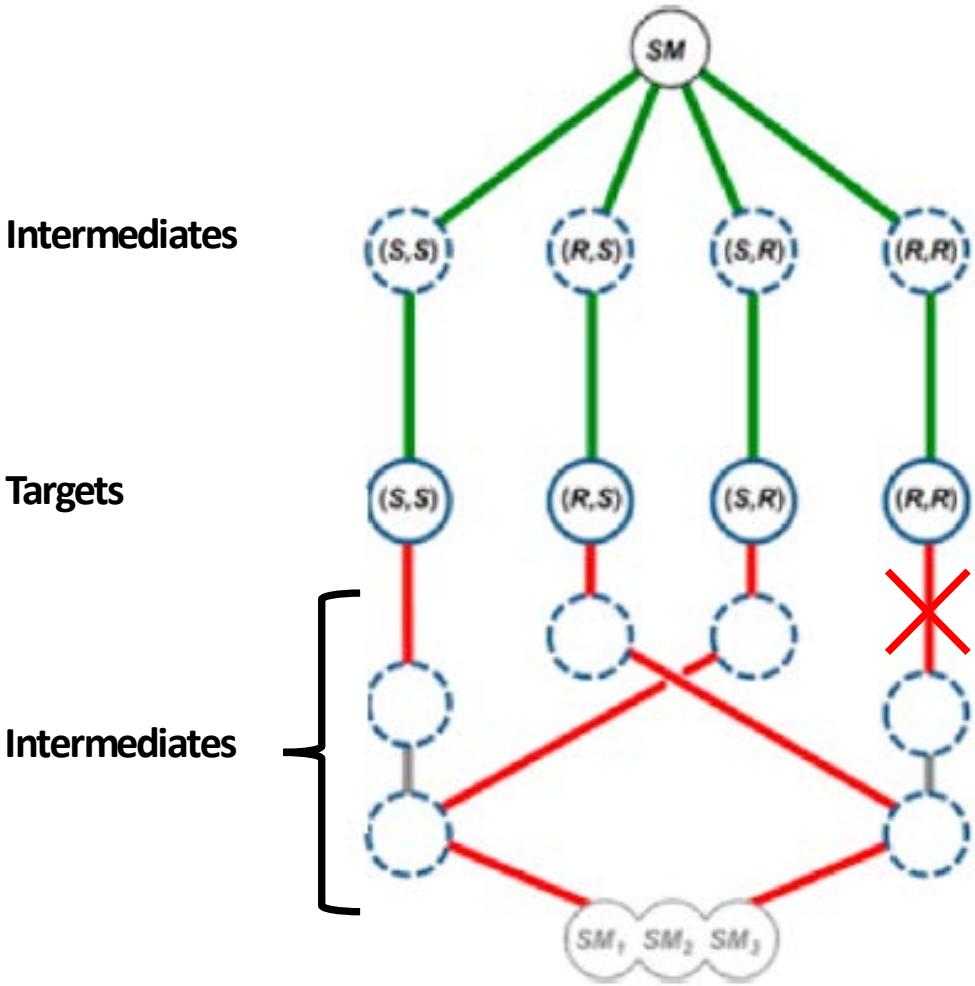
Stereodivergent Dual Catalysis

Hartwig



Carreira

Stereodivergent and Traditional Approaches to Synthesis



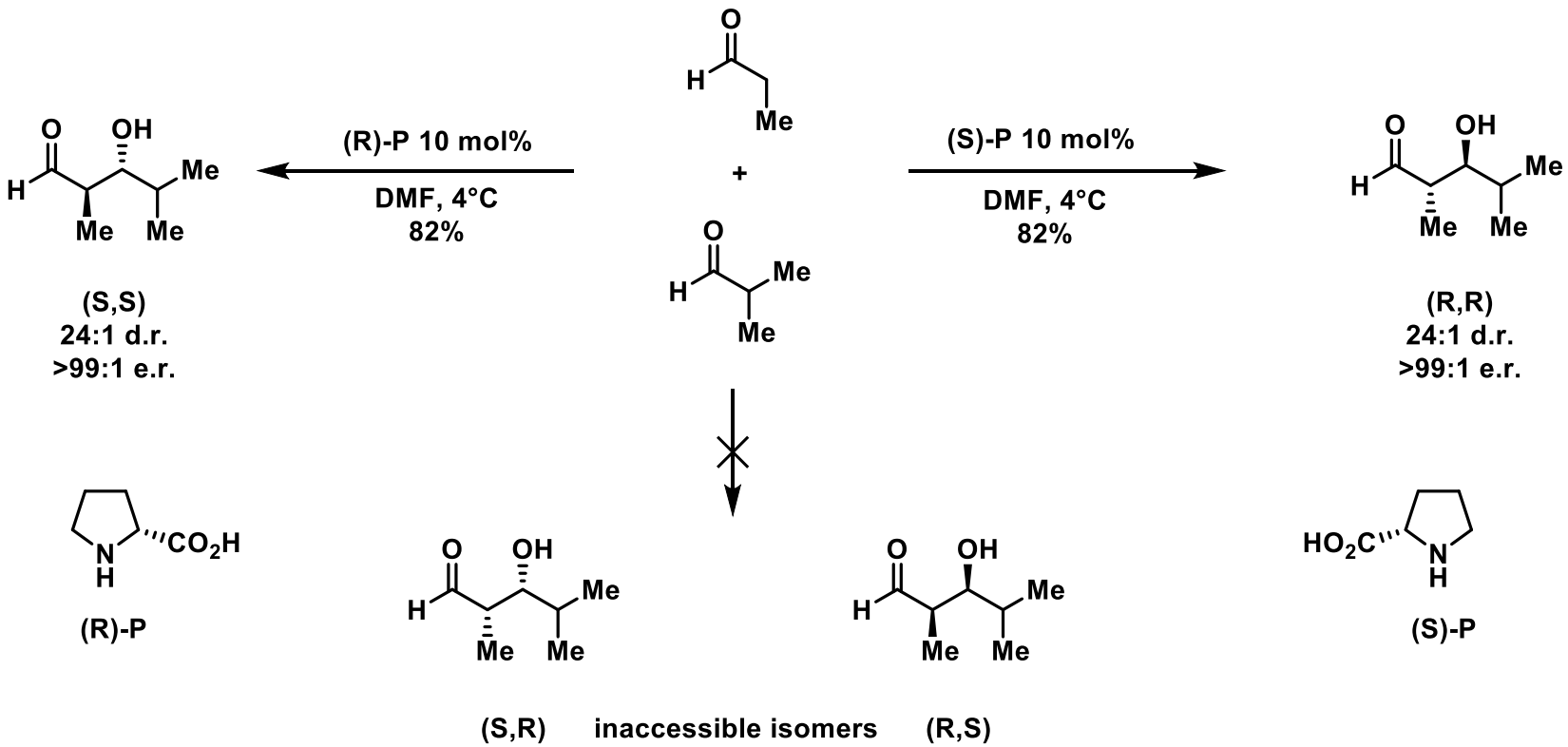
- Same starting material
- Uniform synthetic sequence
- Identical reaction conditions
- Rapid access to any stereoisomer

- Different starting material and/or synthetic routes
- Diastereomer of target might not be accessible

- **Allows to determine the configuration of stereogenic centers in natural products**

J. Am. Chem. Soc. **2017,** *139*, 5627–5639. *Angew. Chem. Int. Ed.* **2014**, *53*, 13898 –13901.

Limitations of Enantioselective Reactions

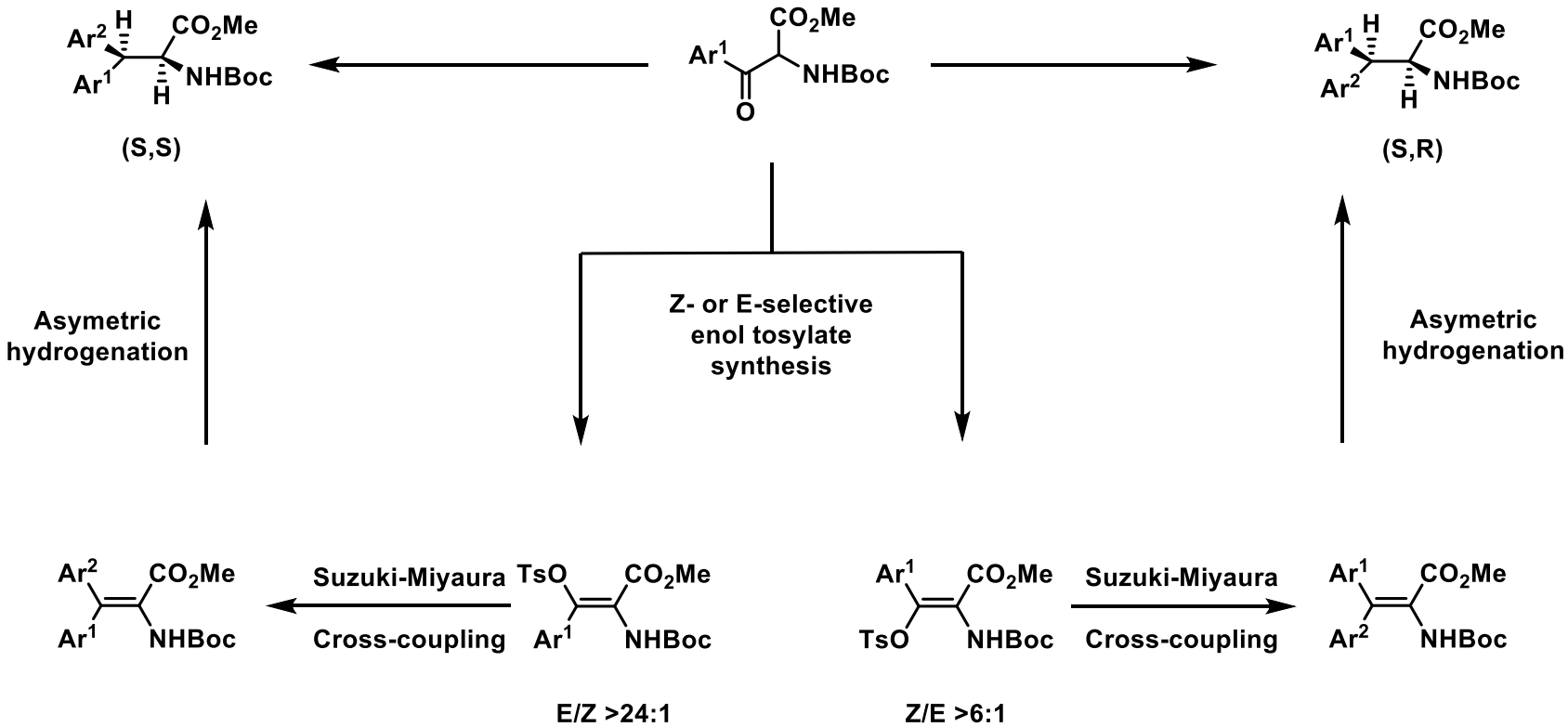


- **Catalyst controls both absolute and relative configurations**
- **Access a single pair of enantiomers**
- **Modern processes optimized for high diastereo- and enantiocontrol**

J. Am. Chem. Soc. **2017,** *139*, 5627–5639.

Limitations of Enantioselective Reactions

Merck Synthesis of β,β'-Diarylamino Acids Derivatives

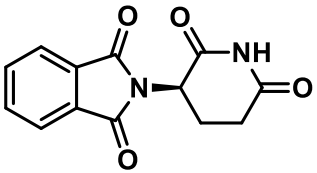


- **Additional steps, time and efforts required**
- **Two distinct protocols for stereoselective enolization are needed**
- **Some precursors may be difficult to access**

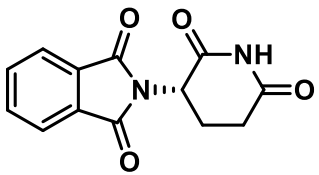
J. Am. Chem. Soc., **2015** *137*,999.

Chiral Molecules in Drugs and Pharmacology

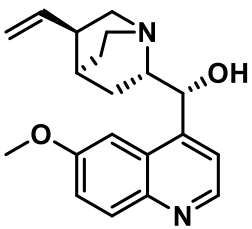
Importance of enantiopure molecules



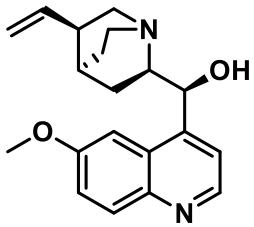
(R)-thalidomide
(sleep-inducing)



(S)-thalidomide
(teratogenic)

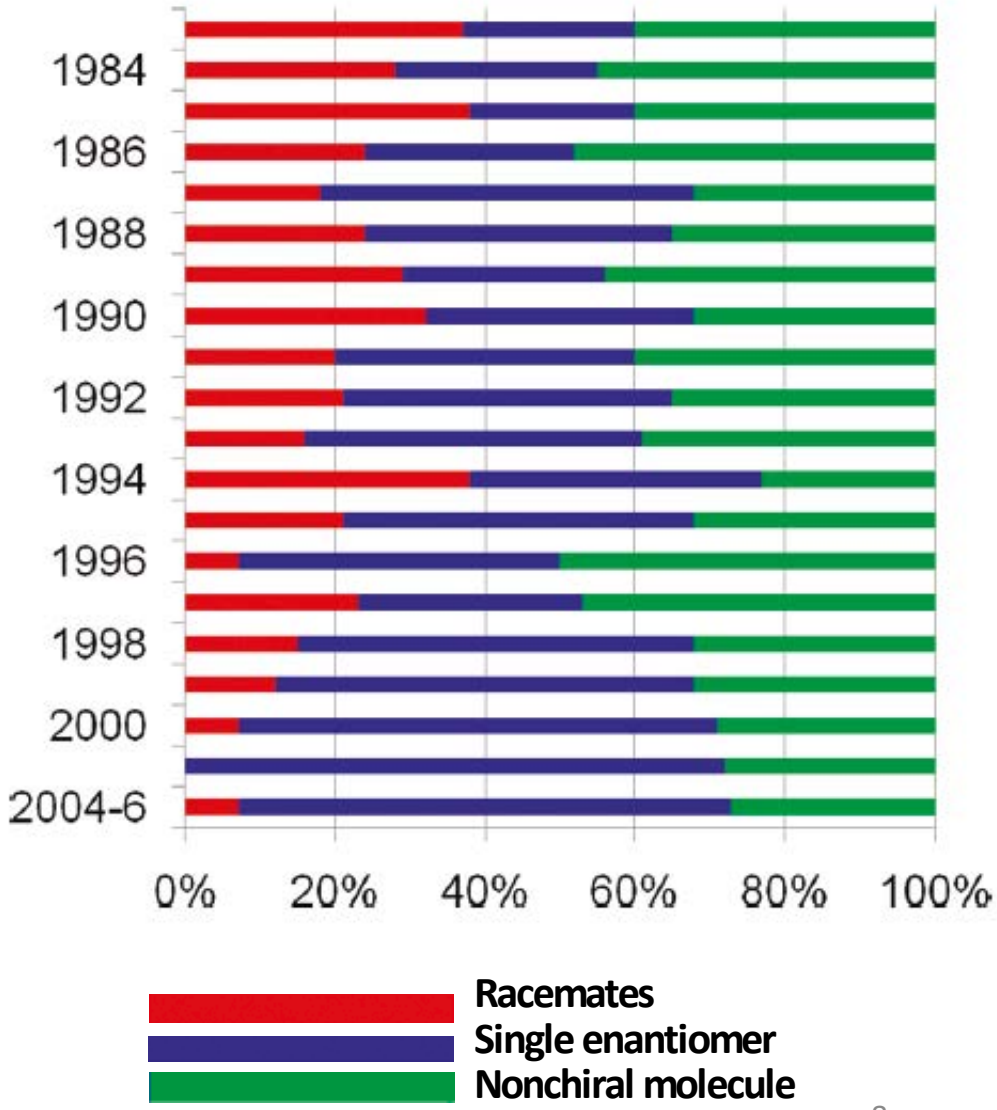


Quinine
(Antimalarial)



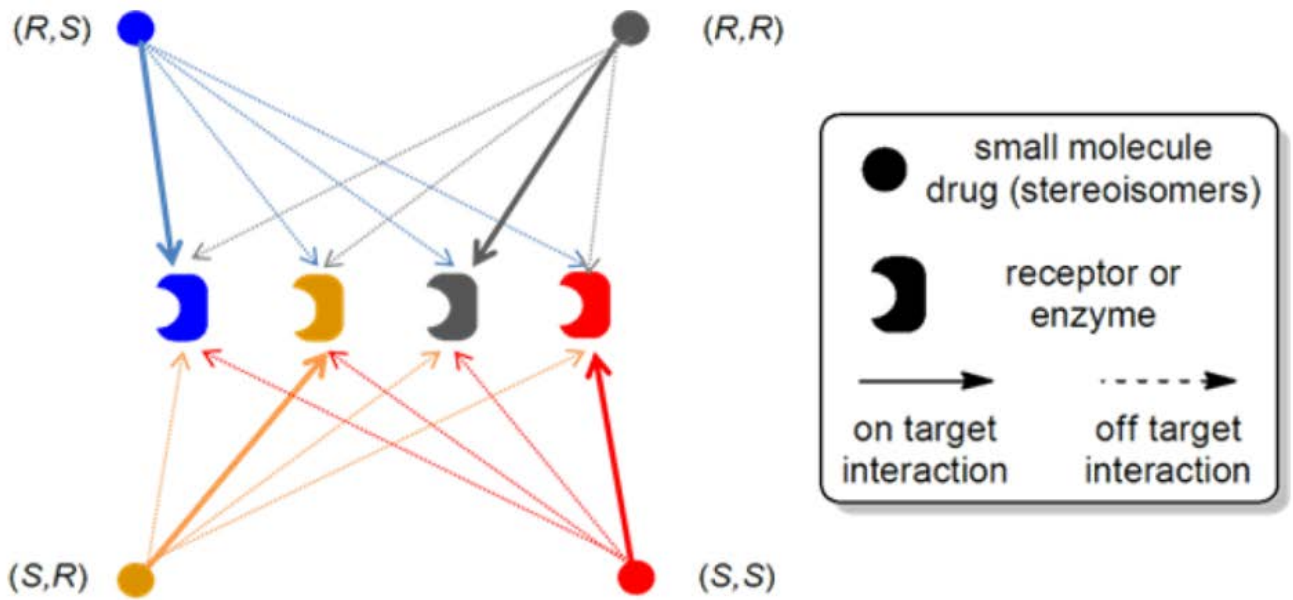
Quinidine
(Antiarrhythmic)

Report on new chemical entities approuved by the FDA



J. Med. Chem. **2011**, *54*, 7005–7022.

Polypharmacology



- **The bioactivity of all stereoisomers of the drug candidate must be known**
- **Manufacturers must develop assays to determine stereochemical purity**
- **All stereoisomers of drug candidate must be synthesized**

J. Am. Chem. Soc. **2017,** *139*, 5627–5639.

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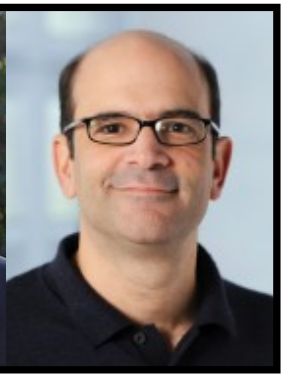
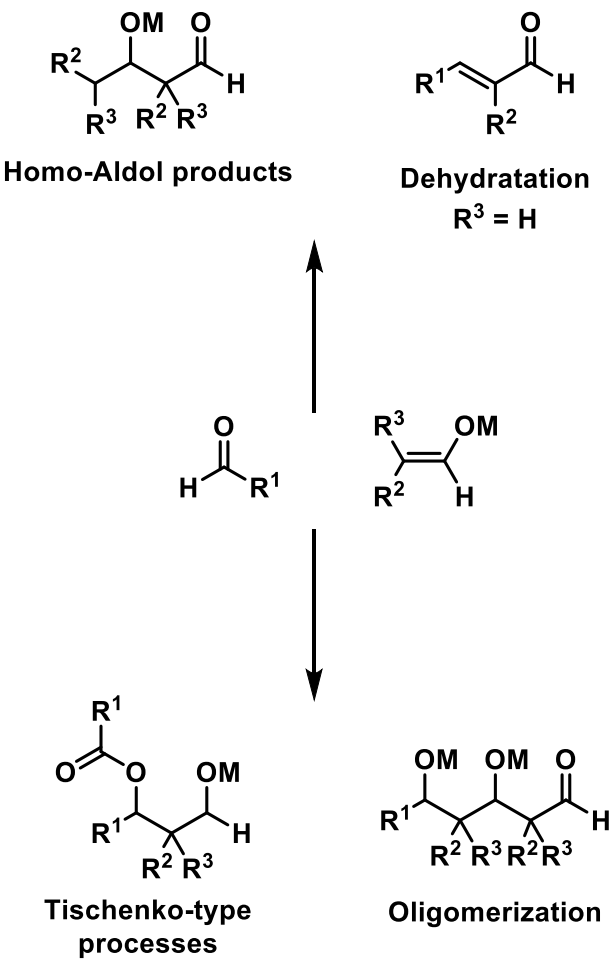
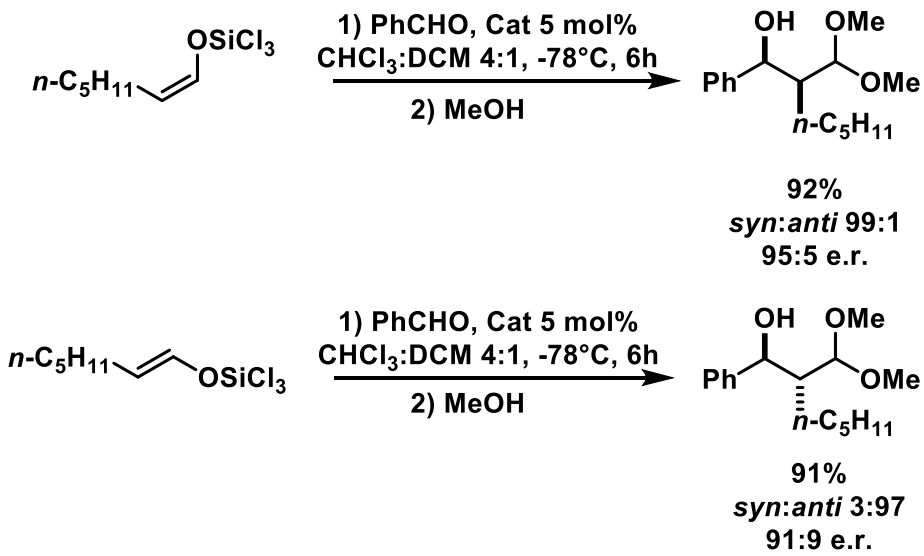


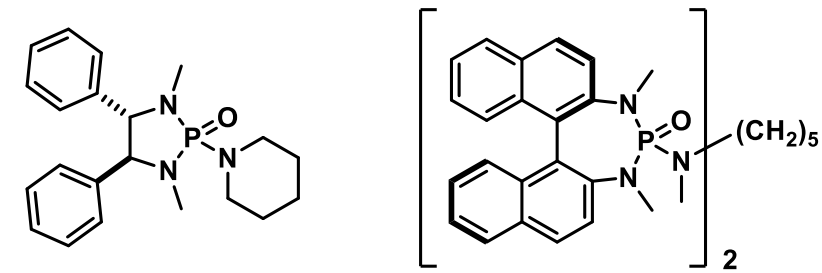
Carreira

The Beginnings

First Catalytic Enantio- and Diastereoselective Crossed-Aldol Reaction







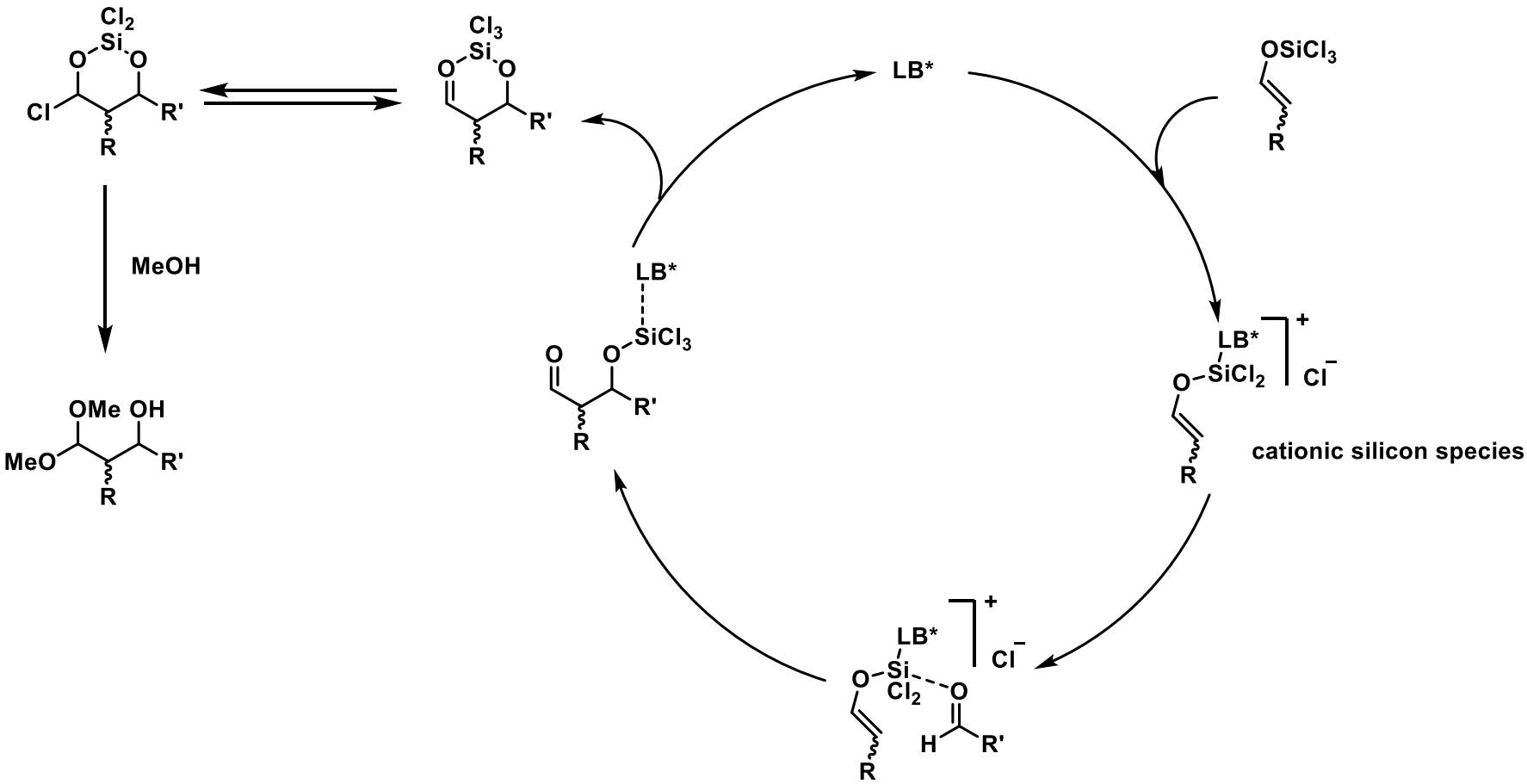
Excellent diastereoselectivity
Poor enantioselectivity

Cat

- **Kinetic studies showed second order in catalyst**

DENMARK and coworkers. *Angew. Chem. Int. Ed*. **2001**, *40*, 4759. *PNAS,* **2004.** *101 (15)* 5439-5444.

Lewis-Base Catalyzed Aldol Reaction Mechanism

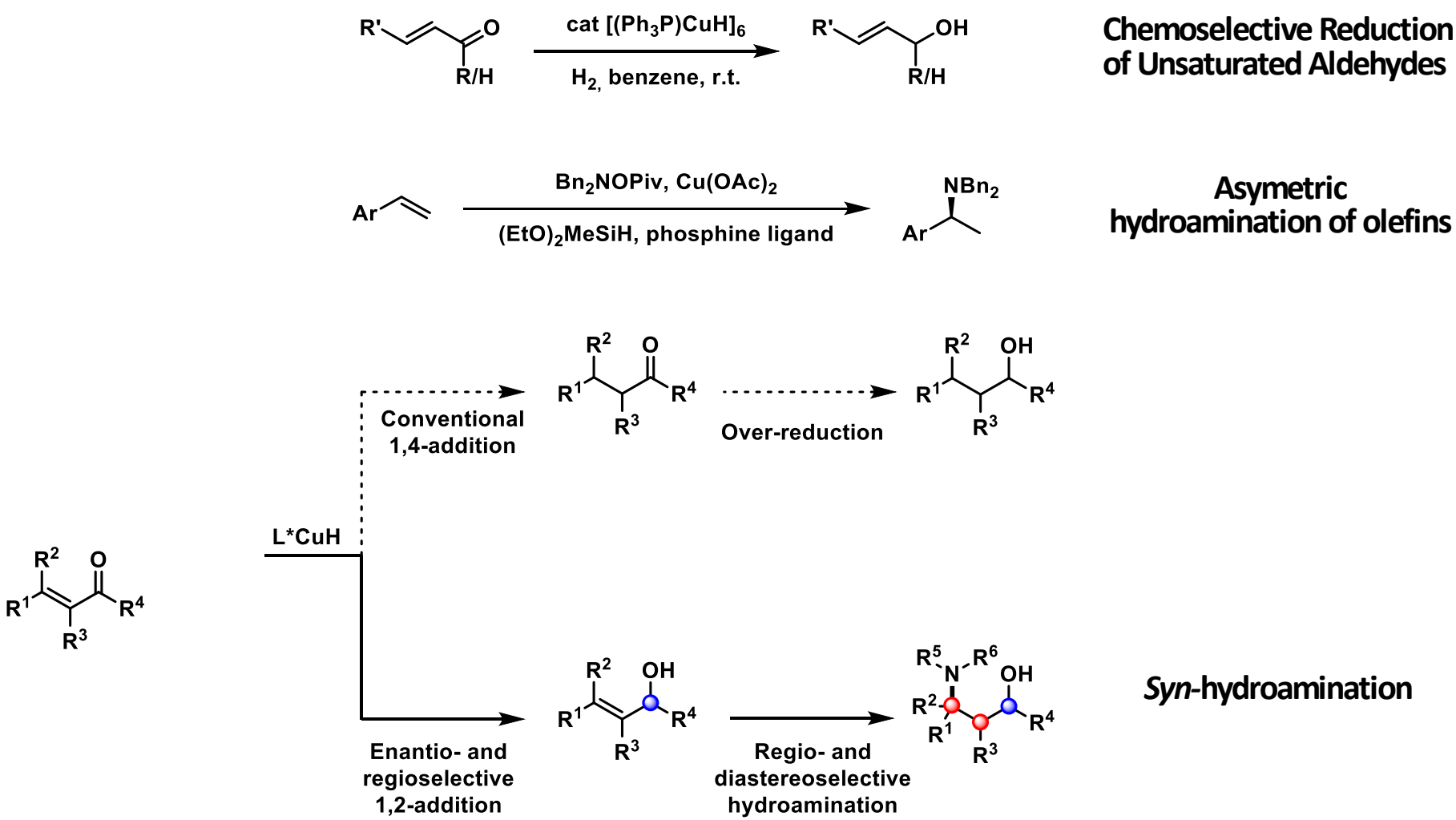


- **Silicon atom act as a organizational center**
- **Chelated species prevent side reactions**
- **Geometrically pure substrate determinate the final stereochemistry**

DENMARK and coworkers. *PNAS,* **2004.** *101 (15)* 5439-5444.

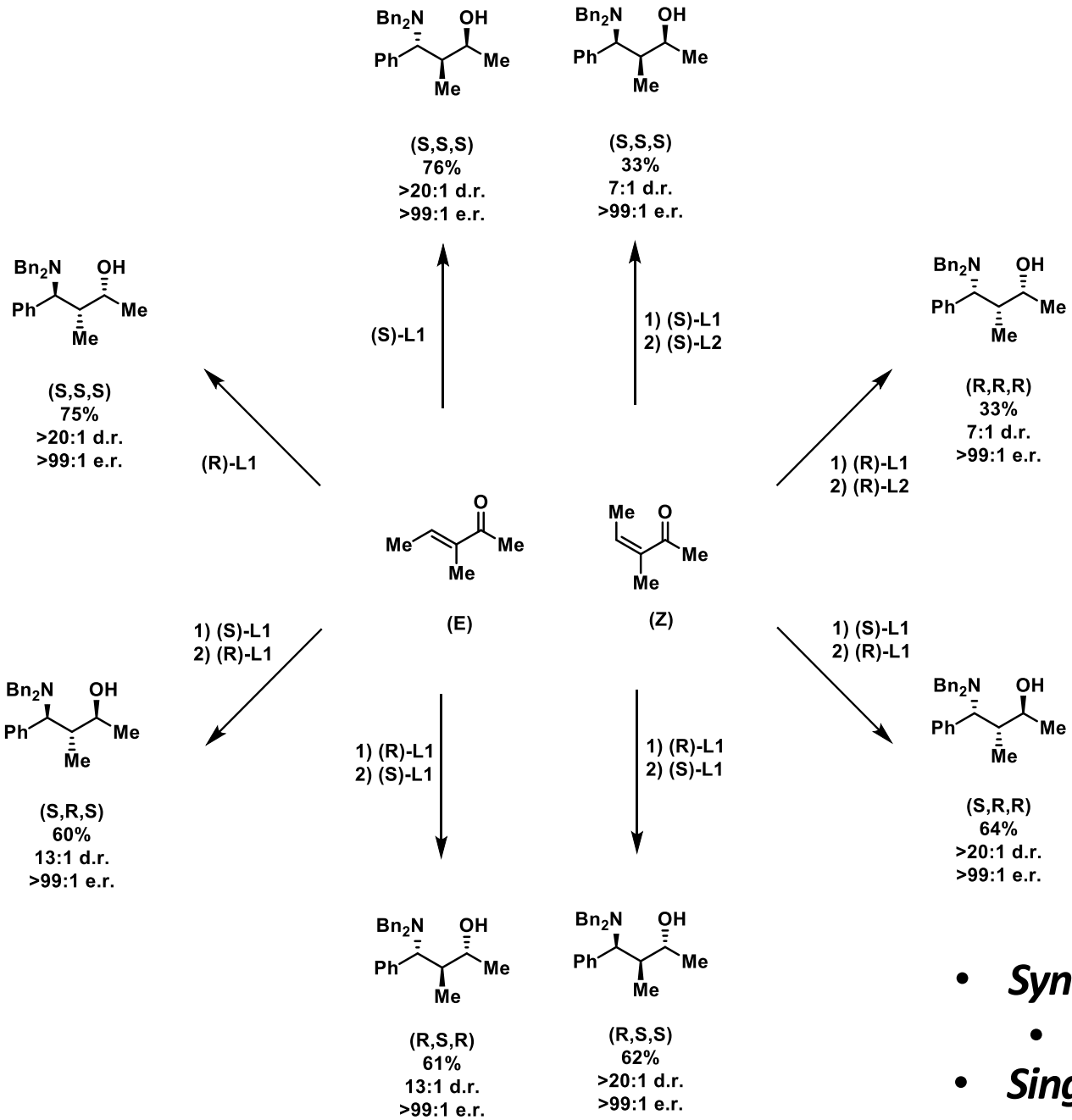
Hydrosilylation/Hydroamination of Enone

Background

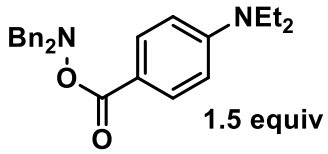


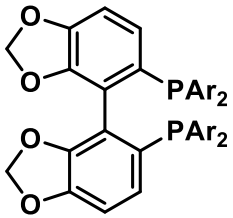
BUCHWALD and coworkers. *Nature,* **2016.** *532,* 353-356. *J. Am. Chem. Soc.* **2003**, *125*, 8779-8789. STRYKER and coworkers. *Tetrahedron 56* (**2000**) 2153-2166.

Hydrosilylation/Hydroamination of Enone



Conditions:
5 mol% Cu(OAc)2, 5.5 mol% Ligand
3-5 equiv (MeO)2MeSiH, THF, r.t., 36-60h





L1 Ar = 3,5-(*t*Bu)$_2$-4-OMe-C$_6$H$_2$
L2 Ar = 3,5-(Me)$_2$-C$_6$H$_3$

- ***Synthetically useful amino alcohols***
  - ***3 contiguous stereocenters***
- ***Single copper/bisphosphine system***

BUCHWALD and coworkers. *Nature,* **2016.** *532,* 353-356.

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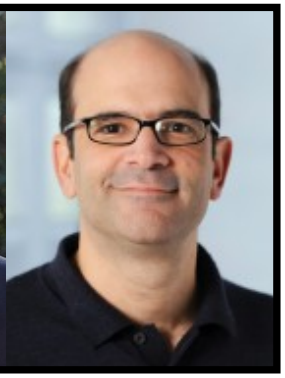
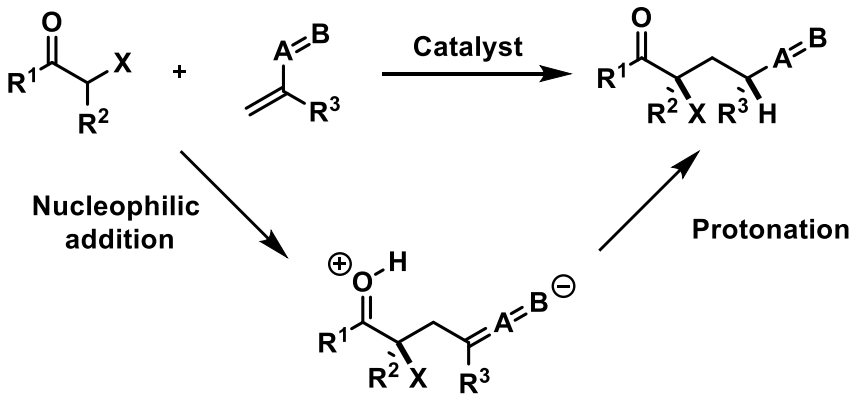


Carreira

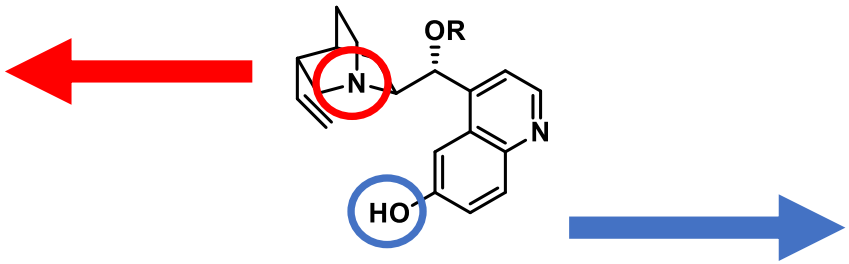
Stereoselective Michael-Addition

General Mechanism



- **Two nonadjacent stereocenters are typically generated in different steps**
- **Protonation step has to be selective**
- **Use of a dual fonction catalyst: 1 site to activate the Michael donor**
  1 site to bind the intermediate

Michael donor activation

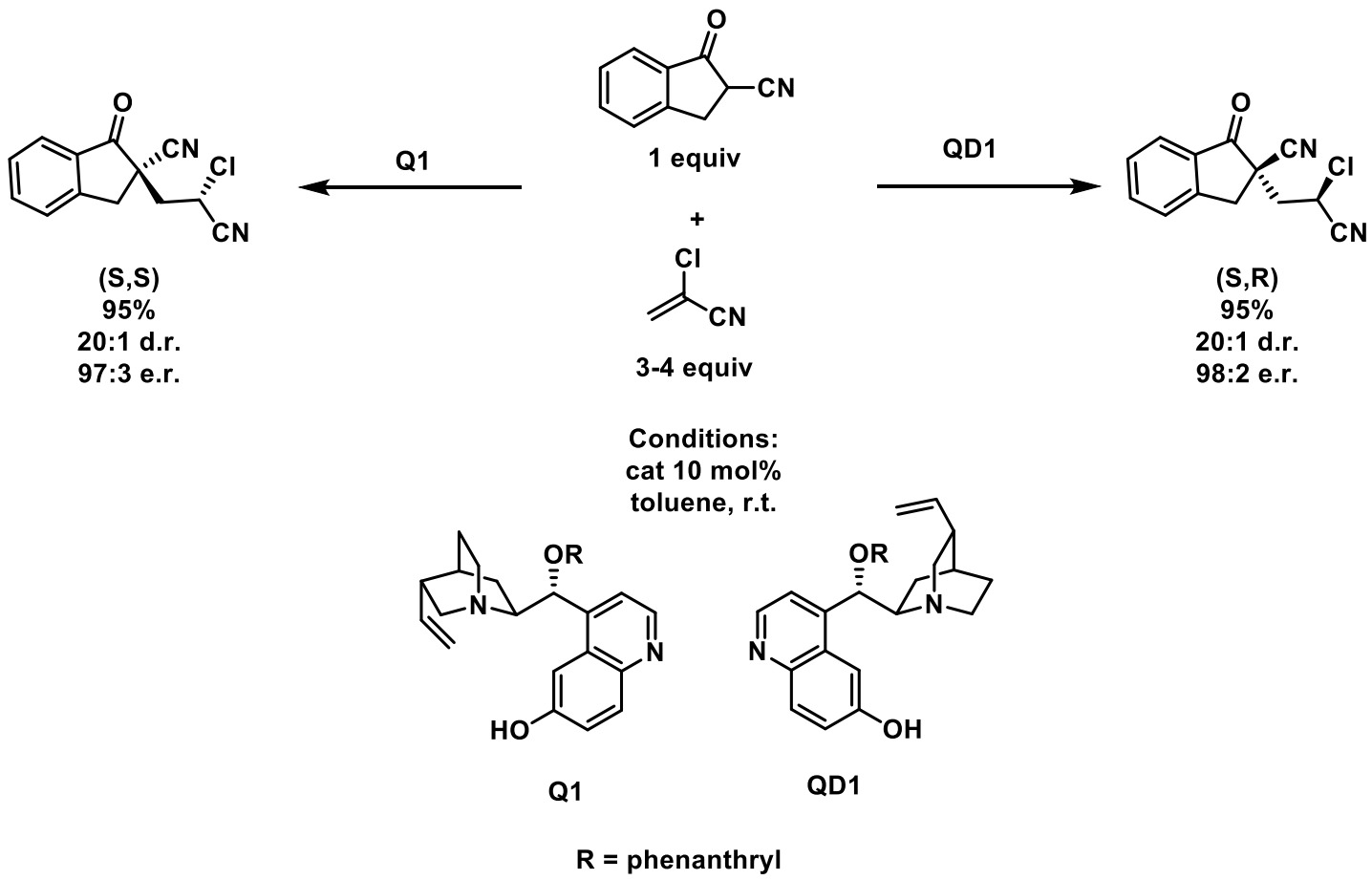


cinchona alkaloid

Binding site

DENG and coworkers. *J. Am. Chem. Soc.* **2006**, *128*, 3928-3930. *J. Am. Chem. Soc.* **2007**, *129*, 768-769.

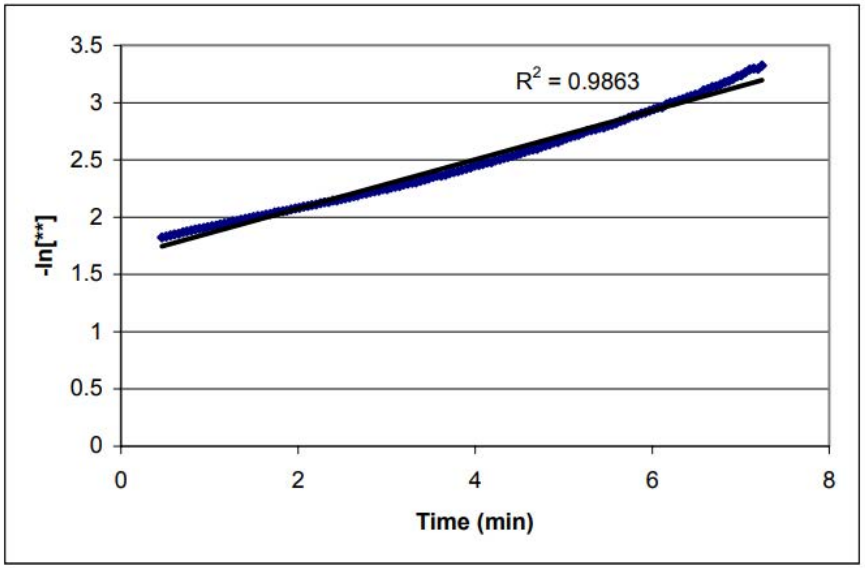
Catalyst Redesign



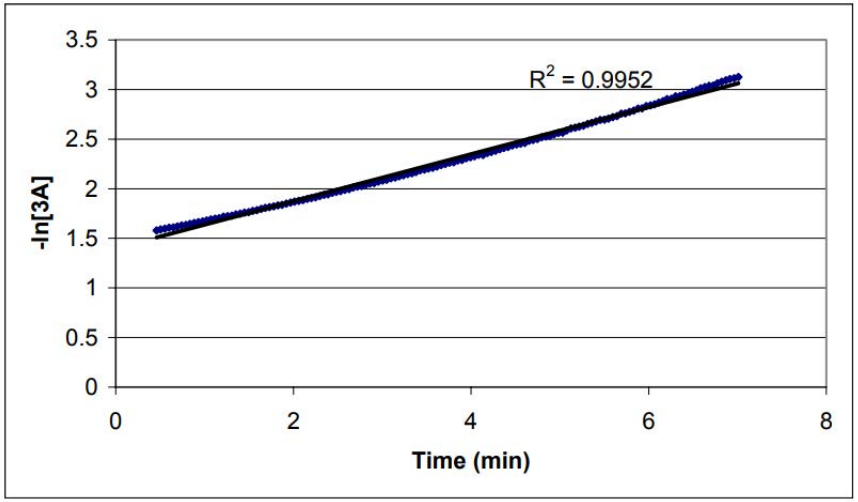
- ***Unable to access the second diasteromeric pair***

DENG and coworkers. *J. Am. Chem. Soc.* **2006**, *128*, 3928-3930. *J. Am. Chem. Soc.* **2007**, *129*, 768-769.

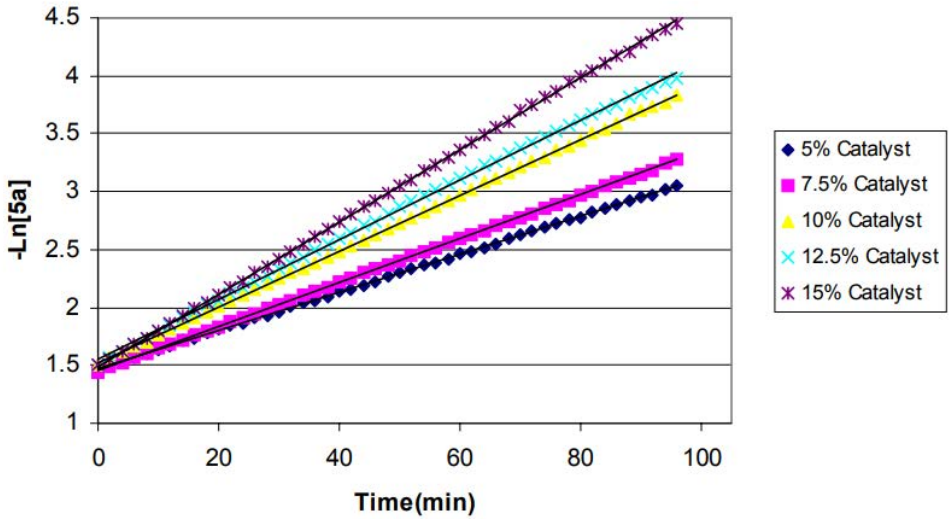
Kinetic Studies



Michael Acceptor



Michael Donor

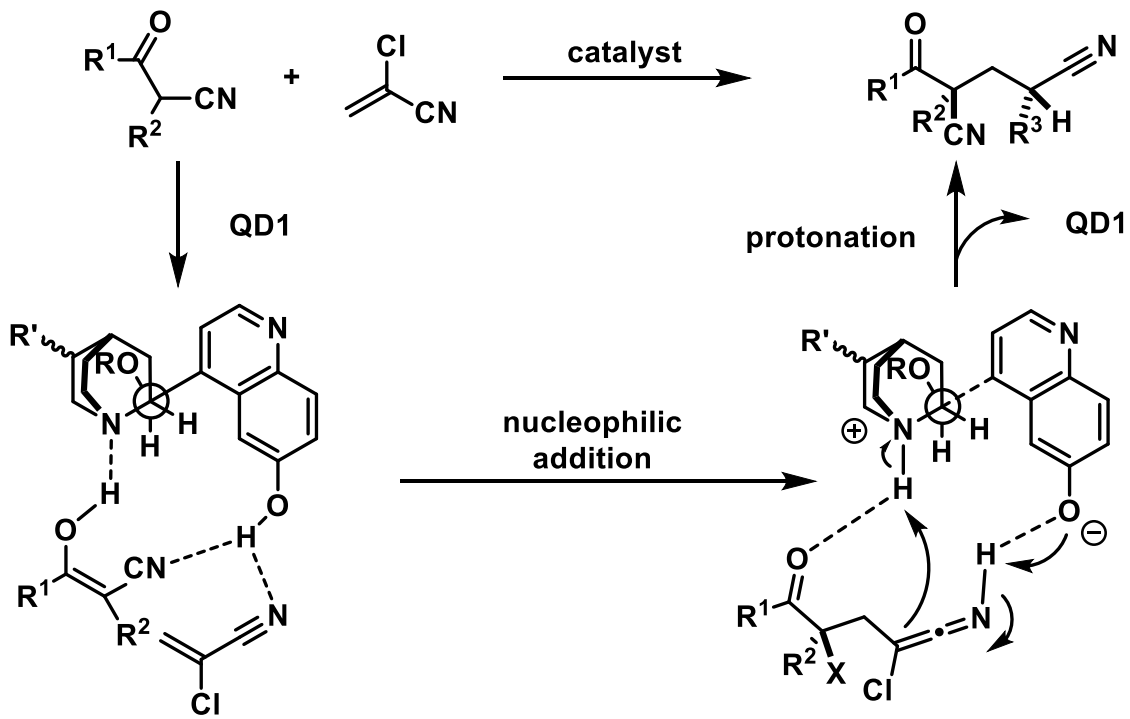


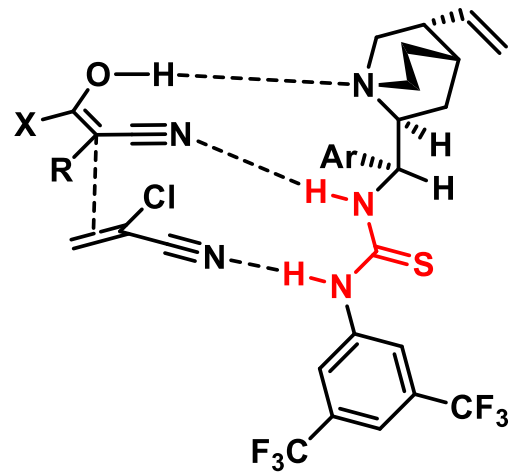
Catalyst

- **First order on: -Michael Donor**
  -Michael Acceptor
  -Catalyst
- **Only one molecule of catalyst in the TS → dual fonction catalyst**

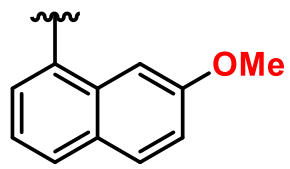
DENG and coworkers. *J. Am. Chem. Soc.* **2006**, *128*, 3928-3930. *J. Am. Chem. Soc.* **2007**, *129*, 768-769.

Selectivity through Hydrogen-Bond Network

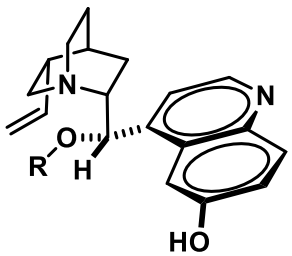




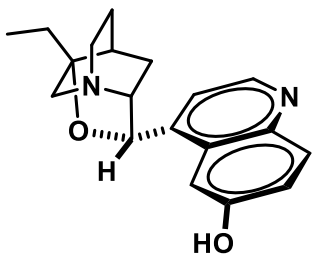
Ar =



- **Decreased rate in protic solvents**
- **Established the conformation using a "locked" quinuclidine**



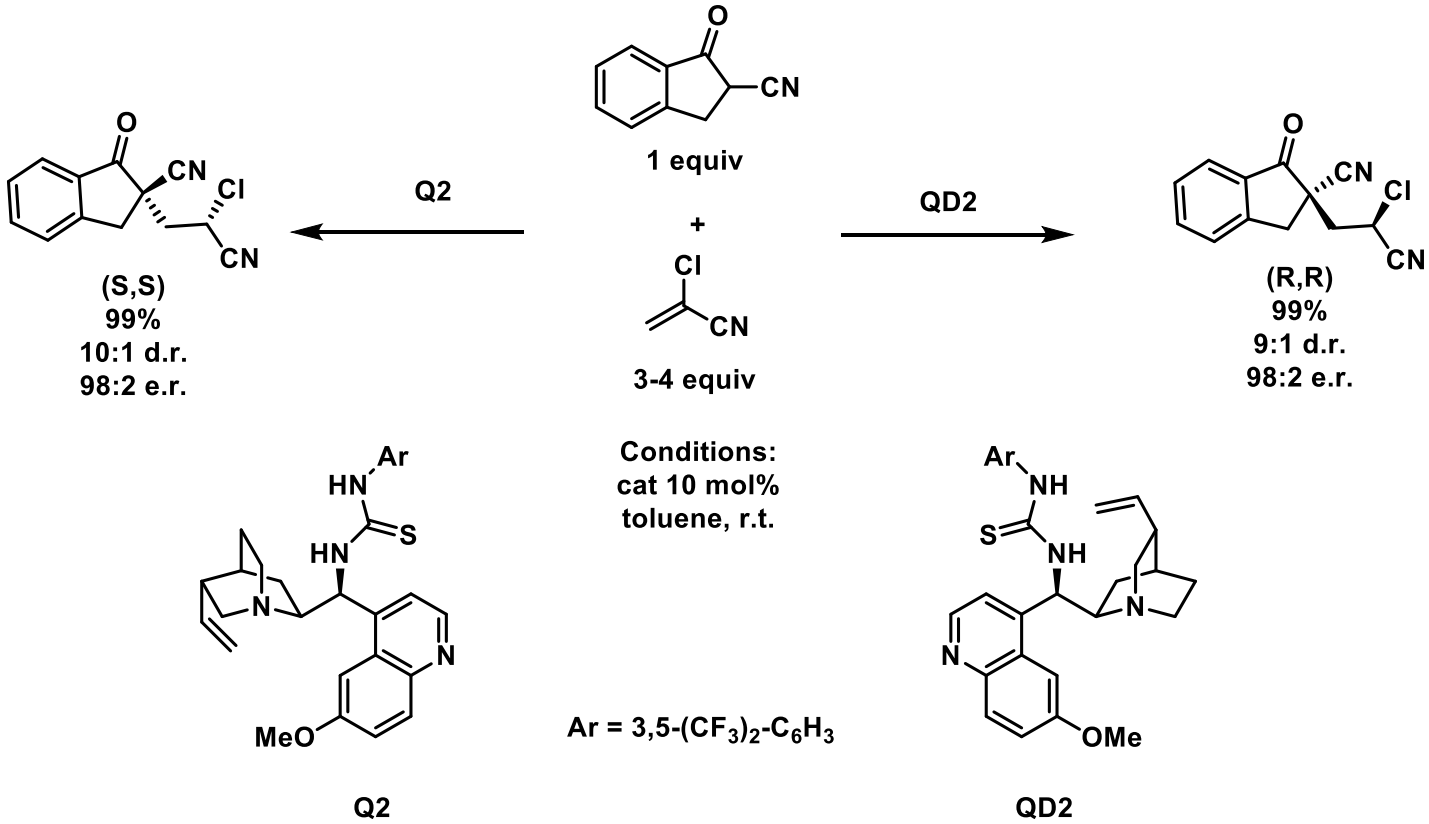
gauche-conformer



rigid structure

DENG and coworkers. *J. Am. Chem. Soc.* **2006**, *128*, 3928-3930. *J. Am. Chem. Soc.* **2007**, *129*, 768-769. *Angew. Chem. Int. Ed.* **2005**, *44*, 105 –108.

Catalyst Redesign

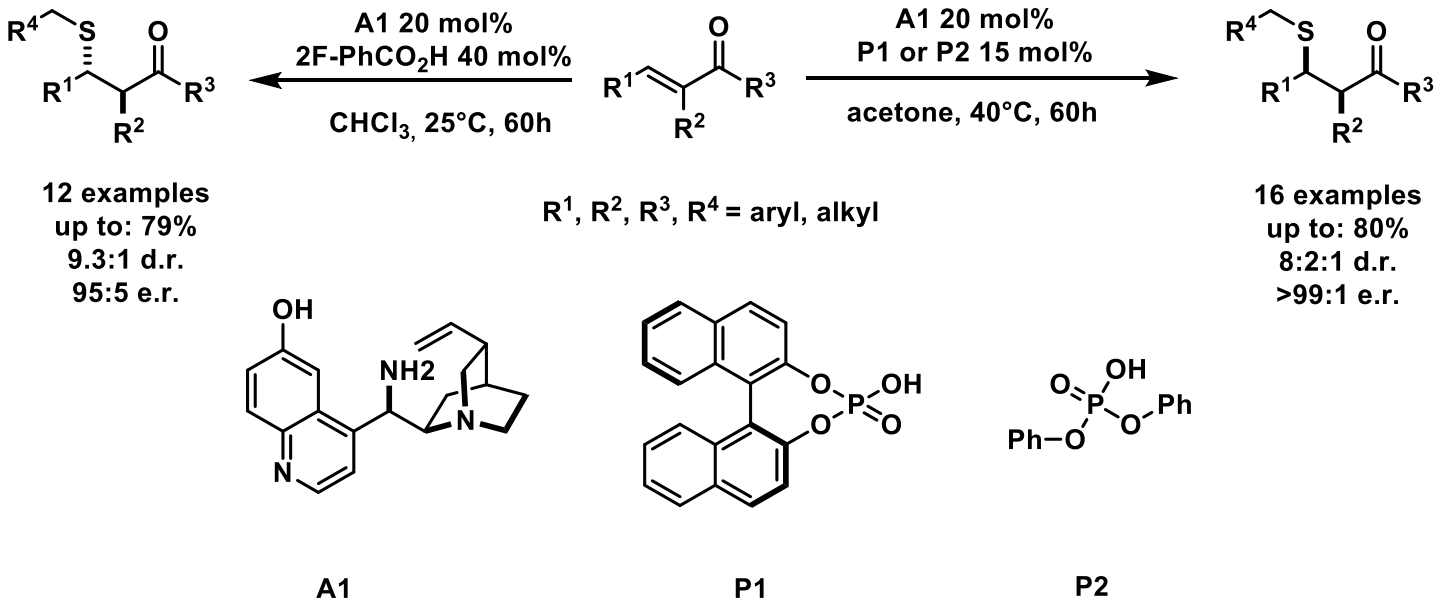


- ***Changing the H-bonding network of the catalyst allowed reorganization of the TS***
- ***Few examples with distal stereocenters***

DENG and coworkers. *J. Am. Chem. Soc.* **2006**, *128*, 3928-3930. *J. Am. Chem. Soc.* **2007**, *129*, 768-769.

Change in Reaction Conditions

Diastereodivergent result



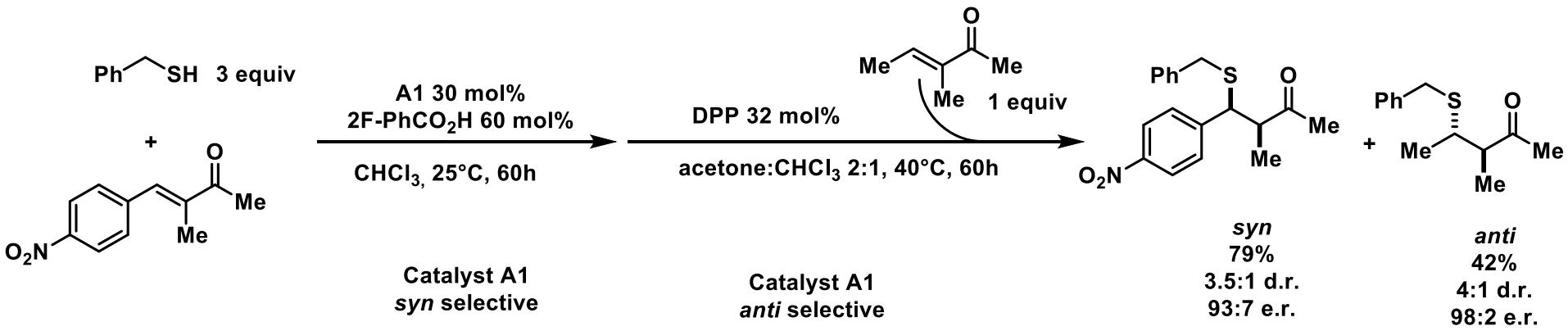
Entry	acid	solvent	Conversion (%)	d.r.
1	2-F-benzoic acid	$CHCl_3$	42	6:1
2	2-F-benzoic acid	Acetone	35	2.1:1
3	P1	$CHCl_3$	28	1:1.3
4	P1	acetone	62	1:6.2

- ***Both change of solvent and acid are needed to invert the diastereoselectivity***

MELCHIORE and coworkers. *J. Am. Chem. Soc.* **2011**, *133*, 17934-17941.

Change in Reaction Conditions

Switching diastereoselection in a single flask

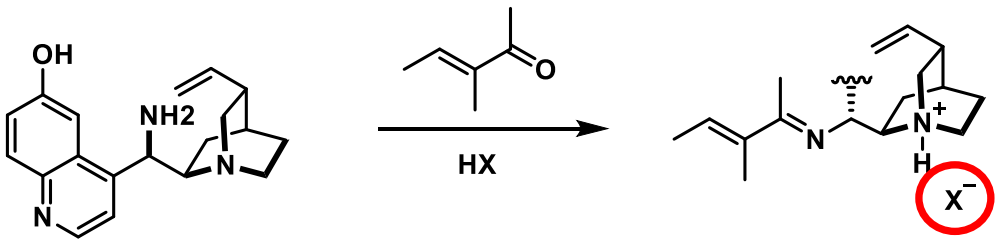


- ***Catalyst can be "re-purposed" simply by choice of an appropriate additive and solvent***
- ***Decided to do some mechanism investigation***

MELCHIORE and coworkers. *J. Am. Chem. Soc.* **2011**, *133*, 17934-17941.

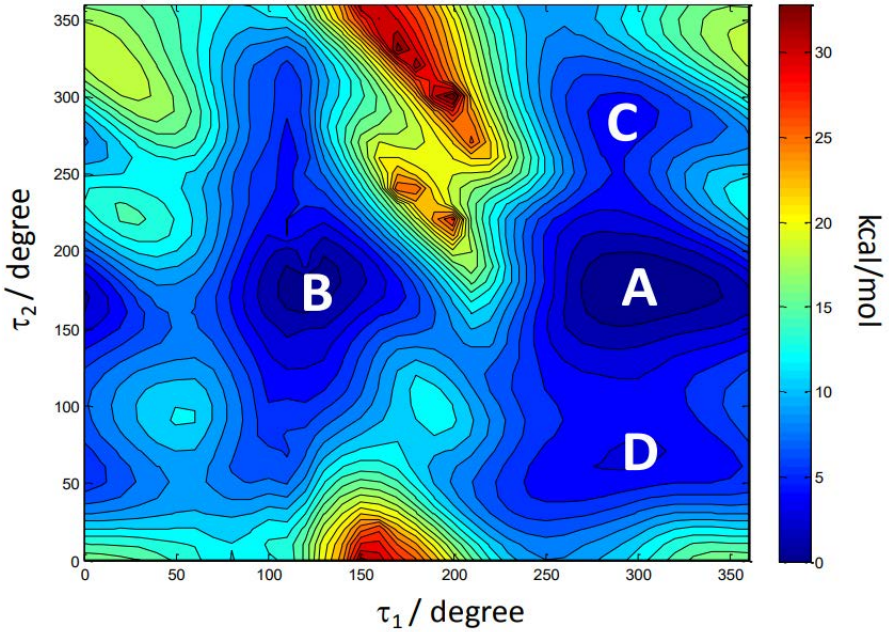
Mechanistic Evidence

Change in Chiral Environment through Ion Pair Assembly and Solvent Effects

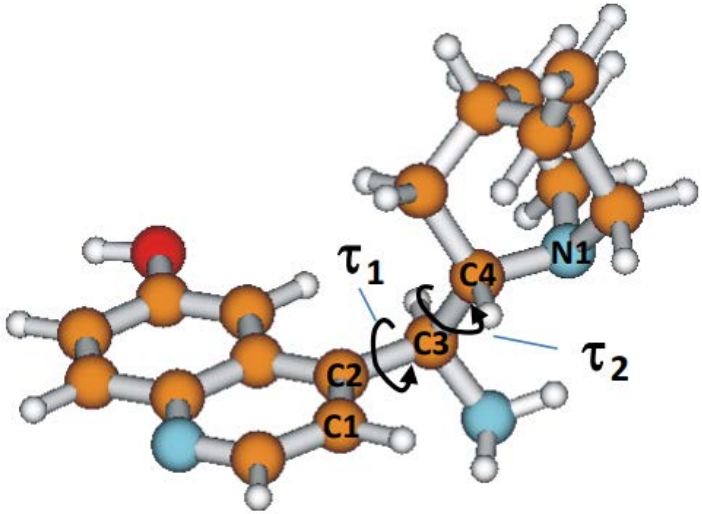


Modulation of the chiral space by tunning of the anion structure and solvent polarity

DFT of the cinchona alkaloid (theoretical in vaccum)

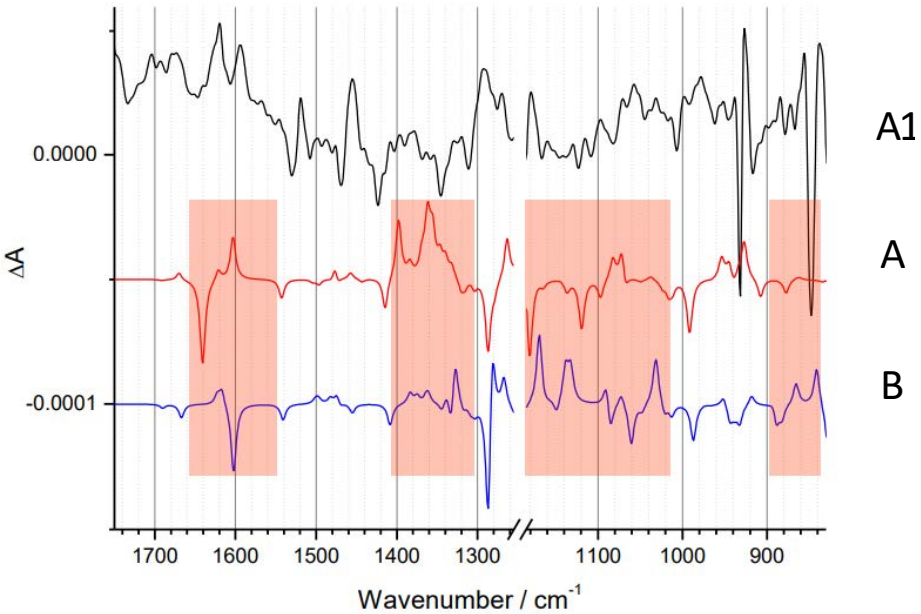


DFT optimized geometry

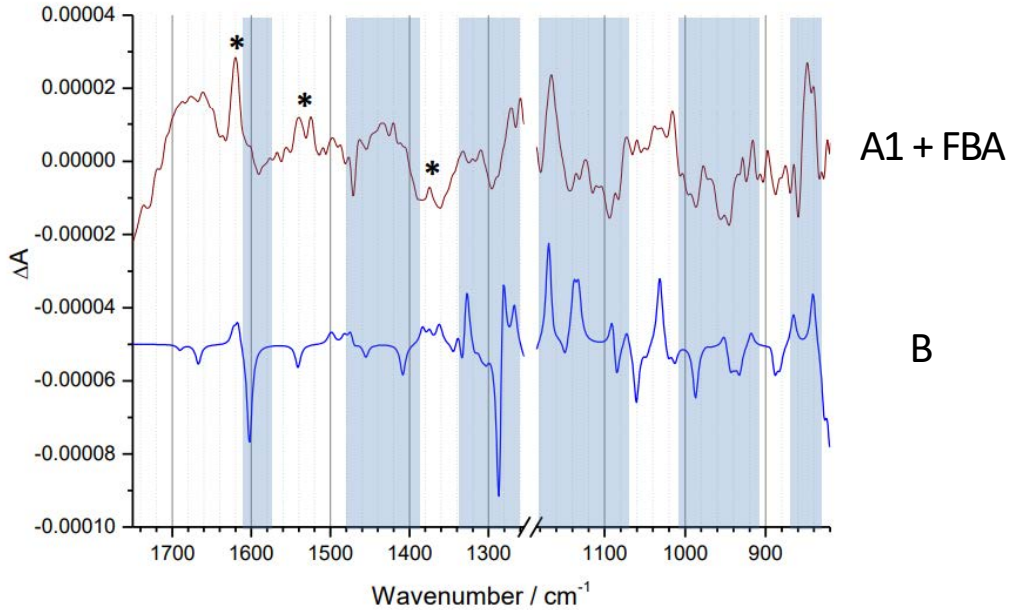


MELCHIORE and coworkers. *J. Am. Chem. Soc.* **2011**, *133*, 17934-17941.

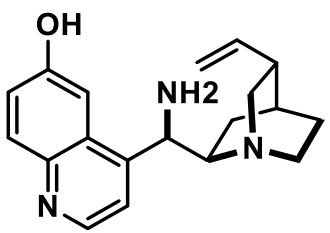
Vibrational Circular Dichroism and DFT



Red highlights the differences between A and B

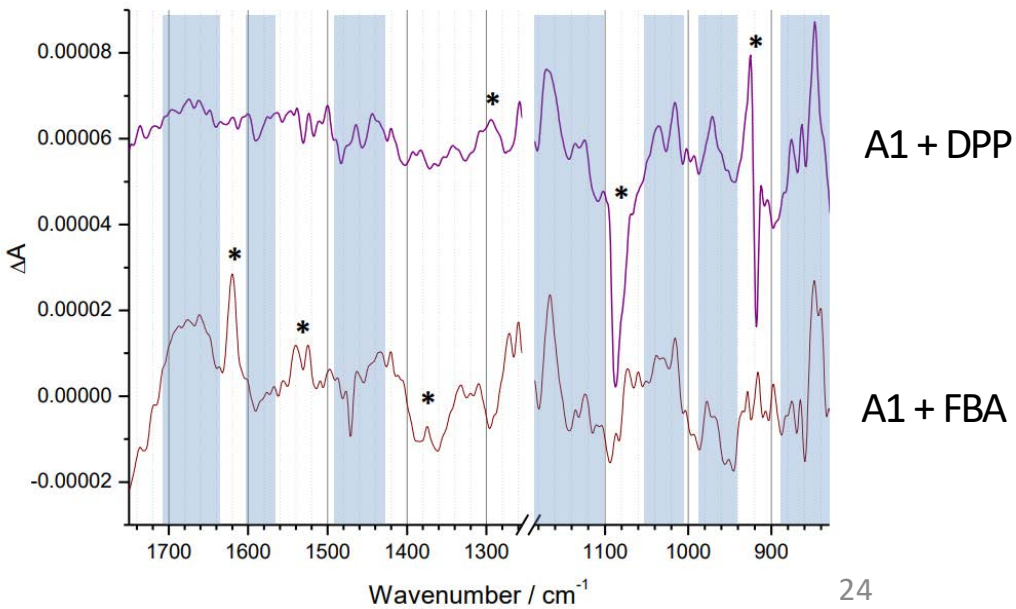


Blue highlights the similarities between A and B



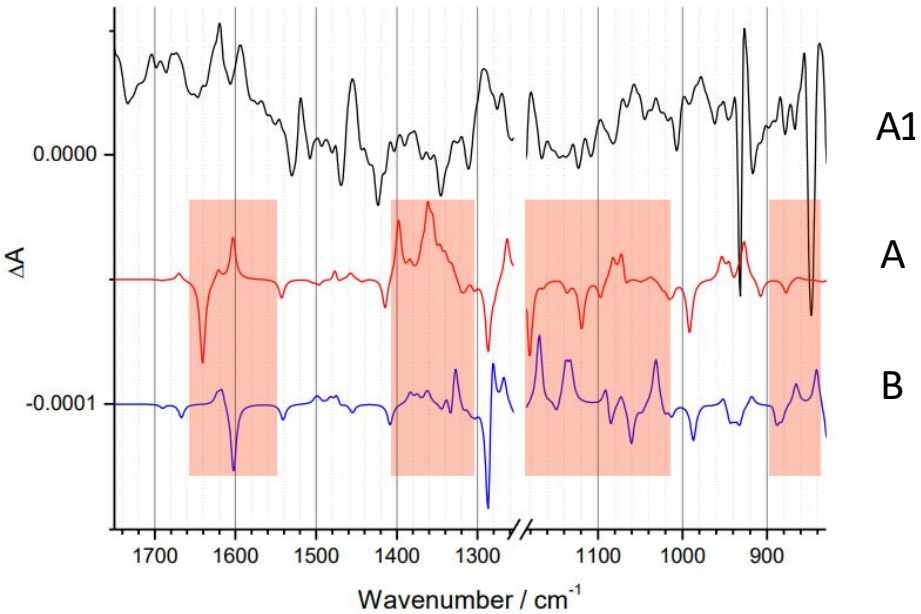
= A1

- ***Acid additives lead to conformation B***
- ***The nature of the acid does not impact the outcome***

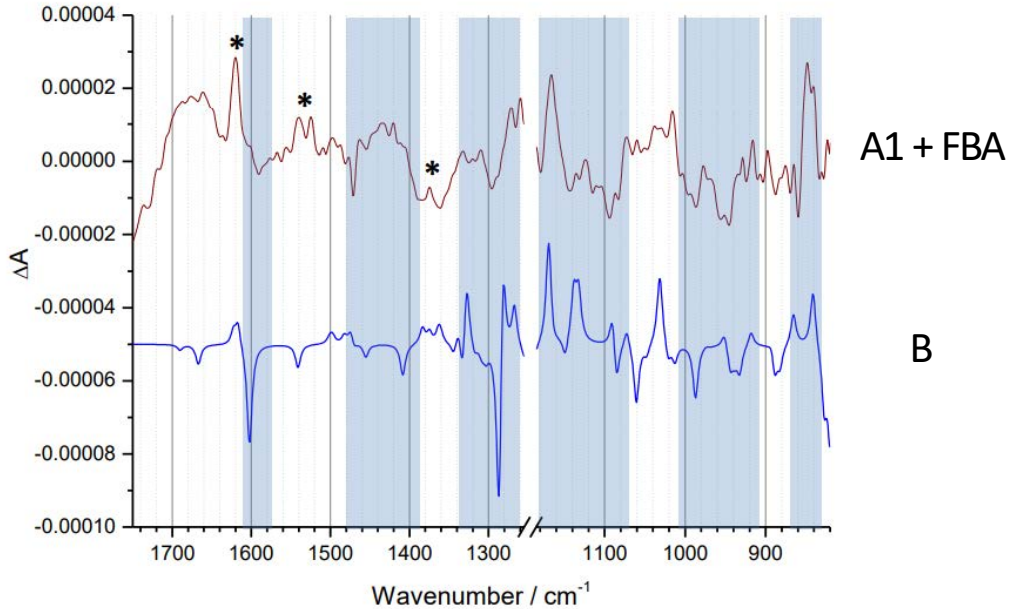


MELCHIORE and coworkers. *J. Am. Chem. Soc.* **2011**, *133*, 17934-17941.

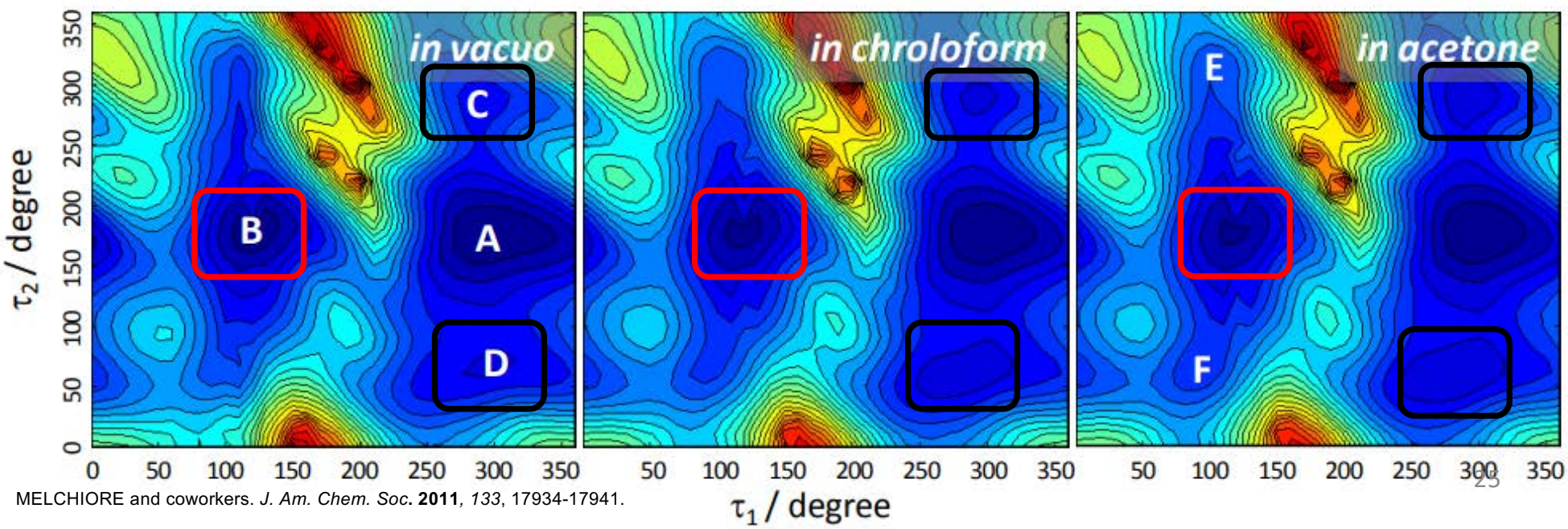
Vibrational Circular Dichroism and DFT



In red features differing between A and B

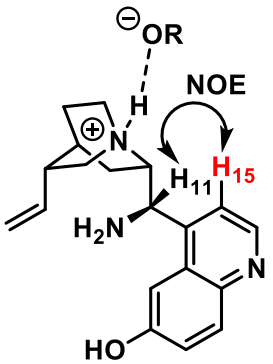


In blue similar features between the spectra

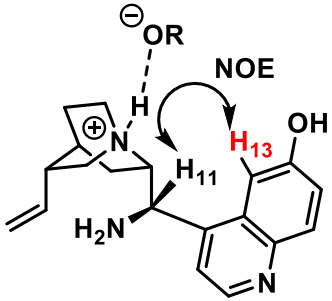


MELCHIORE and coworkers. *J. Am. Chem. Soc.* **2011**, *133*, 17934-17941.

2D-NMR and Electronic Circular Dichroism

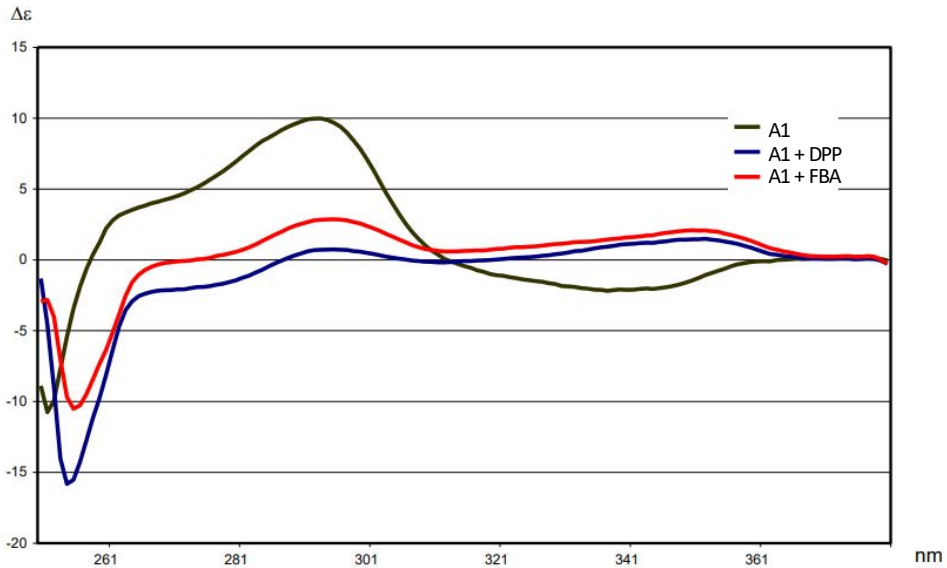


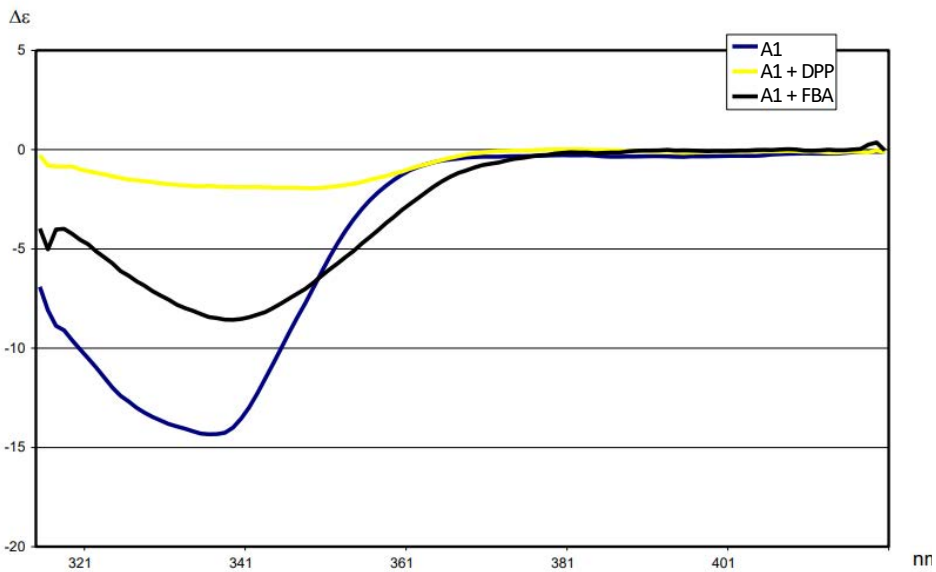
CHCl3

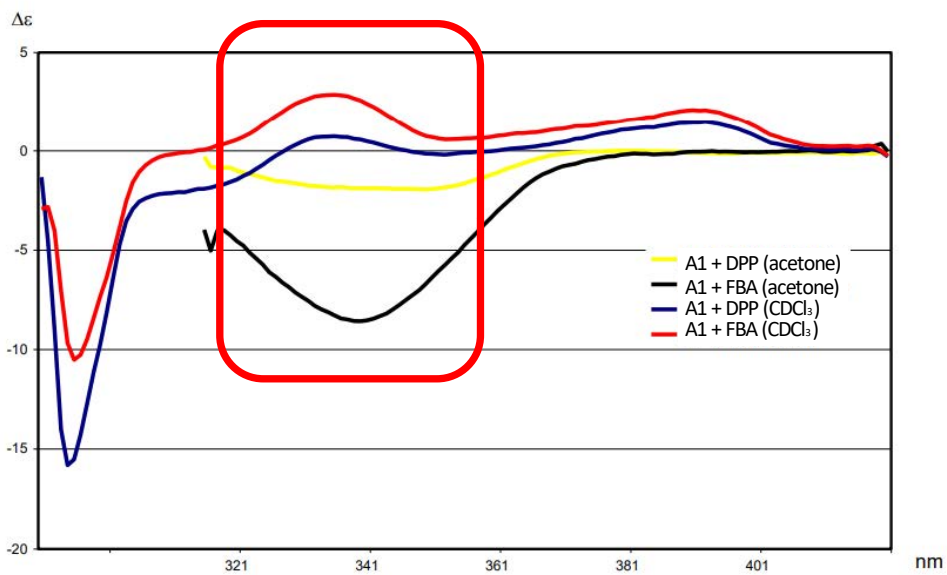


acetone

RO⁻ = (PhO)2P(O)O⁻ or 2-F benzoate

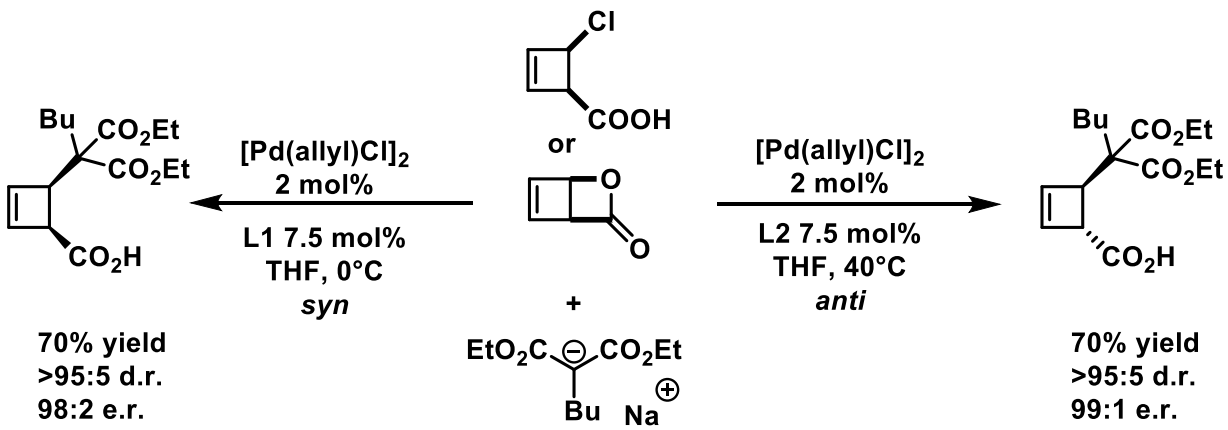


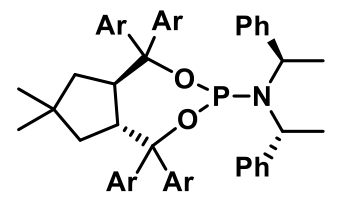




MELCHIORE and coworkers. *J. Am. Chem. Soc.* **2011**, *133*, 17934-17941.

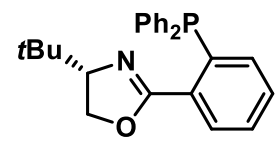
Change in Ligand: Tsuji-Trost Reaction





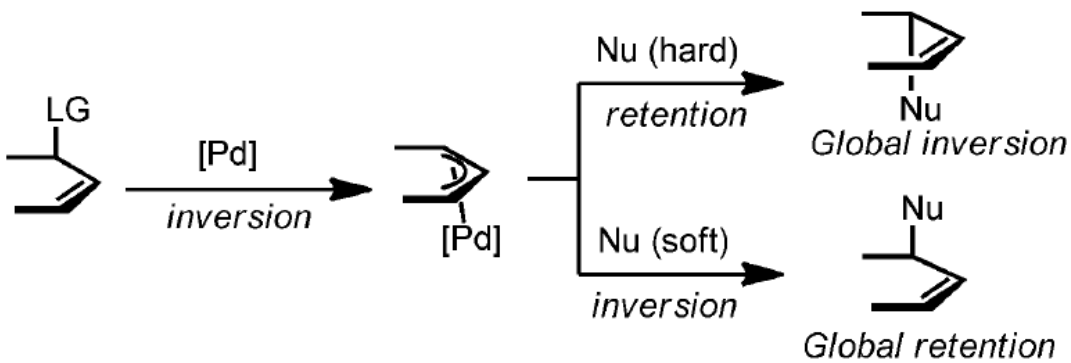
Ar = 3,5-di-*t*-Bu-4-OMeC_6H_2

L1



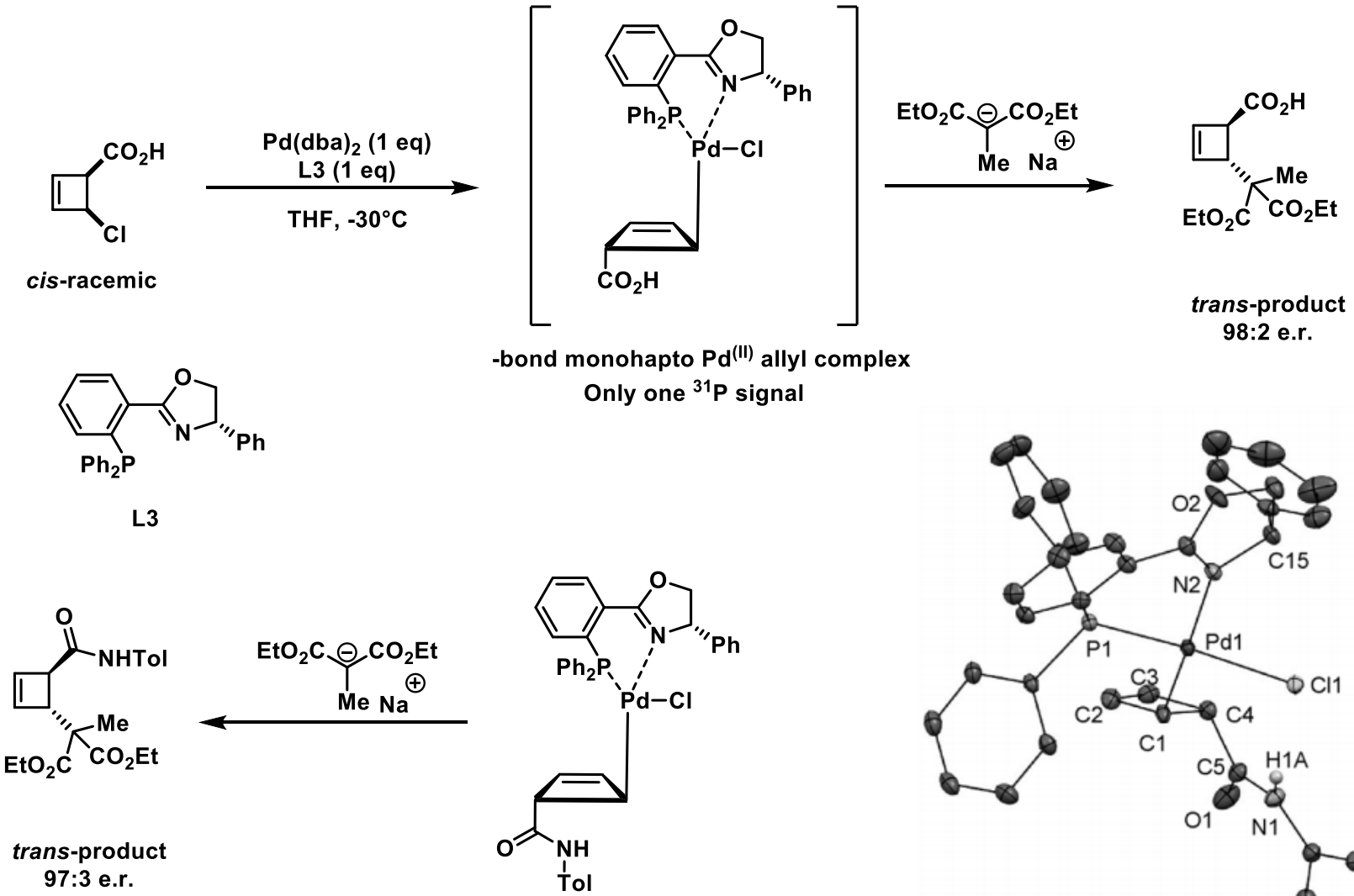
L2

General Mechanism for Tsuji-Trost Reaction



MAULIDE and coworkers. *Adv. Synth. Catal.* **2017**, *359*, 534 – 575.

Mechanistic Evidence



- ***Unusual inner sphere substitution with soft nucleophile***

MAULIDE and coworkers. *Adv. Synth. Catal.* **2017**, *359*, 534 – 575.

History of Stereodivergence

Denmark

Pseudo-divergent Catalysis

Cascade Catalysis

MacMillan

Buchwald

2000 2005 2015

Divergent Catalysis

Deng

Dual Catalysis

Jørgensen

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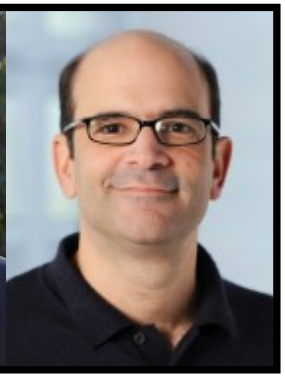
Stereodivergent Dual Catalysis

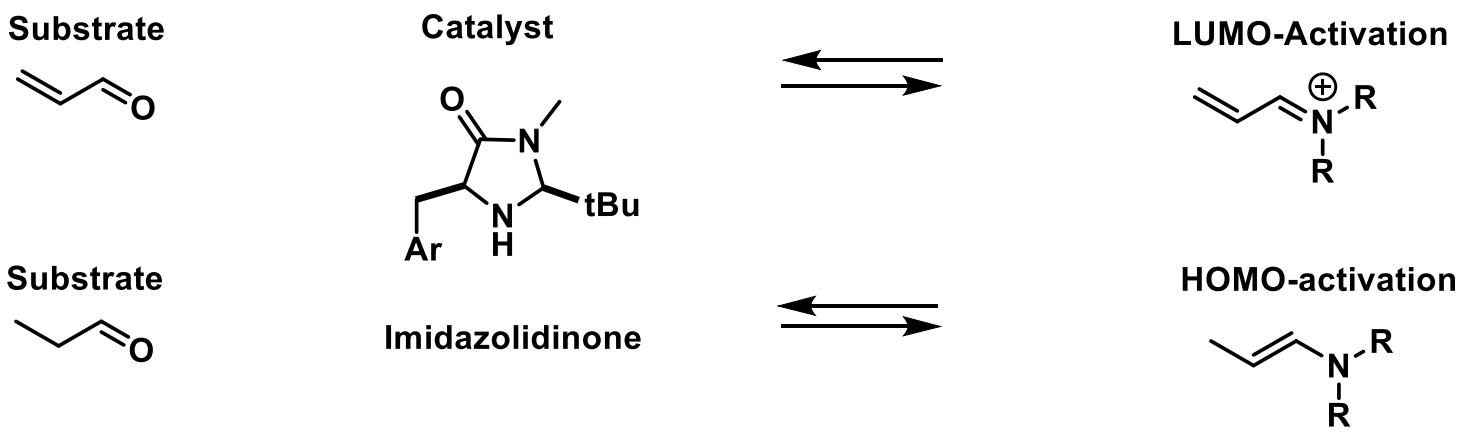
Hartwig



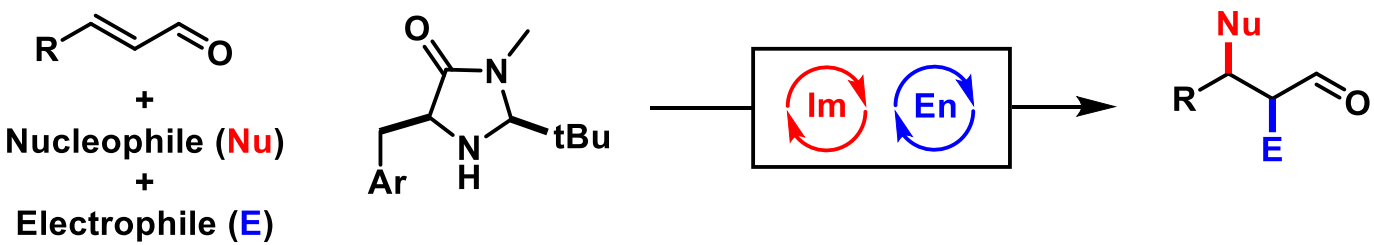
Carreira

Iminium-Enamine Catalysis

Orthogonal Modes for Substrate Activation

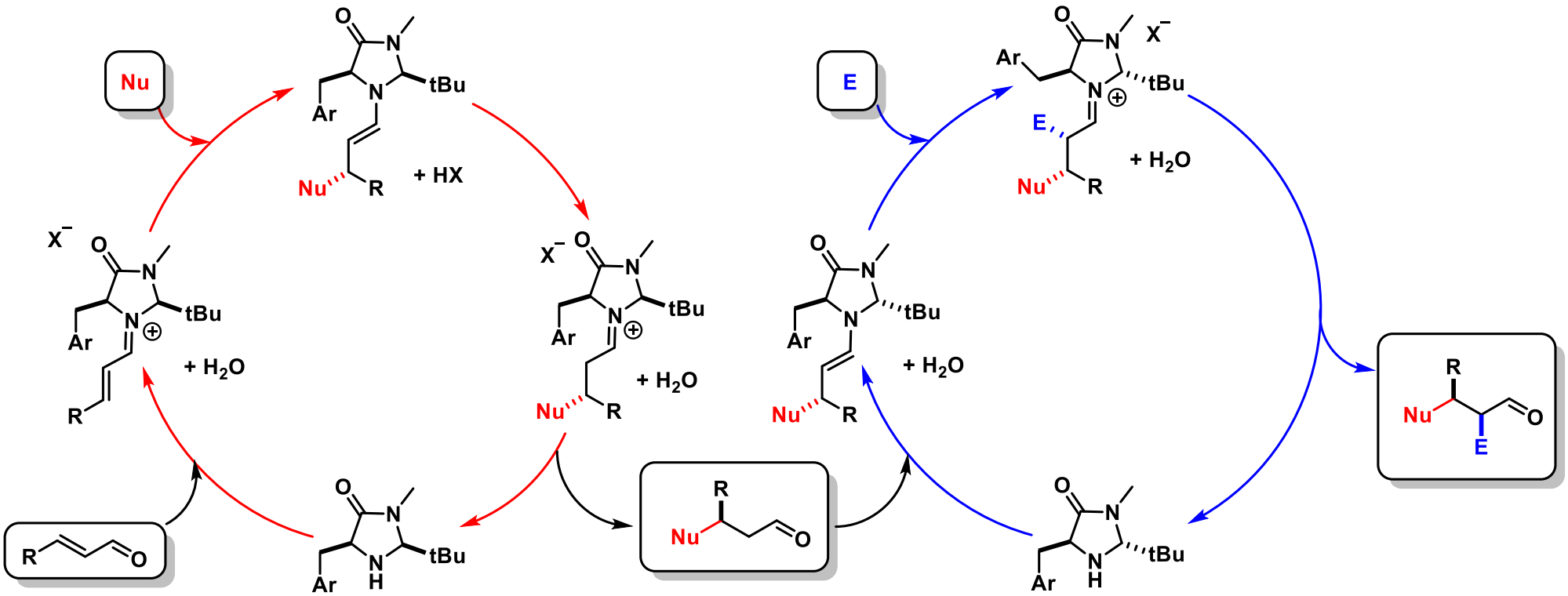


Merging Iminium and Enamine Activation



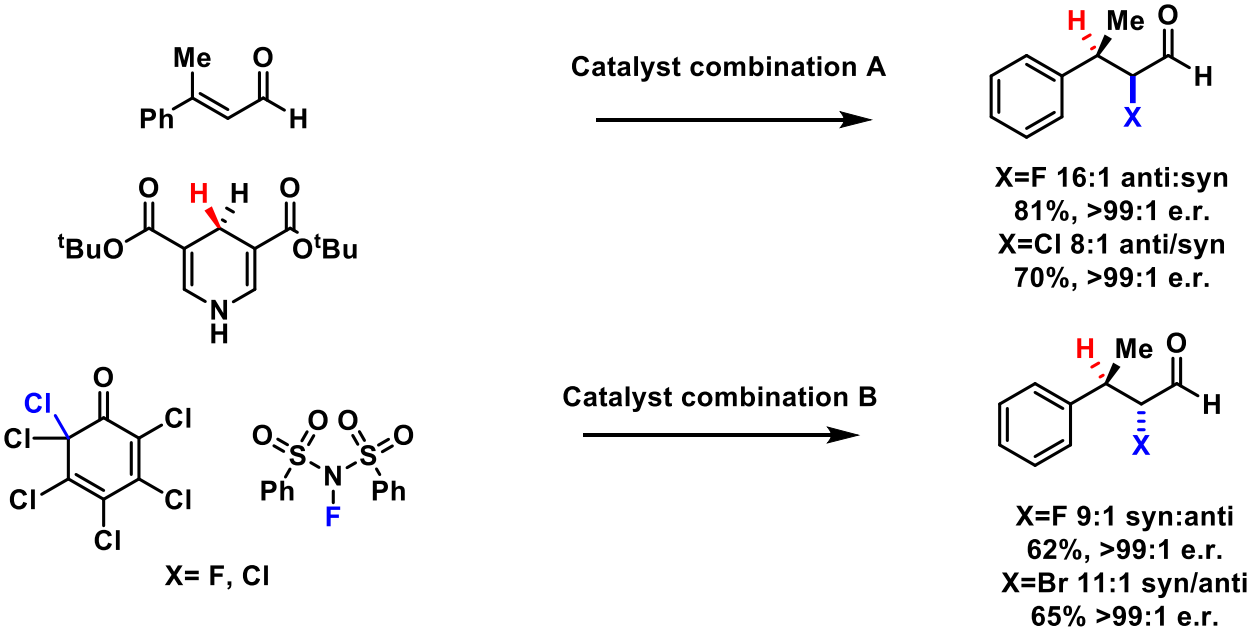
MACMILLAN and coworkers. J. Am. Chem. Soc. **2005**, *127*, 15051-15053.

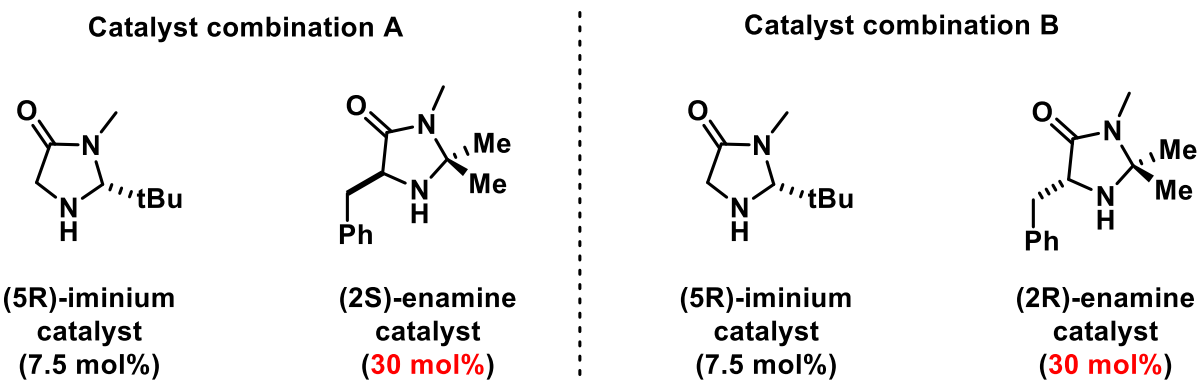
Cascade Catalysis Mechanism



MACMILLAN and coworkers. J. Am. Chem. Soc. **2005**, *127*, 15051-15053.

Formal Hydrohalogenation of Unsaturated Aldehydes

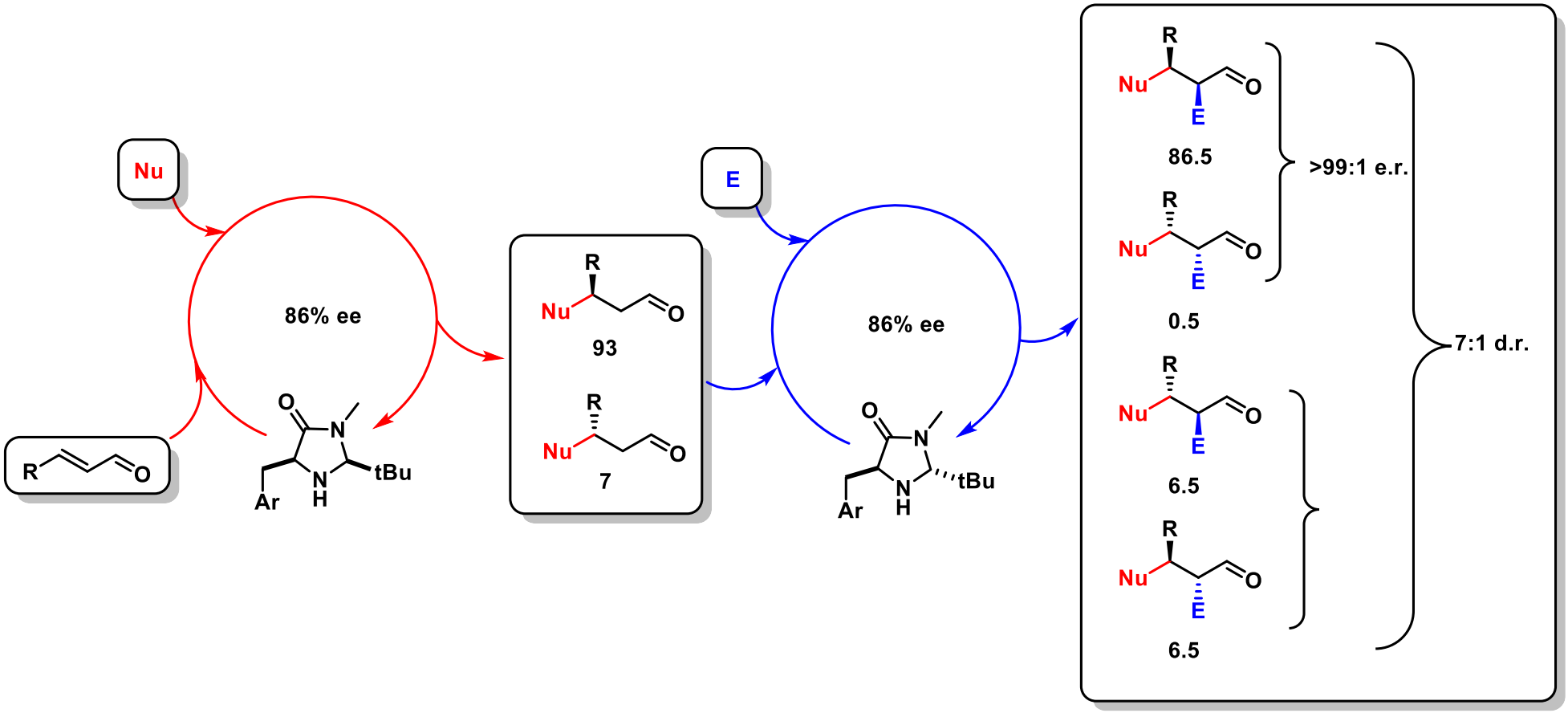




MACMILLAN and coworkers. J. Am. Chem. Soc. **2005**, *127*, 15051-15053.

Consecutive Catalytic Cycles

Benefit of Combining Multiple Cycle



MACMILLAN and coworkers. J. Am. Chem. Soc. **2005**, *127*, 15051-15053.

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Stereodivergent Dual Catalysis

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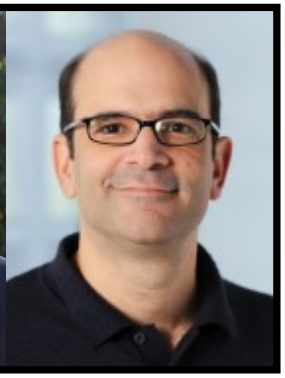
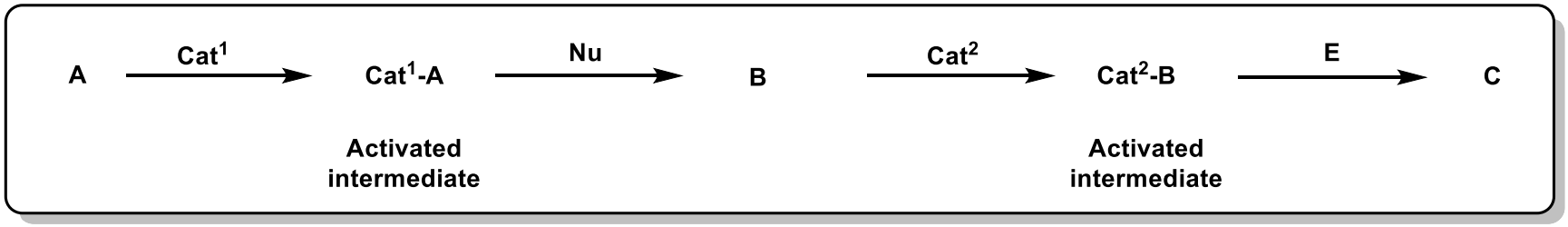


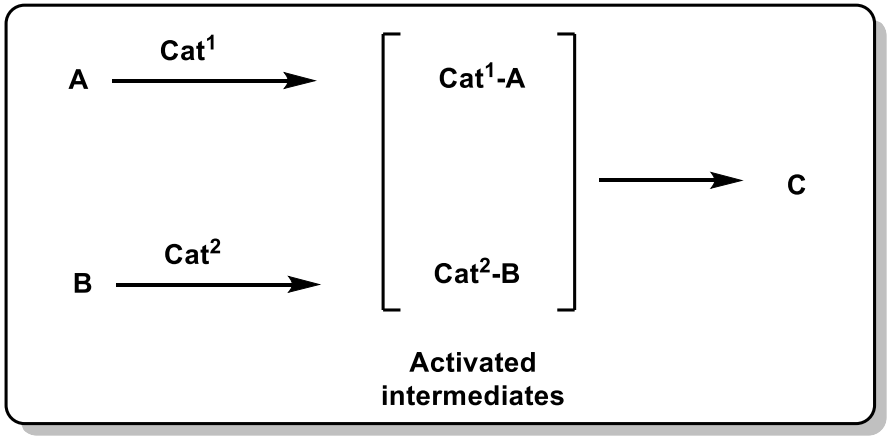
Carreira

Dual Catalysis

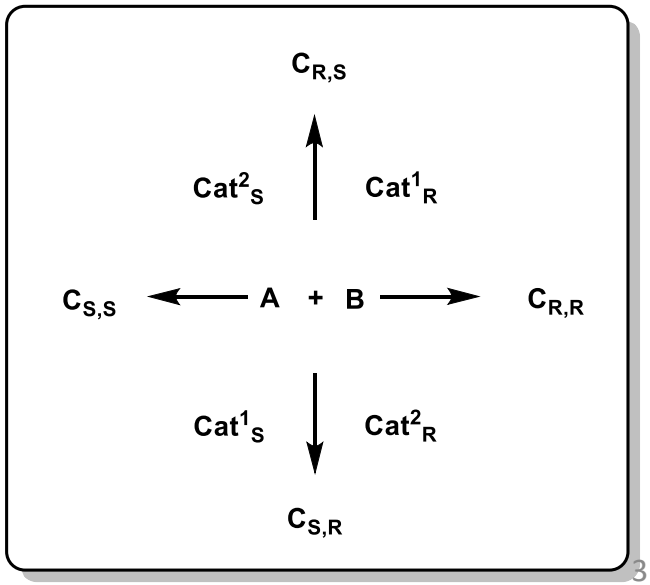
Cascade Catalysis



Dual Catalysis

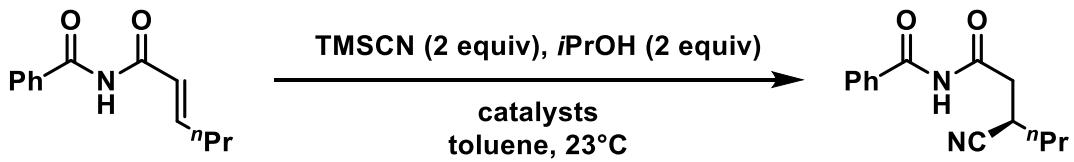


Dual Stereodivergent Catalysis

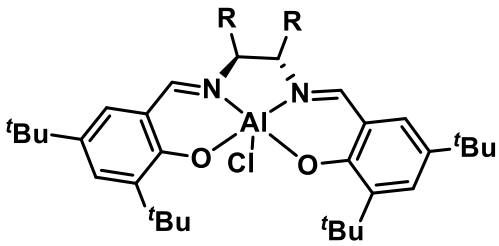


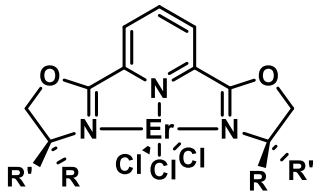
Dual non Divergent Catalysis

First Dual Metal Catalysis



Entry	Al complex	Er complex	Conversion (%)	e.r.
1	(S,S)	-	<3	-
2	-	(S,S)	<3	-
3	(S,S)	(S,S)	87	98:2
4	(S,S)	(R,R)	20	86:14
5	(S,S)	achiral	45	92:8
6	achiral	(S,S)	98	89:11



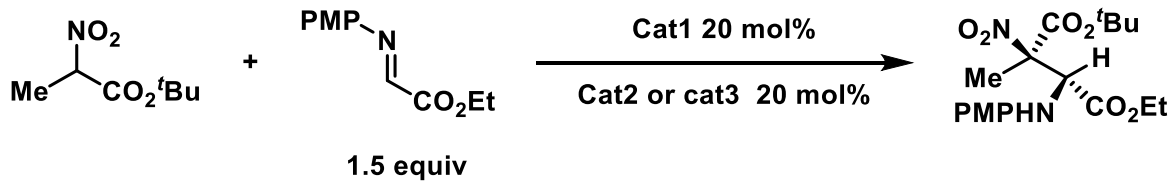


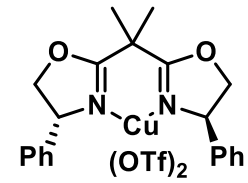
- ***Two catalyst act cooperatively in the rate determining step and asymetric induction***
  - ***Only one stereocenter*** → ***No stereodivergence***
  - ***Simultaneous activation of Nu and E by distinct enantiopure catalysts***

JACOBSEN and coworkers. *J. Am. Chem. Soc.* **2004**, *126*, 9928-9929.

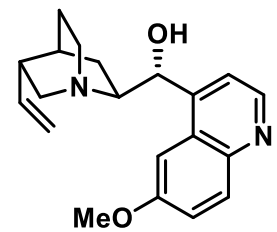
Salient example

Copper/Bisoxazoline/Cinchona Alkaloid Dual Catalysis

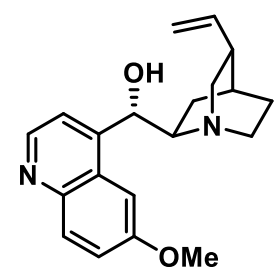




Cat1



Cat2



Cat3

Entry	Ligand	Base	Conversion (%)	d.r.	e.r.
1	(R)-cat1	Et_3N	>90	2:1	80/82
2	No ligand	Quinine	14	1:1	0/0
3	Phenanthroline	Quinine	27	8:1	0/0
4	(R)-cat1	Quinine	90	14:1	99:1
5	(R)-cat1	Quinidine	80	8.5:1	98:2

- ***Chiral ligand controls enantioselectivity and chiral base controls diastereoselectivity***
- ***Two pseudo-enantiomers lead to same pair of diastereomers*** → ***No divergence***

JØRGENSEN and coworkers. *Org. Biomol. Chem.* **2005**, *3*, 1362-1364.

History of Stereodivergence

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Pseudo-divergent Catalysis

Cascade Catalysis

MacMillan

Buchwald

2000 2005 2015

Divergent Catalysis

Deng

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Stereodivergent Dual Catalysis

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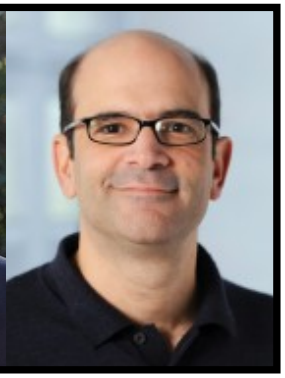
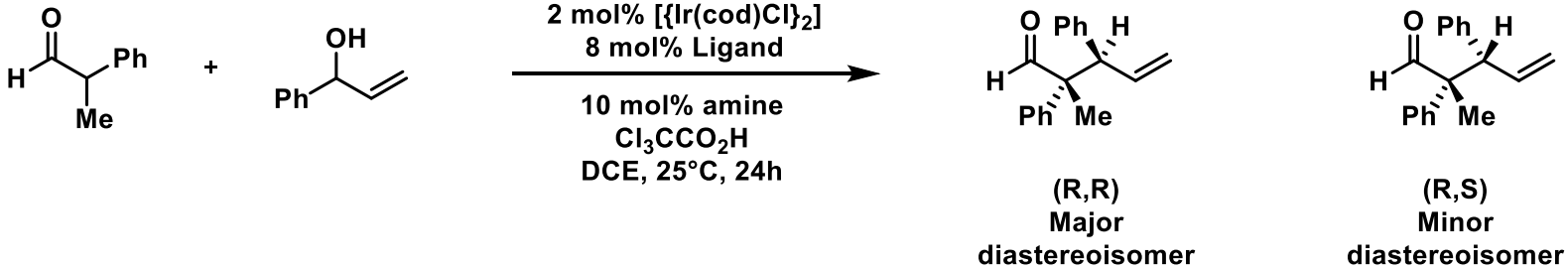


Carreira

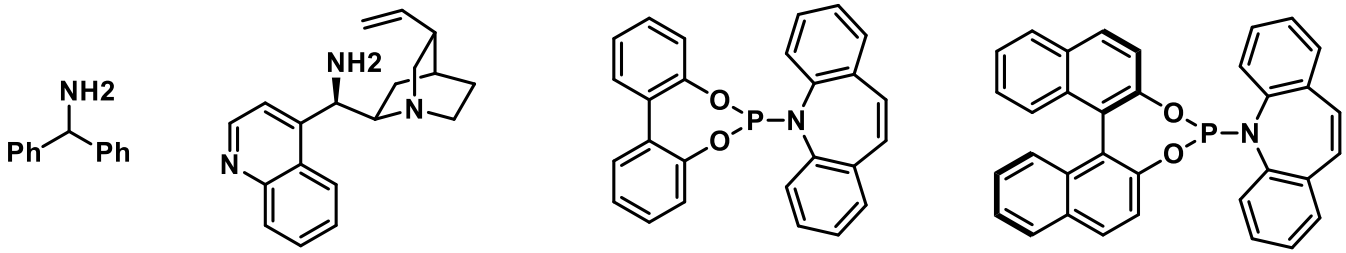
Stereodivergent Dual Catalysis

α-Allylation of Branched Aldehydes



Key Experiments

#1	#2	#3
(R)-L + A1	L1 + A2	(R)-L + A2
69%, 3:1 d.r.	69%, 1.3:1 d.r.	77%, >20:1 d.r.
>99:1 e.r.	84:16 / 96:4 e.r.	>99:1 e.r.
(R)-L control	A2 control	(R)-L + A2 control

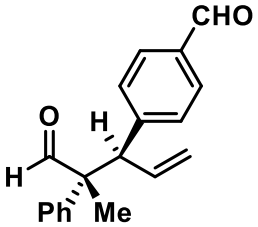


A1 A2 L1 (R)-L

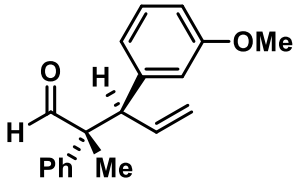
CARREIRA and coworkers. *Science*. **2013**, *340*, 1065.

Example of Stereodivergence

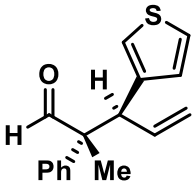
(R)-L + A2	(R)-L + A3	(S)-L + A2	(S)-L + A3
(R,R)-1 72% (>20:1) >99:1 e.r.	(S,R)-1 67% (>20:1) >99:1 e.r.	(R,S)-1 63% (>20:1) >99:1 e.r.	(S,S)-1 75% (>20:1) >99:1 e.r.
(R,R)-2 67% (>20:1) >99:1 e.r.	(S,R)-2 73% (15:1) >99:1 e.r.	(R,S)-2 67% (>20:1) >99:1 e.r.	(S,S)-2 73% (14:1) >99:1 e.r.
(R,R)-3 64% (>20:1) >99:1 e.r.	(S,R)-3 70% (11:1) >99:1 e.r.	(R,S)-3 64% (10:1) >99:1 e.r.	(S,S)-3 70% (>20:1) >99:1 e.r.



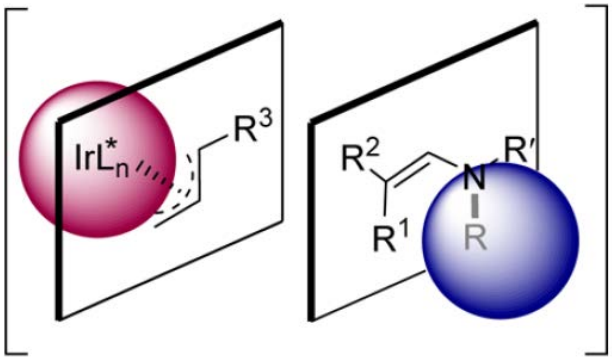
1



2



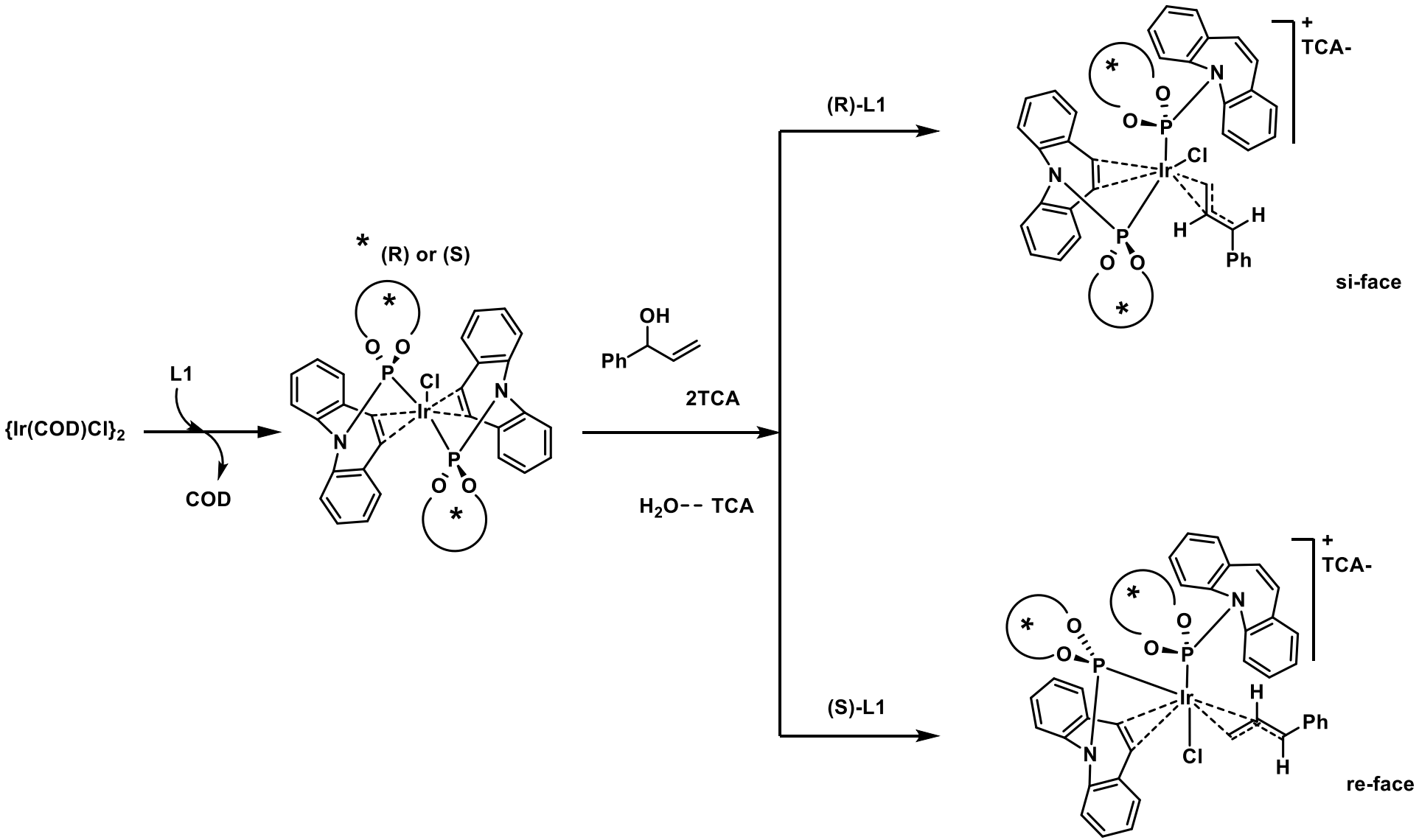
3



- ***Excellent enantio- and diastereoselectivities***
- ***No match/mismatch interractions***
- ***Access to all stereoisomer using the same reaction condition and substrates***

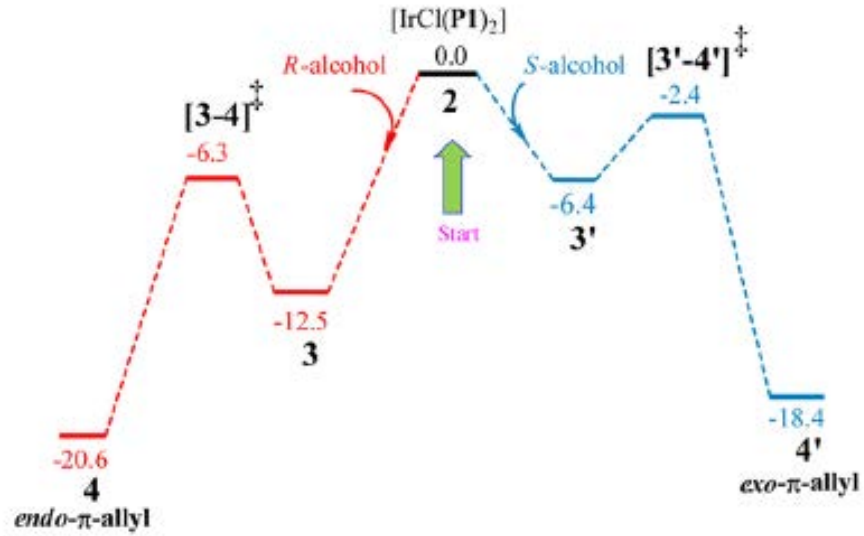
CARREIRA and coworkers. *Science*. **2013**, *340*, 1065.

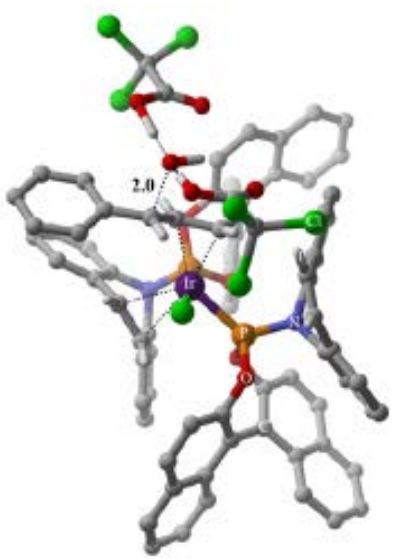
Computational Studies



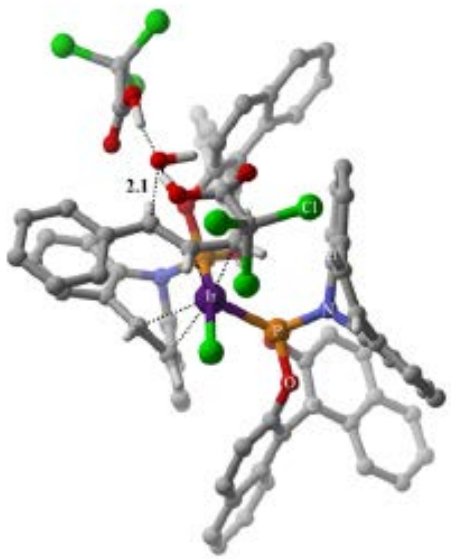
SUNOJ and coworkers. *J. Am. Chem. Soc.* **2015,** *137*, 15712−15722.

Computational Studies

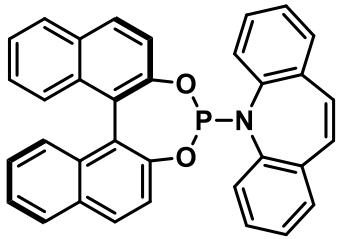




[3-4]‡



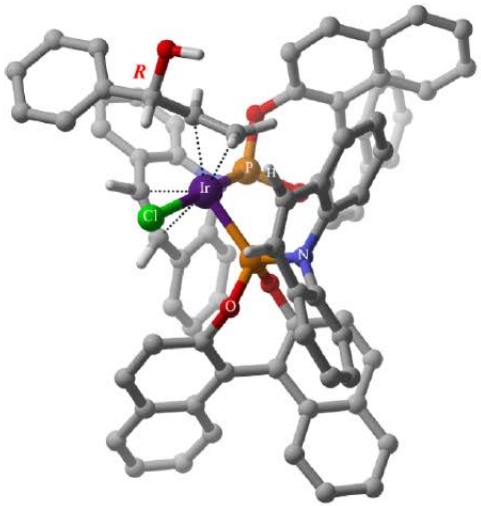
[3'-4']‡



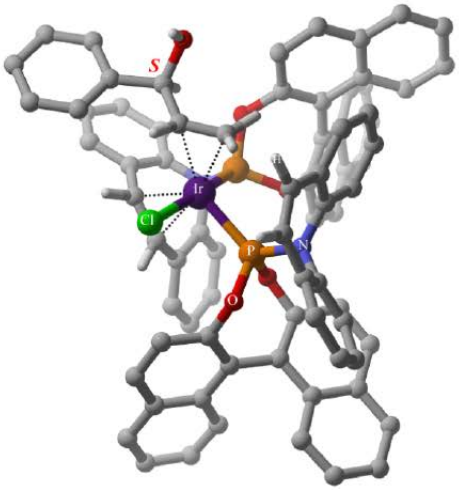
- ***Chiral recognition between (R)Cat and (R) alcohol***
- ***Each enantiomer of the alcohol lead to a different allyl complex***
- ***Yields are around 75-80%***
- ***Implies a deracemization process during the oxidative addition***

SUNOJ and coworkers. *J. Am. Chem. Soc.* **2015,** *137*, 15712−15722.

Transition State Conformations

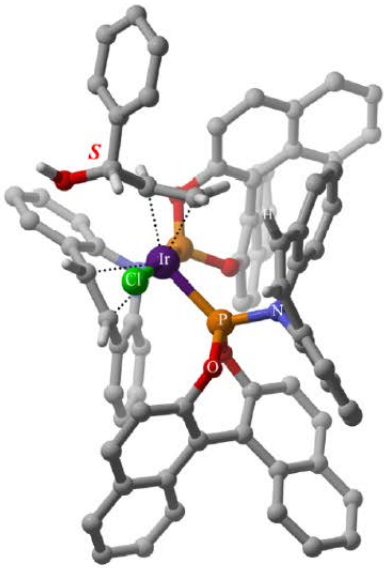


Configuration CR of R-alcohol (0.0)



Configuration CS of S-alcohol (3.6)

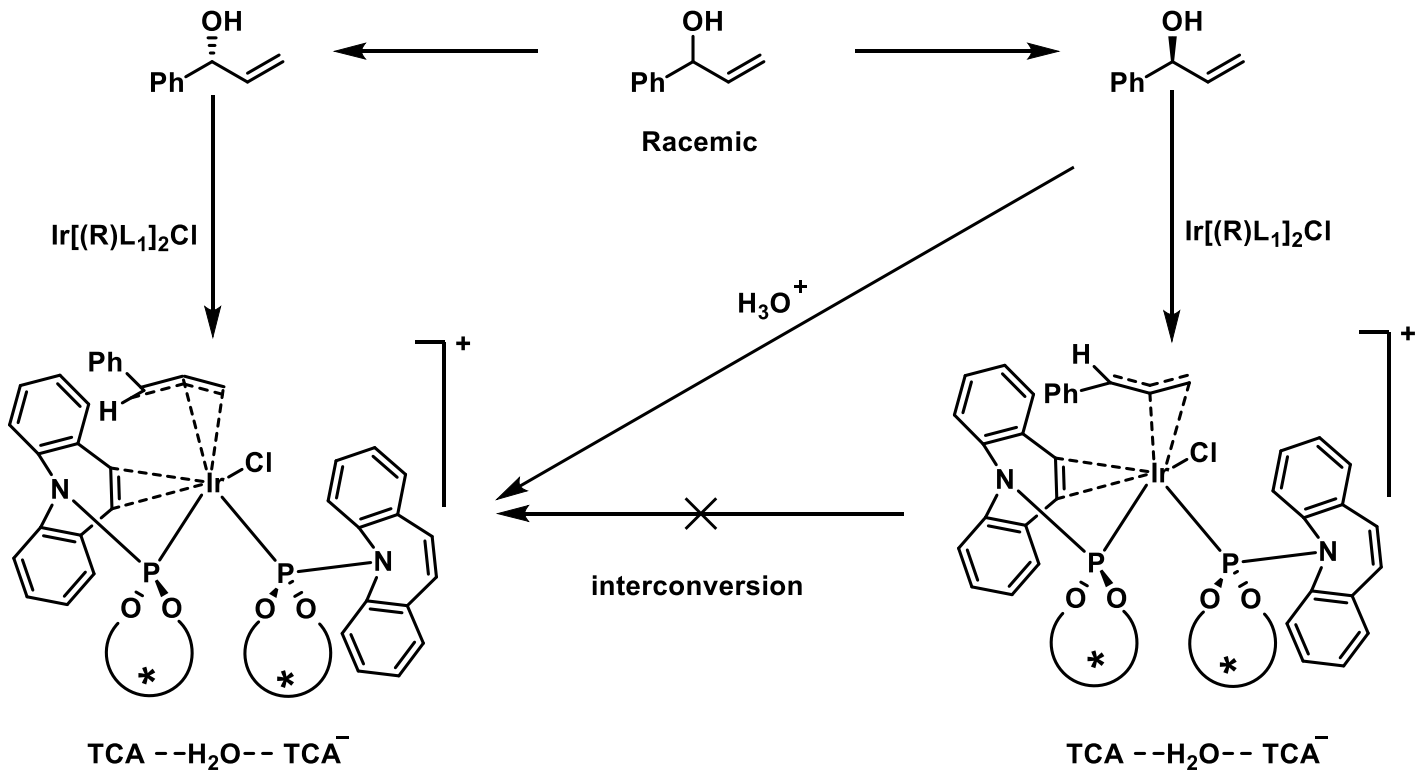
- ***TCA mediated π-ally complex formation higher by 16kcal/mol***
- ***Hydronium mediated dehydration only 5kcal/mol higher***



Configuration CS' of S-alcohol (-2.4)

SUNOJ and coworkers. *J. Am. Chem. Soc.* **2015,** *137*, 15712−15722.

Deracemization of Allylic Alcohol



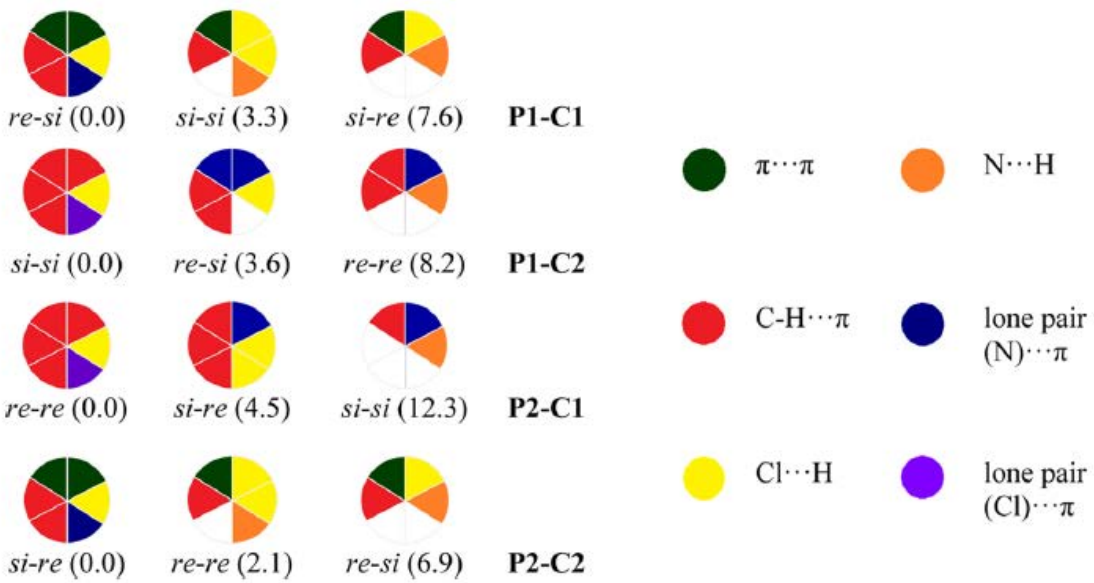
- ***Fast racemization occurs during the oxidative addition step***

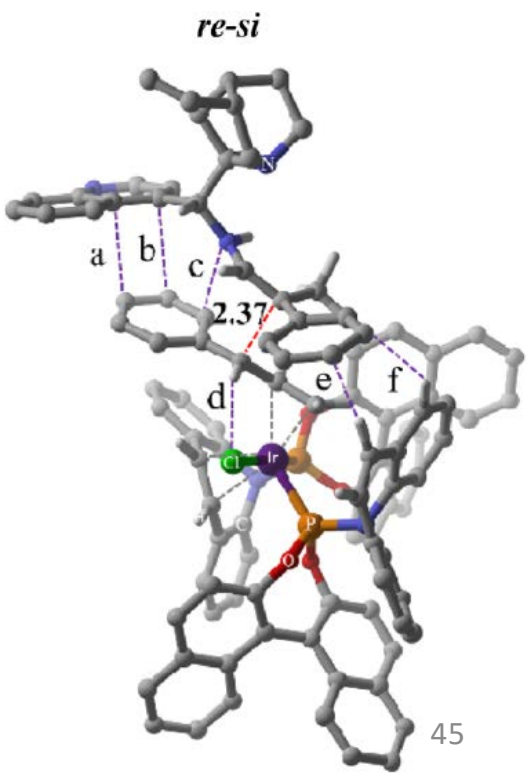
SUNOJ and coworkers. *J. Am. Chem. Soc.* **2015,** *137*, 15712−15722.

Computational Studies and Interaction Wheel Model

Electrophile-Nucleophile	Product configuration	L1-A2	L1-A3	L2-A2	L2-A3
re-si	(2R,3R)	0.0	3.6	5.7	6.9
si-si	(2S,3R)	3.3	0.0	12.3	10.2
si-re	(2S,3S)	7.6	5.2	4.5	0.0
re-re	(2R,3S)	11.3	8.2	0.0	2.1

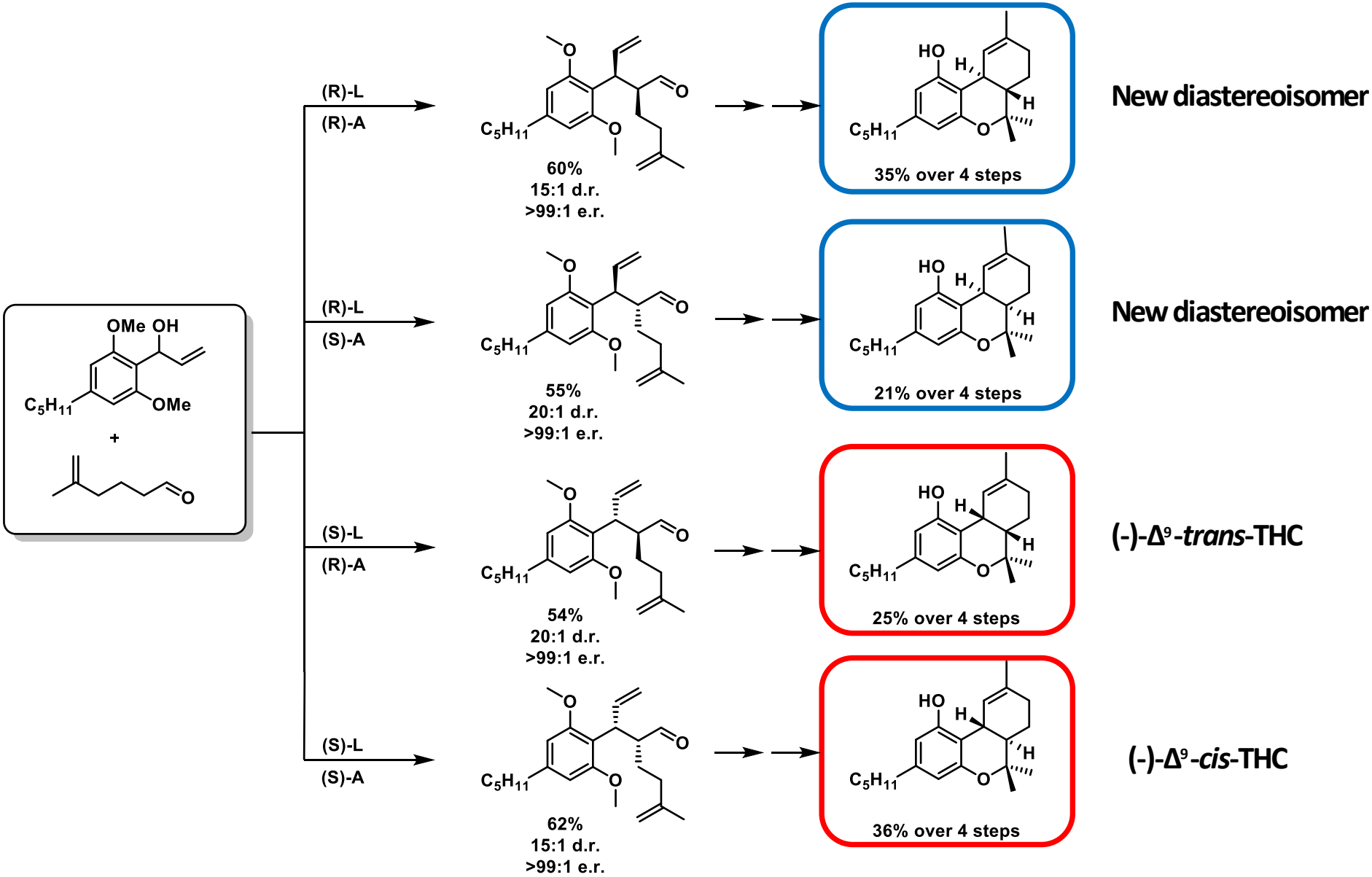
- ***Relative energies of the C-C bond formatio***





SUNOJ and coworkers. *J. Am. Chem. Soc.* **2015,** *137*, 15712−15722.

Application to Total Synthesis



CARREIRA and coworkers. *Angew. Chem. Int. Ed.* **2014**, *53*, 13898 –13901.

Conclusion and Outlook

- *Huge impact in medicinal chemistry*
- *Still relatively recent*
- *Mainly vicinal stereocenters*
- *Lack of mechanistic investigations*
- *Most of discovery is serendipitous*
- *Dual Catalyst as a solution*

To Learn more about Stereodivergent Catalysis

- Stereodivergent Catalysis.
  Chem. Rev. **2018**, *118*, 5080–5200.

- Stereodivergence in Asymmetric Catalysis.
  J. Am. Chem. Soc. **2017**, *139*, 5627–5639.

- Advances in Asymmetric Diastereodivergent Catalysis.
  Adv. Synth. Catal. **2017**, *359*, 534 – 575.

- Mechanistic Insights on Cooperative Catalysis through Computational Quantum Chemical Methods.
  ACS Catal. ***2015****, 5,* 480–503.