Asymmetric Counteranion-Directed Catalysis

M1 Yuki Hirao

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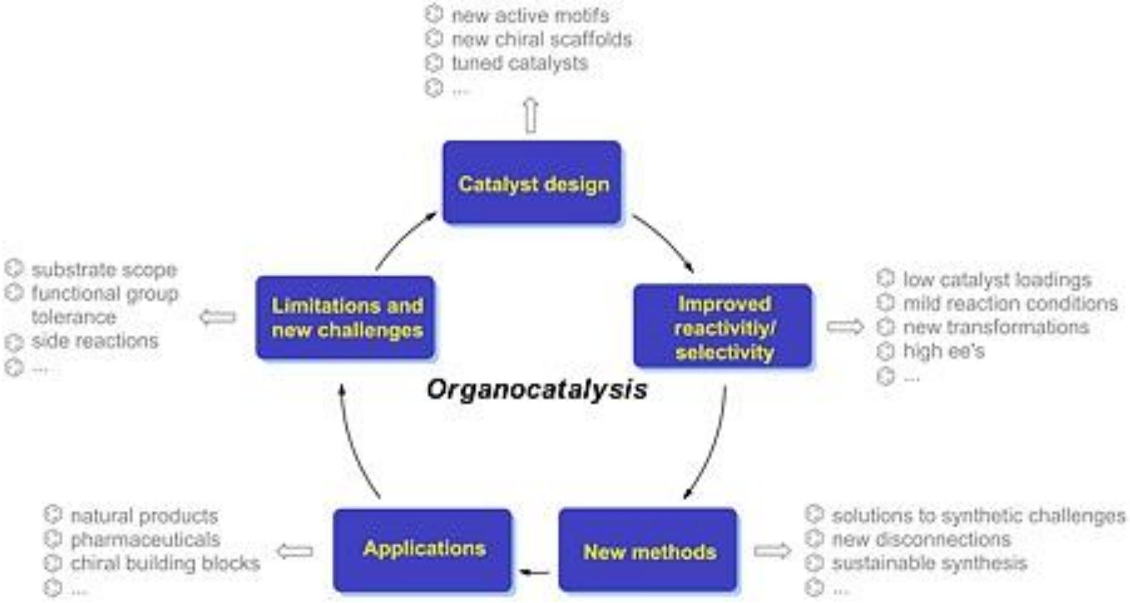
Benjamin List



2012-2014	Managing Director at the Max-Planck-Institut für Kohlenforschung
since 2005	Director at the Max-Planck-Institut für Kohlenforschung
since 2005	Scientific member of the Max-Planck-Society
since 2004	Honorary Professor at the University of Cologne
2003–2005	Group Leader at the Max-Planck-Institut für Kohlenforschung
1999–2003	Assistant Professor (Tenure Track), Scripps Research Institute, La Jolla, USA
1997–1998	Post-Doc, Scripps Research Institute, La Jolla, USA
1997	PhD, University Frankfurt (J. Mulzer)
1993	Chemistry Diplom, Free University Berlin
1968	Born in Frankfurt/Germany

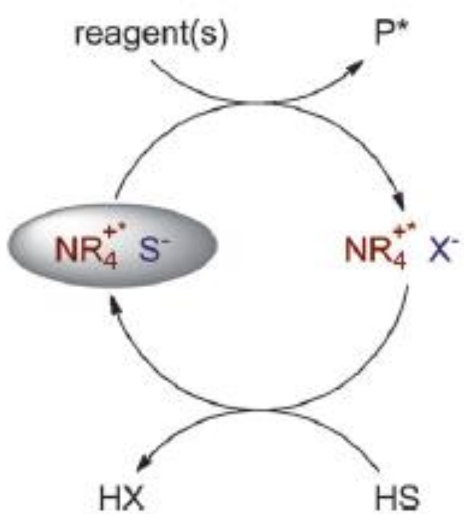
https://www.kofo.mpg.de/en/research/homogeneous-catalysis-

What is ACDC?

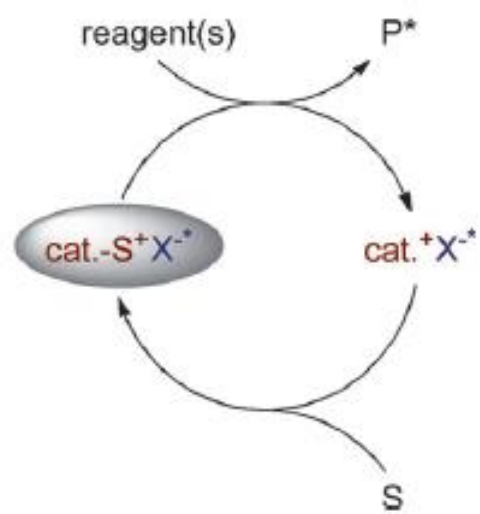
ACDC : Asymmetric Counteranion-Directed Catalysis

Asymmetric counteranion-directed catalysis refers to the induction of enantioselectivity in a reaction proceeding through a cationic intermediate by means of ion pairing with a chiral, enantiomerically pure anion provided by the catalyst.

Phase-Transfer Catalysis



ACDC

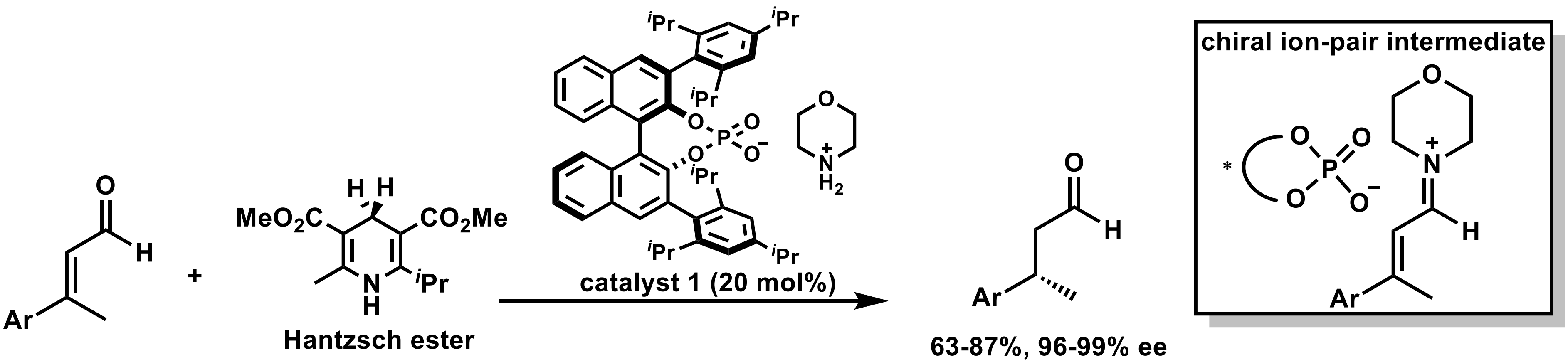


P=product
S=substrate
X=anion

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

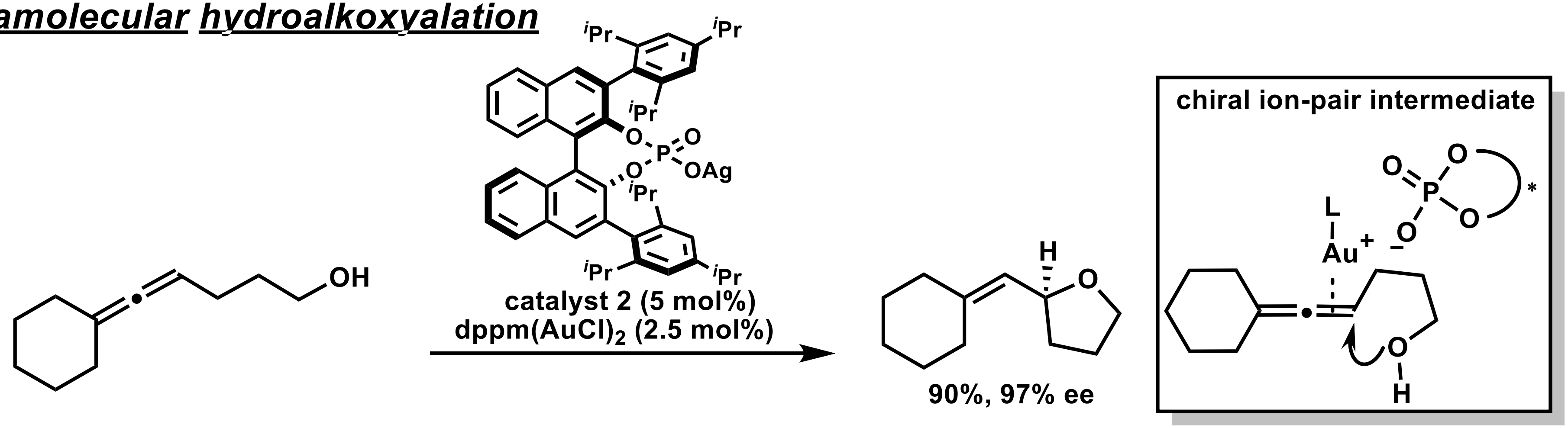
Example of ACDC

asymmetric transfer hydrogenation of α,β-unsaturated aldehydes



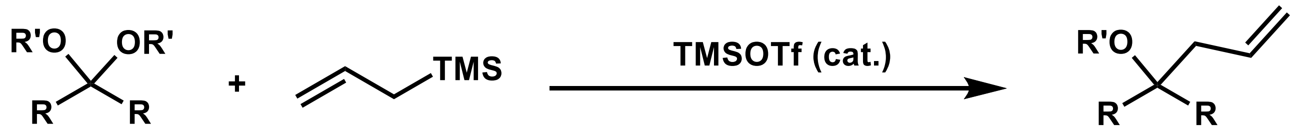
S.Mayer, B. List, *Angew. Chem. Int. Ed*. **2006**, *45*, 4193.

intramolecular hydroalkoxyalation

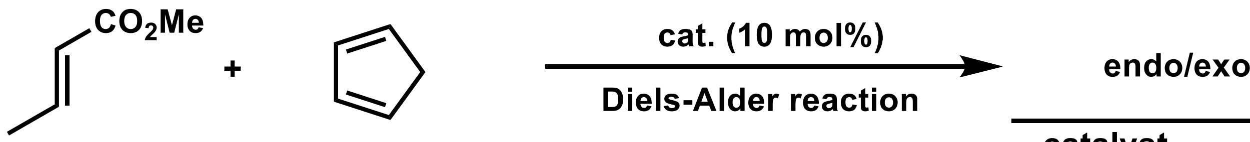


G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science*. **2007**, *317*, 496.

Silylium Lewis Acid Catalysis

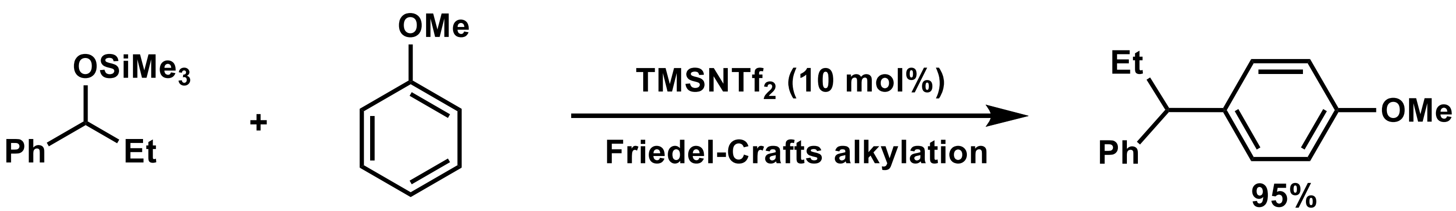


T. Tsunoda, M. Suzuki, R. Noyori, *Tetrahedron Lett*. **1980**, *21*, 71.



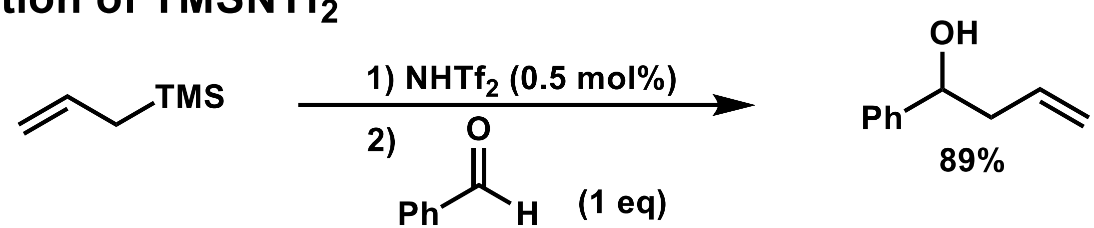
catalyst	yield	endo:exo
TMSOTf	< 5%	13.3:1
$TMSNTf_2$	83%	24:1

B. Mathieu, L. Ghosez, *Tetrahedron Lett*. **1997**, *38*, 5497.



A. Ishii, O. Kotera, T. Saeki, K. Mikami, *Synlett*. **1997**, 1145.

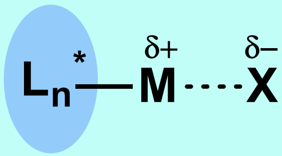
in-situ generation of $TMSNTf_2$



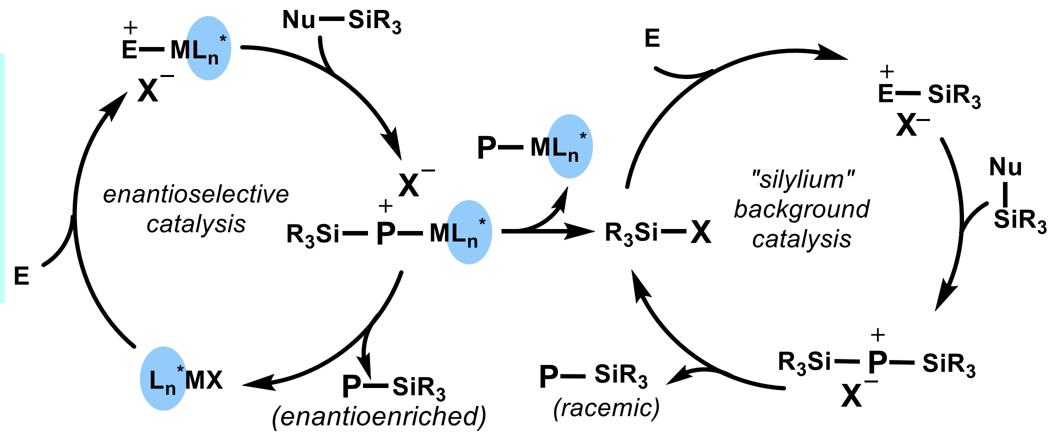
K. Ishihara, Y. Hiraiwa, H. Yamamoto, *Synlett*. **2001**, 1851.

"Silylium" ACDC

previous design of chiral Lewis acid catalysts

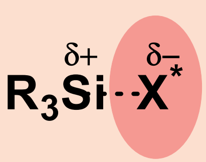


- × ligand (= Lewis base) induces asymmetry but often decreases Lewis acidity
- × potential "silylium" background catalysis

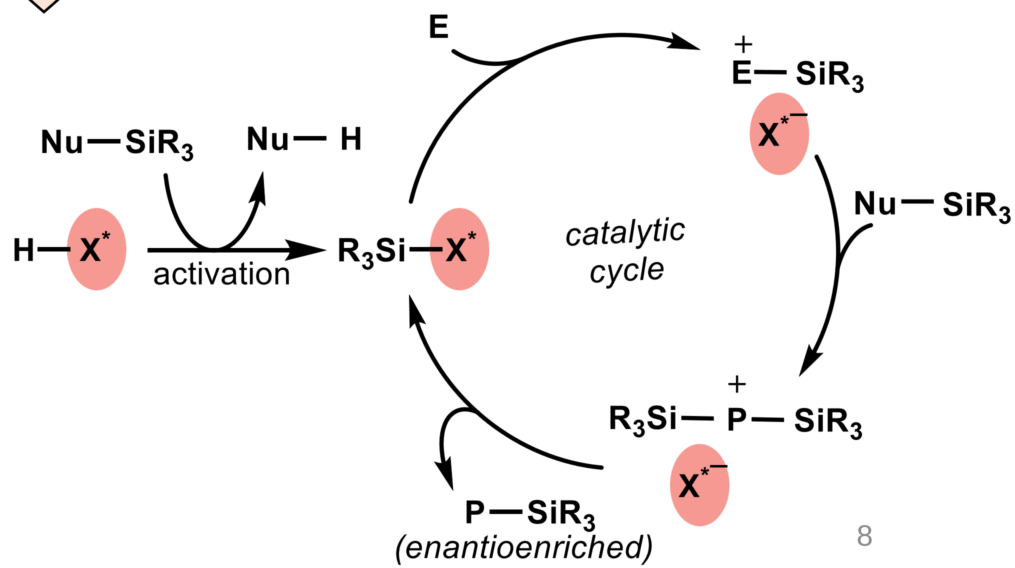


P=product
Nu=nucleophile
E=electrophile

new concept: "silylium" ACDC



- O chiral, enantiopure counteranion induces asymmetry via ion pairing
- O extremly high Lewis acidity
- O no "silylium" background catalysis



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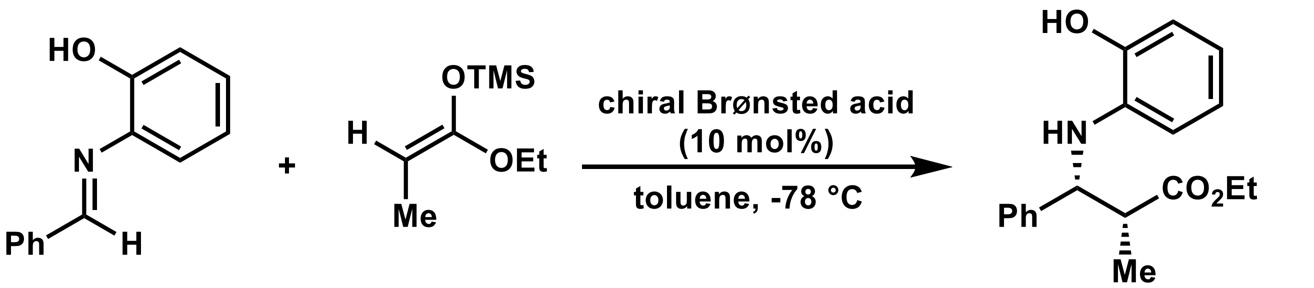
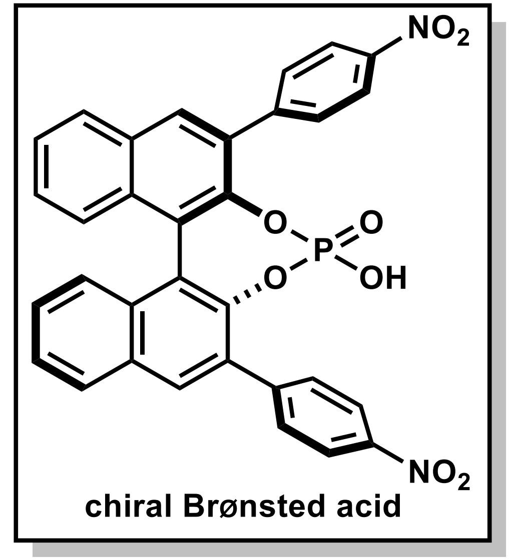
Contents

BINOL-Derived Chiral Catalyst

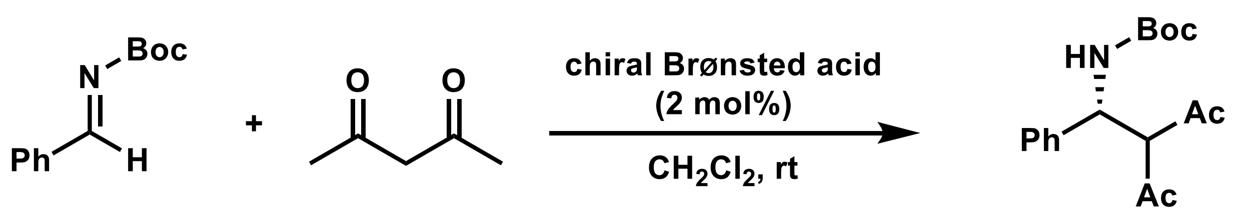
first report of BINOL-derived phosphoric acid



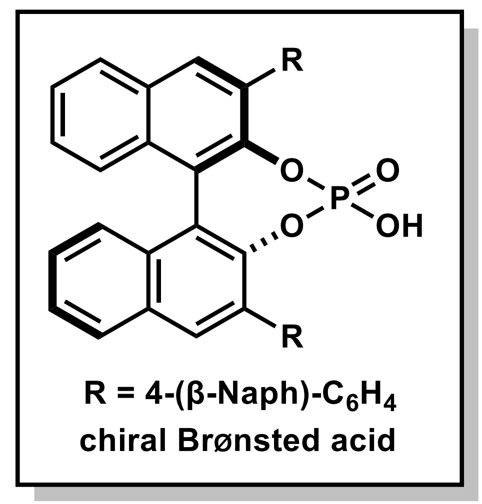
100%, 87:13 (*syn/anti*), 96% ee



T. Akiyama, J. Itoh, K. Yokota, K, Fuchibe, *Angew. Chem. Int. Ed*. **2004**, *43*, 1566.

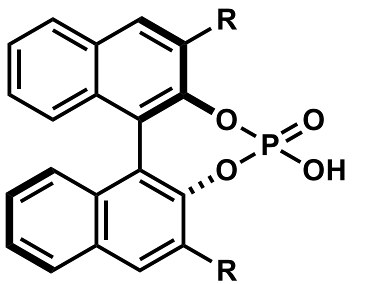


99%, 95% ee

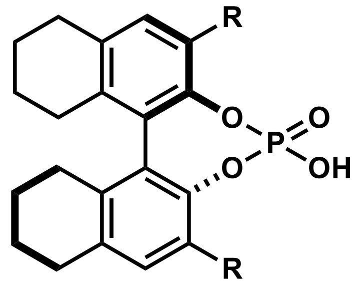


D. Uraguchi, M, Terada, *J. Am. Chem. Soc*. **2004**, *126*, 5356.

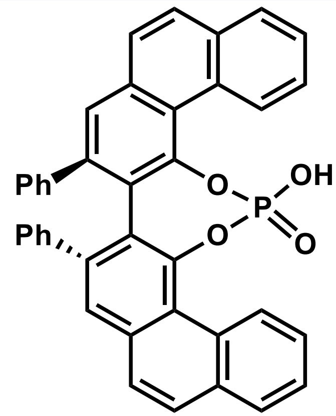
BINOL-Derived Chiral Catalyst



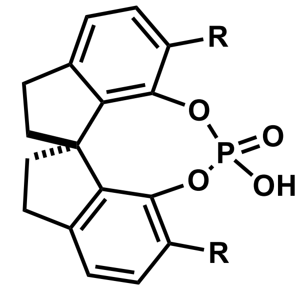
2004 Akiyama
2004 Terada



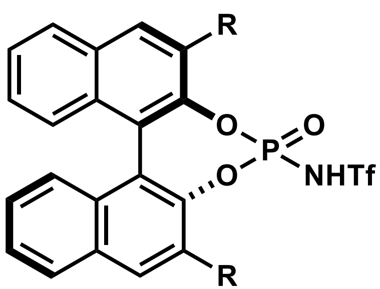
2007 Gong



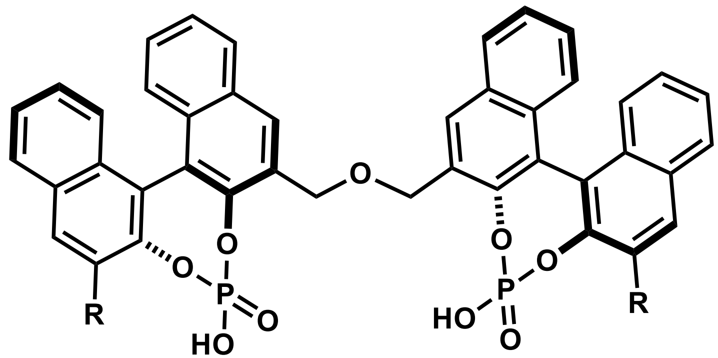
2005 Antilla



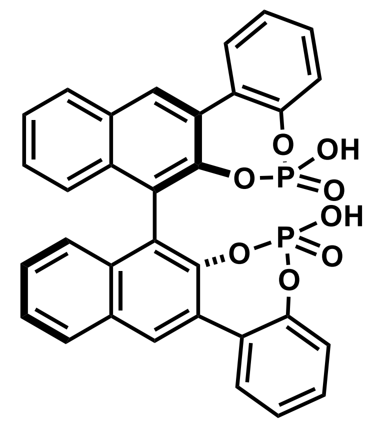
2010 List



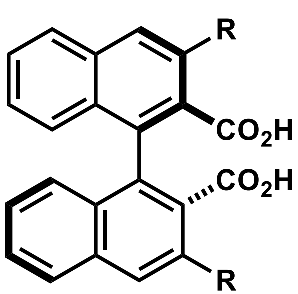
2006 Yamamoto



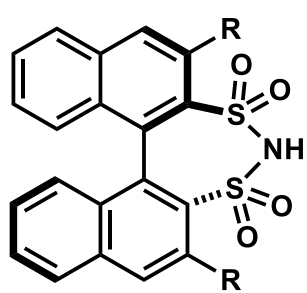
2008 Gong



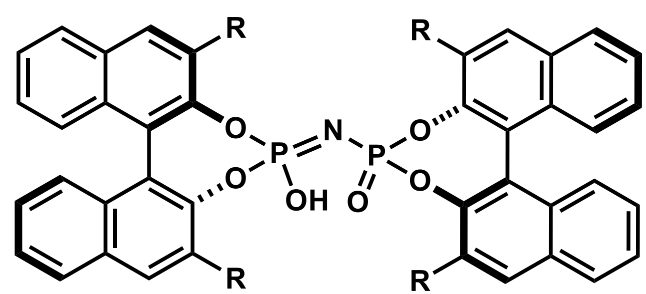
2011 Terada



2008 Maruoka

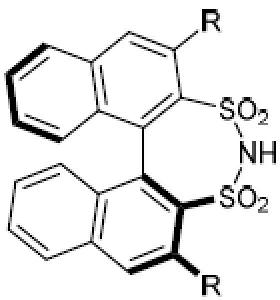


2009 List



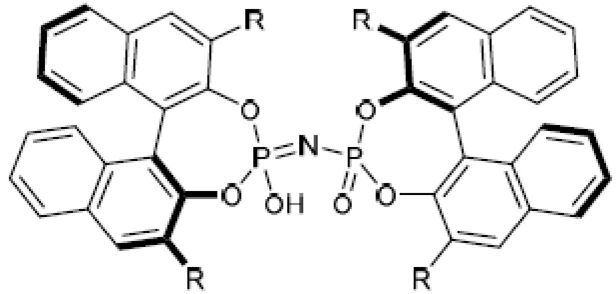
2012 List

Imidodiphosphorimidate (IDPi)



Disulfonimides (DSI)

- \+ highly active Brønsted acids pK_a (MeCN) = 8.4
- \+ active in Lewis acid catalysis
- ~ moderately stereoselective

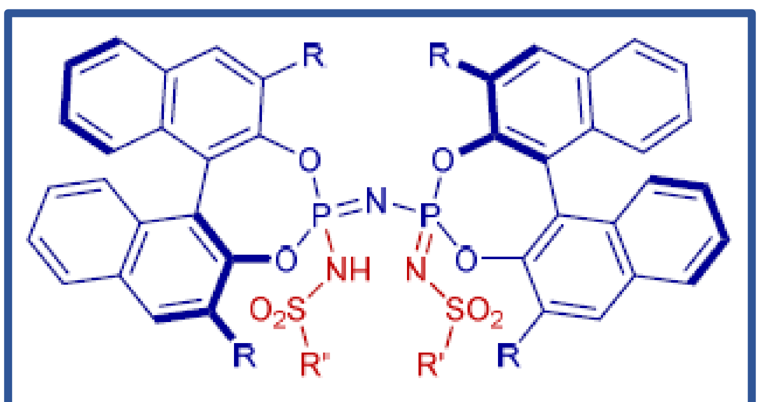


Imidodiphosphates (IDP)

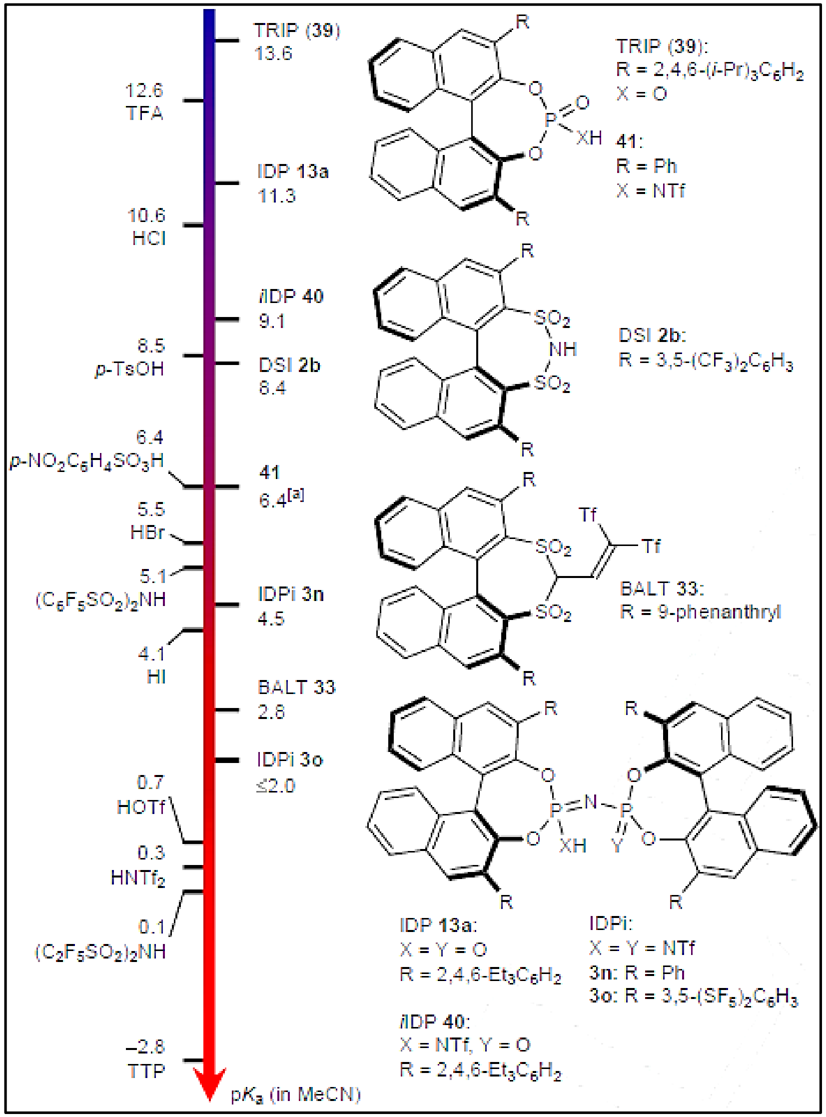
- ~ moderately active Brønsted acids pK_a (MeCN) = 11.5
- – inactive in Lewis acid catalysis
- \+ highly stereoselective

reactivity

selectivity



Imidodiphosphorimidate (IDPi)



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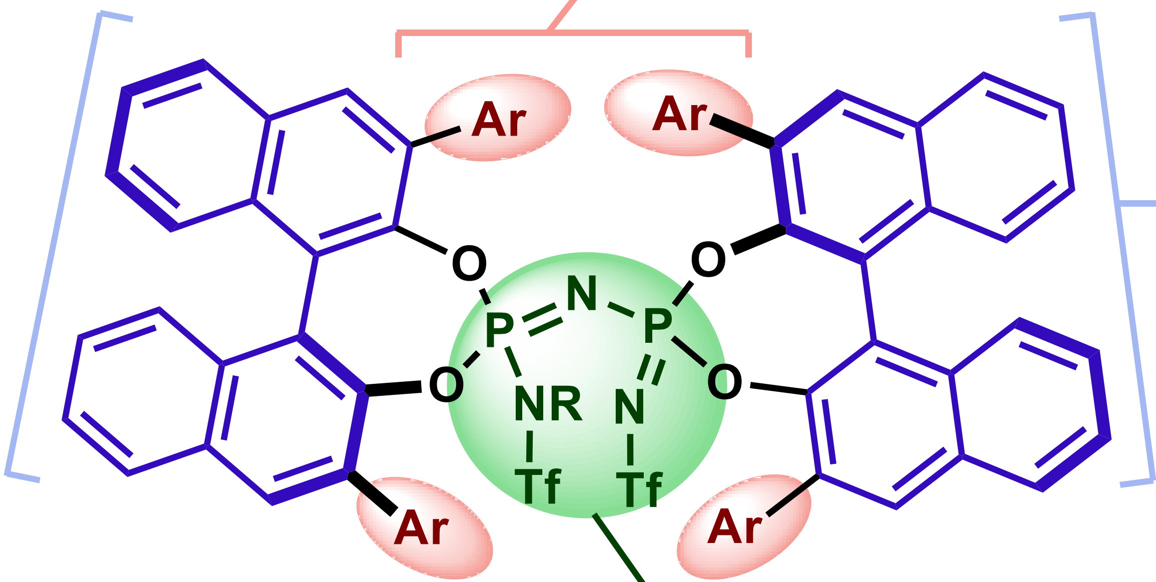
IDPi Catalyst

steric and electronic modulation



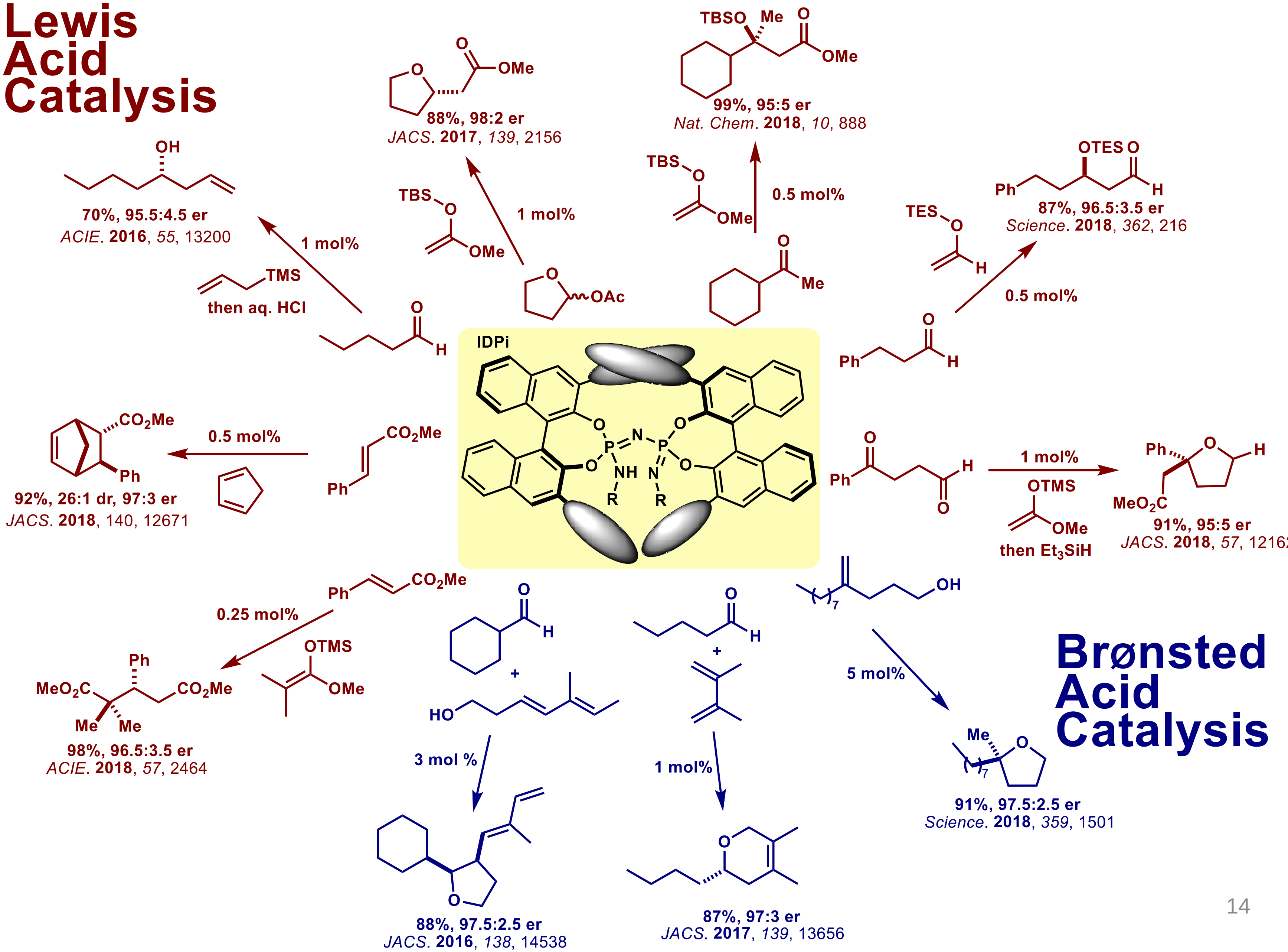
rigid chiral backbone

confined reactive site

R = H; Brønsted acid
R = SiR_3; Lewis acid

- ✓highly active Brønsted acids
  pKa (MeCN) = 4.5 to < 2.0
- ✓active in Lewis acid catalysis
- ✓highly enantioselective

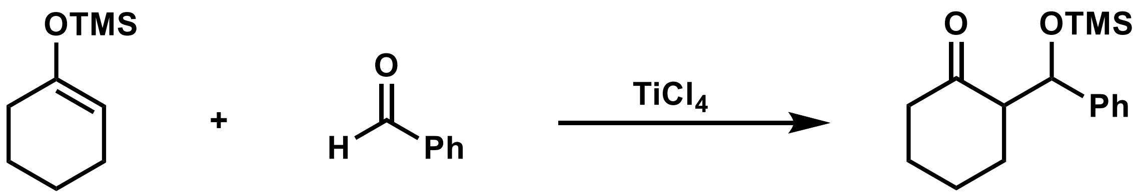
Applications



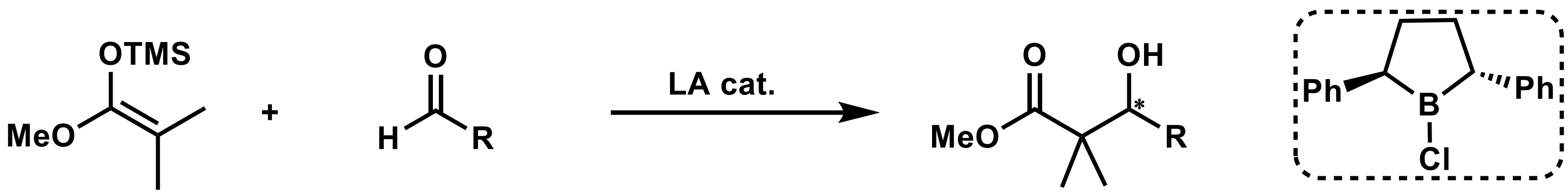
Contents

Mukaiyama Aldol Reaction

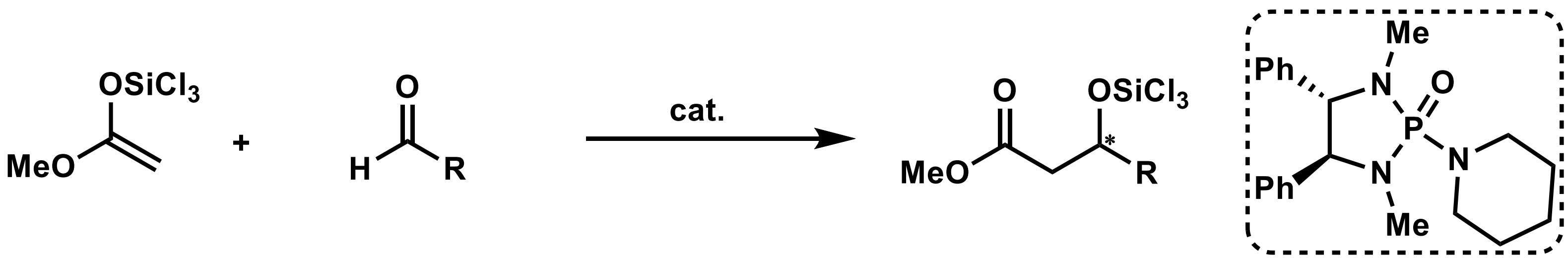
Mukaiyama (1973)



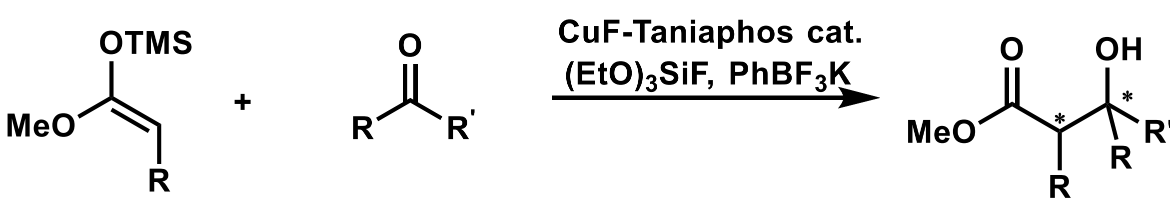
T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett*. **1973**, 1011.



M. T. Reetz, F. Kunisch, P. Heitmann, *Tetrahedron Lett*. **1986**, *27*, 4721.

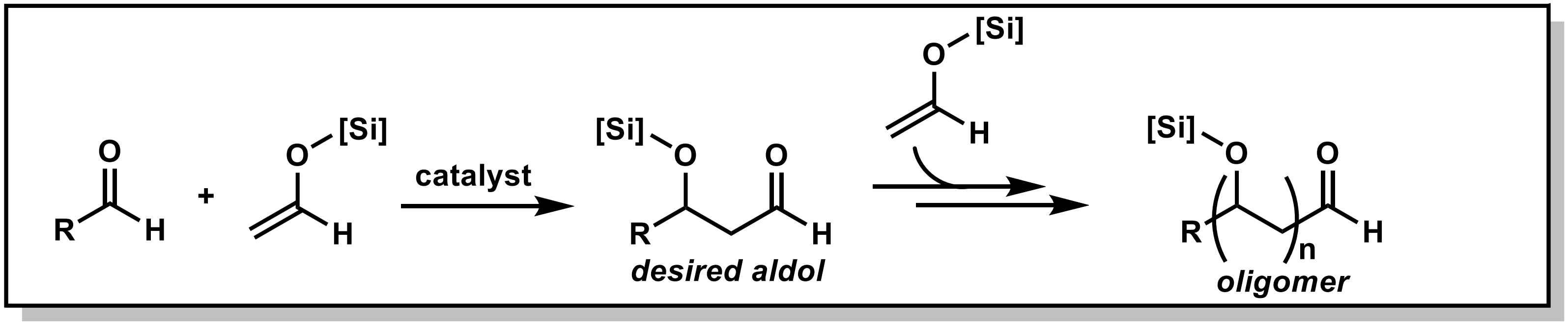


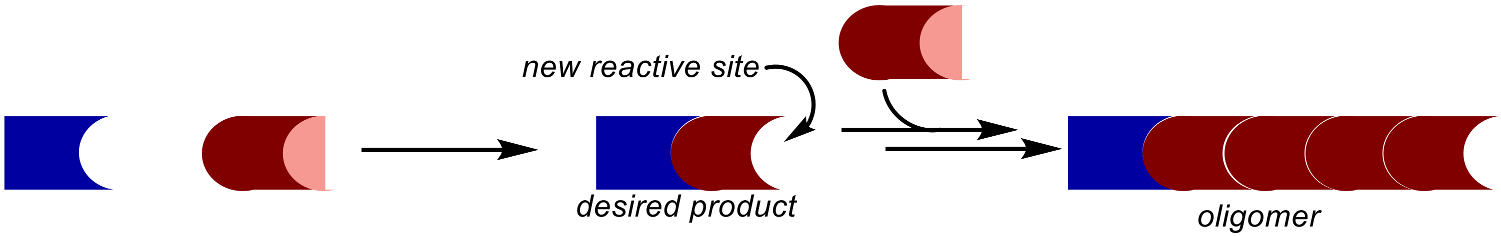
S. E. Denmark, S. B. D. Winter, X. Su, K. T. Wong, *J. Am. Chem. Soc.* **1996**, *118*, 7404.

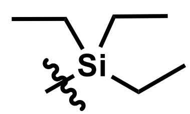
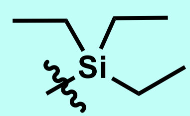


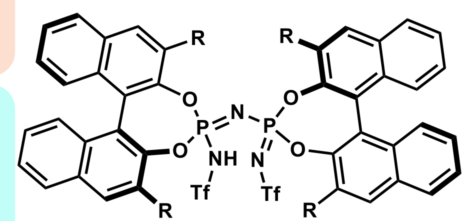
K. Oisaki, D. Zhao, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 7164.

Single Aldolization





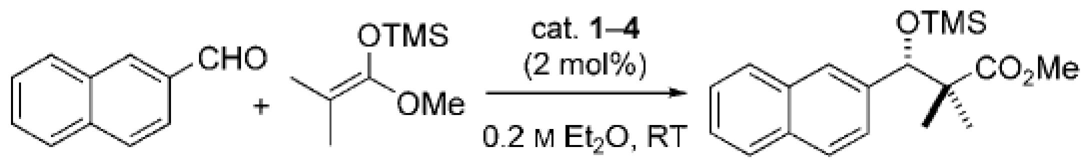
	catalyst	[Si]	% Yield (desired aldol)	e.r.
	$NHTf_2$		<10%	-
Yamamoto *et al.* (2006) ➢reagent control ➢racemic	$NHTf_2$		up to 90%	-
List *et al.* (2018) ➢catalyst control ➢enantioselective	IDPi		up to 95%	up to 99:1



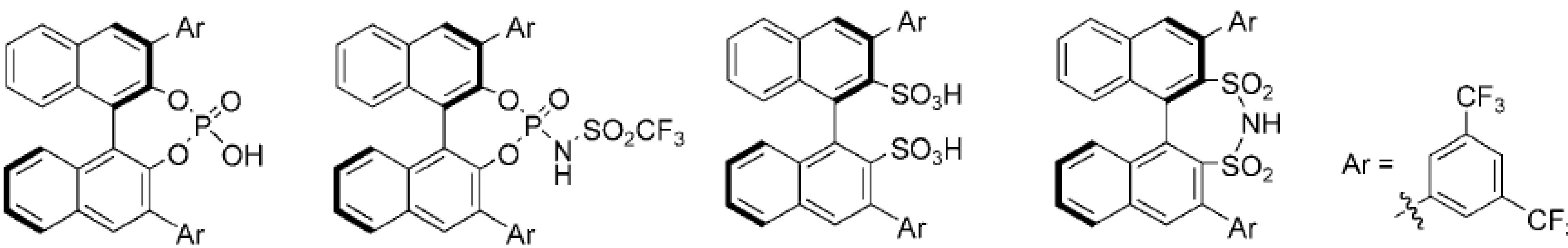
IDPi

M. B. Boxer, H. Yamamoto, *J. Am. Chem, Soc*. **2006**, *128*, 48.
L. Schreyer, P. S. J. Kaib, V. N. Wakchaure, C. Obradors, R. Properzi, S. Lee, B. List, *Science*. **2018**, *362*, 216.

Previously Reported Catalyst



5a 6a 7a

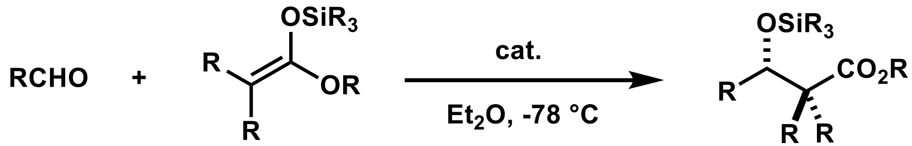


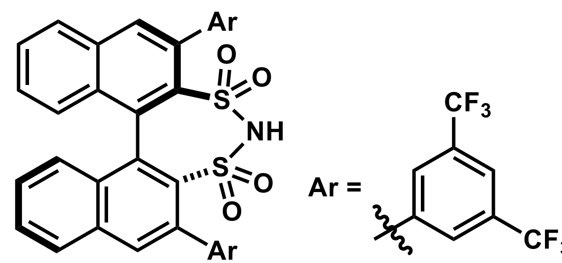
1 2 3 4

Entry	Catalyst	Yield [%][a]	e.r.[b,c]
1	**1**	<2	–
2	**2**	<2	–
3	**3**	<2	–
4	**4**	>99	90:10

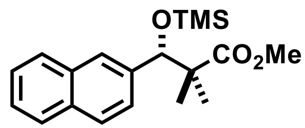
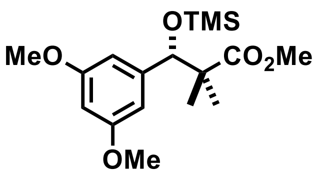
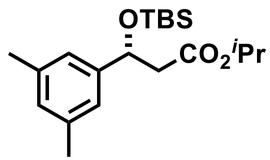
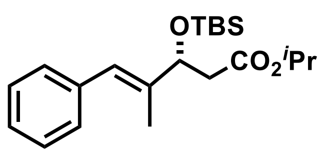
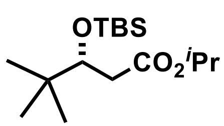
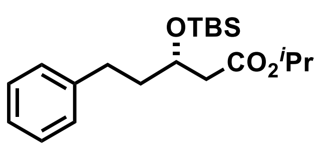
P. Garcia, F. Lay, P. Garcia, C. Rabalakos, B. List, *Angew. Chem. Int. Ed*. **2009**, *48*, 4363.

Previously Reported Catalyst





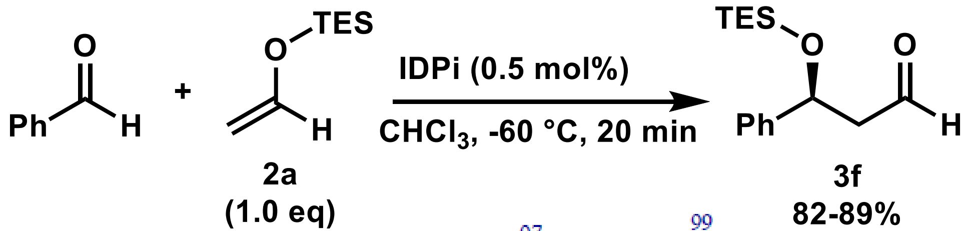
cat.

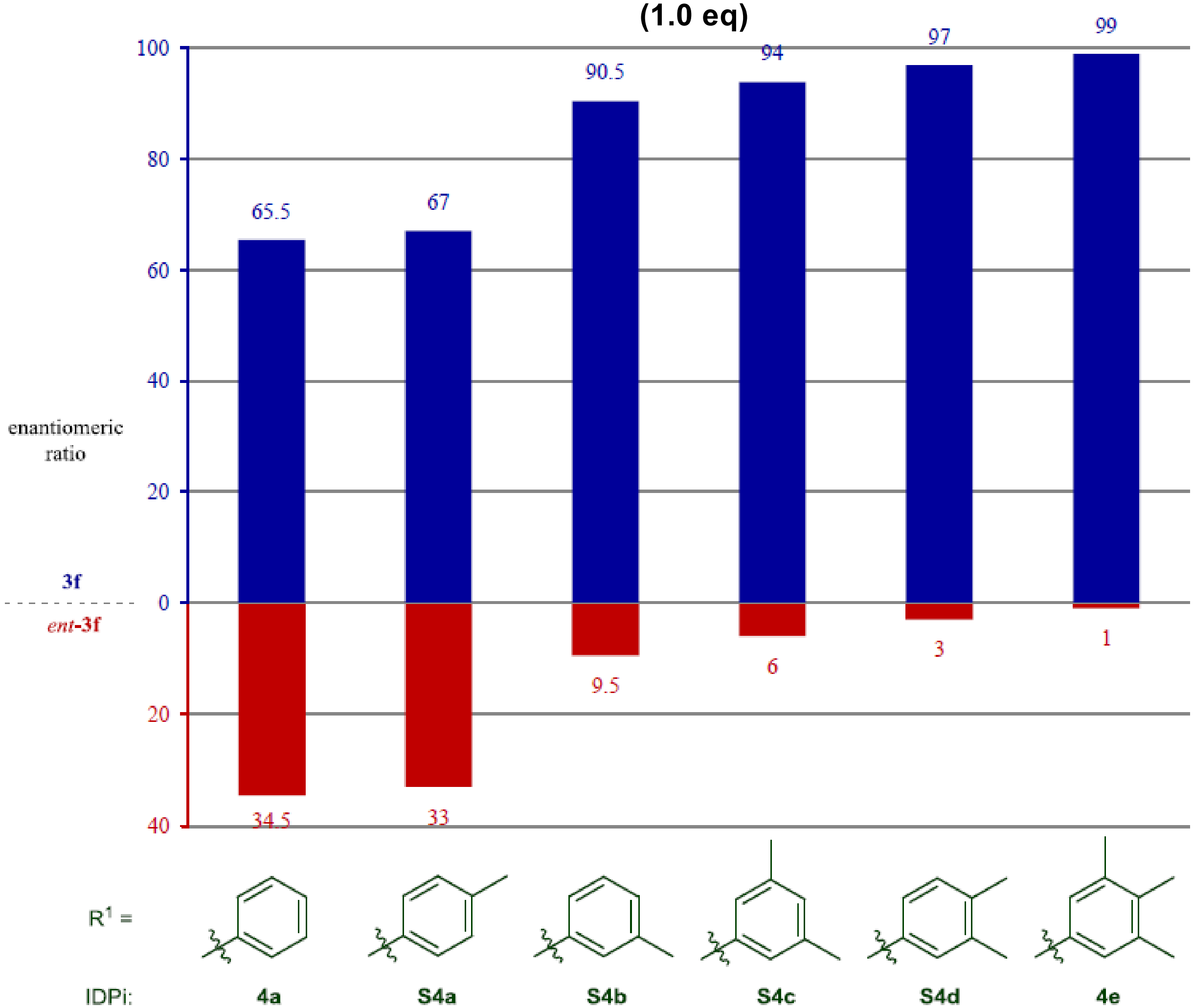
entry	product	catalyst loading (mol%)	yield (%)	e.r.
1		2	98	97:3
2		2	98	96:4
3		2	93	92:8
4		0.1	80	90:10
5		0.05	70	90:10
6		2	95	93:7
7		0.1	90	93:7
8		0.01	88	88:12
9		5	46	91:9
10		5	59	75:25

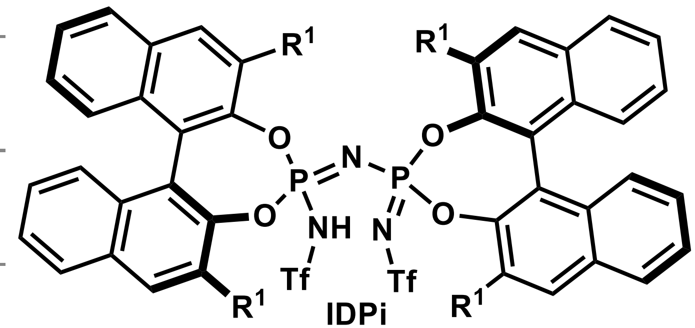
○ aromatic aldehyde
○ catalyst loading
△ ketene silyl acetal
× aliphatic aldehyde

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

Catalyst Optimization (Aromatic Aldehyde)



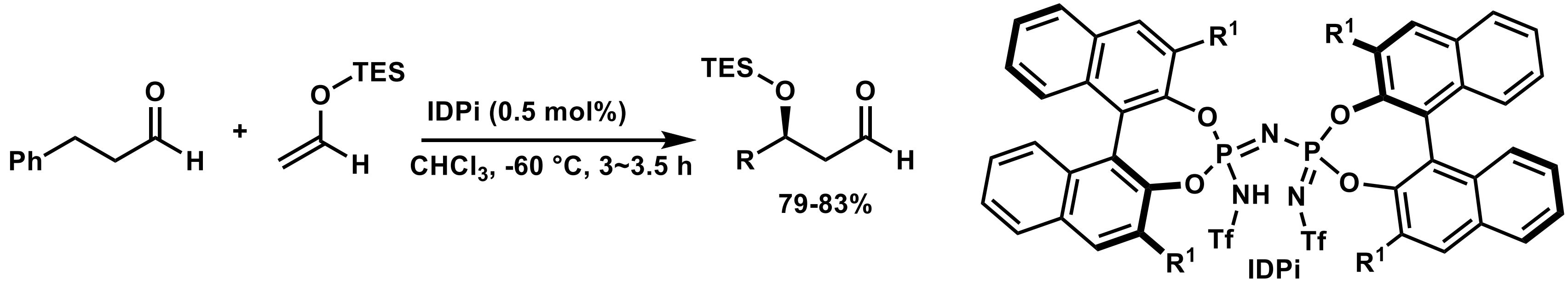


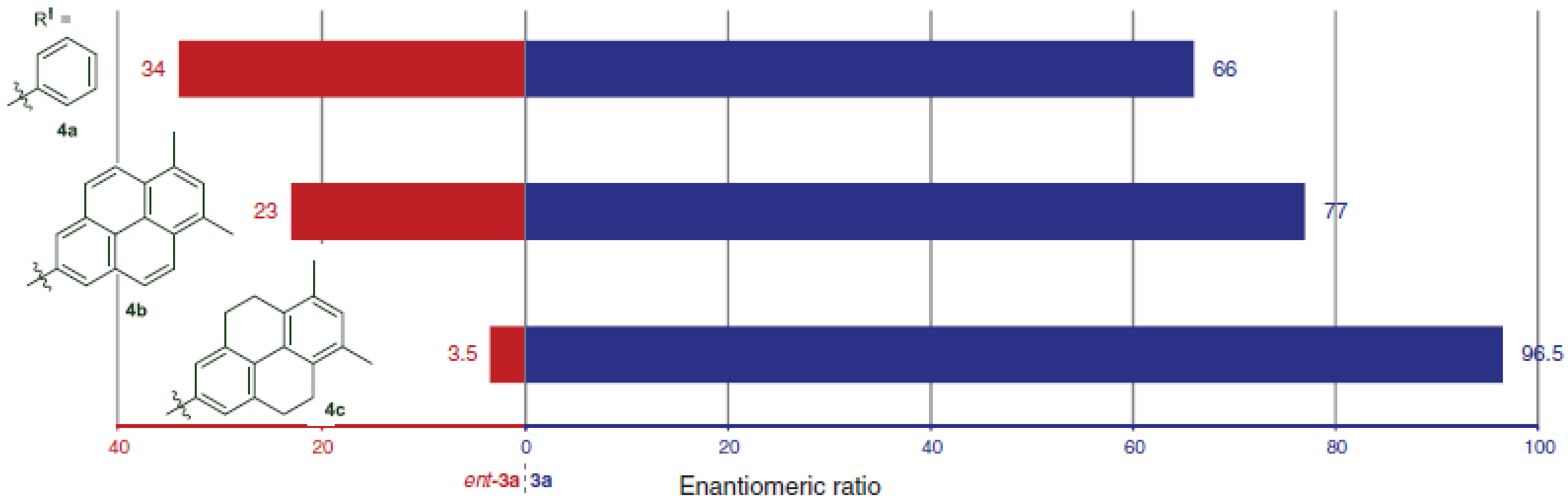


・*meta* and *para*-substituted phenyl group(R^1) of the IDPi revealed a profound enhancement of enantioselectivity.

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

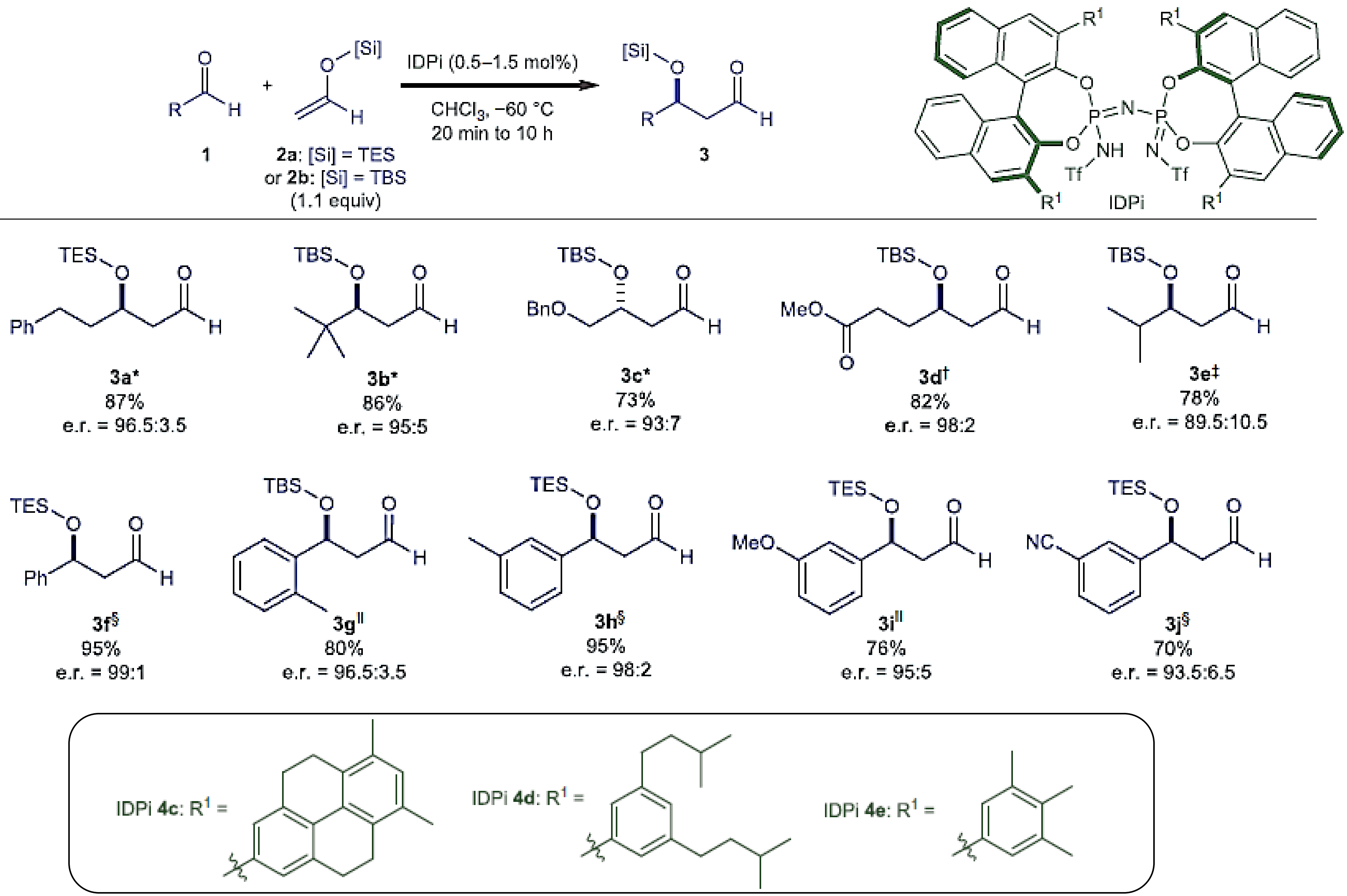
Catalyst Optimization (Aliphatic Aldehyde)





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

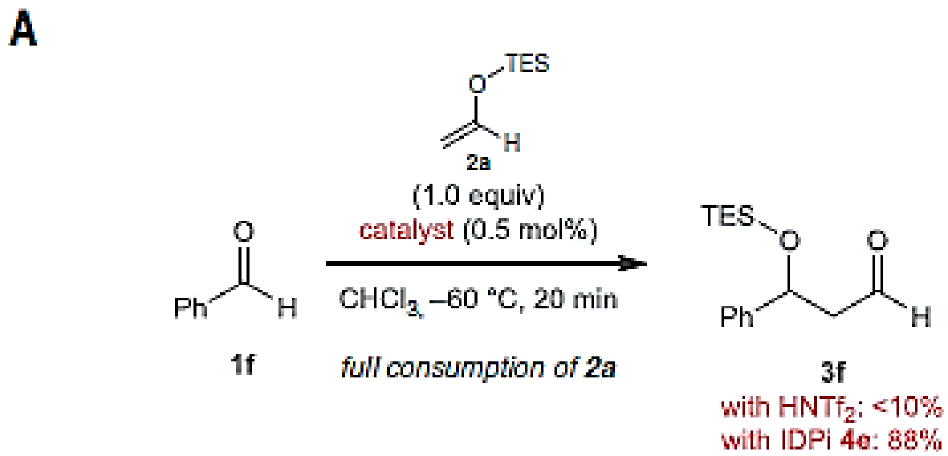
Substrate Scope

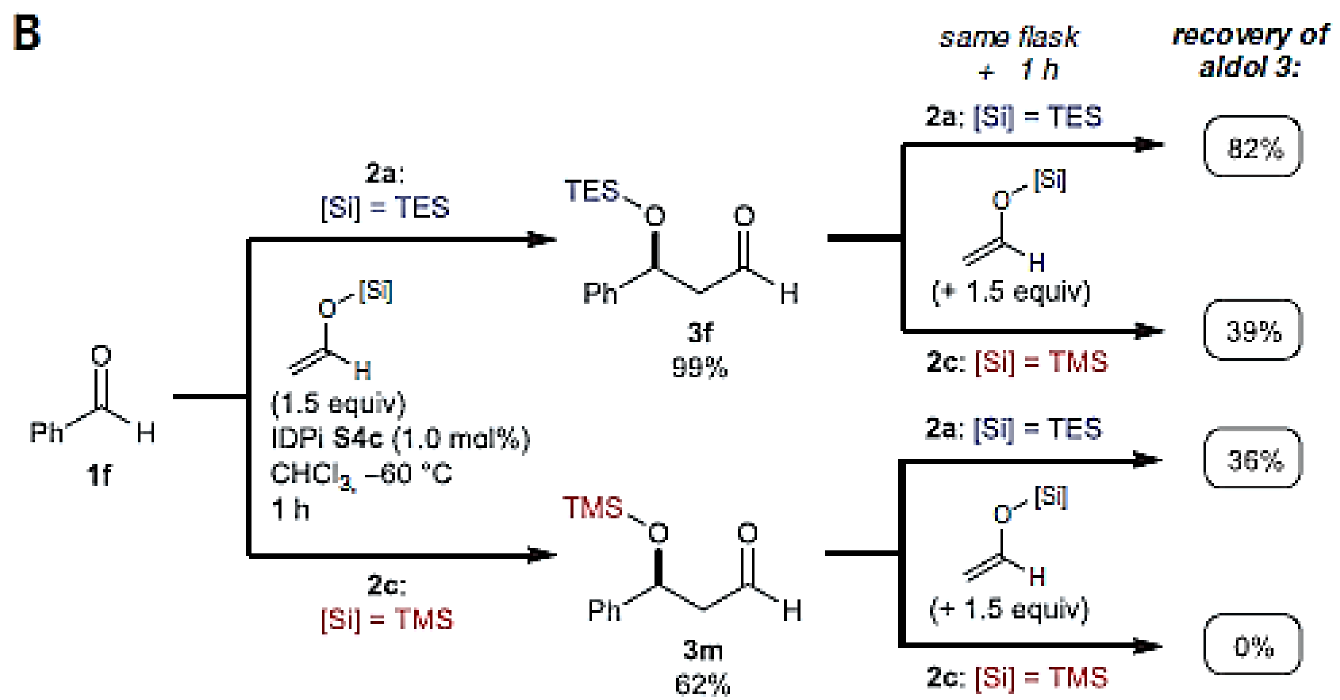


Reactions were performed with 0.5 mmol of aldehydes. *Using IDPi 4c. †Using IDPi 4d and 1.4 equivalents of enolsilane 2b. ‡Using IDPi 4d and 1.2 equivalents of enolsilane 2b. § Using IDPi 4e. ||Reactions were performed in CHCl3/n-hexane (5:4) at −78℃ using IDPi 4e.

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

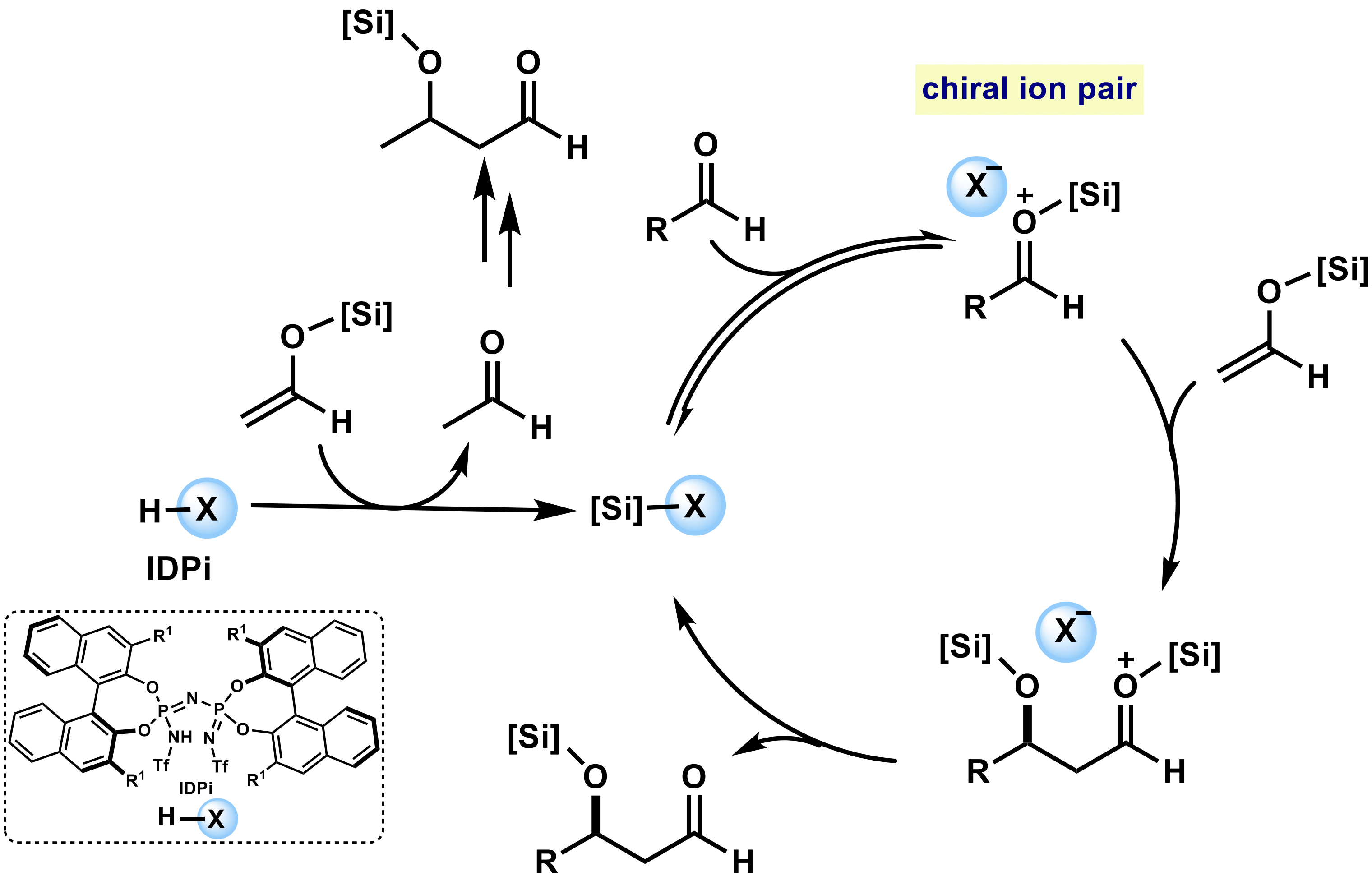
Catalyst and Silyl Group





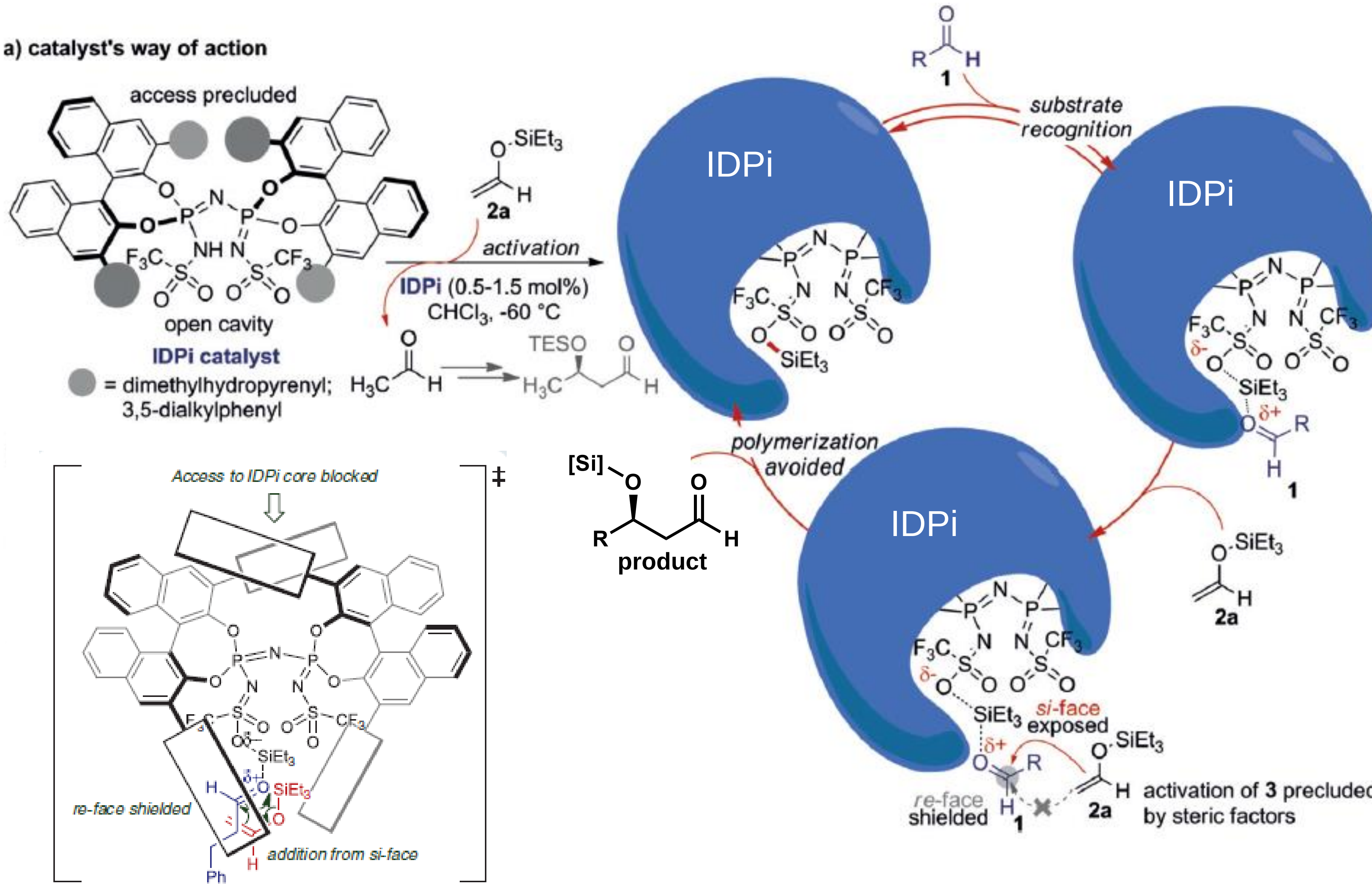
L. Schreyer, P. S. J. Kaib, V. N. Wakchaure, C. Obradors, R. Properzi, S. Lee, B. List, *Science*. **2018**, *362*, 216.

Proposed Catalytic Cycle



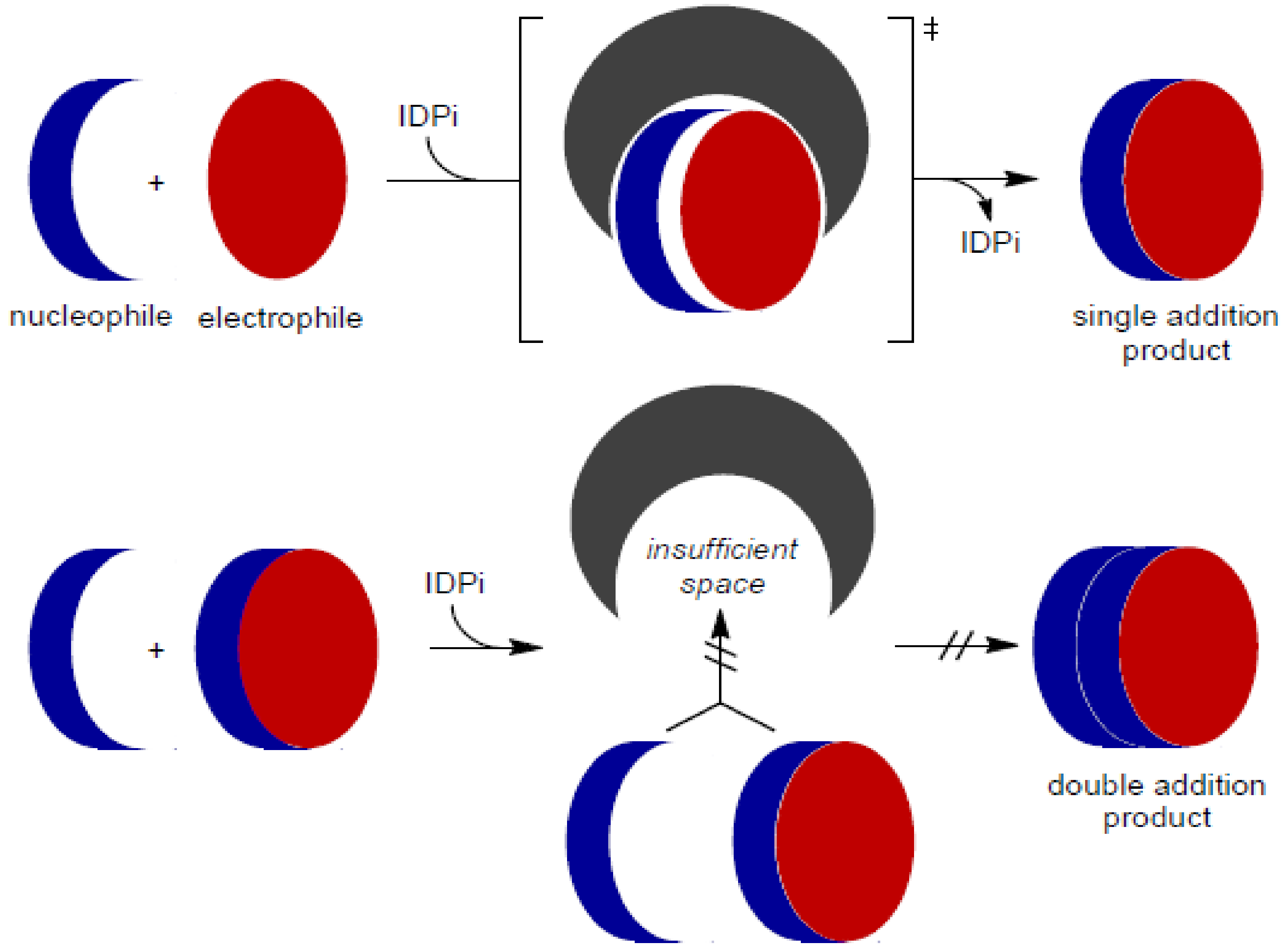
L. Schreyer, P. S. J. Kaib, V. N. Wakchaure, C. Obradors, R. Properzi, S. Lee, B. List, *Science*. **2018**, *362*, 216.

Enantioselectivity



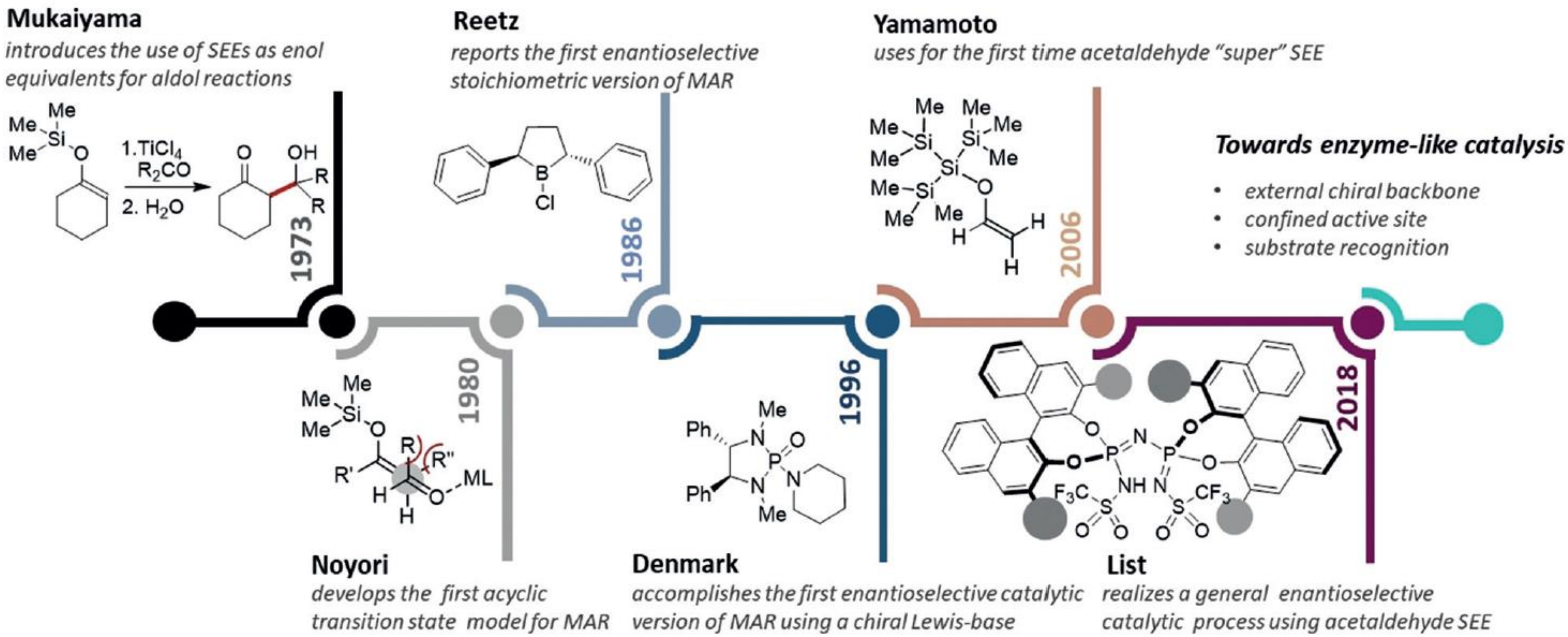
L. D. Amico, F. Zanardi, *Angew. Chem. Int. Ed*. **2019**, *58*, 3264
L. Schreyer, P. S. J. Kaib, V. N. Wakchaure, C. Obradors, R. Properzi, S. Lee, B. List, *Science*. **2018**, *362*, 216.

Single Reaction



DOI: 10.1002/anie.201900932

Mukaiyama Aldol Reaction



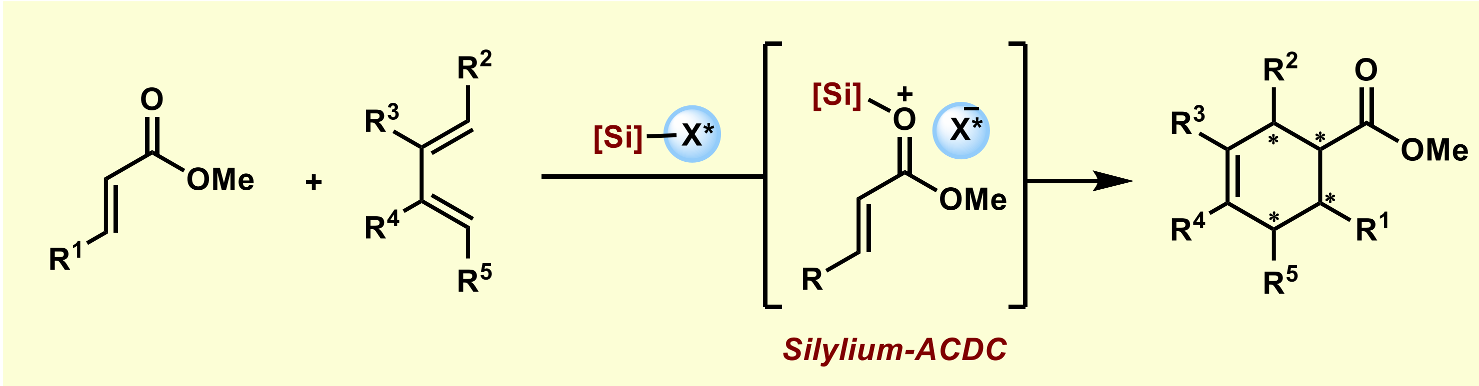
L. D. Amico, F. Zanardi, *Angew. Chem. Int. Ed*. **2019**, *58*, 3264.

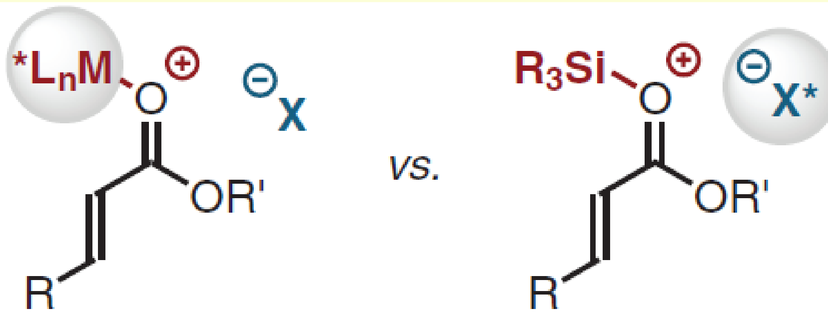
Contents

1. **Introduction**
   - ACDC
   - BINOL-derived chiral catalyst

2. **Applications**
   - Mukaiyama aldol reaction
   - Diels-Alder reaction

Diels–Alder Reaction (ACDC)





Conventional approaches to enantioselective Lewis acid catalysis:

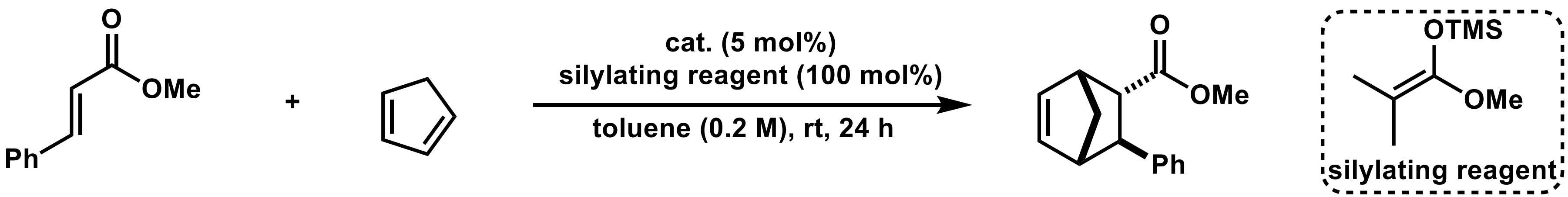
- chirality directly attached to Lewis acid
- complexation between chiral catalyst and substrate
- achiral counteranion present, if Lewis acid is cationic

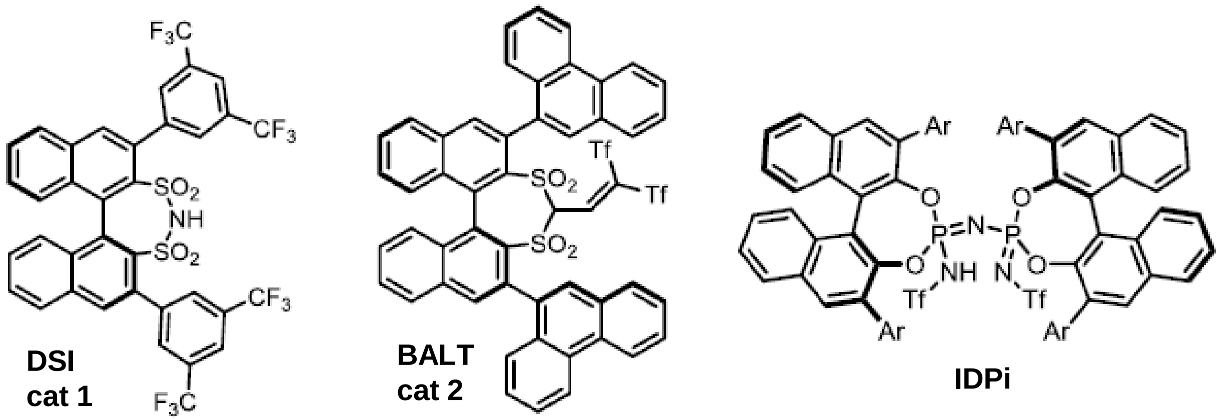
Asymmetric counteranion-directed catalysis with catalytic silylium ion equivalents (silylium ion–ACDC):

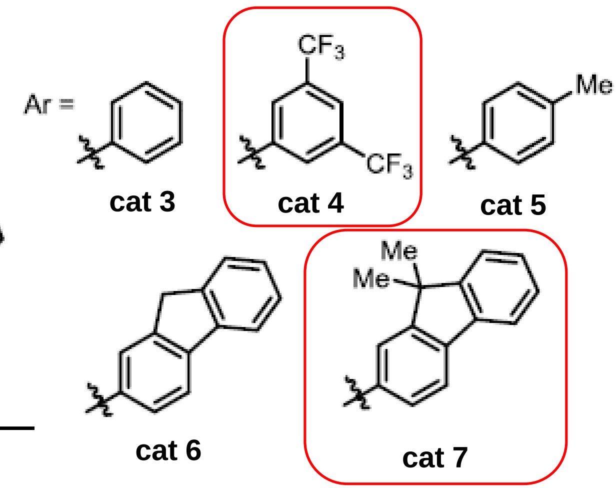
- chirality at the counteranion
- Coulomb interaction between chiral anion and activated substrate
- silylium ion equivalent = highly active Lewis acid catalyst

T. Gatzenmeier, M. Gemmeren, Y. Xie, D. Höfler, M. Leutzsch, B. List, *Science,* **2016**, *351*, 949.
T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12671.

Initial Try



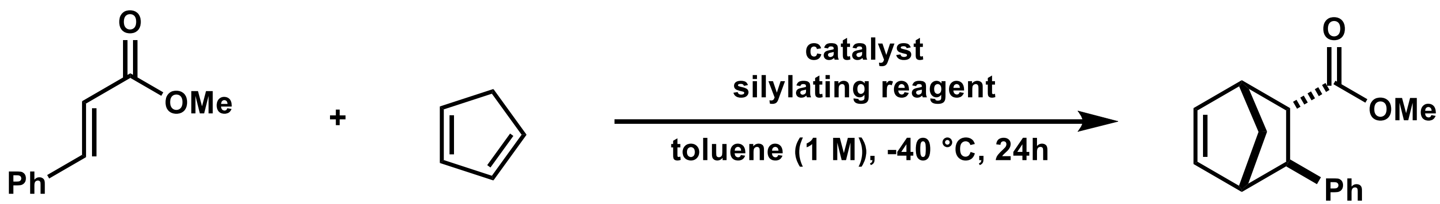




entry	catalyst	conv.(%)	e.r. (endo)	d.r. (endo/exo)
1	cat 1	traces	/	/
2	cat 2	82%	51:49	9:1
3	cat 3	> 99%	70:30	14:1
4	cat 4	> 99%	85:15	11:1
5	cat 5	> 99%	54:46	8:1
6	cat 6	> 99%	74:26	7:1
7	cat 7	> 99%	85:15	8:1

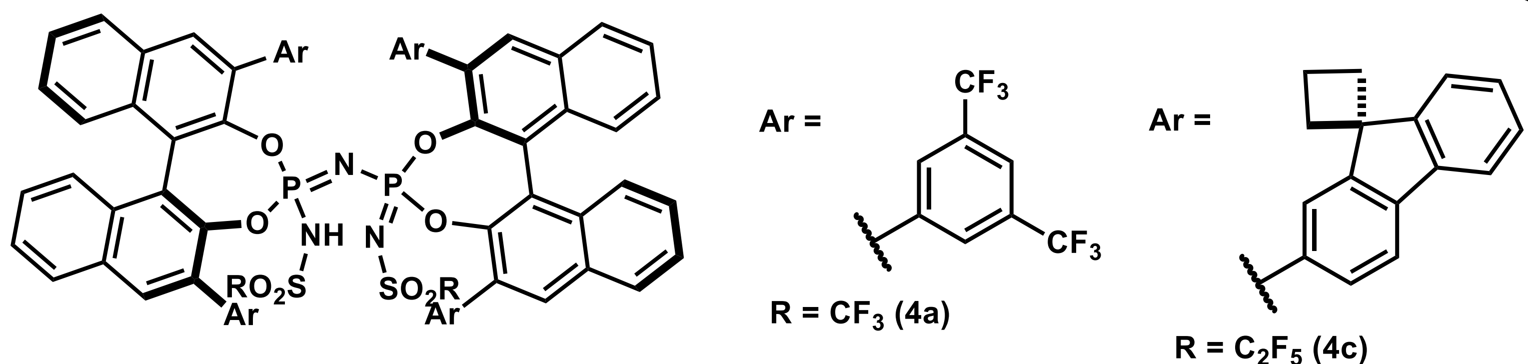
T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12671.

Reaction Development



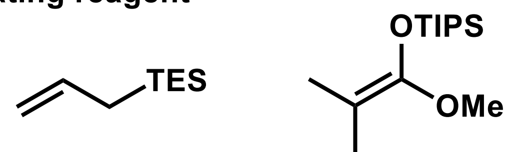
condition A → IDPi 4a (1 mol%), silylating reagent 5a (20 mol%)
92%, d.r. 26:1 (endo/exo), e.r. 97:3 (endo)

condition B → IDPi 4c (1 mol%), silylating reagent 5b (20 mol%)
90%, d.r. 16:1 (endo/exo), e.r. 97.5:2.5 (endo)



IDPi

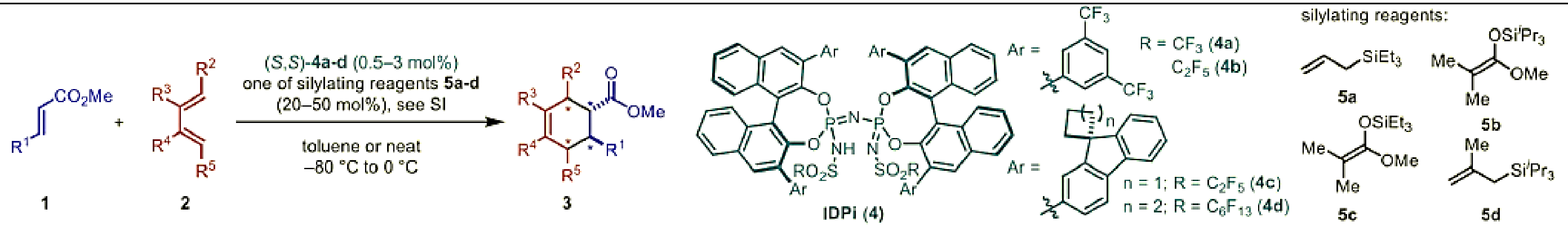
silylating reagent

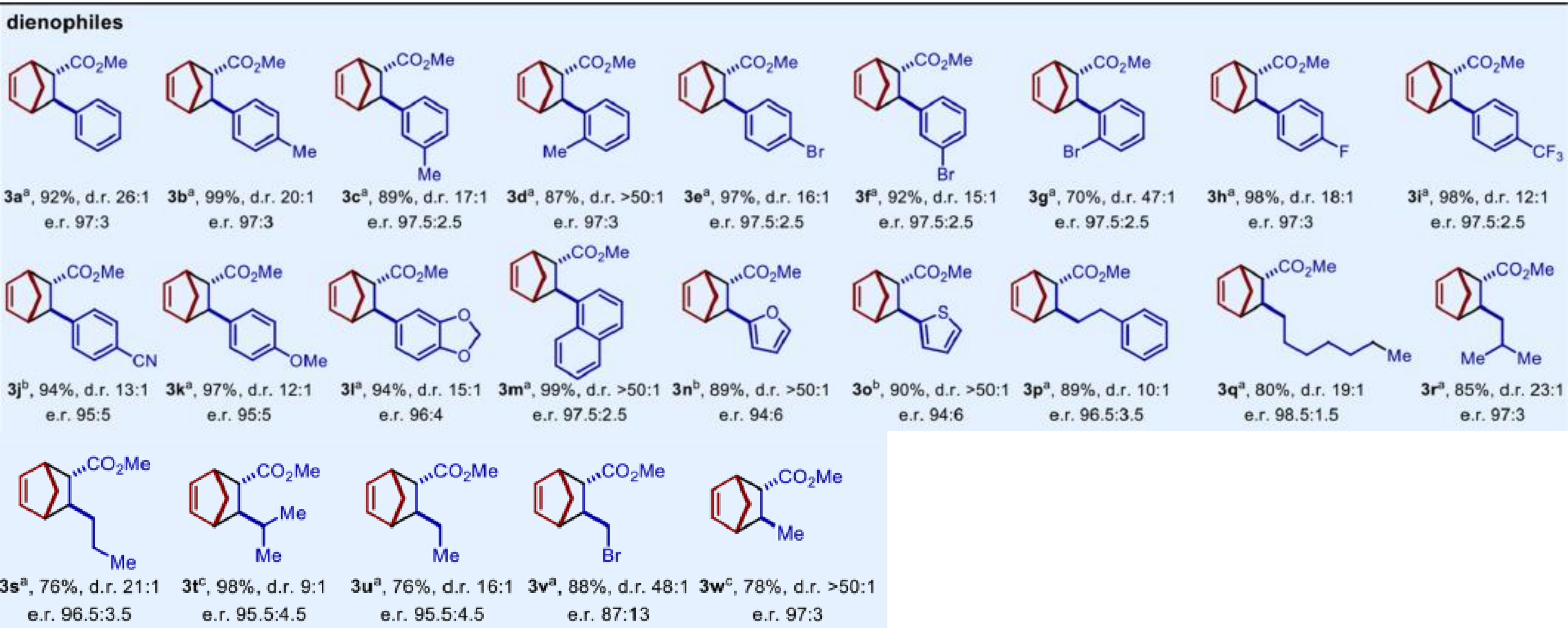


5a 5b

T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12671.

Substrate Scope

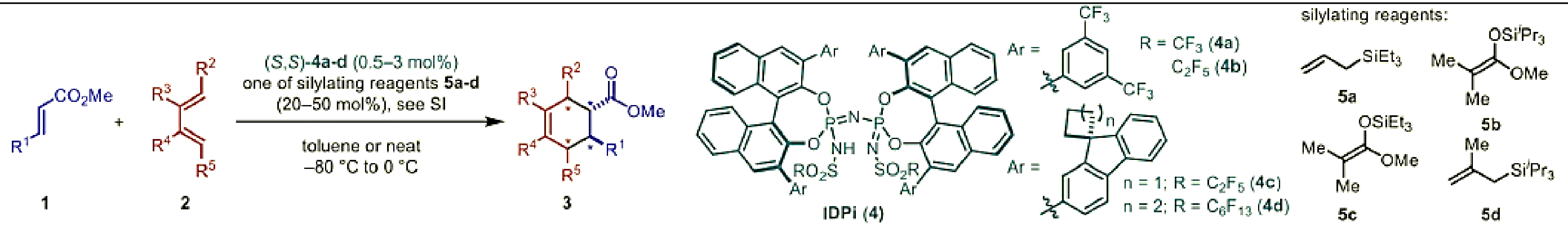


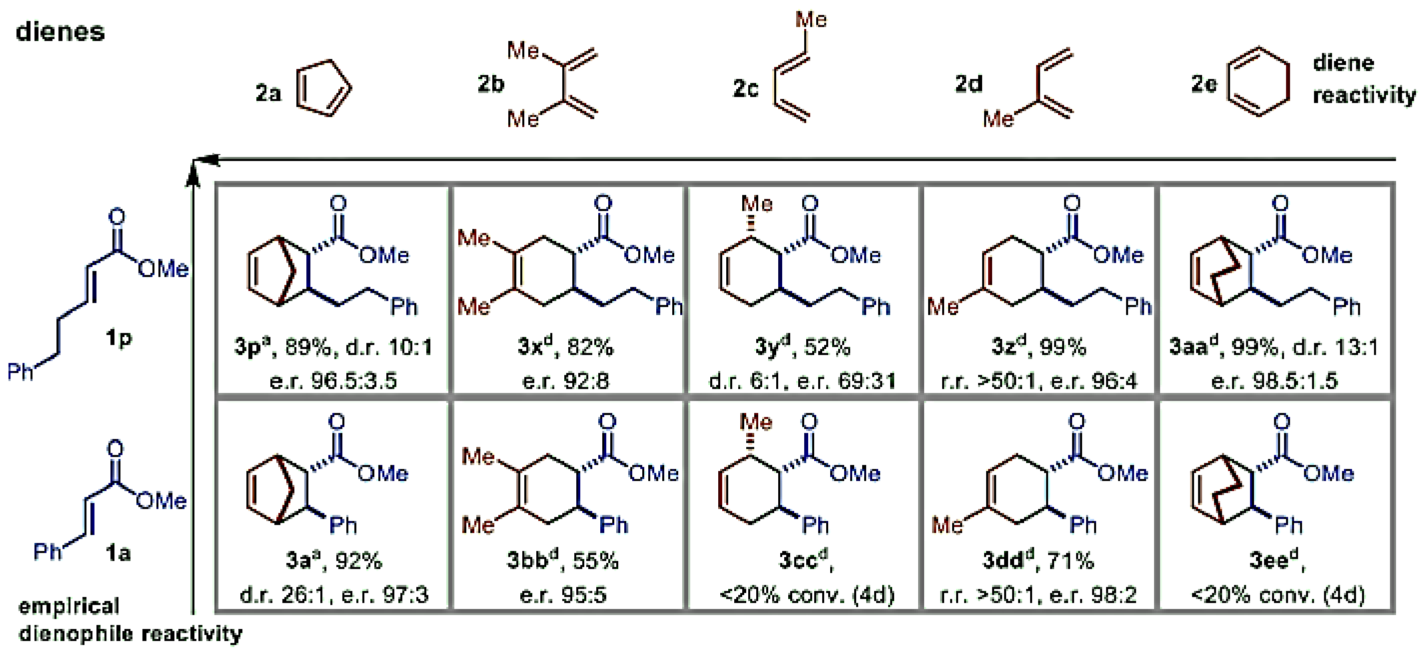


[a]with catalyst 4a; [b]with catalyst 4b;[c]with catalyst 4c; [d]with catalyst 4d (3 mol %).

T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12671.

Substrate Scope

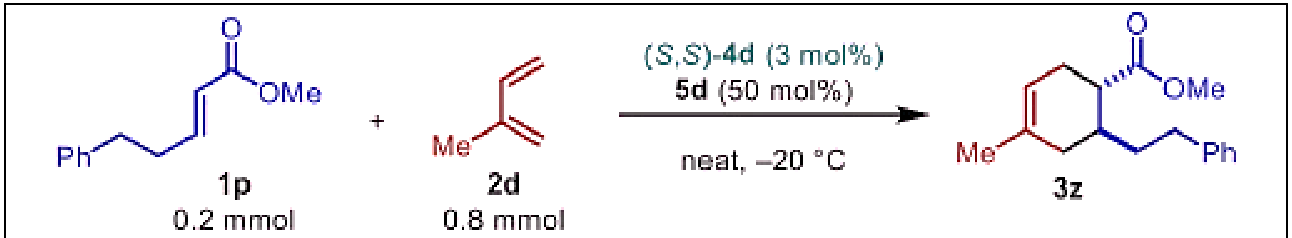


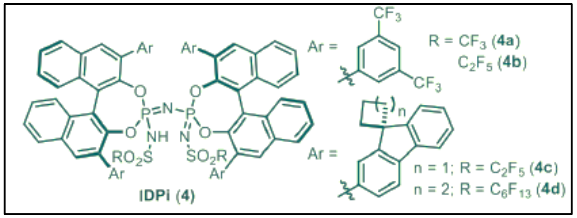


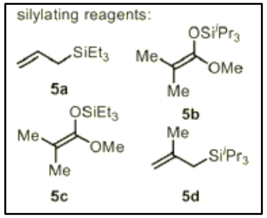
[a]with catalyst 4a; [b]with catalyst 4b;[c]with catalyst 4c; [d]with catalyst 4d (3 mol%).

T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12671.

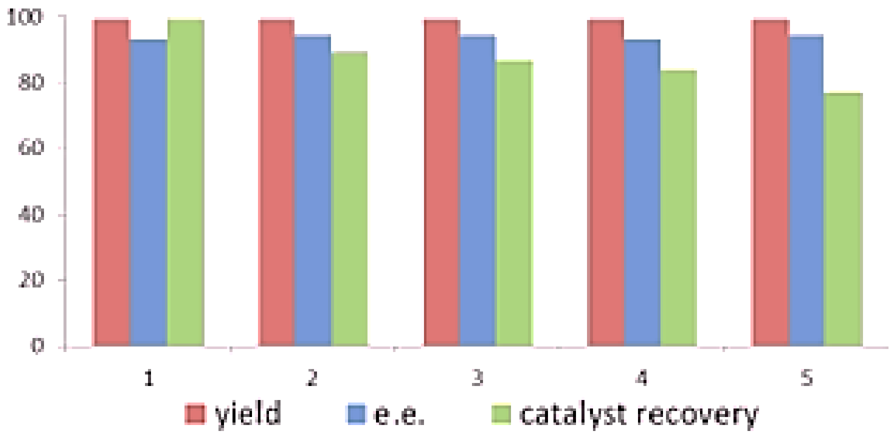
Catalyst Recycling





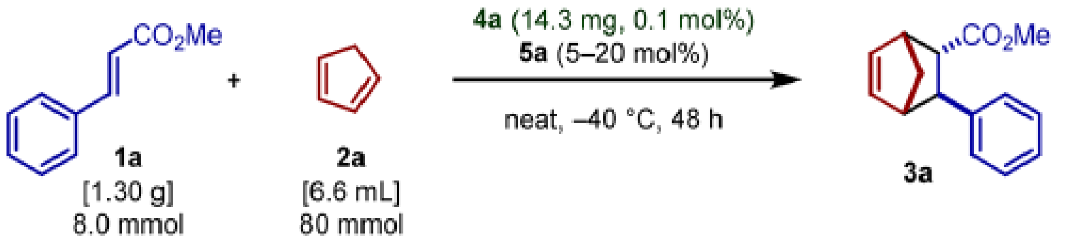


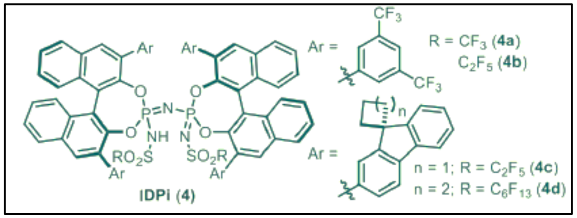
cycle	reaction time	recovered catalyst	yield	e.r.
1	3.5 d	99% (13.8 mg)	99%	96.5:3.5
2	3.5 d	89% (12.4 mg)	99%	97:3
3	4.5 d	87% (12.1 mg)	99%	97:3
4	5 d	84% (11.6 mg)	99%	96.5:3.5
5	5.5 d	77% (10.7 mg)	99%	97:3

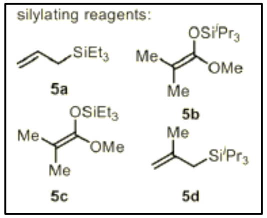


T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12671.

Scale-up Experiments



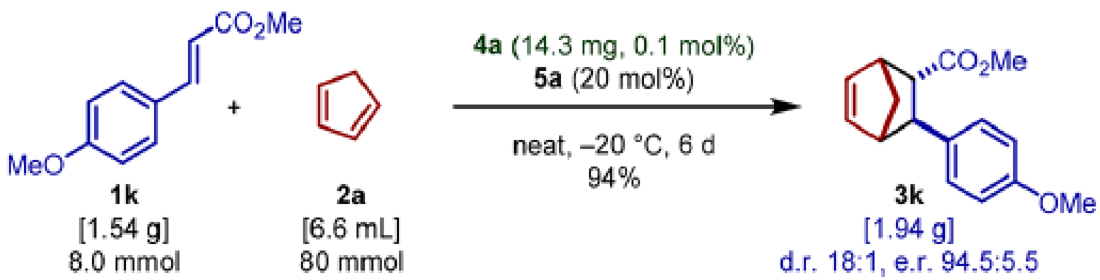


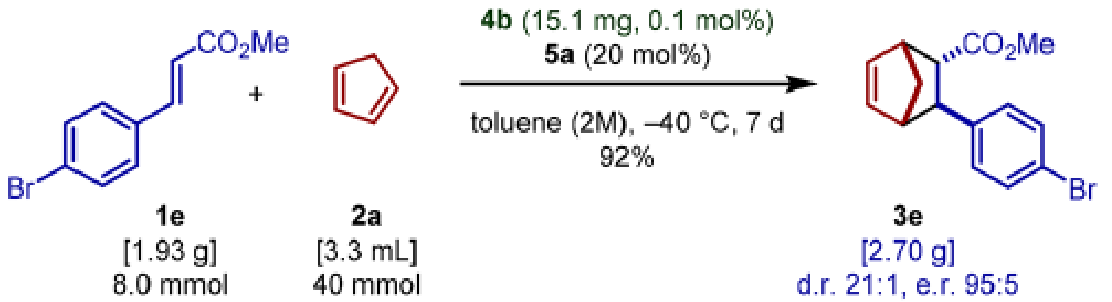


Vial under Argon (20 mol% of **5a**): [1.78 g] 97%, d.r. 21:1, e.r. 96:4

Vial without Argon (20 mol% of **5a**): [1.83 g] 99%, d.r. 22:1, e.r. 96:4

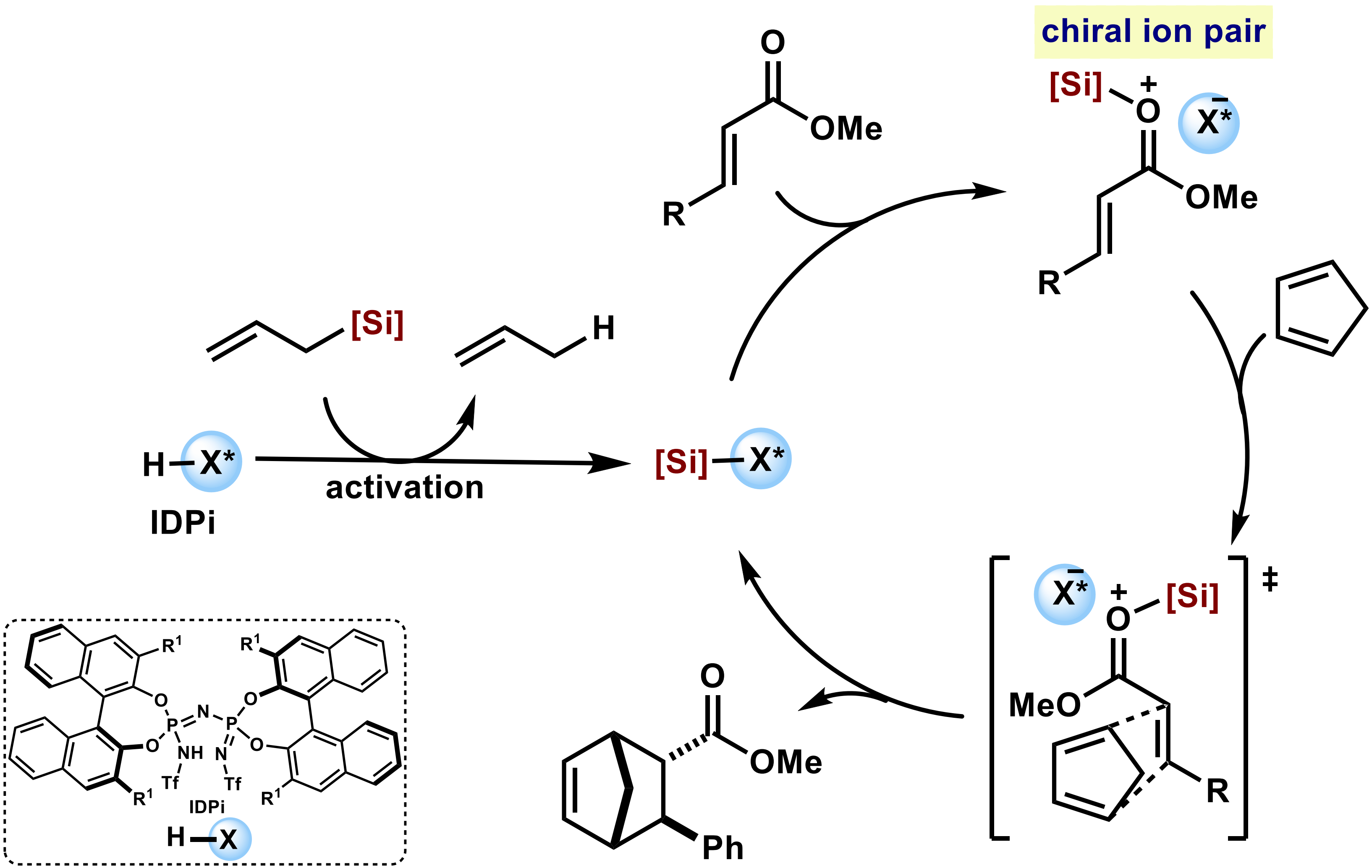
Schlenk flask under Argon (5 mol% of **5a**): [1.73 g] 94%, d.r. 21:1, e.r. 96:4





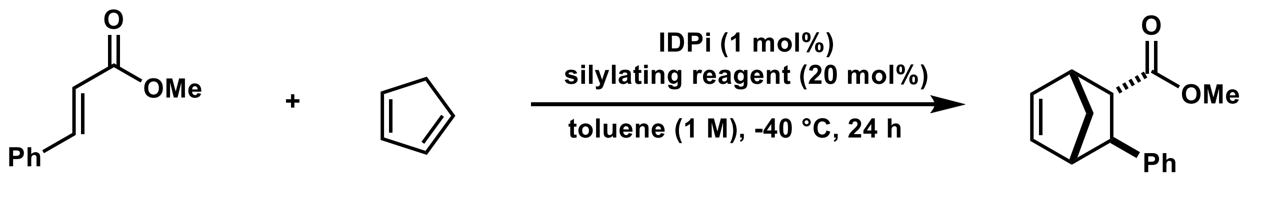
T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12671.

Proposed Catalytic Cycle

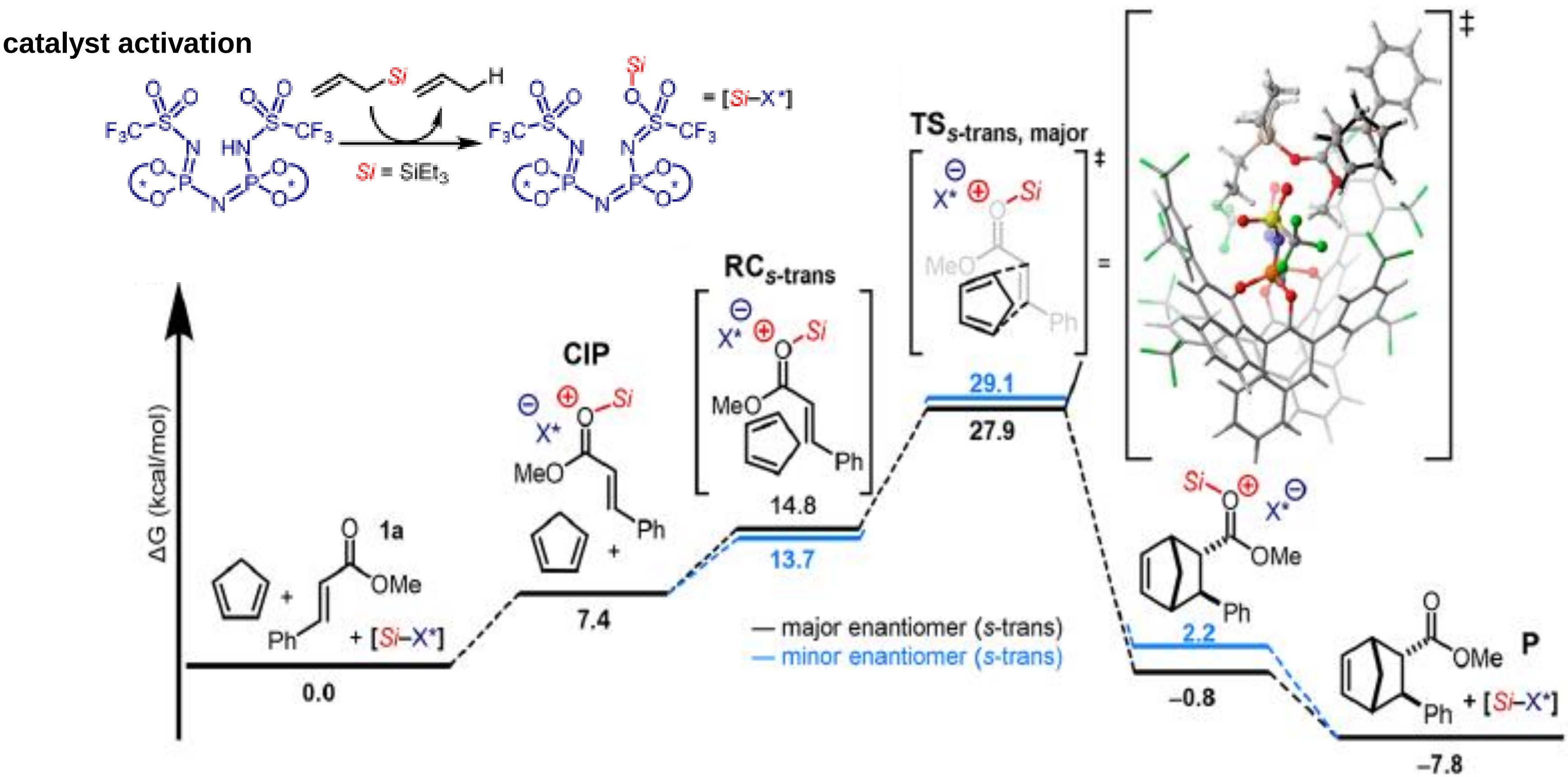


T. Gatzenmeier, M. Gemmeren, Y. Xie, D. Höfler, M. Leutzsch, B. List, *Science.* **2016**, *351*, 949.
T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12671.

Computational Studies

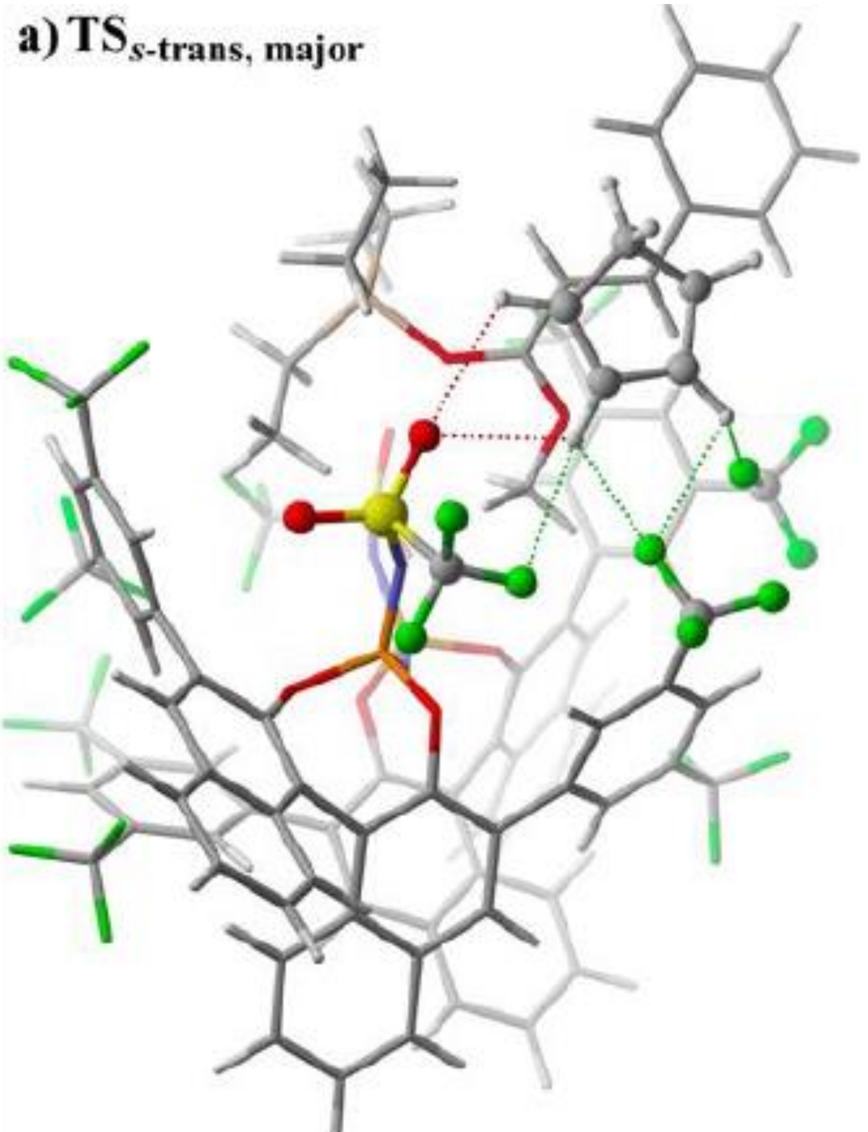


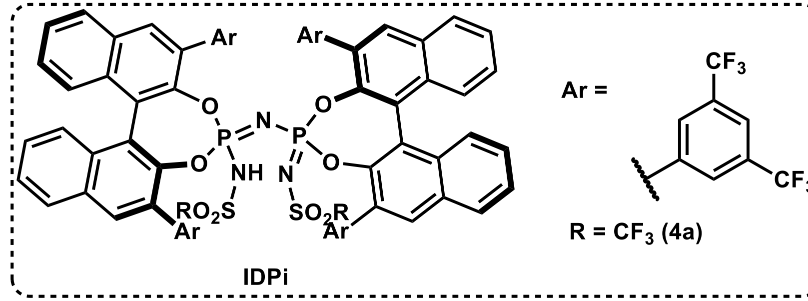
92%, d.r. 26:1, e.r. 97:3

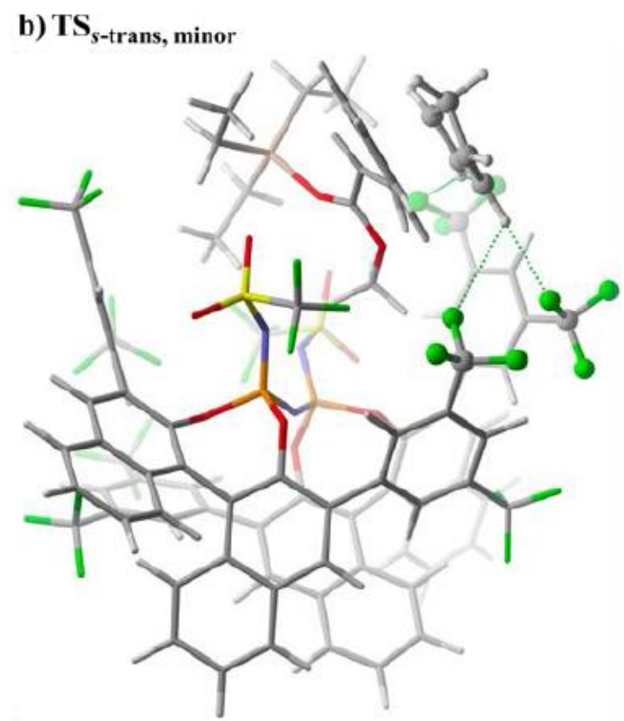


T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12671.

Most Favorable Transition State



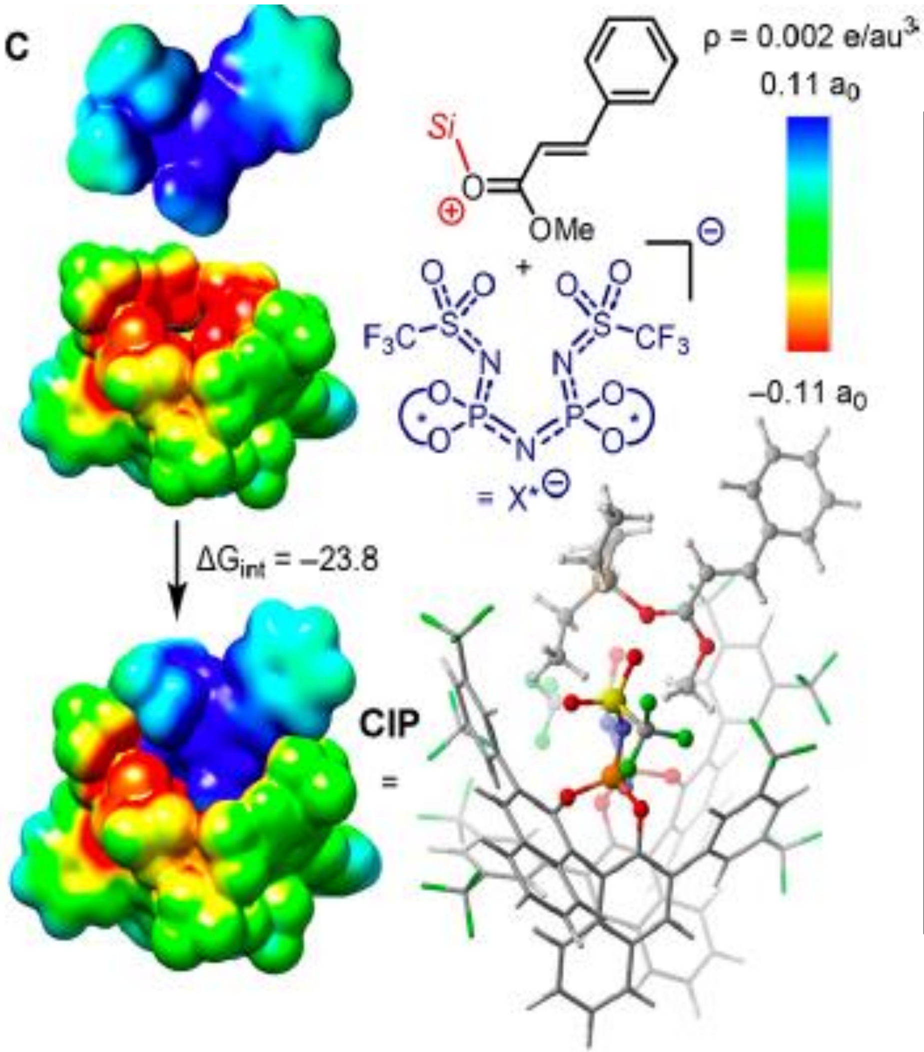


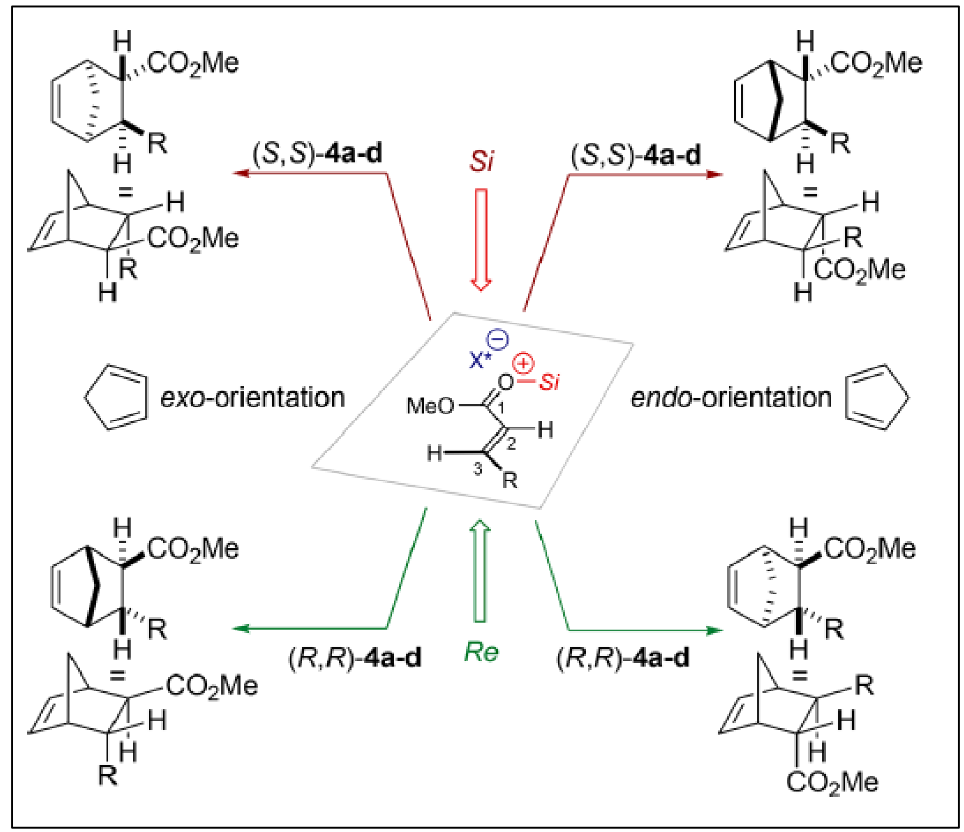


N
O
F
S
P

T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12671.

Interaction with the Chiral Ion Pair

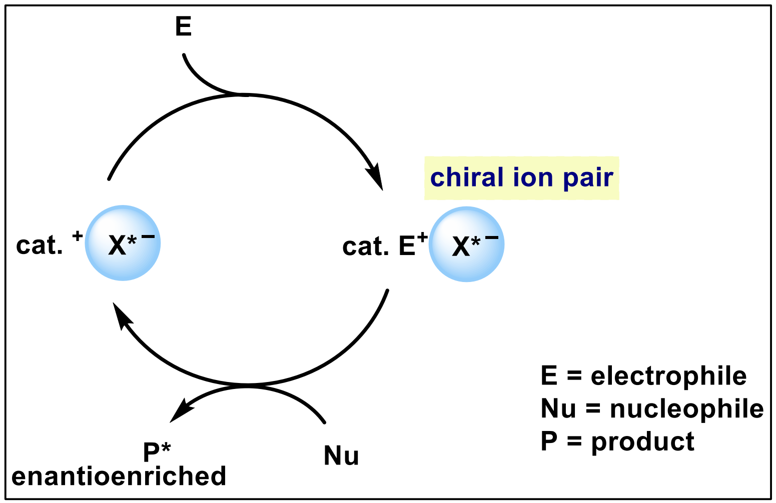




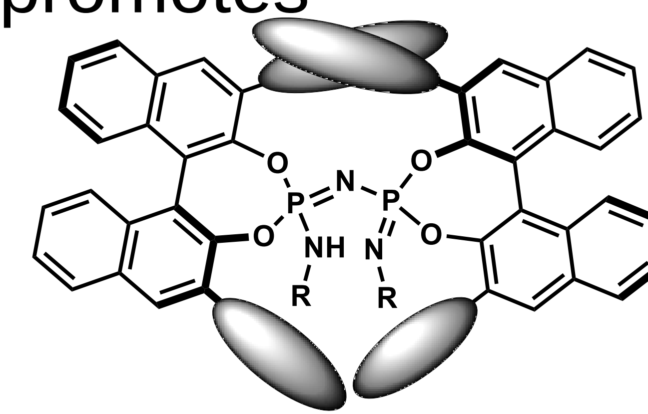
T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12671.

Summary

- Asymmetric Counteranion-Directed Catalysis (ACDC) concept is well developed.



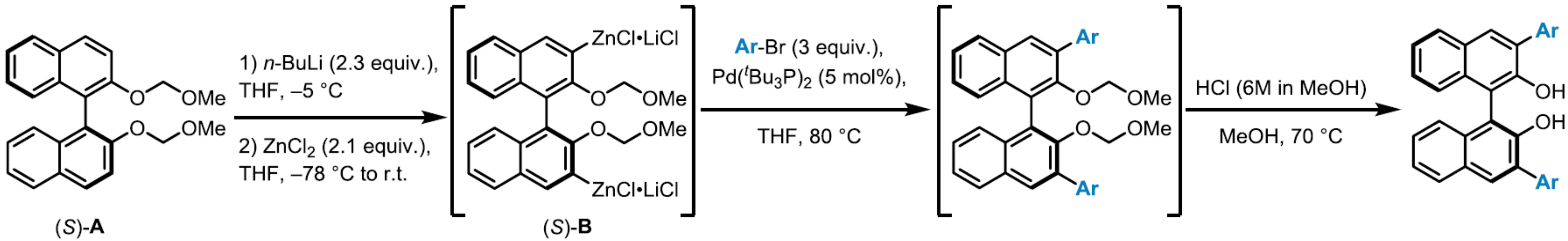
- BINOL-derived new IDPi catalyst promotes various kinds of reactions.
  - ➢ extremely low catalyst loading
    →high turnover, hydrolytically stable
  - ➢ highly selective catalysis
    →highly confined enantiopure catalysis

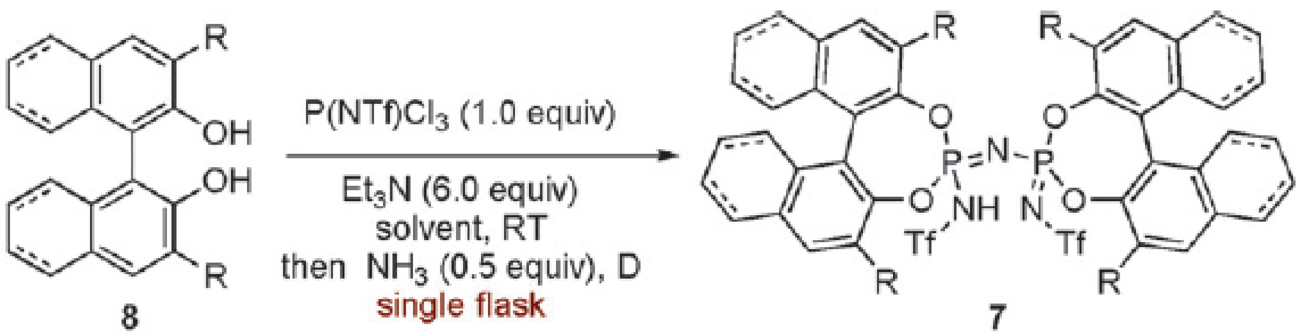


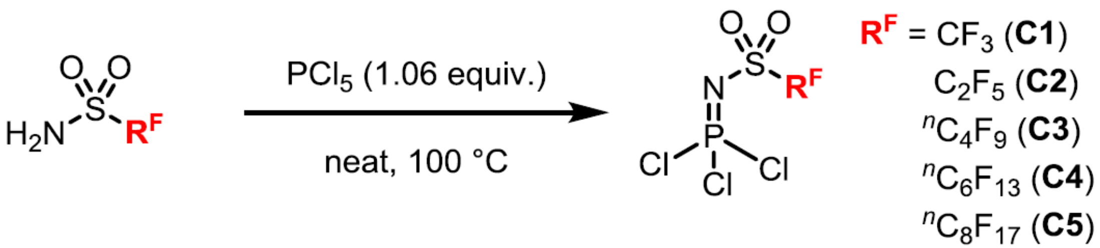
Imidodiphosphorimidates
IDPi

Appendix

Synthesis of Catalysts

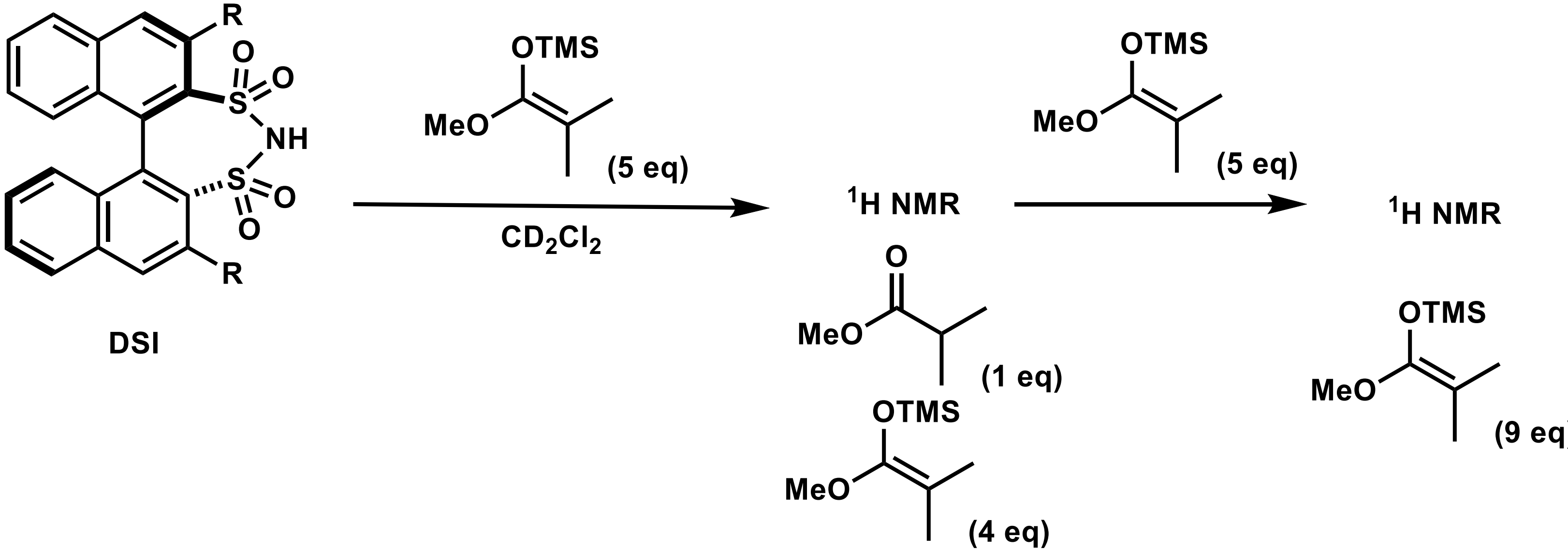






T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12671.

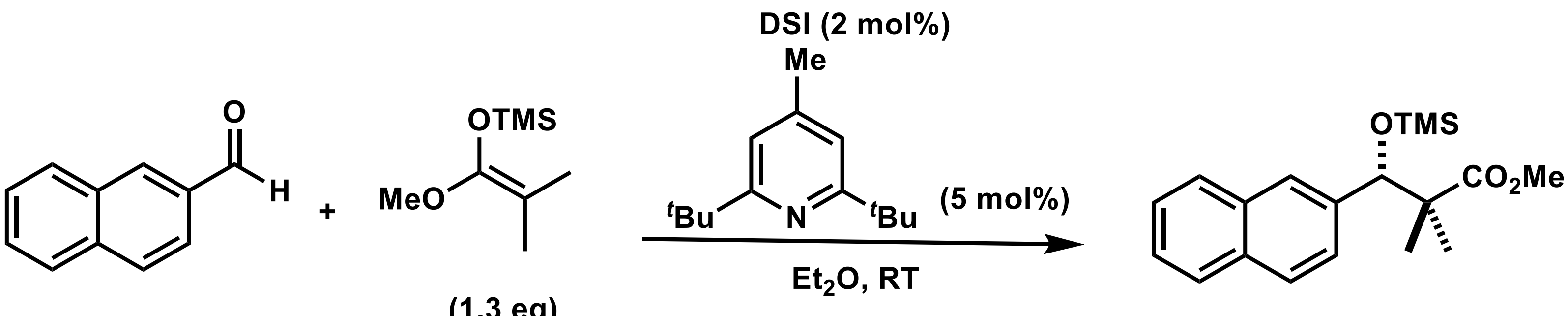
Mechanistic Study (MAR)



new species
(change of the signals in the aromatic region)

---

presence of a hindered base

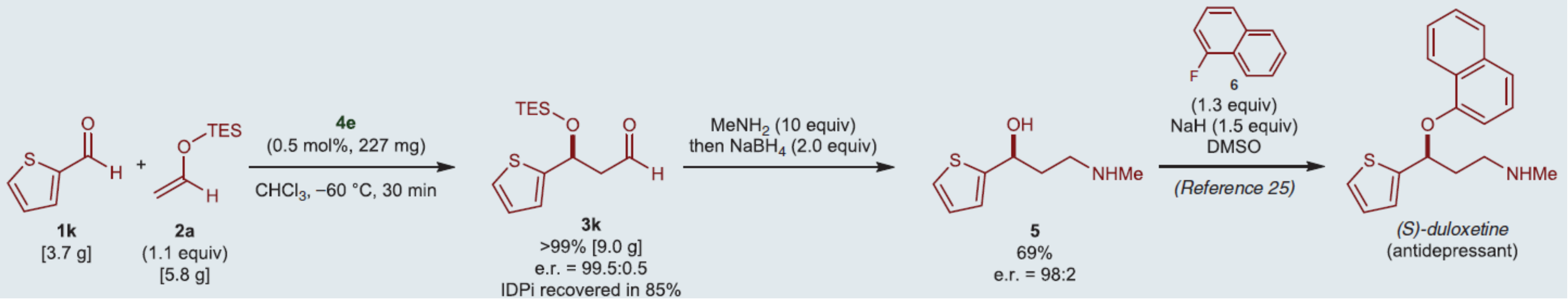


> 99%, 90:10 e.r.

The base inhibits any potential Brønsted acid catalysis.

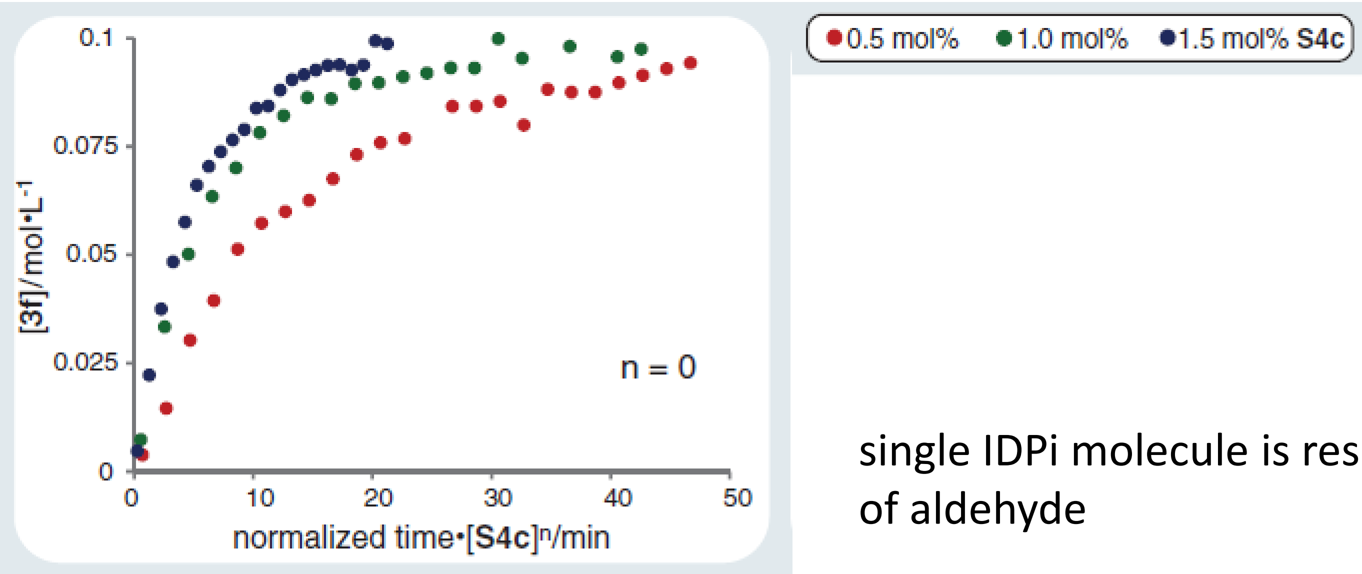
P. Garcia, F. Lay, P. Garcia, C. Rabalakos, B. List, *Angew. Chem. Int. Ed*. **2009**, *48*, 4363.

Scaled-up Aldol Reaction

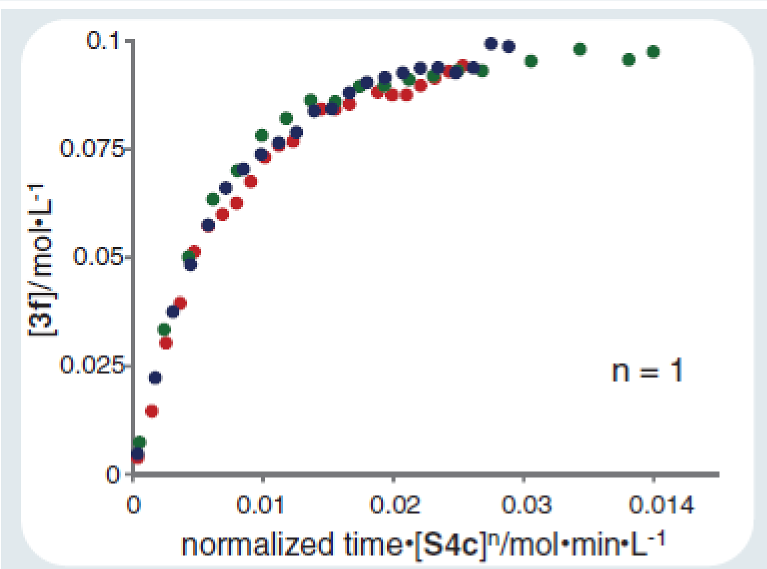


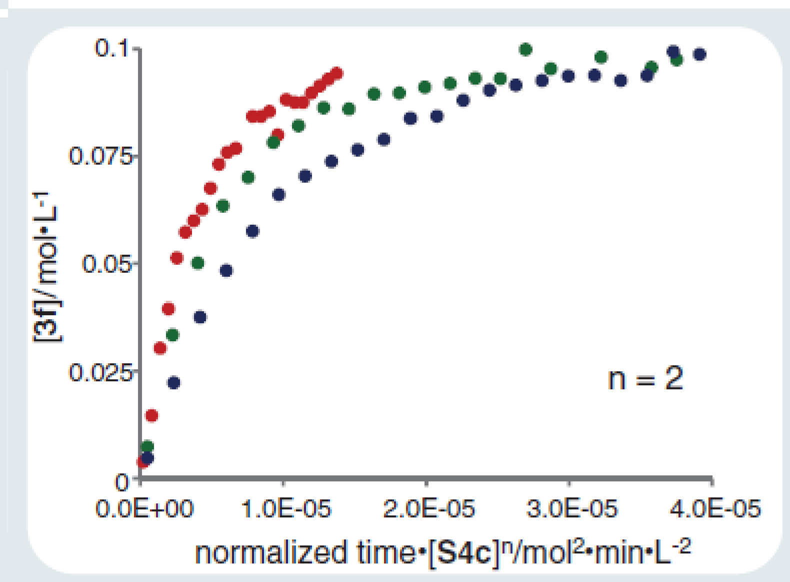
L. Schreyer, P. S. J. Kaib, V. N. Wakchaure, C. Obradors, R. Properzi, S. Lee, B. List, *Science*. **2018**, *362*, 216.

Graphical Method of Burés



single IDPi molecule is responsible for the activation of aldehyde





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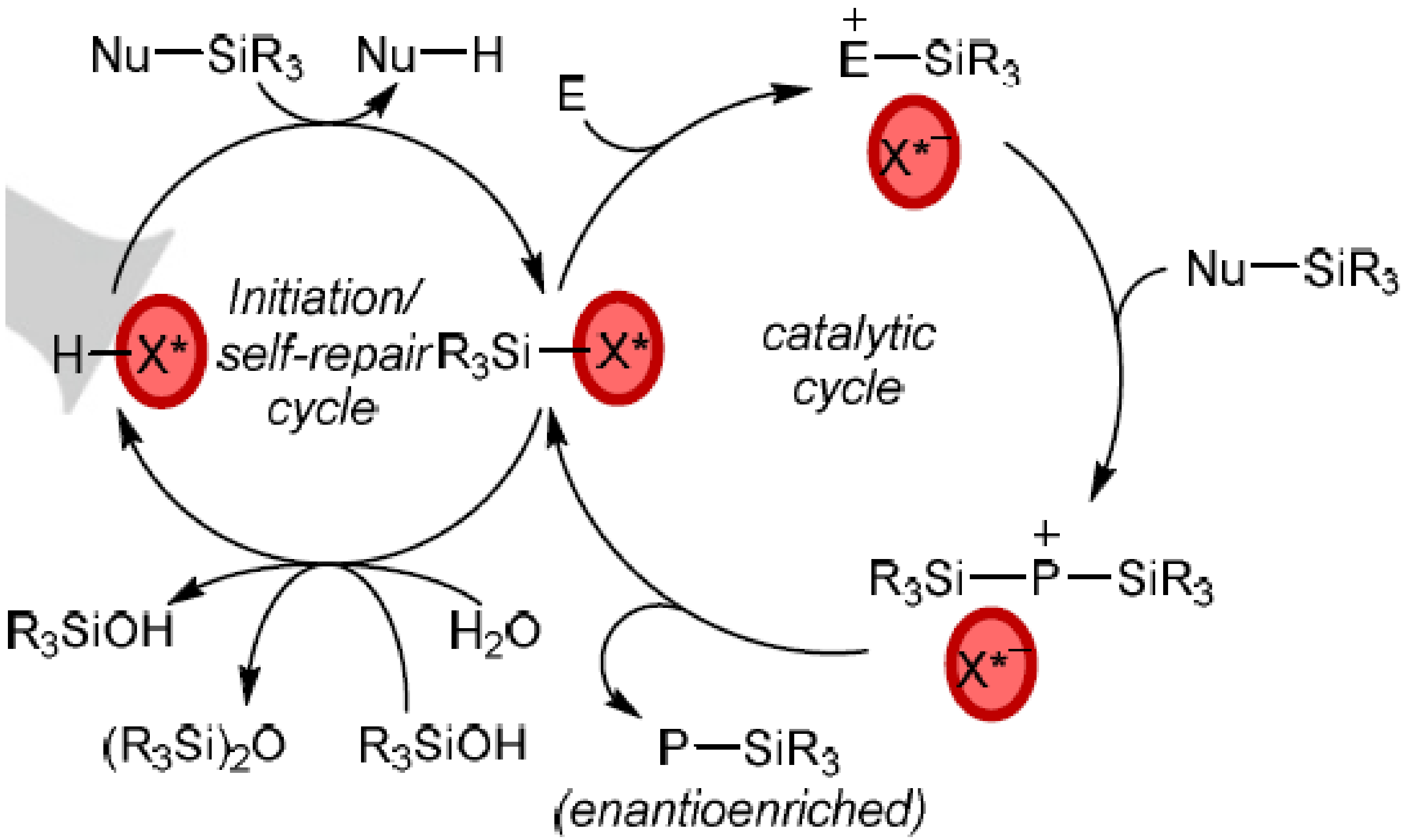
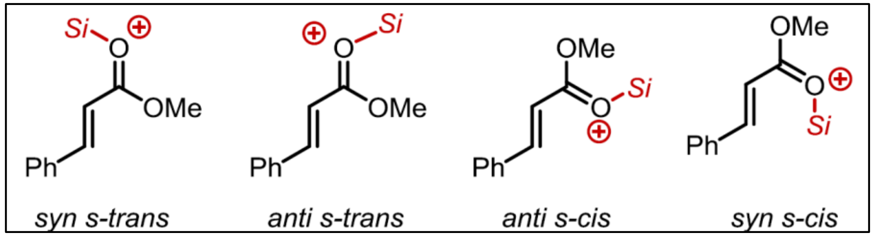
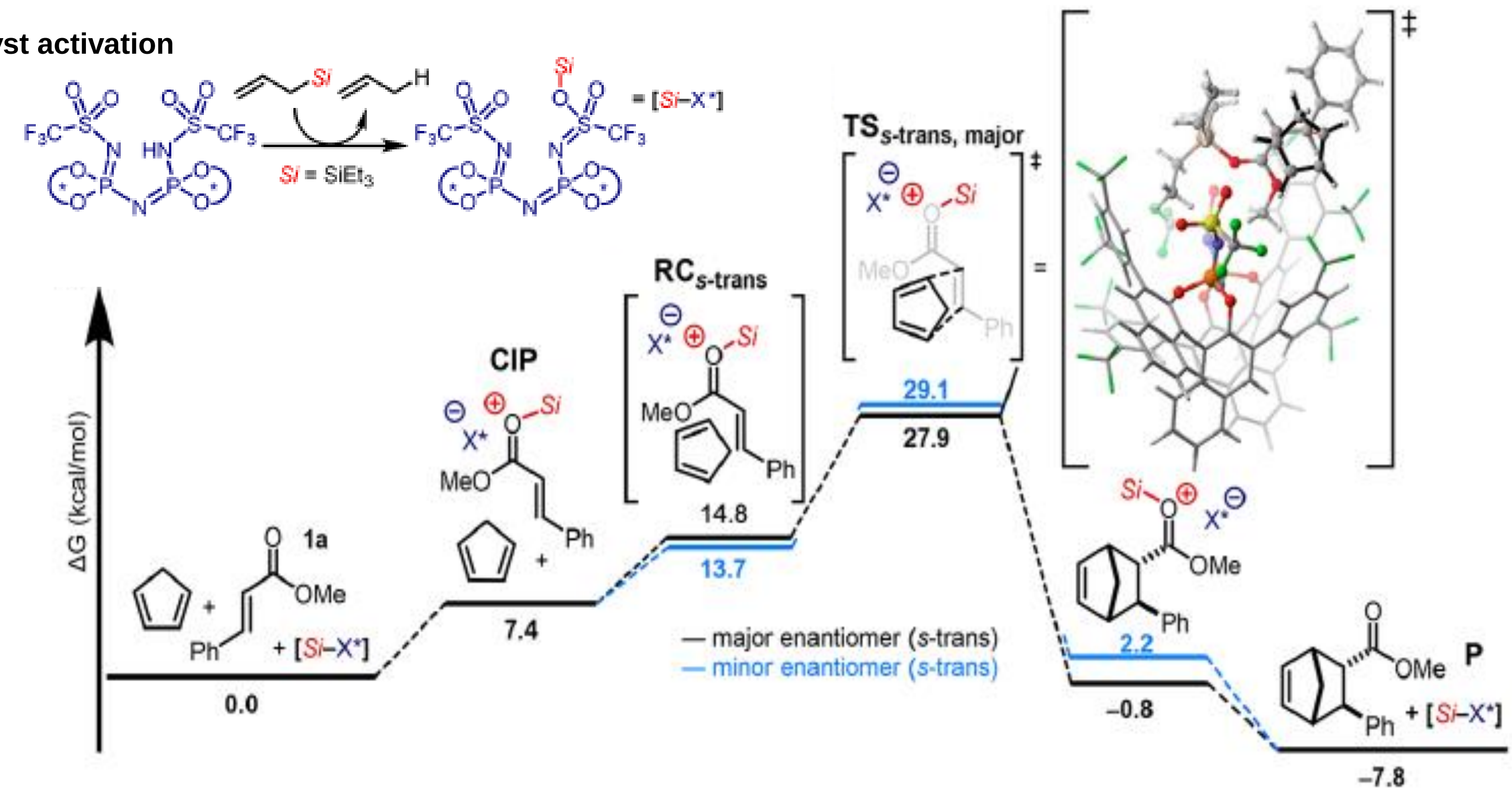
Self Repair Cycle



Computational Studies

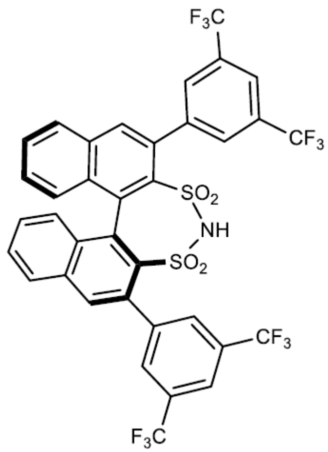


catalyst activation

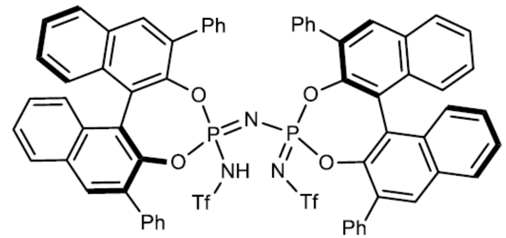


T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12671.

pKa of Catalyst



(*S*)-DSI **C-1**



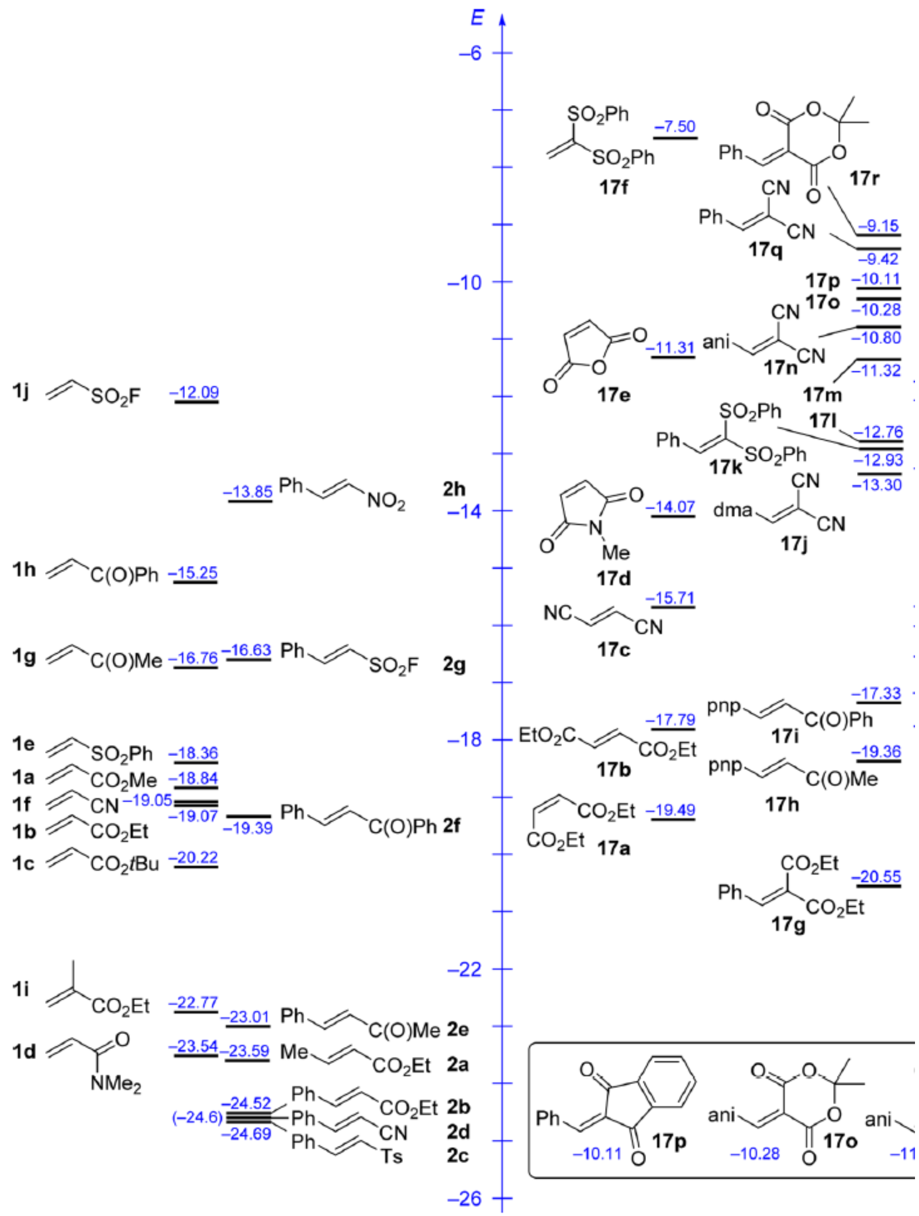
(*S*,*S*)-IDPi **C-3**

Acid	Reference acid	pK_a (reference)[a]	ΔpK_a[b]	pK_a(Acid)	Assigned pK_a
DSI **C-1**	2,4,6-($SO_2OCH_2CF_3$)$_3$-Phenol	7.97	–0.5	8.5	**8.4±0.1**
	(CF_3)$_5C_6CH(CN)_2$	8.86	0.5	8.4	
IDPi **C-3**	2,3,5-tricyanopentadiene	3.68	–0.8	4.5	**4.5±0.2**

[a]Data from Ref. 11. [b]ΔpK_a = pK_a(Reference acid) – pK_a(Studied acid). The pK_a values of other achiral acids displayed on the Fig. 4b in the main text are from Ref.9 and Ref.11.

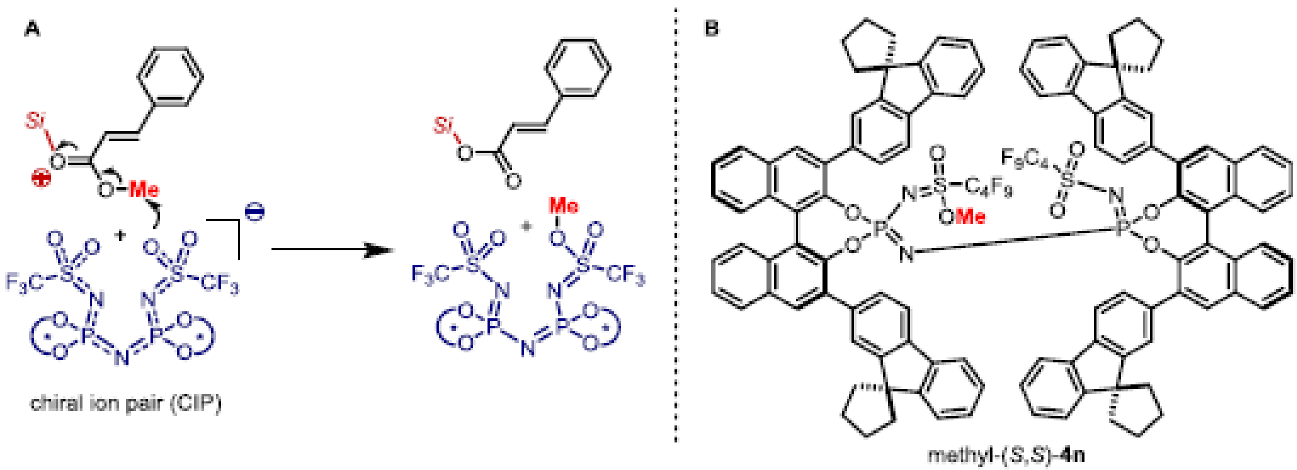
H. Y. Bae, D. Höfler, P. S. J. Kaib, P. Kasaplar, C. K. De, A. Döhring, S. Lee, K. Kaupmees, I. Leito, B. List, *Nat. Chem.* **2018**, *10*, 888

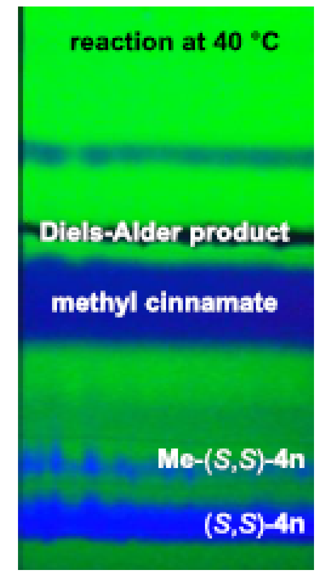
Electrophilic Reactivities of Michael Acceptors



D. S. Allgauer, H. Jangra, H. Asahara, Z. Li, Q. Chen, H. Zipse, A. R. Ofial, H. Mayr, *J. Am. Chem. Soc.* **2017**, *139*, 13318.

Catalyst Methylation





T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12671