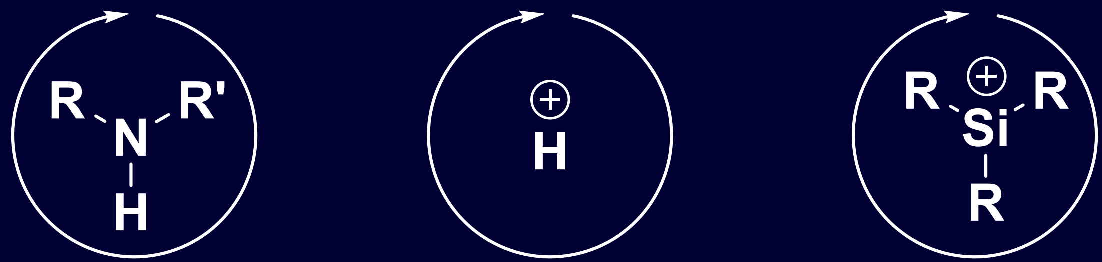
Benjamin List : From Enamine Catalysis to Brønsted-acid(Lewis-acid) Catalysis



Lingran Kong

College of Chemistry and Molecular Engineering

12/4/2021

Introduction

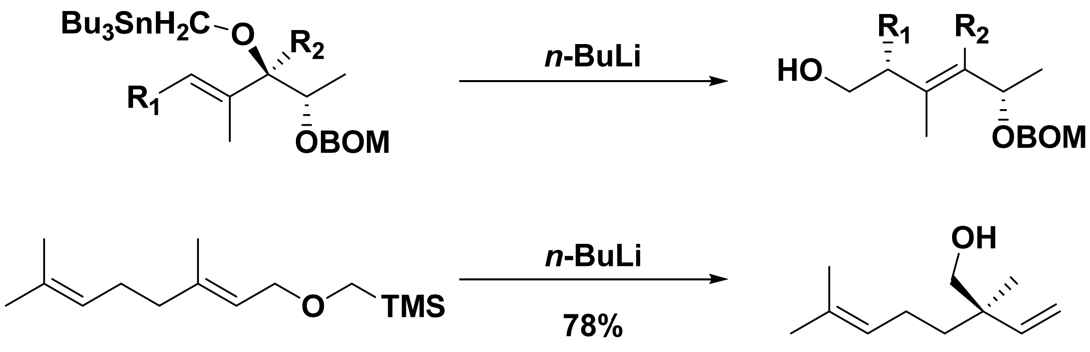
since 2003 Director at the Max-Planck-Institut für Kohlenforschung

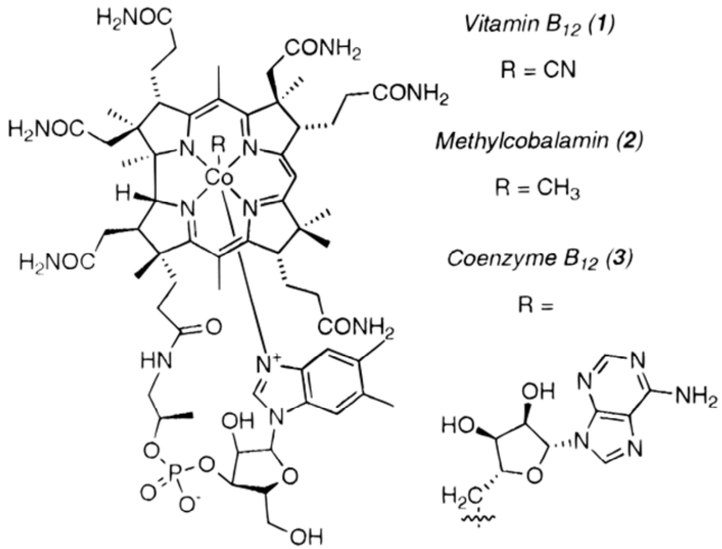
1999 - 2003 Assistant Professor, Scripps Research Institute

1993-1997 PhD, University Frankfurt (J. Mulzer)

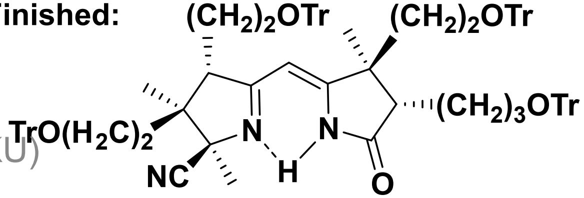
1993 Chemistry Diplom, Free University Berlin

1968 Born in Frankfurt/Germany



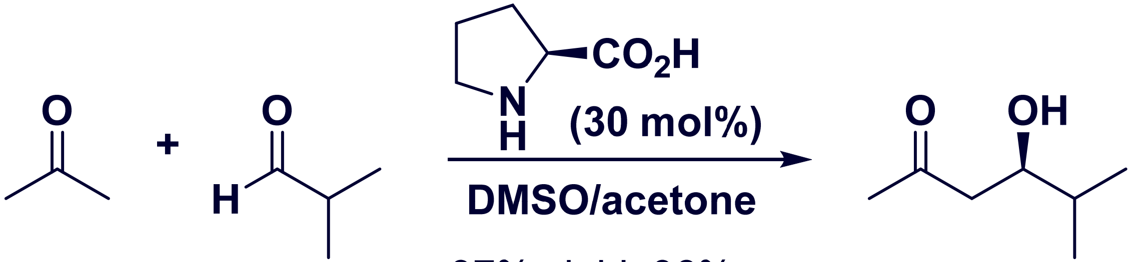


Finished:

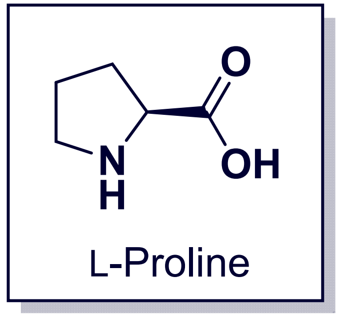


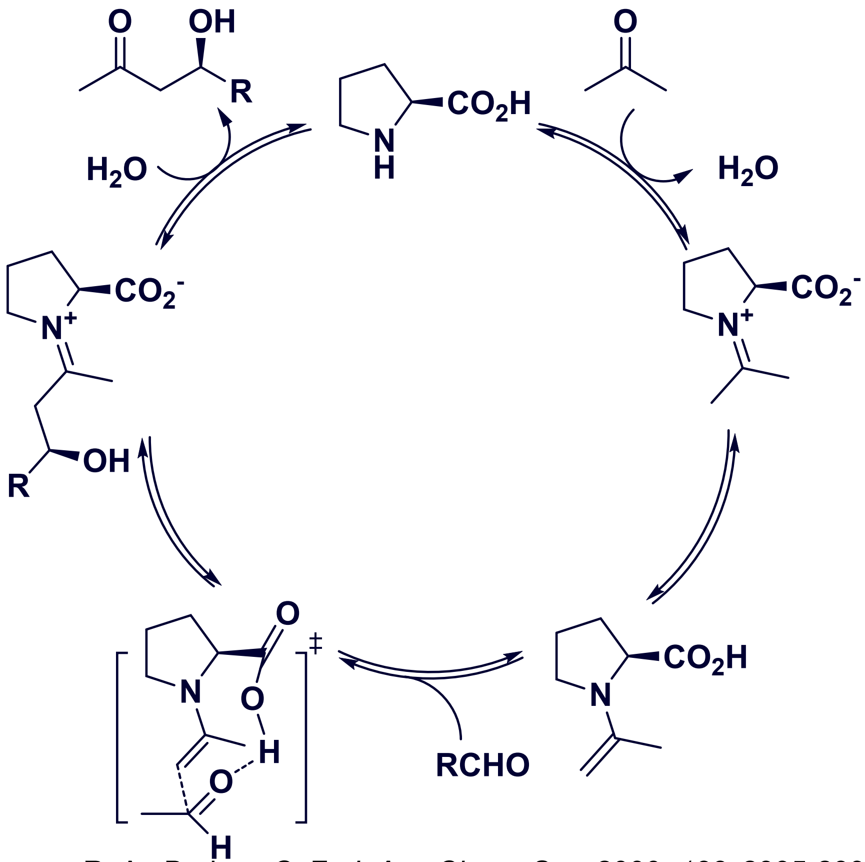
Mulzer, J.; List, B. *Tetrahedron Lett*. **1994**, *35*, 9021.
Mulzer, J.; List, B. *Tetrahedron Lett.* **1996**, *37*, 2403.
Mulzer, J.; List, B.; Bats, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 5512.

Proline Catalyzed Transformations



97% yield, 96% ee





Transformations Covered:

Aldol Rections

Mannich Reactions

Michael Reactions

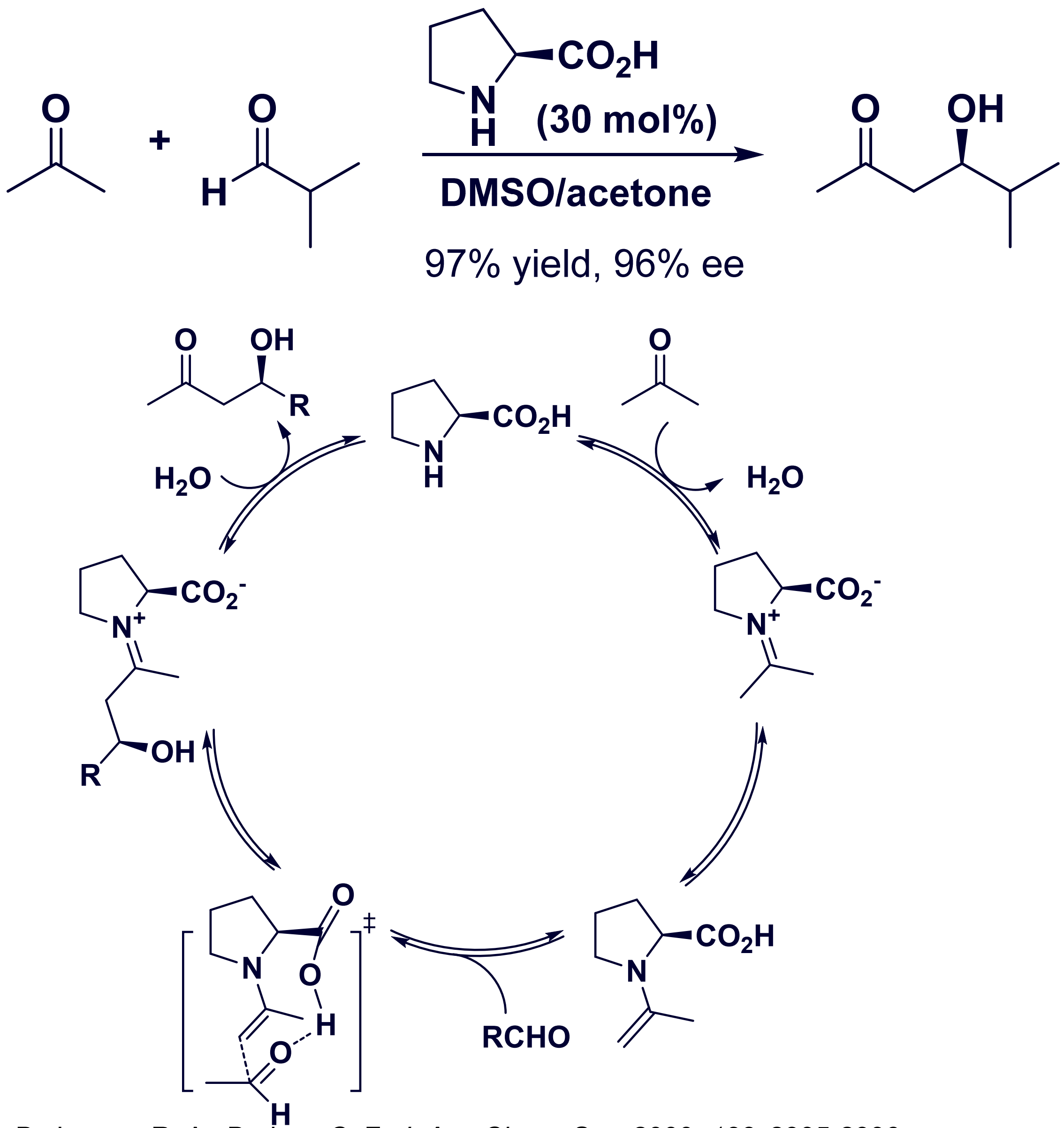
A lot of other

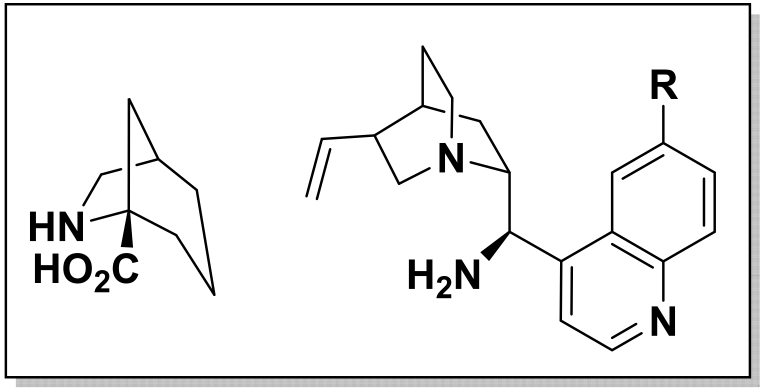
transformations

List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, 107, 5471-5569.

Other Chiral Amines Catalyzed Transformations





Transformations Covered:

Alkylation

Epoxidation

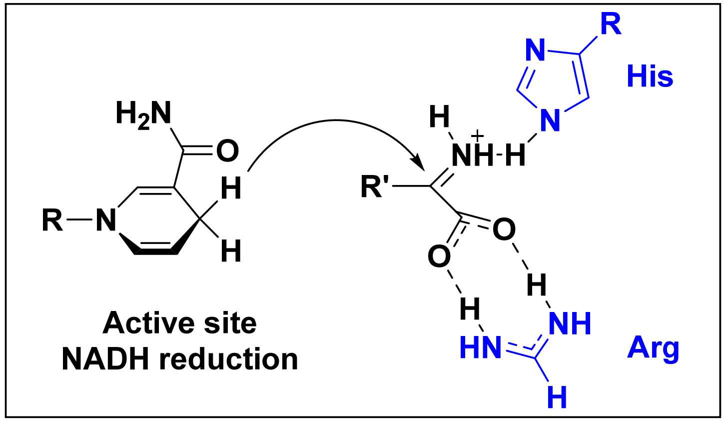
A lot of other transformations

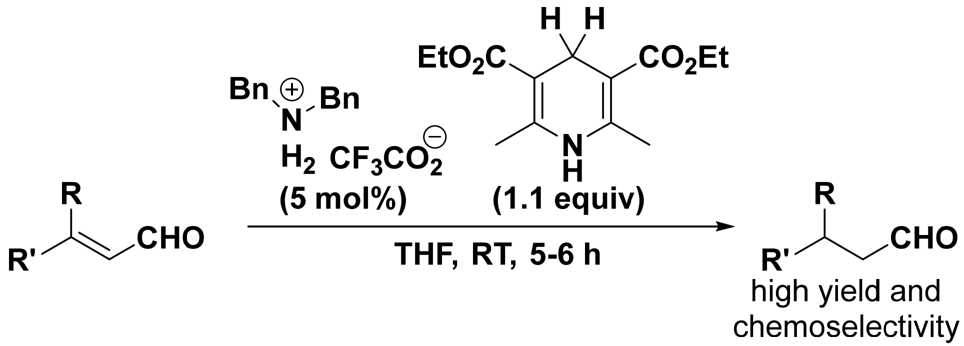
List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.

Mahlau, M.; List, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 518.

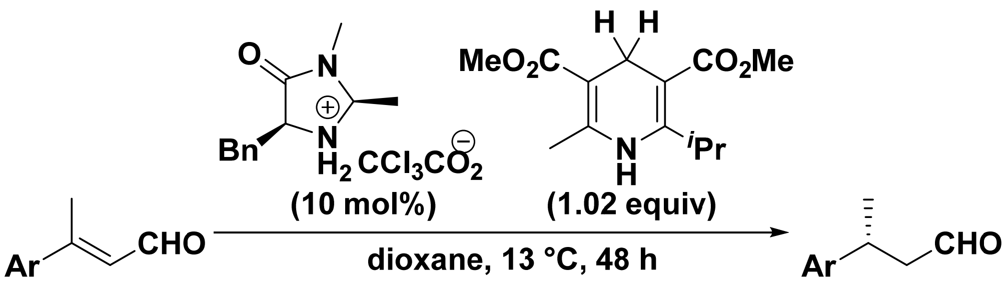
Asymmetric Transfer Hydrogenation

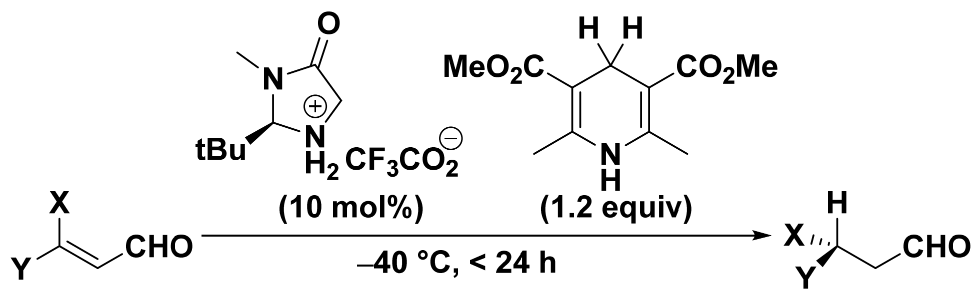
NADH: Natures Reduction (Hydrogenation)
Reagent (Coenzyme)





List, B. et al. *Angew. Chem. Int. Ed*. **2004**, *43*, 6660. Received: August 28, 2004



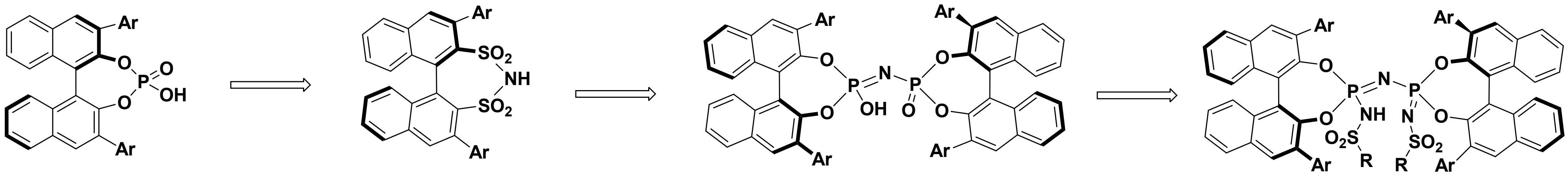


List, B. et al. *Angew. Chem. Int. Ed*. **2005**, *44*, 108.
Received: October 26, 2004

Macmillan, D. W. C. et al. *J. Am. Chem. Soc*. **2005**, *127*, 32.
Received: October 10, 2004

Chiral Phosphoric Acid: Bifunctional Activation

Organocatalysts developed by List group：

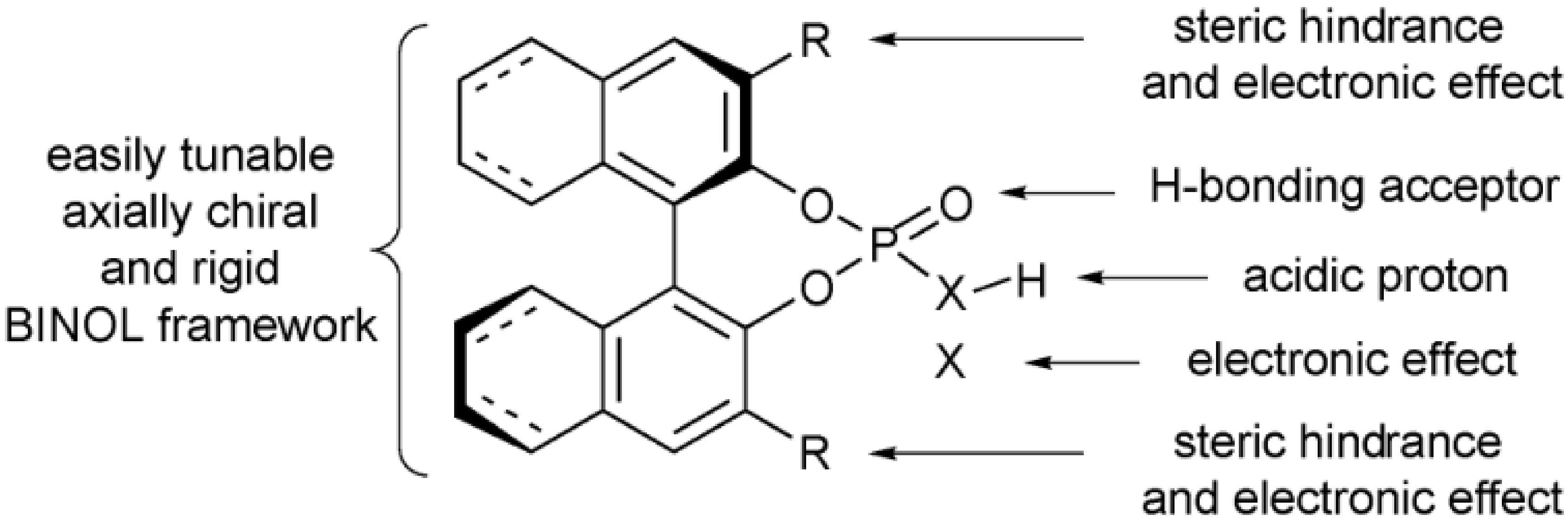


Ar = phenanthryl
pKa = 13.3 (MeCN)

Disulfonimides (DSI)
pKa = 8.4 (MeCN)

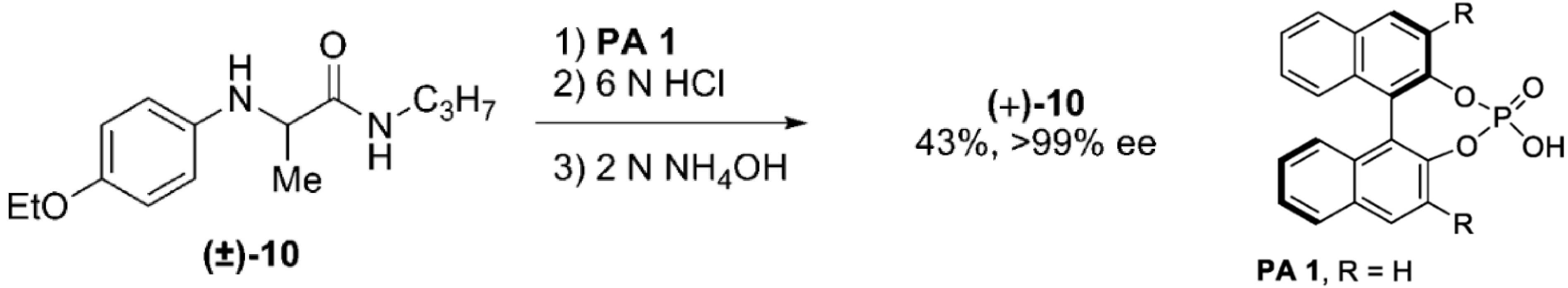
Imidodiphosphates (IDP)
pKa = 11.5 (MeCN)

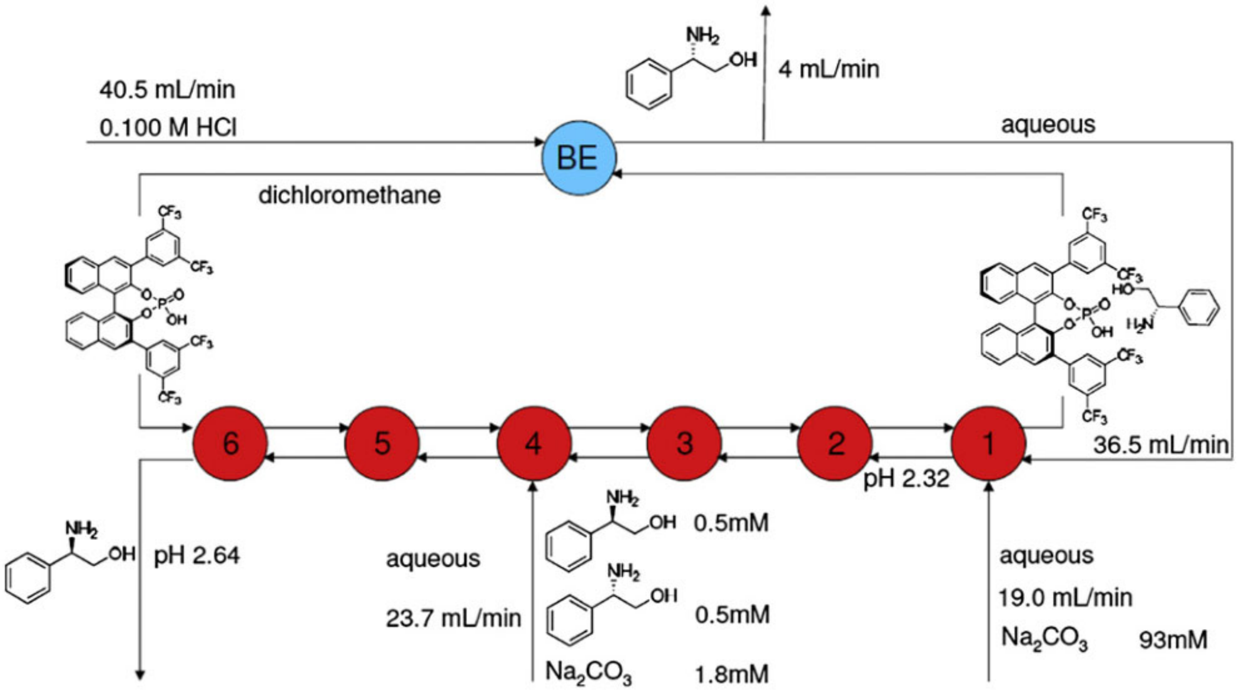
Imidodiphorimidates (IDPi)
pKa = 4.5 to <2.0 (MeCN)

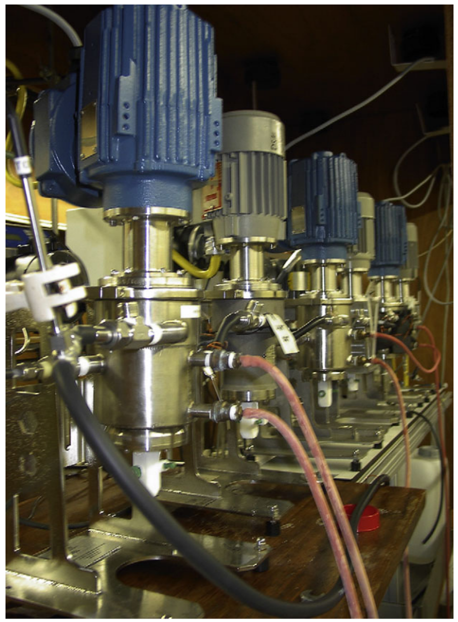


Chiral Phosphoric Acid

- 1971: Chiral phosphoric acid were used as resolving agents for chiral amines



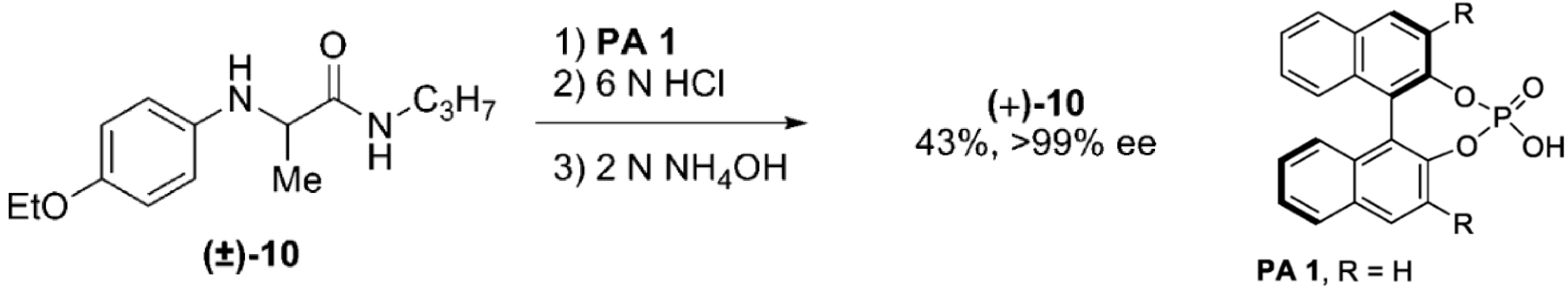




Jacques, J.; Fouquey, C.; Viterbo, R. *Tetrahedron Lett*. **1971**, *4617*.
Wilen, S. H.; Qi, J. Z.; Williard, P. G. *J. Org. Chem*. **1991**, *56*, 485.
Schuur, B.; Verkuijl, B. J. V.; Bokhove, J.; Minnaard, A. J.; de Vries, J. G.; Heeres, H. J.; Feringa, B. L. *Tetrahedron*. **2011**, *67*, 462.

Chiral Phosphoric Acid

- 1971: Chiral phosphoric acid were used as resolving agents for chiral amines

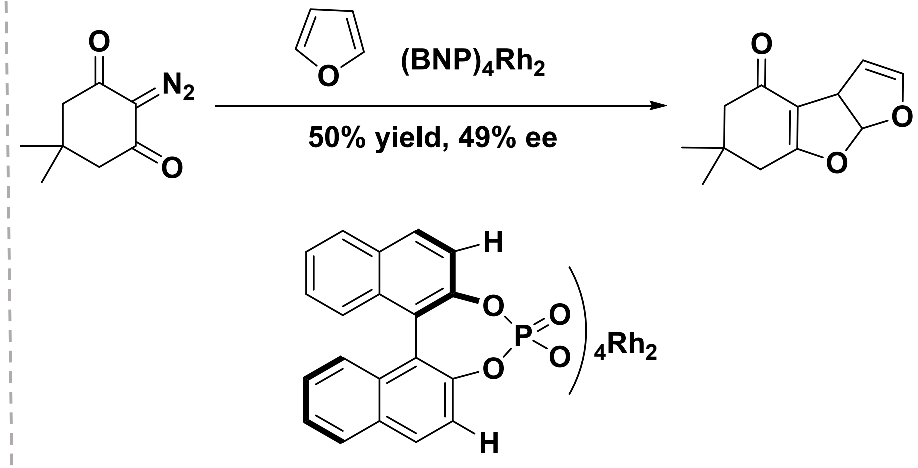


- From 1990s: Chiral phosphoric acid were used as ligands in transition-metal catalysis

$$RCH{=}CH_2 + CO + H_2O \xrightarrow[PdCl_2,\ CuCl_2,\ HCl,\ \text{room temperature, 1 atm}]{O_2,\ THF,\ L^*} RC^*H(CH_3)COOH \quad (2)$$

Table I. Hydrocarboxylation of *p*-Isobutylstyrene (**1**) and 2-Vinyl-6-methoxynaphthalene (**2**)

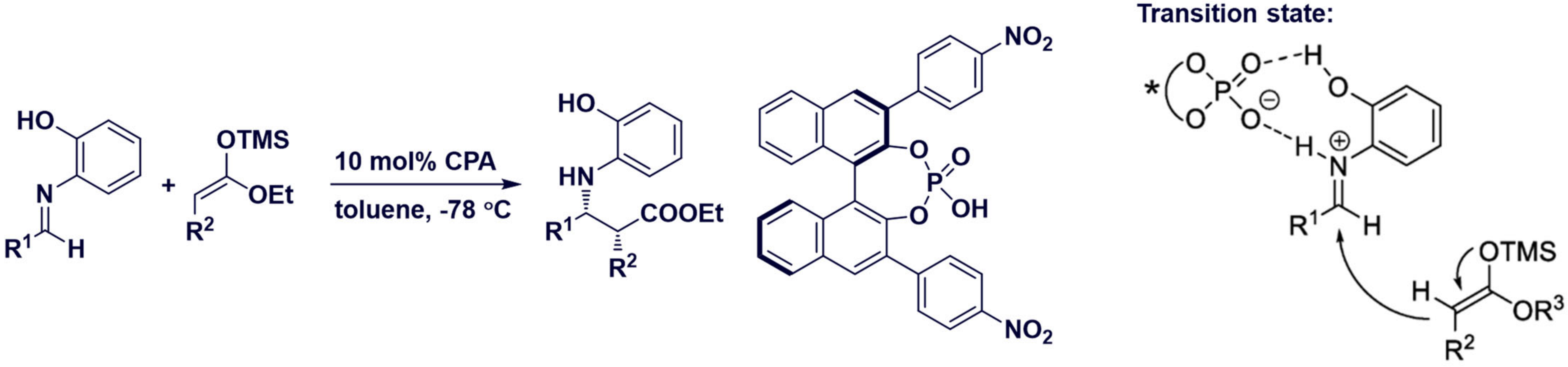
substrate	L*	**1** (or **2**)/ L*/$PdCl_2$	product yield,[a] %	optical yield,[b] %
1	(*S*)-BNPPA	7.7/0.38/1.0	89	83 (*S*)
	(*S*)-BNPPA	7.7/0.77/1.0	80	55 (*S*)
	(*R*)-BNPPA	7.7/0.38/1.0	81	84 (*R*)
2	(*S*)-BNPPA	4.2/0.42/1.0	46	72 (*S*)
	(*S*)-BNPPA	10/0.5/1.0	71	85 (*S*)
	(*R*)-BNPPA	4.2/0.42/1.0	48	76 (*R*)
	(*R*)-BNPPA	7.7/0.38/1.0	64	91 (*R*)



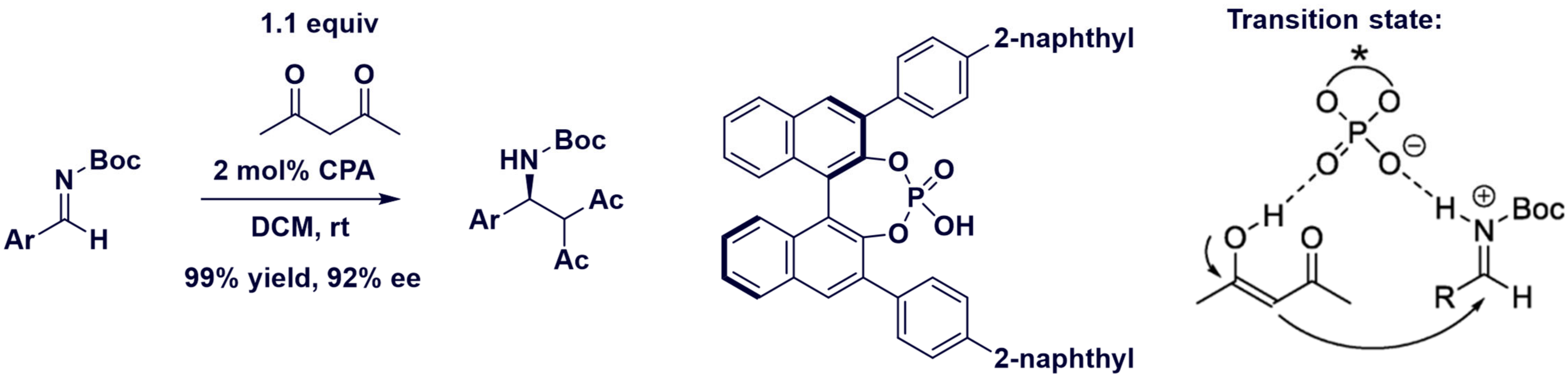
Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803.
Pirrung, M. C.; Zhang, J. *Tetrahedron Lett.* **1992**, *33*, 5987.
Inanaga, J.; Furuno, H.; Hayano, T. *Chem. Rev.* **2002**, *102*, 2211.

Chiral Phosphoric Acid: Organocatalysts

- 2004: Chiral phosphoric acid were used as organocatalysts



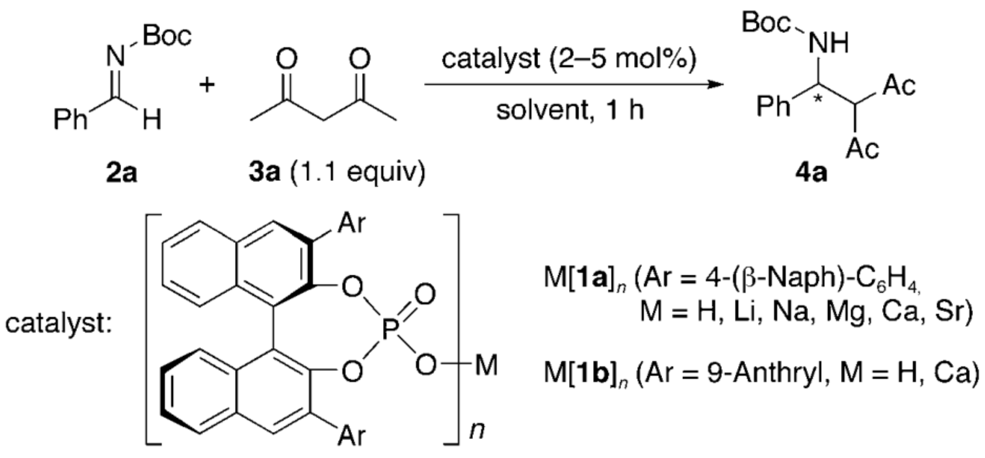
Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566.
Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc*. **2007**, *129*, 6756.

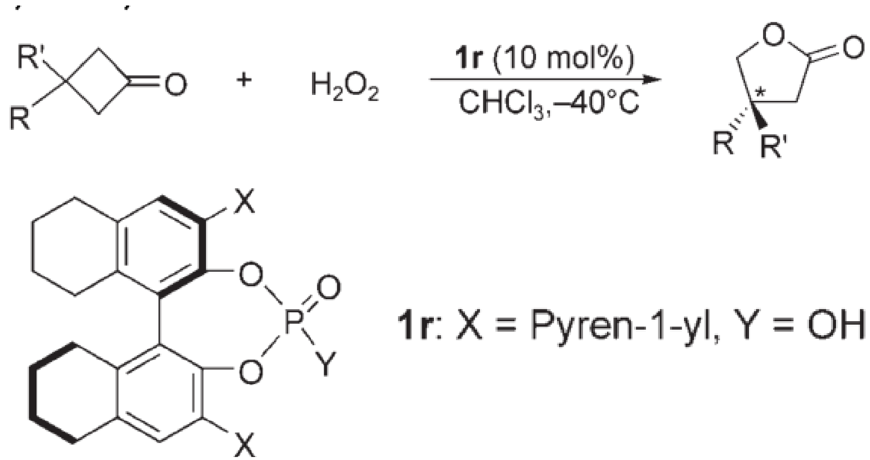


Uraguchi, D.; Terada, M. *J. Am. Chem. Soc*. **2004**, *126*, 5356.
Simón, L.; Goodman, J. M. *J. Org. Chem.* **2011**, *76*, 1775.

Actual Catalyst: Chiral Phosphoric Acid or Chiral Calcium Phosphate？

- BINOL-derived phosphoric acids are readily neutralized to alkali or alkaline-earth metal salts by purification on silica gel





Entry	Catalyst (mol %)[a]	Solvent	T [°C]	Yield [%][b]	*ee* [%][c] (config.)
1	Li[**1a**] (5)	CH_2Cl_2	RT	99	11 (*S*)
2	Na[**1a**] (5)	CH_2Cl_2	RT	88	9 (*S*)
3	Mg[**1a**]$_2$ (2.5)	CH_2Cl_2	RT	> 99	43 (*R*)
4	Ca[**1a**]$_2$ (2.5)	CH_2Cl_2	RT	> 99	92 (*R*)
5	Sr[**1a**]$_2$ (2.5)	CH_2Cl_2	RT	> 99	59 (*R*)
6	H[**1a**] purified on silica gel (2)	CH_2Cl_2	RT	86[d]	92 (*R*)[d]
7	H[**1a**] washed with HCl (2)	CH_2Cl_2	RT	88	27 (*S*)
8	H[**1b**] washed with HCl (5)	CH_2Cl_2	RT	> 99	49 (*S*)
9[e]	H[**1b**] washed with HCl (5)	toluene	−30	> 99	93 (*S*)
10	Ca[**1b**]$_2$ (2.5)	CH_2Cl_2	RT	93	30 (*S*)

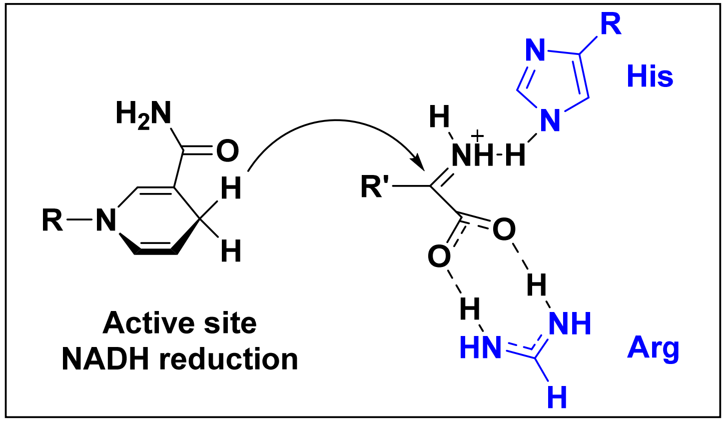
Interestingly, when catalyst **1r** was washed with 4 N HCl and water prior to use, its activity was significantly improved without loss of enantioselectivity (Table 1, entry 20). The exact reason for the improvement of the activity is not yet clear, but it might be attributed to the removal of some trace amounts of impurities that poison the catalyst.

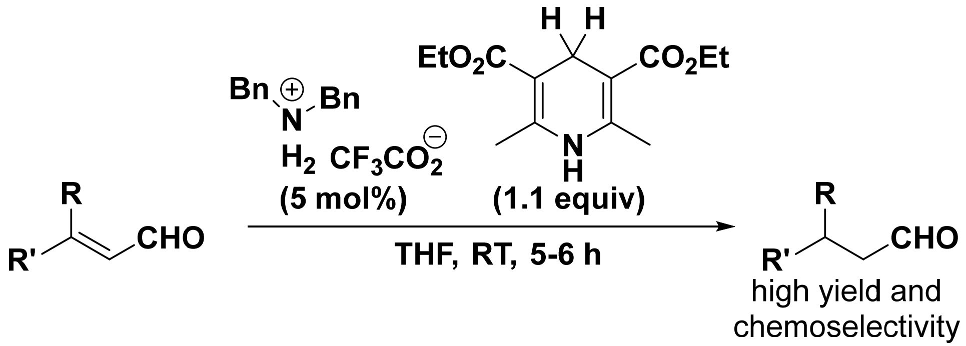
- Key to receiving the free acid in pure form was a thorough washing of CPA with hydrochloric acid after the final step

a) Hatano, M.; Moriyama, K.; Maki, T.; Ishihara, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 3823. b) Xu, S.; Wang, Z.; Zhang, X.; Zhang, X.; Ding, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 2840. c) Klussmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. *Synlett.* **2010**, 2189. d) Parmar, D.; Sugion, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047.

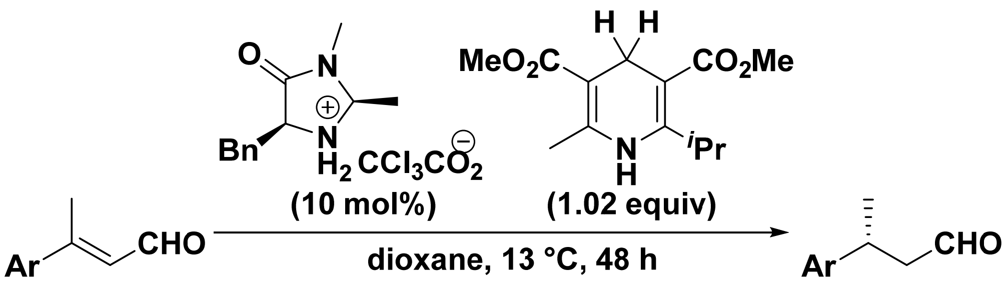
Asymmetric Transfer Hydrogenation

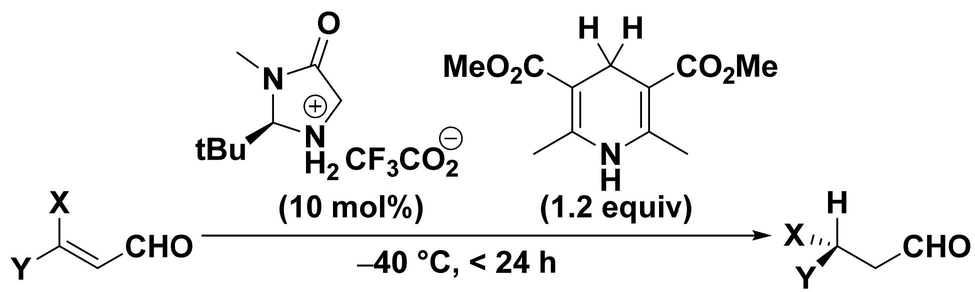
NADH: Natures Reduction (Hydrogenation)
Reagent (Coenzyme)





List, B. et al. *Angew. Chem. Int. Ed*. **2004**, *43*, 6660. Received: August 28, 2004

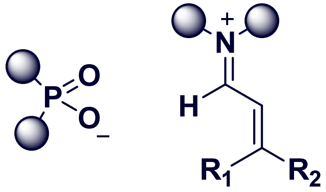




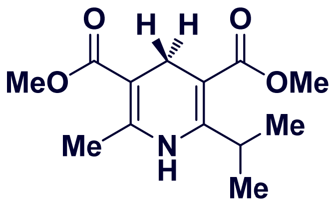
List, B. et al. *Angew. Chem. Int. Ed*. **2005**, *44*, 108.
Received: October 26, 2004

Macmillan, D. W. C. et al. *J. Am. Chem. Soc*. **2005**, *127*, 32.
Received: October 10, 2004

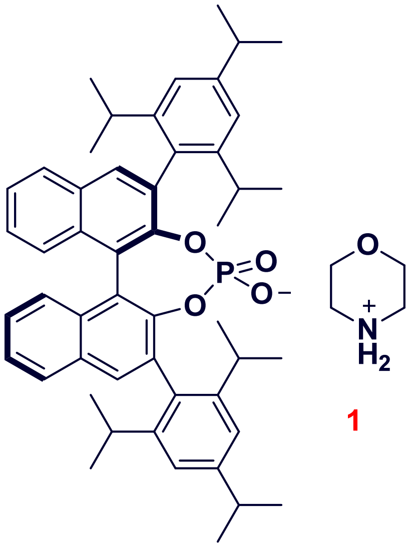
List: Asymmetric Counteranion-Directed Catalysis(ACDC)



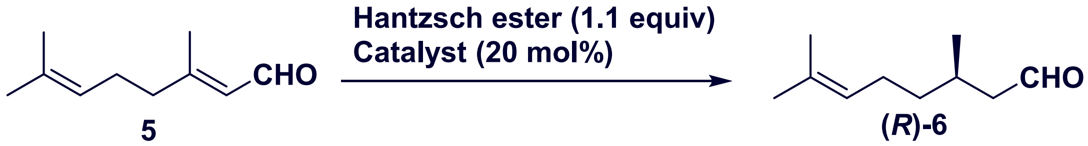
chiral counteranion

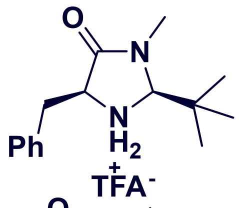
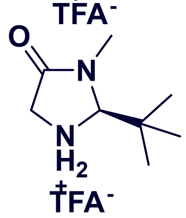


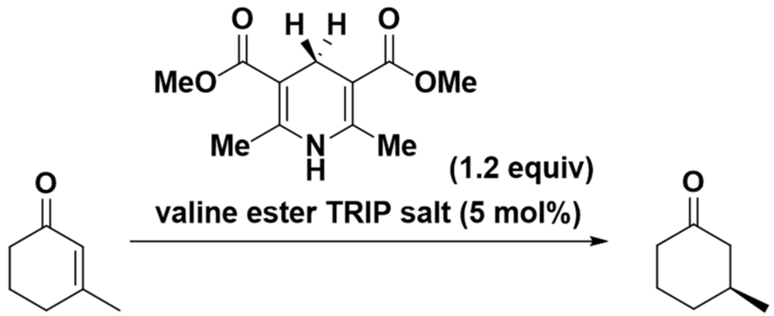
Hantzsch Ester



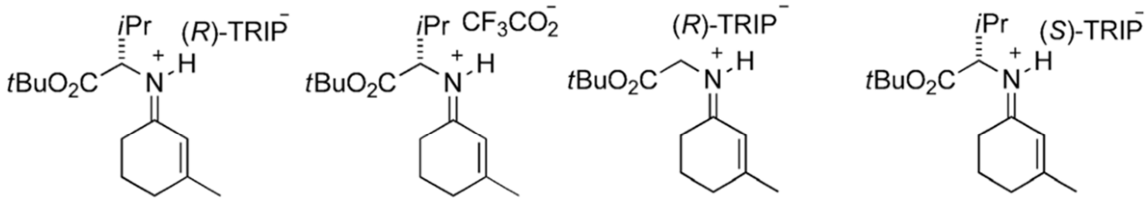
1



Catalyst	Product	Yield [%]	e.r.
	(*S*)-6	58	70:30
	(*S*)-6	82	70:30
1	(*R*)-6	71	95:5



chiral ion-pair intermediates:

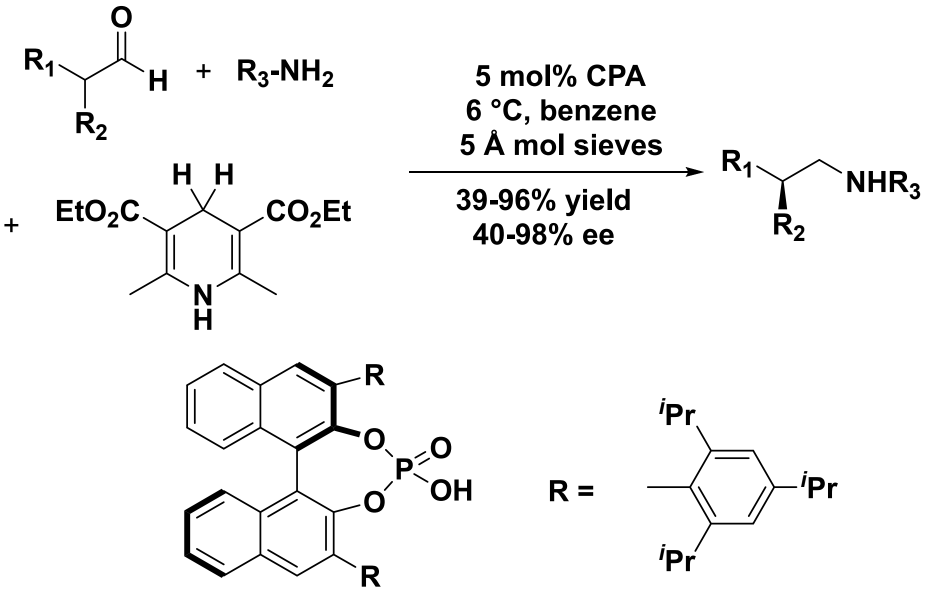


26a	26b	26c	26d
e.r. 97:3	e.r. 77:23	e.r. 76:24	e.r. 58:42
optimal	achiral anion	achiral cation	mismatch

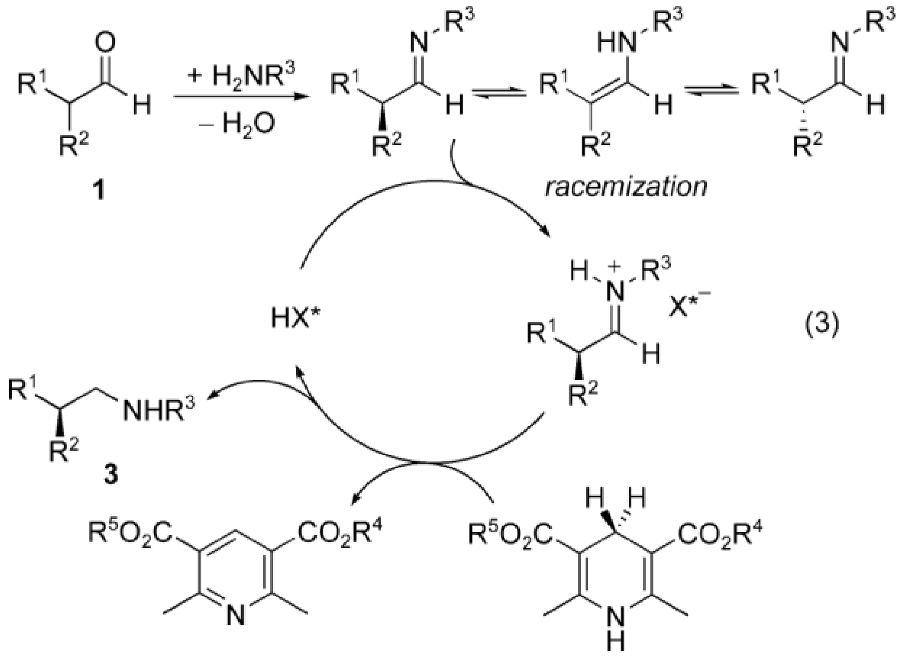
Mayer, B.; List, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 4193.
Martin, N. J. A.,; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368.

Reductive Amination

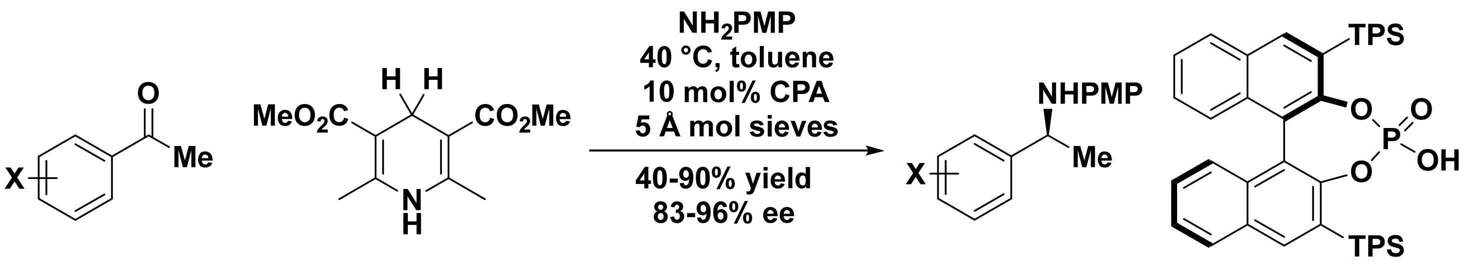
➢ Dynamic kinetic resolution via reductive amination by List

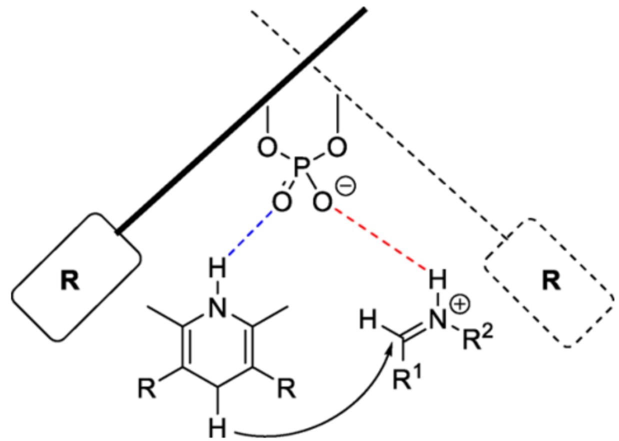


TRIP



Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074.

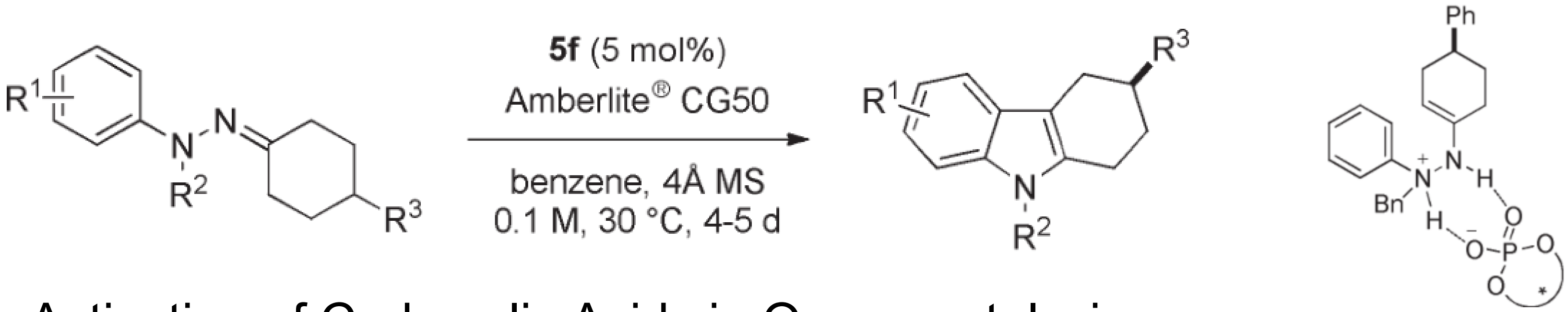




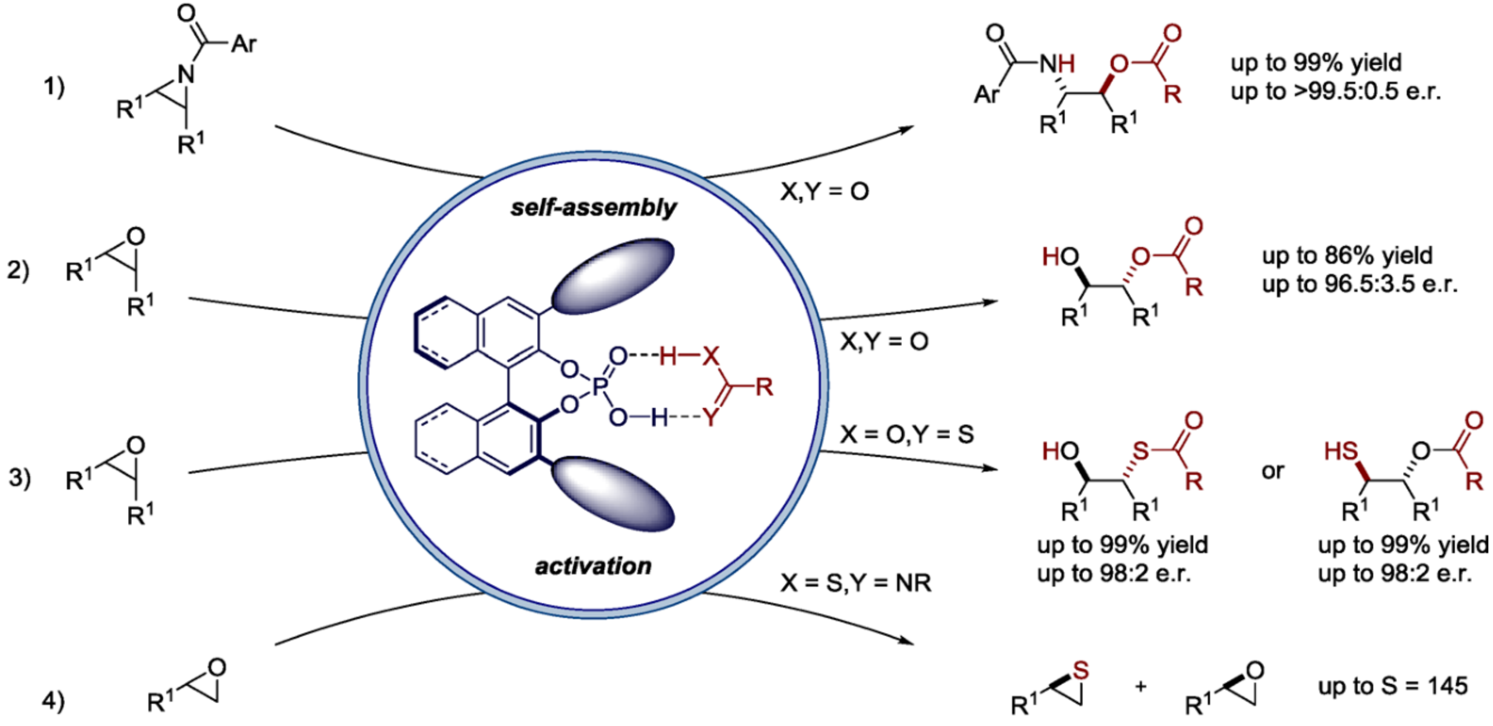
Storer, R. I.; Carrera, D. E.; Ni, Y.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84.
Simón, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 8741.
Marcelli, T.; Hammar, P.; Himo, F. *Chem. Eur. J.* **2008**, *14*, 8562.

Chiral Phosphoric Acid Catalytic Asymmetric Transformations

- Catalytic Asymmetric Fischer Indolization



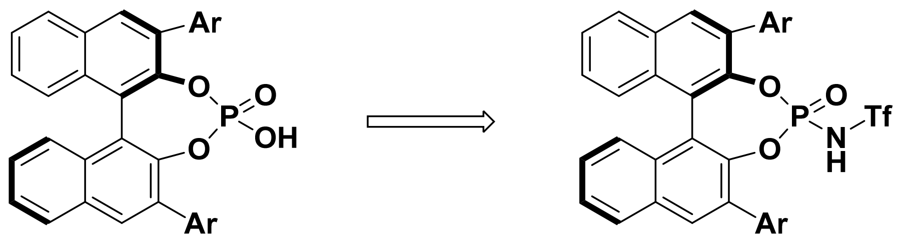
- Activation of Carboxylic Acids in Organocatalysis



Muller, S.; Webber, M. J.; List, B. *J. Am. Chem. Soc.* **2011**, *133*, 18534.
Monaco, M. R.; Fazzi, D.; Tsuji, N.; Leutzsch, M.; Liao, S.; Thiel, W.; List, B. *J. Am. Chem. Soc.* **2016**, *138*, 14740.

Chiral Brønsted Acid Catalyst Activates Ketones (The first example)

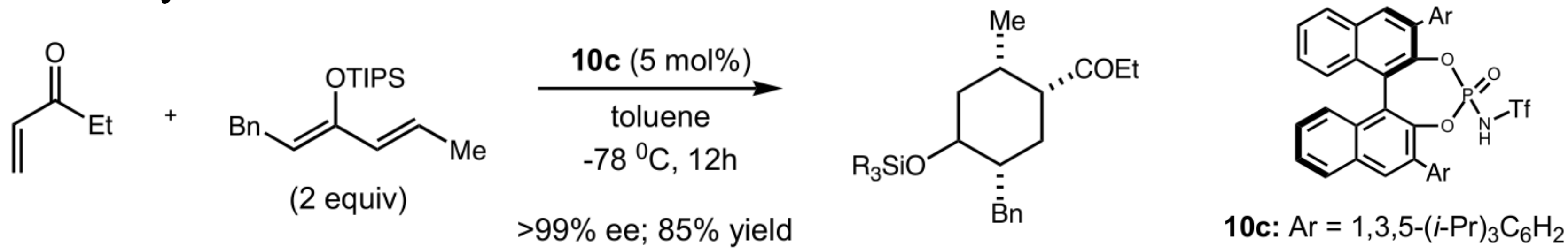
- Limitation has been the requirement for relatively basic substrates such as imines

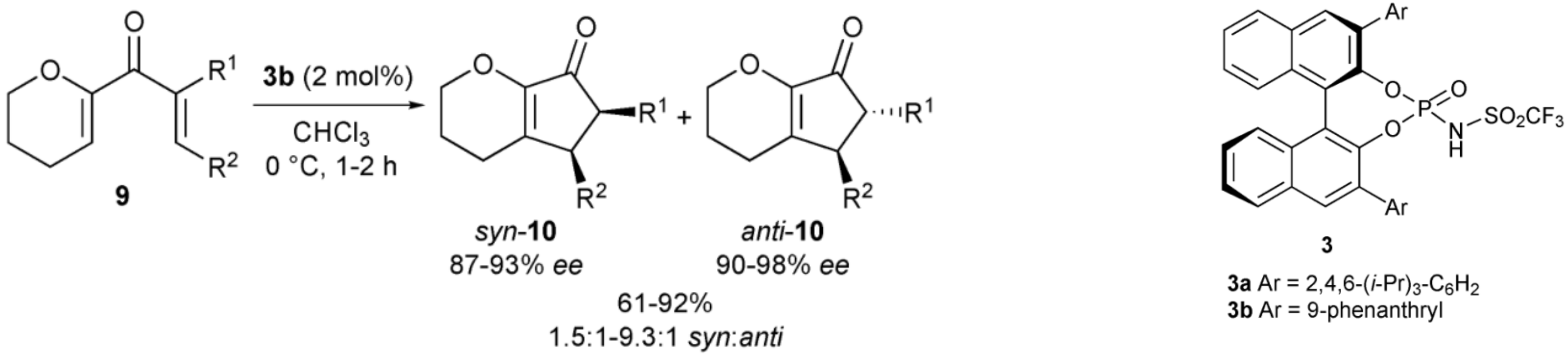


Ar = phenanthryl
pKa = 13.3 (MeCN)

Ar = phenyl
pKa = 6.4 (MeCN)

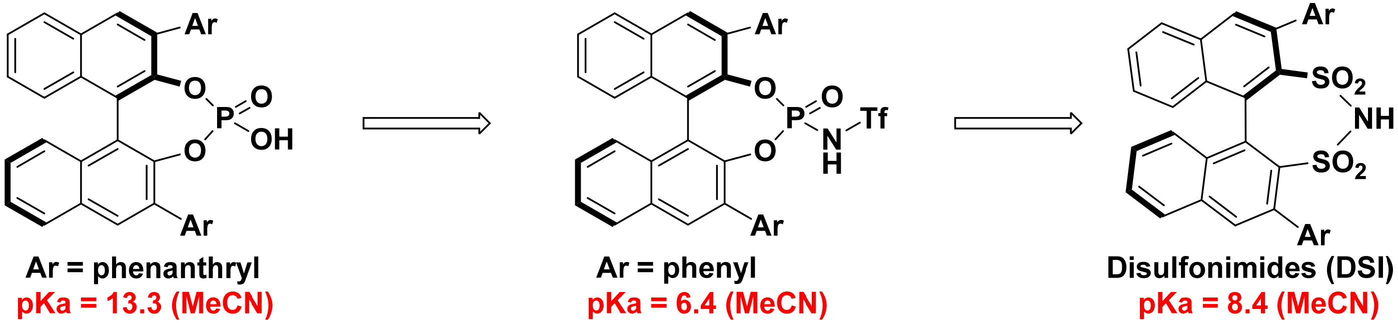
- Activation of α,β-unsaturated ketones in an asymmetric Diels–Alder reaction or Nazarov cyclization



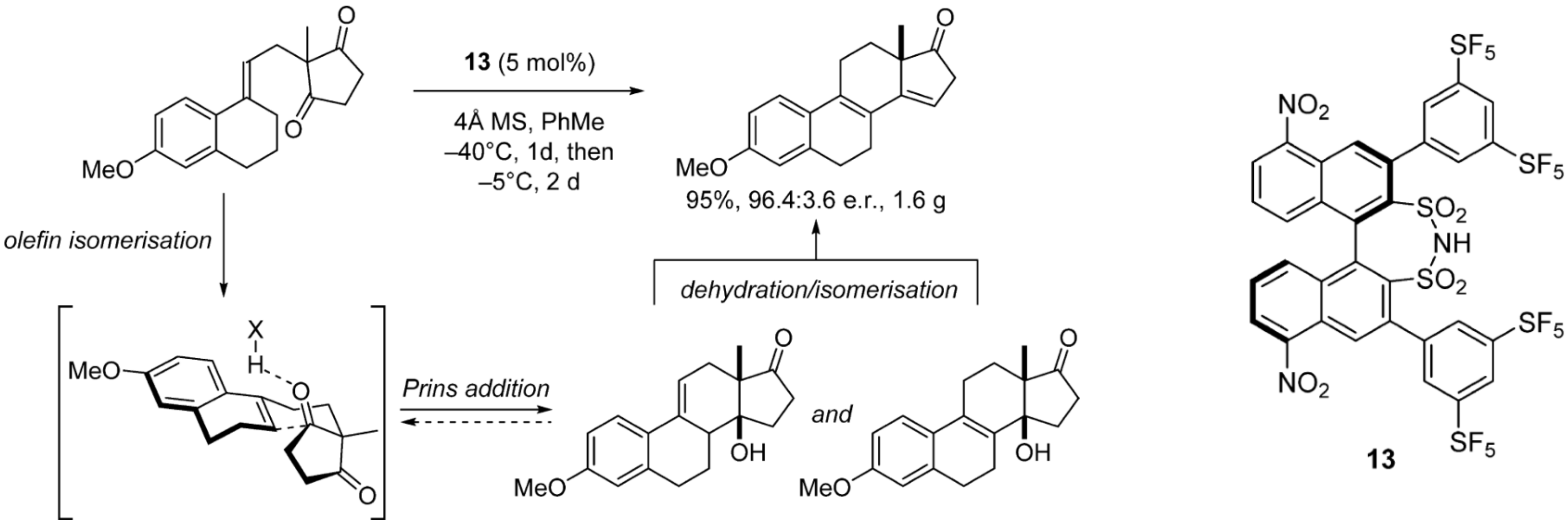


Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626.
Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2097.
Rueping,M.; Kuenkel, A.; Atodiresei, L. *Chem. Soc. Rev.* **2011**, *40*, 4539.

Disulfonimides Catalytic Asymmetric Torgov Cyclization (Brønsted acid catalysis)

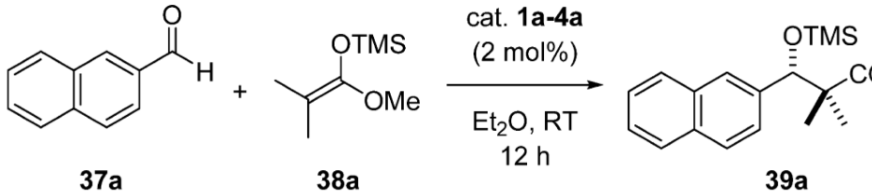


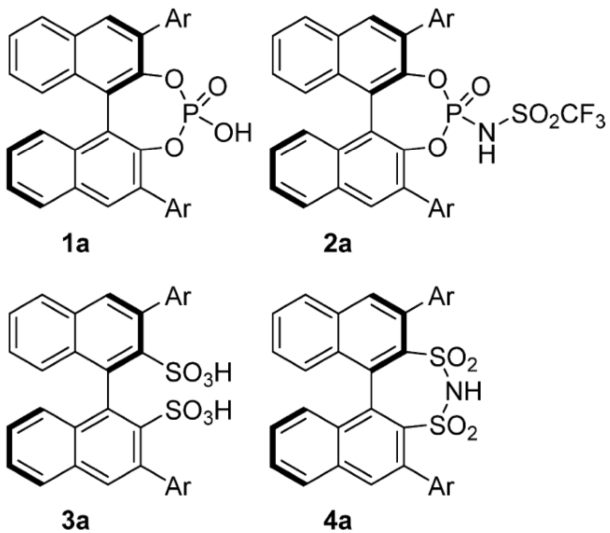
- Development of the highly acidic disulfonimide, allowed low-temperature reaction



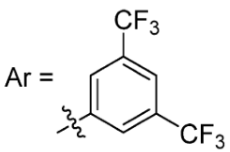
Révost, S.; Dupré, N.; Leutzsch, M.; Wang, Q.; Wakchaure, V.; List, B. *Angew. Chem., Int. Ed*. **2014**, *53*, 8770.
James, T,; van Gemmeren, M.; List, B. *Chem. Rev*. **2015**, *115*, 9388.

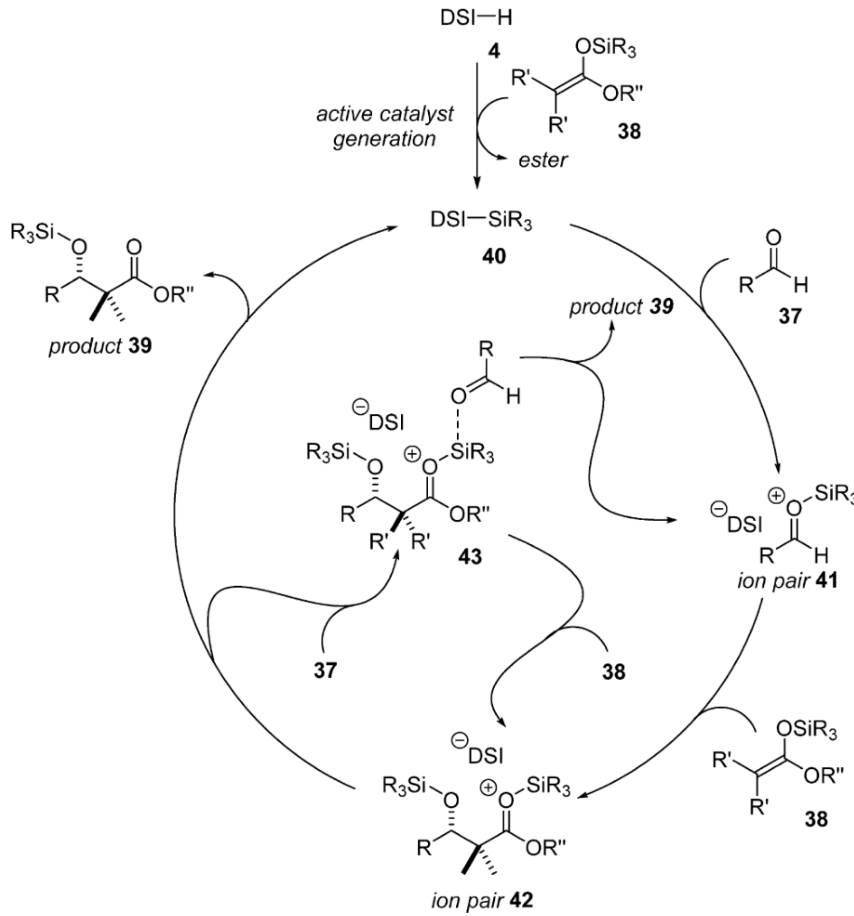
Disulfonimides in Lewis Acid Catalysis





Entry	Catalyst	Yield (%)	e.r.
1	**1a**	<2	–
2	**2a**	<2	–
3	**3a**	<2	–
4	**4a**	>99	90:10

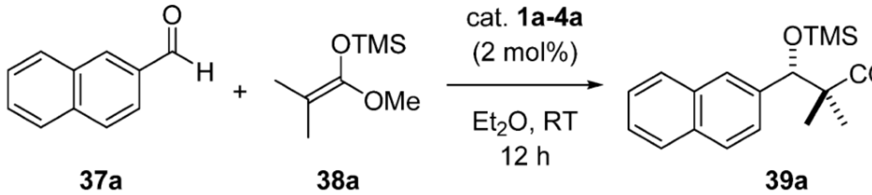


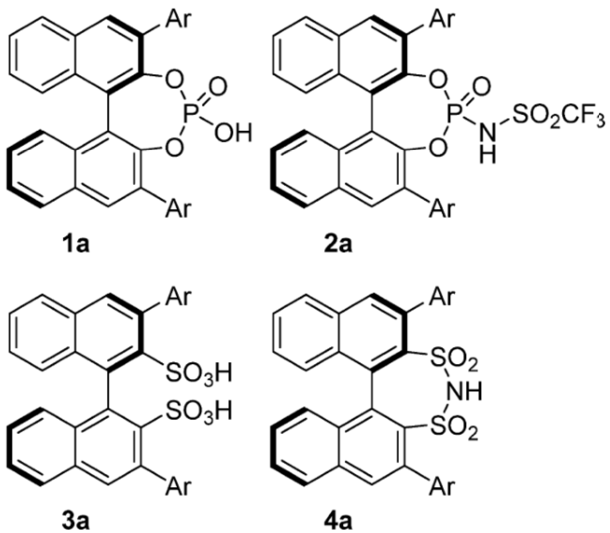


- NMR studies show that silyl ketene acetal 38 readily silylates the disulfonimide 4, validating the initial Lewis acid formation.
- The presence of the Brønsted-basic 2,6-di-tert-butyl-4-methylpyridine was tolerated within this transformation, eliminating any potential Brønsted acid aldehyde activation.

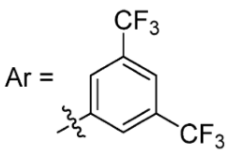
García-García, P.; Lay, F.; García-García, P.; Rabalakos, C.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 4363.

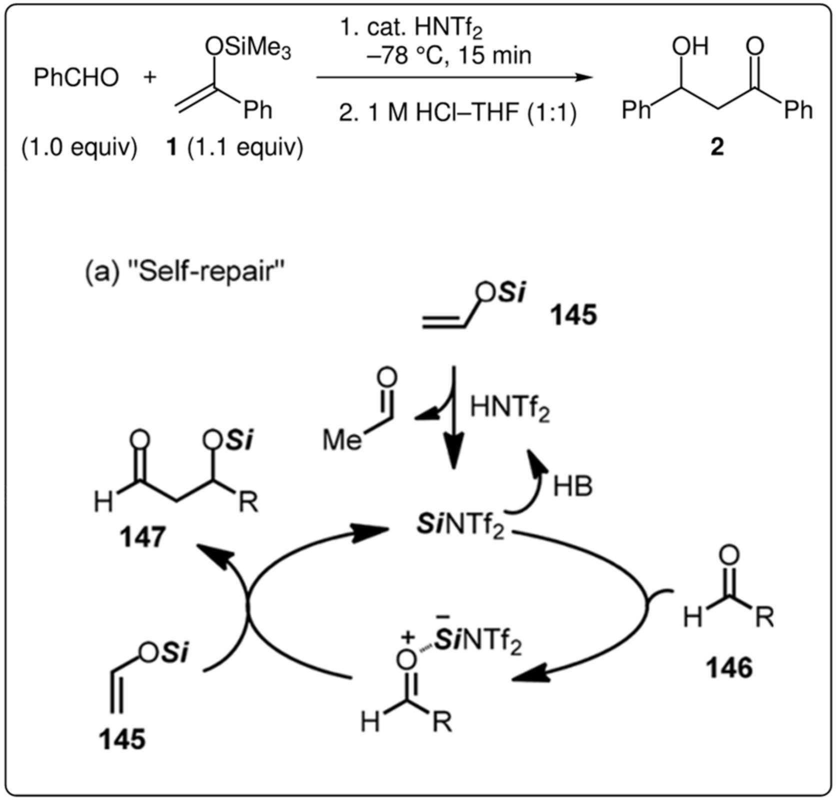
Disulfonimides in Lewis Acid Catalysis





Entry	Catalyst	Yield (%)	e.r.
1	**1a**	<2	–
2	**2a**	<2	–
3	**3a**	<2	–
4	**4a**	>99	90:10

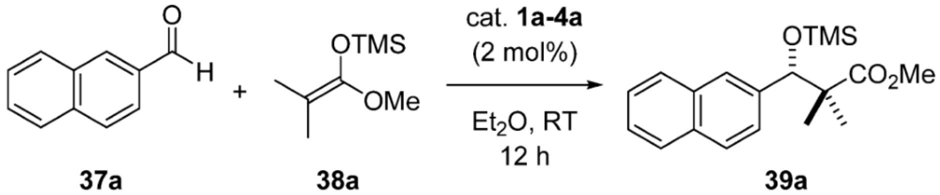


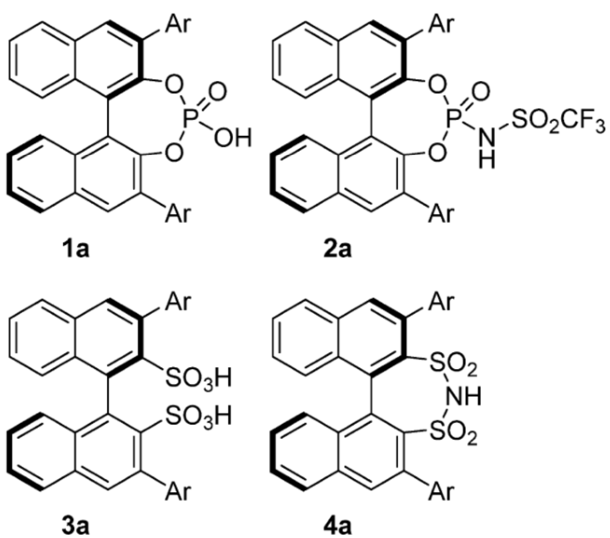


- ➢ In 2001, Yamamoto discovered that silyl triflimide(generated in situ) could efficiently catalyze Mukaiyama aldol reaction.(Self-repair mechanism)

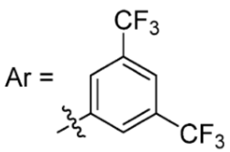
García-García, P.; Lay, F.; García-García, P.; Rabalakos, C.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 4363.
Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett*. **2001**, *2001*, 1851.

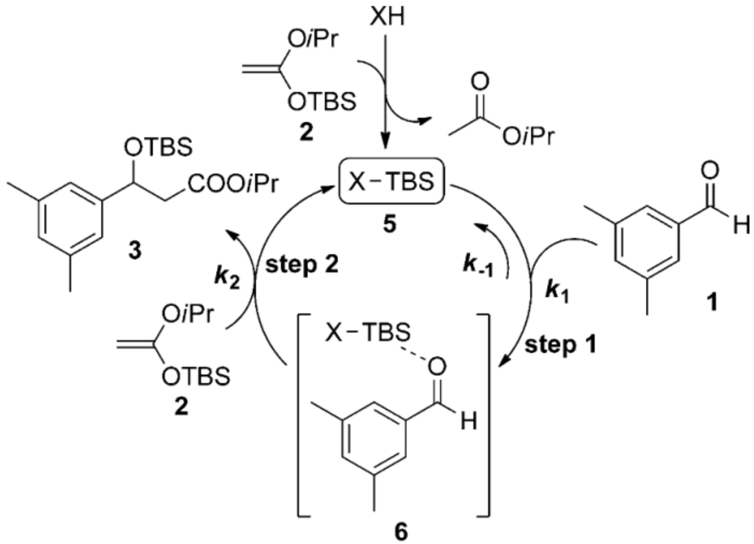
Disulfonimides in Lewis Acid Catalysis

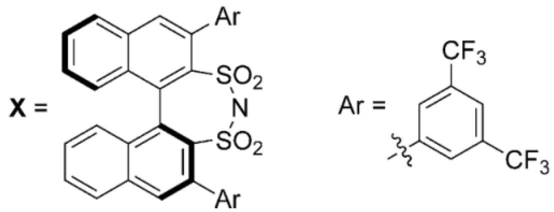




Entry	Catalyst	Yield (%)	e.r.
1	**1a**	<2	–
2	**2a**	<2	–
3	**3a**	<2	–
4	**4a**	>99	90:10







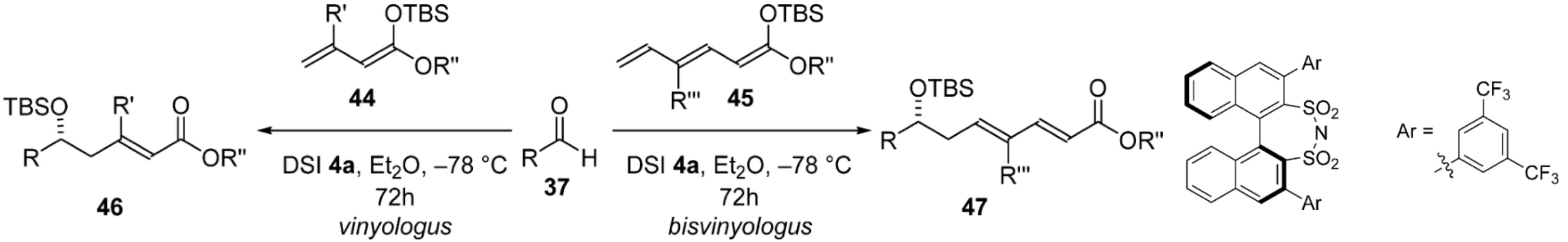
$$\text{rate} = k \cdot [\mathbf{1}]^{0.55} \cdot [\mathbf{2}] \cdot [\mathbf{4}]$$

- The attack of the silyl ketene acetal on the activated oxonium ion is the slowest step of the catalytic cycle
- Aldehyde activation is an equilibrium, the aldehyde concentration can partially influence the rate

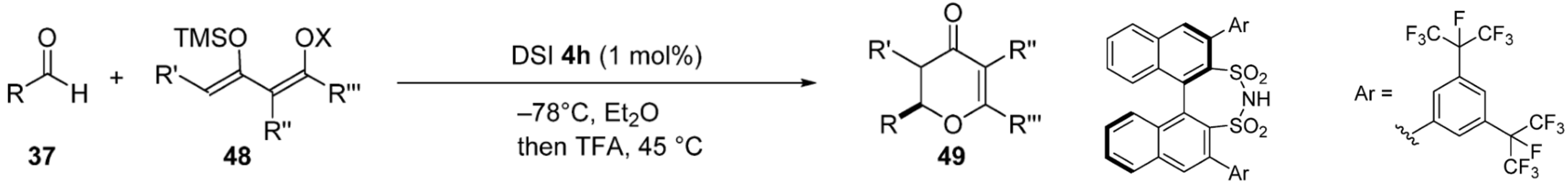
Zhang, Z.; List, B. *Asian J. Org. Chem.* **2013**, 2, 957.

Disulfonimide-Catalyzed Asymmetric Transformations

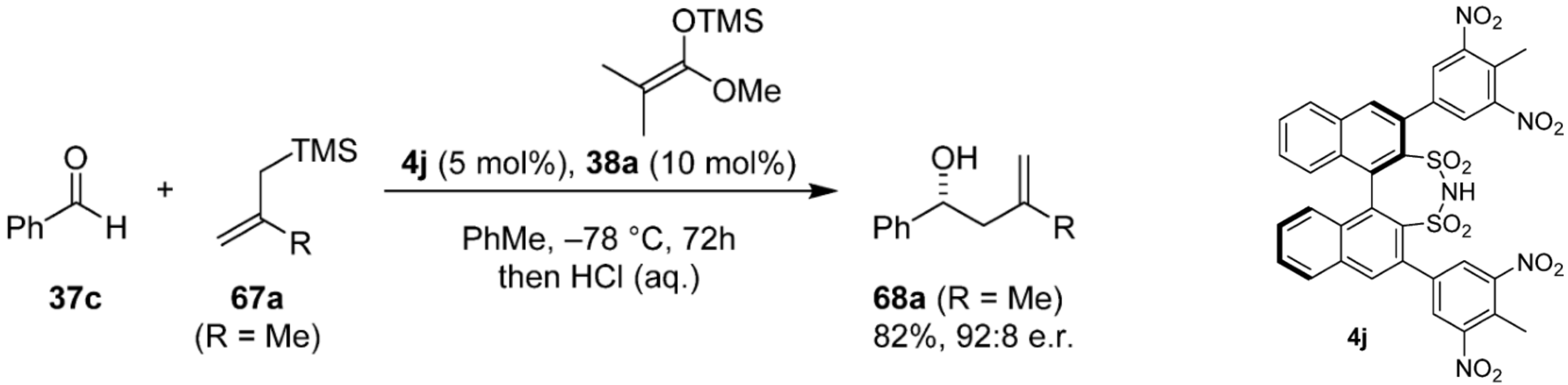
- Vinylogous and Bisvinylogous Mukaiyama Aldol Reactions



- Formal Hetero-Diels−Alder Reactions



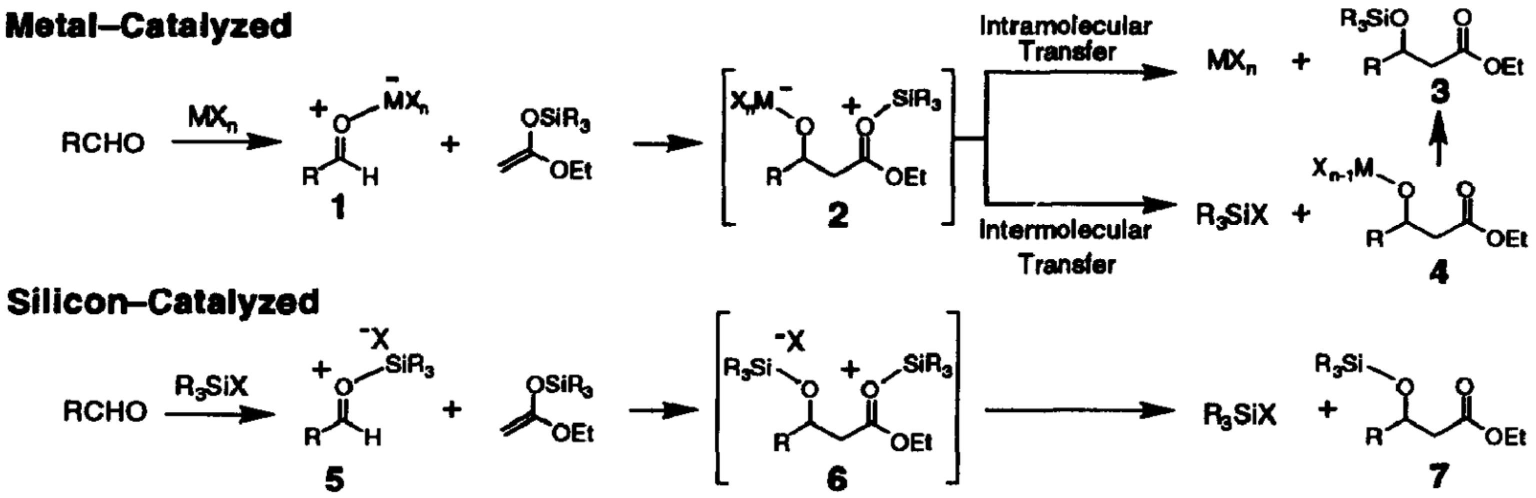
- Hosomi−Sakurai Reaction with Methallyltrimethylsilane



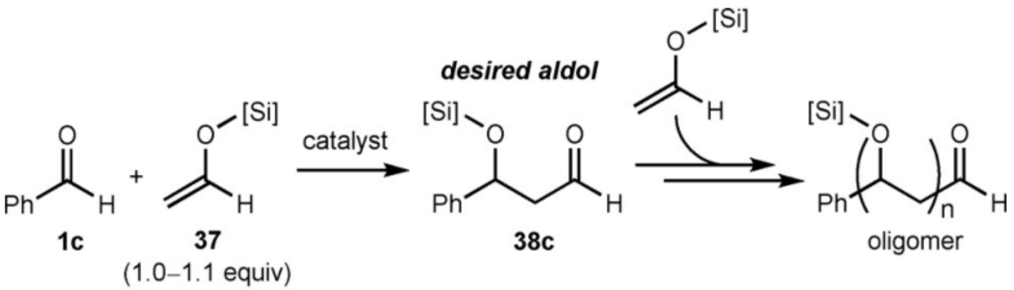
a) Ratjen, L.; García-García, P.; Lay, F.; Beck, M. E.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 754. b) Guin, J.; Rabalakos, C.; List, B.. *Angew. Chem., Int. Ed.* **2012**, *51*, 8859. c) Mahlau, M.; García-García, P.; List, B. *Chem.Eur. J.* **2012**, *18*, 16283. d) James, T,; van Gemmeren, M.; List, B. *Chem. Rev.* **2015**, *115*, 9388.

Challenges in Asymmetric Mukaiyama Aldol Reactions

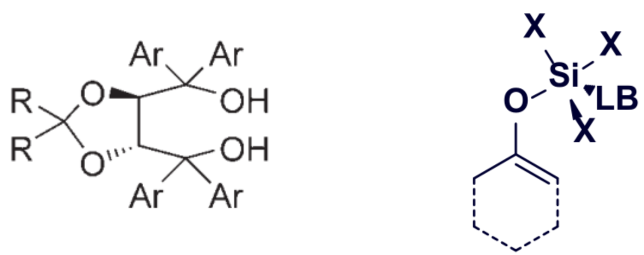
- ➢ Open transition model
- ➢ Metal-based catalyst: require high to very high catalyst loadings (often 20%) due to the competition with a nonenantioselective silylium ion background catalysis pathway.



➢ Inability to discriminate between the starting acetaldehyde acceptor and the product aldehyde, thus leading to extensive polymerization



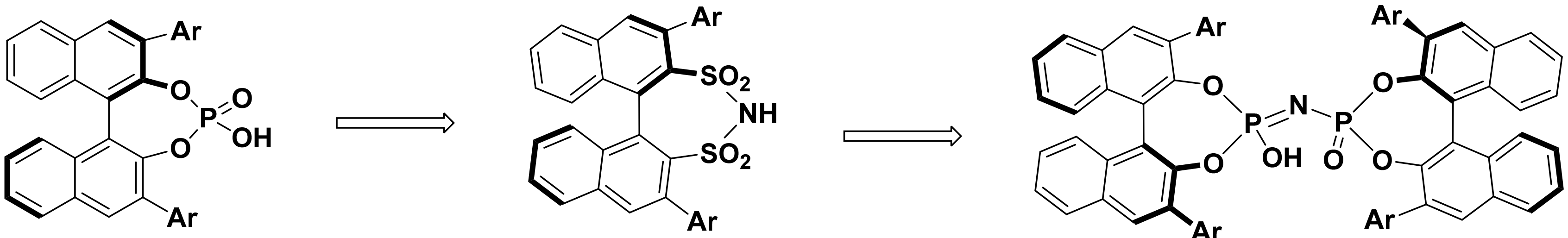
➢ Lewis bases catalysis(Denmark), chiral diols(Rawal): high catalyst loadings and highly activated substrates



a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011. b) Carreira, E. M.; Singer, R. A. *Tetrahedron, Lett*. **1994**, *35*, 4323. c) Denmark, S. E.; Wynn, T.; Beutner, G. L. *J. Am. Chem. Soc.* **2002**, *124*, 13405. d) McGilvra, J. D.; Unni, A. K.; Modi, K.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 6130.

Imidodiphosphate(IDP) Catalyst

- Difficult to further modify steric environment of CPA: 3,3-substituents on BINOL radiate away from the active site

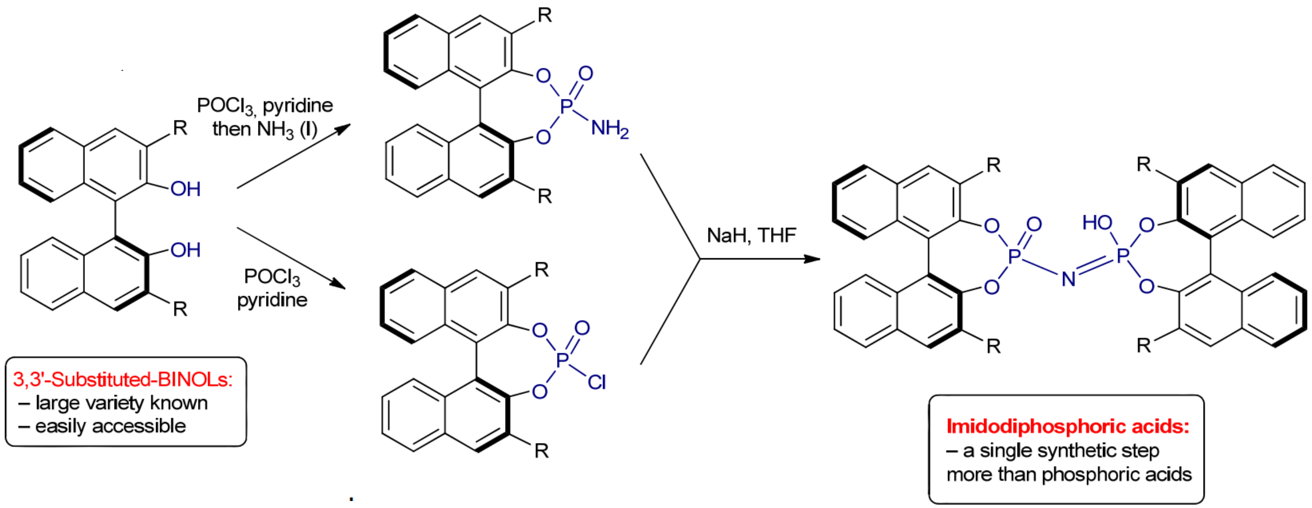


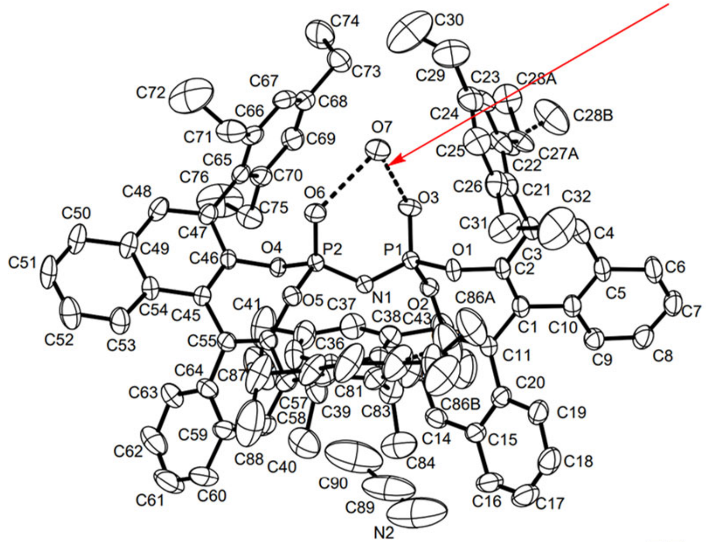
Ar = phenanthryl
pKa = 13.3 (MeCN)

Disulfonimides (DSI)
pKa = 8.4 (MeCN)
moderately stereoselective

Imidodiphosphates (IDP)
pKa = 11.5 (MeCN)

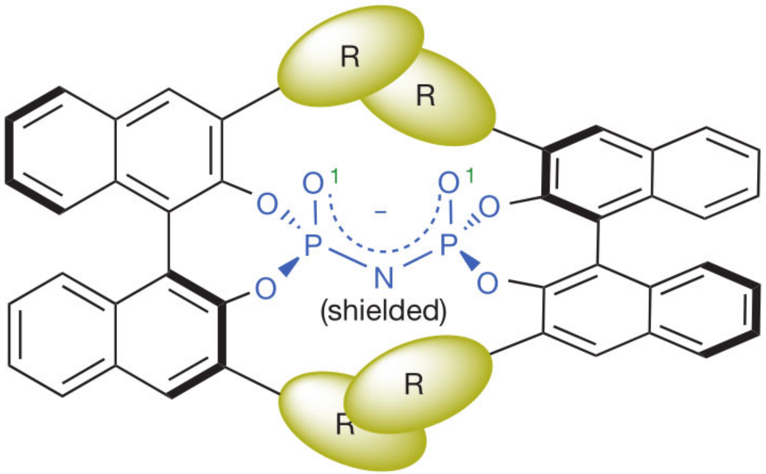
- Imidodiphosphori cacid co-crystallized with a molecule of water, are consistent with a hydronium ion bridging the two imidodiphosphate oxygen atoms，which supports proton location on oxygen rather than on nitrogen.

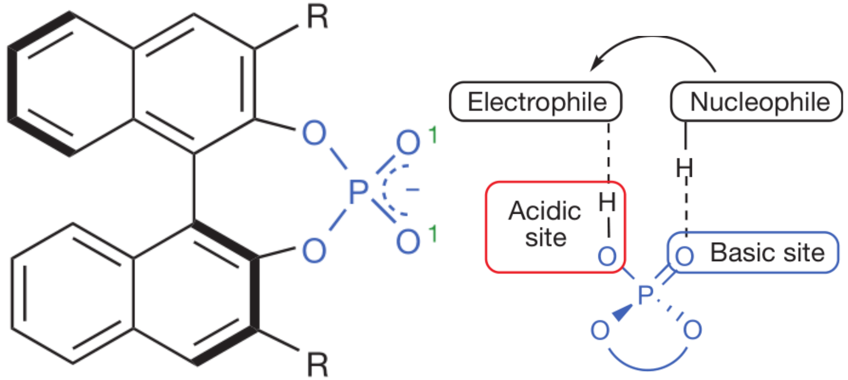


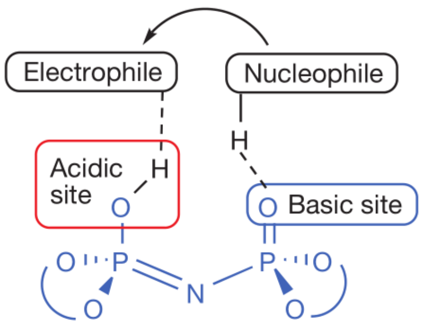


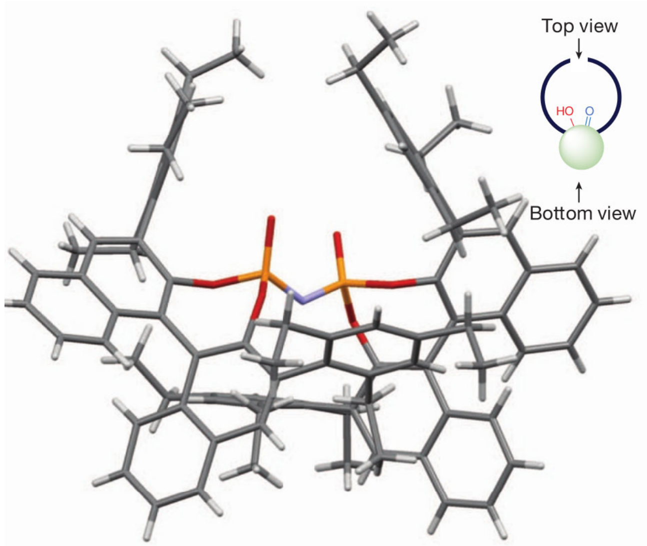
Ćorić, I.; List, B. *Nature*, **2012**, 483, 315.

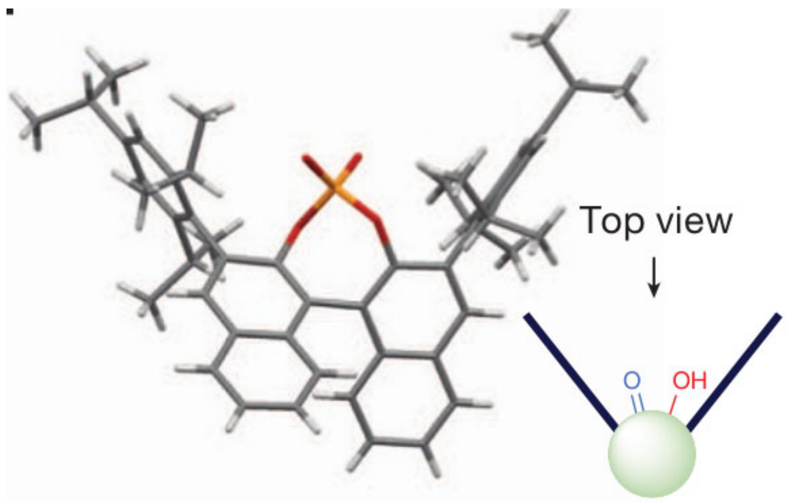
Features of Imidodiphosphate Catalyst











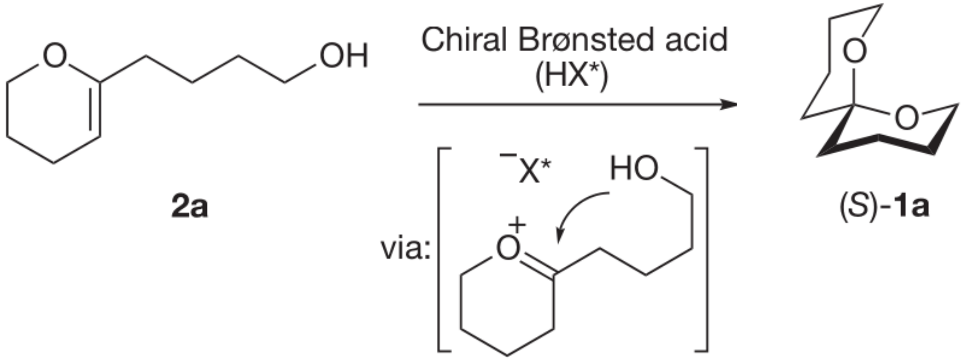
A chiral pocket

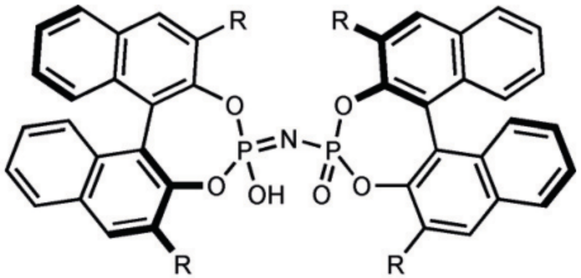
Broad open cone

- The interlocking of BINOL-subunits are unable to freely rotate and the resulting molecular structure possesses a very high rigidity.
- Anion is C2 -symmmetric, and has therefore only a single type of catalytically relevant Brønsted basic site

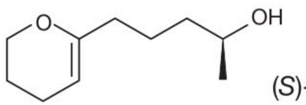
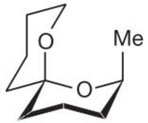
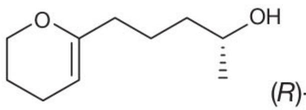
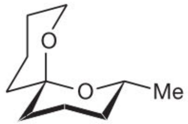
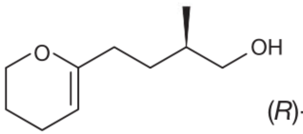
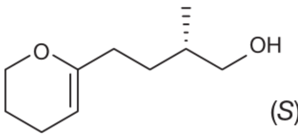
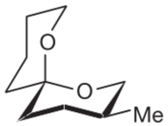
Ćorić, I.; List, B. *Nature*, **2012**, *483*, 315.

Asymmetric Spiroacetalization(Brønsted acid catalysis）





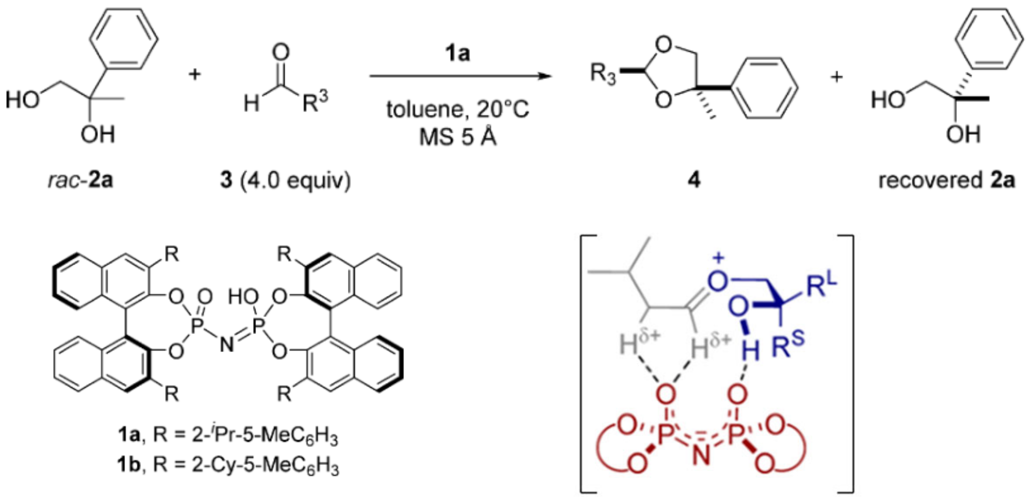
Imidodiphosphates (IDP) **R=2,4,6-$Et_3C_6H_2$**

8	 (*S*)-**2g**	**6a** (5 mol%), −35 °C, MTBE	 **1g**	83%	d.r. 5:1, non-thermodynamic spiroacetal (thermodynamic d.r. 1:124)
9	 (*R*)-**2g**		 **1h**	89%	d.r. 65:1
10	 (*R*)-**2i**	**6a** (5 mol%), −35 °C, MTBE	 **1i**	70%	d.r. 23:1, non-thermodynamic spiroacetal (thermodynamic d.r. 1:9)
11	 (*S*)-**2i**		 **1j**	70%	d.r. 50:1

Čorić, I.; List, B. *Nature*, **2012**, 483, 315.

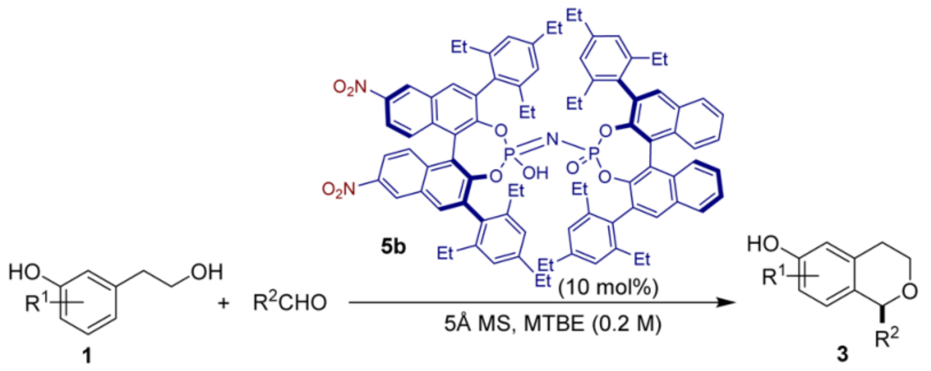
Activation of Oxocarbenium Ion(Brønsted acid catalysis）

- Resolution of Diols



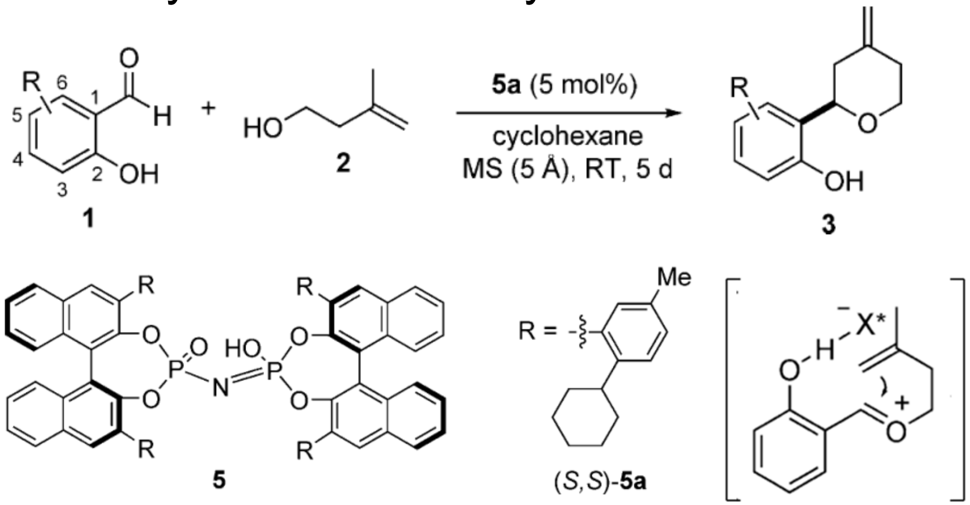
Kim, J. H.; Coric, I.; Palumbo, C.; List, B.
J. Am. Chem. Soc. **2015**, *137*, 1778.

- Asymmetric Oxa-Pictet−Spengler Reaction



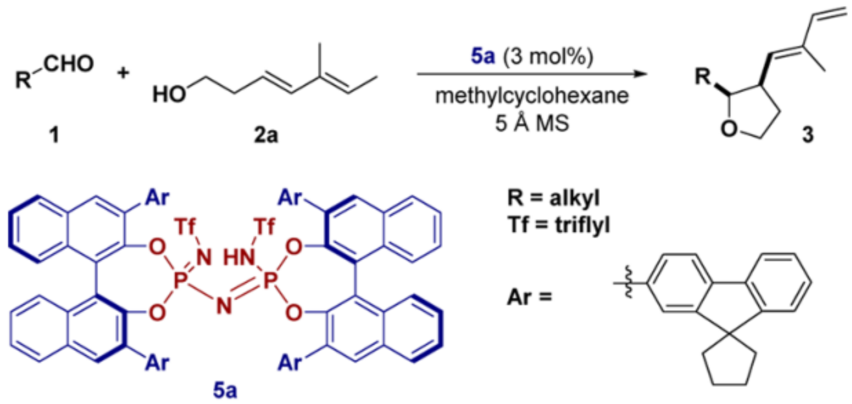
Das, S.; Liu, L.; Zheng, Y.; Alachraf, M. W.; Thiel, W.; De, C. K.; List, B.
J. Am. Chem. Soc. **2016**, *138*, 9429.

- Asymmetric Prins Cyclization



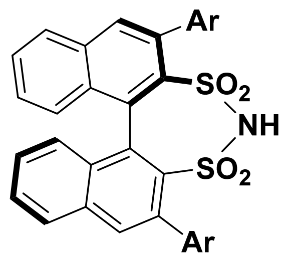
Tsui, G. C.; Liu, L.; List, B.
Angew. Chem., Int. Ed. **2015**, *54*, 7703.

- Asymmetric Vinylogous Prins Cyclization

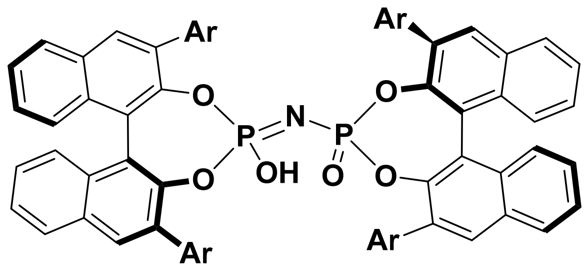


Xie, Y.; Cheng, G. J.; Lee, S.; Kaib, P. S.; Thiel, W.; List, B.
J. Am. Chem. Soc. **2016**, *138*, 14538.

Imidodiphorimidates(IDPi) Catalyst



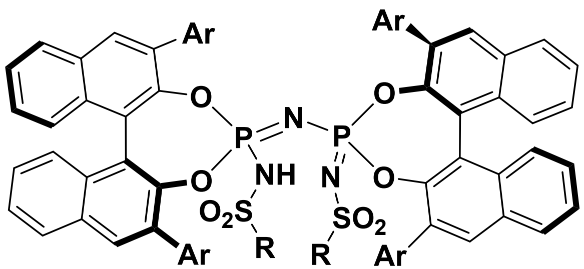
Disulfonimides (DSI)
pKa = 8.4 (MeCN)
highly active Bronsted acids
active in Lewis acid catalysis
moderately stereoselective



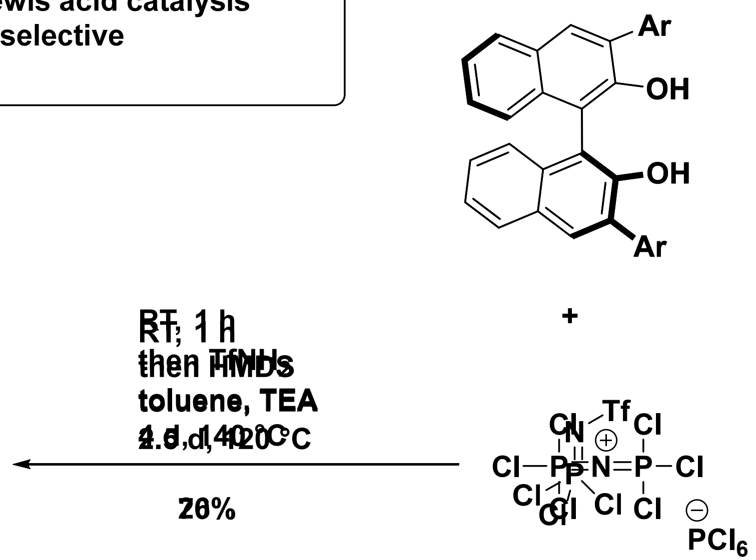
Imidodiphosphates (IDP)
pKa = 11.5 (MeCN)
moderately active Bronsted acids
inactive in Lewis acid catalysis
highly stereoselective

reactivity

selectivity

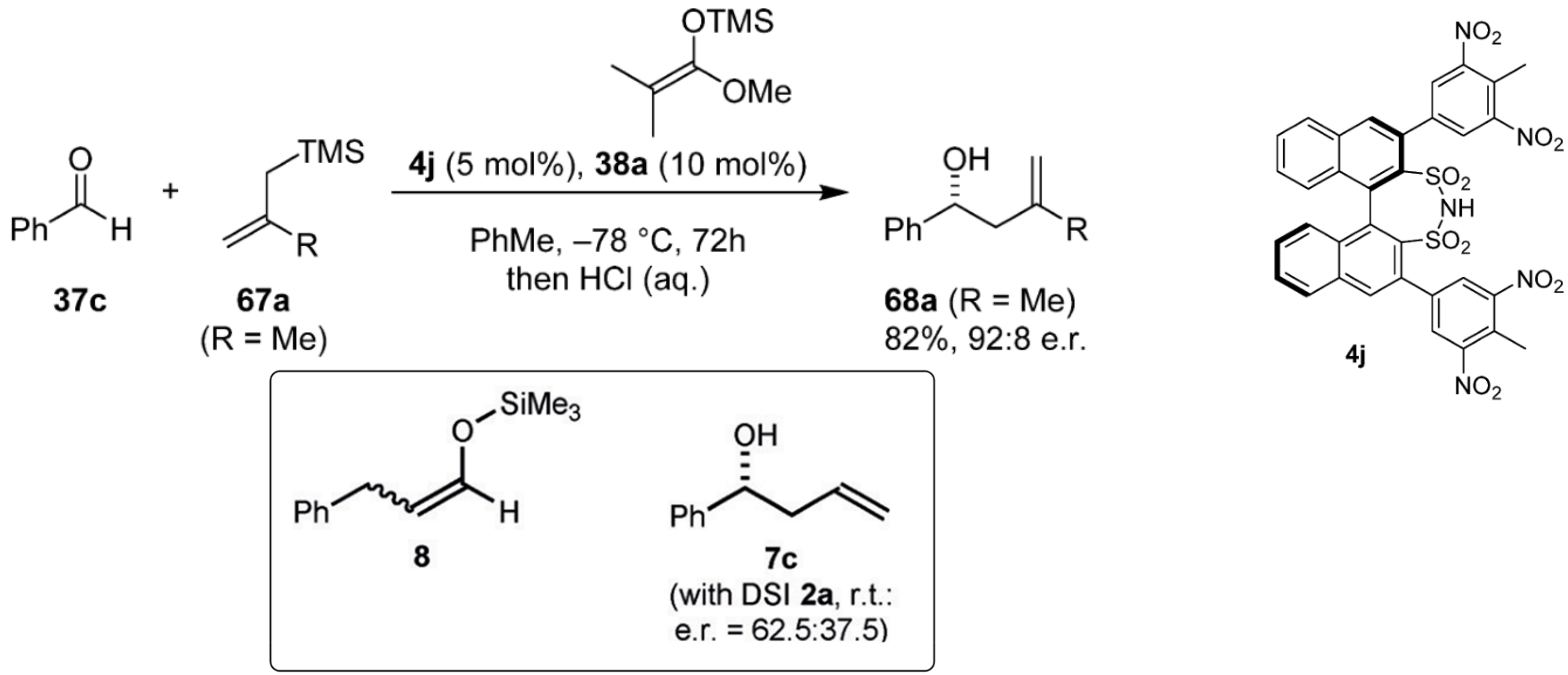


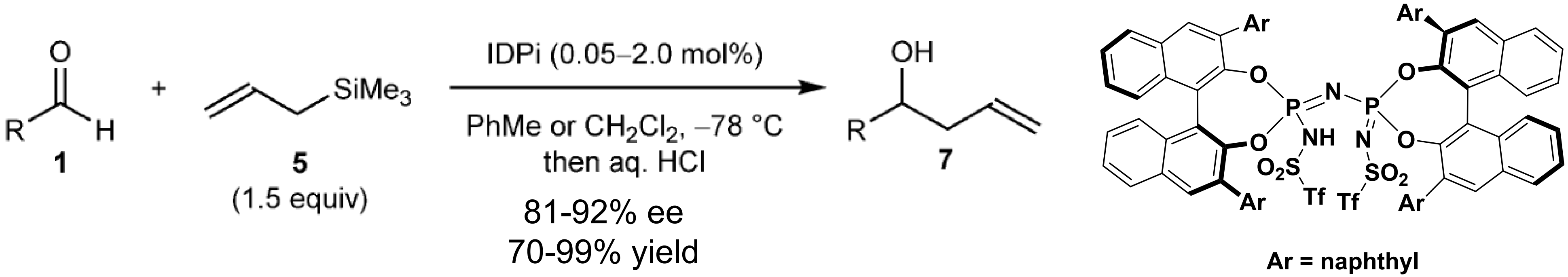
Imidodiphorimidates (IDPi)
pKa = 4.5 to <2.0 (MeCN)
highly active Bronsted acids
active in Lewis acid catalysis
highly stereoselective



Kaib, P. S.; Schreyer, L.; Lee, S.; Properzi, R.; List, B. *Angew. Chem., Int. Ed.* **2016**, *55*, 13200.
List, B. et al. *J. Am. Chem. Soc.* **2021**, *143*, 14835.

Hosomi–Sakurai Reaction with Allyltrimethylsilane(Lewis acid catalysis）

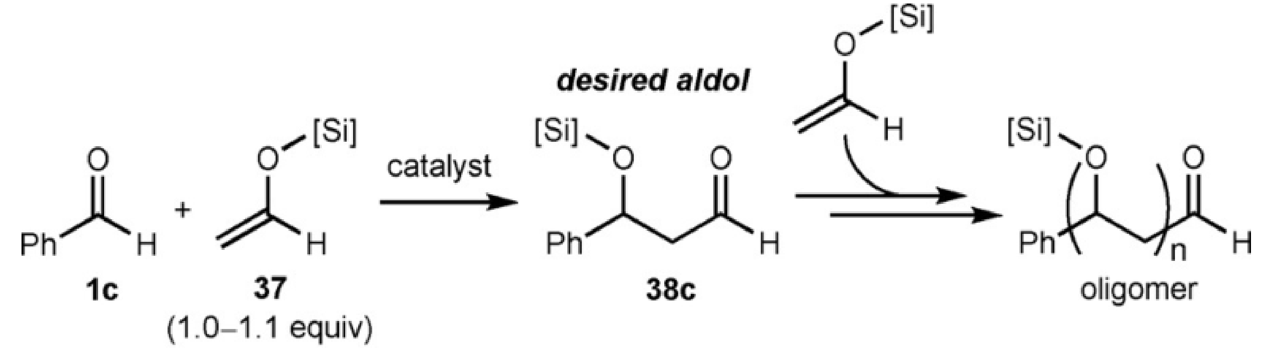


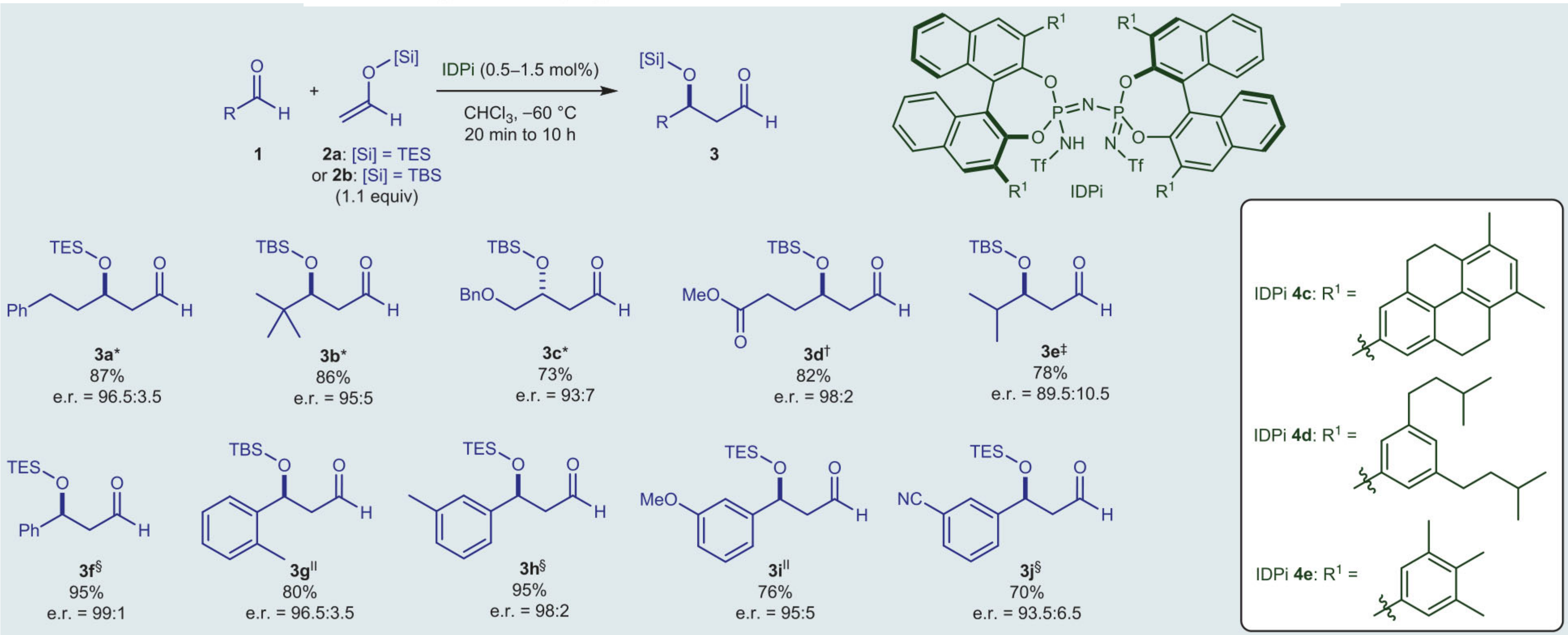


Kaib, P. S.; Schreyer, L.; Lee, S.; Properzi, R.; List, B. *Angew. Chem., Int. Ed.* **2016**, *55*, 13200.

Asymmetric Single Aldolizations of Acetaldehyde Enolates

➢ Inability to discriminate between the starting acetaldehyde acceptor and the product aldehyde, thus leading to extensive polymerization

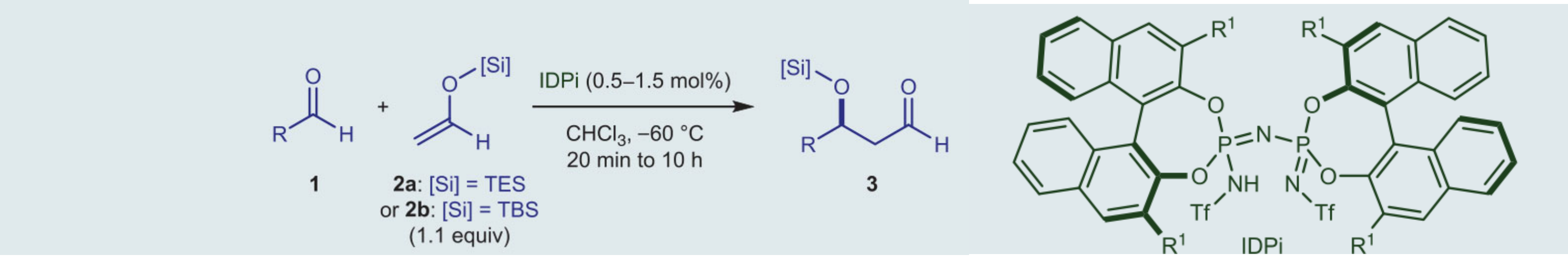


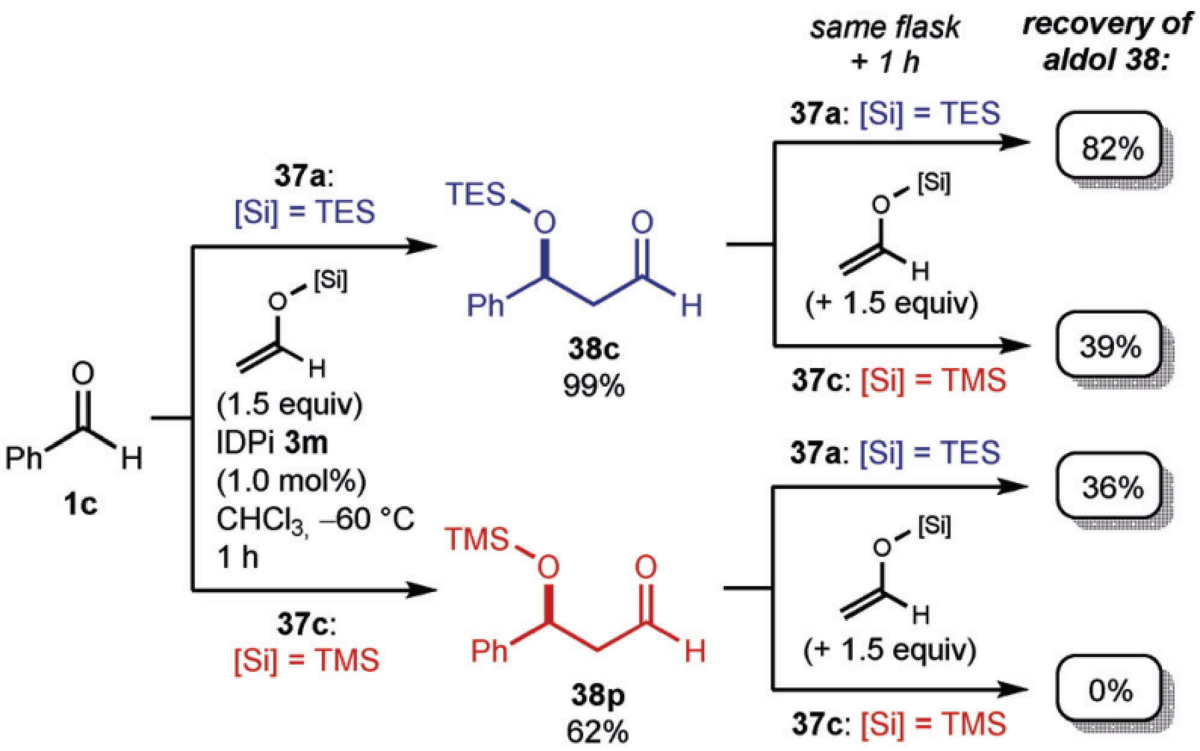


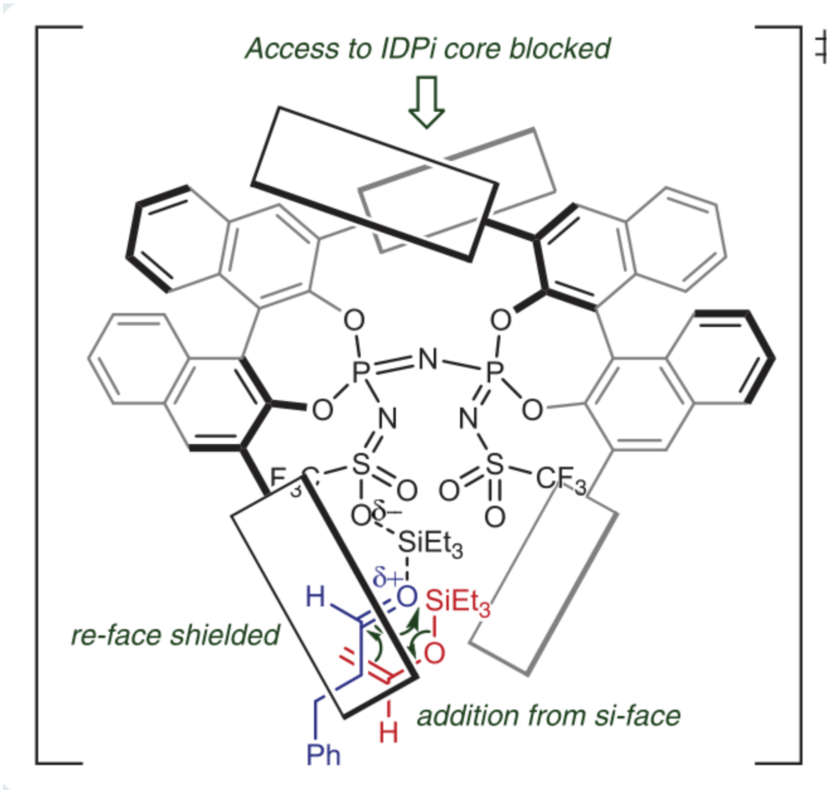
Schreyer, L.; Kaib, P. S. J.; Wakchaure, V. N.; Obradors, C.; Properzi, R.; Lee, S.; List, B. *Science*. **2018**, *362*, 216.

Asymmetric Single Aldolizations of Acetaldehyde Enolates

➢ The steric bulk of the silyl group greatly affected reaction

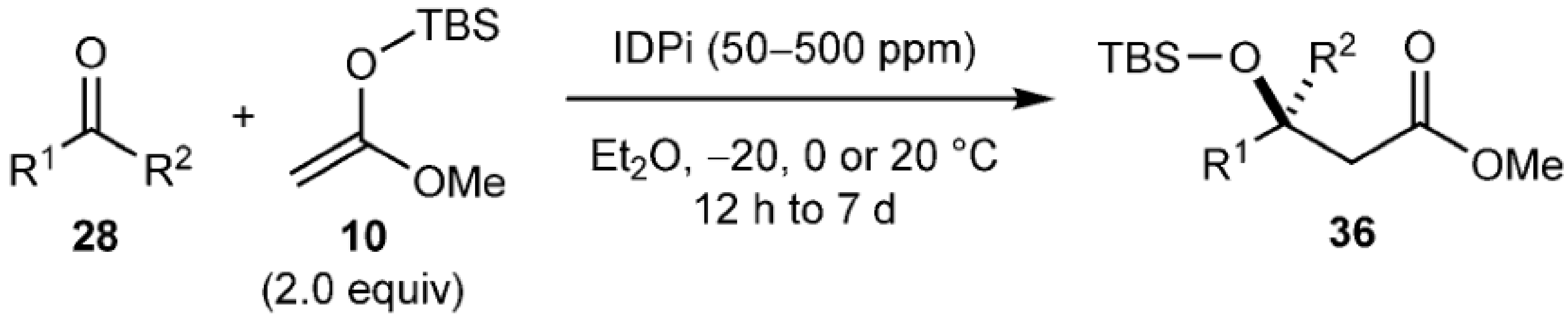


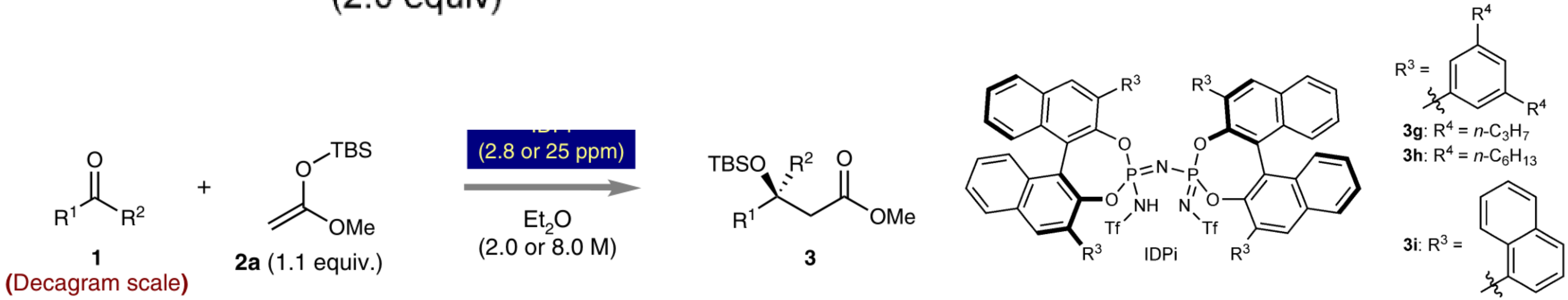


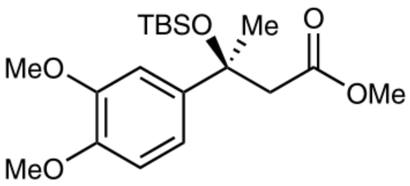


Schreyer, L.; Kaib, P. S. J.; Wakchaure, V. N.; Obradors, C.; Properzi, R.; Lee, S.; List, B. *Science.* **2018**, *362*, 216.

Sub-ppm-level Asymmetric Organocatalysis

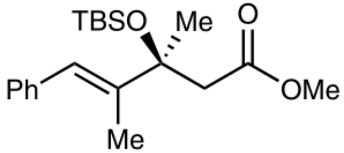






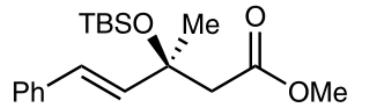
From **1i** (10.0 g)/**C-8** (25 ppm: 2.1 mg)
2.0 M, 10 °C, <0.5 d

3i
>99% (20.5 g), TON 40,000, 95:5 e.r.



From **1v** (10.0 g)/**C-8**(2.8 ppm: 0.34 mg)
8.0 M, 24 °C, 2 d

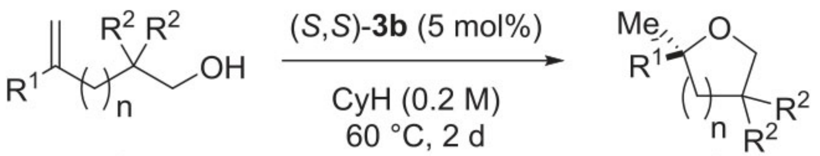
3v
92% (20.1 g)[a], TON 329,000, 96:4 e.r.



From **1u** (30.0 g)/**C-8** (2.8 ppm: 1.1 mg)
8.0 M, 5 °C, 13 d

3u
86% (59.2 g)[b], TON 307,000, 95:5 e.r.

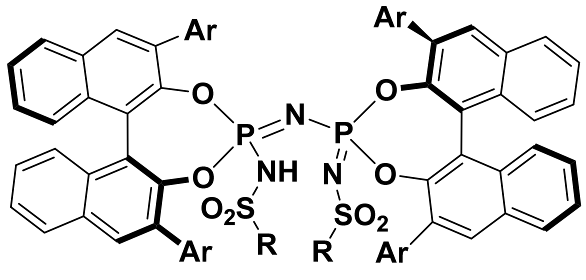
Intramolecular Hydroalkoxylation of Simple Olefins(Brønsted acid catalysis）



1

n = 1, 2

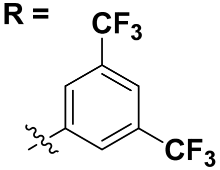
2

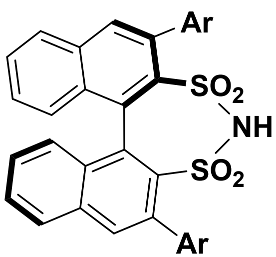


(*S, S*)-3b

Ar = 4-*t*Bu$_2$C$_6$H$_4$

R =



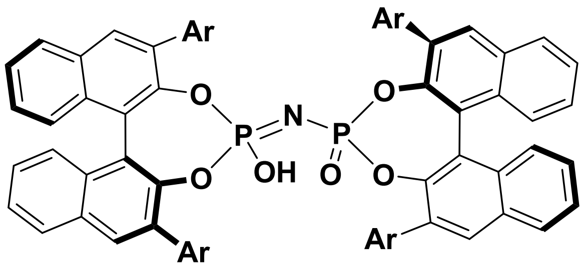


Disulfonimides (DSI)

Ar = 3,5-(CF$_3$)$_2$C$_6$H$_3$

55% yield

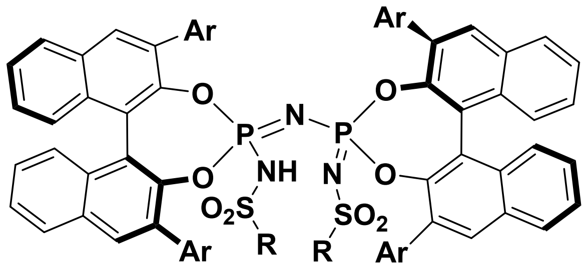
7% ee



Imidodiphosphates (IDP)

Ar = 2,4,6-Et$_3$C$_6$H$_2$

N. D.



Imidodiphorimidates (IDPi)

Ar = 4-*t*Bu$_2$C$_6$H$_4$

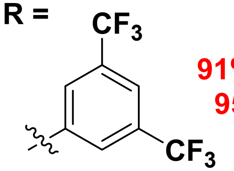
R = CF$_3$

84% yield

71% ee

Ar = 4-*t*Bu$_2$C$_6$H$_4$

R =

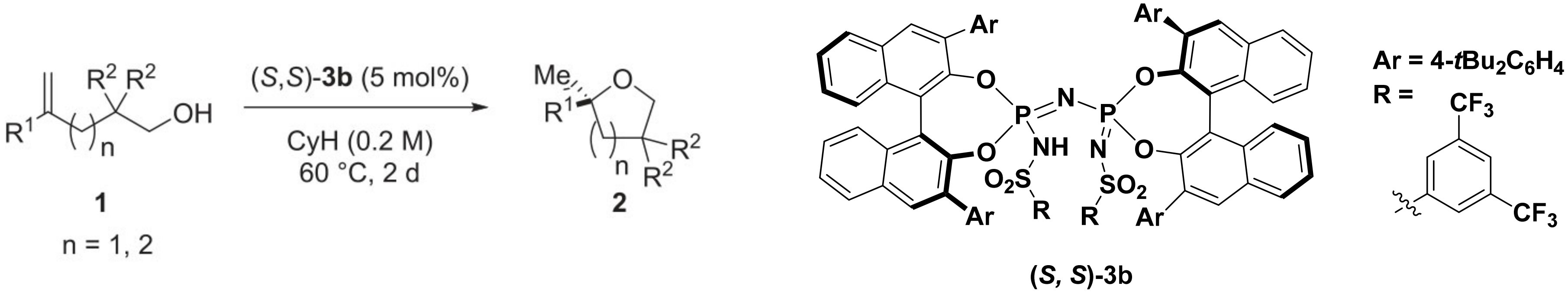


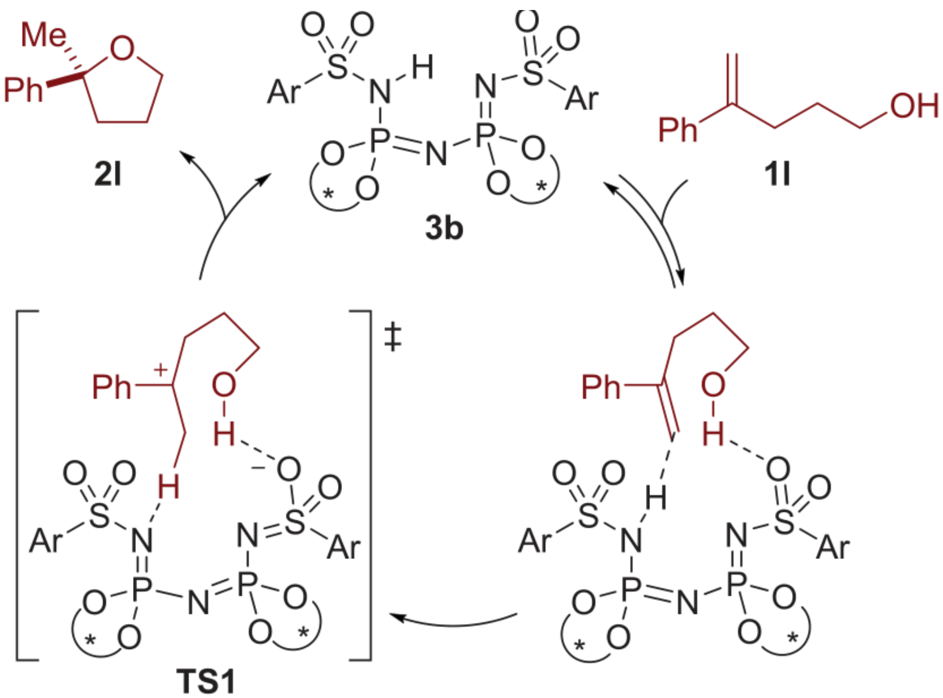
91% yield

95% ee

Tsuji, N.; Kennemur, J. L.; Buyck, T.; Lee, S.; Prévost, S.; Kaib, P. S. J.; Bykov, D.; Farès, C.; List, B. *Science*. **2018**, *359*, 1501.

Intramolecular Hydroalkoxylation of Simple Olefins(Brønsted acid catalysis）



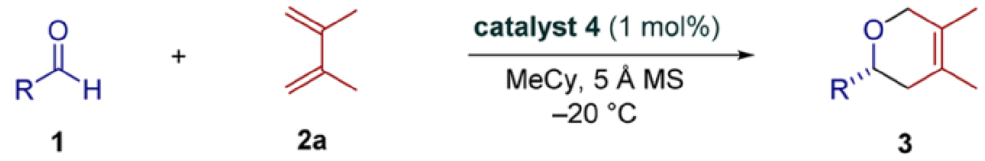


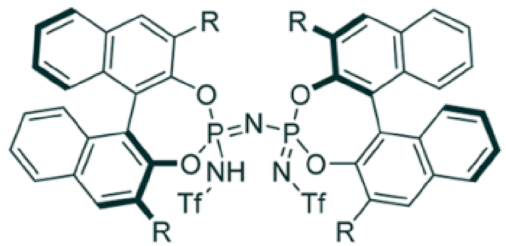
- DFT studies gave an asynchronous concerted mechanism(protonation of the olefin, followed by the C-O bond).
- Hammett analysis gave a linear correlation with a negative slope(r =−2.08±0.04), consistent with the proposed carbocationic intermediate in the transition state.

Tsuji, N.; Kennemur, J. L.; Buyck, T.; Lee, S.; Prévost, S.; Kaib, P. S. J.; Bykov, D.; Farès, C.; List, B. *Science*. **2018**, *359*, 1501.

Activation of Ketones(Brønsted acid catalysis）

➢ Asymmetric [4+2]-Cycloaddition of Dienes with Aldehydes

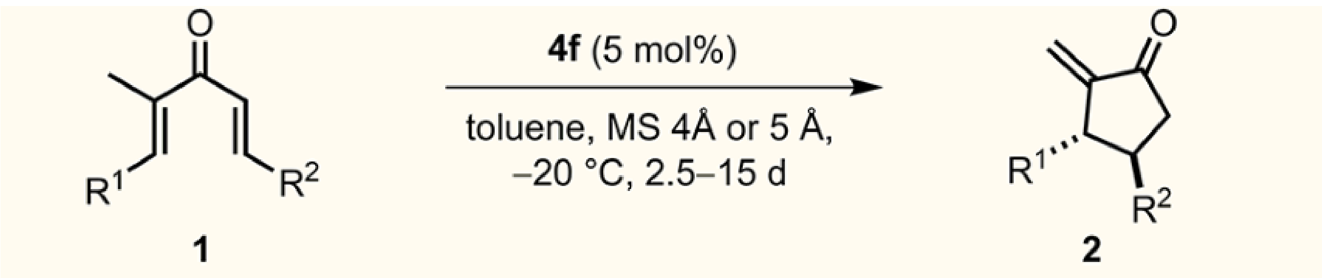


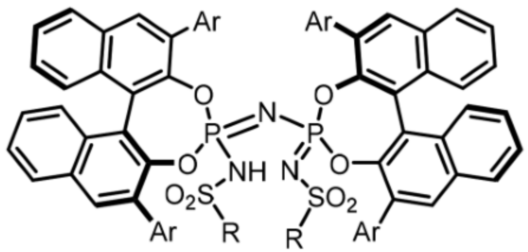


4c: R = 3,5-$(SF_5)_2C_6H_3$; **4d:** R = 3,5-$(n\text{-}C_3F_7)_2C_6H_3$

Liu, L.; Kim, H.; Xie, Y.; Fares, C.; Kaib, P. S. J.; Goddard, R.; List, B. J. Am. Chem. Soc. 2017, 139, 13656.

➢ Catalytic Asymmetric Nazarov Cyclization of Simple Divinyl Ketones

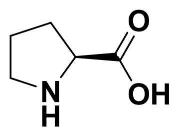




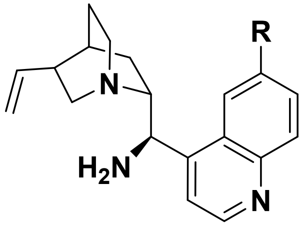
(*S*,*S*)-IDPi-**4d**: Ar = Ph, R = CF_3
(*S*,*S*)-IDPi-**4e**: Ar = 2-triphenylenyl, R = CF_3
(*S*,*S*)-IDPi-**4f**: Ar = 2-triphenylenyl, R = C_2F_5

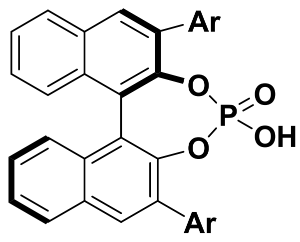
Ouyang, J.; Kennemur, J. L.; De, C. K.; Farès, C.; List, B. *J. Am. Chem. Soc.* **2019**, *141*, 3414.

Summary

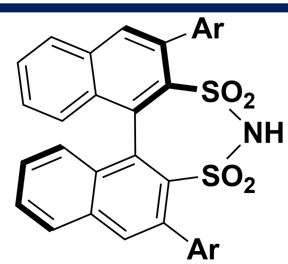


L-Proline
2000

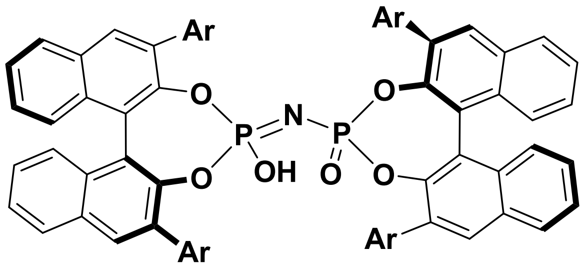




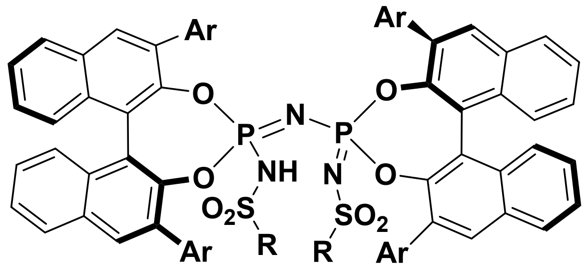
Ar = phenanthryl
pKa = 13.3 (MeCN)
2004, Akiyama



Disulfonimides (DSI) 2009
pKa = 8.4 (MeCN)
highly active Bronsted acids
active in Lewis acid catalysis
moderately stereoselective



Imidodiphosphates (IDP) 2012
pKa = 11.5 (MeCN)
moderately active Bronsted acids
inactive in Lewis acid catalysis
highly stereoselective



Imidodiphorimidates (IDPi) 2016
pKa = 4.5 to <2.0 (MeCN)
highly active Bronsted acids
active in Lewis acid catalysis
highly stereoselective
one-pot synthesis

High activity, high efficiency, high stereoselectivity(IDPi):

- **Sub-ppm-level asymmetric Organocatalysis**
- **Asymmetric single aldolizations of acetaldehyde enolates**
- **Activation of olefins**

Detailed mechanism, case by case ?