

# **Reactions with Chiral Amplification**

**Literature Seminar  
2023/07/08**

**Yuuki Watanabe**

## 1. Introduction

## 2. Main Paper

ACS  
central  
science

ACS AuthorChoice

Research Article

 Cite This: ACS Cent. Sci. 2019, 5, 1235–1240

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**Asymmetric Catalysis in Chiral Solvents: Chirality Transfer with Amplification of Homochirality through a Helical Macromolecular Scaffold**

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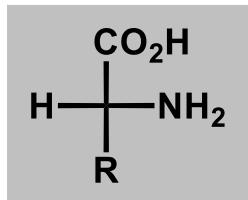
<http://pubs.acs.org/journal/acscii>

Asymmetric Catalysis in Chiral Solvents: Chirality Transfer with  
Amplification of Homochirality through a Helical Macromolecular  
Scaffold

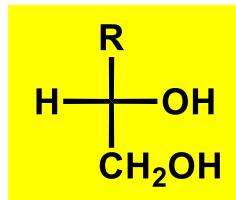
# Homochirality

Homochirality: A uniformity of chirality

In nature, amino acids/sugars are homochiral.

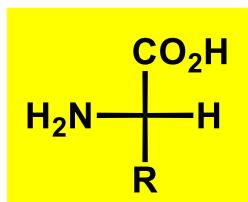


D-amino acid

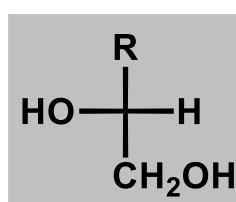


D-sugar

: common in biology

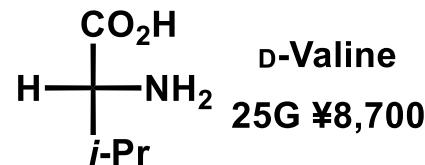
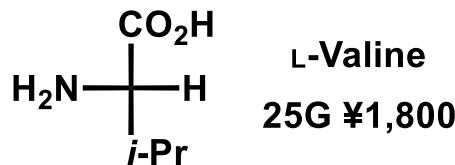


L-amino acid



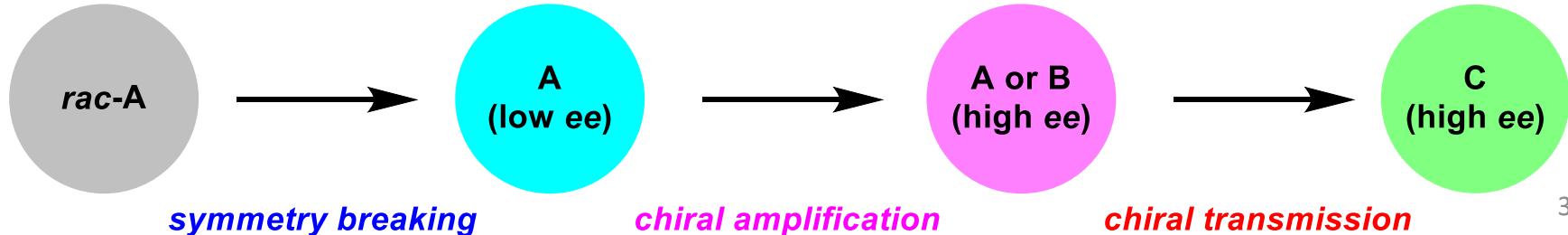
L-sugar

: uncommon in biology



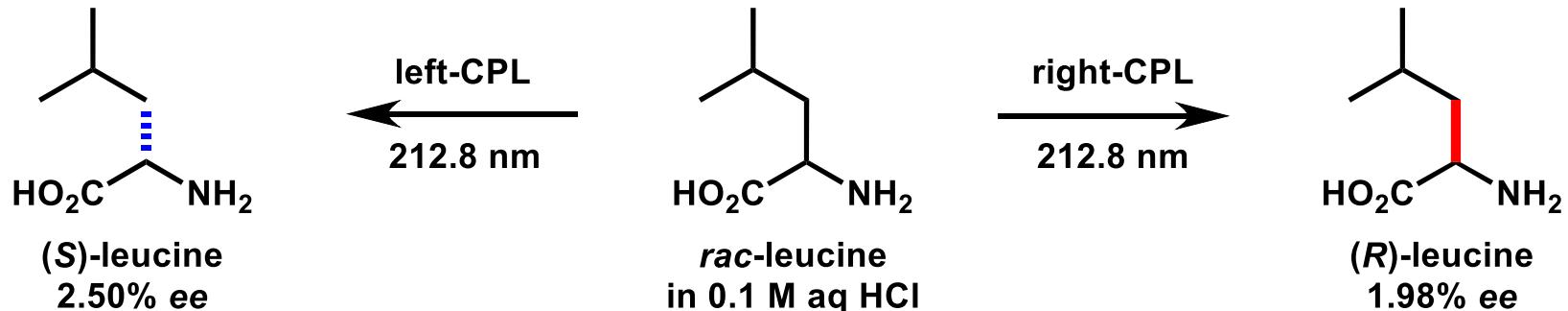
Q: What is the origin and the mechanism of homochirality in biology?

<Possible hypothesis>

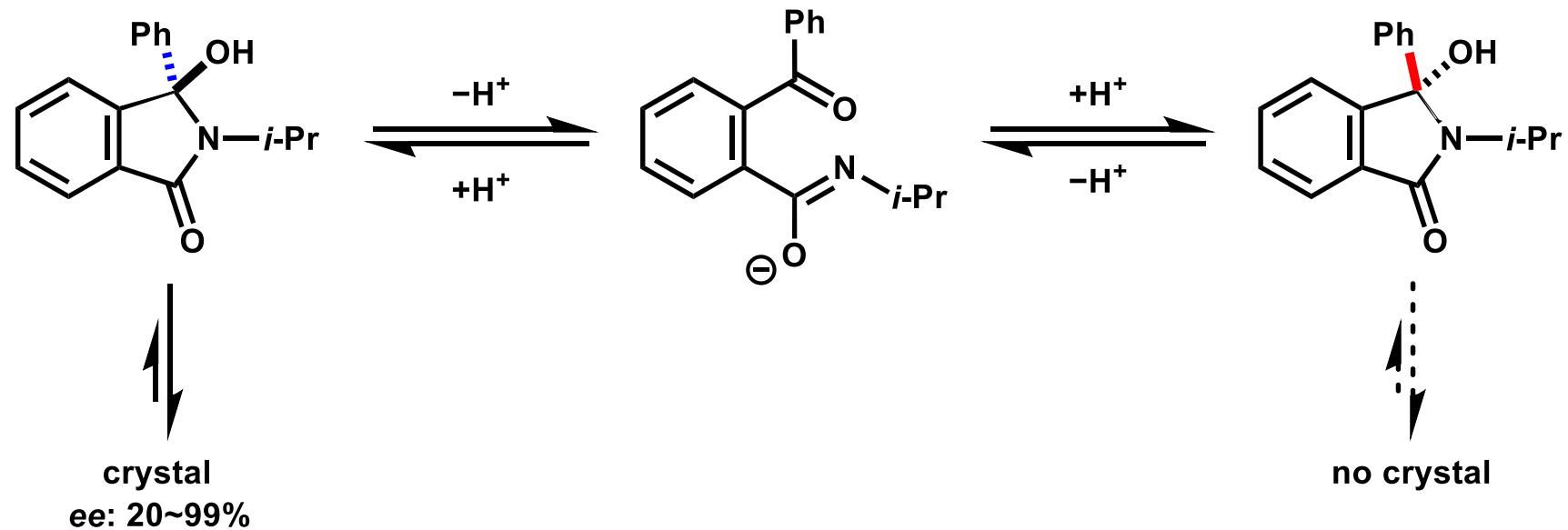


# Symmetry Breaking

<circularly polarized light, CPL>



<Recrystallization with CPL>

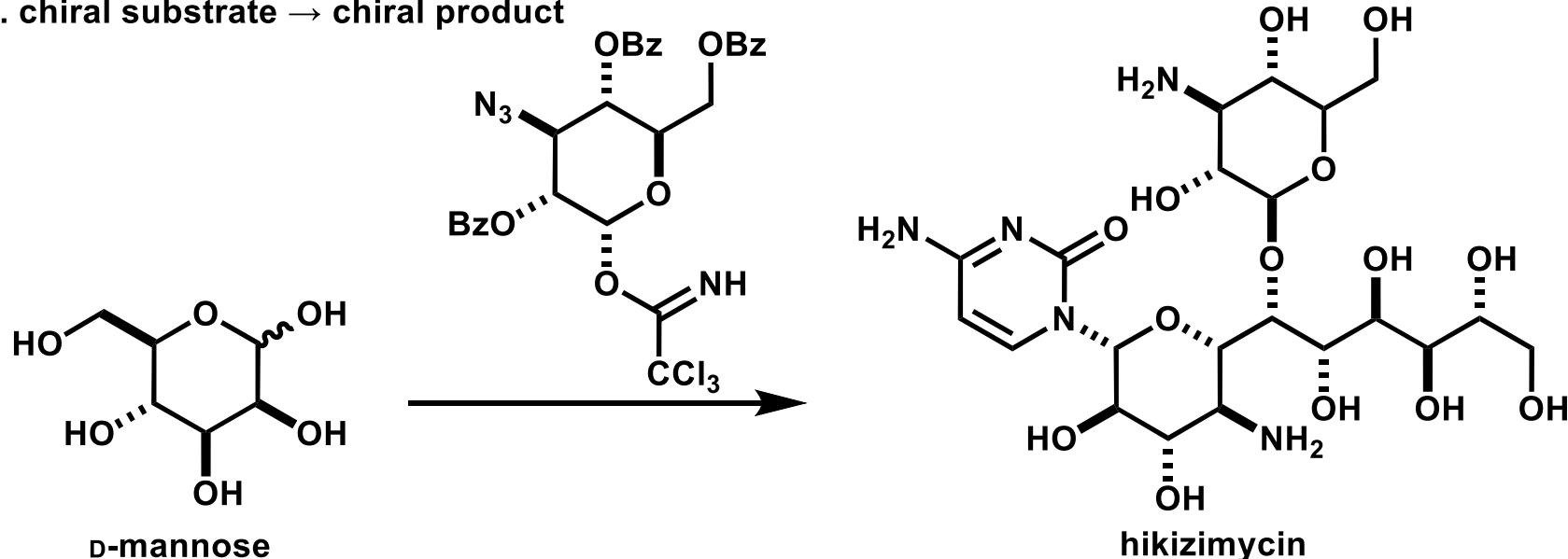


1. Flores, J. J.; Bonner, W. A.; Massey, G. A. *J. Am. Chem. Soc.* **1977**, *99*, 3622.

2. Sakamoto, M.; Uemura, N.; Saito, R.; Shimobayashi, H.; Yoshida, Y.; Mino, T.; Omatsu, T. *Angew. Chem., Int. Ed.* **2021**, *60*, 12819.

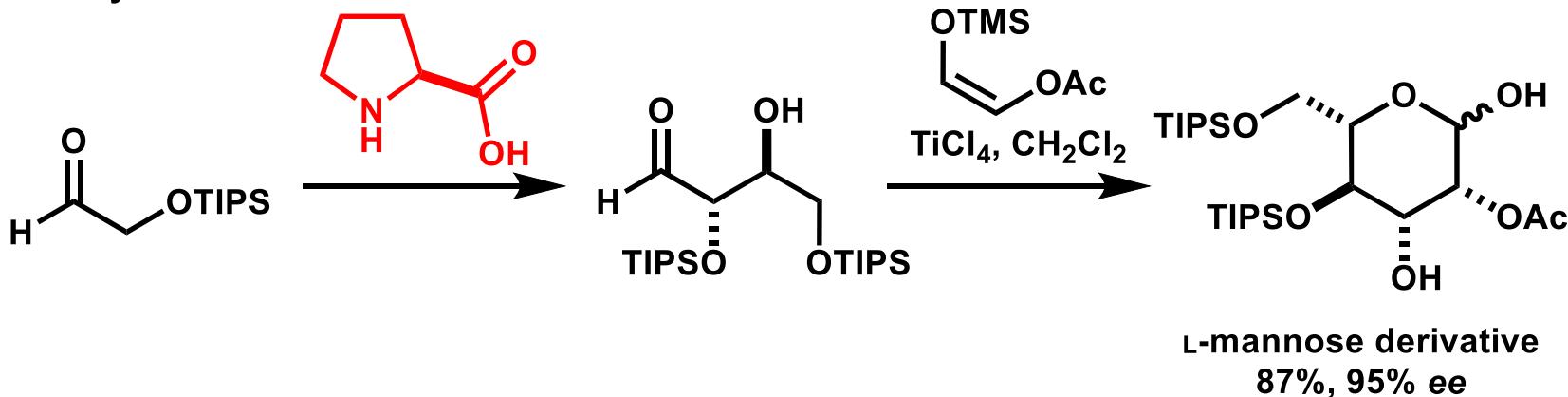
# Chiral Transmission

1. chiral substrate → chiral product



2. achiral substrate → chiral product (with chiral catalyst)

Most asymmetric reactions are "chiral transmission" reactions.



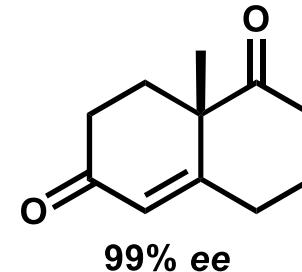
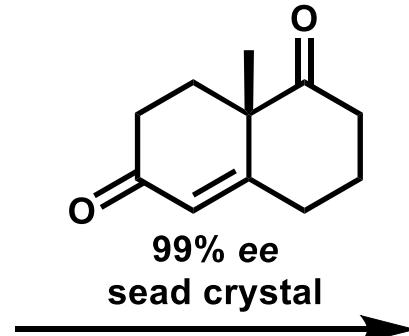
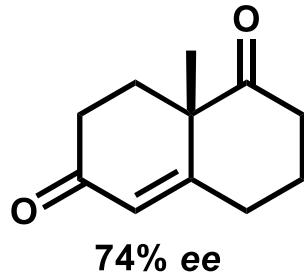
1. Fujino, H.; Fukuda, T.; Nagatomo, M.; Inoue, M. *J. Am. Chem. Soc.* **2020**, 142, 13277.

2. a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, 124, 6798.

b) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, 305, 5691.

# Chiral Amplification

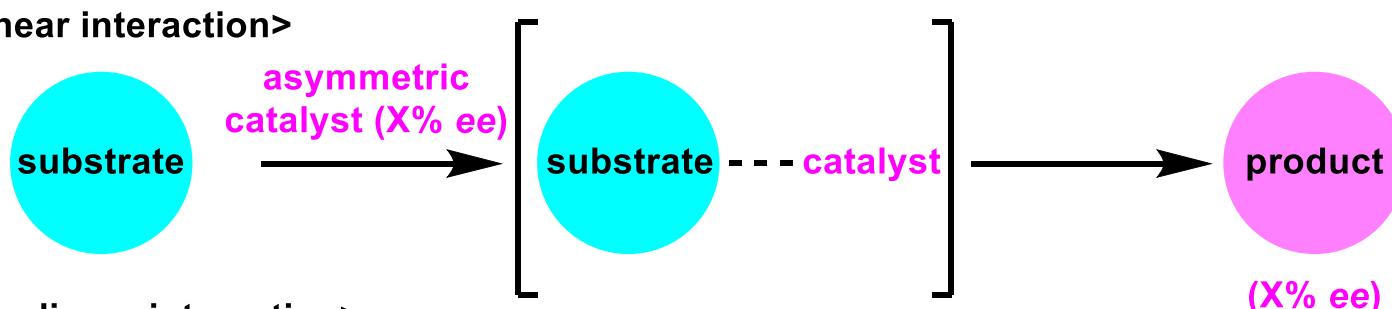
<Recrystallization>  
to obtain the higher ee product  
(with seed crystal)



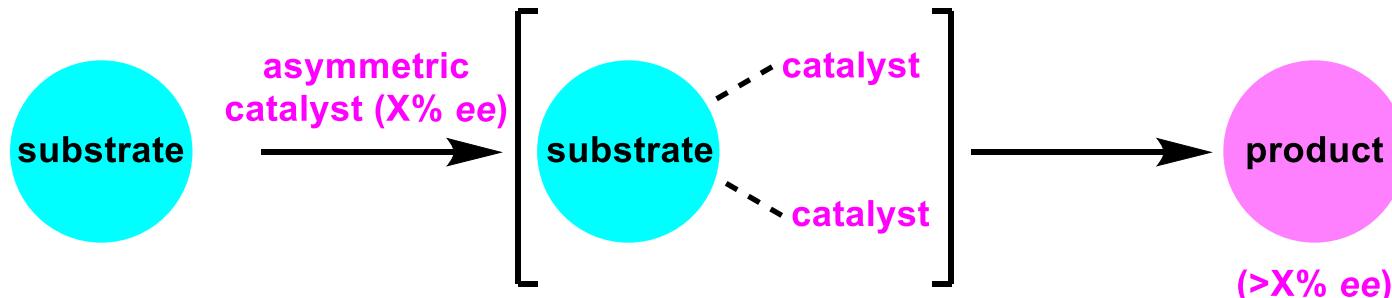
<Reaction>

Nonlinear phenomena of "the ee of product" and "the ee of asymmetric catalyst"

<linear interaction>

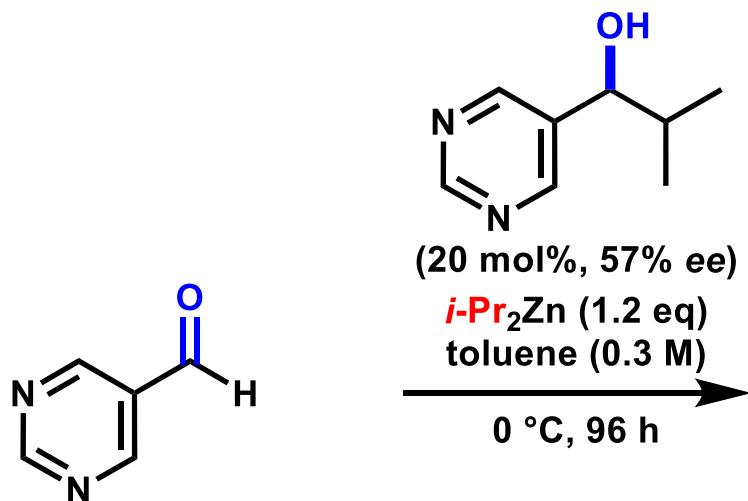


<nonlinear interaction>

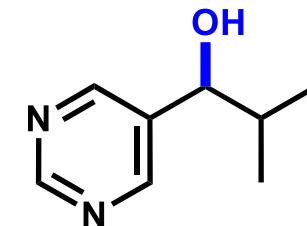
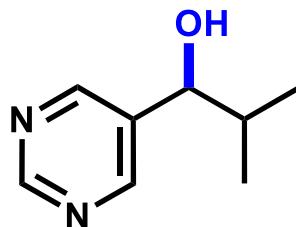


In this case, if  $X = 50$ , the ee of product would be up to 80%.

# Asymmetric Autocatalyst

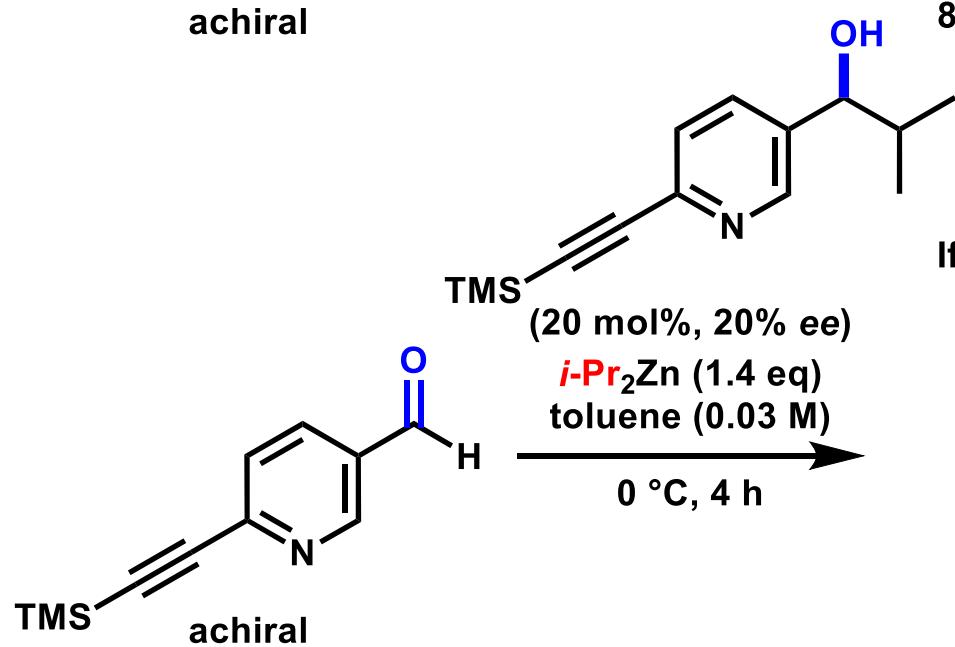


If the catalyst were completely recovered,  
newly formed alcohol:

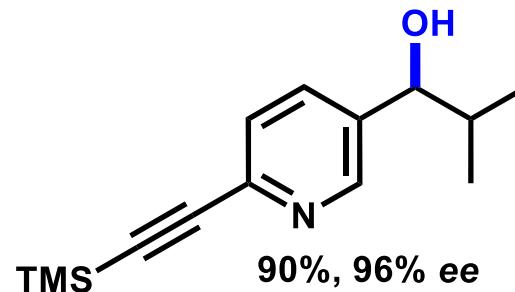


80%, 81% ee

60%, 89% ee



If the catalyst were completely recovered,  
newly formed alcohol:

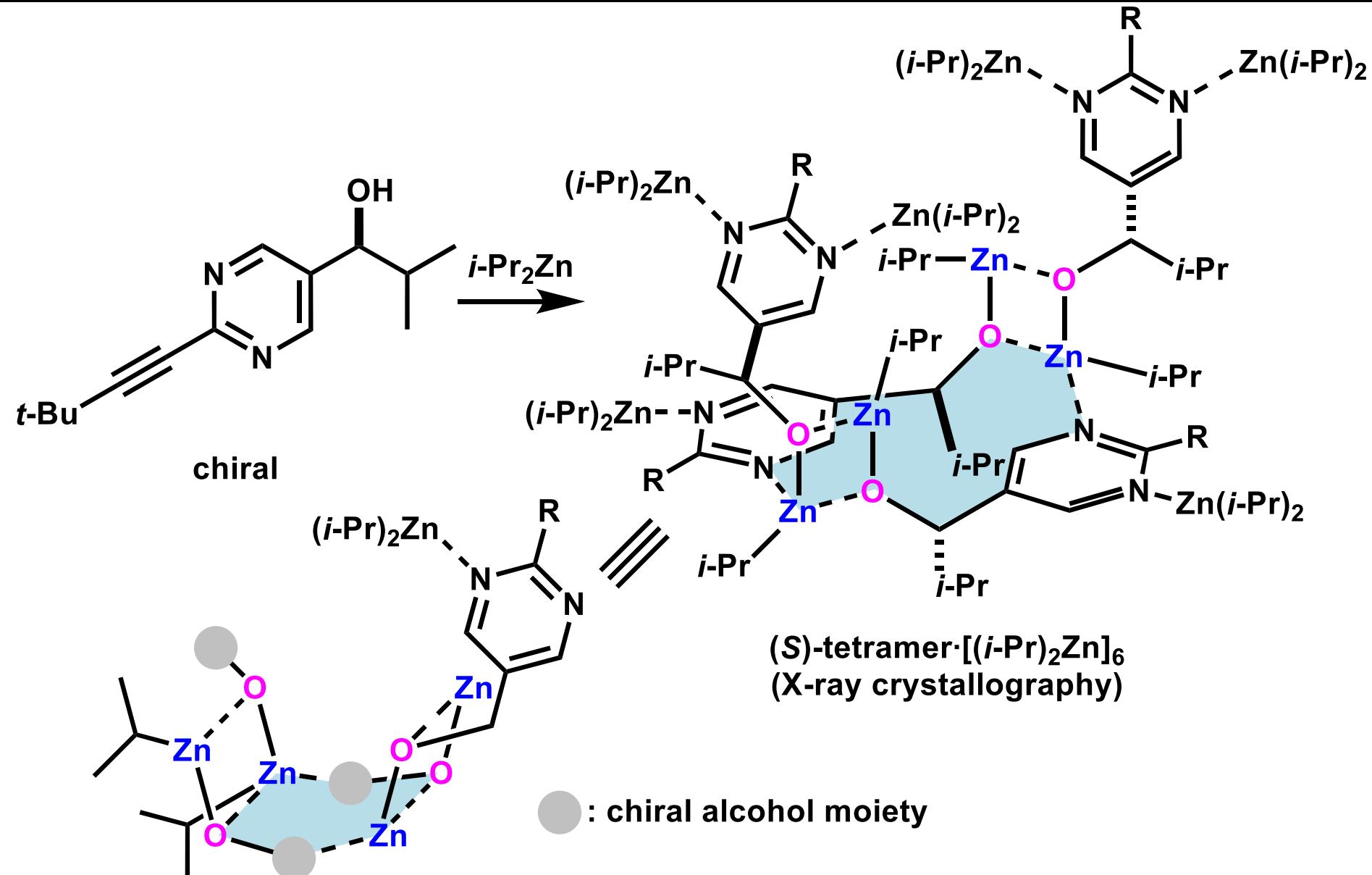


90%, 96% ee

1. Soai, K.; Niwa, S.; Hori, H. *J. Chem. Soc., Chem. Commun.* **1990**, 1990, 982.

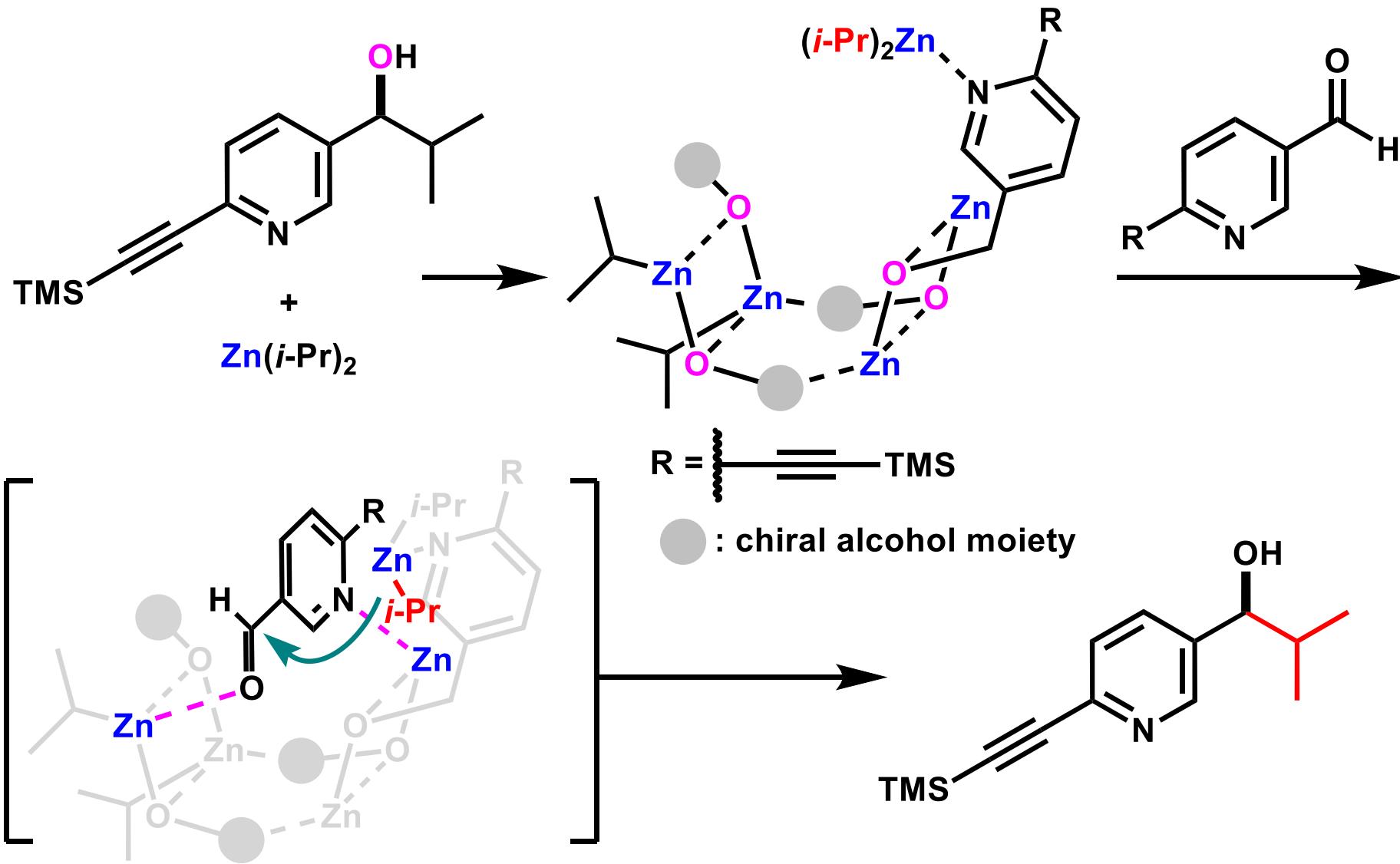
2. Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature* **1995**, 378, 767.

# **Possible Reaction Mechanism (1)**



1. Matsumoto, A.; Abe, T.; Hara, A.; Tobita, T.; Sasagawa, T.; Kawasaki, T.; Soai, K. *Angew. Chem. Int. Ed.* **2015**, *54*, 15218.

# Possible Reaction Mechanism (2)



1. Matsumoto, A.; Abe, T.; Hara, A.; Tobita, T.; Sasagawa, T.; Kawasaki, T.; Soai, K.  
*Angew. Chem. Int. Ed.* **2015**, *54*, 15218.

2. Athavale, S. V.; Simon, A.; Houk, K. N.; Denmark, S. E. *J. Am. Chem. Soc.* **2020**, *142*, 18387.

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**Asymmetric Catalysis in Chiral Solvents: Chirality Transfer with Amplification of Homochirality through a Helical Macromolecular Scaffold**

# *Prof. Michinori Suginome*



## **Education**

1988: B.S. @Kyoto University (Prof. Itoh Yoshihiko/Prof. Yoshida Zen-ichi)  
1993: Ph. D. @Kyoto University (Prof. Itoh Yoshihiko)  
1993~2002: Assistant Professor @ Kyoto University  
1998-1999: Visiting Researcher with Prof. Gregory C. Fu  
2002~2004: Associate Professor @ Kyoto University  
2004~: Professor @ Kyoto University

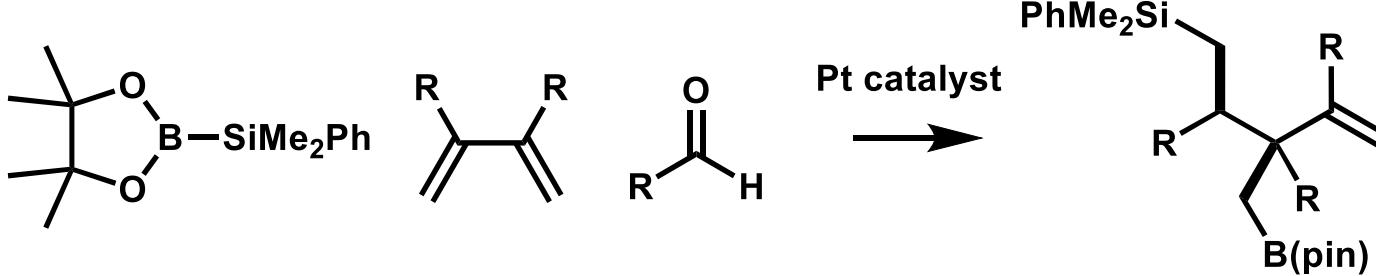


**Prof. Michinori Suginome**

## **Research Area**

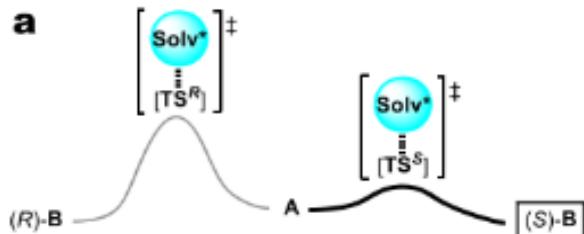
1. Reaction development
2. Polymer reaction

**Prof. Harusada Suginome  
(grandfather)**

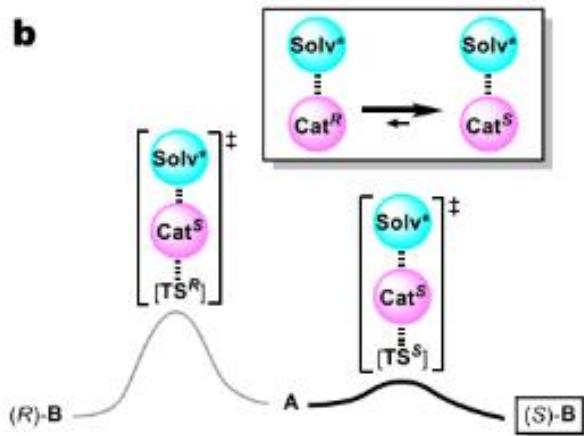


# Solvent Effect for Asymmetric Reactions

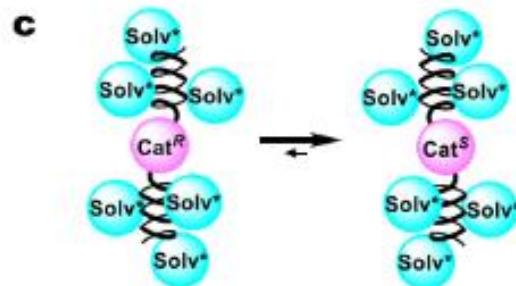
<Possible effect of chiral solvents on asymmetric reactions>



the direct interaction  
○ strong interaction  
✗ narrow reaction scope



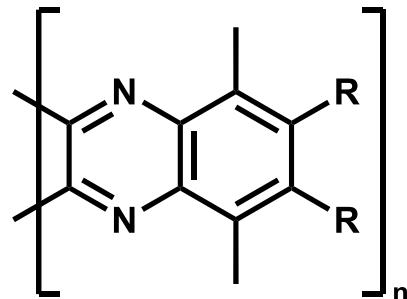
catalyst-solvent interaction  
○ wide reaction scope (catalytic site doesn't change)  
✗ weak interaction



polymer-solvent interaction  
○ wide reaction scope  
○ strong interaction with multisites

? the preparation of the flexible polymer  
? the chiral amplification

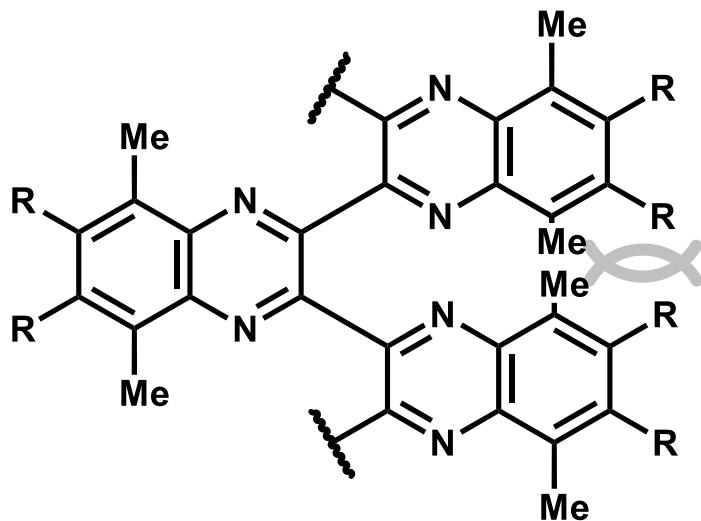
# Poly(quinoxaline-2,3-diyl)s (PQXs)



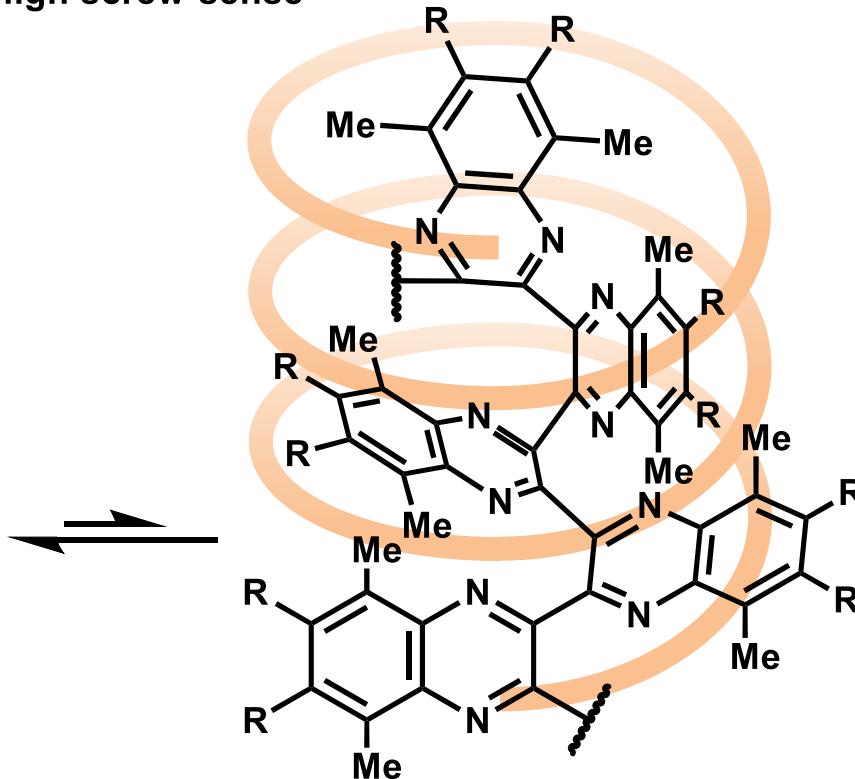
Synthesis: Ito (1990)

Features: robust helical structure  
(stable at 80 °C in solution)  
high screw-sense

poly(quinoxaline-2,3-diyl)s (PQXs)



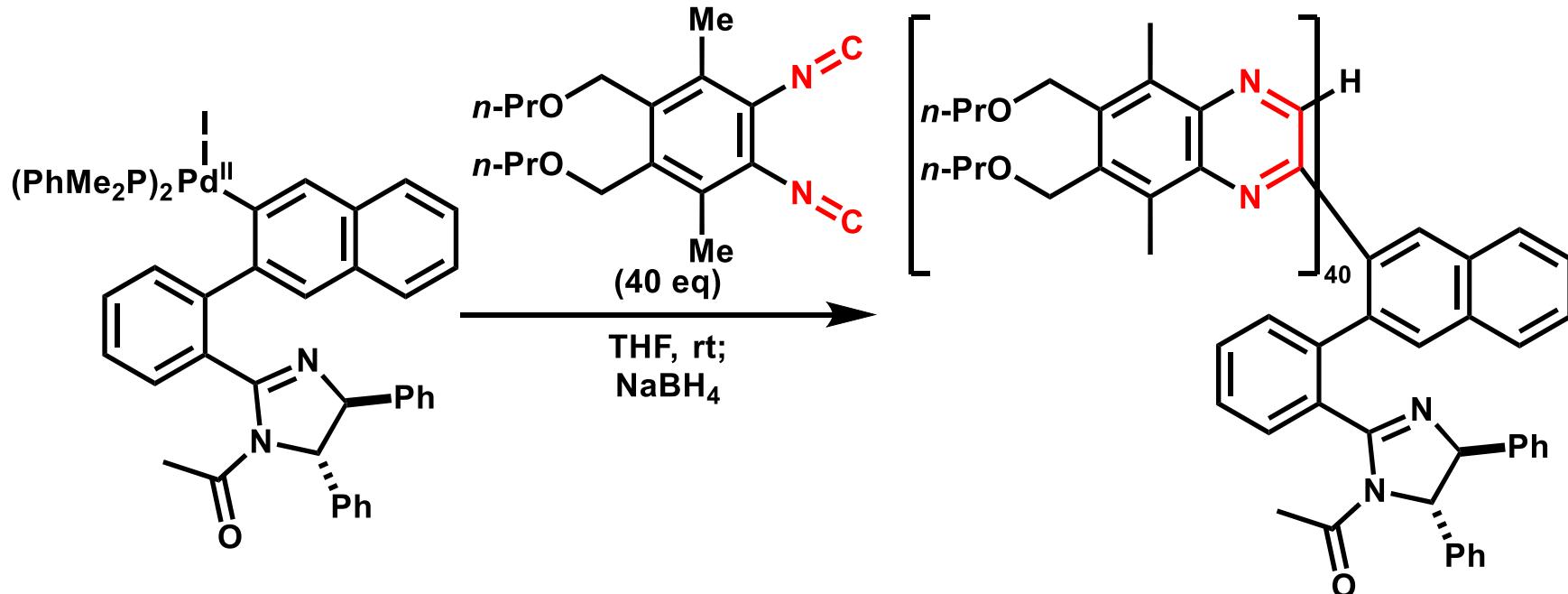
planar structure



helical structure

1. Ito, Y.; Ihara, E.; Murakami, M.; Shiro, M. *J. Am. Chem. Soc.* **1990**, 112, 6446.
2. Ito, Y.; Miyake, T.; Hatano, S.; Shima, R.; Ohara, T. Suginome, M. *J. Am. Chem. Soc.* **1998**, 120, 11880.
3. Yamamoto, T.; Suginome, M. *Angew. Chem. Int. Ed.* **2009**, 48, 539.
4. Nagata, Y.; Takeda, R.; Suginome, M. *ACS Cent. Sci.* **2019**, 5, 1235.

# *Helically Chiral Conformation of PQXs*



71%, >99% *se* (*P*)  
*se*: screw-sense excess

<helicity>

*P*-helix (plus)



*M*-helix (minus)



The high *se* was achieved derived from one chiral unit.



Is the high *se* achieved derived from solvent chirality?

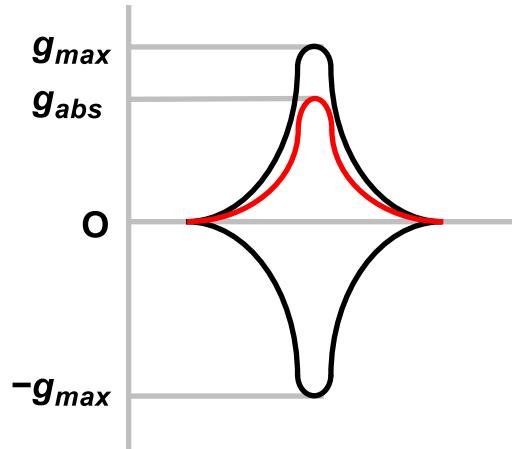
1. Nagata, Y.; Takeda, R.; Suginome, M. ACS Cent. Sci. 2019, 5, 1235.

2. Suginome, M.; Coolet, S.; Ito, Y. Org. Lett. 2002, 4, 351.

# *Estimation of Screw-Sense Excess (SE) (1)*

polymer: the structures of the products are uneven (the number of monomer)  
 → the screw-sense excess is estimated (impossible to measure se like ee)

## 1. the measurement of CD spectrum



$$\Delta G = -RT \ln \frac{[P]}{[M]}$$

R: the constant, T: temperature

$$\Delta G = G_h N = -RT \ln \frac{[P]}{[M]}$$

$G_h$ : the energy difference between P- and M-helices  
 N: the number of units

$$[P] = [M] \exp \left( -\frac{G_h N}{RT} \right)$$

Substitution for the se formula:

$$se = \frac{g_{abs}}{g_{max}}$$

$$se = \frac{\exp \left( -\frac{G_h N}{RT} \right) - 1}{\exp \left( -\frac{G_h N}{RT} \right) + 1} = \tanh \left( -\frac{G_h N}{2RT} \right)$$

[P], [M]: the concentration of each polymer

$$g_{abs} = g_{max} \cdot \tanh \left( -\frac{G_h N}{2RT} \right)$$

1. Lifson, S.; Andreola, C.; Peterson, N. C.; Green, M. M. *J. Am. Chem. Soc.* **1989**, 111, 8850–8858
2. Nagata, Y.; Yamada, T.; Adachi, T.; Alao, Y.; Yamamoto, T.; Sugino, M. *J. Am. Chem. Soc.* **2013**, 135, 10104.
3. Nagata, Y.; Takeda, R.; Sugino, M. *ACS Cent. Sci.* **2019**, 5, 1235.

# *Estimation of Screw-Sense Excess (SE) (2)*

## 2. Fitting

$$g_{abs} = g_{max} \cdot \tanh\left(-\frac{G_h N}{2RT}\right)$$

R: the constant, T: temperature

$G_h$ : the energy difference  
between P- and M-helices

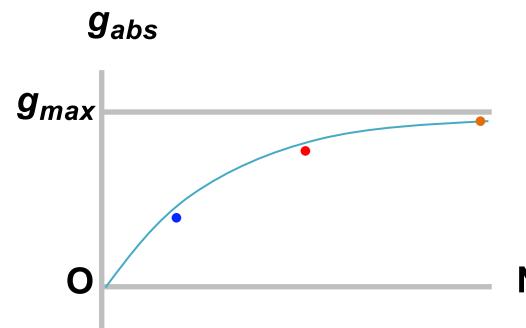
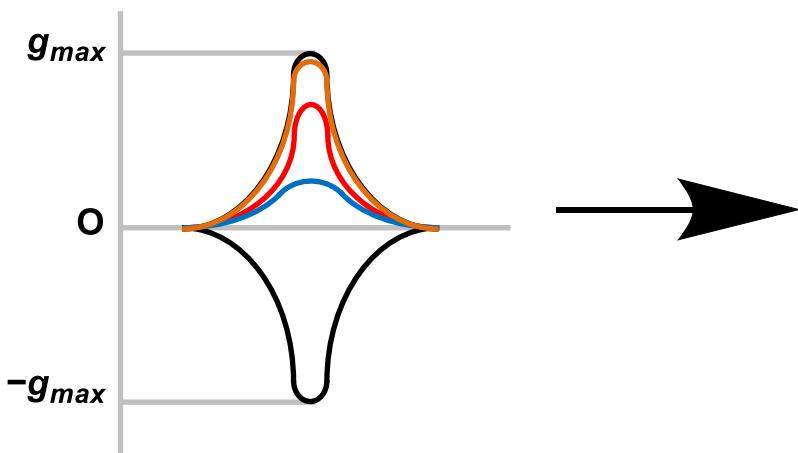
N: the number of units

unknown constant:  $g_{max}$ ,  $G_h$

$g_{abs}$ : measurable



To synthesize the various polymers with different N and to measure the  $g_{abs}$ , the trendline can be obtained.



From the trendline (shown in blue),  
 $g_{max}$  can be estimated.  
Using the formula

$$se = \frac{g_{abs}}{g_{max}}$$

the se value can also be calculated.

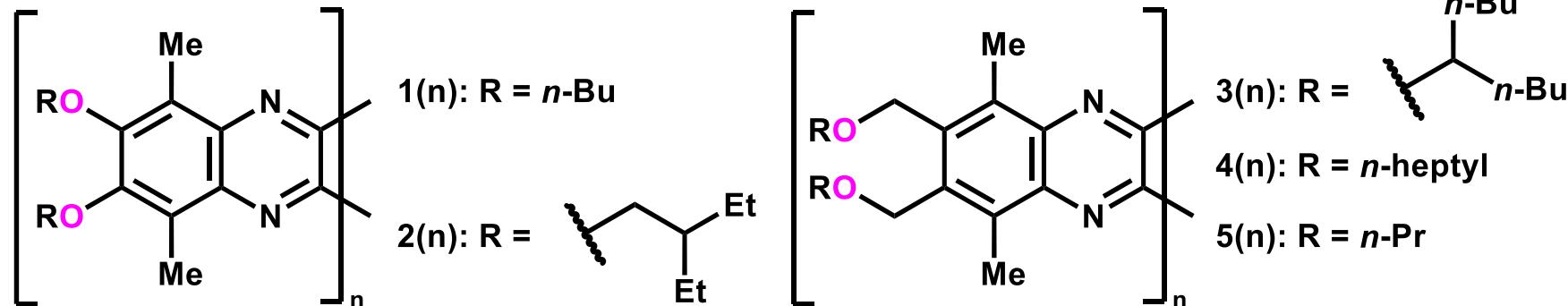
1. Lifson, S.; Andreola, C.; Peterson, N. C.; Green, M. M. *J. Am. Chem. Soc.* **1989**, 111, 8850–8858

2. Nagata, Y.; Yamada, T.; Adachi, T.; Alao, Y.; Yamamoto, T.; Sugino, M. *J. Am. Chem. Soc.* **2013**, 135, 10104.

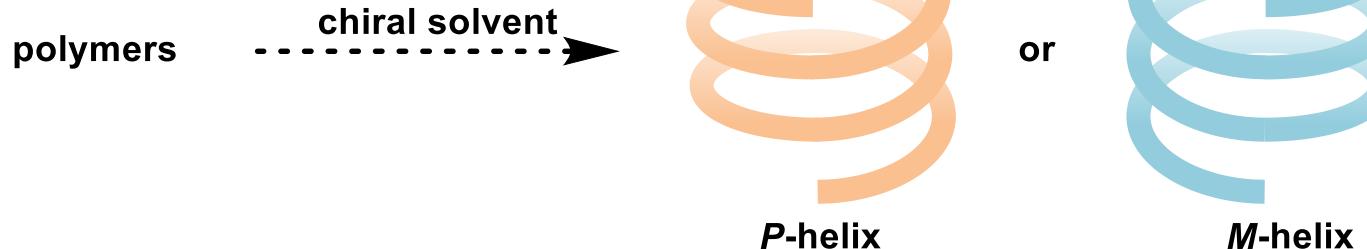
3. Nagata, Y.; Takeda, R.; Sugino, M. *ACS Cent. Sci.* **2019**, 5, 1235.

# Research Design

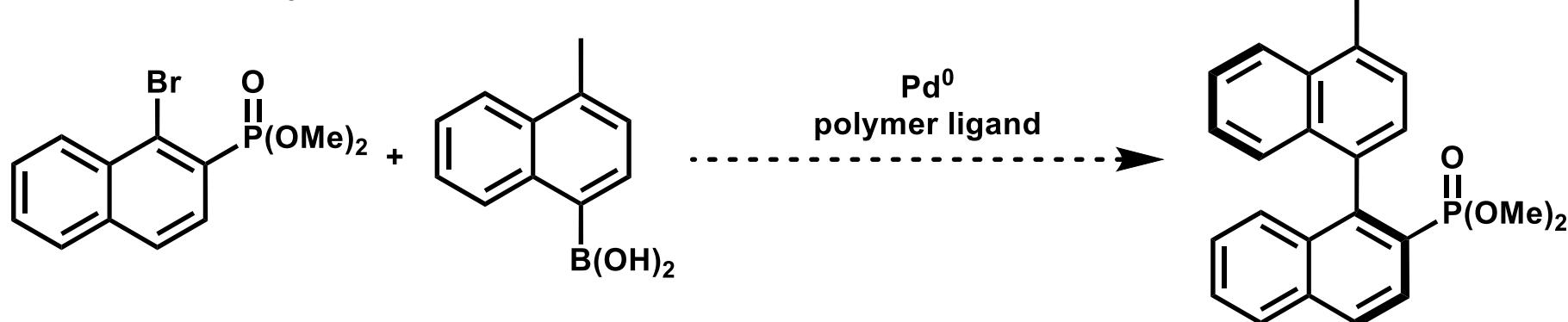
<possible polymers>



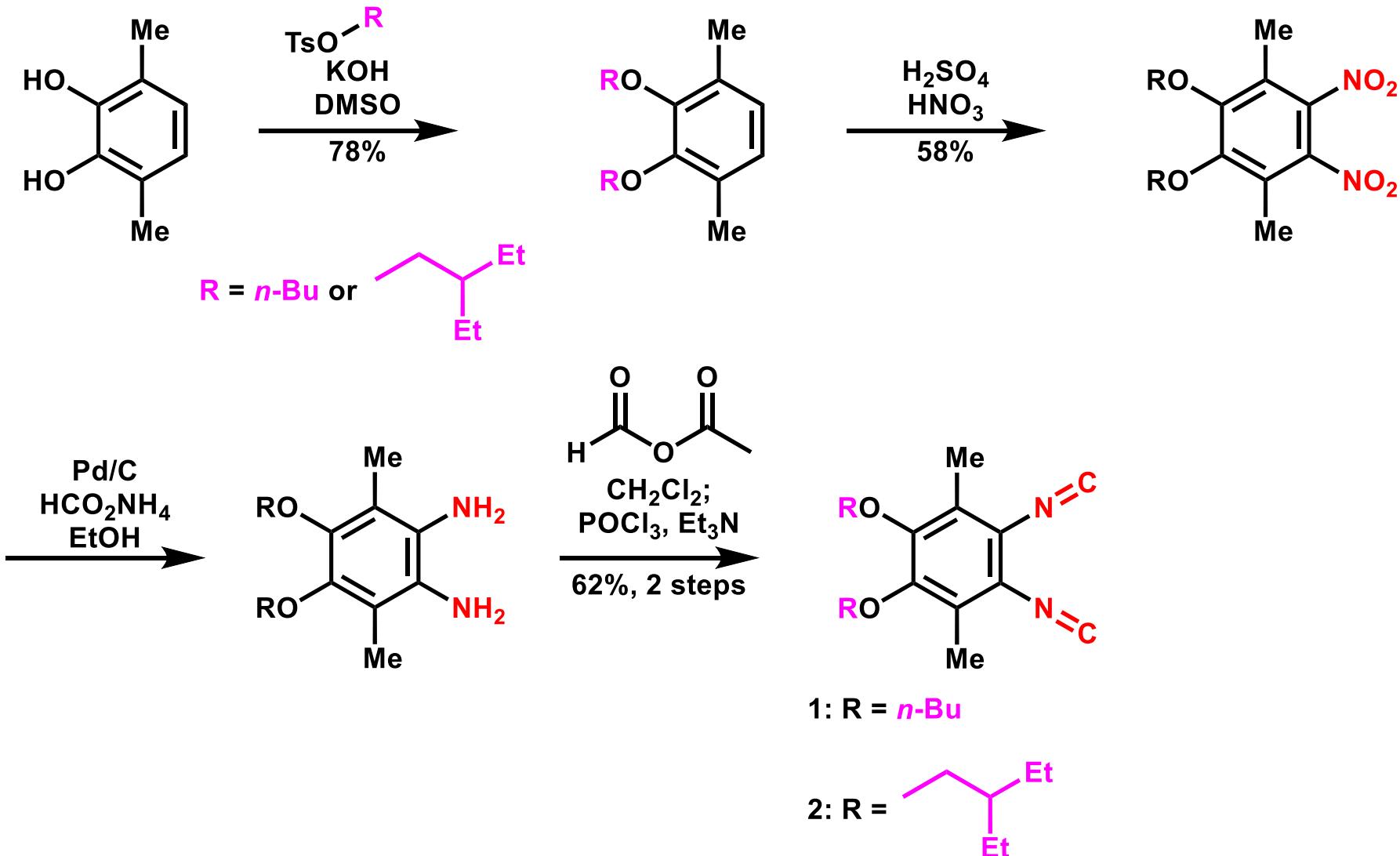
<determination of se>



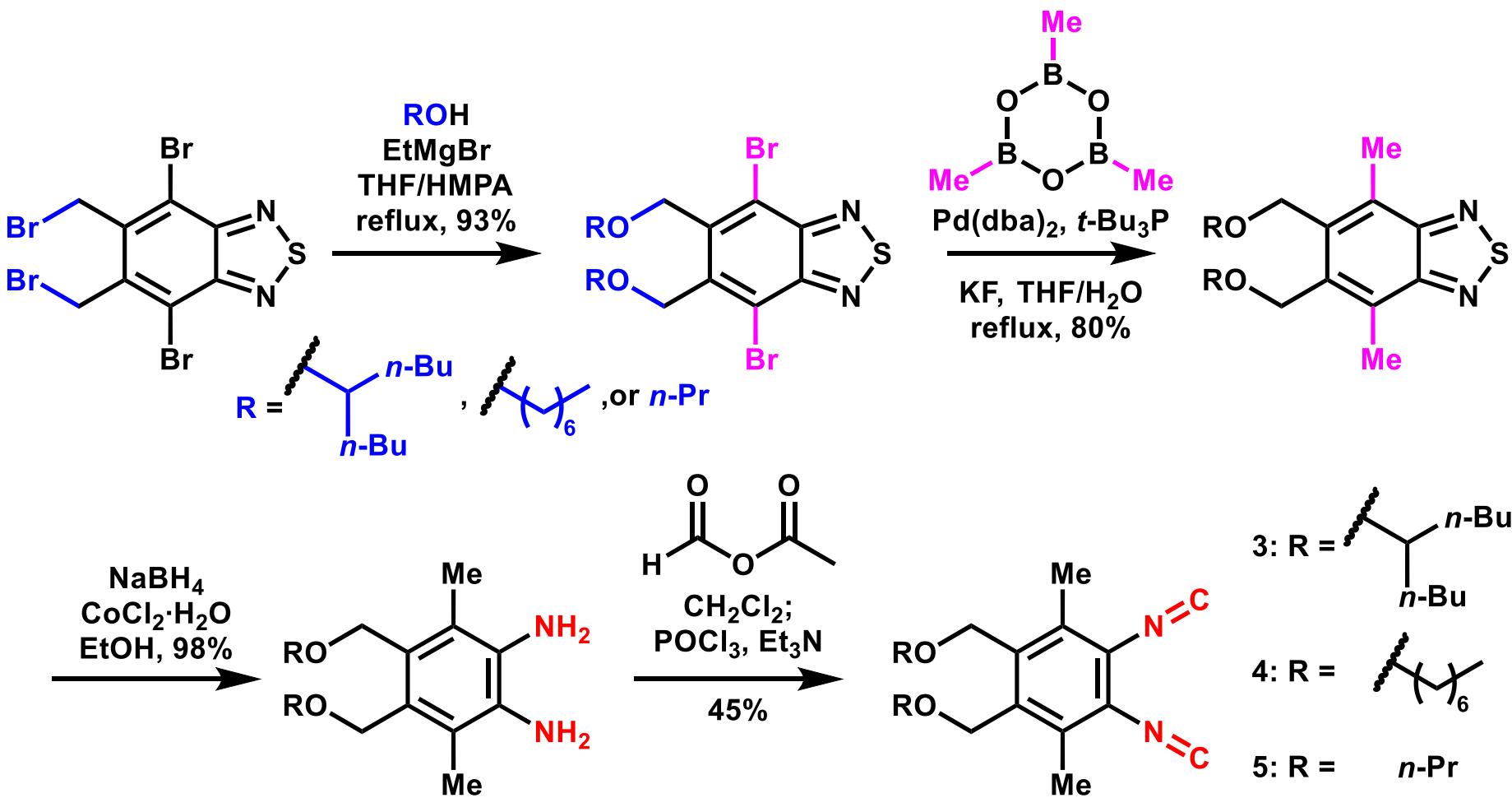
<application to the asymmetric reaction>



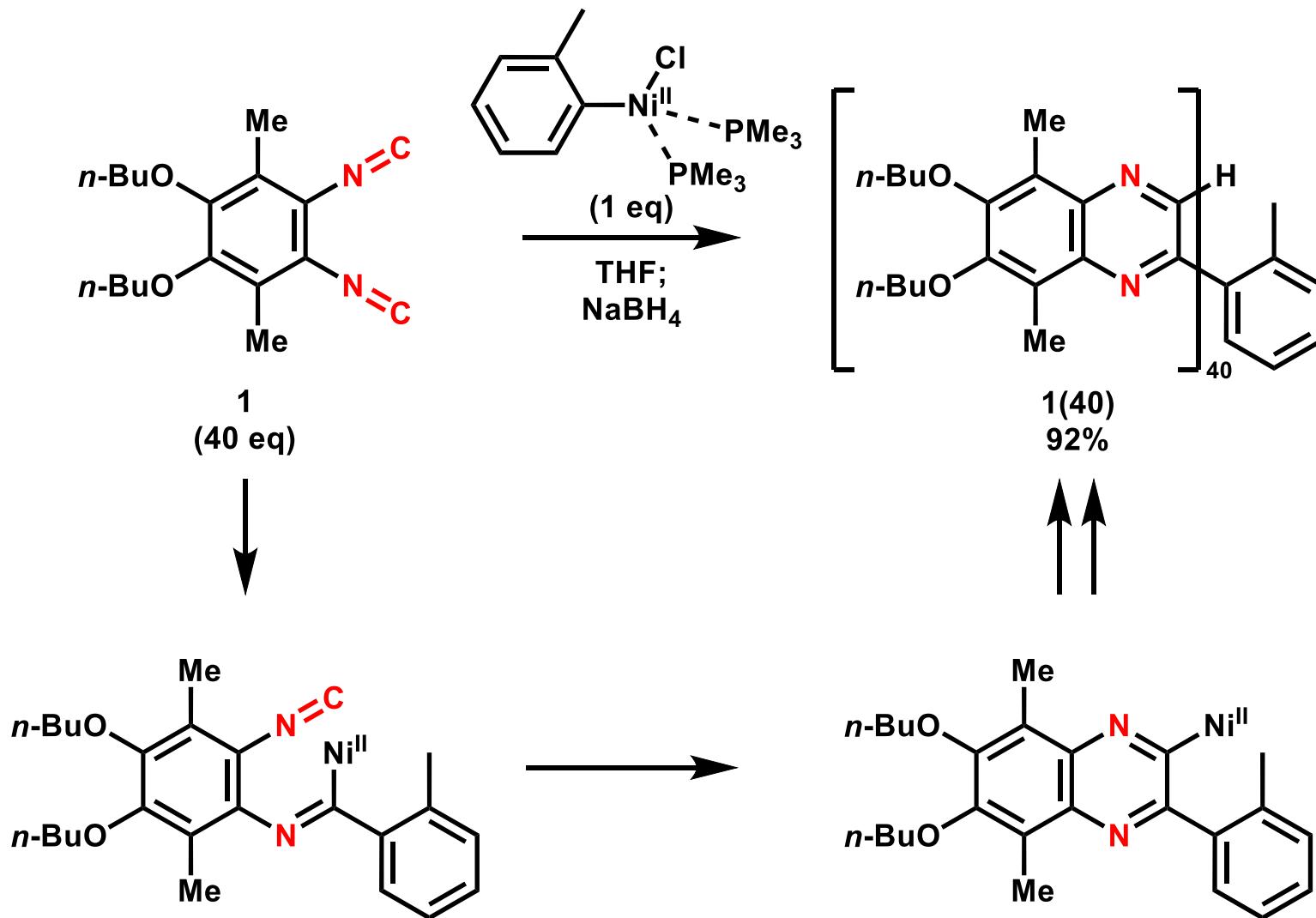
# Preparation of PQXs Monomer (1)



# Preparation of PQXs Monomer (2)

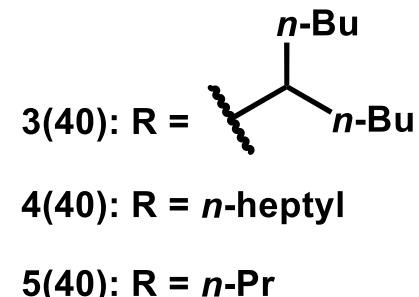
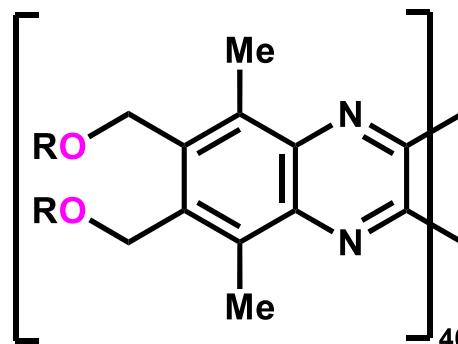
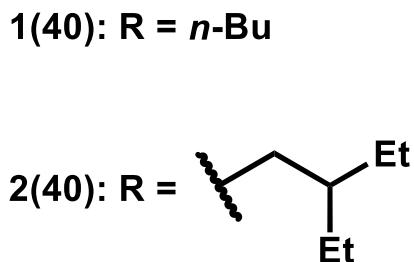
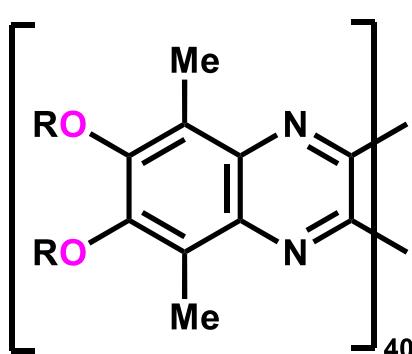


# *Preparation of PQXs Polymer*



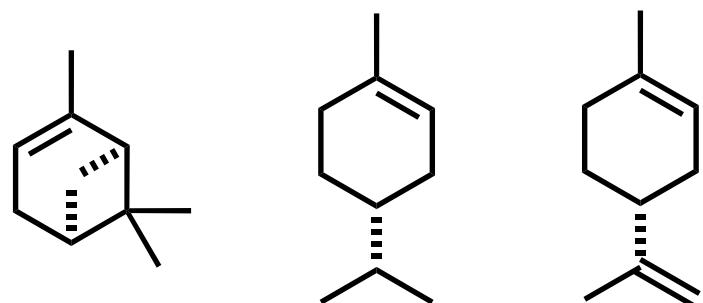
**2(40), 3(40), 4(40), and 5(40) were prepared with the same process.**

# Investigation of Chiral Solvent



## screw-sense excess (se)

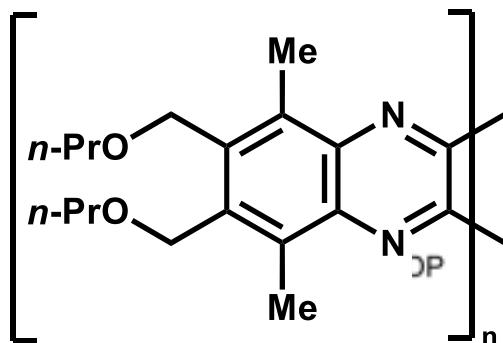
polymer	(1 <i>S</i> )- $\alpha$ -pinene	( <i>R</i> )-menthene	( <i>R</i> )-limonene
1(40)	2% ( <i>P</i> )	insoluble	51% ( <i>P</i> )
2(40)	6% ( <i>M</i> )	4% ( <i>P</i> )	30% ( <i>P</i> )
3(40)	14% ( <i>P</i> )	21% ( <i>P</i> )	44% ( <i>P</i> )
4(40)	12% ( <i>P</i> )	33% ( <i>P</i> )	59% ( <i>P</i> )
5(40)	20% ( <i>P</i> )	40% ( <i>P</i> )	72% ( <i>P</i> )



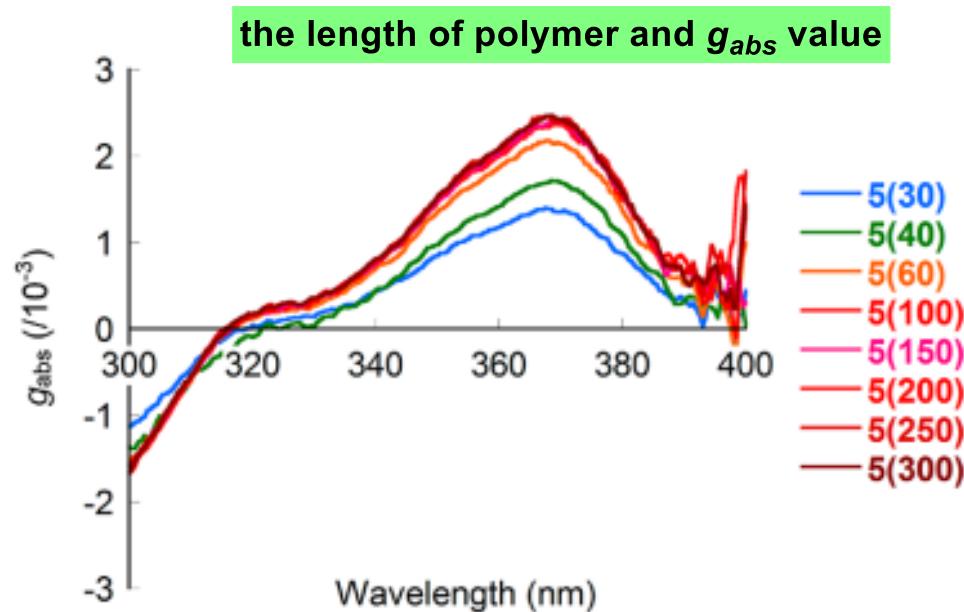
Each se was estimated with the measured  $g_{abs}$  and the estimated  $g_{max}$ .

$$g_{max} = 2.37 \times 10^{-3} \text{ at } 366.0 \text{ nm.}$$

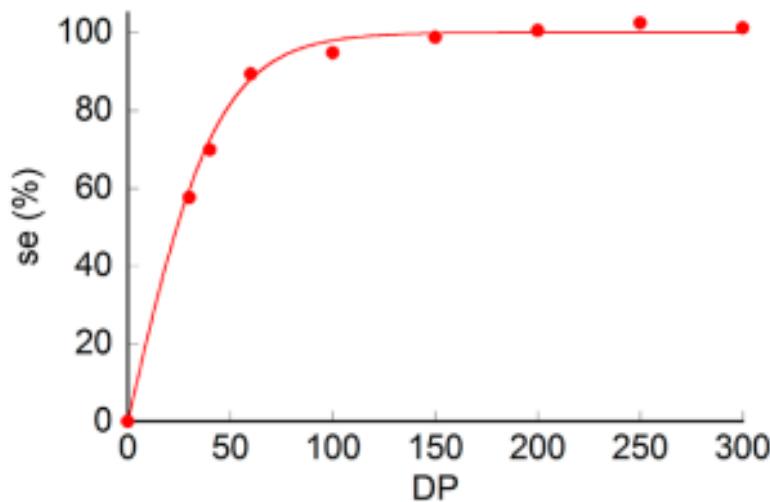
# Optimization of Polymer Length



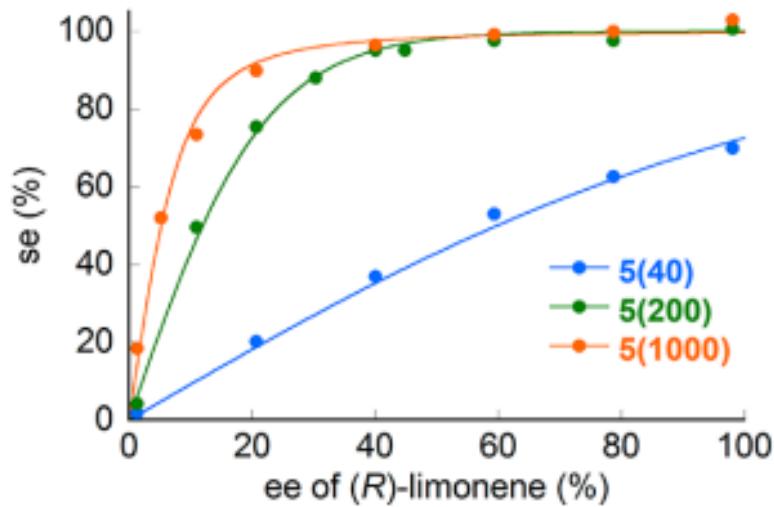
5(n)  
n: the number of monomer  
(=DP)



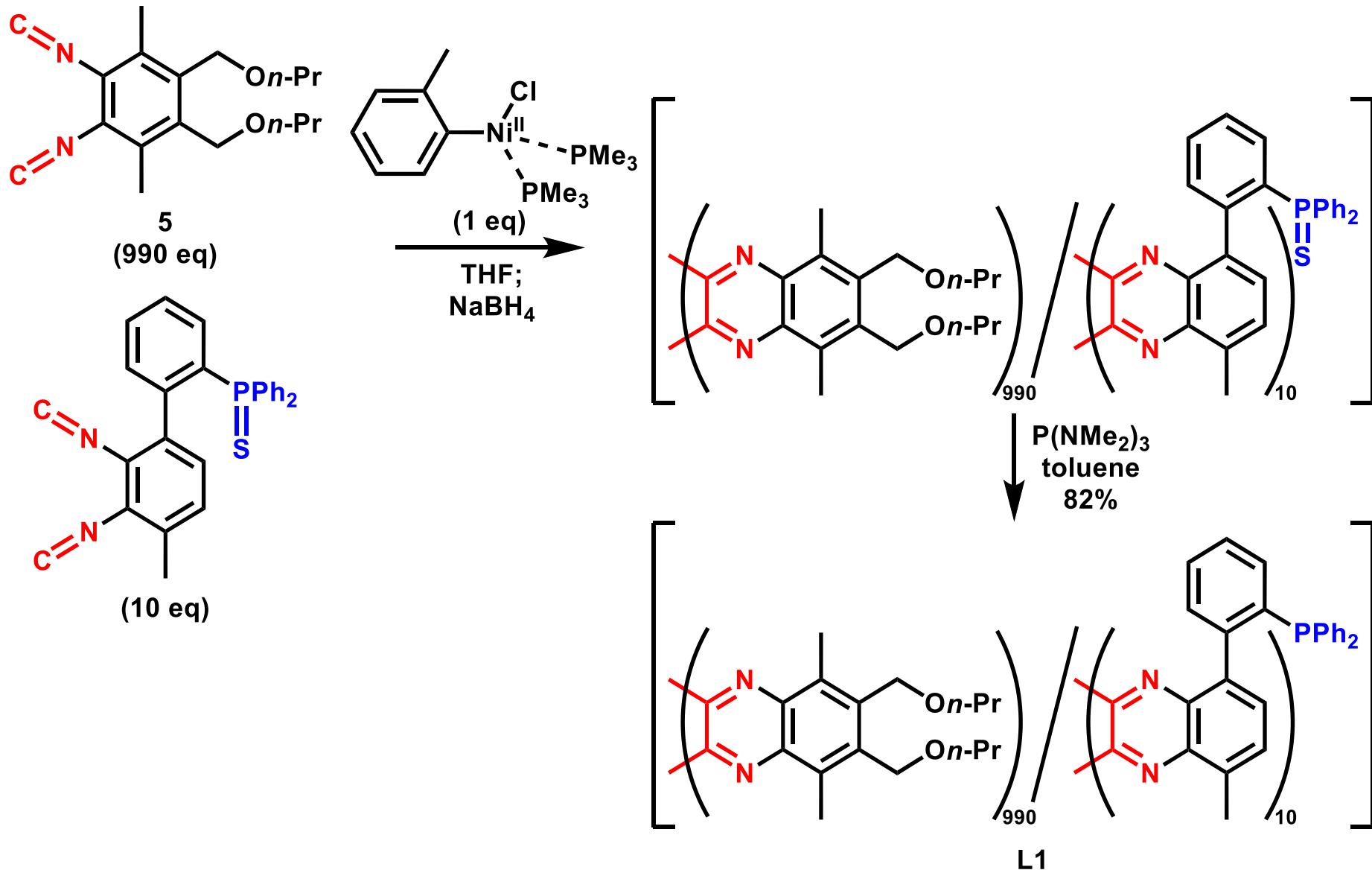
the length of polymer and the se value



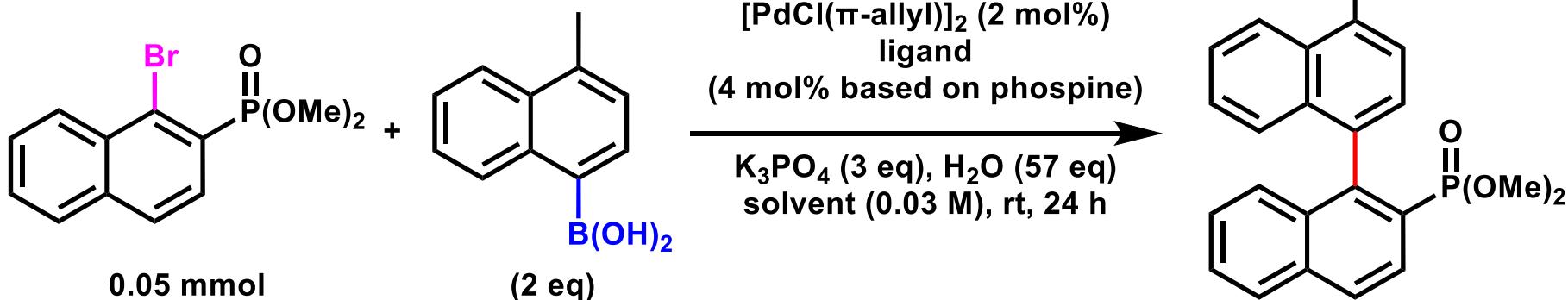
the ee of limonene and the se value



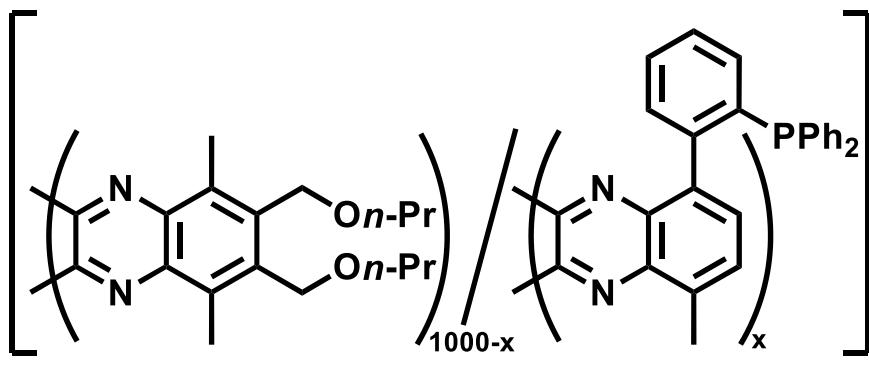
# Preparation of Polymer Ligand



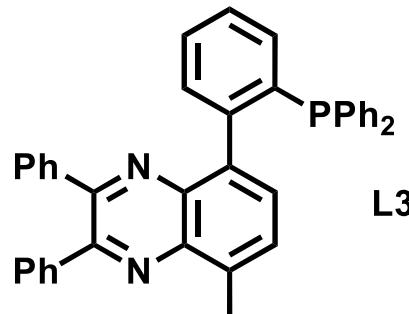
# **Asymmetric Suzuki-Miyaura Coupling (1)**



entry	ligand	solvent	result
1	L1	THF	70%, <1% ee
2	L1	( <i>R</i> )-limonene <sup>a)</sup> /THF (95/5)	66%, 98% ee ( <i>S</i> )
3	L2	( <i>R</i> )-limonene <sup>a)</sup> /THF (95/5)	55%, 85% ee ( <i>S</i> )
4	L3	( <i>R</i> )-limonene <sup>a)</sup> /THF (95/5)	59%, <1% ee
5	L1	( <i>S</i> )-limonene <sup>a)</sup> /THF (95/5)	54%, 98% ee ( <i>R</i> )
6	L1	( <i>R</i> )-limonene <sup>b)</sup> /THF (95/5)	69%, 70% ee ( <i>S</i> )



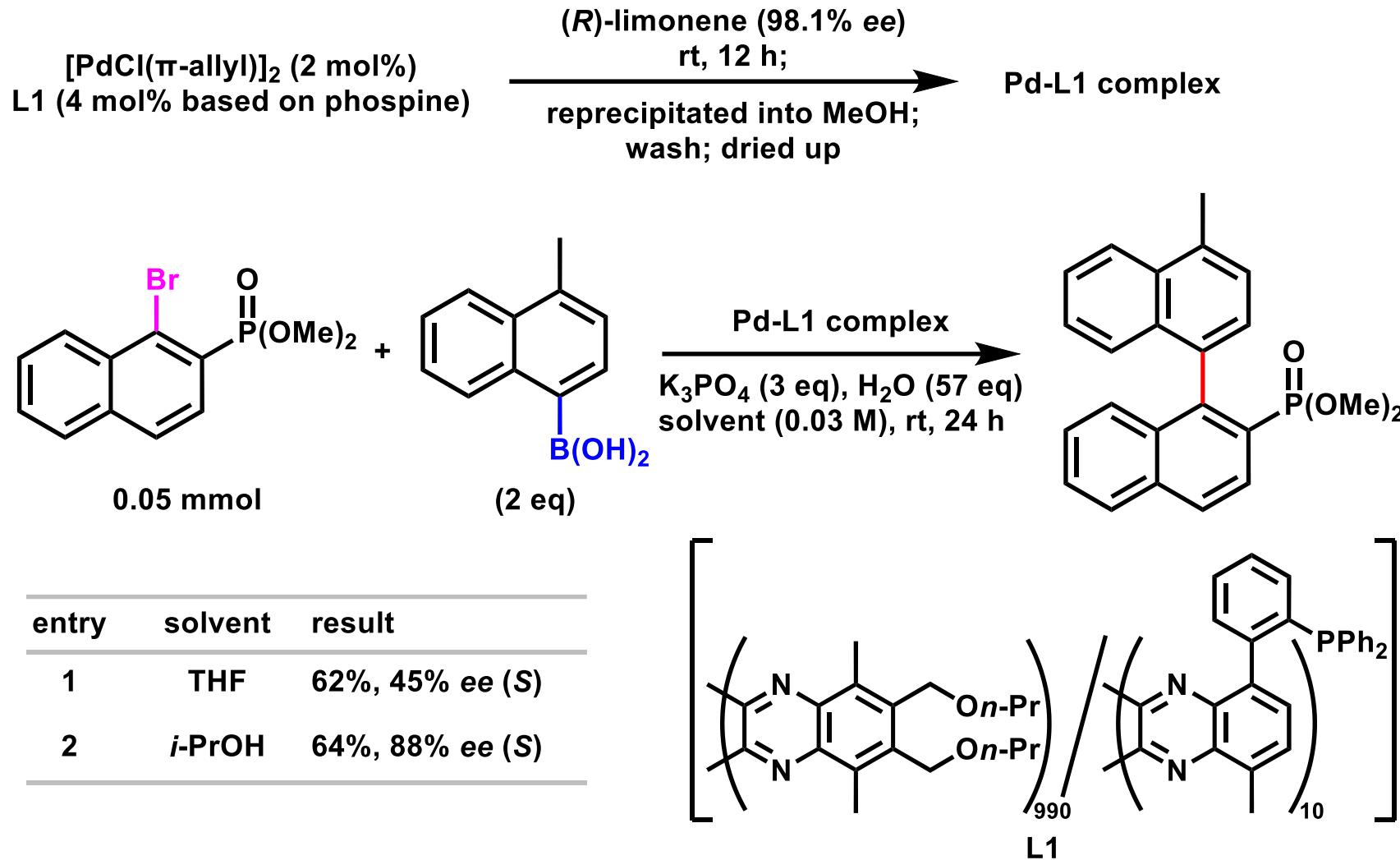
L1: x = 10  
L2: x = 50



a) 98.1% ee, b) 12.6% ee

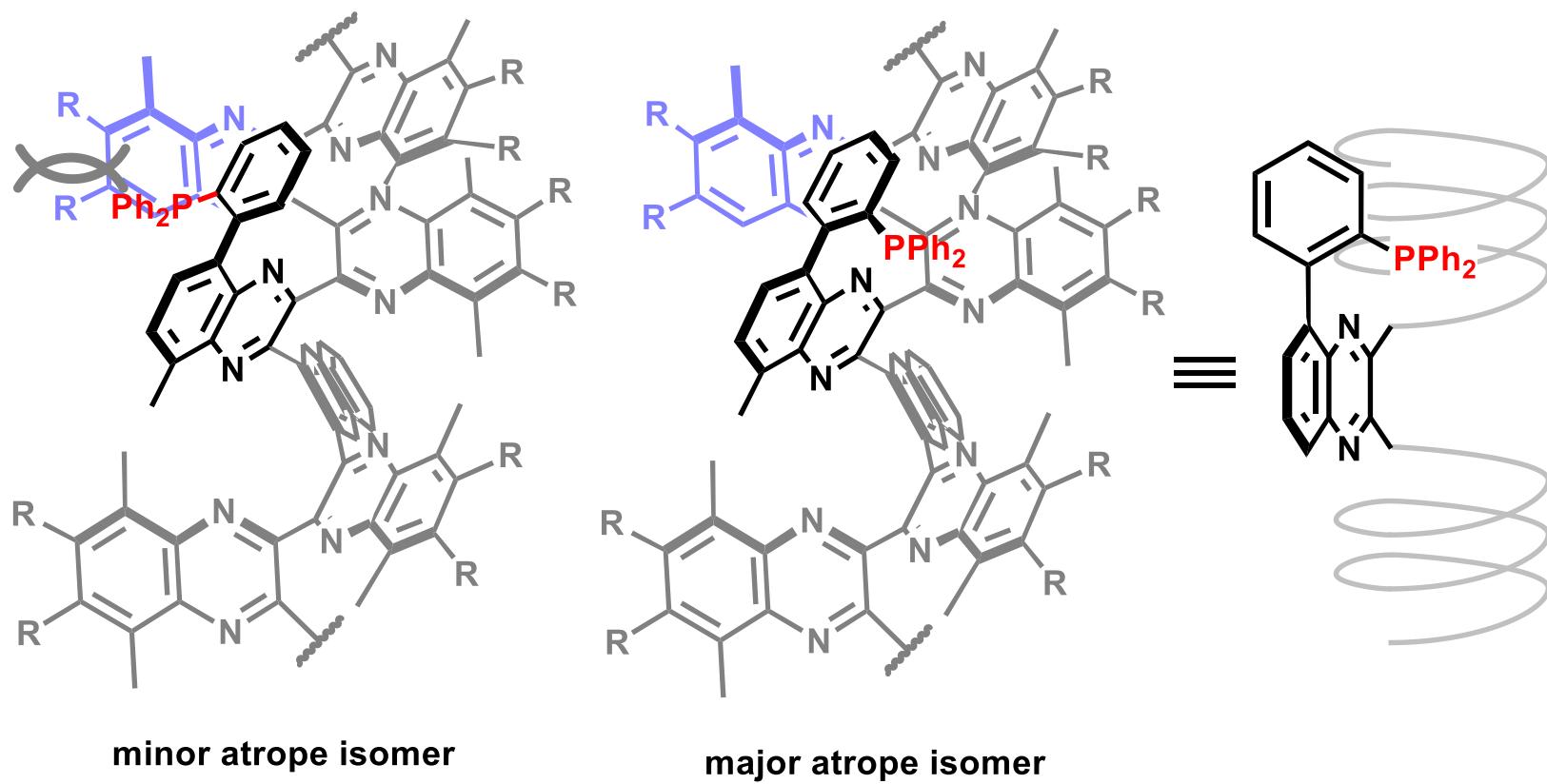
chiral amplification was observed as expected.

# Asymmetric Suzuki-Miyaura Coupling (2)

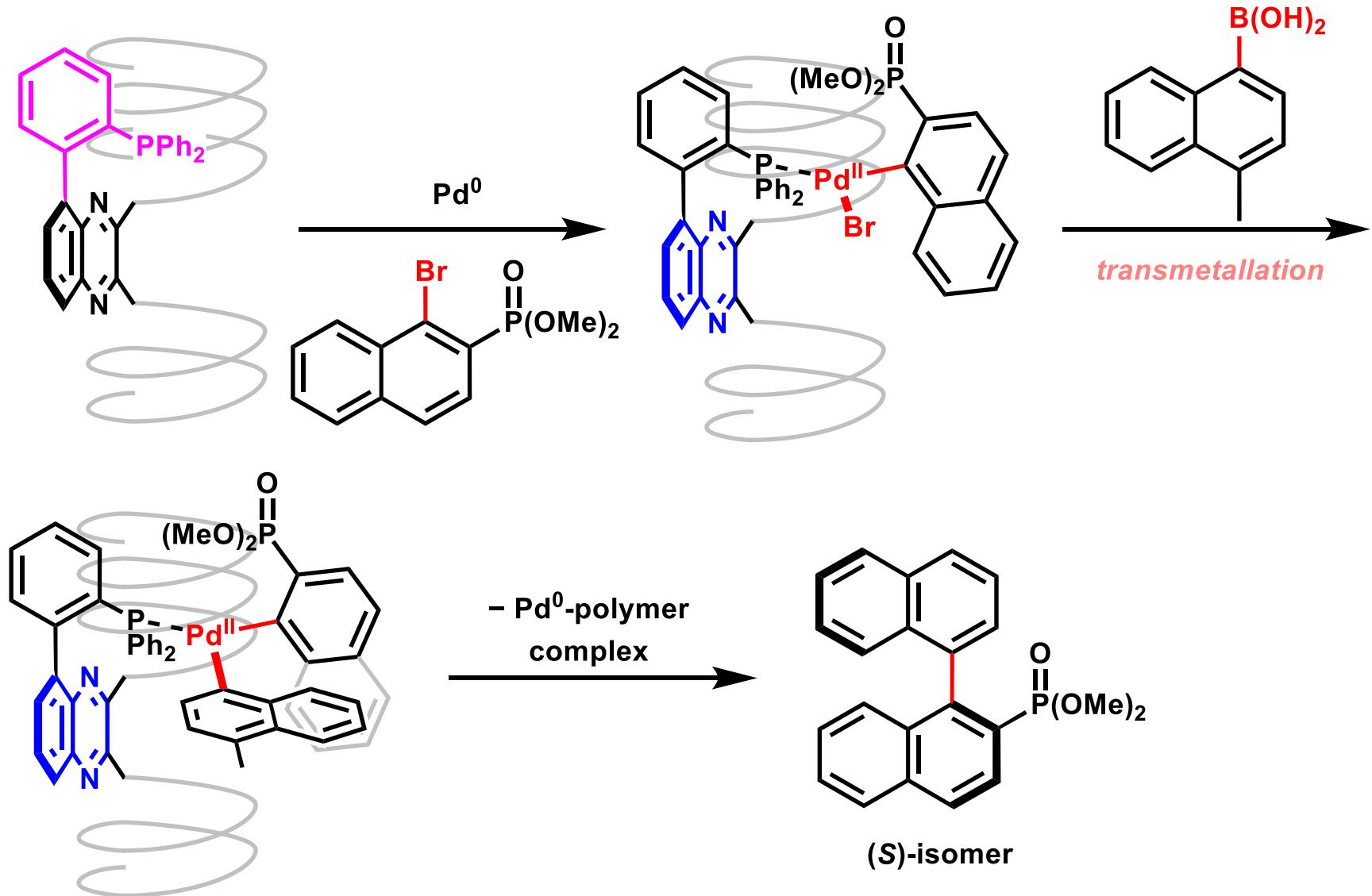


The less-solubility of Pd-L1 complex in *i*-PrOH memory would pronounce the memory of chirality.

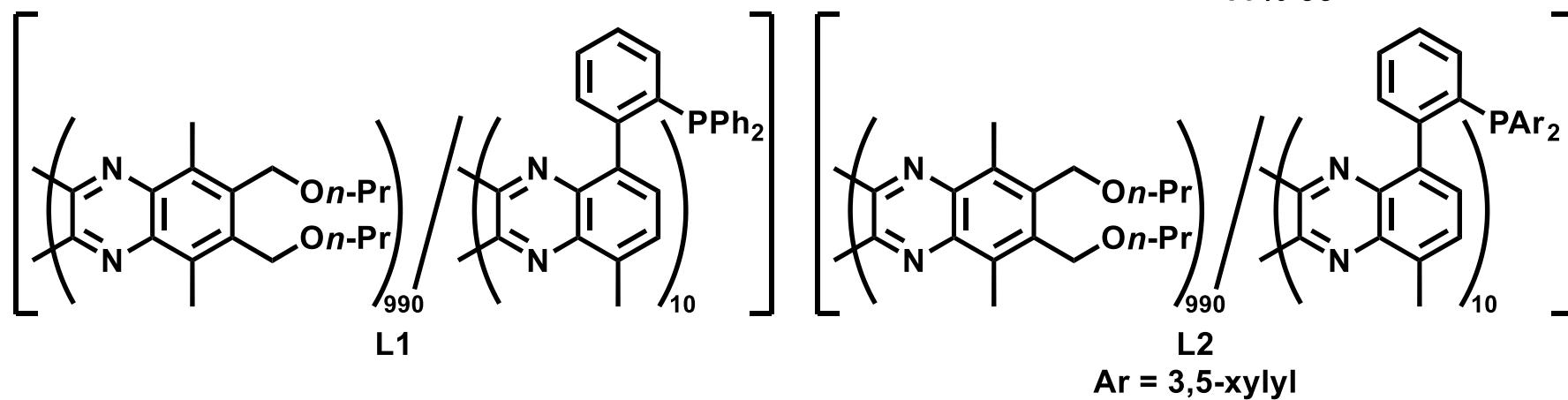
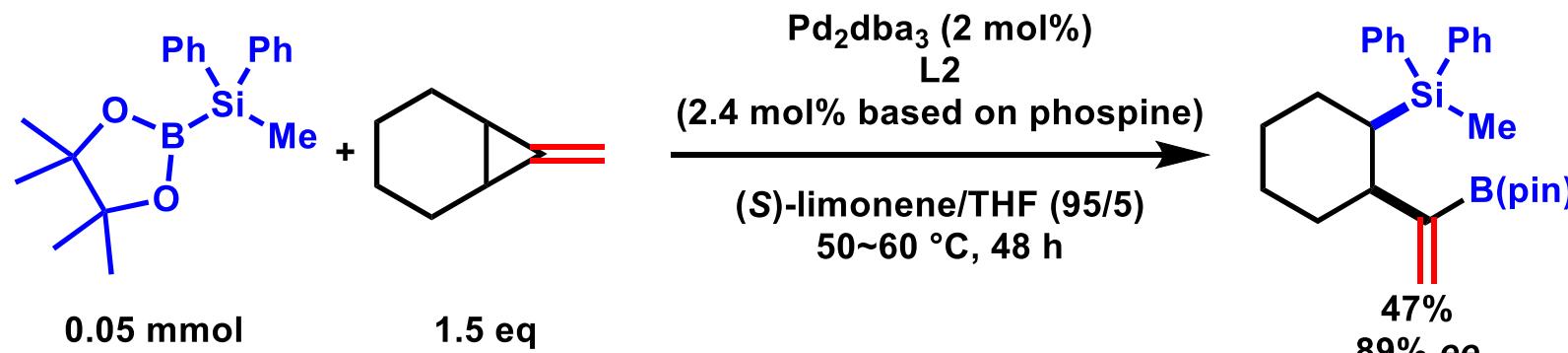
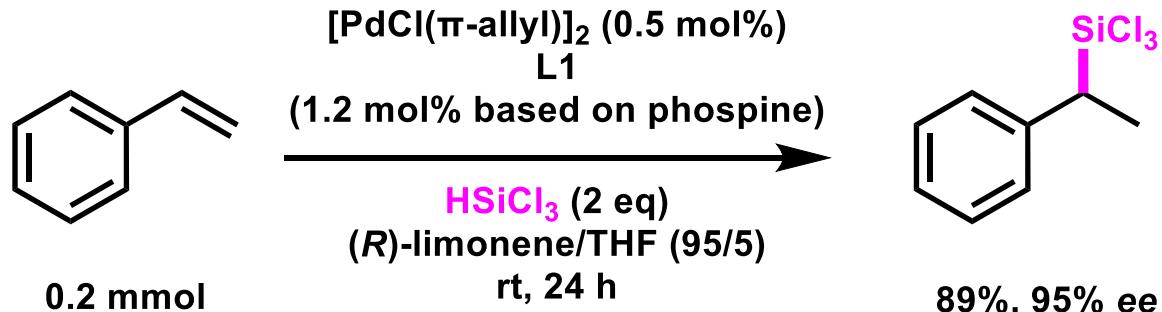
# *Plausible Mechanism of Enantioselectivity*



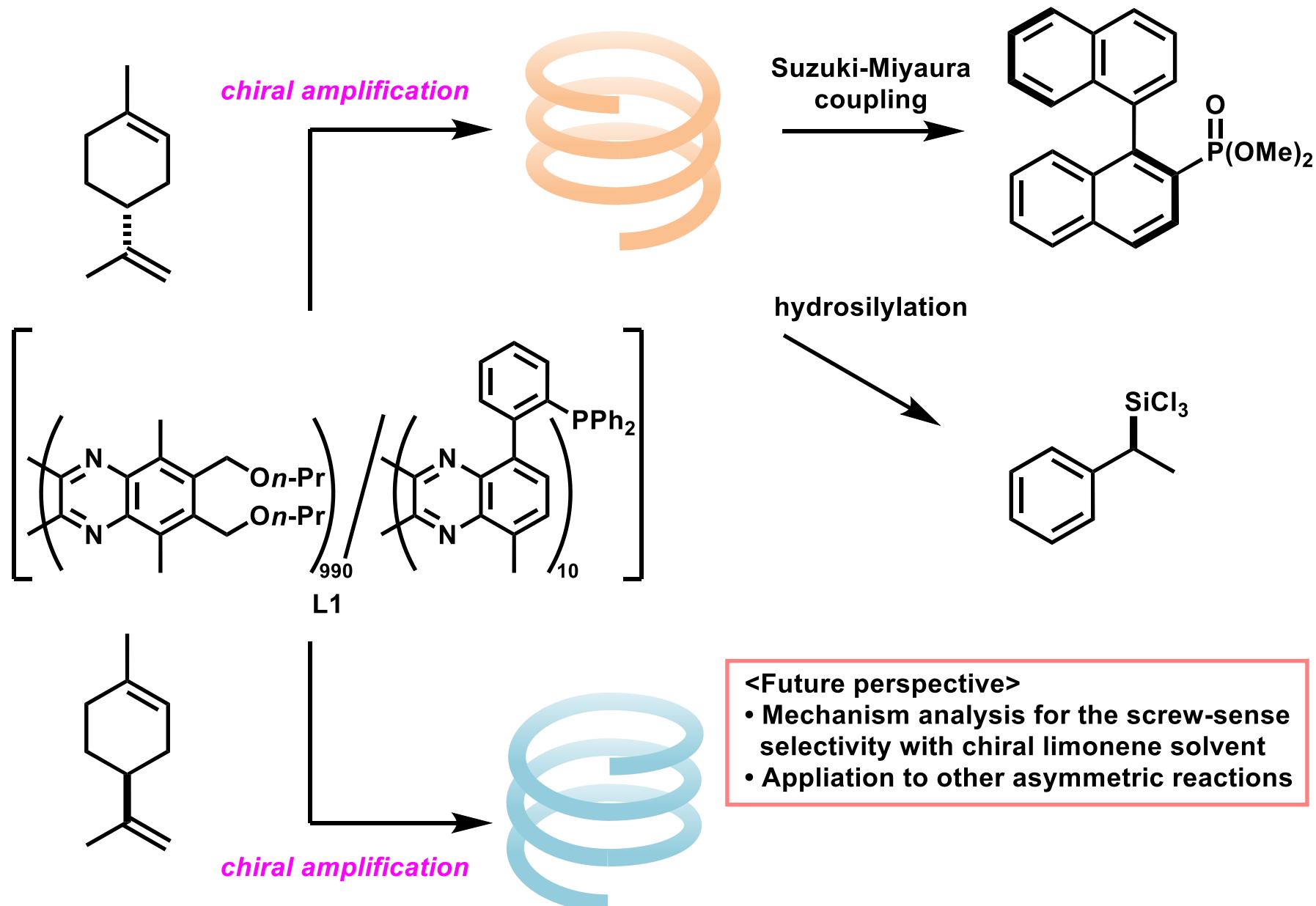
# Plausible Mechanism of Enantioselectivity (2)



# Other Application of PQXs

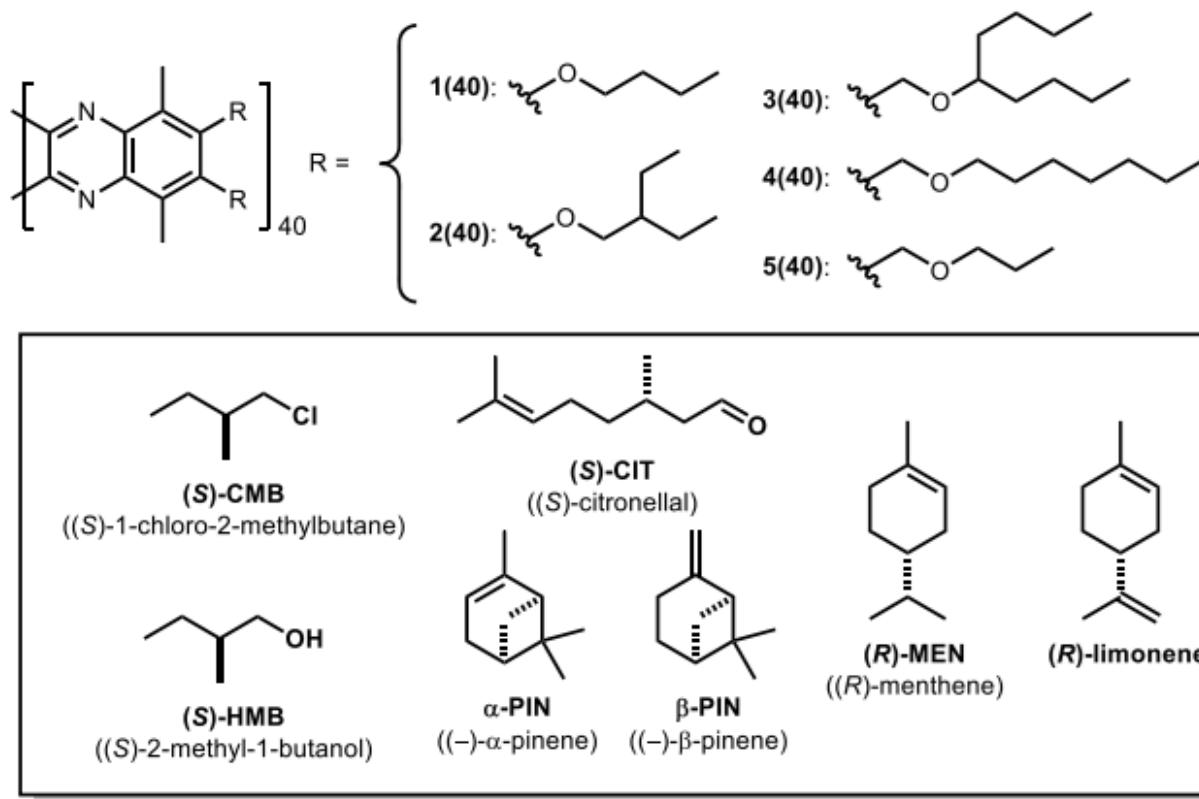


# Summary



# *Appendix*

# All Results



polymer	se (%) <sup>b</sup>						
	(S)-CMB	(S)-HMB	(S)-CIT	$\alpha$ -PIN	$\beta$ -PIN	(R)-MEN	(R)-limonene
1(40)	c	c	c	2 (P)	c	c	51 (P)
2(40)	5 (P)	c	3 (P)	6 (M)	4 (P)	4 (P)	30 (P)
3(40)	5 (M)	31 (M)	20 (P)	14 (P)	24 (P)	21 (P)	44 (P)
4(40)	3 (M)	29 (M)	8 (P)	12 (P)	17 (P)	33 (P)	59 (P)
5(40)	10 (P)	34 (M)	11 (P)	20 (P)	27 (P)	40 (P)	72 (P)

# Asymmetric Suzuki-Miyaura Coupling (1)

