# *Asymmetric Brønsted acid catalysis developed by Benjamin List's group*

2018. 6. 30. LS
Tsukasa Shimakawa

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1. Introduction

2. New concenpts for asymmetic Brønsted acid catalysis (2012, 2016)

LETTER

doi:10.1038/nature10932

Asymmetric spiroacetalization catalysed by confined Brønsted acids

Ilija Čorić[1] & Benjamin List[1]

**Organocatalysis**

International Edition: DOI: 10.1002/anie.201607828
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3. Asymmeric hydroalkoxylation of olefin (2018)

REPORT

ORGANIC CHEMISTRY

**Activation of olefins via asymmetric Brønsted acid catalysis**

**Nobuya Tsuji,[1] Jennifer L. Kennemur,[1] Thomas Buyck,[1] Sunggi Lee,[1] Sébastien Prévost,[1] Philip S. J. Kaib,[1] Dmytro Bykov,[2,3] Christophe Farès,[1] Benjamin List[1]***

# Prof. Benjamin List

**Education and professional appointment:**

1993: Chemistry Dipolm, Free University Berlin
1997: Ph. D, University of Frankfurt (Prof. John. Mulzer)

1997-1998: Posdoc, Scripps Research Institute (Prof. Richard Lerner)
1998-2003: Assistant Professor, Scripps Research Institute
2003- : Group Leader, Director, Max Plank Institute for Coal Research

**Awards**:
2007: AstraZeneca Research Award
2012: Otto Bayer Prize
2013: Mukaiyama Award
2014: Arthur C. Cope Scholar Award etc...

**Research topic**:
Development of new concepts for chemical synthesis and catalysis

1. Organocatalysis
1-1. Aminocatalysis

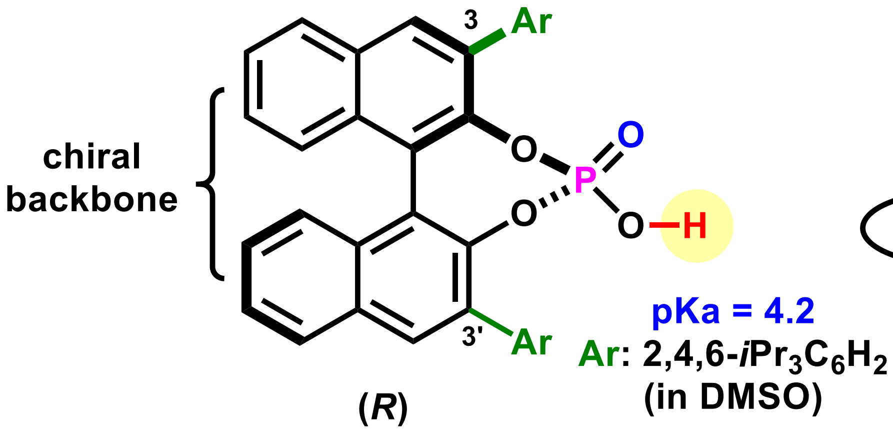
1-2. Brønsted acid catalysis

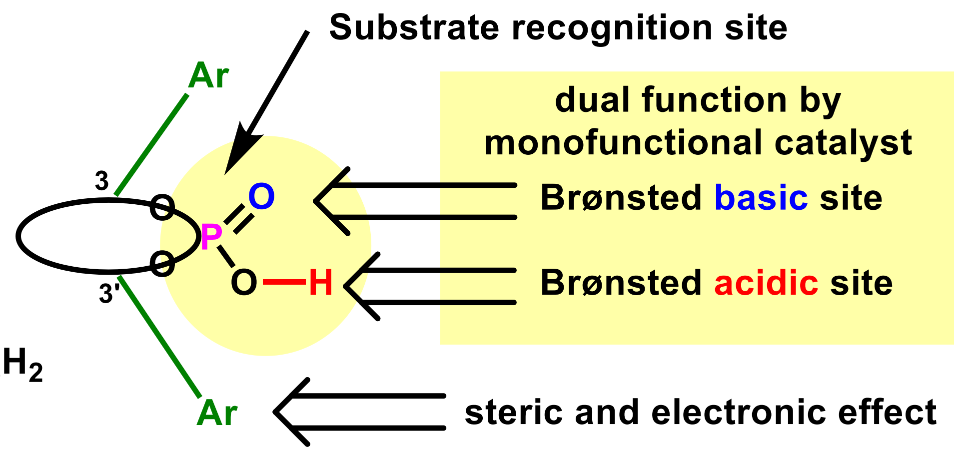
1-3. Organic Lewis acid catalysis

2. ACDC catalysis
(Asymmeric Counteranion Directed Catalysis)

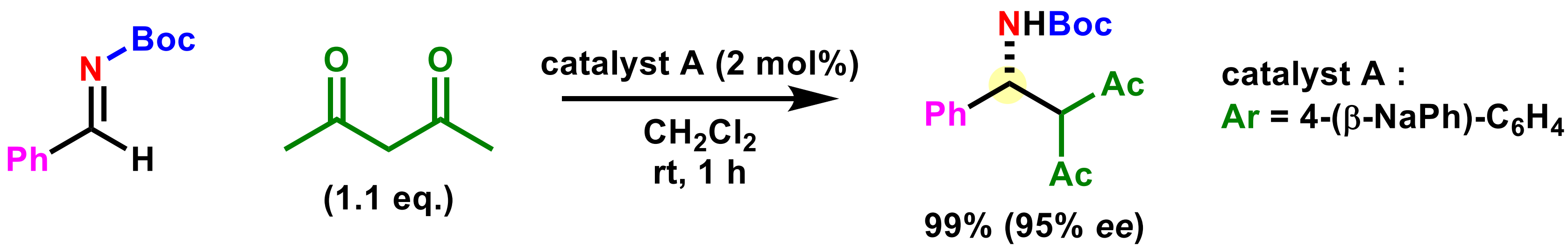
https://www.kofo.mpg.de/en/research/homogeneous-catalysis-

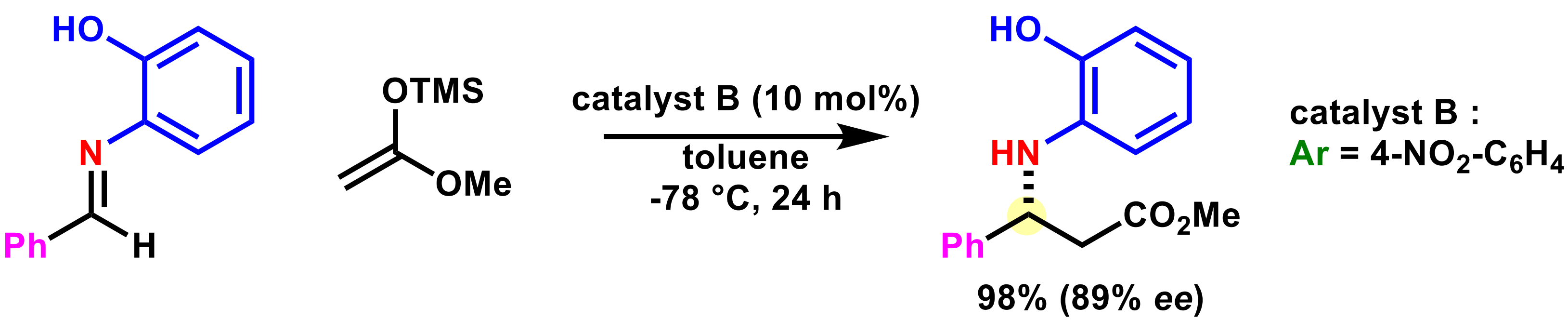
# Chiral phosphoric acid catalyst



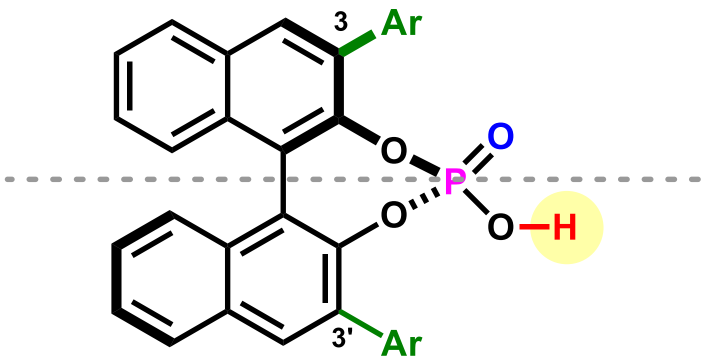

In 2004, Akiyama and Terada reported Mannich-type reaction independently.

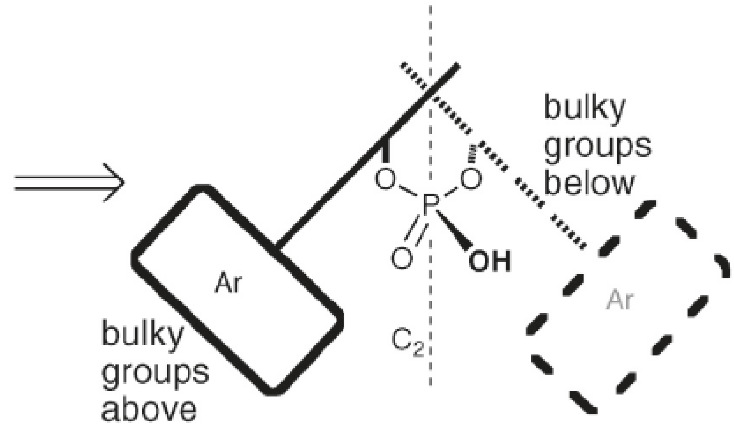


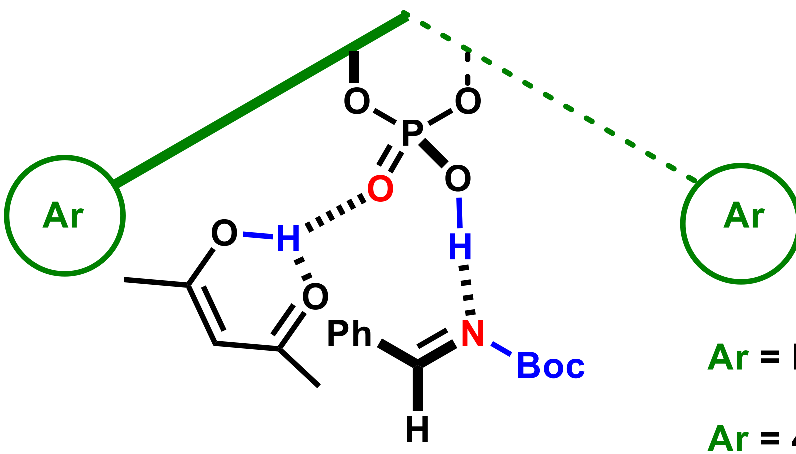

1) Terada, M. *Synthesis* **2010**, *12*, 1929. 2) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem. Int. Ed*. **2004**, *43*, 1566.
3) Uraguchi, D. and Terada, M. *J. Am. Chem. Soc*. **2004**, *126*, 5356.

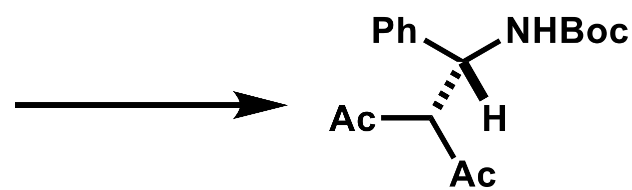
# Mode of action




**Terada's reaction**




**Ar = H, 12% ee** **Ar = Ph, 56% ee**

**Ar = 4-Ph-$C_6H_4$, 90% *ee*** **Ar = 4-(β-NaPh)-$C_6H_4$, 95% *ee***

**Substrate**

**1. Hydrogen bonding network**

**2. Sterically bulky group**

**→ Limitation of substrate**

**X**

**Catalyst**

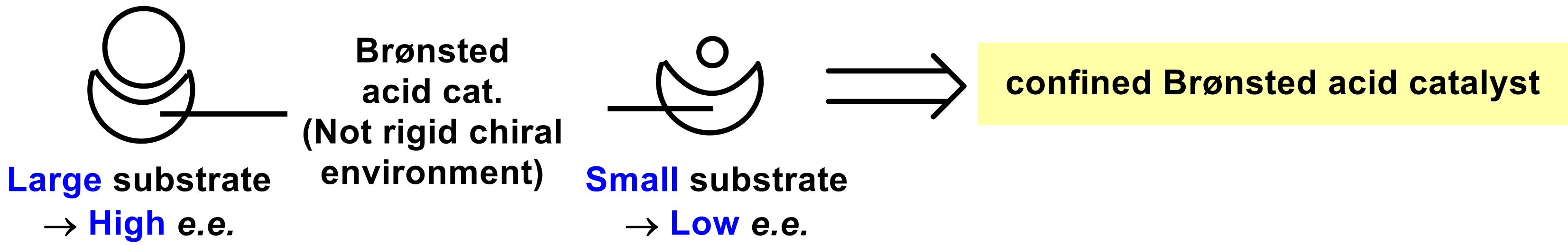
**bulky substituent at C3, C3' position**


1) Uraguchi, D. and Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. 2) Simon, L. and Goodman, J. M. *J. Org. Chem.* **2011**, *76*, 1775.

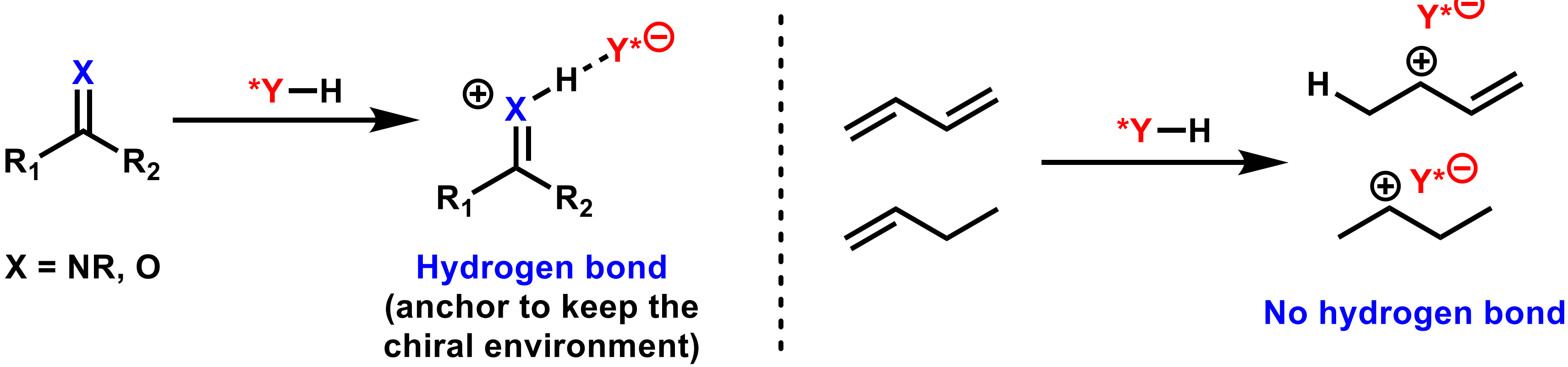
# Remaining tasks in chiral Brønsted acid catalysis

**Application toward unbiased substrates**

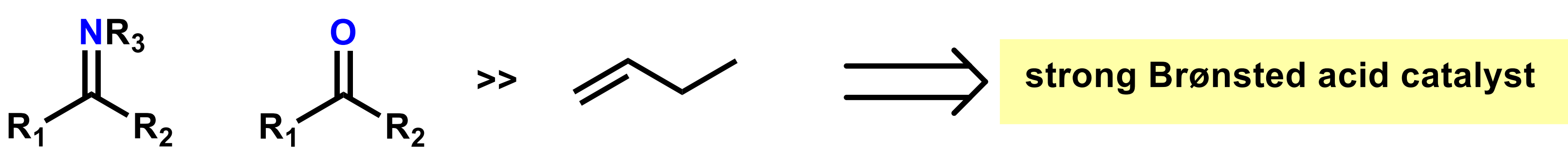
**1-1. Small substrates**




**1-2. Substrates lacking hydrogen bond interaction**




**1-3. Application toward low basic substrates**



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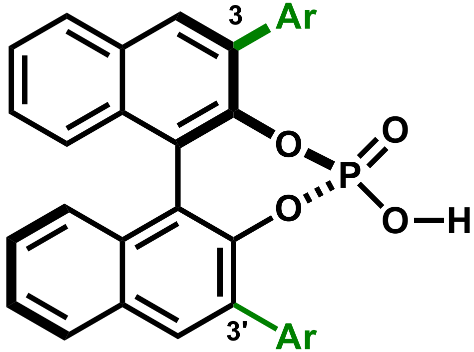
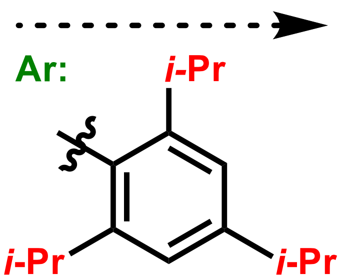
# How to introduce steric demand?

**Plan A:** Introduce bulky group at C3 and C3'




(*R*)-TRIP



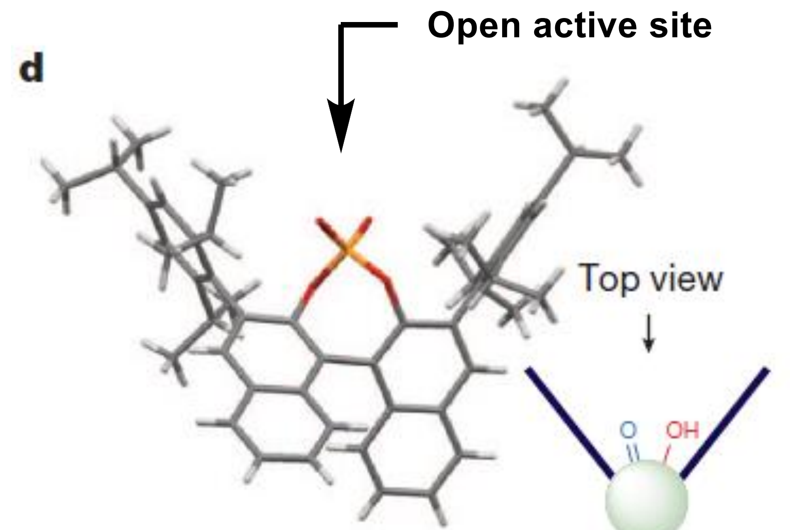
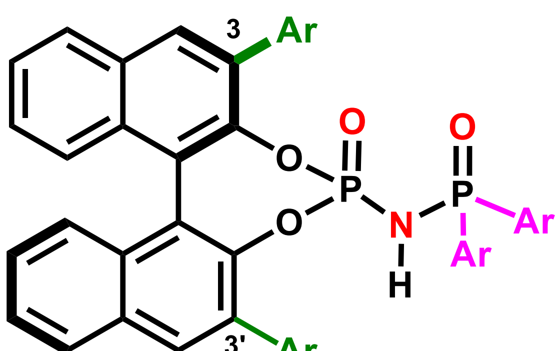



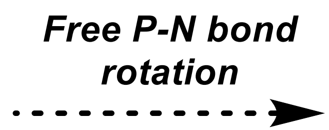

**Fig 1. Structure of (*R*)-TRIP**

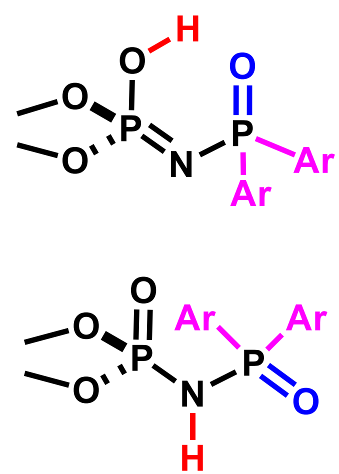
**Plan B**: Introduce other steric control groups




↓ pKa

**Ar group: too far**

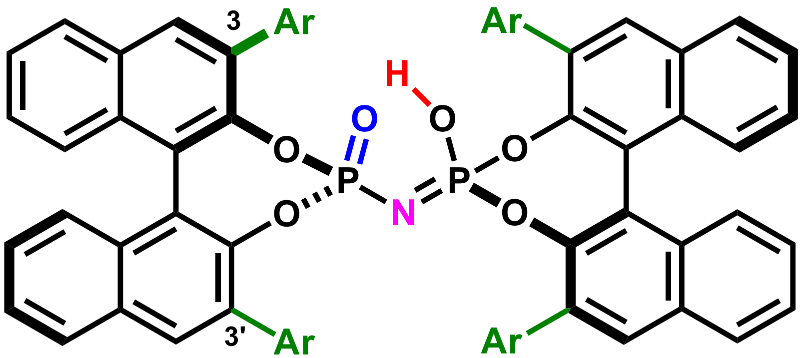



**many distinct acid/base pair** → **Low ee**

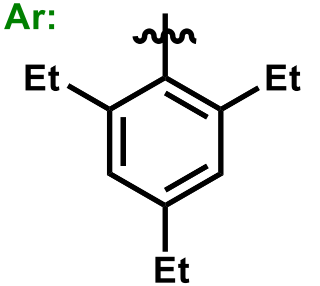
1) Klussmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. *Synlett* **2010**, 2189. 2) Coric, I. and List, B. *Nature* **2012**, *483*, 315.

# Imidodiphosphoric Brønsted acid catalyst

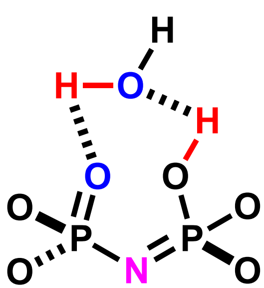



IDP catalyst

Ar:




co-crystallized with $H_2O$ (in MeCN)




Proton located on oxygen atom

rigid environment

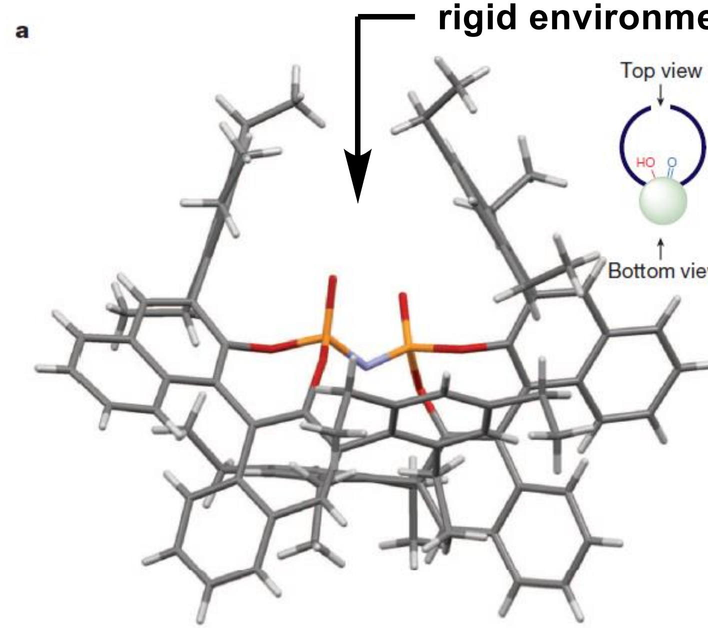



Fig 2. X-ray structure of IDP catalyst

1. Block one Brønsted basic site (N)
2. Free P-N bond rotation was impossible

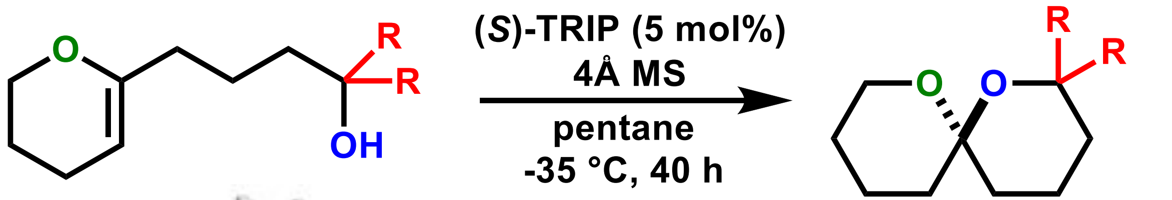
→ single acid/base pair

rigid chiral environment

Coric, I. and List, B. *Nature* **2012**, *483*, 315.

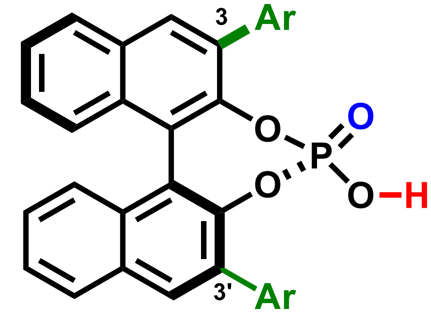
# Asymmetric spiroacetalization

**Nagorny's group**

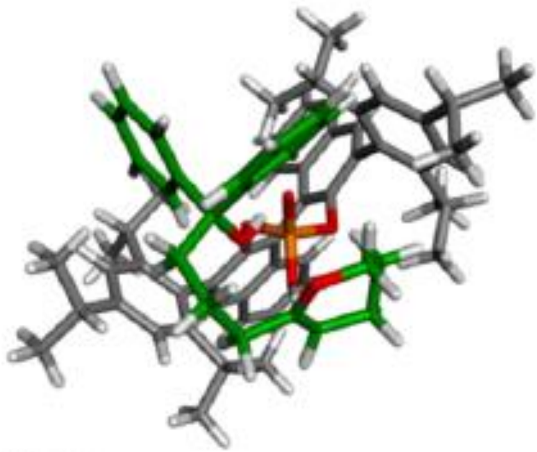



R = Ph, 96%, 92% *ee*

R = Bn, 82%, 75% *ee*

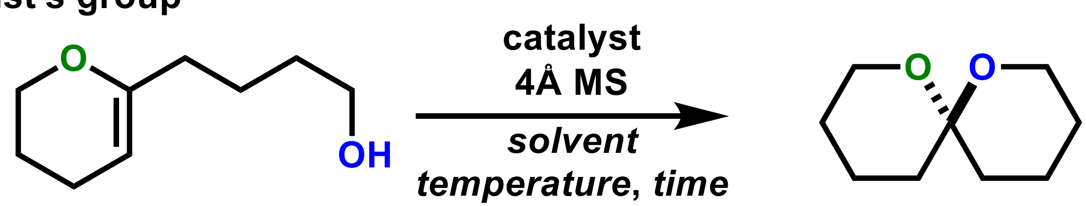



(*S*)-TRIP
Ar :2,4,6-*i*$Pr_3C_6H_2$



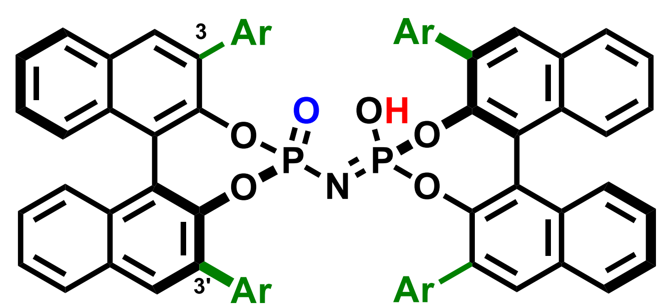
***gem***-**Ph group was necessary for highly enentioselective spiroacetalization**

**List's group**




(*S*)-TRIP (1 mol%)
benzene, rt, 30 min — 14% ee (>90% conversion)

(*R, R*)-IDP (5 mol%)
MTBE, -25 °C, 24 h — 70%, 95% *ee*

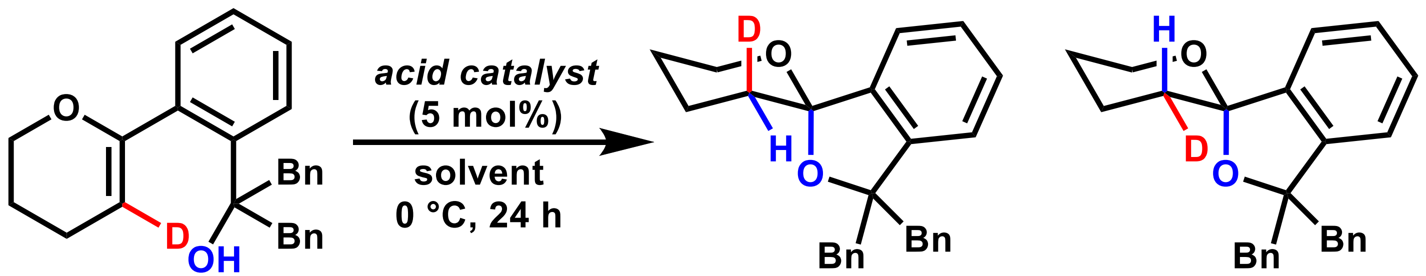


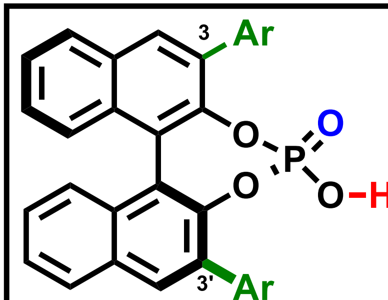

(*S, S*)-IDP
Ar :2,4,6-$Et_3C_6H_2$


1) Sun, Z.; Winschel, G. A.; Borovika, A.; Nagorny, P. *J. Am. Chem. Soc*. **2012**, *134*, 8074. 2) Khomutnyk, Y. Y.; Argüelles, A. J.; Winschel, G. A.; Sun, Z.; Zimmerman, P. M.; Nagorny, P. *J. Am. Chem. Soc*. **2016**, *138*, 444. 3) Coric, I. and List, B. *Nature* **2012**, *483*, 315.

# Mechanistic study by Nagorny's group

## 1. Deuterium labeling



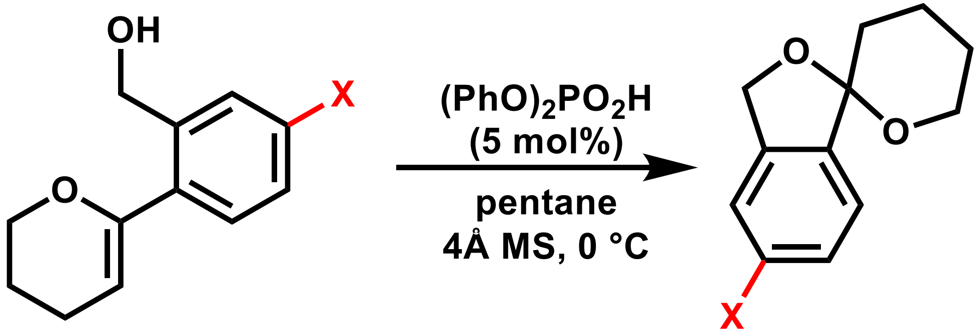



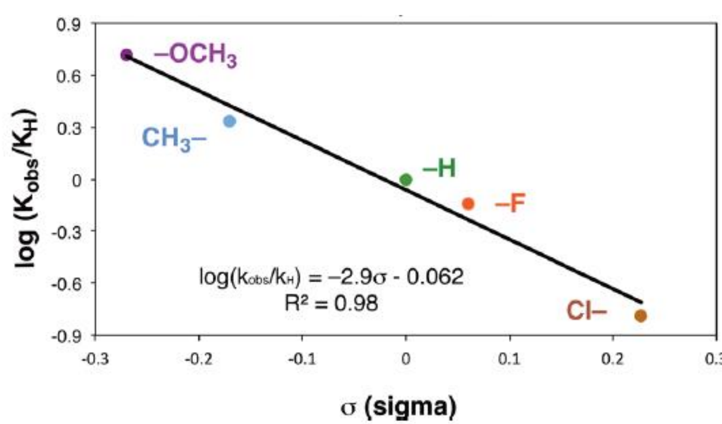

(*S*)-TRIP
Ar :2,4,6-*i*$Pr_3C_6H_2$

| | *syn*-O, H derivative | *anti*-O, H derivative |
|---|---|---|
| (*S*)-TRIP, solvnet (pentane, toluene, $CH_2Cl_2$) | 99 | 1 |
| PTSA, $CH_2Cl_2$ | 1 | 1 |

**Highly selective *syn* H-O addition→ No formation of oxonium cation intermediate**

## 2. Hammett studies



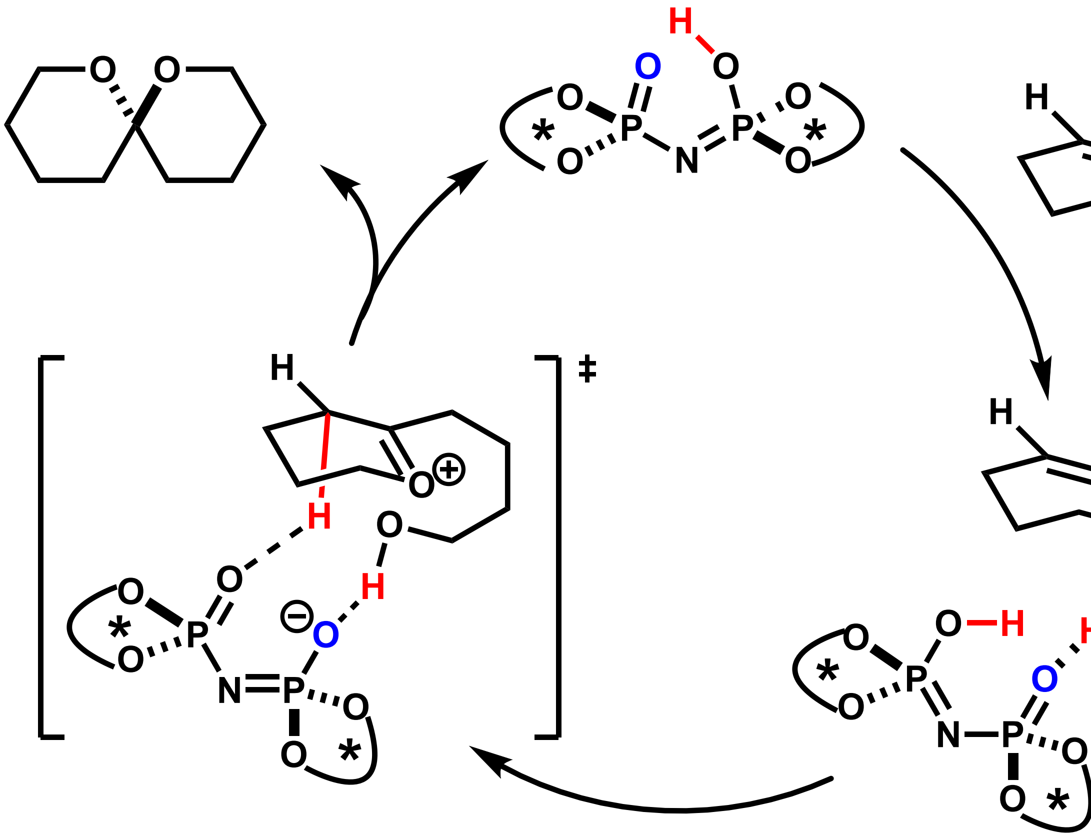




**Build up of positive charge in the TS of the rate determining step**

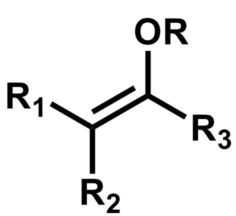
Hammett $\rho = -2.9$

Khomutnyk, Y. Y.; Argüelles, A. J.; Winschel, G. A.; Sun, Z.; Zimmerman, P. M.; Nagorny, P. *J. Am. Chem. Soc.* **2016**, *138*, 444.

# Proposed catalytic cycle

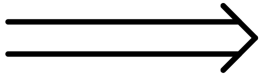


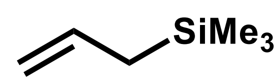
Concerted asynchronous mechanism




· Application for simple enolether was accomplished

*Less basic substrate ?*

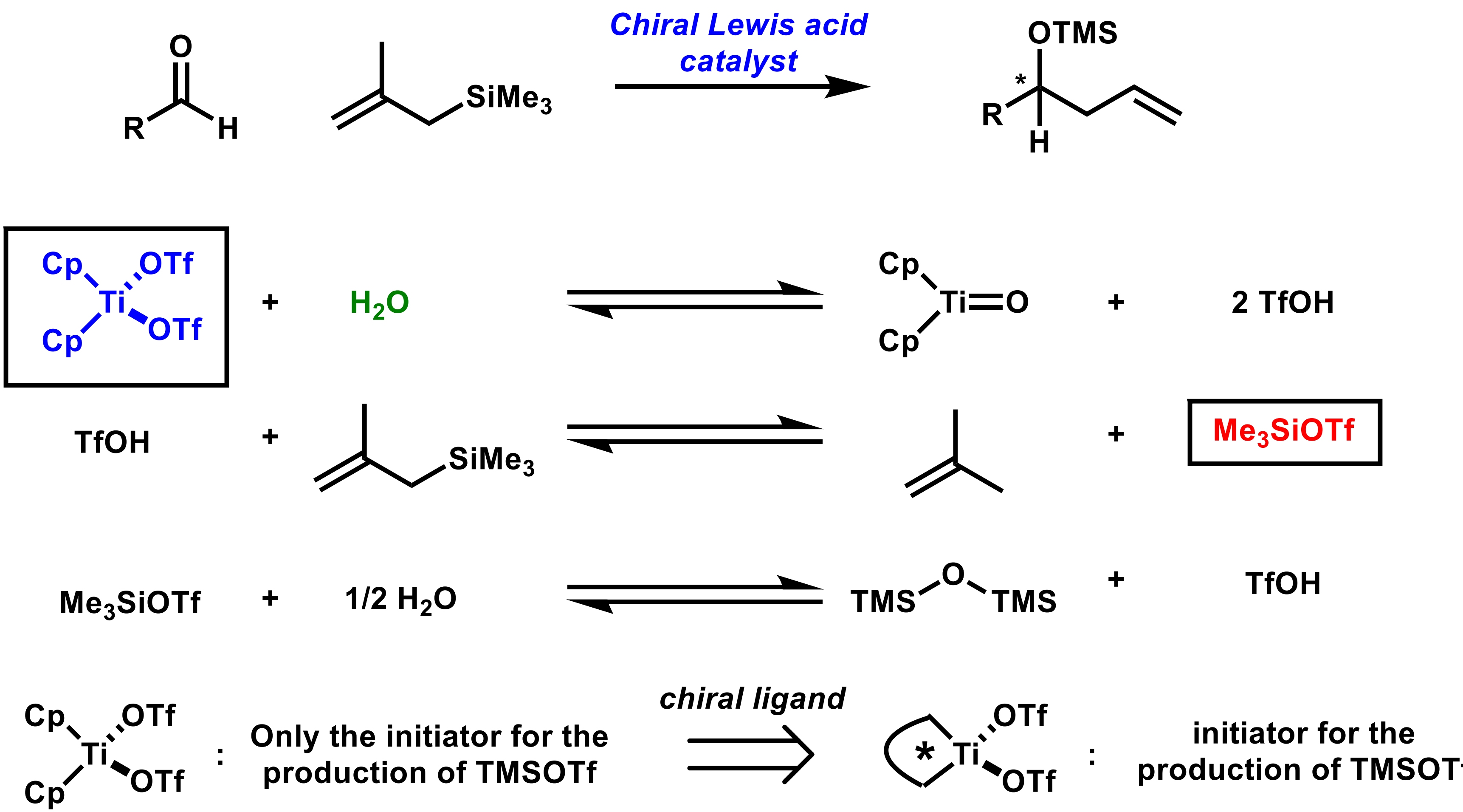





Application for trimethylsilane

Khomutnyk, Y. Y.; Argüelles, A. J.; Winschel, G. A.; Sun, Z.; Zimmerman, P. M.; Nagorny, P. *J. Am. Chem. Soc*. **2016**, *138*, 444.

# Achiral $Me_3Si^+$ species in asymmetric reaction



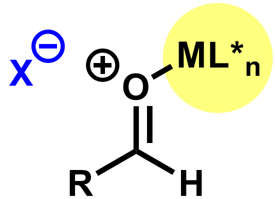

To conduct asymmetric Hosomi-Sakurai reaction...

Slow addition of substrates together with high catalyst loadings ⟹ New catalytic system

Hollis, T. K. and Bosnich, B. *J. Am. Chem. Soc*. **1995**, *117*, 4570.

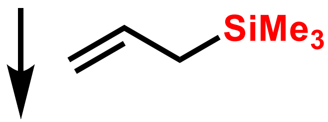
# Silylium-based ACDC catalyst

**Conventional enantioselective Lewis acid catalysis**



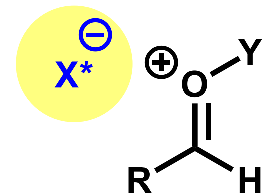

**achiral counteranion**

**If X = OTf**



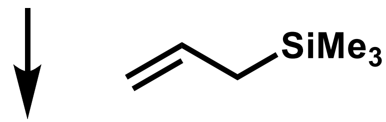

**Generation of $Me_3SiOTf$ ?**

**" ACDC " = Asymmetric Counteranion Directed Catalysis**



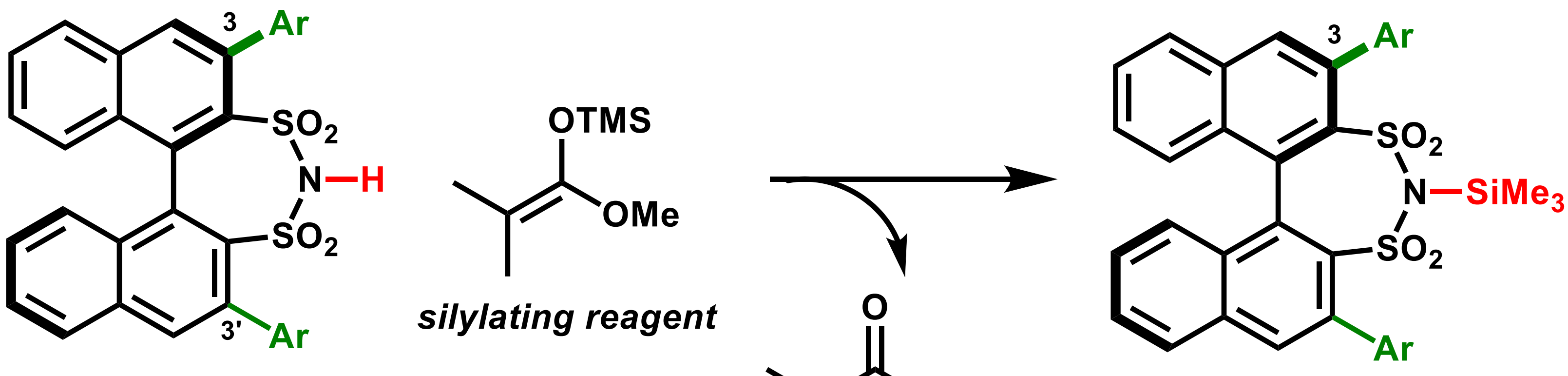

**Y = $SiMe_3$ (Lewis acid cat.)**

**chiral counteranion**




**No generation of achiral $Me_3Si^+$ species**

**How to generate chiral $Me_3Si$ specie ?**

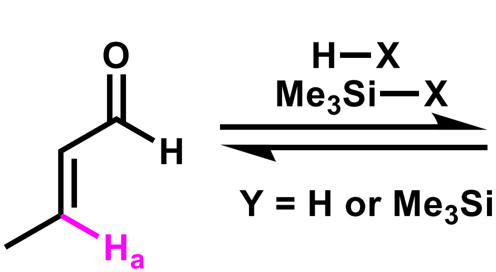


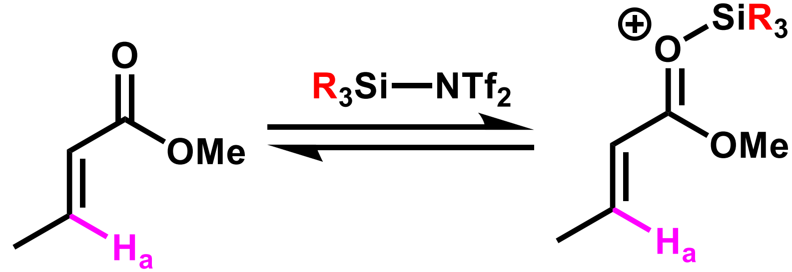

**NH Brønsted acid catalyst**

**Lewis acid catalyst**
**(generation of $R_3Si^+$ species)**

1) Mahlau, M. and List, B. *Angew. Chem. Int. Ed*. **2013**, *52*, 518.
2) Gatzenmeier, T.; Gemmersen, M. V.; Xie, Y.; Höfler, D.; Leutzseh, M.; List, B. *Science* **2016**, *351*, 949.

# NH acid for silylium-based ACDC catalyst



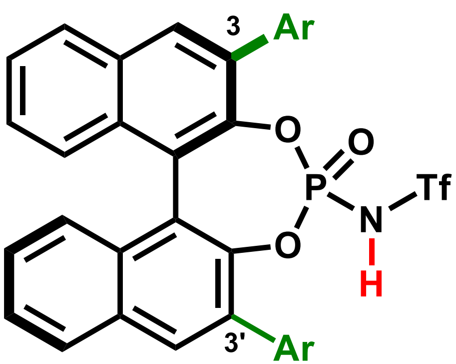




| HX | Δδ ($H_a$) | $Me_3SiX$ | Δδ ($H_a$) |
|---|---|---|---|
| TfOH | 1.27 | TMSOTf | 0.003 |
| $Tf_2NH$ | 0.76 | $TMSNTf_2$ | 1.74 |

NH acid would be better than OH acid for silylium Lewis acid ACDC catalyst

| $R_3SiNTf_2$ | Δδ ($H_a$) |
|---|---|
| $TMSNTf_2$ | 0.89 |
| $TIPSNTf_2$ | 1.09 |

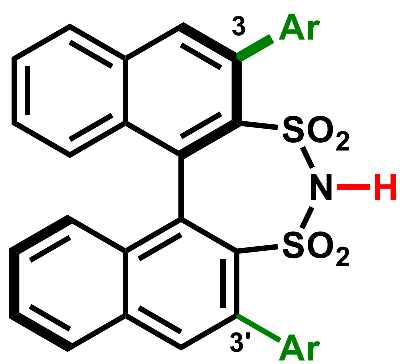
Bulky substituent group increase the Lewis acidity.




A

pKa = 3.3 (in DMSO)

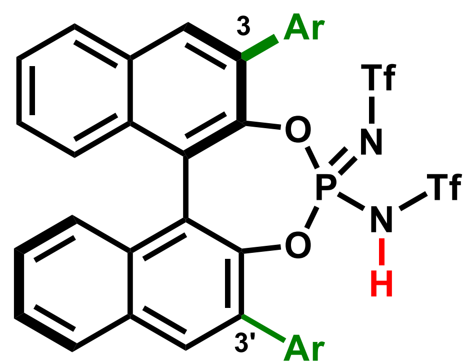
pKa = 6.4 (in MeCN)




B

pKa = 1.8 (in DMSO)

not reported



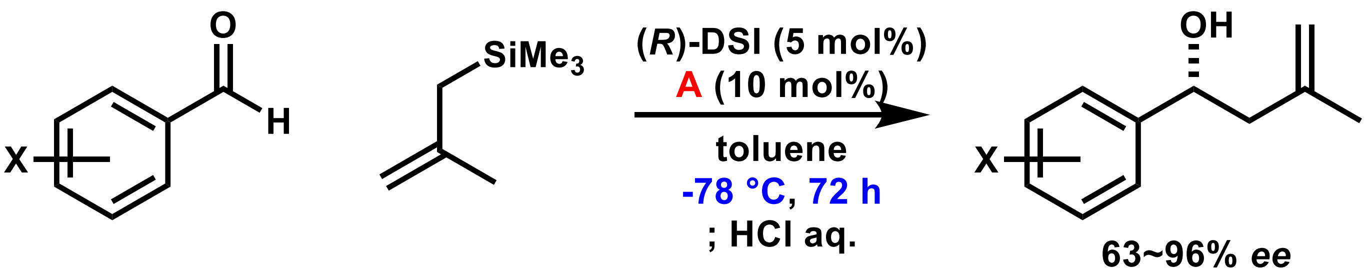

C

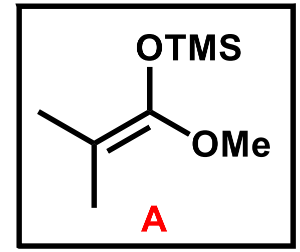
not reported

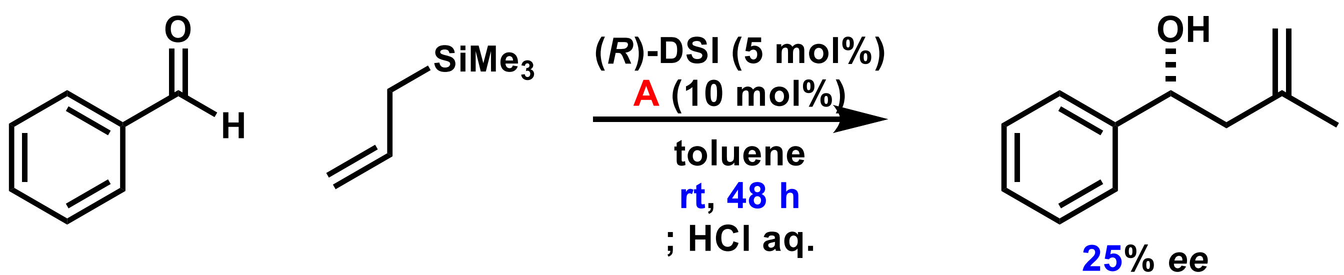
pKa = 2 (in MeCN)

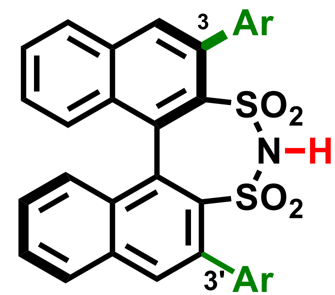
1) Hasegawa, A.; Ishihara, K.; Yamamoto, H. *Angew. Chem. Int. Ed*. **2003**, *42*, 573. 2) Mathieu, B.; Fays, L.; Ghosez, L. *Tetrahedron Lett.* **2000**, *41*, 9561. 3) Nakashima, D. and Yamamoto, H. *J. Am. Chem. Soc*. **2006**, *128*, 9626. 3) Garcia-Garcia, P.; Lay, F.; Rabalakos, C.; List, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 4363. 4) Kaib, P. S. and List, B. *Synlett* **2016**, *27*, 156.

# Previous study by List's group




(*R*)-DSI

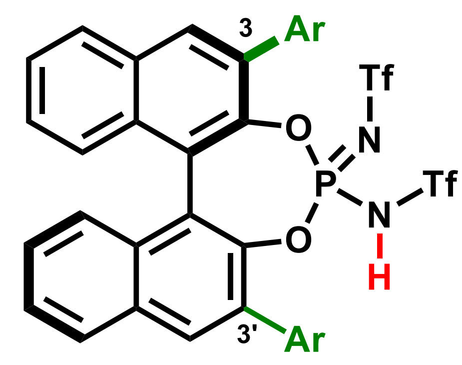
1. A rather than allyltrimethylsilane would be serve as the silylating reagent.

2. Lewis acidity of N-$SiMe_3$ species derived from (*R*)-DSI was insufficient for addition of allyltrimethylsilane

Remaining tasks

1. Strong NH acid catalyst
   → Like catalyst C shown in right box ??

2. Improvement of enantioselectivity
   → Dimerization of BINOL backbone shown in previous section ??




C

Mahlau, M.; Garcia-Garcia, P.; List, B. *Chem. Eur. J*. **2012**, *18*, 16283.

# Imidodiphosphorimidate Brønsted acid catalyst

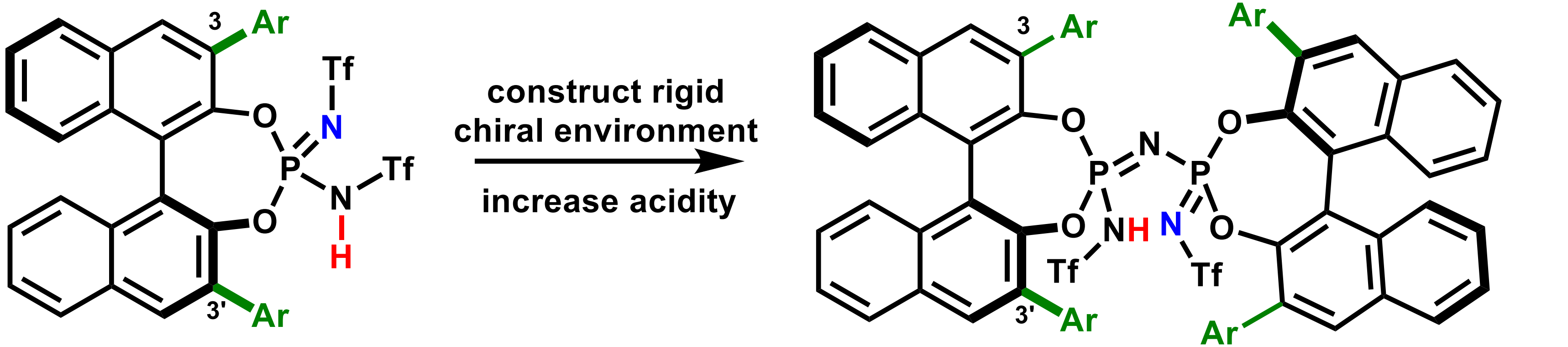
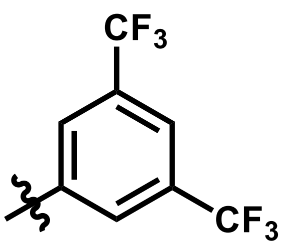
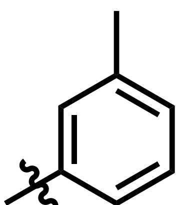
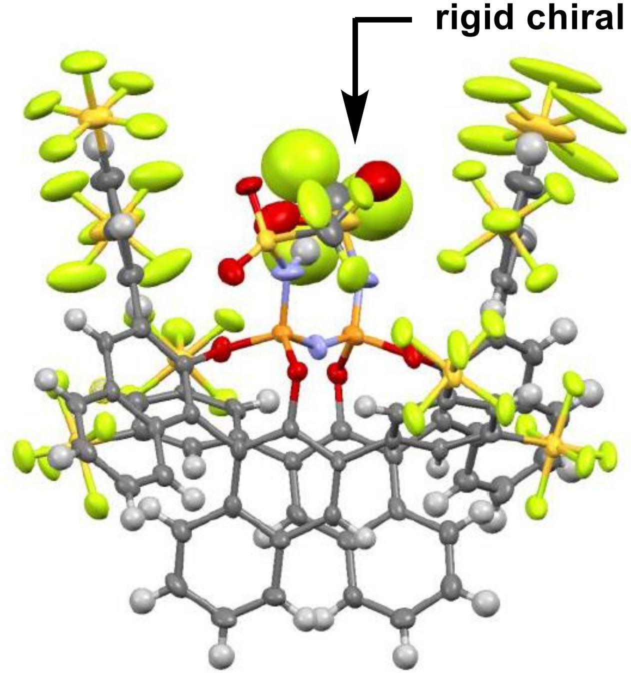



*Table 1*: P-N-P bond angle of IDPi catalyst

| entry | Ar | P-N-P bond angle |
|---|---|---|
| 1 |   | 160.1 ° |
| 2 |  | 161.5 ° |

Acidic proton located on a triflyl-bond nitrogen atom
→ Only single acid/base pair formation



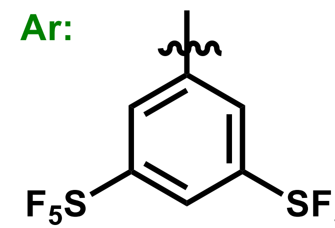
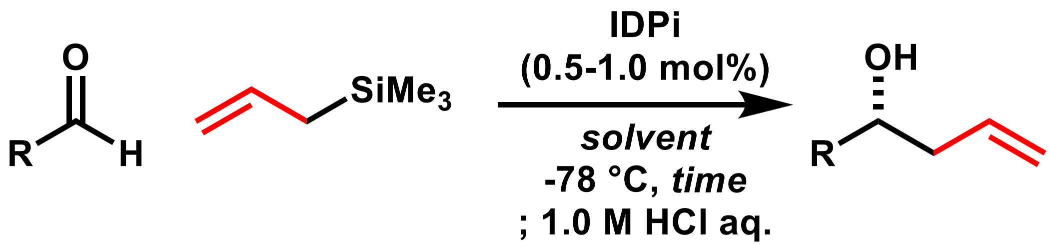
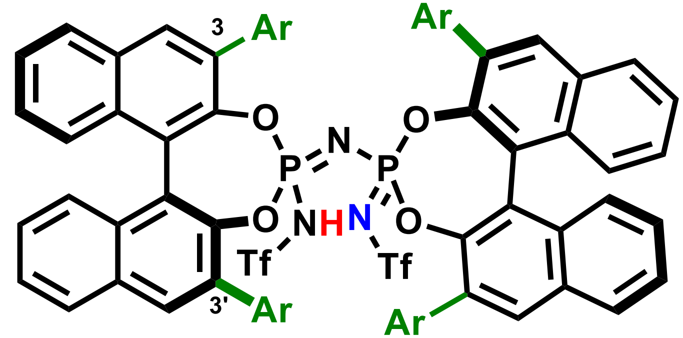




Fig 3. : X-ray structure of IDPi acid

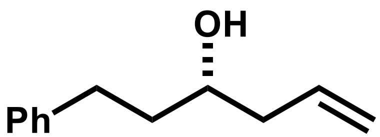

1) Kaib, P. S. J.; Schreyer, L.; Lee, S.; Properzi, R.; List, B. *Angew. Chem. Int. Ed*. **2016**, *55*, 13200.
2) Liu, L.; Kim, H.; Xie, Y.; Fares, C.; Kaib, P. S. J.; Goddard, R.; List, B. *J. Am. Chem. Soc*. **2017**, *139*, 13656.

# Asymmetric Hosomi-Sakurai reaction

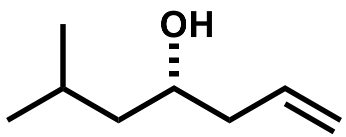


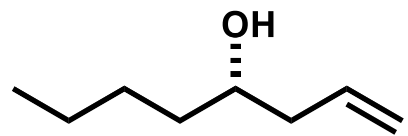

IDPi catalyst



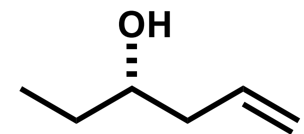

$CH_2Cl_2$, 5 days
93%, 96% *ee*



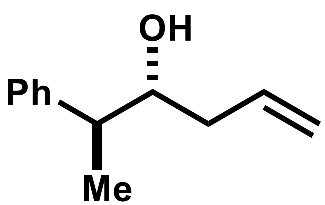

$CH_2Cl_2$, 22 h
73%, 92% *ee*



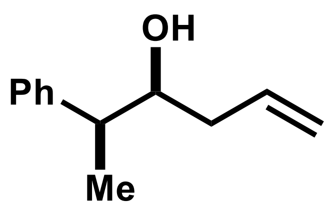

$CH_2Cl_2$, 18 h
70%, 91% *ee*




$CH_2Cl_2$, 2 days
87%, 91% *ee*

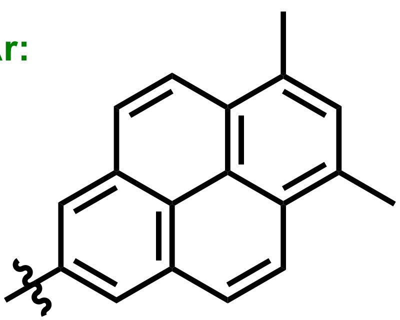



$CHCl_3$, 2 days
90%, 97% *ee*



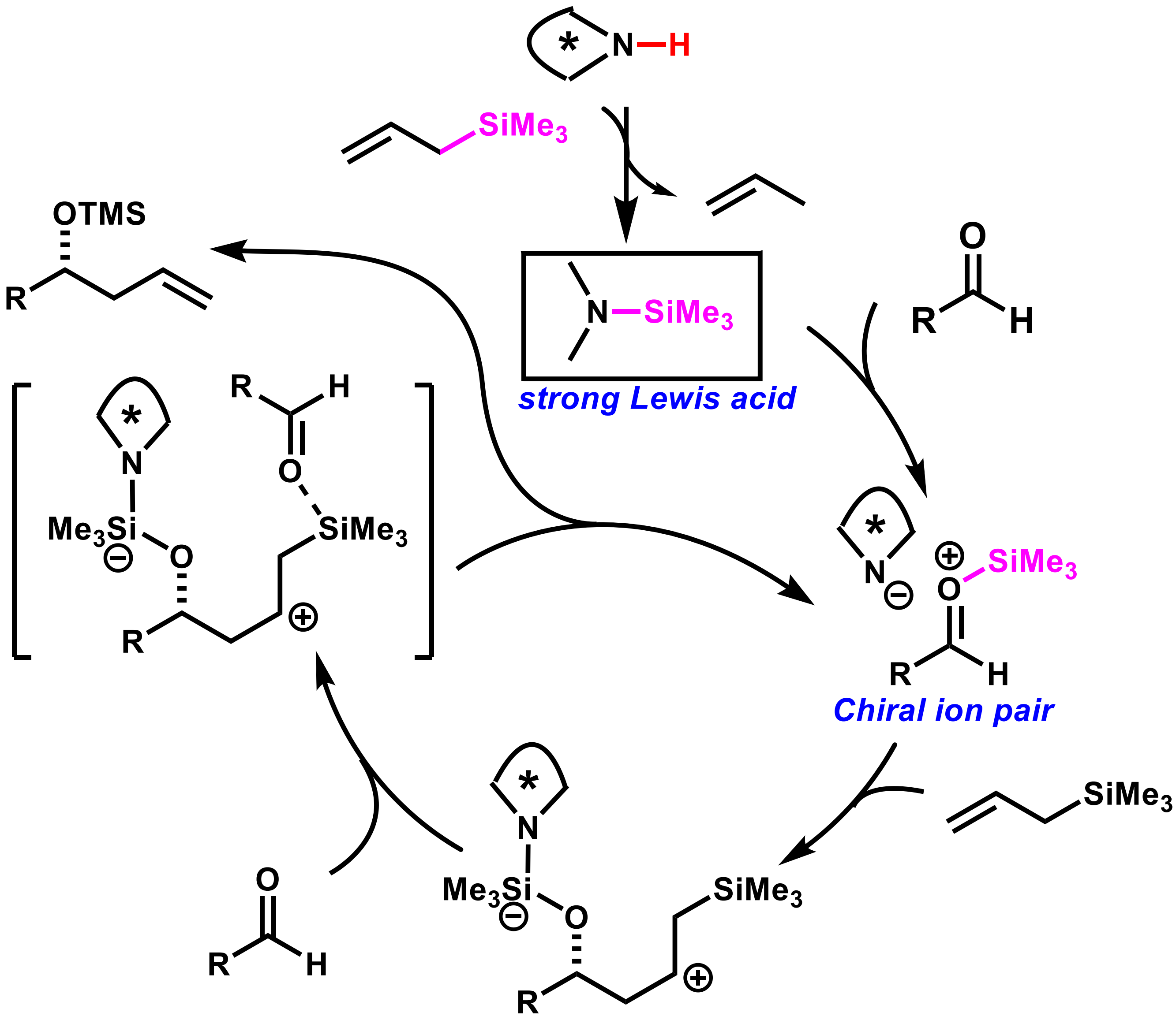

$CHCl_3$, 2 days
*ent*-IDPi catalyst
90%, 30% *ee*

Ar:



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

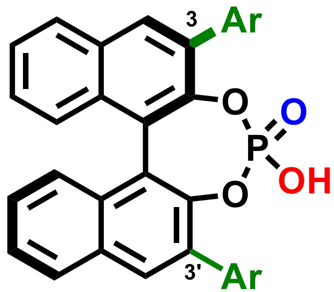
# Proposed catalytic cycle



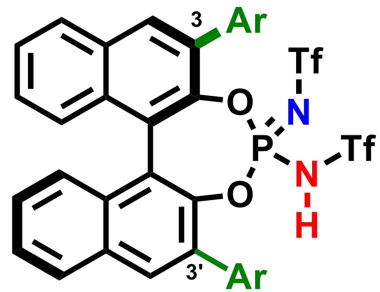


1) Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Chem. Commun*. **2002**, 1564.
2) Hiraiwa, Y.; Ishihara, K.; Yamamoto, H. *Eur. J. Org. Chem*. **2006**, 1837.

# Short Summary



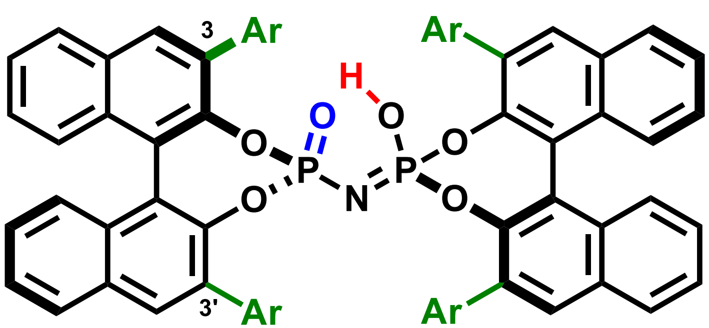

or



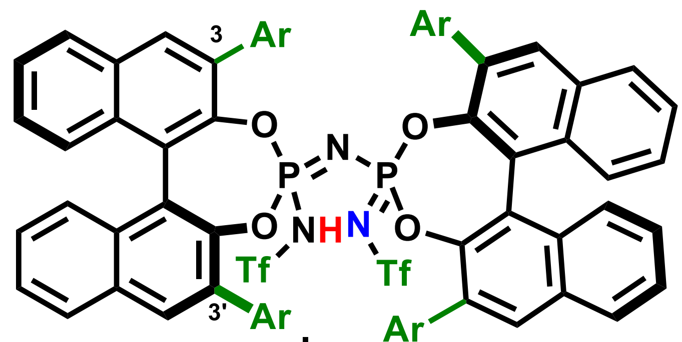

*Construction of rigid chiral environment*

*single acid/base pair*

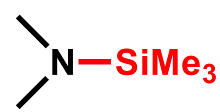
*Construction of rigid chiral environment*




**Application toward small substrates**

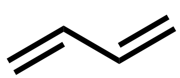



*silylating reagent*

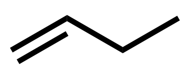



***Silylium-based ACDC catalyst***
**(OrganoLewis acid catalyst)**

**Remaining class of substrates**



or



# Contents

1. Introduction

2. New concepts toward asymmetic Bronsted acid catalysis (2012, 2016)

LETTER

doi:10.1038/nature10932

**Asymmetric spiroacetalization catalysed by confined Brønsted acids**

Ilija Čorić[1] & Benjamin List[1]

**Organocatalysis**

International Edition: DOI: 10.1002/anie.201607828
German Edition: DOI: 10.1002/ange.201607828

**Extremely Active Organocatalysts Enable a Highly Enantioselective Addition of Allyltrimethylsilane to Aldehydes**

*Philip S. J. Kaib, Lucas Schreyer, Sunggi Lee, Roberta Properzi, and Benjamin List**

3. Asymmeric hydroalkoxylation of olefin (2018)

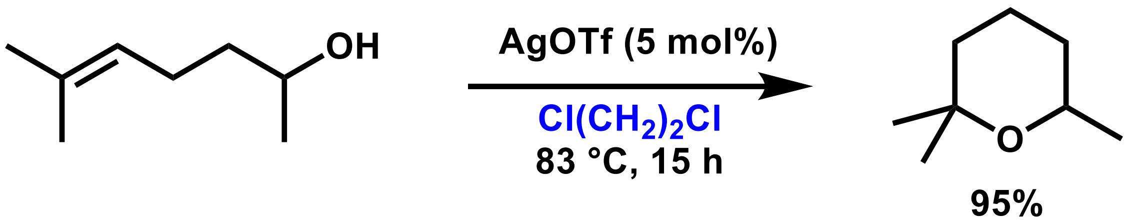
REPORT

ORGANIC CHEMISTRY

**Activation of olefins via asymmetric Brønsted acid catalysis**

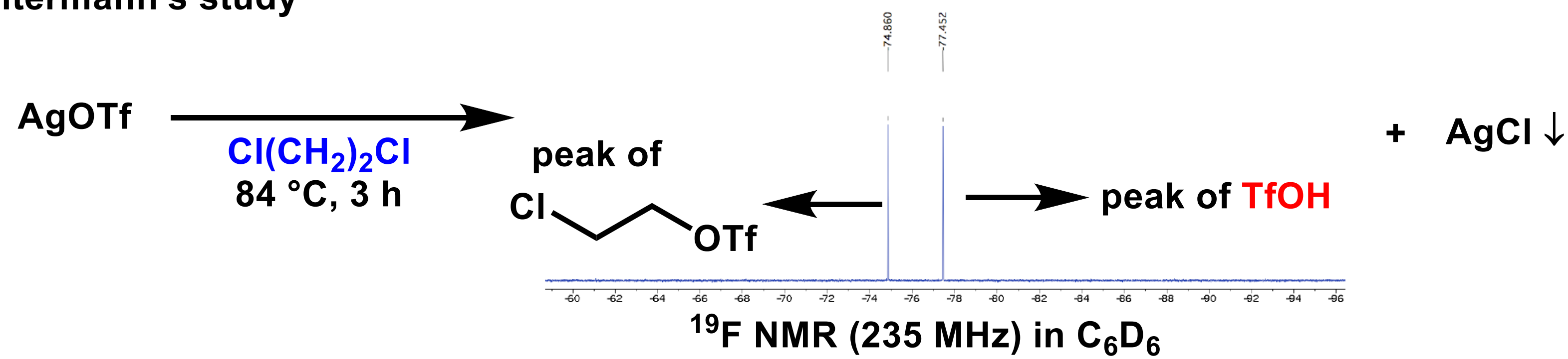
Nobuya Tsuji,[1] Jennifer L. Kennemur,[1] Thomas Buyck,[1] Sunggi Lee,[1] Sébastien Prévost,[1] Philip S. J. Kaib,[1] Dmytro Bykov,[2,3] Christophe Farès,[1] Benjamin List[1]*

# Hidden Brønsted acid catalysis

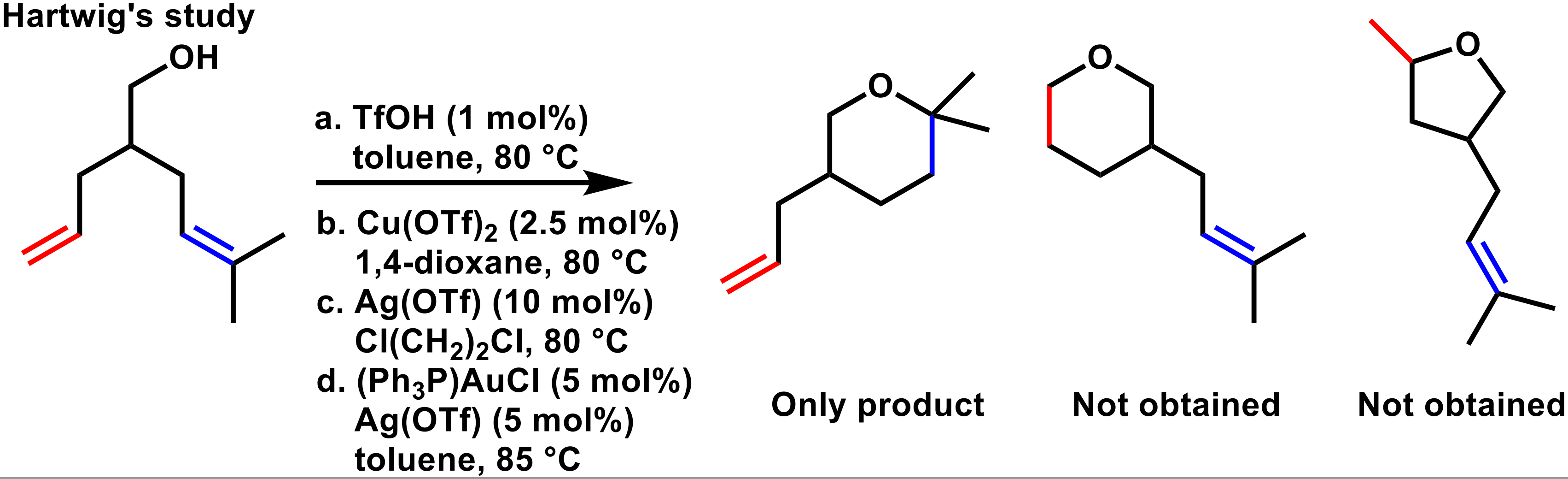



**Asymmetric hydroalkoxylation would be possible if we use chiral ligand, but...**

**Hintermann's study**




**Hartwig's study**

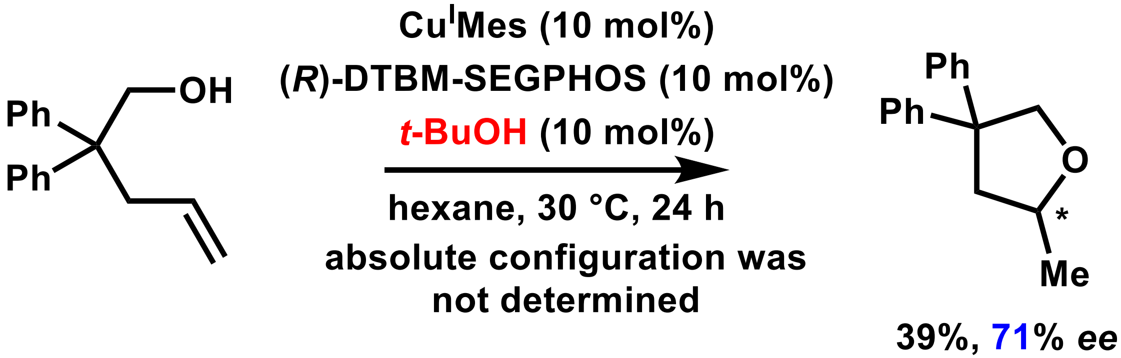


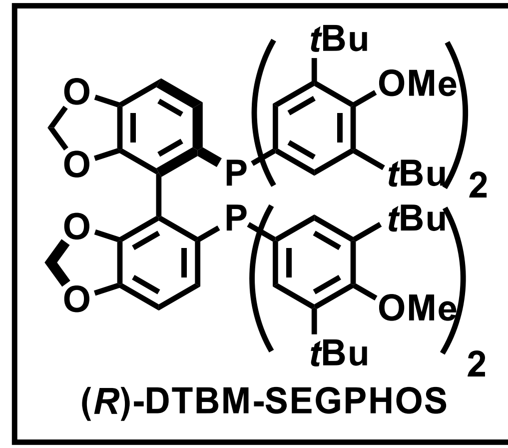


1) Yang, C-G.; Reich, N. W.; Shi, Z.; He, C. *Org. Lett*. **2005**, *7*, 4553. 2) Dang, T. T.; Boeck, F.; Hintermann, L. *J. Org. Chem*. **2011**, *76*, 9353.
3) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M. Hartwig, J. F. *Org. Lett*. **2006**, *8*, 4179.

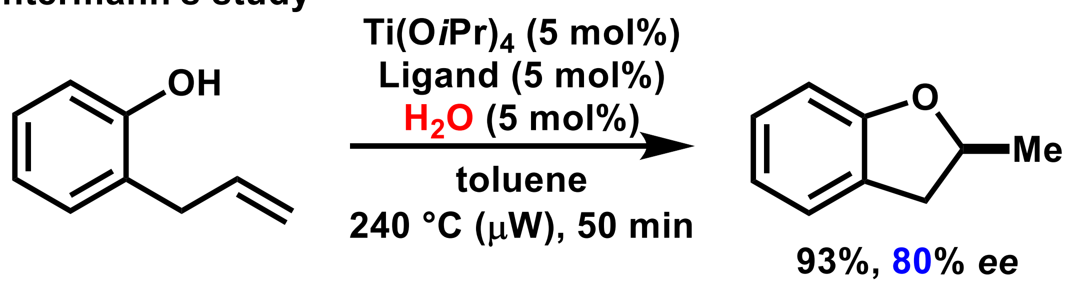
# How to render Hidden Brønsted acid catalysis ?

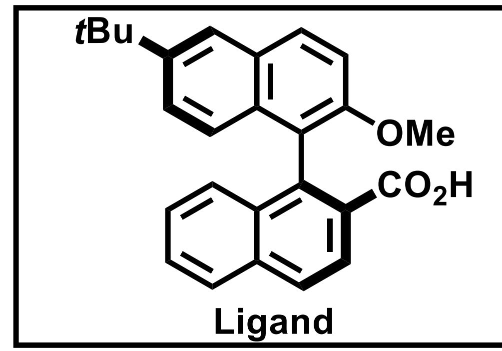
**Sawamura's study**

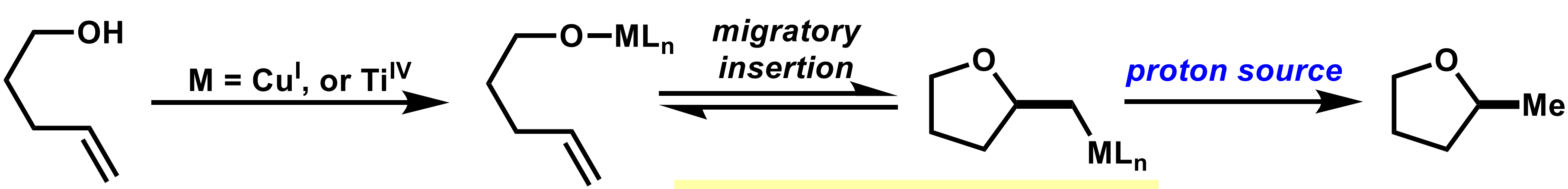



**Hintermann's study**




**1. Kinetic condition** **2. Not electrophilic activation**

1) Murayama, H.; Nagao, K.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2015**, *17*, 2039. 2) Schlüter, J.; Blazejak, F.; Boeck, F.; Hintermann, L. *Angew. Chem. Int. Ed.* **2015**, *54*, 4014. 3) Stollenz, M. and Meyer, F. *Organometallics* **2012**, *31*, 7708.

# Screening of catalyst

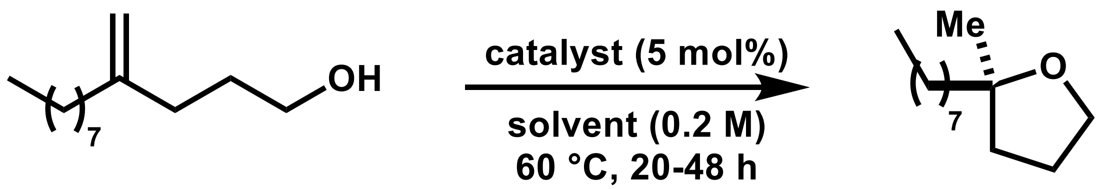
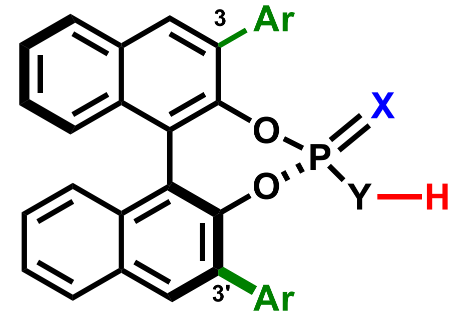
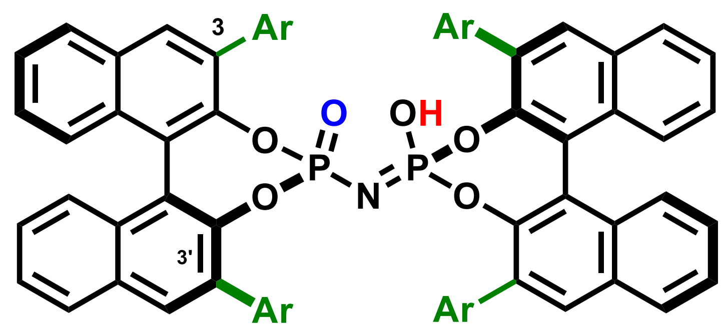



*Table* 2 : Catalyst screenings

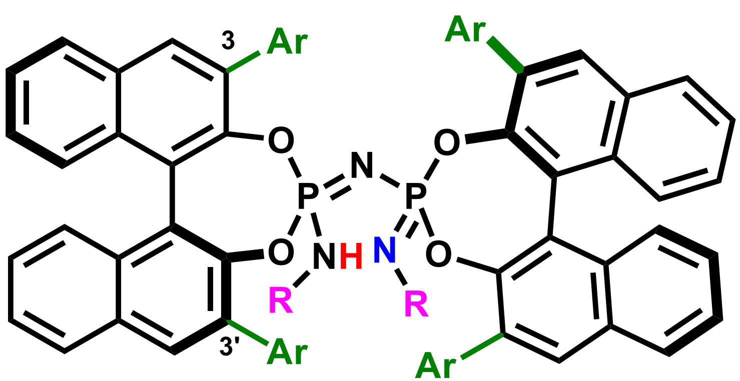
| entry | catalyst | solvent | yield | *ee* |
|---|---|---|---|---|
| 1 | A | toluene | n. d. | — |
| 2 | B | toluene | 73% | 1% |
| 3 | C | toluene | n. d. | — |
| 4 | D | toluene | 85% | 27% |
| 5 | E | cyclohexane | 91% | 95% |




Ar :2,4,6-*i*$Pr_3C_6H_2$
A: X = O, Y = O
B: X = O, Y = NTf



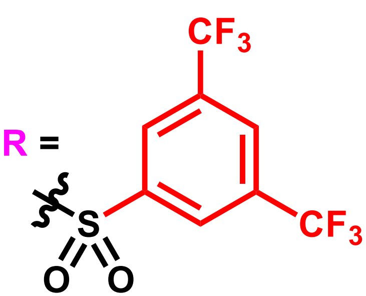

C
Ar: 2,4,6-$Et_3C_6H_2$




(*S*, *S*)-IDPi

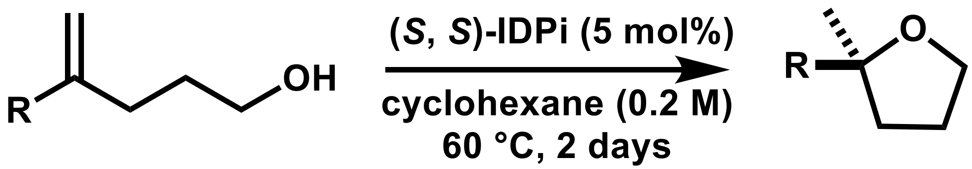
D: Ar= Ph, R= Tf

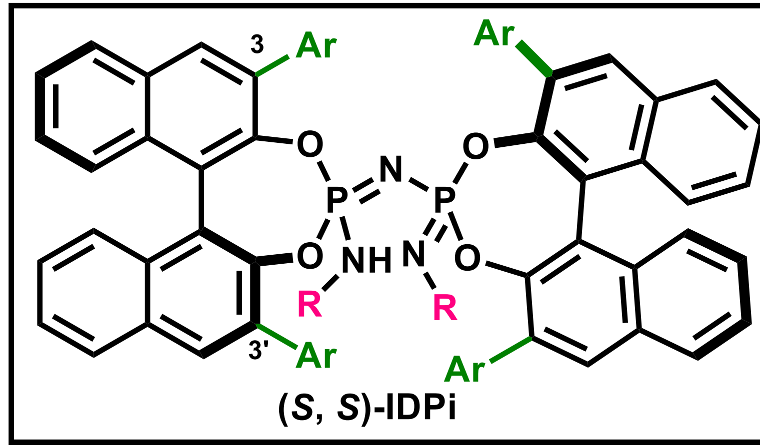
E: Ar = 4-*t*$BuC_6H_4$ R =

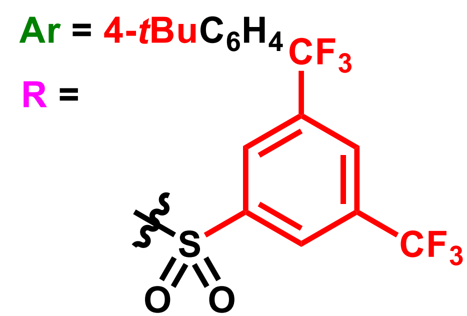


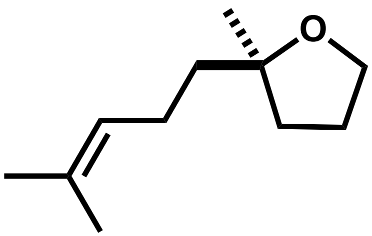

Tsuji, N.; Kennemur, J. L.; Buyek, T.; Lee, S.; Prevost, S.; Kaib, P. S. J.; Bykov, D.; Fares, C.; List, B. *Science* **2018**, *359*, 1501.

# Substrate scope

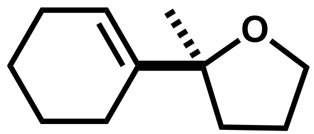


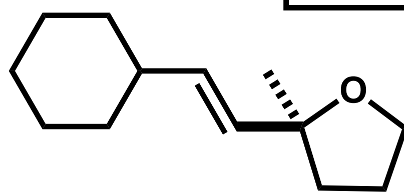



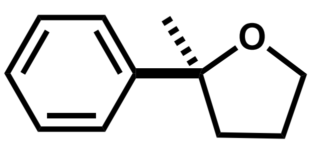
94%, 90% *ee*



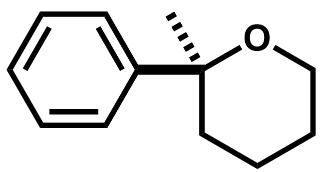
72%, 96% *ee*
(10 °C, 7days)



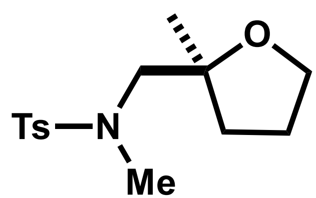
85%, 95% *ee*
(10 °C, 7days)



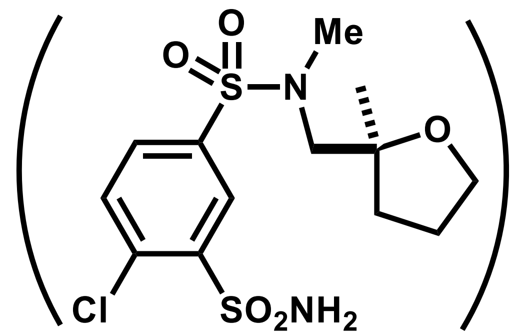
84%, 97% *ee*



53%, 85% *ee*

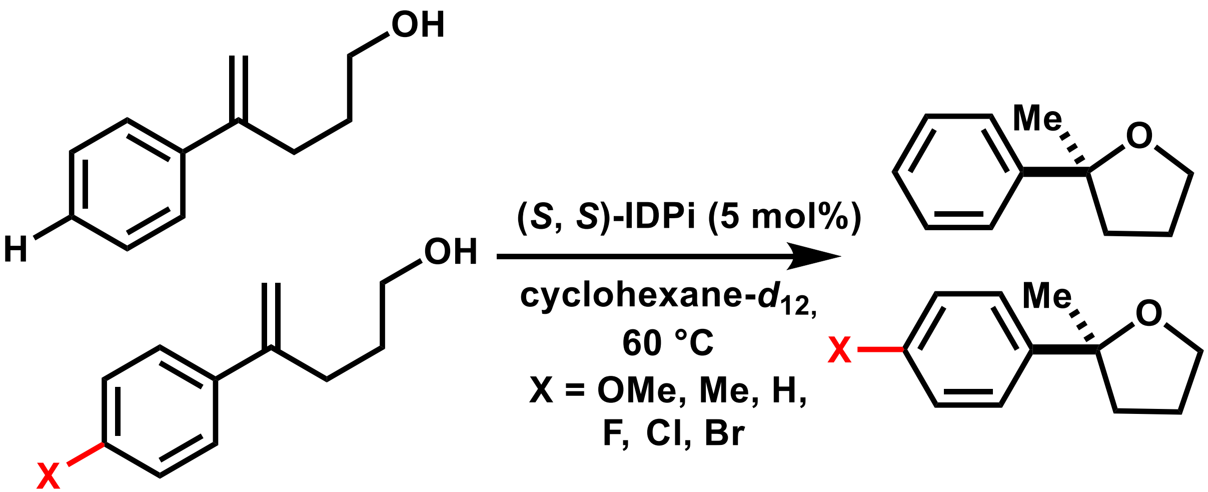


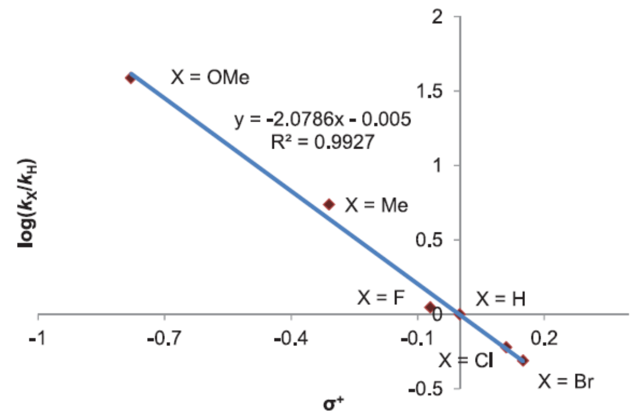

66%, 94% *ee*




(*S*)-Mefruside

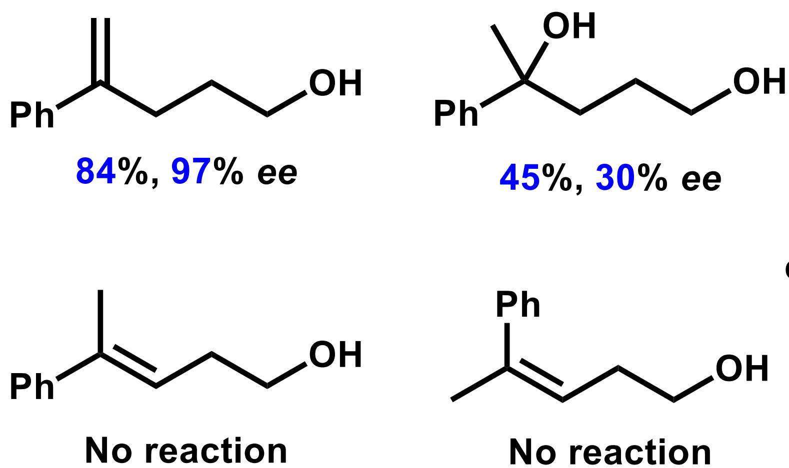
# Mechanistic study

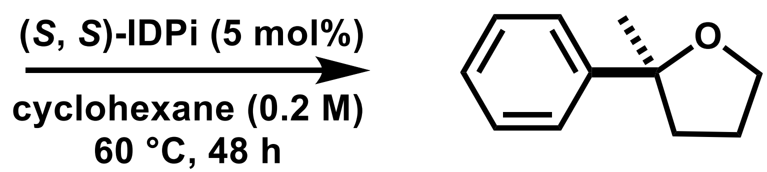



$\rho$ = -2.08 ± 0.04

Positive charge in the TS of this reaction



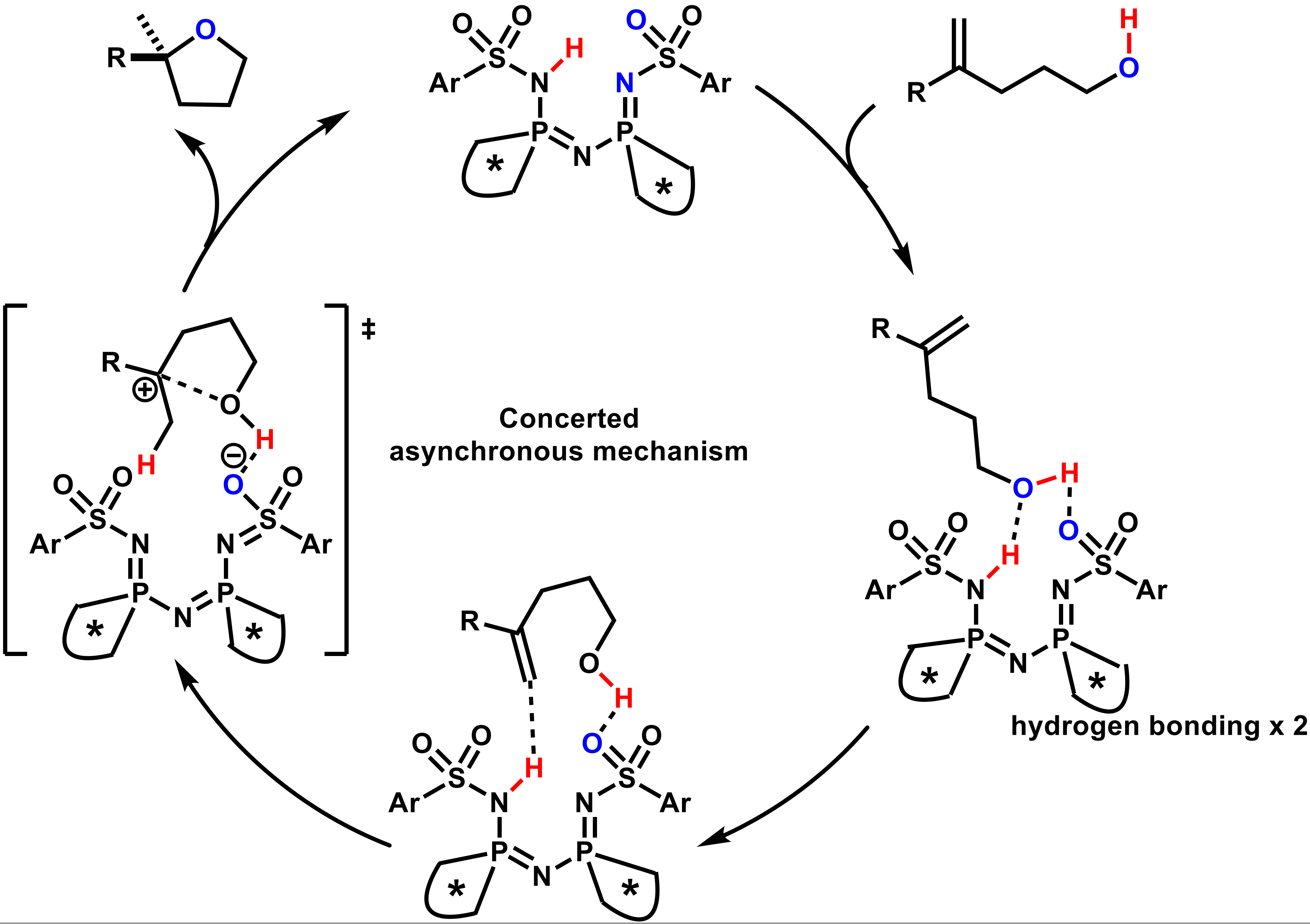




Formation of carbocation intermediate was rejected.

→ Concerted asynchronous mechanism is plausible ?

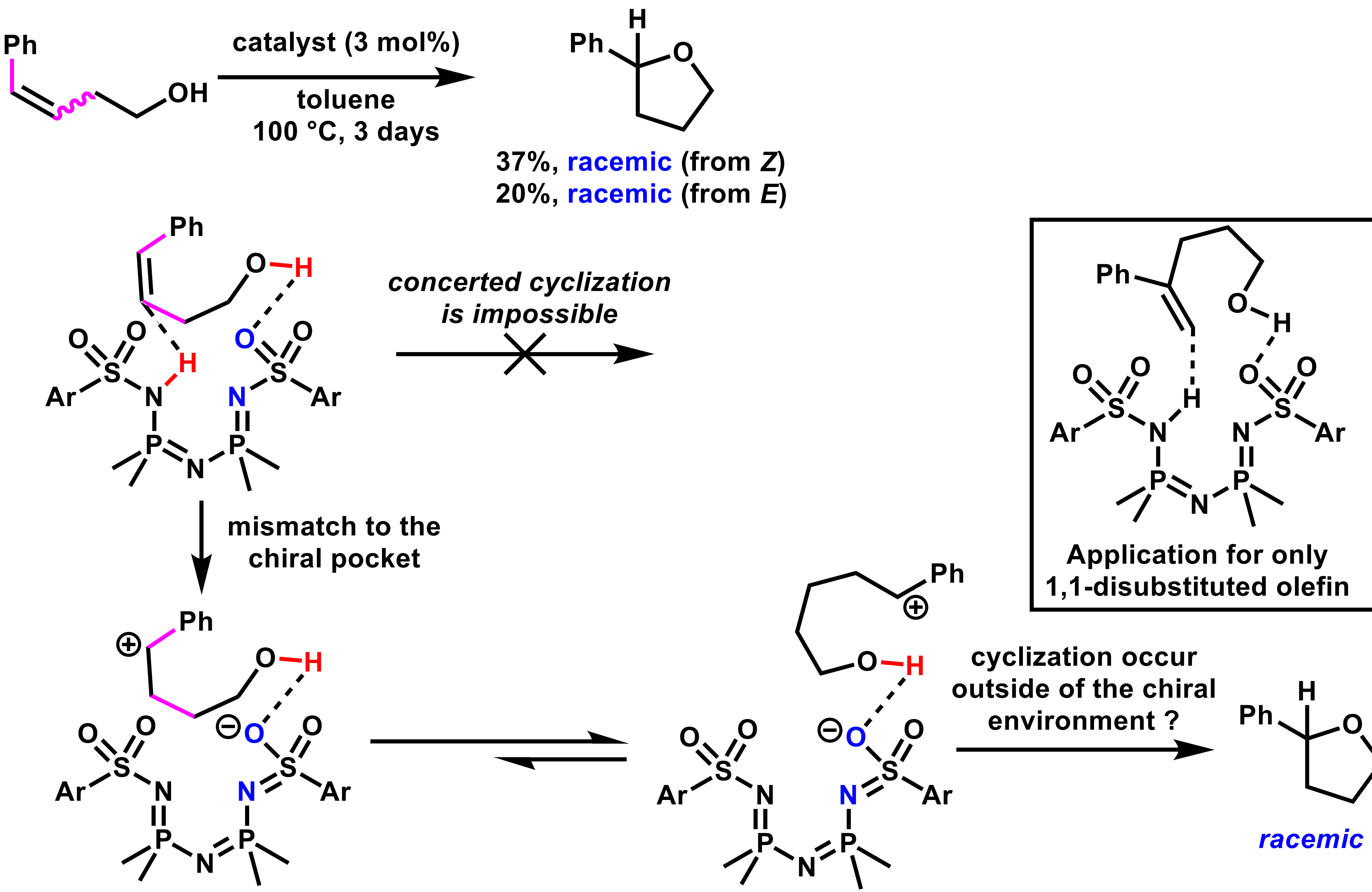
Tsuji, N.; Kennemur, J. L.; Buyek, T.; Lee, S.; Prevost, S.; Kaib, P. S. J.; Bykov, D.; Fares, C.; List, B. *Science* **2018**, *359*, 1501.

# Proposed catalytic cycle



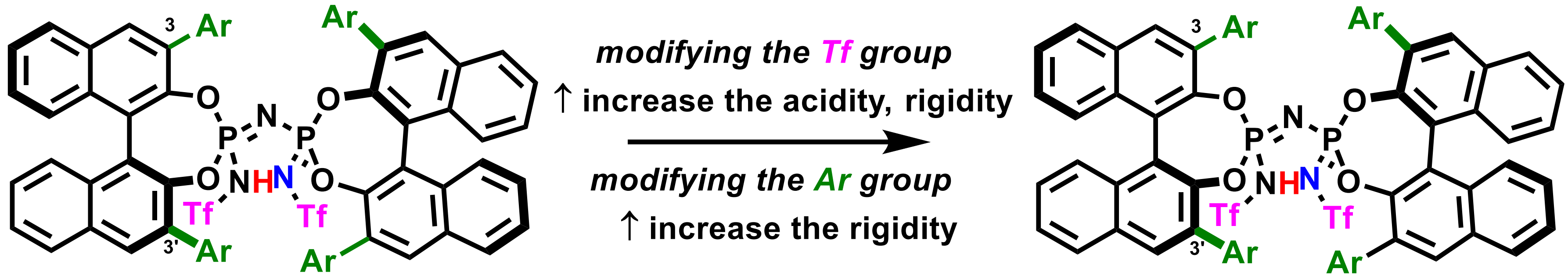

Tsuji, N.; Kennemur, J. L.; Buyek, T.; Lee, S.; Prevost, S.; Kaib, P. S. J.; Bykov, D.; Fares, C.; List, B. *Science* **2018**, *359*, 1501.

# Difference of the reactivity of olefin (Proposed)




Tsuji, N.; Kennemur, J. L.; Buyek, T.; Lee, S.; Prevost, S.; Kaib, P. S. J.; Bykov, D.; Fares, C.; List, B. *Science* **2018**, *359*, 1501.

# Summary





Low basicity
simple substrate

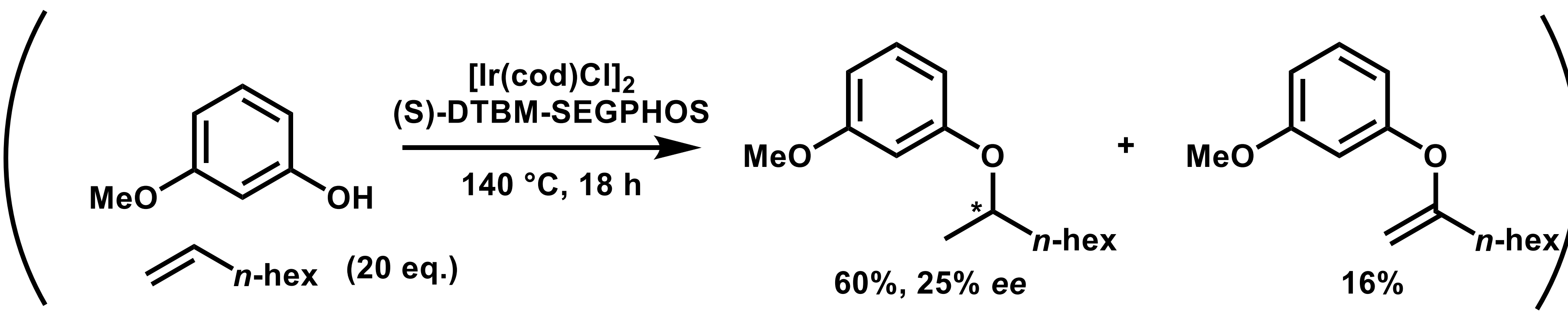
high yield
high *ee*

---

Future perspective

1. Application for another substituted type olefin
→ modify the catalyst folding

2. Application for intermolecular reaction




Sevov, C. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 9303.