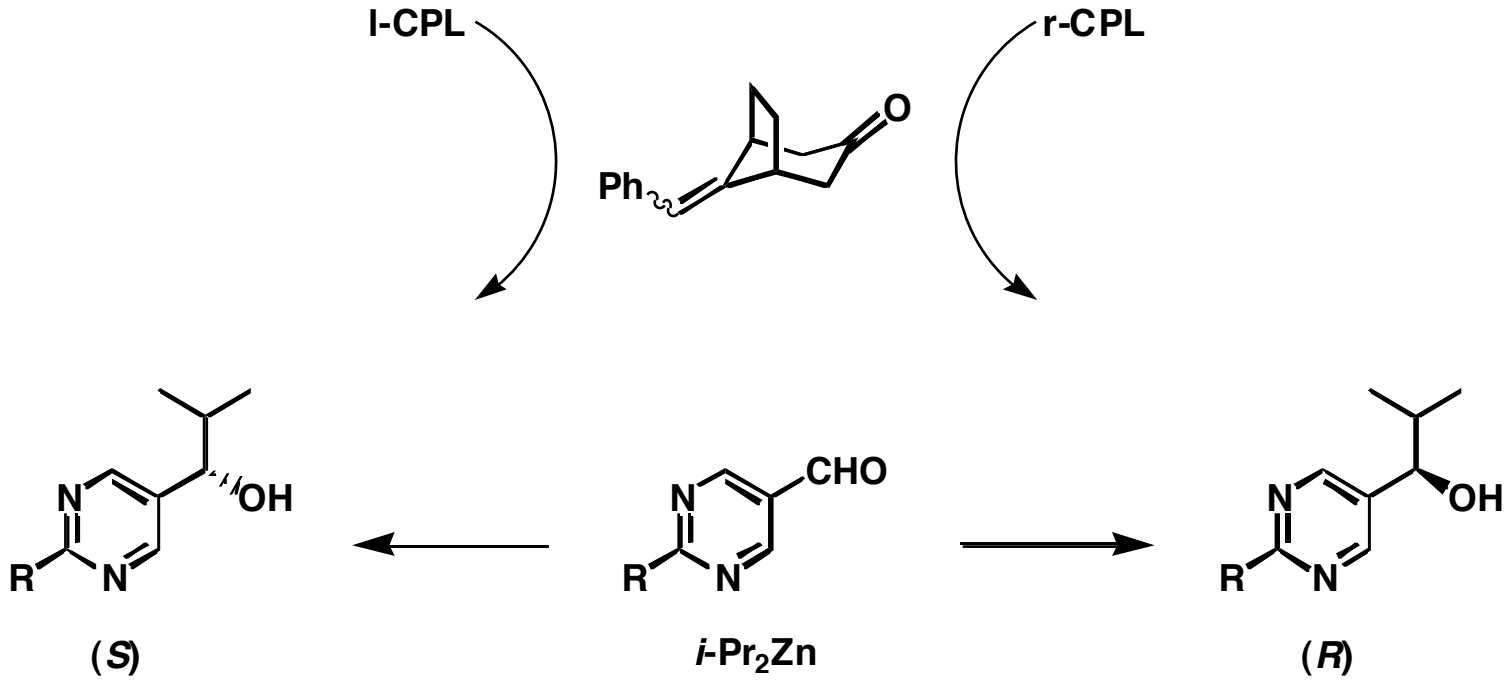
Asymmetric Synthesis Utilizing Circularly Polarized Light Mediated by the Photoequilibration of Chiral Olefins in Conjuction with Asymmetric Autocatalysis



Sato, I.; Sugie, R.; Matsueda, Y.; Furumura, Y.; Soai, K. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 4490

Presentation Outline

- ***Concept of Asymmetric Autocatalysis***

- ***Earlier Examples of Asymmetric Autocatalysis (Soai's Work)***

  Examples for which the autocatalyst is the chiral initiator (with or without amplification)

  Examples for which the chiral initiator is different from the autocatalyst

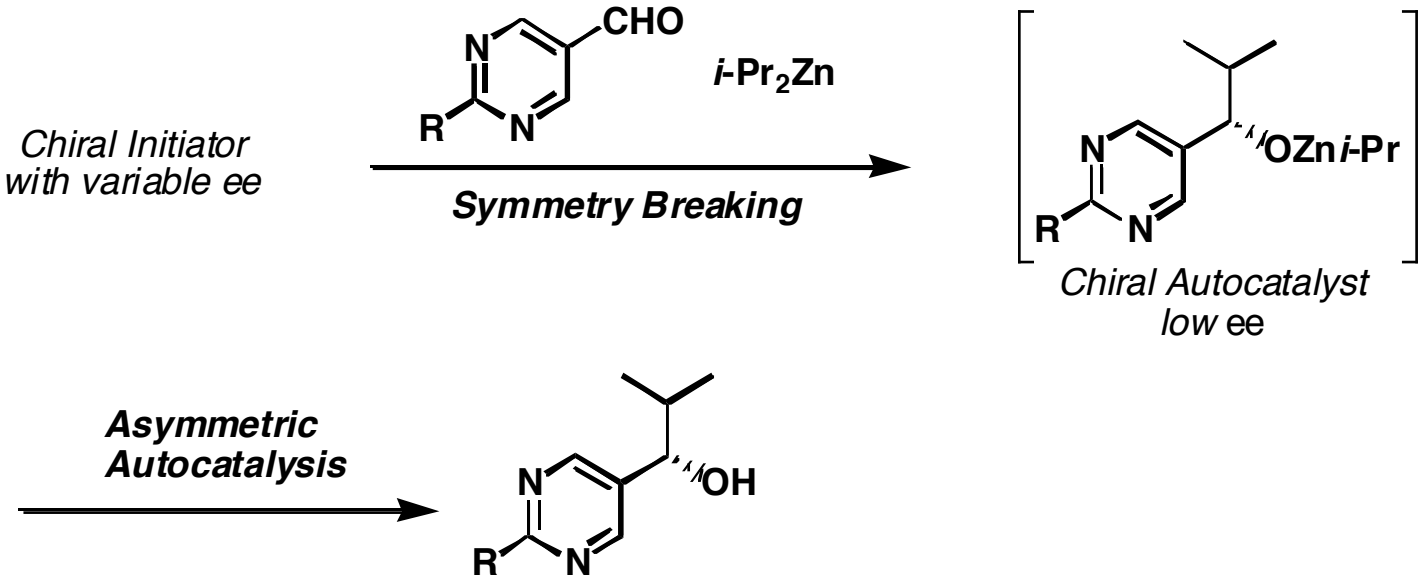
- ***Asymmetric Synthesis Utilizing Circularly Polarized Light (CPL) Mediated by the Photoequilibration of Chiral Olefins in Conjunction with Asymmetric Autocatalysis***

  Asymmetric autocatalysis with chiral olefins as initiators

  CPL-induced photoequilibration of racemic olefins in conjuction with asymmetric autocatalysis

Enantiomeric Amplification Based on Asymmetric Autocatalysis: The Concept

"A slight symmetry breaking induced by the presence of a chiral initiator of very low ee is dramatically amplified by asymmetric autocatalysis. [...], the slight ee in the chiral initiator is enhanced in the alkylated product. The subsequent addition of i-Pr_2Zn and aldehyde to the reaction mixture leads to an asymmetric autocatalytic reaction by the slightly enantiomerically enriched alkanol as an asymmetric autocatalyst, and highly enantiomerically enriched alkanol is obtained."



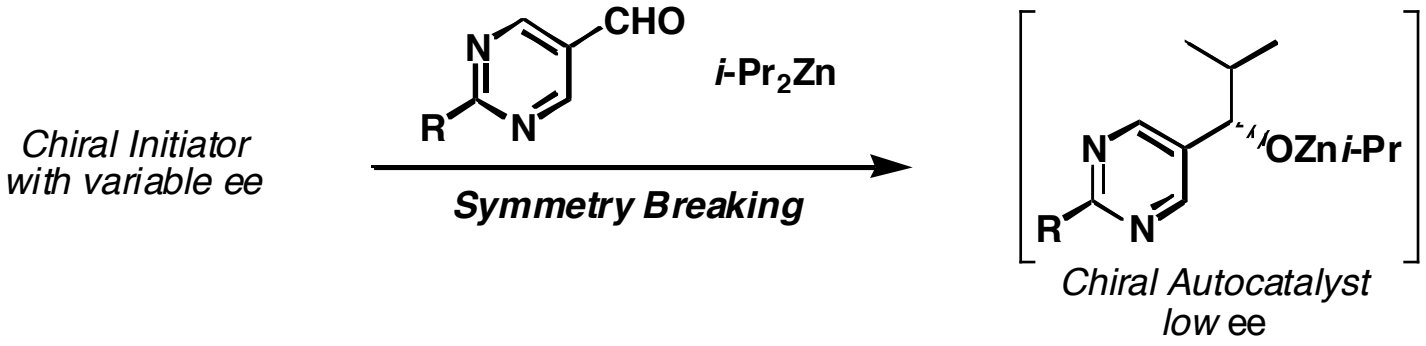
Shibata, T.; Yamamoto, J.; Matsumoto, N.; Yonekubo, S.; Osanai, S.; Soai, K.
J. Am. Chem. Soc. **1998**, *120*, 12157

Enantiomeric Amplification Based on Asymmetric Autocatalysis: The Concept

- *Autocatalytic Asymmetric Reaction when Chiral Autocatalyst = Product*

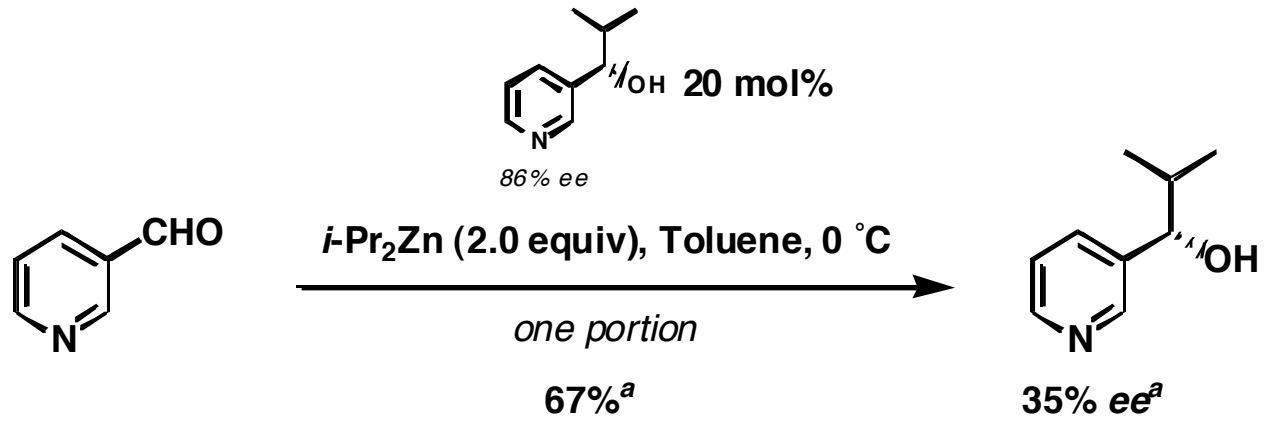
  Product formed catalyses the reaction that forms itself

- *Key Features: unlike conventionnal asymmetric catalysis, purification of the product from the chiral catalyst is not necessary*

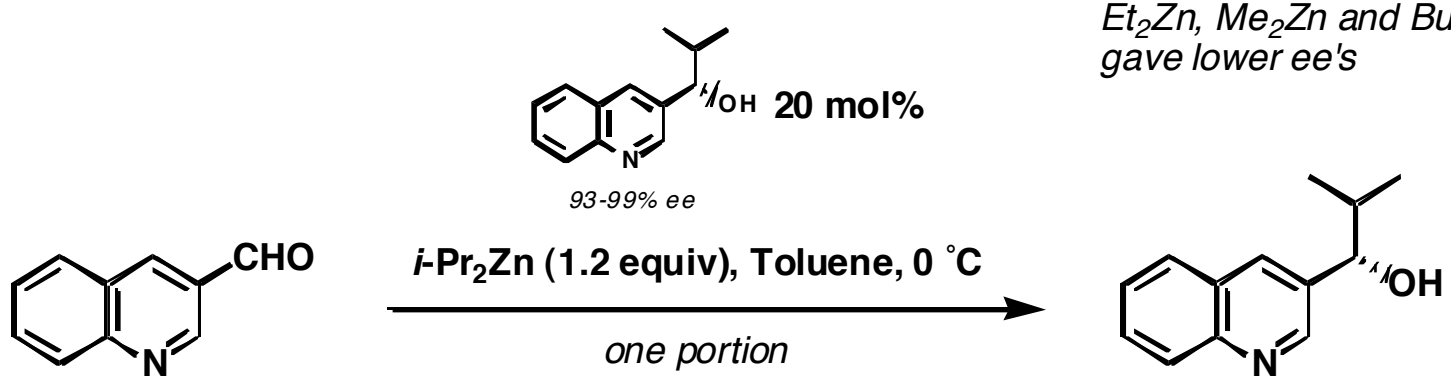


Shibata, T.; Yamamoto, J.; Matsumoto, N.; Yonekubo, S.; Osanai, S.; Soai, K.
J. Am. Chem. Soc. **1998**, *120*, 12157

Asymmetric Autocatalysis: Earlier Work by Soai



Et_2Zn, Me_2Zn and Bu_2Zn gave lower ee's

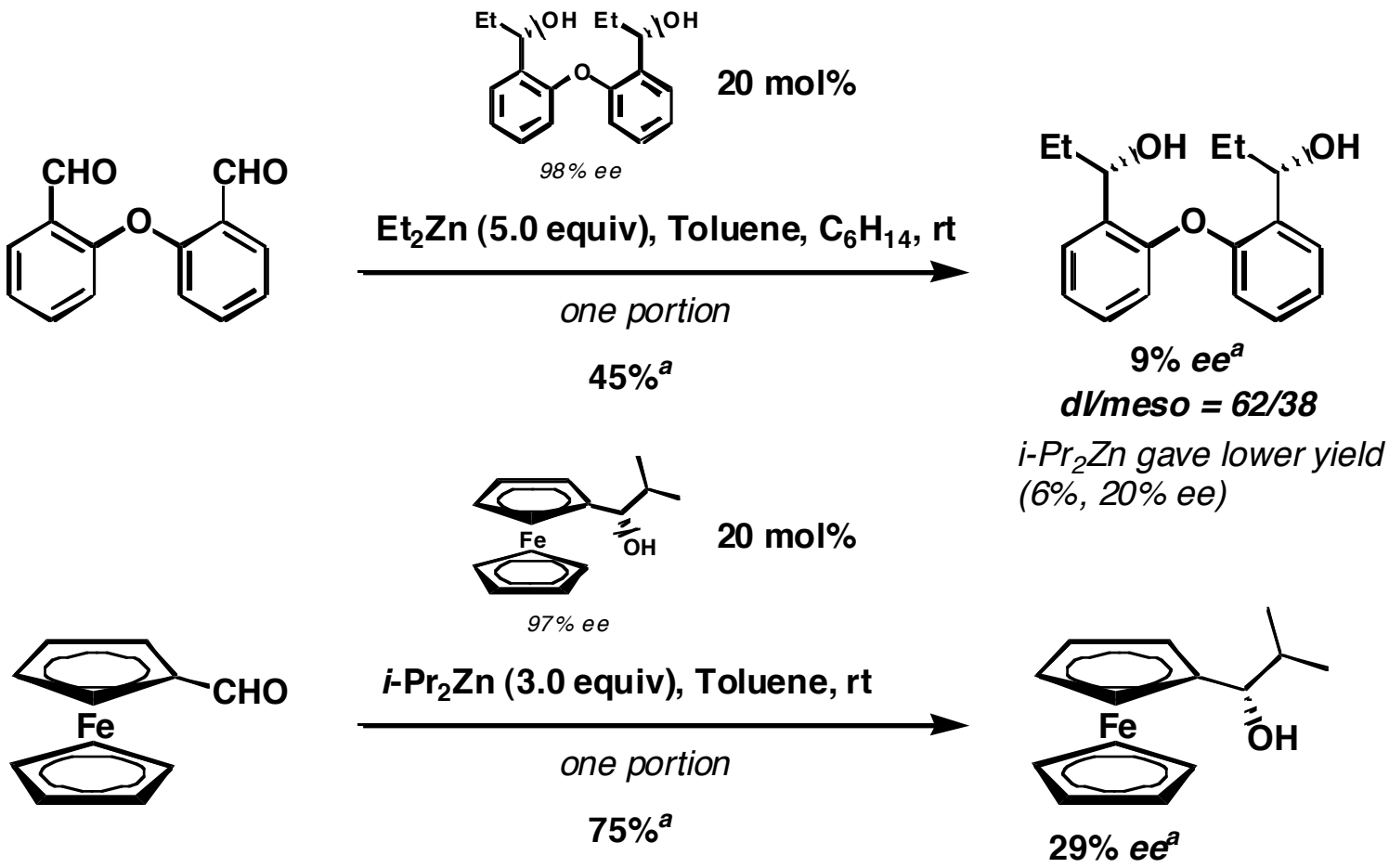


Cumene also a good solvent (DCM is not)

[a] Yield and *ee* of newly formed product (catalyst not included)

Soai, K.; Niwa, S.; Hori, H. *J. Chem. Soc., Chem. Commun.* **1990**, 982
Shibata, T.; Choji, K.; Morioka, H.; Hayase, T.; Soai, K. *J. Chem. Soc., Chem. Commun.* **1996**, 751

Asymmetric Autocatalysis: Earlier Work by Soai

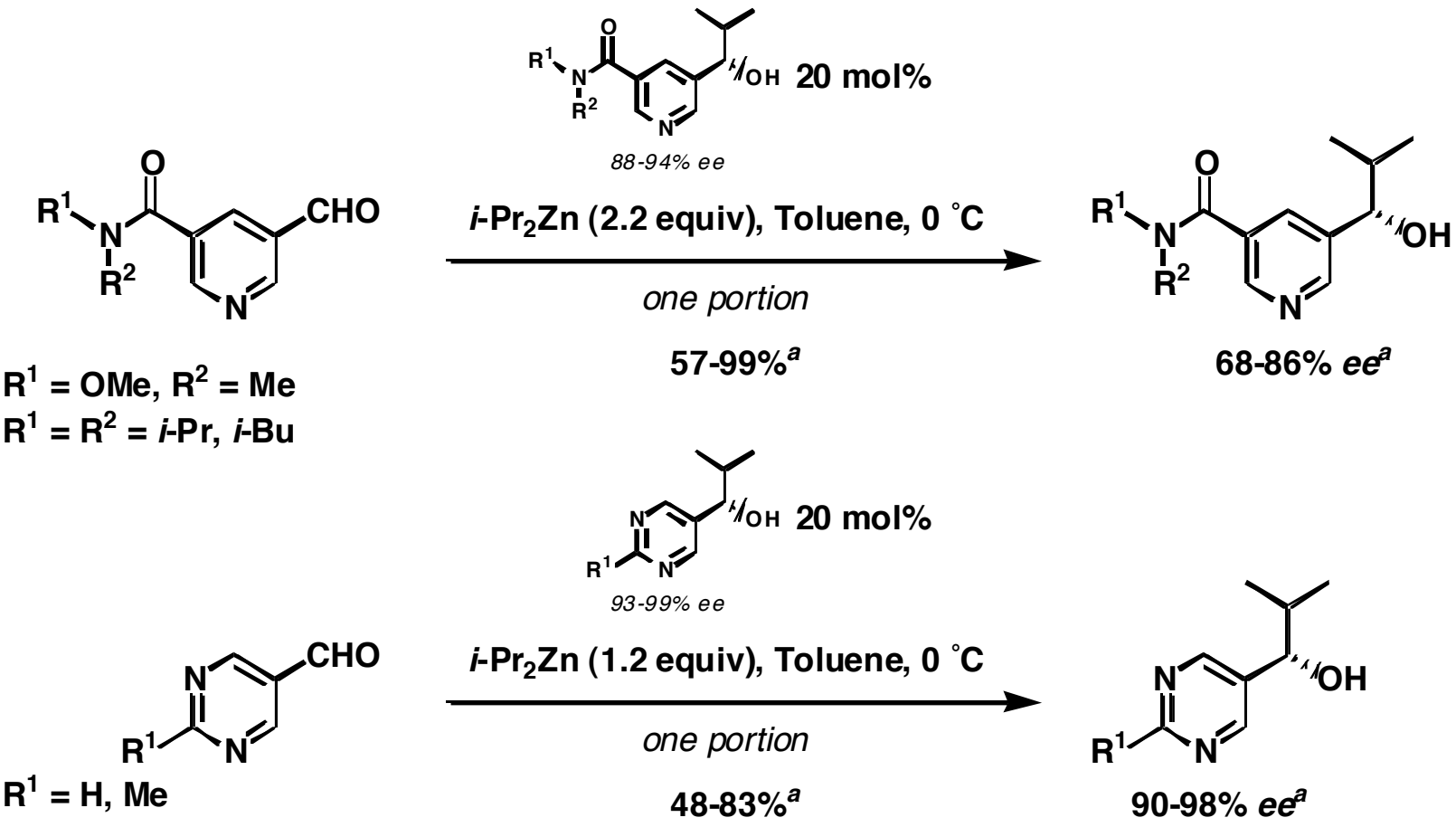


[a] Yield and *ee* of newly formed product (catalyst not included)

With 50 mol%, 35% ee

Soai, K.; Hayase, T.; Shimada, C.; Isobe, K. *Tetrahedron: Asymmetry* **1994**, *5*, 789
Soai, K.; Hayase, T.; Takai, K. *Tetrahedron: Asymmetry* **1995**, *6*, 637

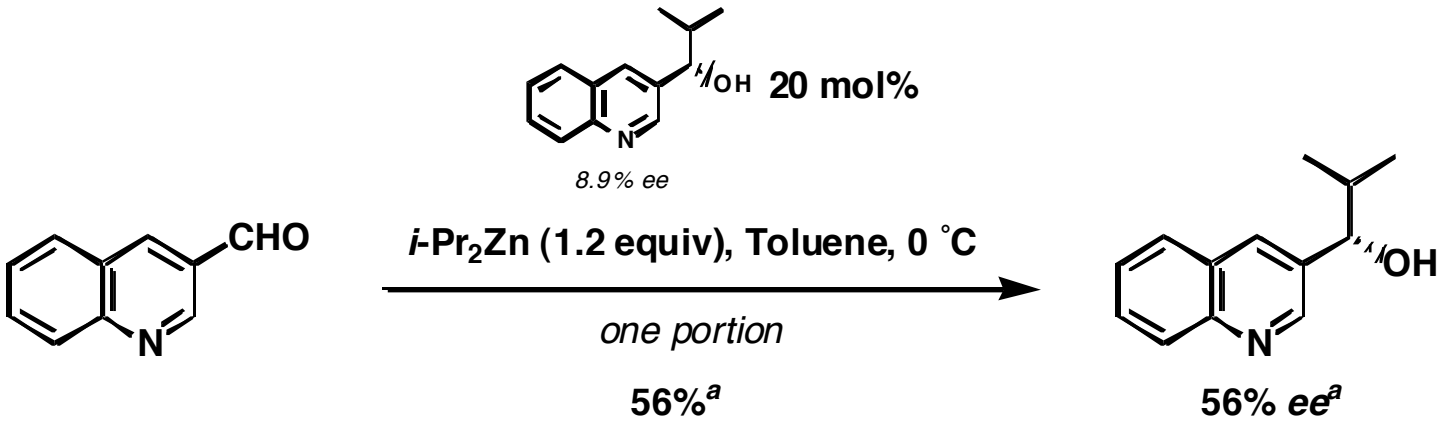
Asymmetric Autocatalysis: Earlier Work by Soai



[a] Yield and *ee* of newly formed product (catalyst not included)

Shibata, T.; Morioka, H.; Tanji, S.; Hayase, T.; Kodaka, Y.; Soai, K *Tetrahedron Lett.* **1996**, *37*, 8783
Shibata, T.; Morioka, H.; Hayase, T.; Choji, K.; Soai, K. *J. Am. Chem. Soc.* **1996**, *118*, 471

Enantiomeric Amplification Based on Asymmetric Autocatalysis: Earlier Work by Soai



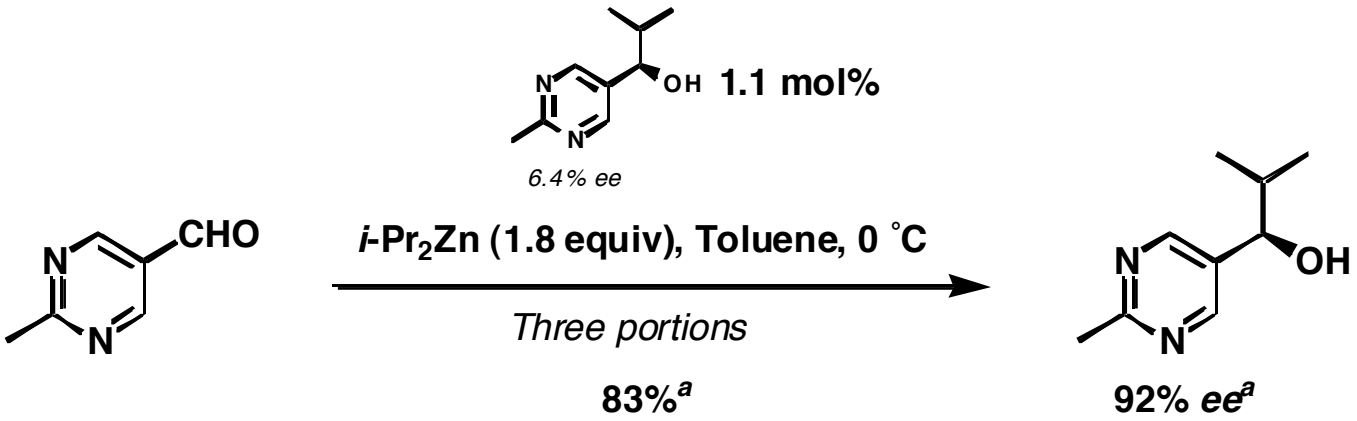
- *The ee of the product is higher than the ee of the catalyst (evidence of a non linear effect)*
- *The product obtained from this reaction can be used as a catalyst for the next one so that after a few iterations, a product with high ee can be obtained (>90% ee after 6 reactions)*

[a] Yield and *ee* of newly formed product (catalyst not included)

Shibata, T.; Choji, K.; Hayase, T.; Aizu, Y.; Soai, K. *J. Chem. Soc., Chem. Commun.* **1996**, 1235
First example, see; Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature* **1995**, *378*, 767

Enantiomeric Amplification Based on Asymmetric Autocatalysis: Earlier Work by Soai

- *A dramatic increase in ee's can be obtained if the aldehyde and i-Pr_2Zn are added portionwise to the reaction mixture*



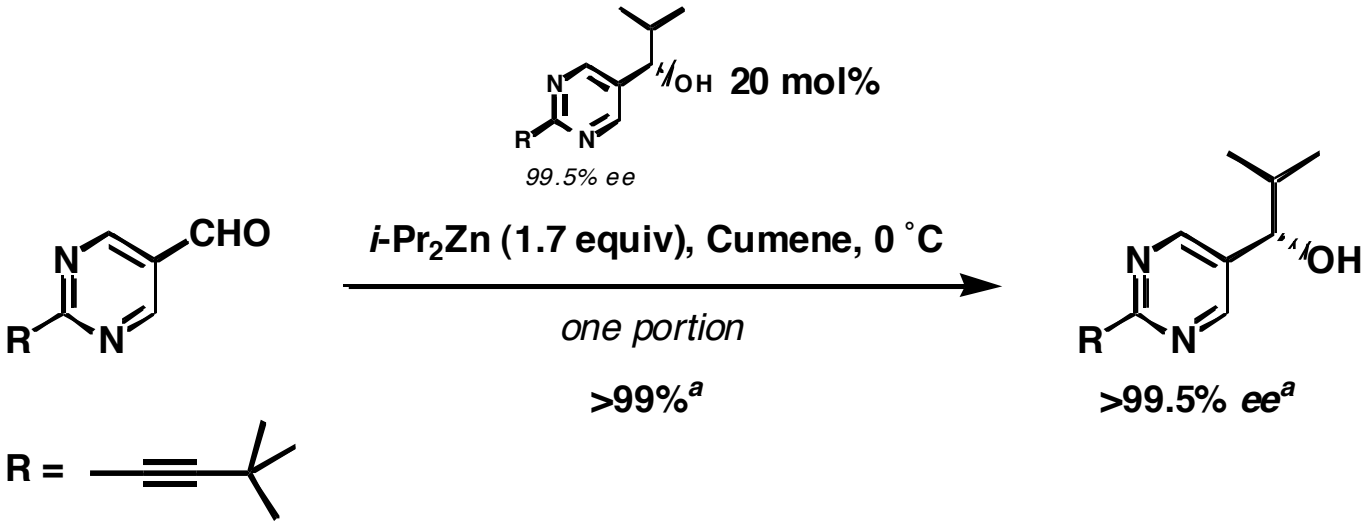
- *Still a one-pot reaction*

- *The amount and the ee of the autocatalyst increases with every portion (after two portions, ee of the newly formed product is 60%)*

[a] Yield and *ee* of newly formed product (catalyst not included)

Shibata, T.; Hayase, T.; Yamamoto, J.; Soai, K. *Tetrahedron: Asymmetry* **1997**, *8*, 1717

Enantiomeric Amplification Based on Asymmetric Autocatalysis: Earlier Work by Soai



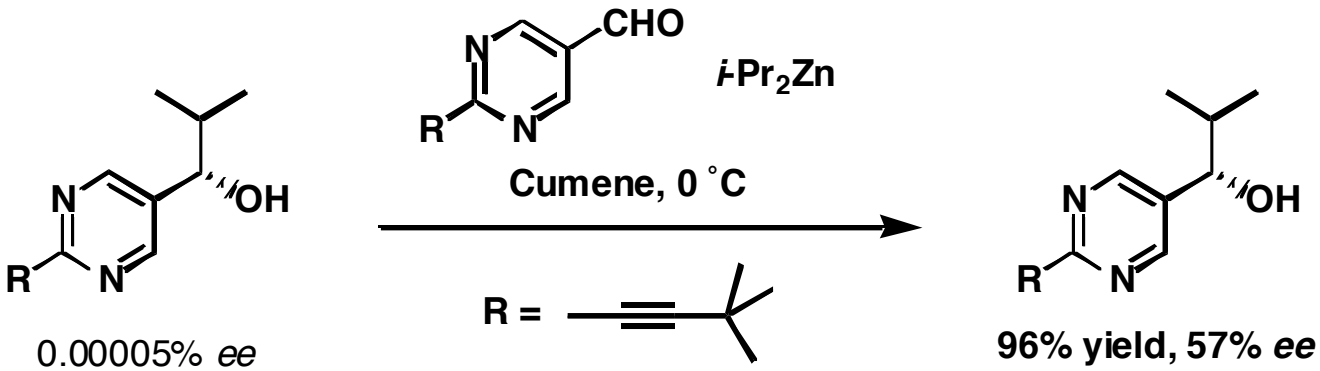
- *Under these conditions, the reaction was performed successively, with the products of one round serving as the reactants for the next one. Even after 10 rounds, all the asymmetric autocatalytic reactions proceeded perfectly (>99% yield, >99.5% ee)*

[a] Yield and *ee* of newly formed product (catalyst not included)

Shibata, T.; Yonekubo, S.; Soai, K. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 659

Enantiomeric Amplification Based on Asymmetric Autocatalysis

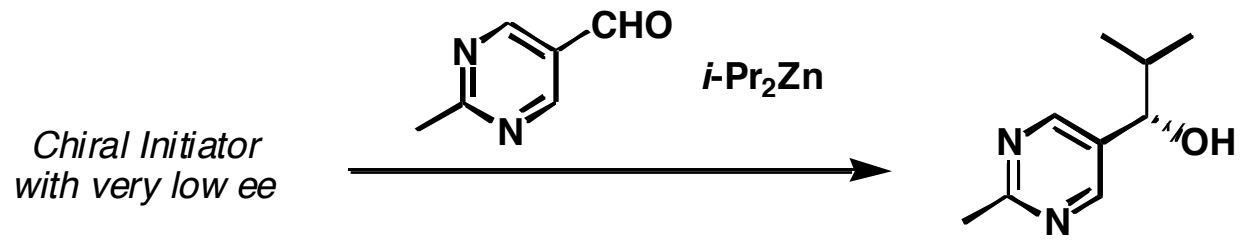
How low can you go?



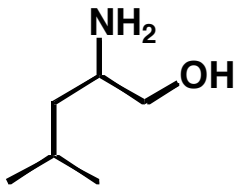
- *Aldehyde and i-Pr$_2$Zn were added in four portions*
- *Autocatalyst loading of 0.8 mol% (relative to the total amount of aldehyde used)*

Sato, I.; Urabe, H.; Ishiguro, S.; Shibata, T.; Soai, K. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 315

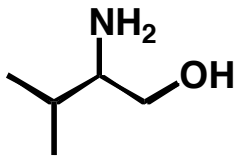
Enantiomeric Amplification Based on Asymmetric Autocatalysis: Other Chiral Initiators



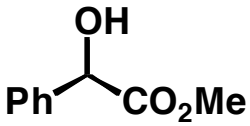
Chiral Initiators



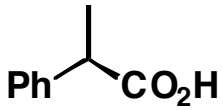
2% (26%)



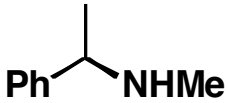
1% (51%)



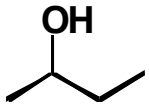
0.1% (70%)



0.1% (76%)



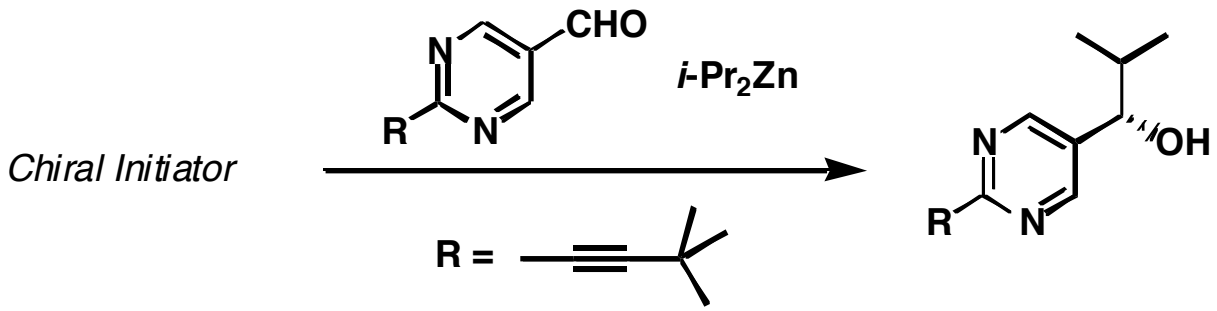
0.1% (85%)



0.1% (76%)

Shibata, T.; Yamamoto, J.; Matsumoto, N.; Yonekubo, S.; Osanai, S.; Soai, K.
J. Am. Chem. Soc. **1998**, *120*, 12157

Enantiomeric Amplification Based on Asymmetric Autocatalysis: Other Chiral Initiators



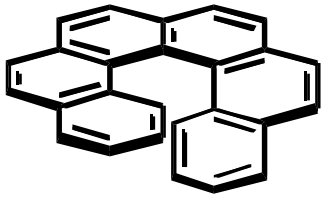
d-$NaClO_3$ crystal (98% *ee*)[1]

Toluene, 0 ˚C
190 mol% $NaClO_3$
Aldehyde and *i*-Pr_2Zn added
in three portions

d-Quartz crystal (93-97% *ee*)[3]

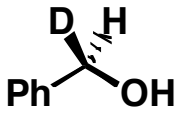
Toluene, 0 ˚C
190 mol% quartz
Aldehyde and *i*-Pr_2Zn added
in three portions

[6]- and [5]-Helicenes (95% *ee*)[2]



Toluene, 0 ˚C
6-11 mol% Helicene
Aldehyde and *i*-Pr_2Zn added
in two portions

α-Deuterated alcohols (90-96% *ee*)[4]



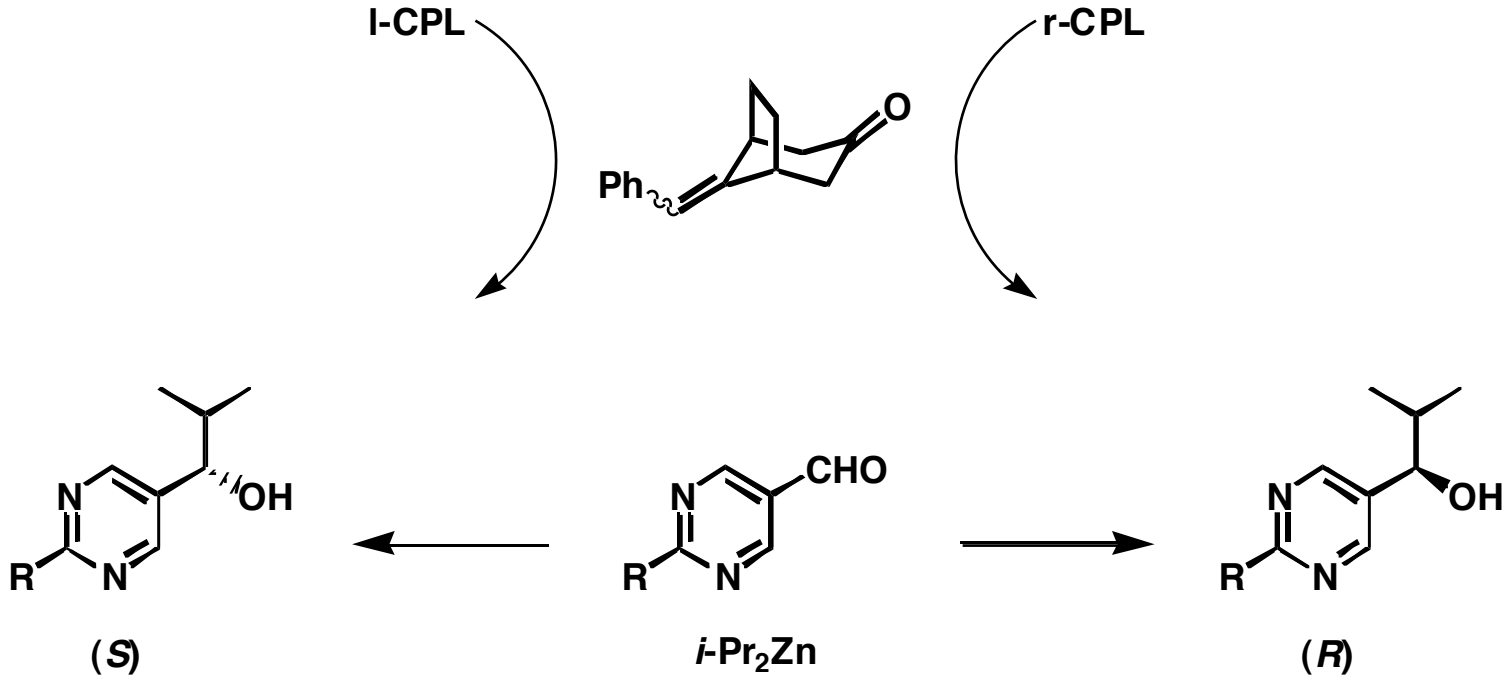
Toluene, 0 ˚C
1.6 mol% alcohol
Aldehyde and *i*-Pr_2Zn added
in four portions

[1] Sato, I.; Kadowaki, K.; Soai, K. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 1510 [2] Sato, I.; Yamashima, R.; Kadowaki, K.; Yamamoto, J.; Shibata, T.; Soai, K. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1096 [3] Soai, K.; Osanai, S.; Kadowaki, K.; Yonekubo, S.; Shibata, T.; Sato, I. *J. Am. Chem. Soc.* **1999**, *121*, 11235
[4] Sato, I.; Omiya, D.; Saito, T.; Soai, K. *J. Am. Chem. Soc.* **2000**, *122*, 11739

Asymmetric Synthesis Utilizing Circularly Polarized Light Mediated by the Photoequilibration of Chiral Olefins in Conjuction with Asymmetric Autocatalysis

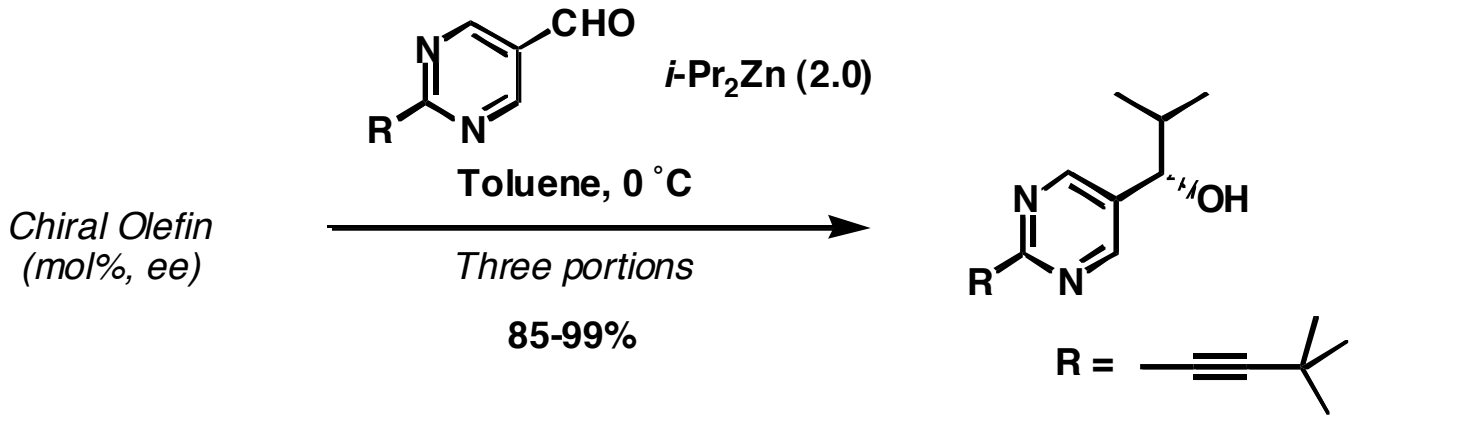
Basic concept

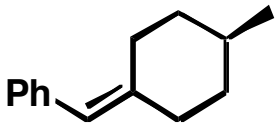
Use right or left-circularly polarized light to induce a slight enantiomeric enhancement of a chiral olefin, which translates to a slight enantiomeric enrichement in the reaction product. The product then acts as an autocatalyst to produce itself in high ee's



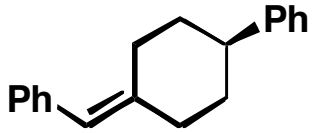
Sato, I.; Sugie, R.; Matsueda, Y.; Furumura, Y.; Soai, K. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 4490

Asymmetric Autocatalysis using Chiral Olefins as Initiators

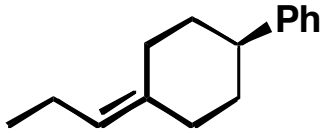




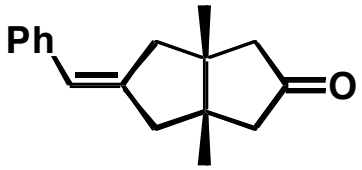
5 mol% of 98% *ee* (95% *ee*)
5 mol% of 86% *ee* (95% *ee*)



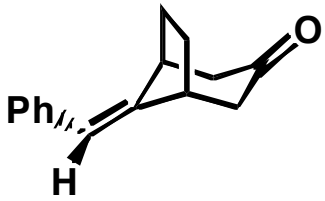
5 mol% of 56% *ee* (96% *ee*)



5 mol% of 56% *ee* (96% *ee*)

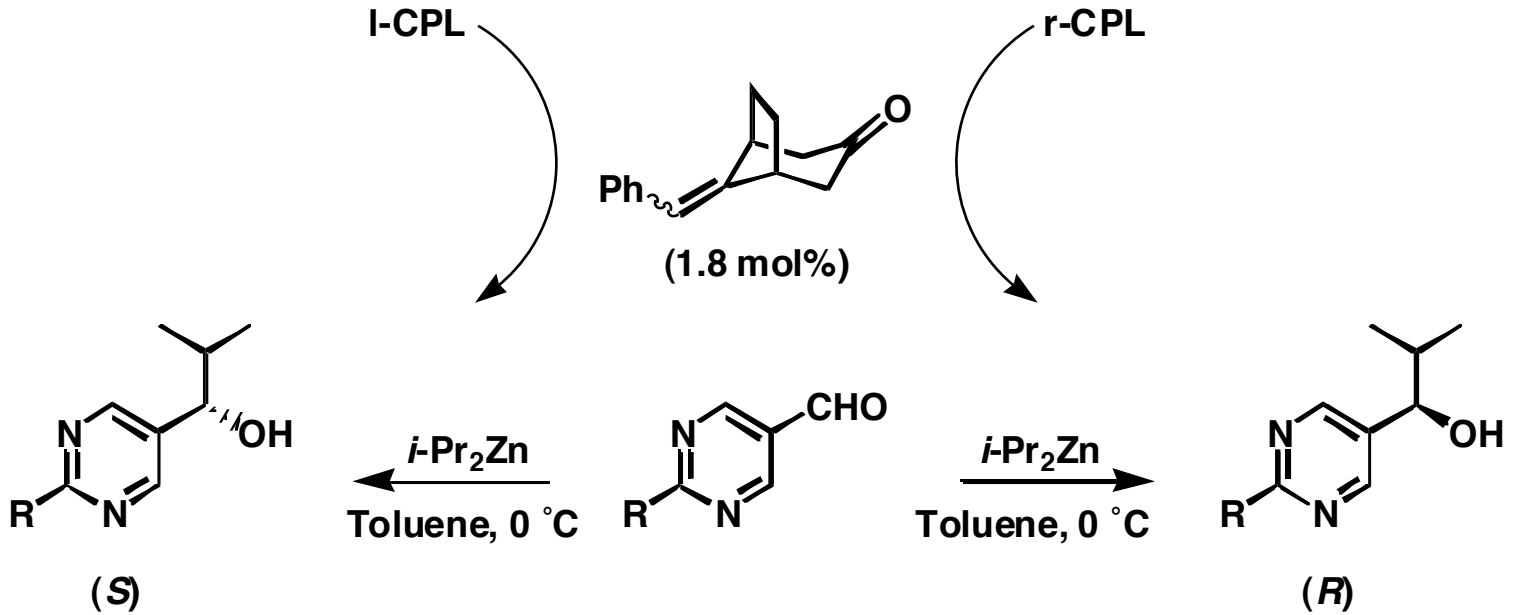


5 mol% of 87% *ee* (90% *ee*)
5 mol% of 30% *ee* (96% *ee*)



2 mol% of 98% *ee* (98% *ee*)
10 mol% of 5% *ee* (97% *ee*)
10 mol% of 1.3% *ee* (95% *ee*)

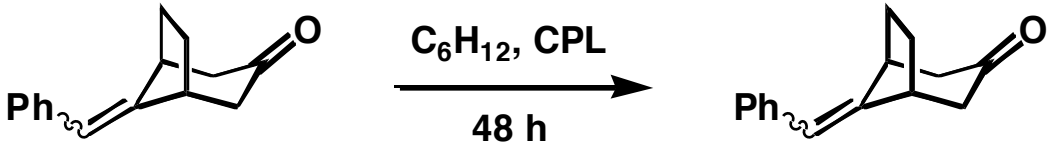
Asymmetric Autocatalysis using a Chiral Olefin Generated by Photoequilibration with CPL



Entry	Chiral Source	Yield (%)	*ee* (%)
1	l-CPL	96	97
2	r-CPL	96	93
3	l-CPL	92	91
4	r-CPL	91	90
5	l-CPL	93	90
6	r-CPL	97	90

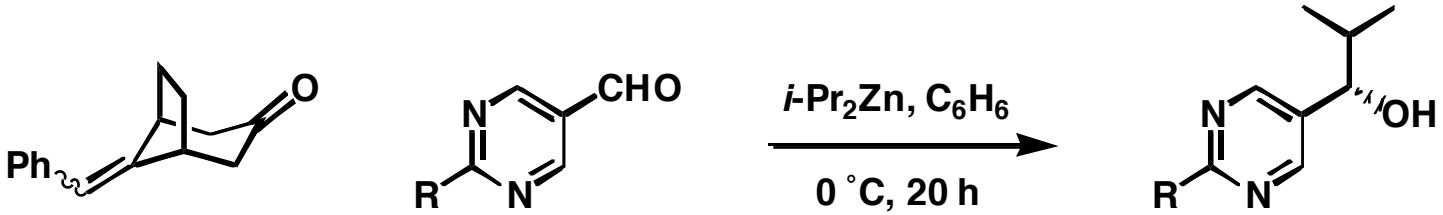
Representative Procedure

▷ **Step 1:** *Dissolve racemic alkene in cyclohexane and irradiate the solution with CPL for 48 h*



racemic *ca. 2% ee*

▷ **Step 2:** *Concentrate, dissolve in methylcyclohexane and treat with aldehyde and i-Pr_2Zn*



ca. 2% ee (0.024 mmol) (0.025 mmol)

▷ **Step 3:** *Add 3 other portions of aldehyde and i-Pr_2Zn at different intervals*

Aldehyde	***i*-Pr_2Zn**	**Time**
(0.1 mmol)	(0.2 mmol)	2 h
(0.4 mmol)	(0.8 mmol)	5 h
(0.8 mmol)	(1.6 mmol)	2 h