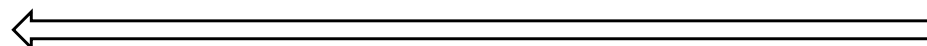
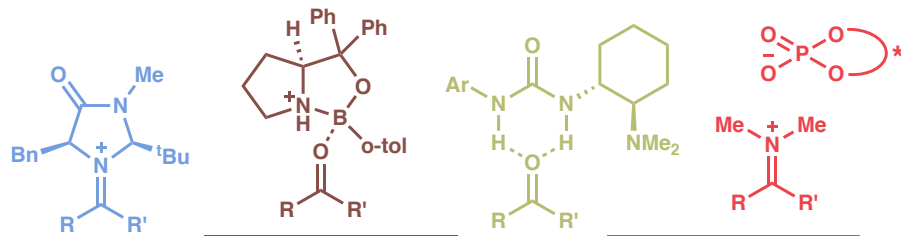


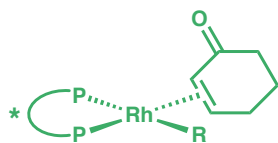
- Iminium/enamine catalysis (covalent)
- Lewis acid catalysis
- Hydrogen bonding/Brønsted acid catalysis
- Transition metal catalysis
- Ion pairing/ion directed catalysis

"... high stereinduction is often achieved through highly directional catalyst-substrate interactions."

- Eric Jacobsen



Directionality



"An ion pair is defined to exist when a cation and anion are close enough in space that the energy associated with their electrostatic attraction is larger than the thermal energy available to separate them."

- Anslyn and Dougherty, *Modern Physical Organic Chemistry*

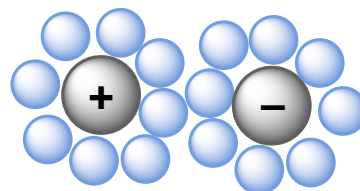
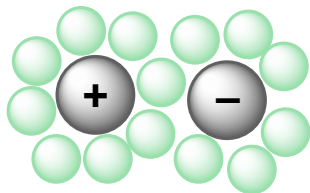
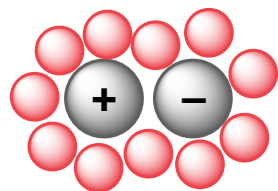
$$E = \frac{q_1 q_2}{4\pi\epsilon_r \epsilon_0 r}$$

ϵ_r = relative permittivity or dielectric constant

Contact ion pair

Solvent shared ion pair

Solvent separated ion pair



Low dielectric solvent

Medium dielectric solvent

High dielectric solvent

ϵ_r

Key Players in the Field



Prof. Eric Jacobsen, Harvard University
Coined "asymmetric ion-pairing catalysis"



Prof. Magnus Rueping, KAUST Catalysis Center
Asymmetric Brønsted acid catalysis



Prof. Dean Toste, UC Berkeley
Chiral anionic phase transfer catalysis

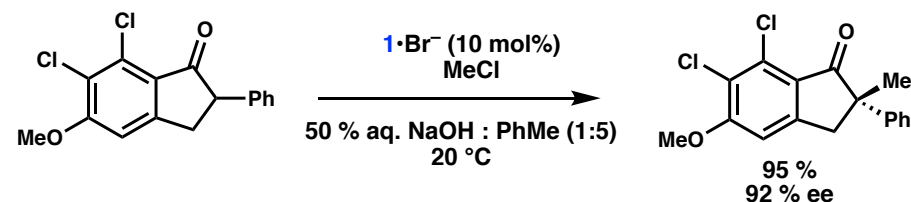


Prof. Benjamin List, Max Planck Institut für Kohlenforschung
Coined "asymmetric counteranion directed catalysis (ACDC)"

Reviews:

Maruoka and Ooi. *Angew. Chem. Int. Ed.* **2007**. 4222
Lacour and Moraleda. *Chem. Commun.* **2009**. 7073
Mahlau and List. *Angew. Chem. Int. Ed.* **2013**. 518
Brak and Jacobsen. *Angew. Chem. Int. Ed.* **2013**. 534

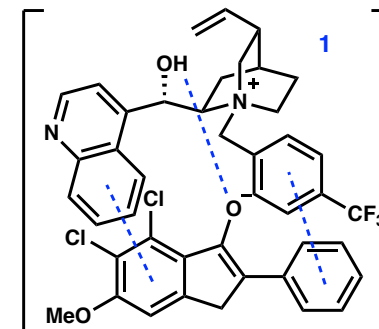
Cationic phase transfer

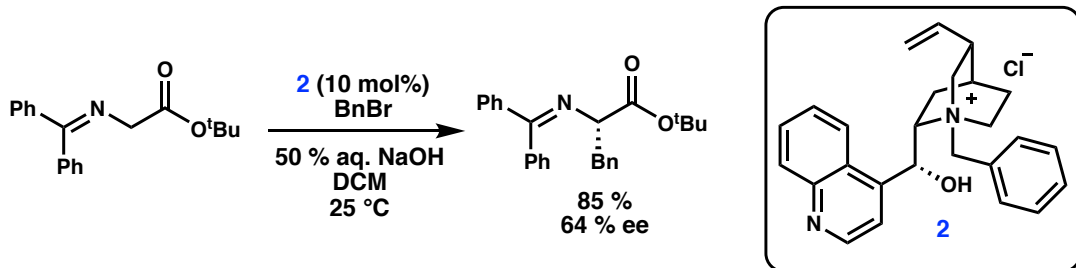


- First example of successful chiral phase transfer catalysis

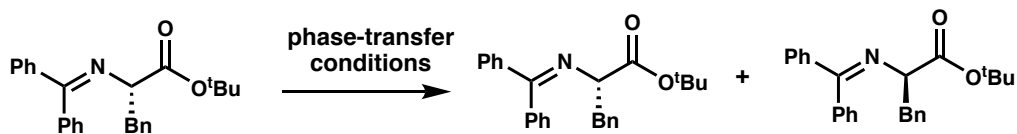
- ee's improved with less polar solvents and with lower temperatures

- proposed key interactions accounting for selectivity

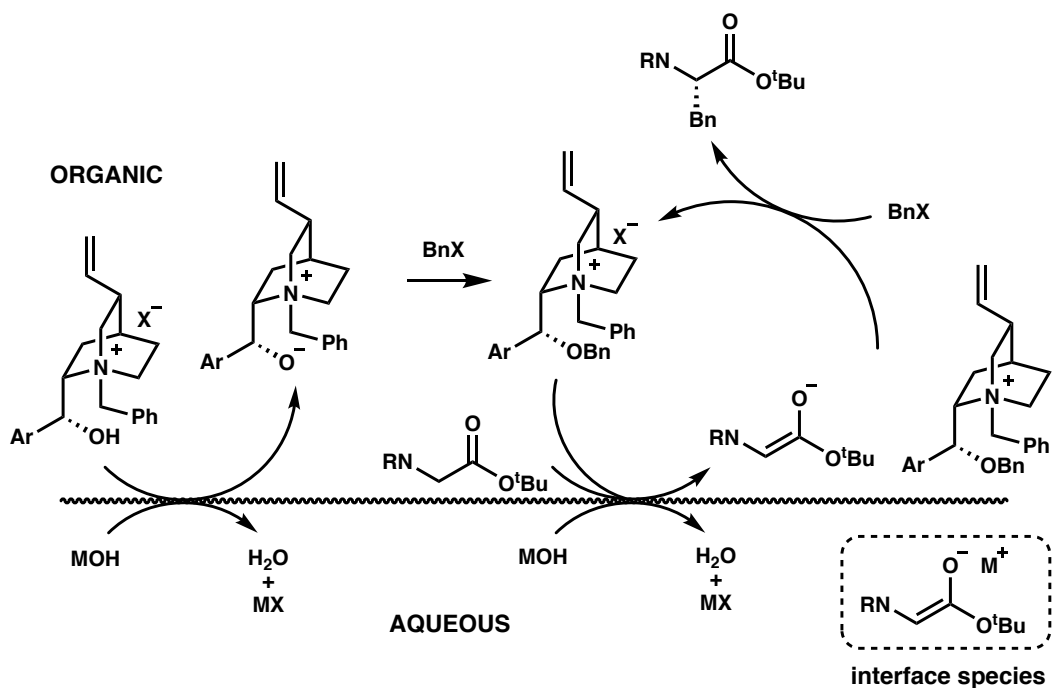




- Assumed salt metathesis at interface to generate chiral, soluble ionic pair

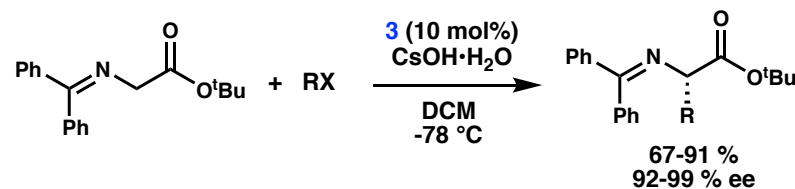


Entry	Catalyst	BnBr	Racemization (%)	
1	none	no	0	- Different racemization outcomes suggests that 2 quickly reacts with BnBr
2	2	no	30	
3	2	yes	0	- Catalyst is benzylated 2 (Bn·2), no free hydroxyl, no H-bond!
4	Bn·2	no	0	



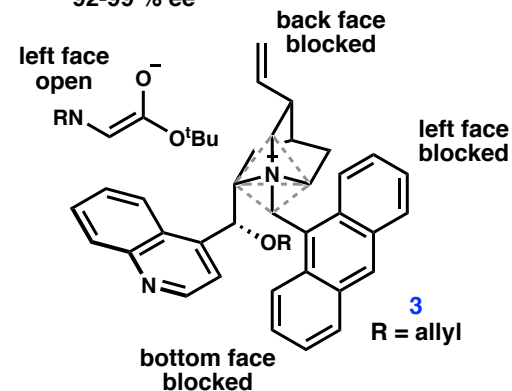
O'Donnell. *JACS*. **1989**. 2353
O'Donnell. *Tetrahedron*. **1994**. 4507

Corey developed anthracenyl derivative for a variety of primary alkyl halides

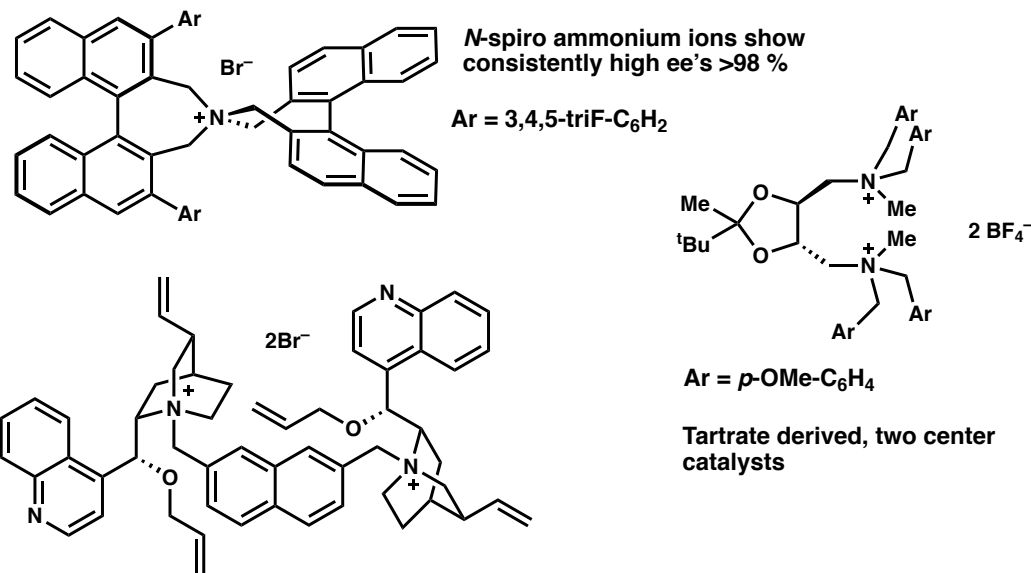


- Proposed tetrahedral model for selectivity

- Computation shows enolate two oxygens and a carbon interaction with three hydrogens next to ammonium nitrogen



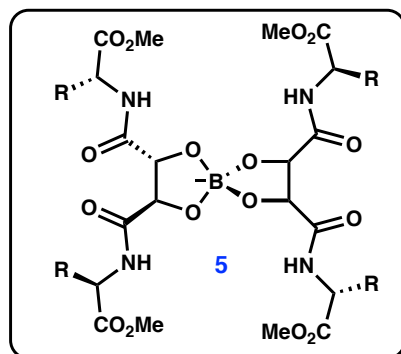
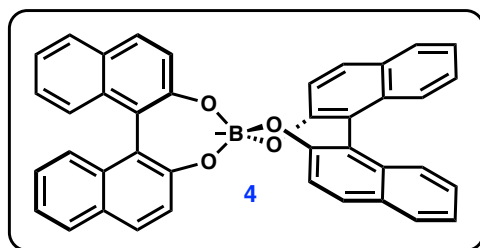
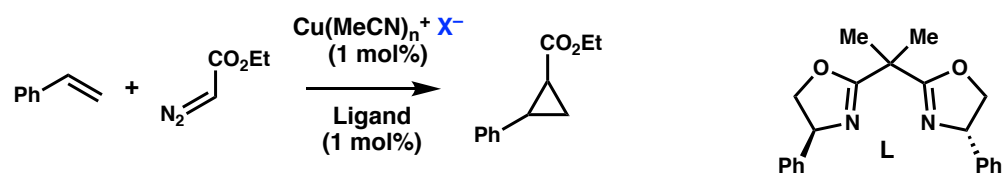
The alkylation of glycine Schiff bases using a catalytic chiral phase transfer counterion has been extensively investigated



Multimeric conchina alkaloids can dramatically improve selectivity

Corey. *JACS*. **1997**. 12414
Houk. *JACS*. **2002**. 7163
Shibasaki. *Tetrahedron*. **2004**. 7743
Maruoka. *Chem Comm*. **2007**. 1487
Park. *Angew. Chem. Int. Ed*. **2002**. 3036

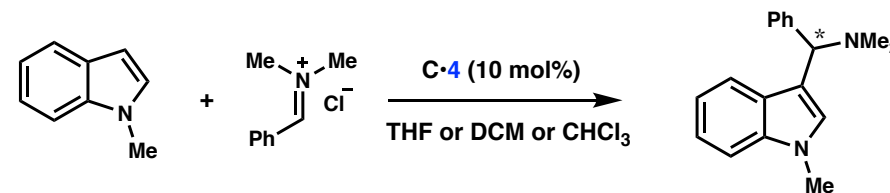
Beginnings of chiral anions in catalysis



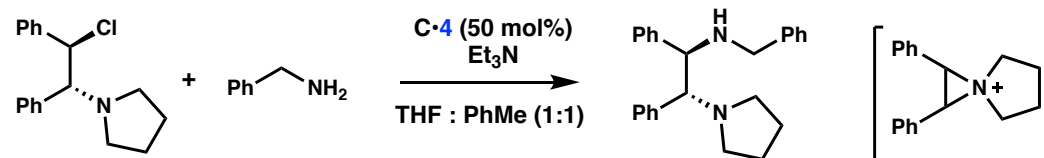
Entry	X ⁻	Ligand	Solvent	Temperature	ee cis/trans (%)	Yield (%)
1	S-(4)	L	PhH	rt	6 / 15	34
2	R-(4)	L	PhH	rt	8 / 12	34
3	S-(4)	L	PhH	0 °C	6 / 21	12
4	R-(4)	L	PhH	0 °C	28 / 10	20
5	Ph-(5)	none	DCM	25 °C	15 / 8	57
6	Ph-(5)	none	DCM	0 °C	18 / 17	35
7	Ph-(5)	none	PhH	0 °C	26 / 17	21
8	^t Bu-(5)	none	PhH	0 °C	19 / 34	3

- First report of chiral anion giving selectivity in catalysis
- Matched and mismatched effects small but significant
- Selectivity depends on dielectric constant and on temperature

Arndtsen. *Org. Lett.* **2000**. 4165
 Arndtsen. *Organometallics*. **2004**. 2838
 Arndtsen. *Tetrahedron Asymm.* **2005**. 1789



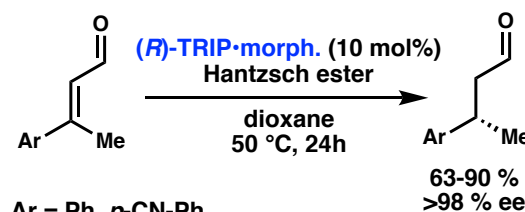
- Cations (C) Et₂NH₂⁺, Et₃NH⁺, Na⁺, Ag⁺ were explored
- Yields ranged from 0-98 % with no trend between solvents or cation
- ee's < 12 %, no consistent sign inversion for enantiomer of 4



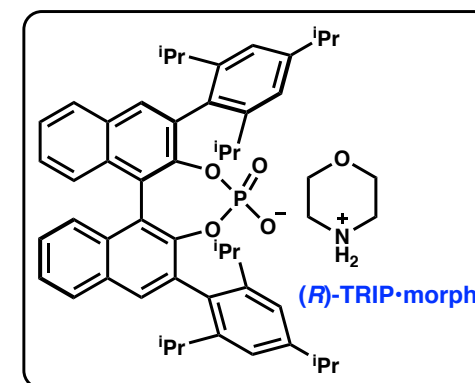
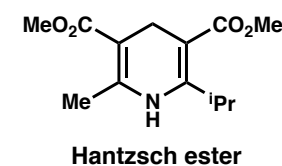
- Yields < 30 %
- Highest ee for Et₃NH⁺ 2, 13-15 % with consistent sign inversion for enantiomer of 4

Nelson. *Tetrahedron Asymm.* **2003**. 1995

Organocatalysis

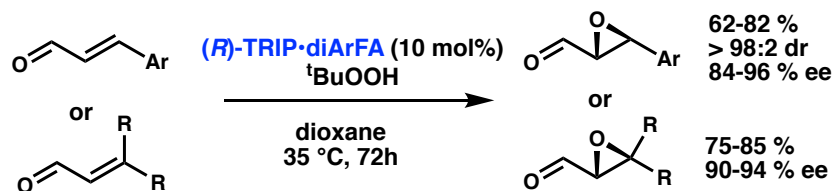


Ar = Ph, *p*-CN-Ph,
p-NO₂-Ph, *p*-Br-Ph,
p-CF₃-Ph, naph.

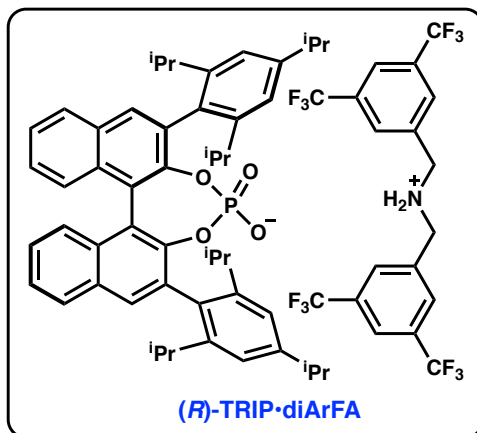


- Breakthrough report of first highly selective chiral anion catalyst
- Enantioselective reduction of citronellal (90 % ee) better than chiral amine (40 % ee)

List. *Angew. Chem Int. Ed.* **2006**. 4193

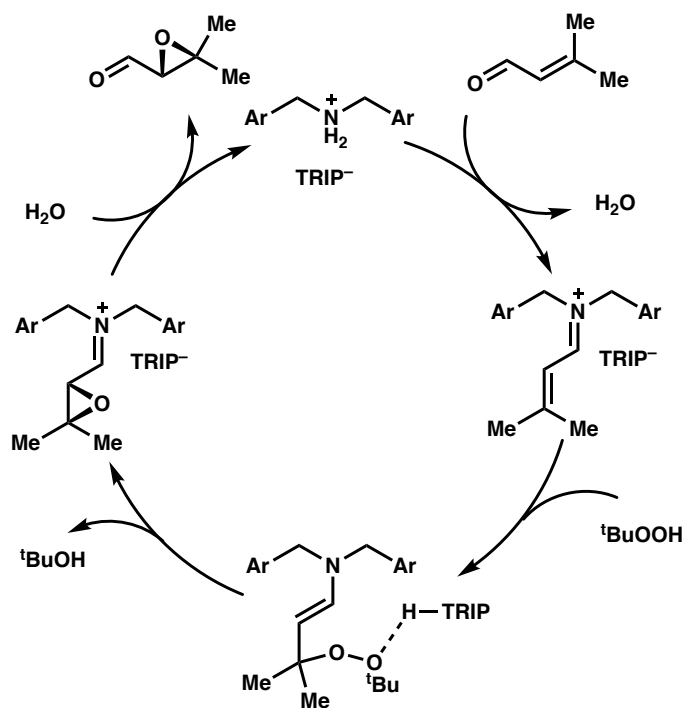


Ar = Ph, 1/2-naph, *o*/*m*/*p*-tol, *o*/*m*/*p*-F-C₆H₄
 R = Me, Et, -C₅H₁₀

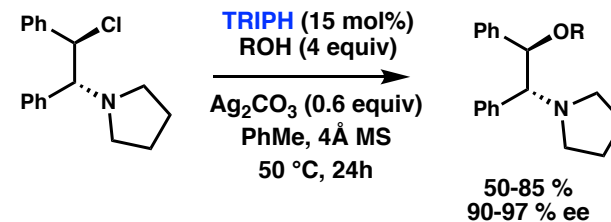


- Termed ACDC, but anion not involved in enantiodetermining step

- More H-bonding catalysis?

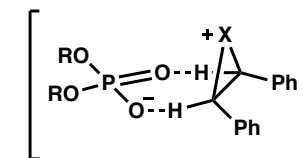
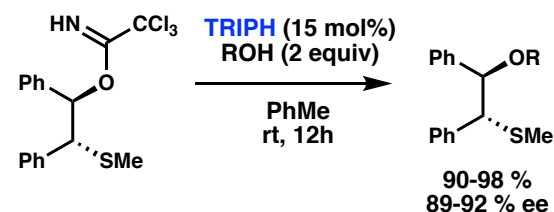


List. *Angew. Chem Int. Ed.* **2008.** 1119



Presumably secondary H-bonding interaction between TRIP base and incoming alcohol

R = neopentyl, 2-indane, 2,6-diMe-4-OMe-C₆H₂,
 N-Bs-indole, CH(allyl)₂, ^tBu (30 equiv)

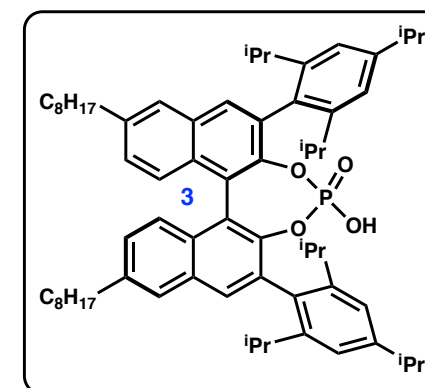
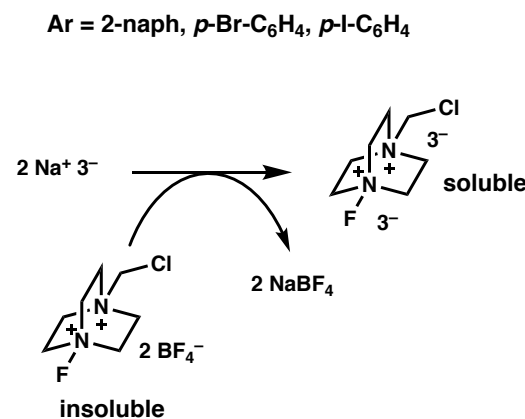
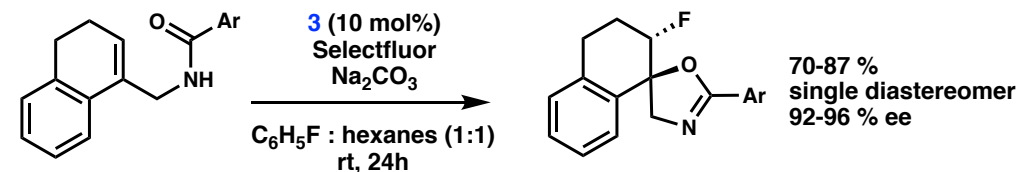


- Later studies show ion pair formation of this kind

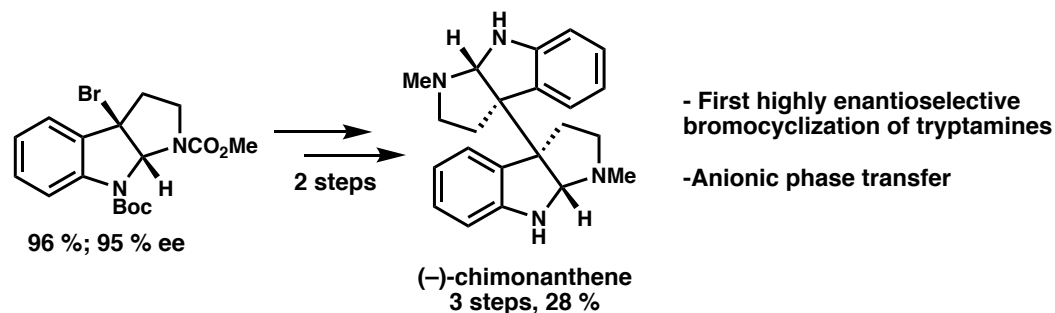
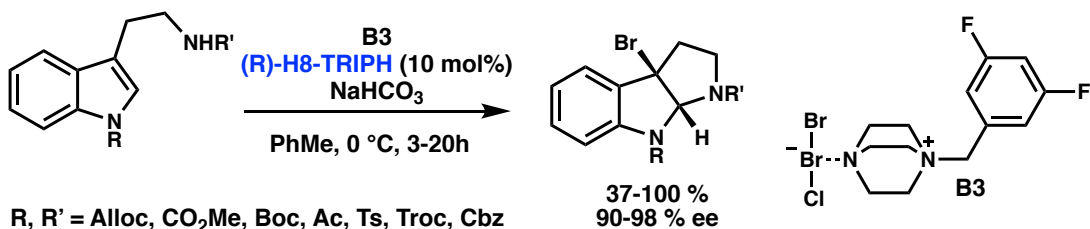
R = neopentyl, 2-indane, 2-Bs-ethyl

Toste. *JACS.* **2008.** 14984
 Paton. *JACS.* **2017.** 8886

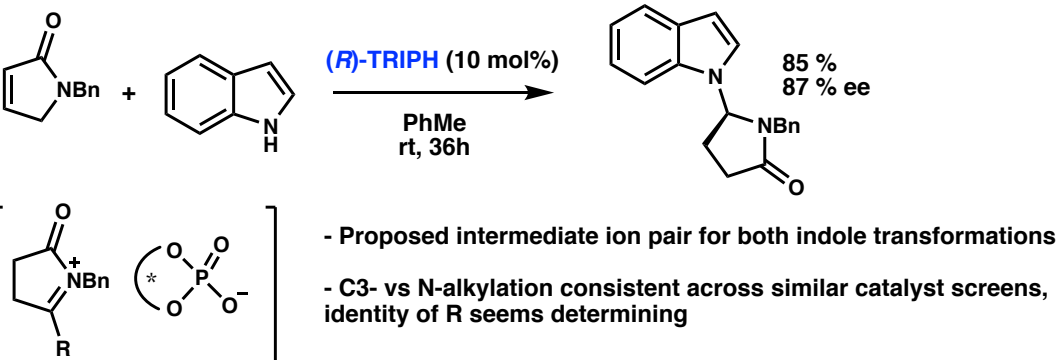
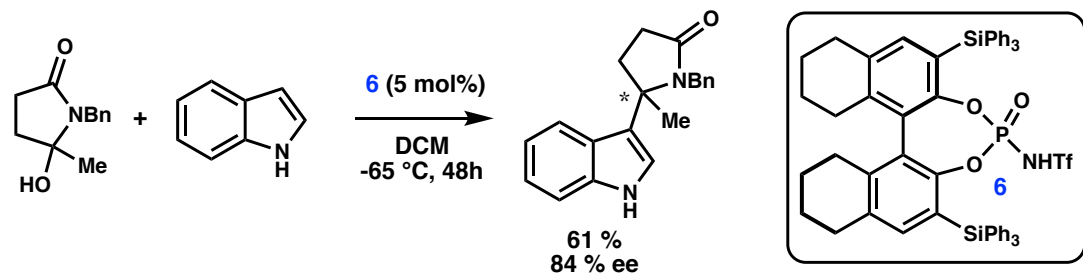
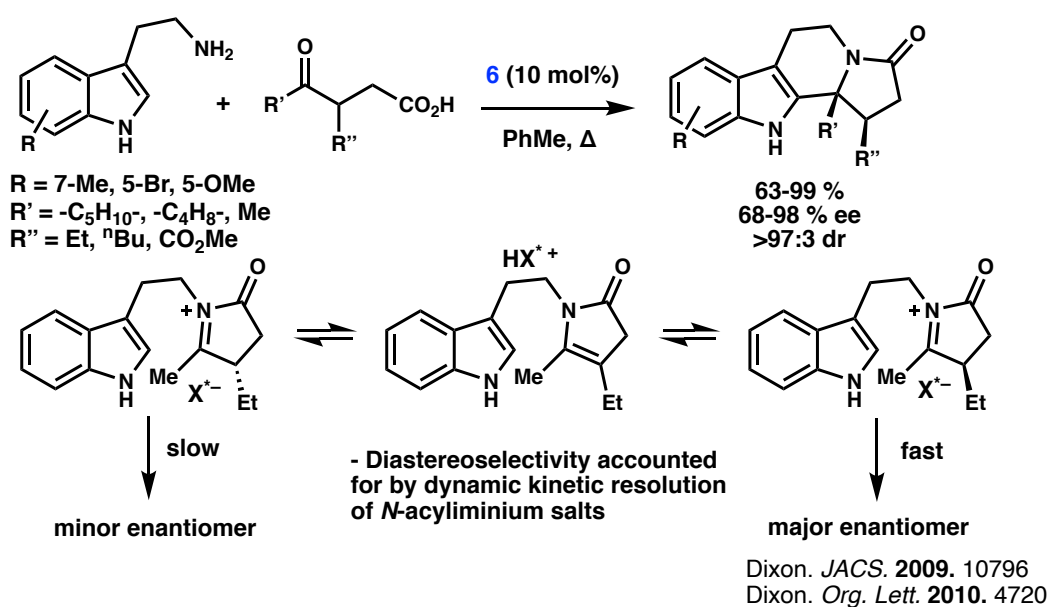
Anionic phase transfer



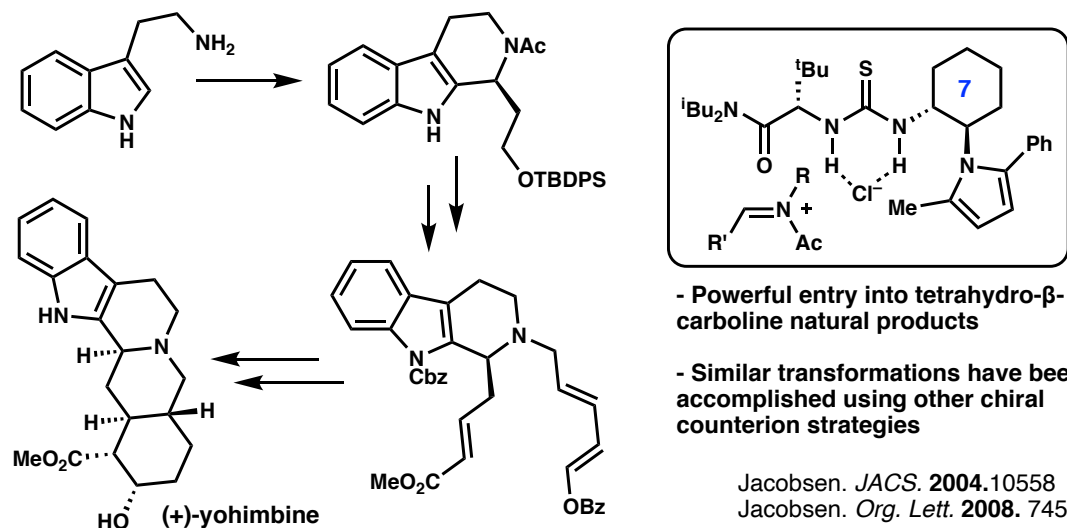
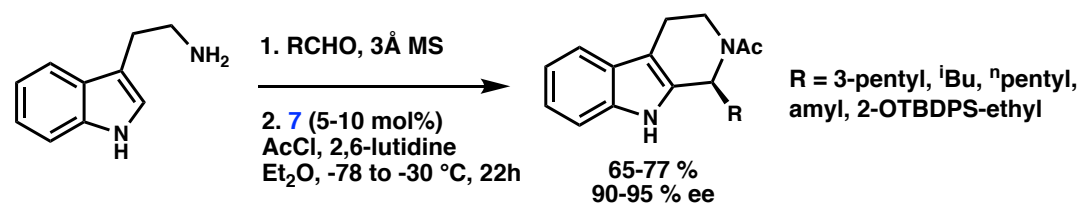
Toste. *Science.* **2011.** 1681

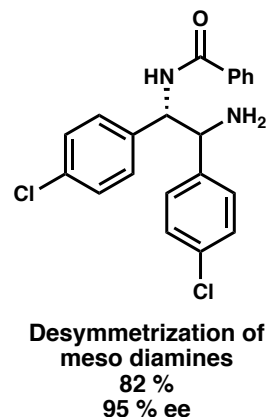
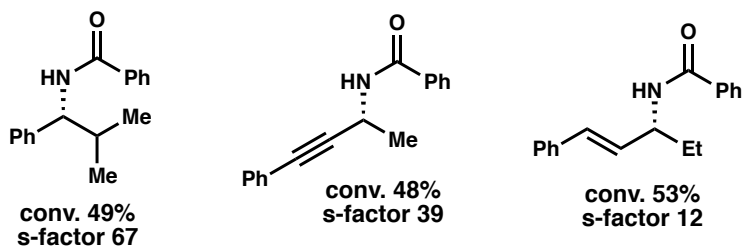
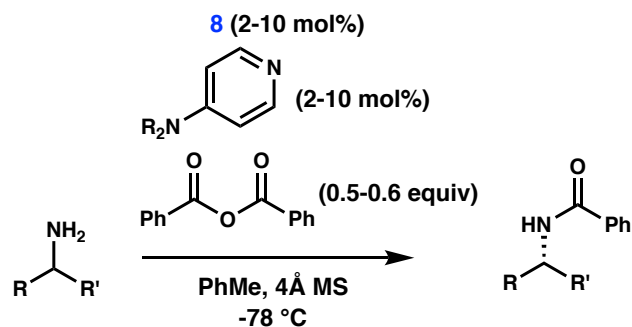
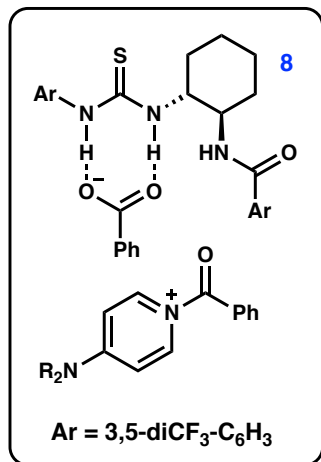
Ma. *Angew. Chem. Int. Ed.* **2013.** 12924

Friedel-Crafts type

Rueping. *Synlett.* **2010.** 119
Huang. *Angew. Chem. Int. Ed.* **2011.** 5682

Chiral anion binders

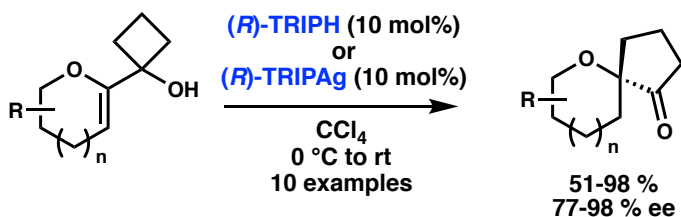




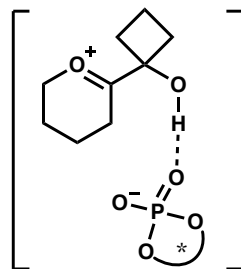
- Remarkably all substrates and methodologies work under nearly identical conditions

Seidel. *Org. Lett.* **2012**. 3084
Seidel. *JACS.* **2010**. 13624
Seidel. *Org. Lett.* **2011**. 2464
Seidel. *JACS.* **2011**. 14538

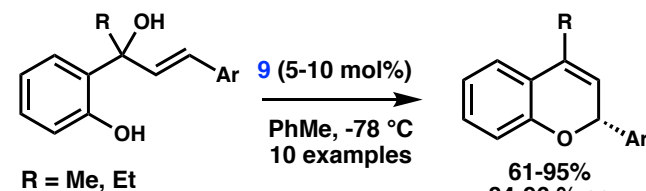
Oxocarbenium and carbocations



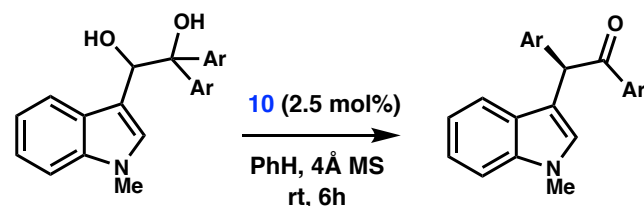
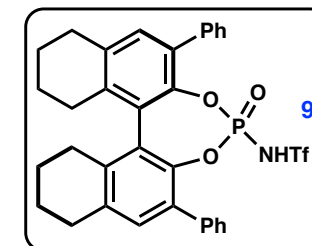
- Ag salt catalyst performs comparably to the Brønsted acidic catalyst; presumed silver-proton exchange with cyclobutyl alcohol



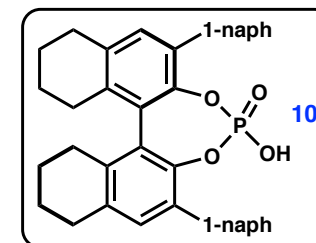
Tu. *Angew. Chem. Int. Ed.* **2009**. 8572



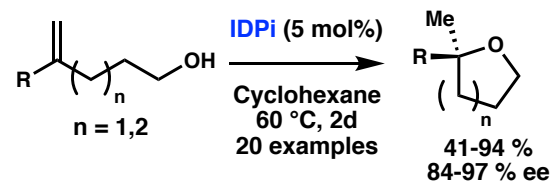
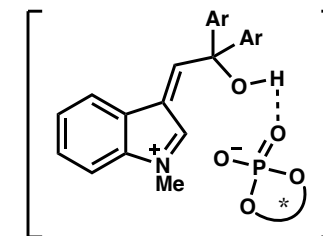
- Strong chiral Brønsted acid generates allylic carbocation
- Efficient access to stereodefined 2*H*-chromenes



Ar = Ph, *p*-tol, 4-OMe-C₆H₄, 4-Cl-C₆H₄,
4-F-C₆H₄, 2-naph, 3,5-diMe-C₆H₃



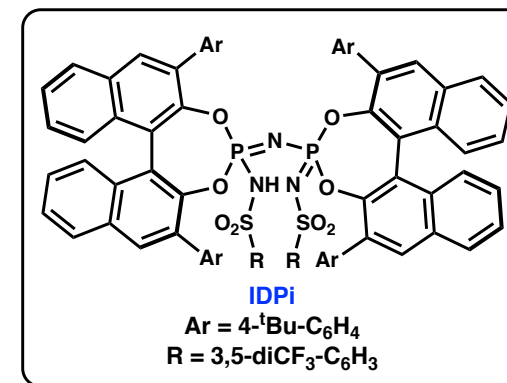
- First enantioselective pinacol rearrangement
- Likely H-bonding involved in key step



- Extremely acidic chiral acid

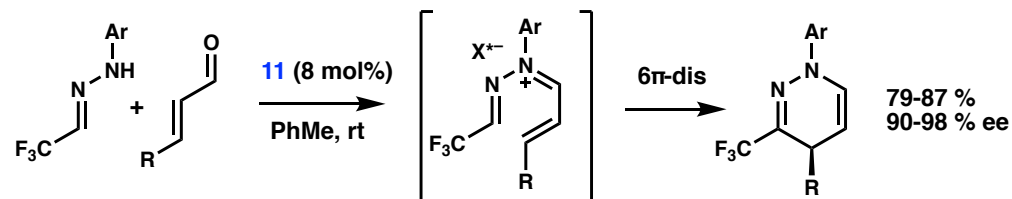
- pK_a MeCN : TRIPH (13.6), HCl (10.6), IDPi (~2), HOTf (0.7)

- Deep chiral pocket reminiscent of enzyme



Rueping. *JACS.* **2011**. 3732
Antilla. *Angew. Chem. Int. Ed.* **2010**. 9734
List. *Science.* **2018**. 1501

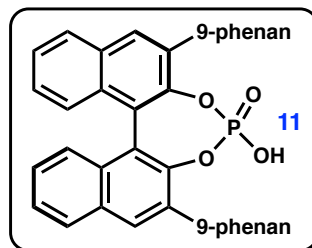
Electrocyclization



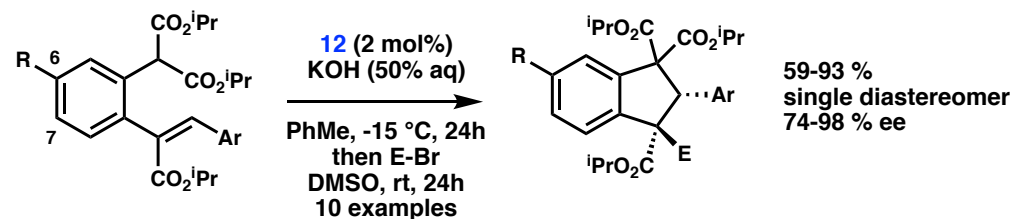
Ar = 4-Br-naph

R = Ph, 2-Br-C₆H₄, 2-Cl-C₆H₄, 2-OMe-C₆H₄,
2-NO₂-C₆H₄, 4-CO₂Me-C₆H₄,
4-CN-C₆H₄, 4-F-C₆H₄, 4-Br-C₆H₄, C₆F₅

- Controlling enantioselectivity in electrocyclizations is a challenging problem
- Simple and robust method

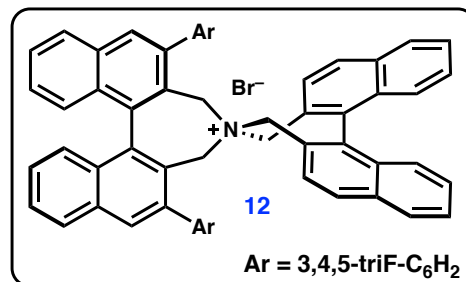
Rueping. *Angew. Chem. Int. Ed.* 2013. 8008

5-endo-trig

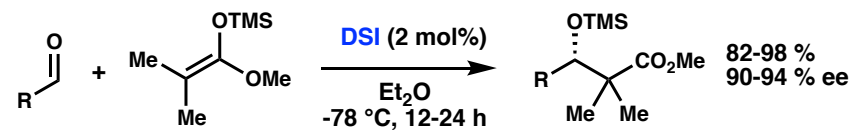
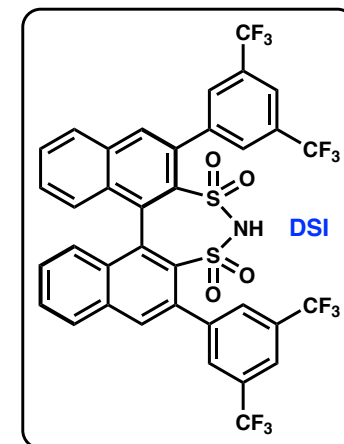
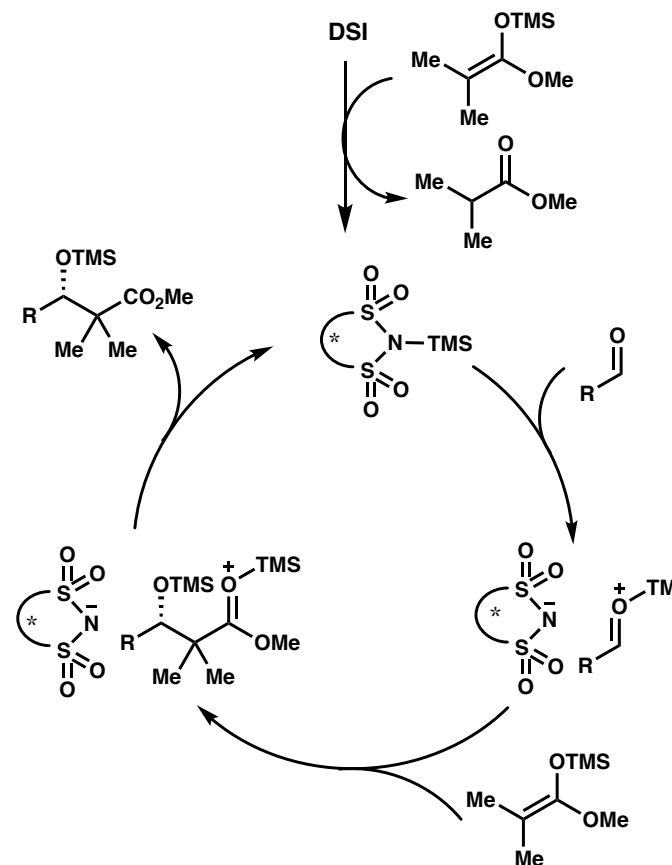


- Anti Baldwin 5-endo-trig cyclization previously unexplored for indane formation

- Heavy enantio-erosion seen with C7 substitution; catalyst substrate geometry optimization shows C7 hydrogen points into naphthyl wall

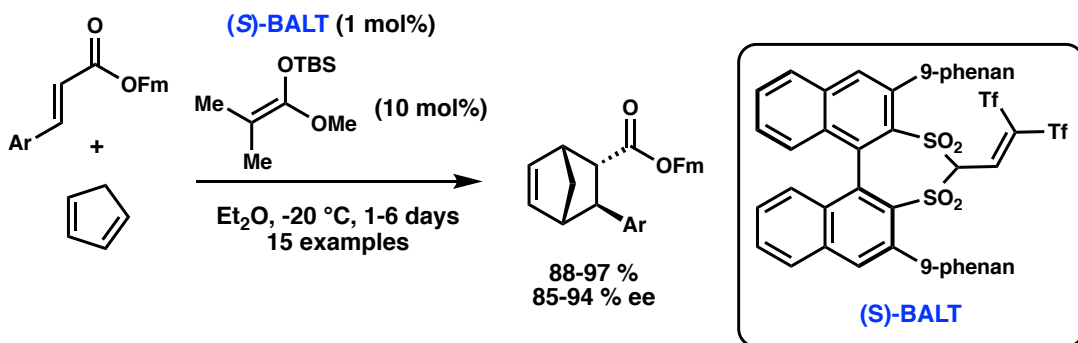
Smith. *Nat. Chem.* 2015. 171

Silylium ions

R = naph, 3,5-diOMe-Ph, *E*-styrene

- No correlation between Brønsted acidity of catalyst and reactivity
- NMR studies show rapid formation of silylated catalyst
- Reaction can proceed in the presence of hindered amine bases
- Catalyst loading can be dropped to 0.01 mol% in some cases with little loss of enantioselectivity and yield

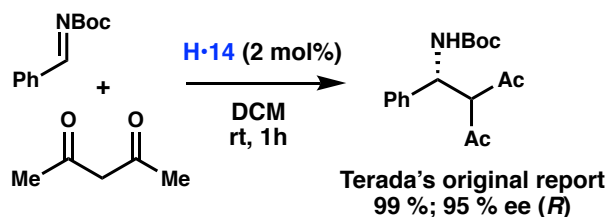
List. *Angew. Chem Int. Ed.* 2009. 4363



- Highly acidic chiral C-H acid required for activity and Lewis acidity
- $pK_{a \text{ MeCN}}$: TRIPH (13.6), HCl (10.6), DSI (8.4), BALT (2.8), IDPi (~2), HOTf (0.7)

List. *Science*. 2016. 949

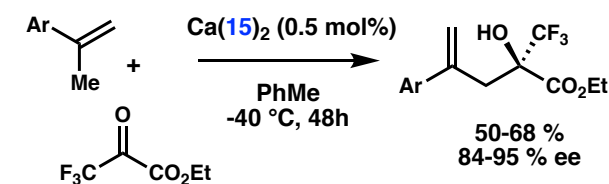
Lewis acids



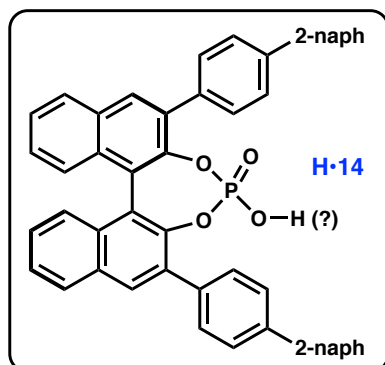
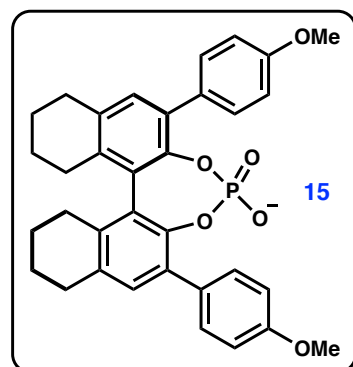
Terada reports a Brønsted catalysis method

Ishihara investigates:

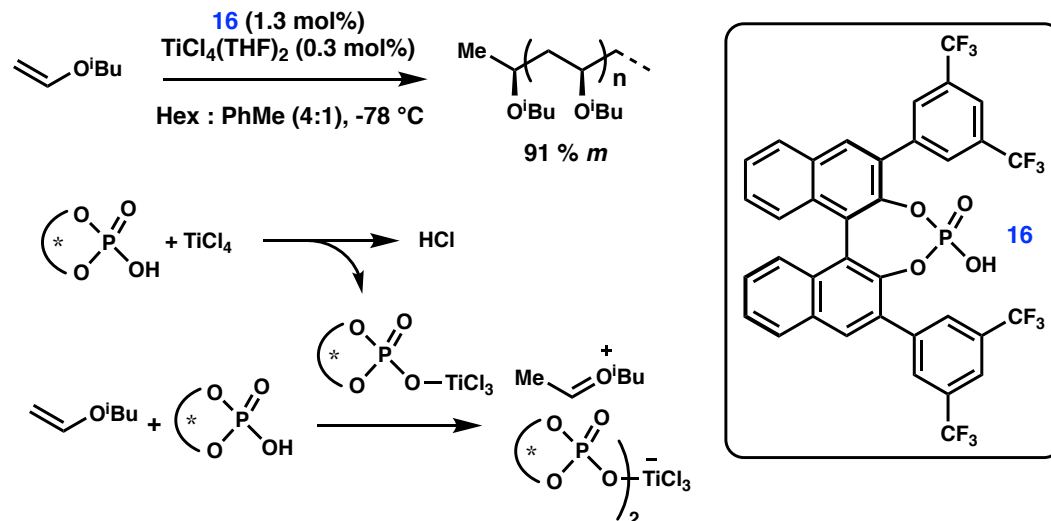
- H·14 purified on silica gel: 86 %; 92 % ee (*R*)
- H·14 washed with HCl: 88 %; 27 % ee (*S*)
- Ca(14)₂: 99%; 92% (*R*)

R = Ph, *p*-tol, *m*-tol, *p*-^tBu-C₆H₄, *p*-F-C₆H₄, 2-naph

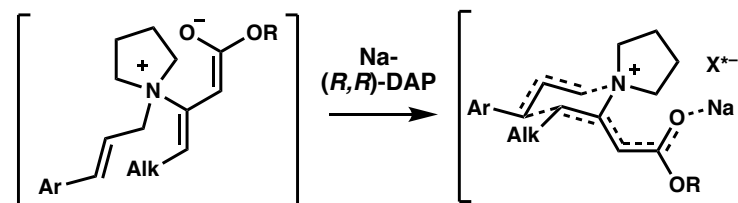
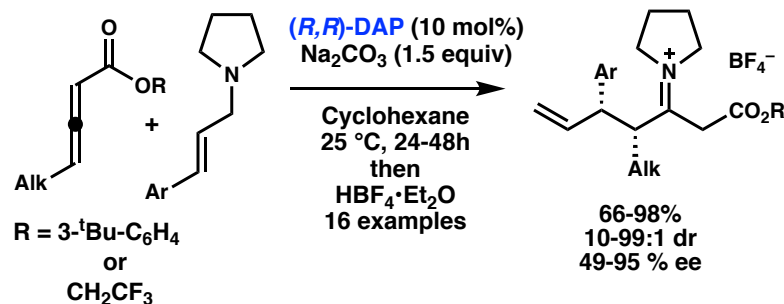
- Lewis acid activated carbonyl ene reaction

Which is the actual catalyst?
Most likely Ca(14)₂

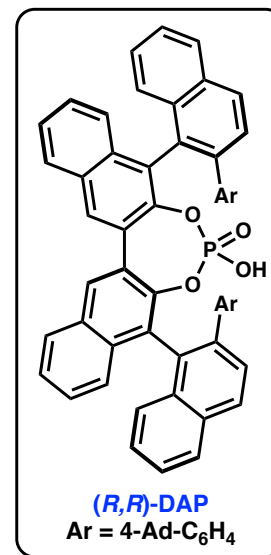
Terada. *JACS*. 2004. 5356
 Ishihara. *Angew. Chem. Int. Ed.* 2010. 3823
 Rueping. *Chem. Asian J.* 2012. 1195



- Selective general catalyst for many alkyl vinyl ethers, not achieved by other systems

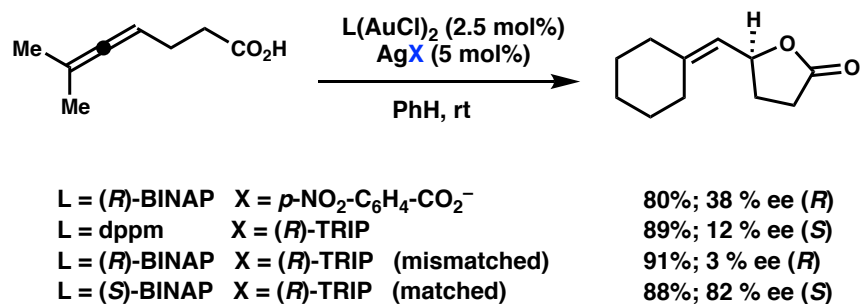
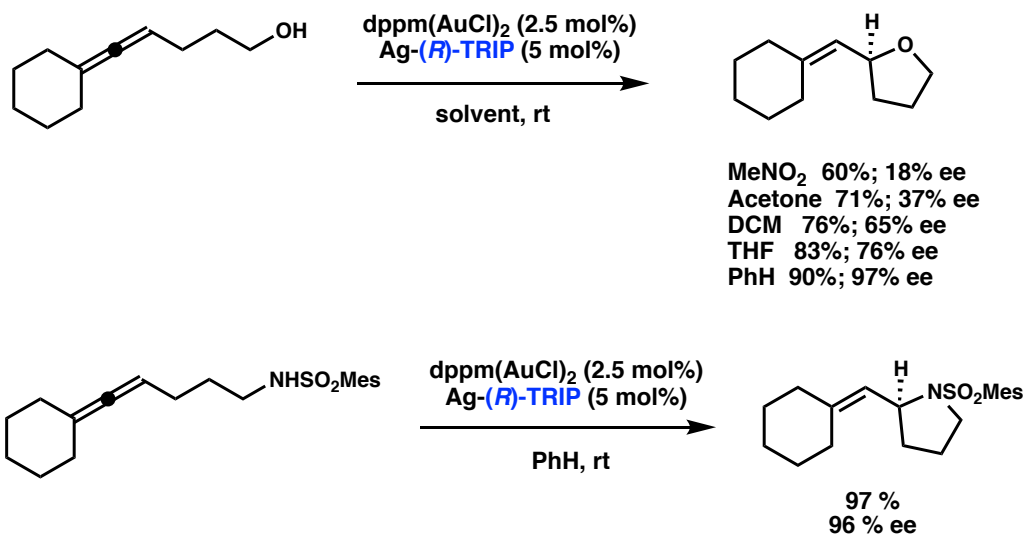


- Example of catalyst substrate interactions dominated by electrostatics
- Computation shows cation- π and π - π stacking interactions to be important for chiral organization

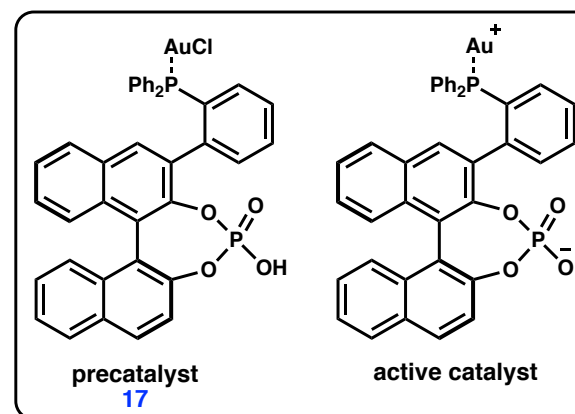
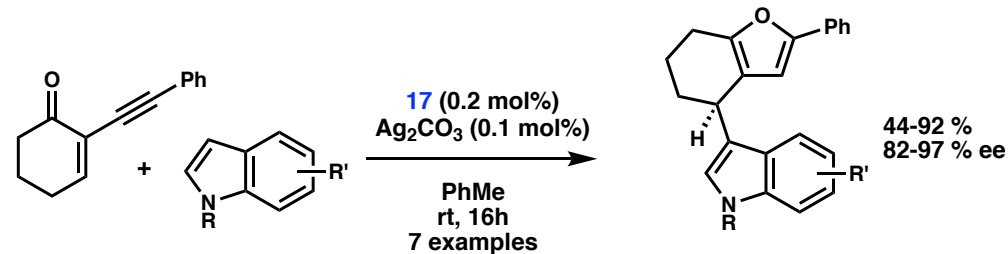
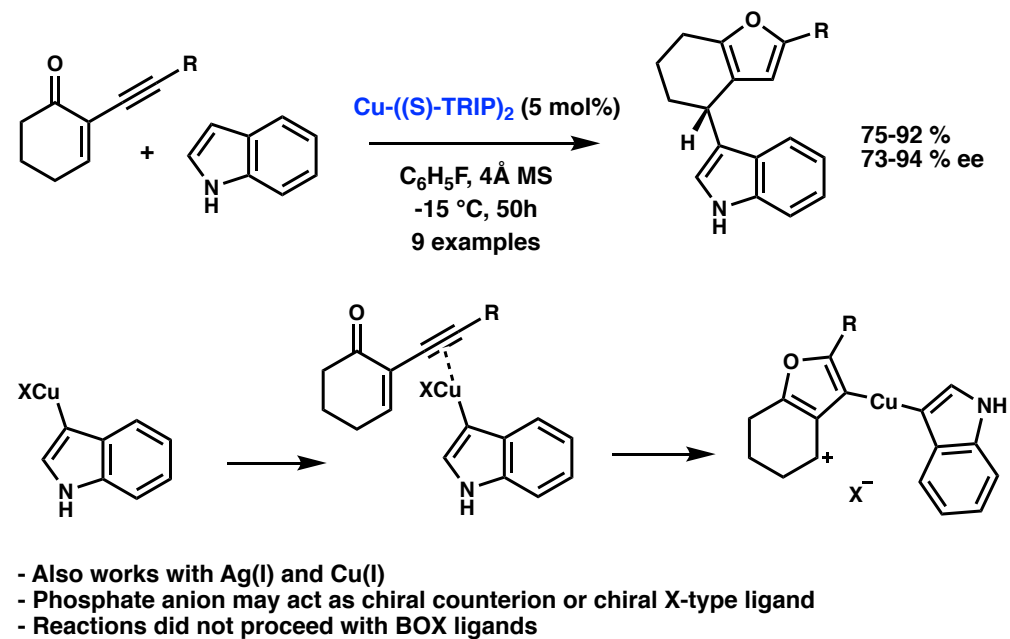


Leibfarth. *Science*. 2019. 1439
 Toste. *JACS*. 2020. 6390

Coinage metals

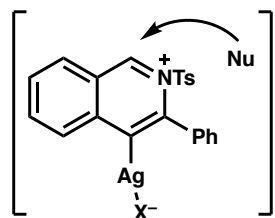
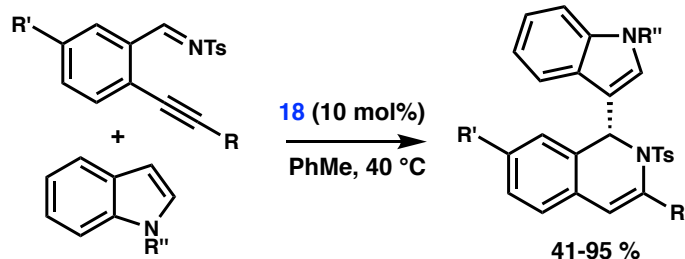
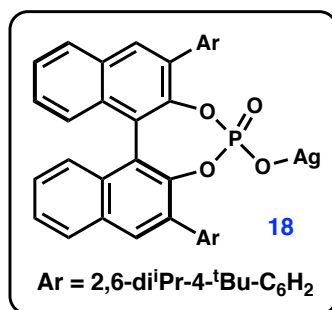


- First successful example of chiral counterion use in transition metal catalysis
- Clear example of synergistic ligand-counterion enantioinduction
- Gold is usually 2 coordinate (180 °) so counterion lends chiral bulk

Toste. *Science*. 2007. 496

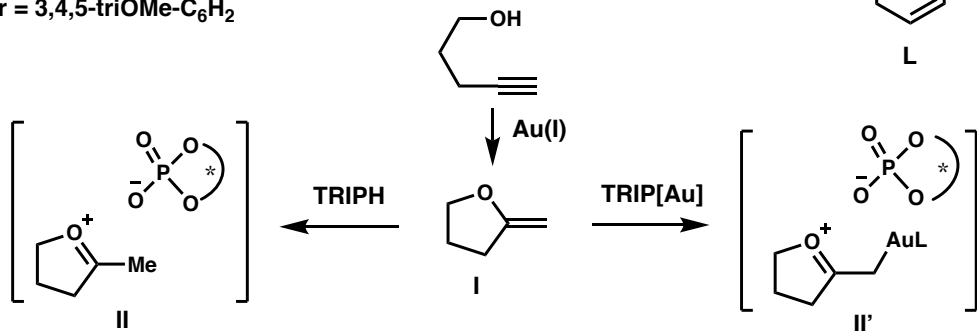
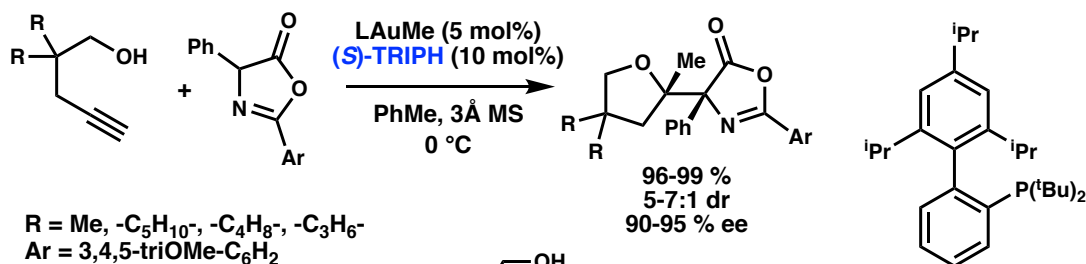
- Tethered counterion strategy
- Higher selectivity than untethered control experiments
- Can be done WITHOUT Ag (slightly lower yields)
- Highly rare to see chloride dissociation in Au catalysis

Toste. *JACS*. 2011. 8486
Guinchard. *JACS*. 2020. 3797



- R = Ph, R' = H, R'' = H; 56 % ee
- R = Ph, R' = F, R'' = H; 89 % ee
- R = ⁿBu, R' = H, R'' = H; 10 % ee
- R = cyclopropyl, R' = H, R'' = H; 54 % ee
- R = Ph, R' = H, R'' = Me; 59 % ee

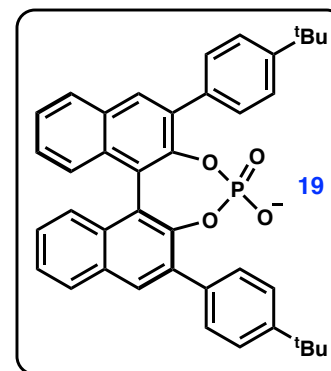
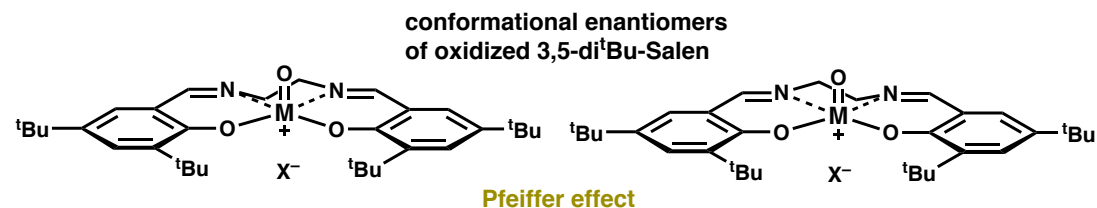
- Structural modifications of the reactive partners show that other secondary interactions may be more important than phosphate H-bonding to nucleophile



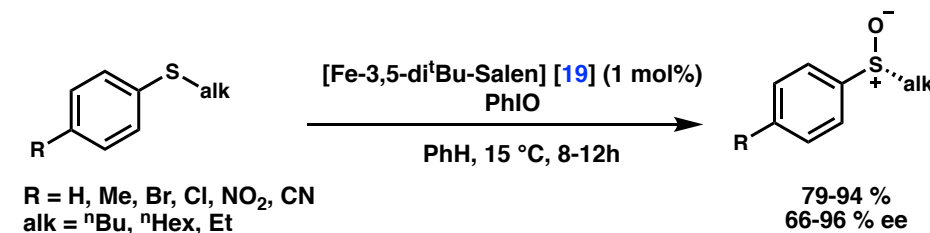
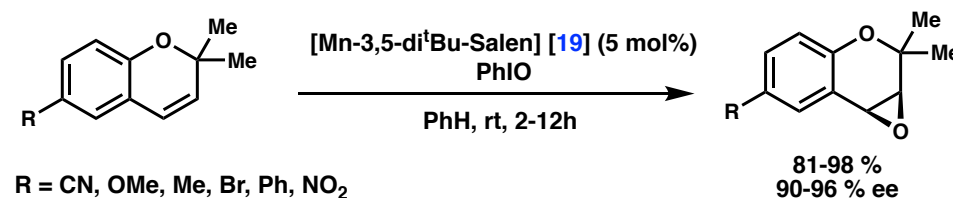
- Powerful relay gold catalysis to selectively generate vicinal quaternary stereocenters
- Experiments show that both intermediate ionic species (II and II') may be active

You. *Tetrahedron*. **2012**. 5263
Gong. *Tetrahedron Lett*. **2011**. 5963

Transition metal oxidations

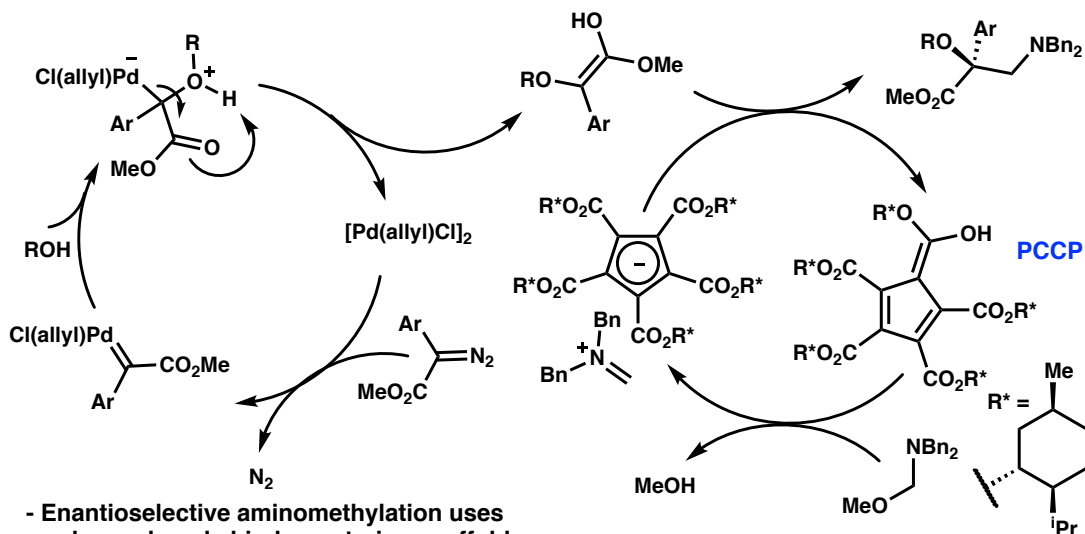
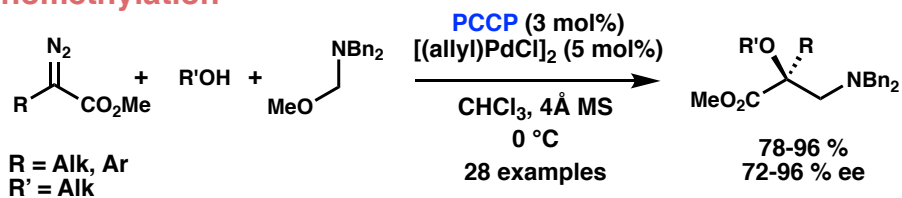


- Chiral anion thought to bias Salen conformation and provide additional surrounding chirality
- Phosphate thought to act as counterion since high reactivity is associated with "naked" catalyst



List. *Angew. Chem Int. Ed*. **2010**. 628
List. *Adv. Synth. Catal*. **2012**. 2363

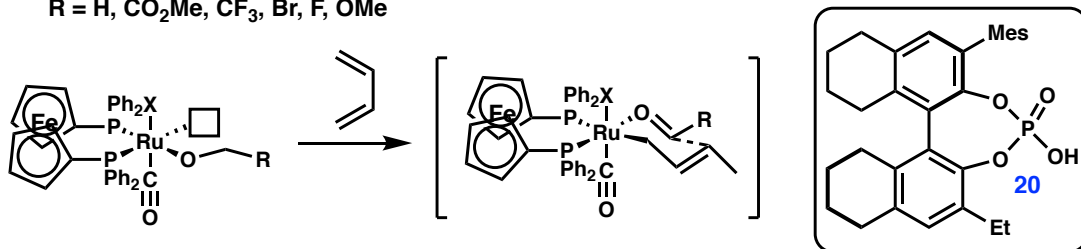
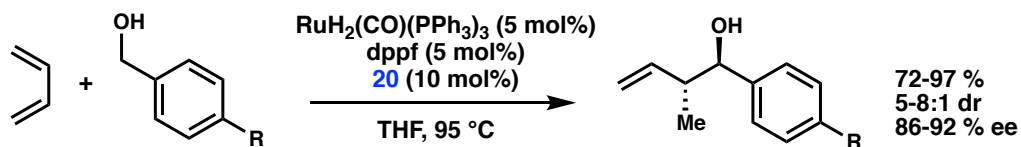
Aminomethylation



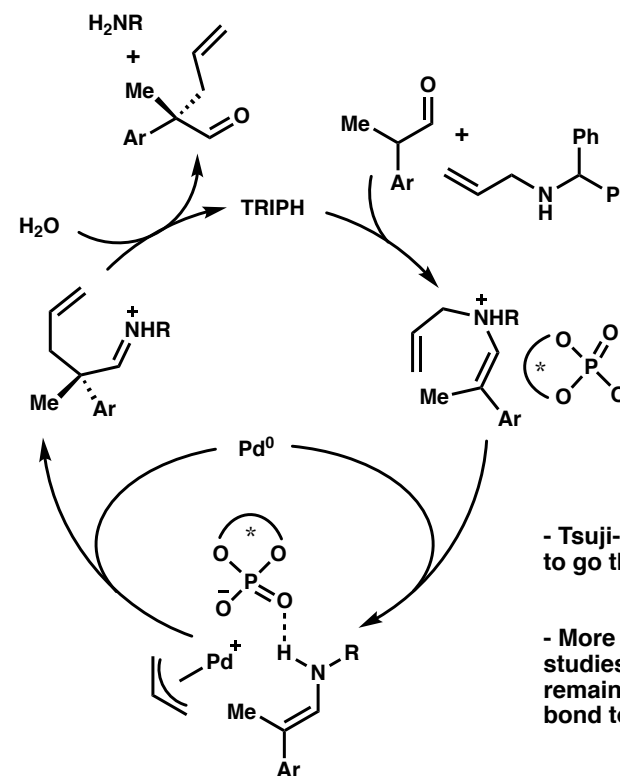
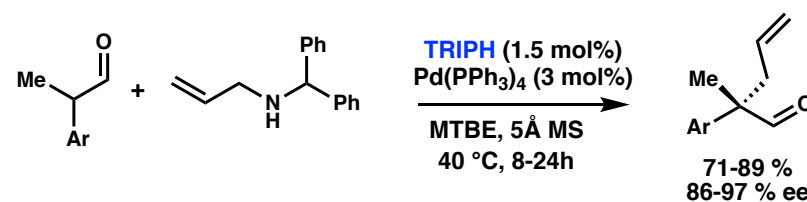
- Enantioselective aminomethylation uses rarely employed chiral counterion scaffold
- $\text{pK}_a \text{ MeCN} : \text{HCl (10.6), PCCP (8.8), HOTf (0.7)}$
- Chiral phosphoric acids gave < 51 % ee

Hu. *JACS*. 2019. 1473

Crotylation and allylation

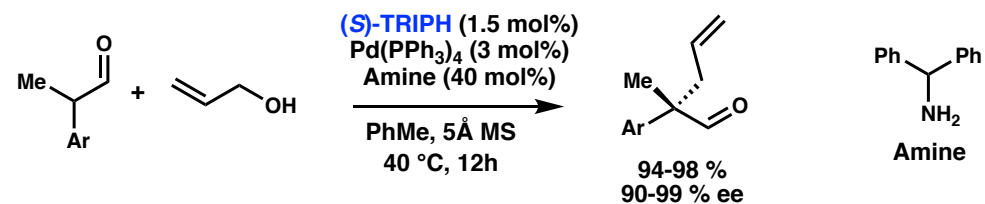


- Rare enantioselective crotylation using simple butadiene (by-product free)
- Transfer hydrogenation using alcohol as hydrogen source (in situ aldehyde formation)
- Counterion promotes (E)-σ-crotyl conformer in transition state

Krische. *Science*. 2012. 324

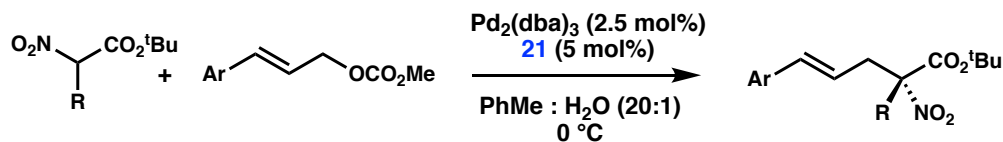
- Tsuji-Trost allylation accepted to go through cationic Pd

- More recent computational studies show that phosphate remains counterion with ionic H-bond to enamine

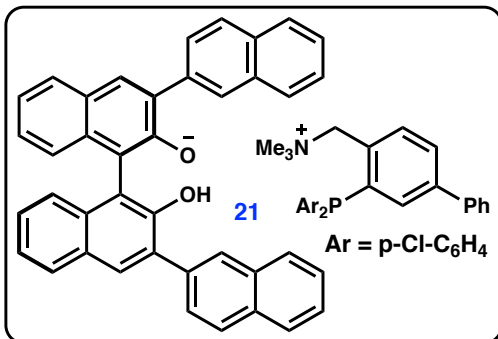


- Reaction proceeds without amine additive but with ee loss (10 % ee)
- Catalytic cycle remains similar but with TRIPH protonation of allyl alcohol to generate Pd-allyl

List. *JACS*. 2007. 11336
List. *Angew. Chem Int. Ed*. 2011. 9471
Sunoj. *JOC*. 2014. 7600



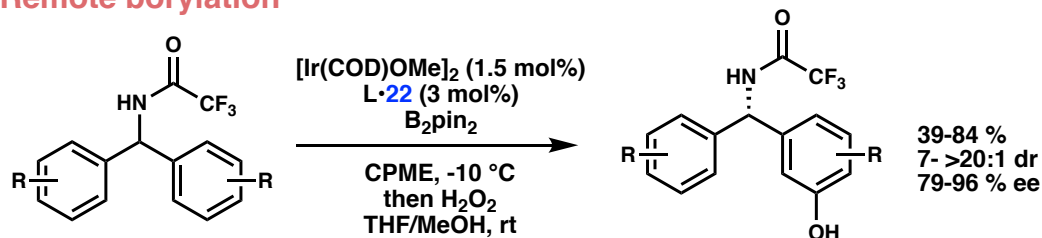
R = Me, Et, ⁱBu, ⁿHex, Bn
 Ar = Ph, *p*-Cl-C₆H₄, *p*-Br-C₆H₄, *p*-OMe-C₆H₄,
 2-naph, 2-thienyl



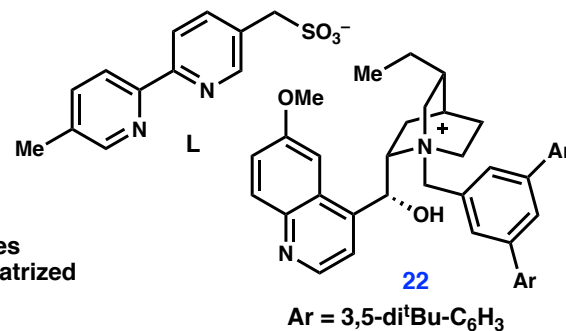
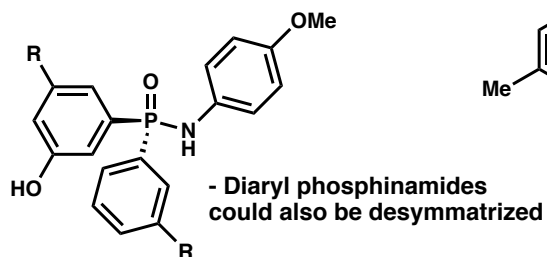
- Chiral anion pairs with achiral cationic ligand
- Allows for rapid modular screening with chiral anions
- Allows chiral anion to control anionic nucleophile
- Remaining BINOL proton likely important for directing nucleophile

Ooi. *Nat. Chem.* 2012. 473

Remote borylation



m-R = CF₃, F, Cl, Br, I, CO₂Et, OCF₃, CN
o-R = Cl, Br, CF₃

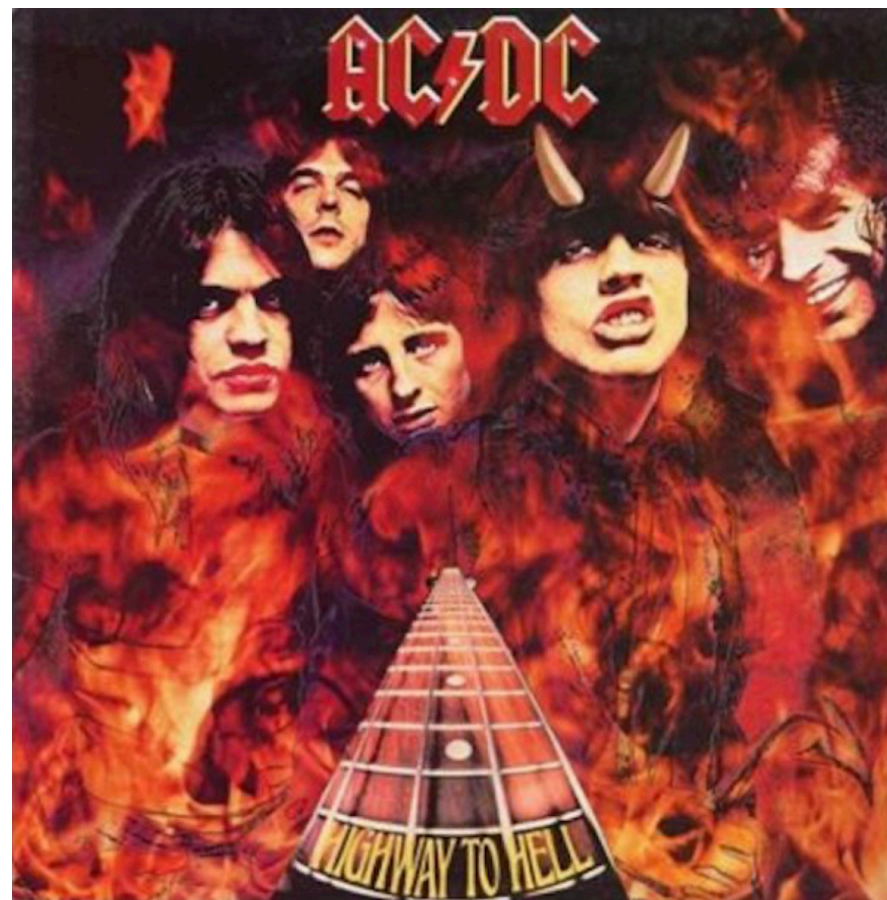


- Ionic linkages have the potential to be screened more rapidly
- Charged ligands may form stronger interactions with the substrate for better control
- Can allow for more distant functionalization

Phipps. *Science.* 2020. 1246

Summary

- Chiral counterion catalysis can be difficult due to inherent non-directionality
- Primary electrostatic interaction amplified at lower temperatures and in solvents with lower dielectric constants
- Many chiral counterions rely on secondary substrate interactions including H-bonding for better enantioinduction
- Synergistic chiral ligand - chiral counterion effects should be considered
- BINOL phosphates and the *Cinchona* alkaloids are the most used catalyst scaffolds by far. A young, growing field will see new innovative catalysts like PCCP and IDPi.
- Powerful strategy for transition states with charged character, BUT neutral ligands with ionic bonds also amenable to neutral transition states (ion pairing within the ligand)



“... ACDC is not “just” a hard rock band from Australia or a label for different types of electronic current.”
 – Benjamin List