

Helically Chiral Polymer Ligand, "PQXphos"

Literature Seminar

2016/9/1

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1 Introduction

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

3 Helix-inversion Mechanism

4 PQX-based Chiral Ligand

5 Chirality-Amplification System

6 Summary

Introduction

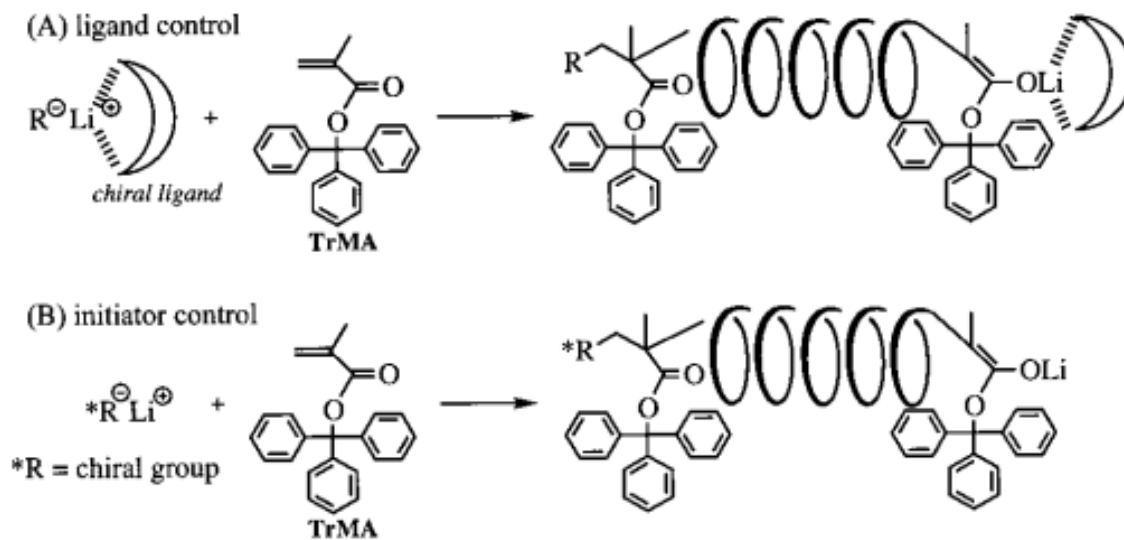


Helical Chiral Polymers

for Asymmetric Synthesis

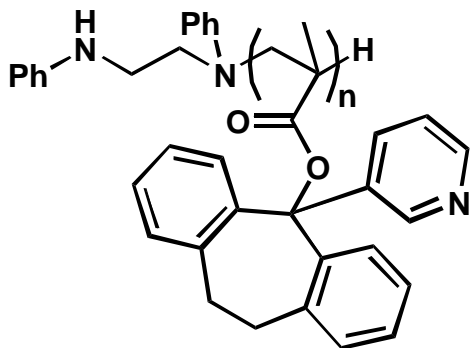
Advantage of helical polymer-based chiral ligands

- ease in recovery and reusability
- large chiral environment

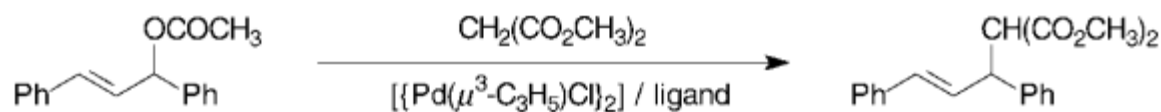
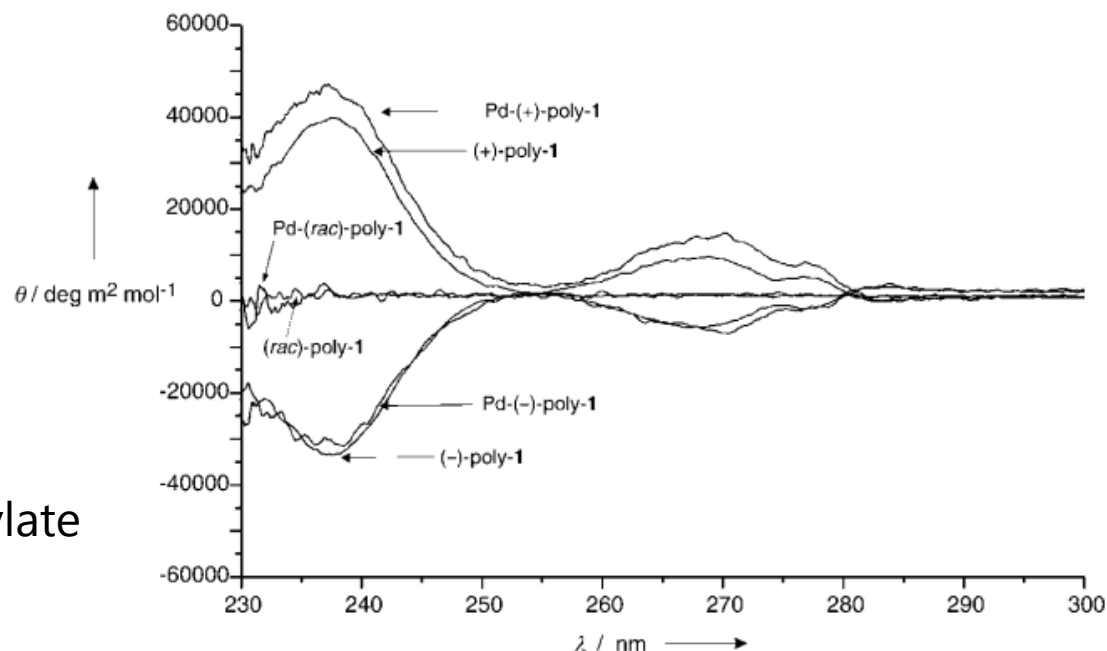


TrMA = triphenylmethyl methacrylate

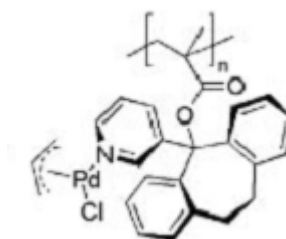
Ex. Poly(triphenylmethyl methacrylate)



Poly(triphenylmethyl methacrylate)
(ligand)



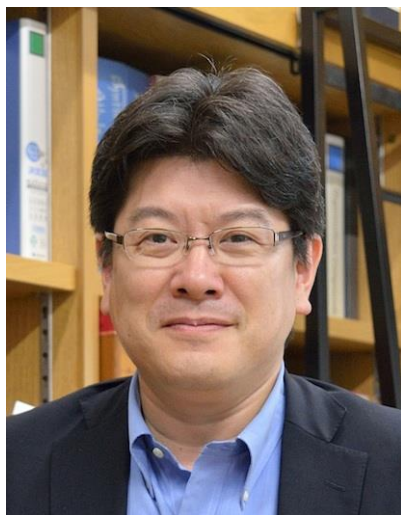
Ligand ^[a]	[Pd] [mol %] ^[b]	Solvent	<i>T</i> [°C]	<i>t</i> [h]	Yield [%] ^[c]	<i>ee</i> [%] ^[d]	Config. ^[e]
(+)-poly-1	10	CH ₂ Cl ₂	25	72	12	29	<i>R</i>
(+)-poly-1	25	CH ₂ Cl ₂	25	72	66 ^[f]	33	<i>R</i>
(+)-poly-1	10	CH ₂ Cl ₂	40	48	74	27	<i>R</i>
(+)-poly-1	25	CH ₂ Cl ₂	40	14	79 ^[f]	32	<i>R</i>
(-)-poly-1	10	CH ₂ Cl ₂	40	70	88 ^[f]	28	<i>S</i>
(-)-poly-1	25	CH ₂ Cl ₂	40	40	81 ^[f]	33	<i>S</i>
<i>rac</i> -poly-1	10	CH ₂ Cl ₂	40	70	92 ^[f]	0	–
<i>rac</i> -poly-1	25	CH ₂ Cl ₂	40	40	78 ^[f]	0	–



Insufficient enantioselectivity
lack of rigidity, homogeneity, etc.

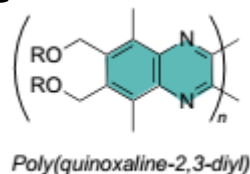
 **Poly(quinoxaline-2, 3-diyl)s**

Today's Main Topic : Poly(quinoxaline-2, 3-diyl)s

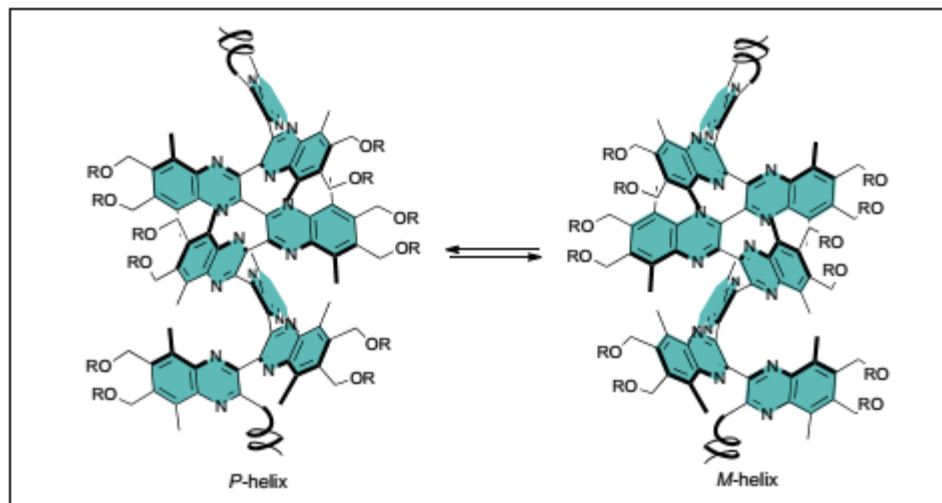


- 1993-2002 **Assistant Professor**
Department of Synthetic Chemistry and Biological Chemistry,
Kyoto University
- 2002-2004 **Associate Professor**
Department of Synthetic Chemistry and Biological Chemistry,
Kyoto University
- 2004-present **Professor**
Department of Synthetic Chemistry and Biological Chemistry,
Kyoto University

Prof. Suginome



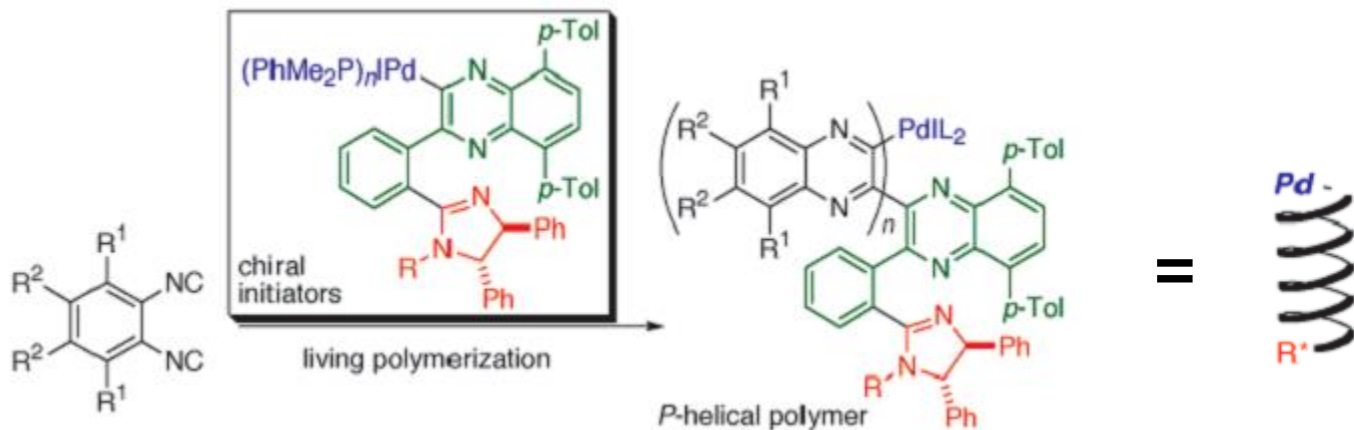
What is PQX?



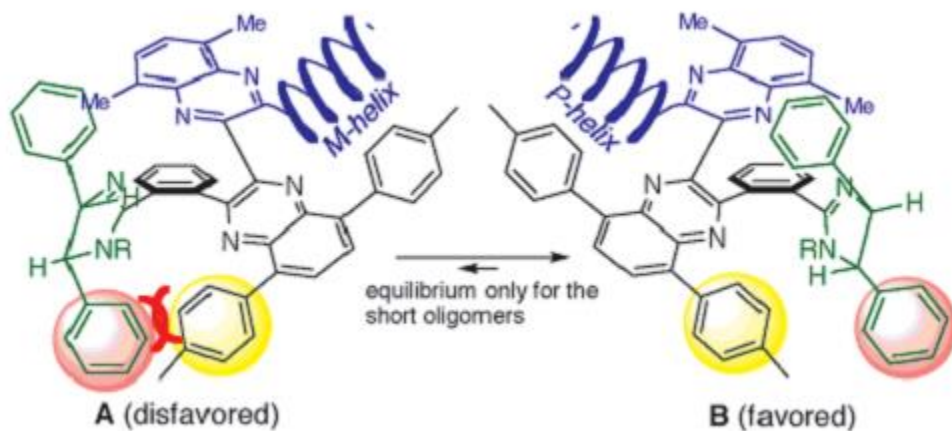
◆ Features

- Single-handed helical polymer
- Chirality-switchability

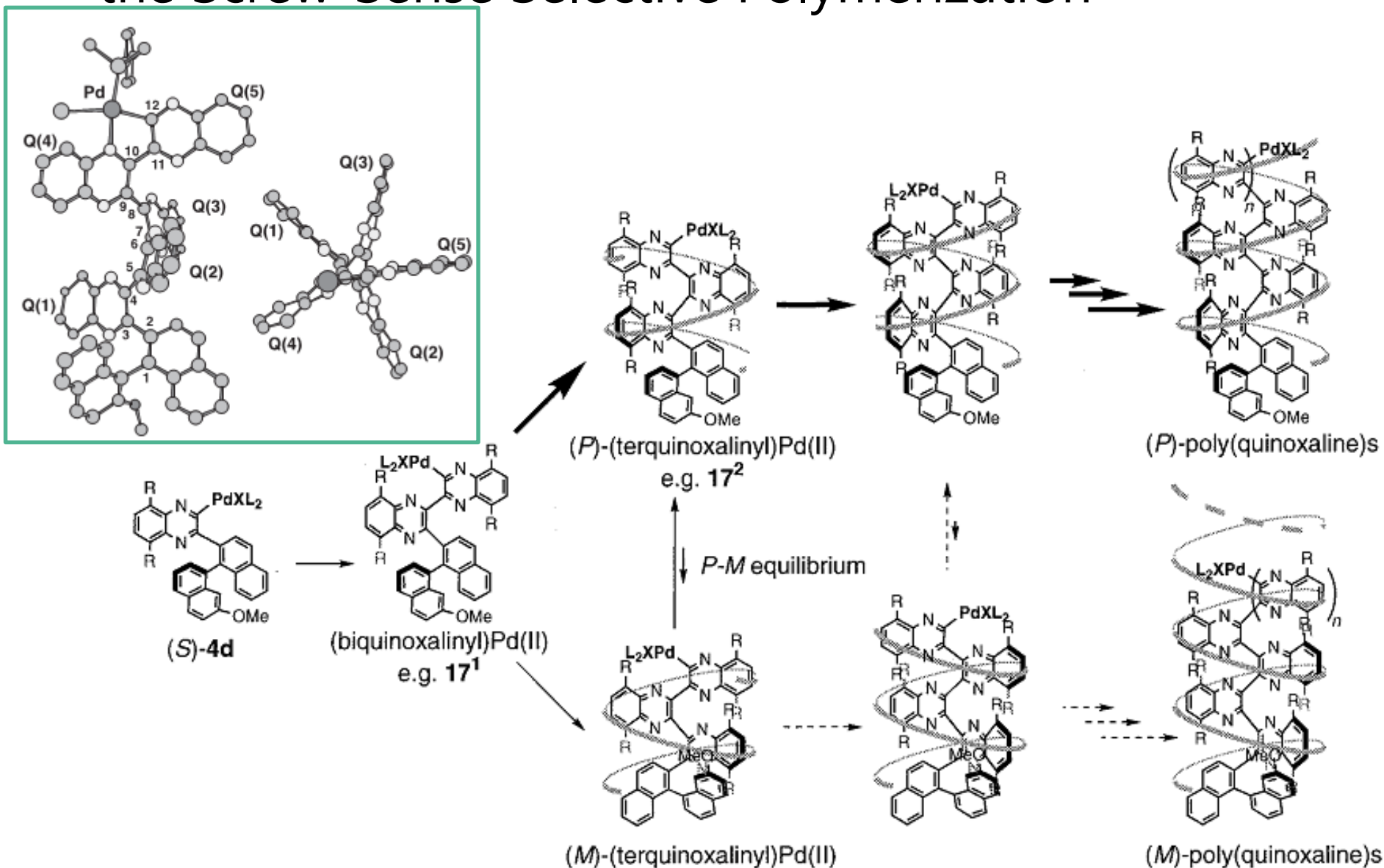
The Chain-End Control Mechanism of the Screw-Sense Selective Polymerization



P = right handed helix, M = left handed helix

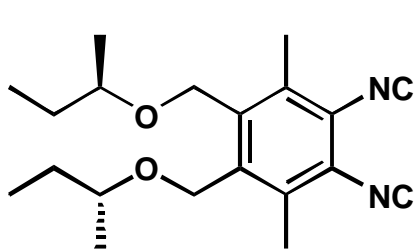


The Chain-End Control Mechanism of the Screw-Sense Selective Polymerization



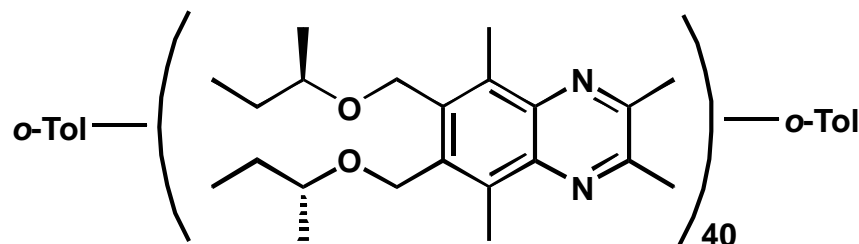


Solvent-Dependent Switch of Helical Main-Chain Chirality

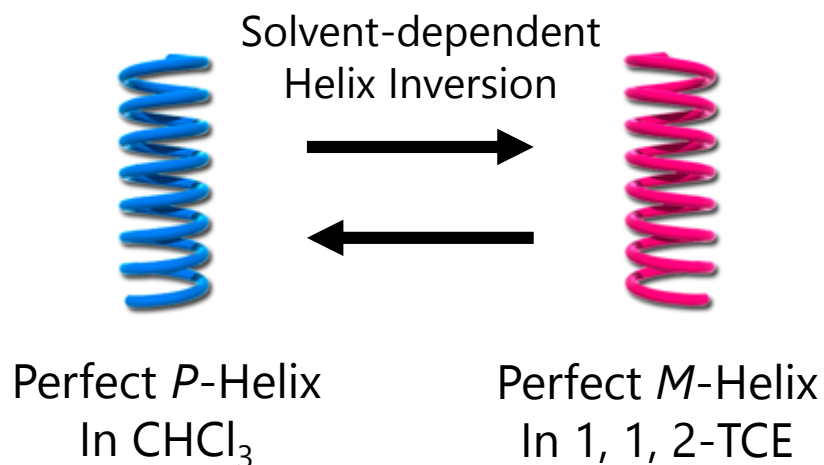
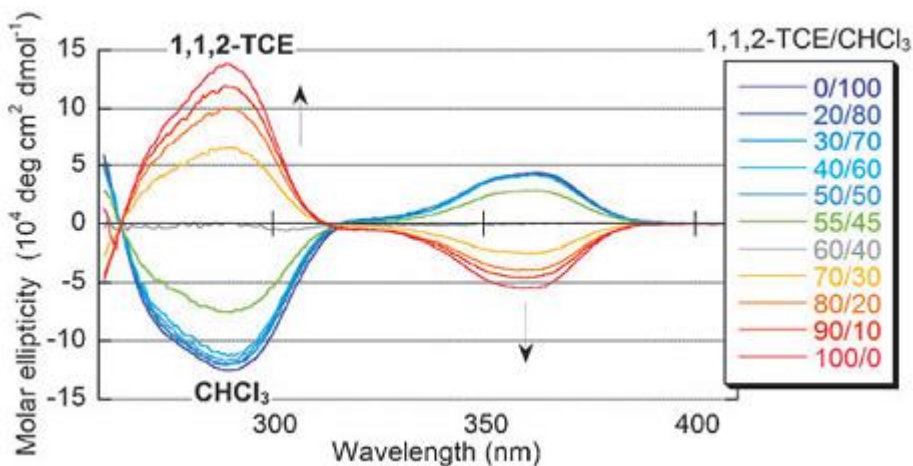


(*R*)-monomer

1) *o*-TolNiCl(PMe₃)₂
PMe₃, THF, rt, 3 h
2) *o*-TolMgBr

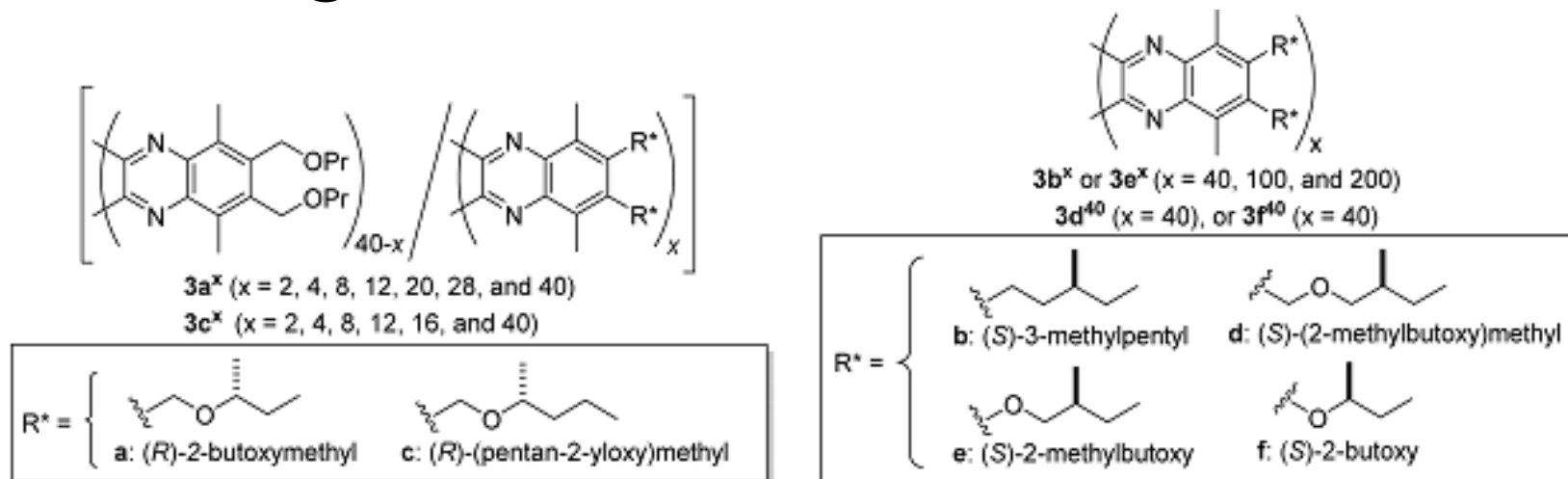


1, 1, 2-TCE = 1, 1, 2-trichloroethan



Helix-inversion Mechanism

Screening of Chiral Side Chains



polymer in CHCl_3 in 1, 1, 2-TCE

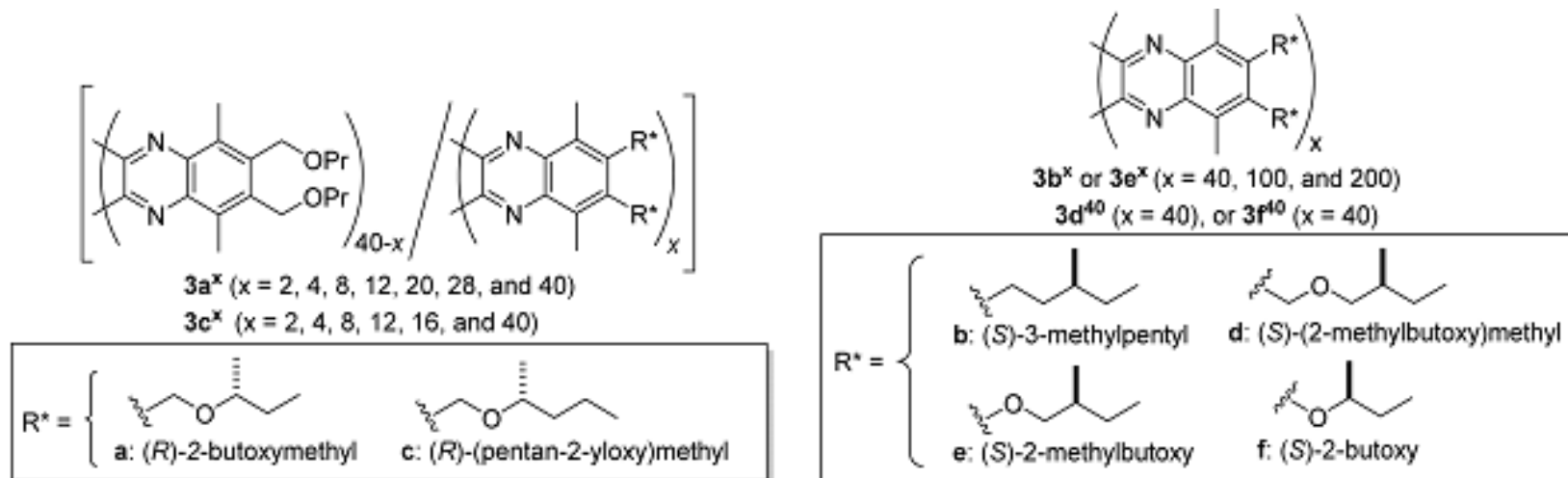
a^{40}	$R^* =$	P	M
b^{40}	$R^* =$	M	P
c^{40}	$R^* =$	P	M
d^{40}	$R^* =$	M	M
e^{40}	$R^* =$	M	P
f^{40}	$R^* =$	P	P

◆ No correlation between helical direction and configuration of side chains

◆ Oxygen atom were not essential.

◆ Switchable polymer commonly have the chiral center at third position.

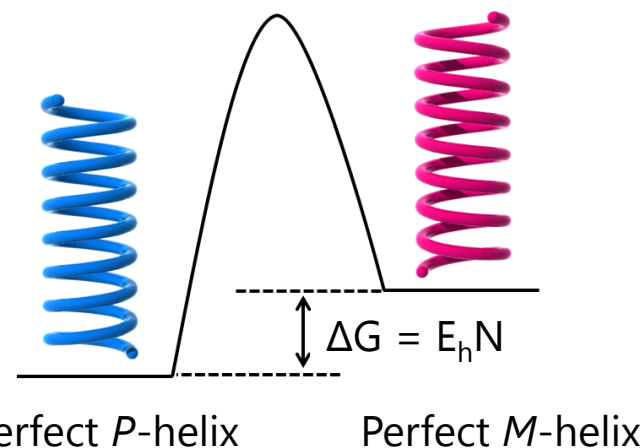
Gained Energy Difference Between *P* and *M* helix



Calculated E_h and g_{\max} Values

polymer	CHCl_3		1,1,2-TCE	
	E_h (kJ mol^{-1})	$g_{\max} / 10^{-3}$	E_h (kJ mol^{-1})	$g_{\max} / 10^{-3}$
3a	-0.59 <i>P</i>	+2.37	-0.32 <i>M</i>	-2.87
3c	-0.70 <i>P</i>	+2.23	-0.46 <i>M</i>	-2.81
3b	-0.05 <i>M</i>	+1.26	- ^a	- ^a
3e	-0.10 <i>M</i>	+2.40	- ^a	- ^a

^aCollected data were not sufficient for the nonlinear least-squares fitting.

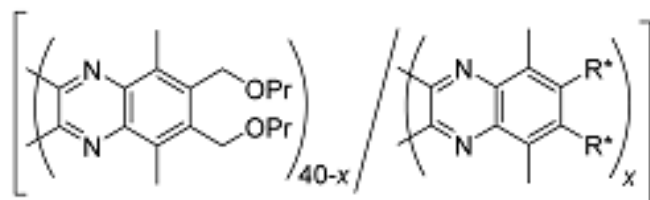


The large E_h value played a central role in the highly efficient control of the screw sense.

g = dissymmetry factor ($\Delta\epsilon/\epsilon$)

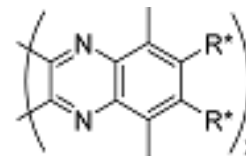
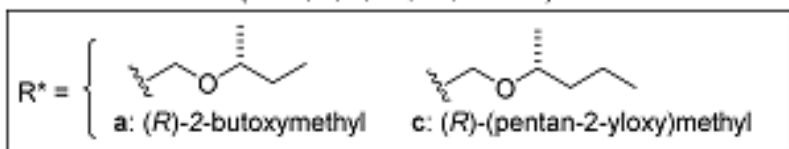
cf. other helical polymers : $E_h = 0.005\text{-}0.06 \text{ kJ mol}^{-1}$

Relationships Between Number of Chiral Units and se



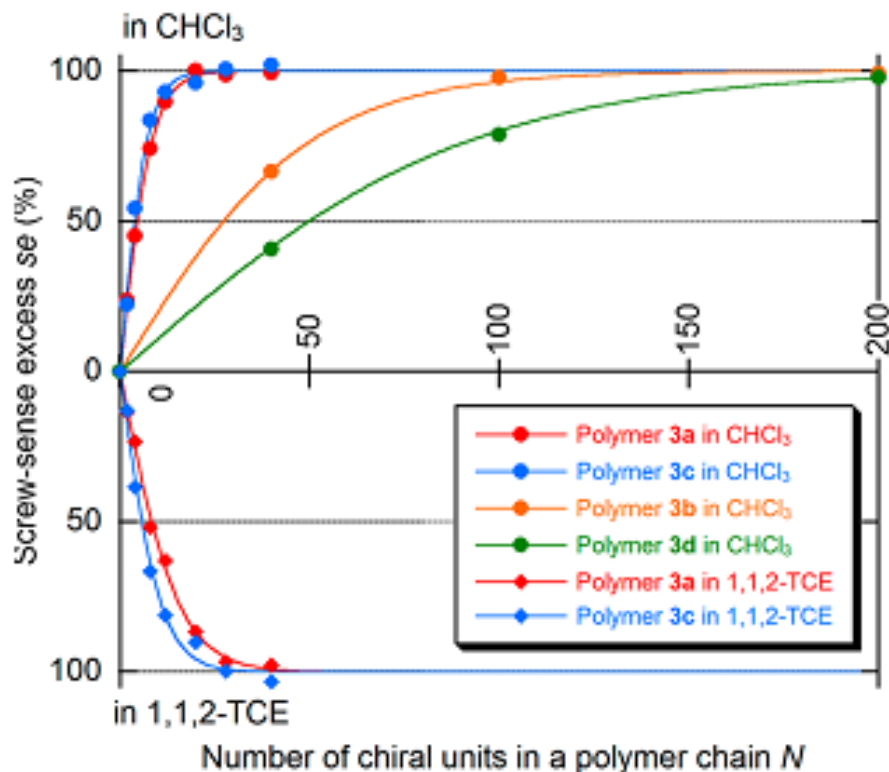
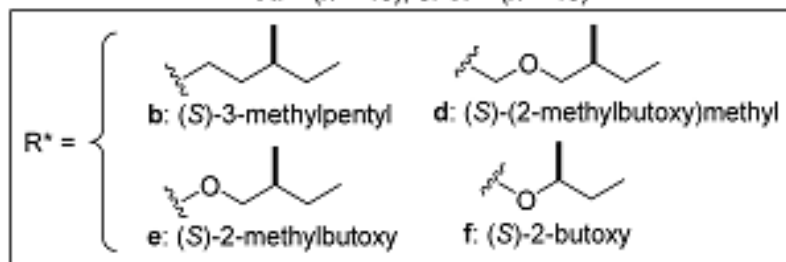
$3a^x$ ($x = 2, 4, 8, 12, 20, 28, \text{ and } 40$)

$3c^x$ ($x = 2, 4, 8, 12, 16, \text{ and } 40$)



$3b^x$ or $3e^x$ ($x = 40, 100, \text{ and } 200$)

$3d^{40}$ ($x = 40$), or $3f^{40}$ ($x = 40$)



Polymer 3a and 3c
Helix induction was achieved very efficiency.

Polymer 3b and 3d
Many chiral units are required to maintain a single-handed helical main chain.

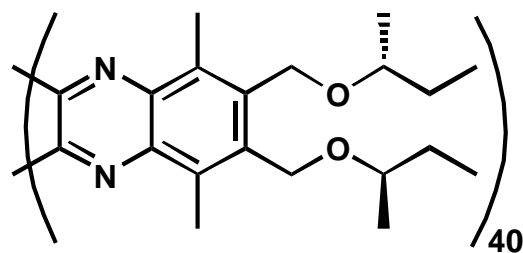
$$\ast se = g_{abs}/g_{max}$$

3b : low solubility

3d : no inversion



Helix induction by various solvents

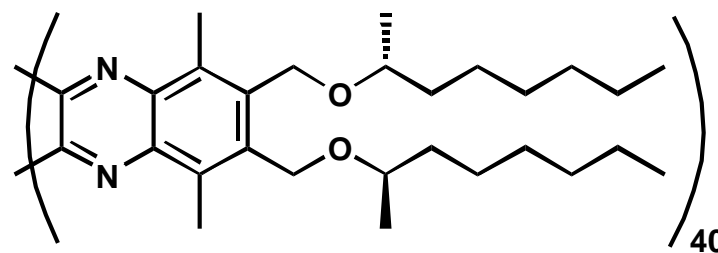


CHCl₃

E_h (kJ mol⁻¹) $g_{max}/10^{-3}$

-0.59 +2.37
(P)

improve



CHCl₃

E_h (kJ mol⁻¹) $g_{max}/10^{-3}$

-1.01 +2.29
(P)

1, 1, 2-TCE

E_h (kJ mol⁻¹) $g_{max}/10^{-3}$

-0.32 -2.87
(M)

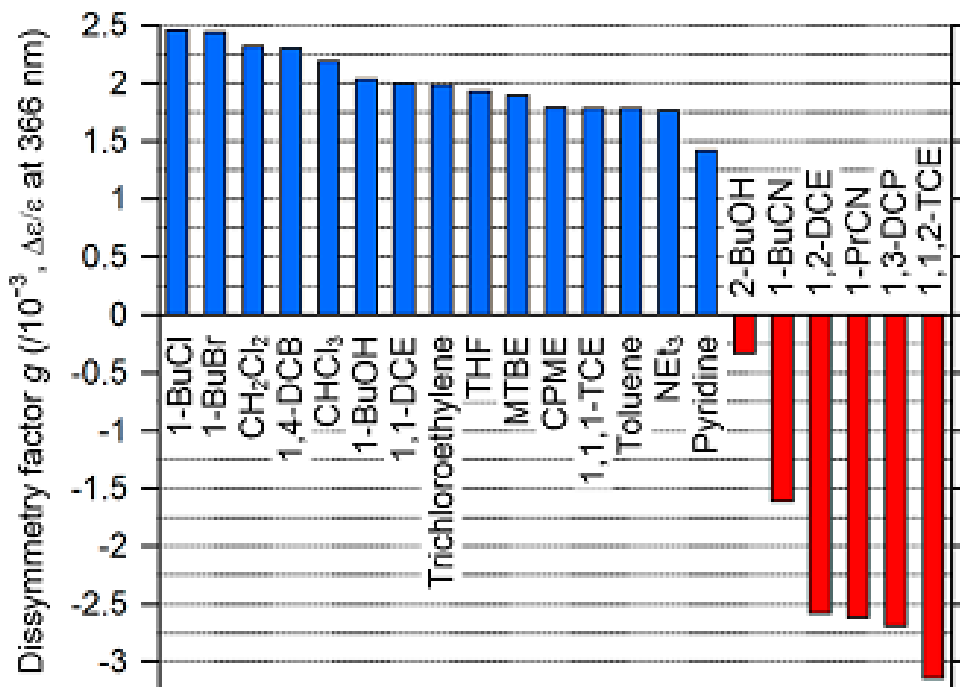
1, 1, 2-TCE

E_h (kJ mol⁻¹) $g_{max}/10^{-3}$

-0.70 -2.79
(M)

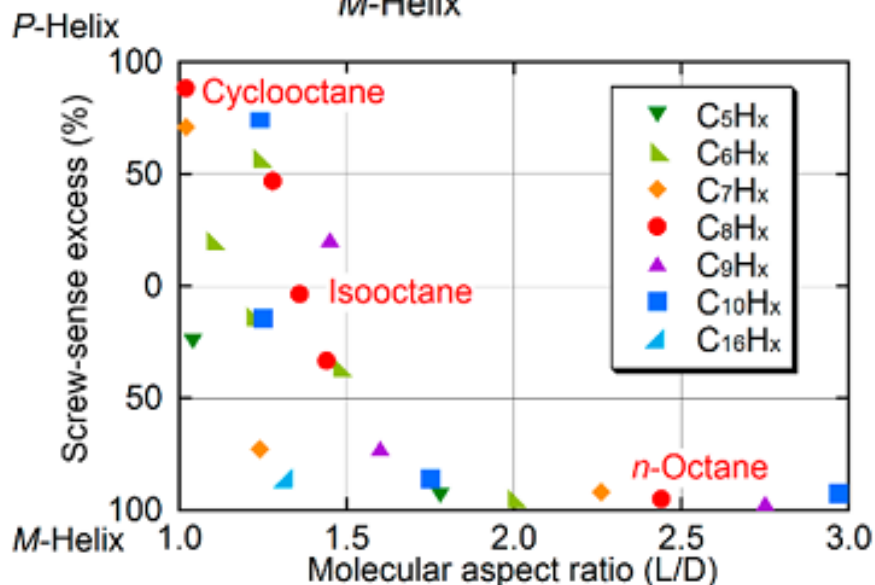
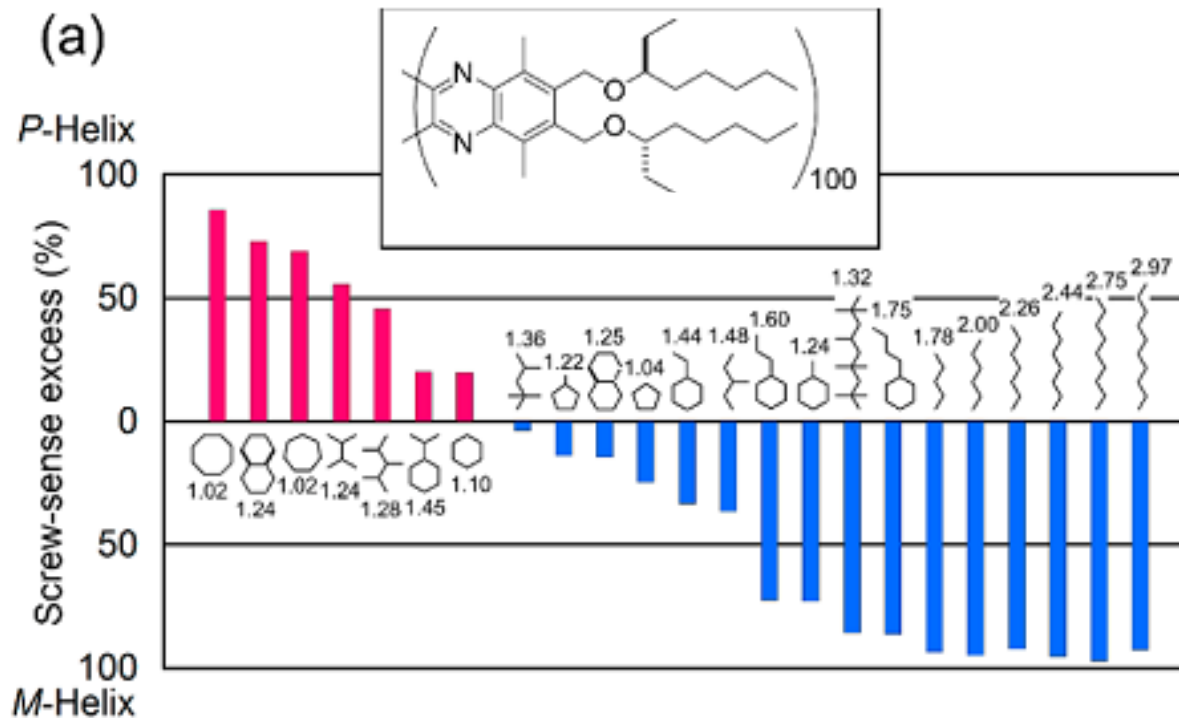
3a⁴⁰

3h⁴⁰





Helix induction by Alkane solvents

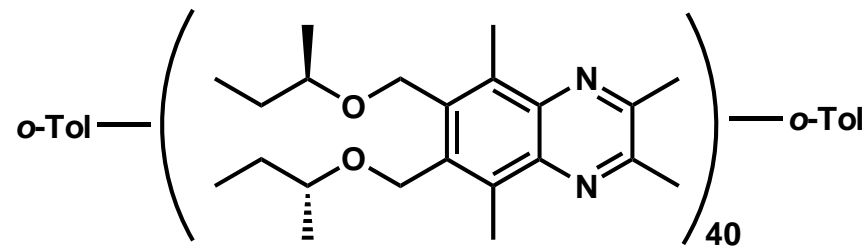


Linear alkanes (larger molecular aspect ratio) induced *M*-helical structure.

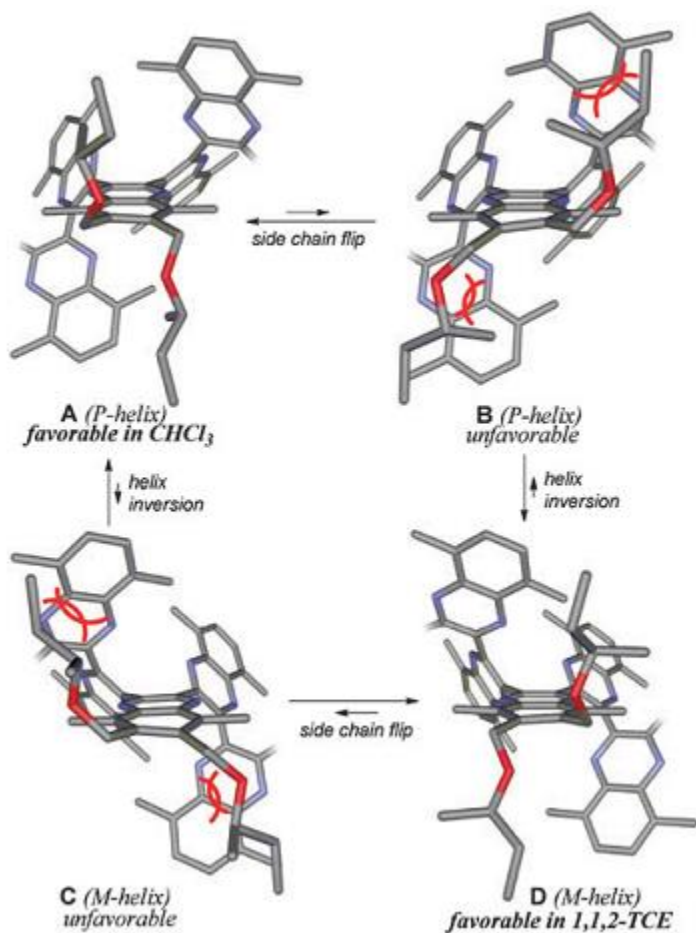
Branched or cyclic alkanes (smaller molecular aspect ratio) induced *P*-helical structure.

※Molecular aspect ratio =
 L (major axis)/ D (minor axis)

Possible conformations



Conformation A is favored
in CHCl_3 ?

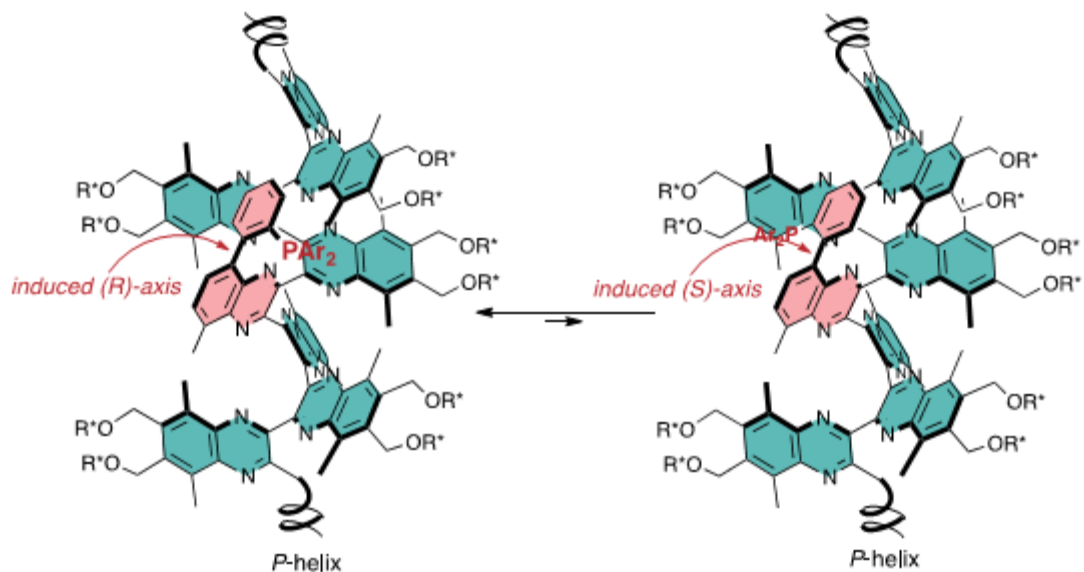
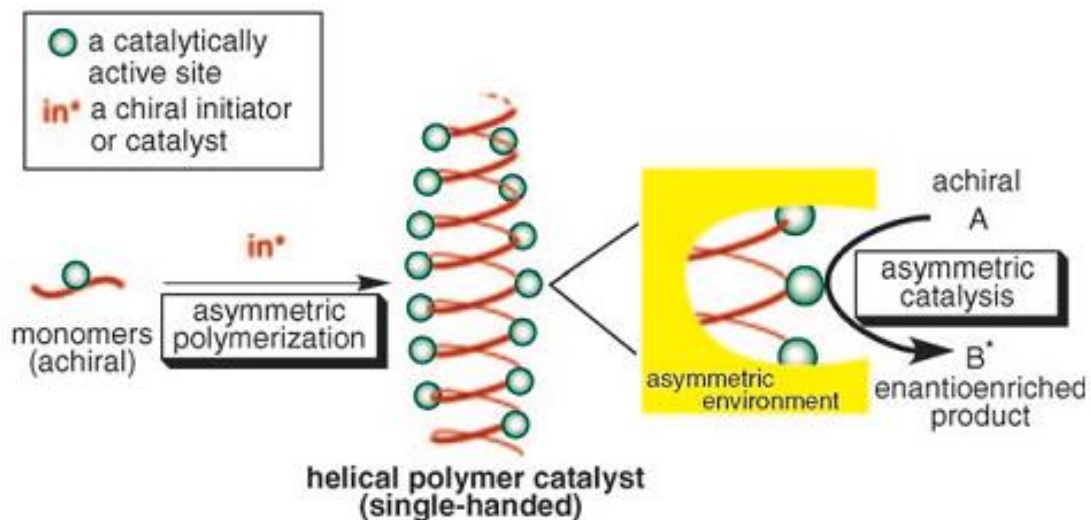


Conformation D is favored
in 1,1,2-TCE?

Chiral side chains except for those on the central quinoxaline ring
are omitted for clarity.

PQX-based Chiral Ligand

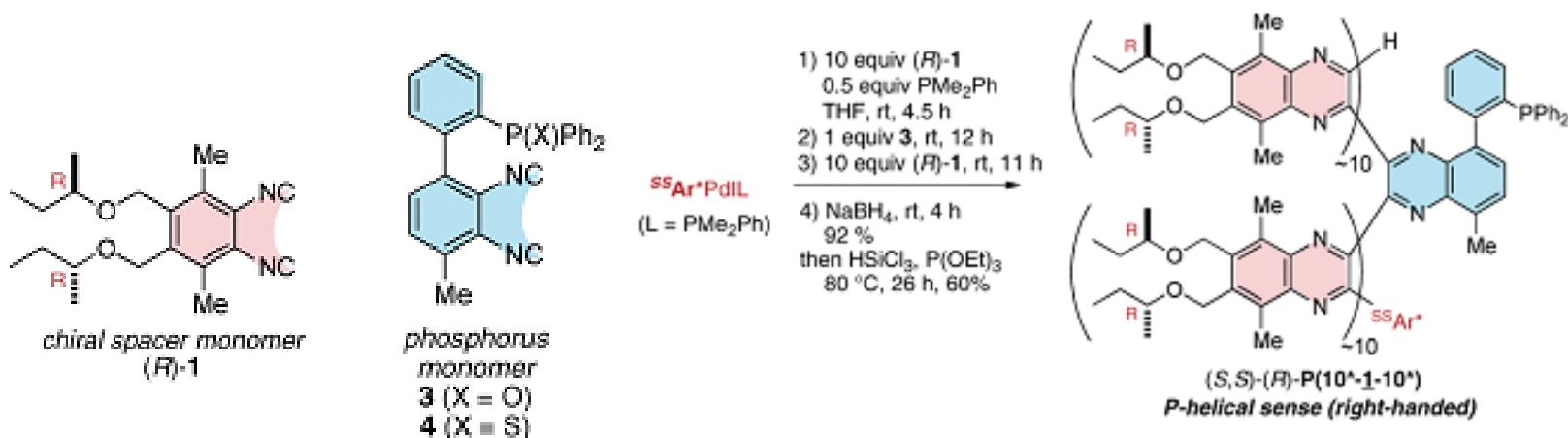
PQXphos Ligand



Axial chirality induced by *P*-helix



Catalytic Asymmetric Hydrosilylation of Styrene



entry	ligand	R	R'	% yield ^b	% ee ^c
1	(S,S)-(R)-P(10*-1-10*)	H	H	91	96 (S)
2	(S,S)-(R)-P(10*-1-10*)	2-Me	H	94	95 (S)
3	(S,S)-(R)-P(10*-1-10*)	3-Me	H	93	91 (S)
4	(S,S)-(R)-P(10*-1-10*)	4-Me	H	96	95 (S)
5	(S,S)-(R)-P(10*-1-10*)	4-MeO	H	96	91 (S)
6	(S,S)-(R)-P(10*-1-10*)	4- <i>t</i> -Bu	H	92	84 (S)
7	(S,S)-(R)-P(10*-1-10*)	4-F	H	94	92 (S)
8	(S,S)-(R)-P(10*-1-10*)	H	Me	93	96 (S)

^a A styrene derivative (1.0 mmol) and trichlorosilane (2.0 mmol) were stirred at 0 °C in the presence of $[\text{PdCl}(\pi\text{-allyl})]_2$ (0.50 μmol) with a polymer ligand (2.0 μmol P). ^b Isolated yield (bulb-to-bulb distillation). ^c Determined by chiral HPLC after conversion to the corresponding α -phenylethyl alcohol by $\text{H}_2\text{O}_2/\text{KHCO}_3/\text{KF}$ oxidation.

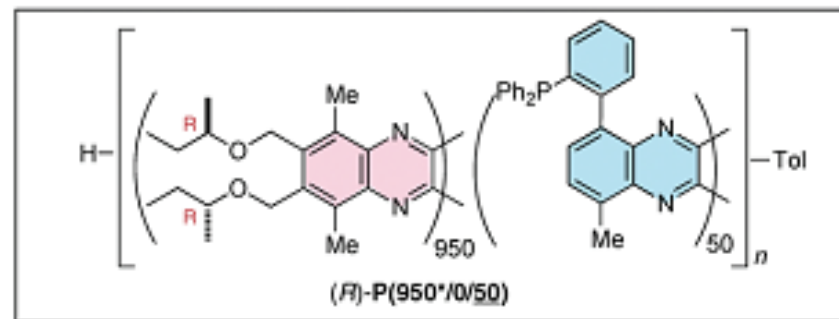
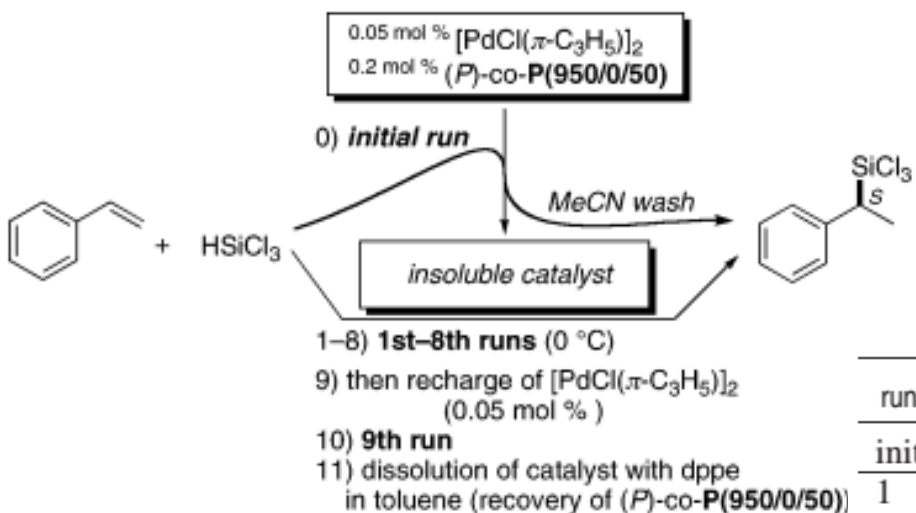
High reactivity and enantioselectivity



Catalytic Asymmetric Hydrosilylation of Styrene

Random copolymer (P)-co-P(950/0/50)

- easy accessible than block copolymer

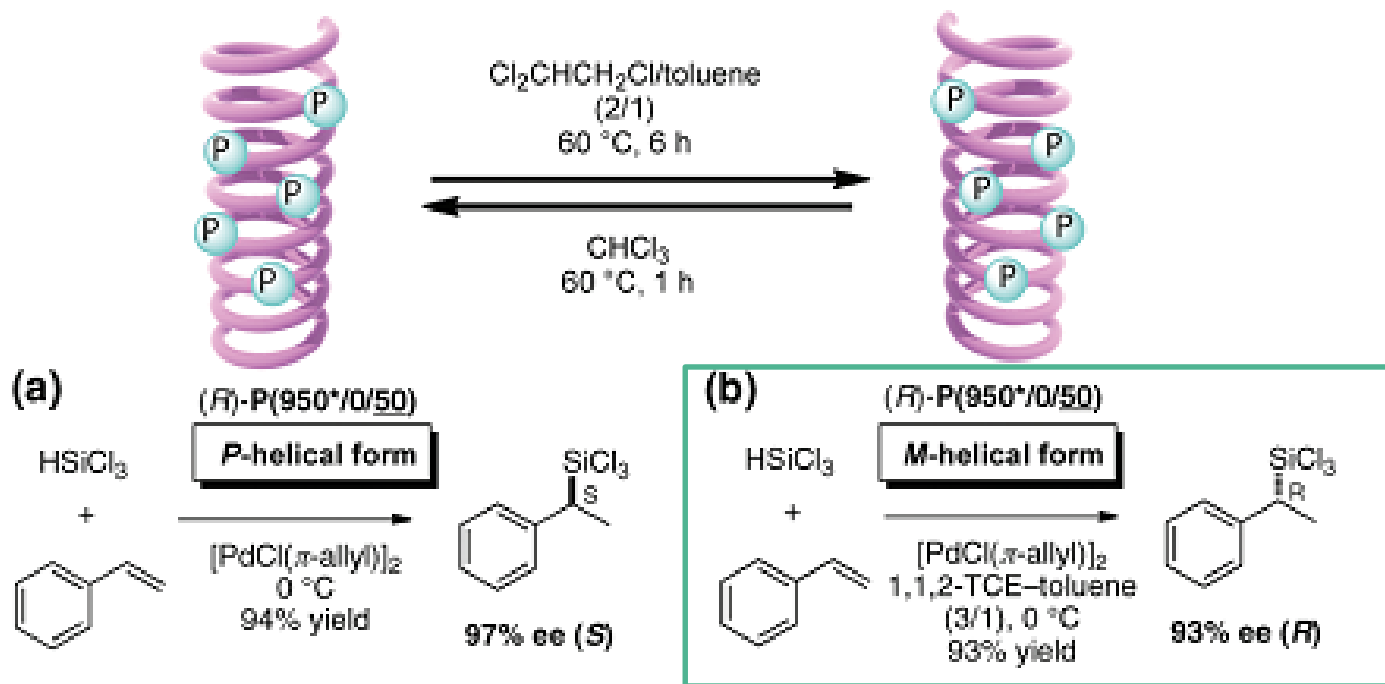


run	time/h	%yield ^b	%ee ^c	run	time/h	%yield ^b	%ee ^c
init	12	94	96	5	37	98	97
1	24	95	97	6	50	97	98
2	24	96	98	7	64	99	98
3	24	97	97	8	70	97	98
4	32	97	97	9	12	98	96

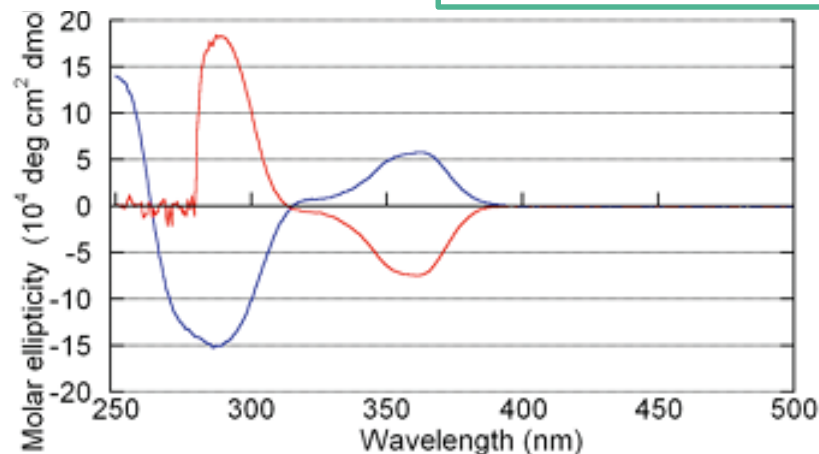
Recoverable and reusable

^a See footnote a in Table 2 for the reaction conditions. Product was isolated by washing the reaction flask with acetonitrile three times followed by bulb-to-bulb distillation. ^b Isolated yield. ^c Determined after oxidation.

Catalytic Asymmetric Hydrosilylation of Styrene



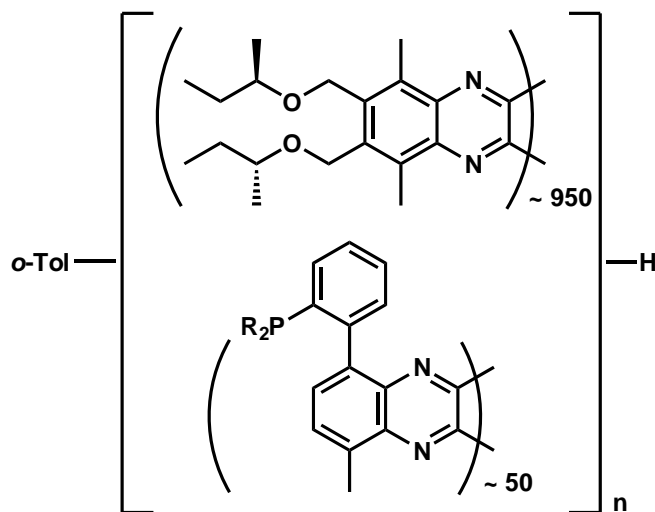
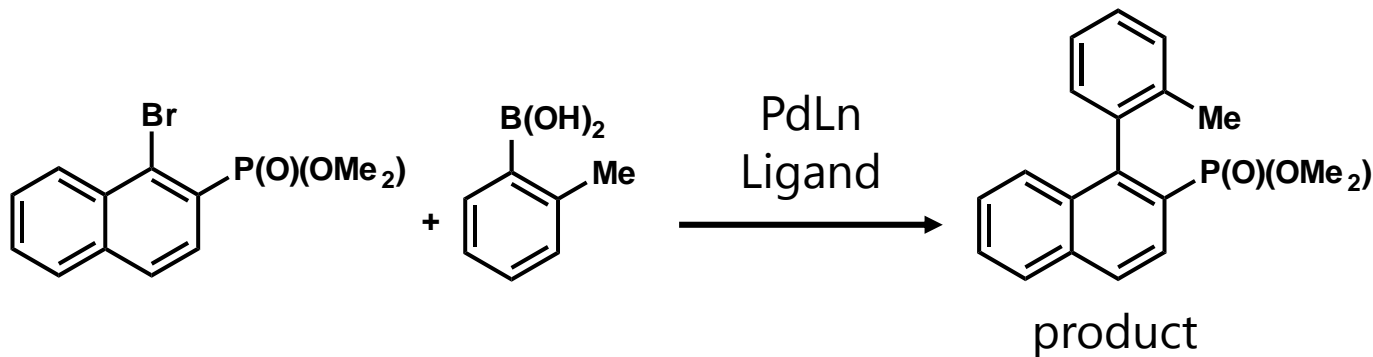
Chirality-switchable



CD spectra of (R) -P(950*/50) in chloroform (blue line) and in a 1, 1, 2-TCE/toluene (2/1) mixture (red line)



Catalytic Asymmetric Suzuki-Miyaura Coupling



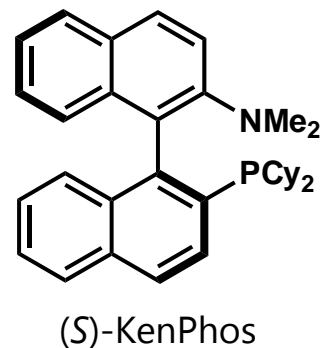
(P)-(R)-PQXphos

R = 2-nap
R = Cy

y. 80% ee 94%] (-)-(S)-product
y. 72% ee 40%	

J. Am. Chem. Soc. **2000**, 122, 12051-12052

One of the first system reported by Buchwald and co-workers

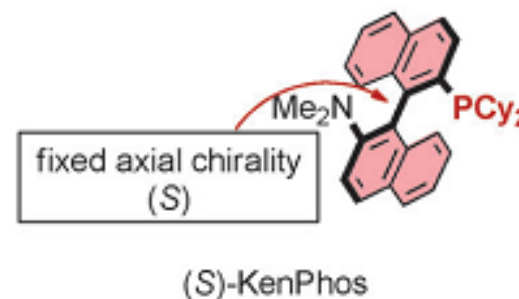
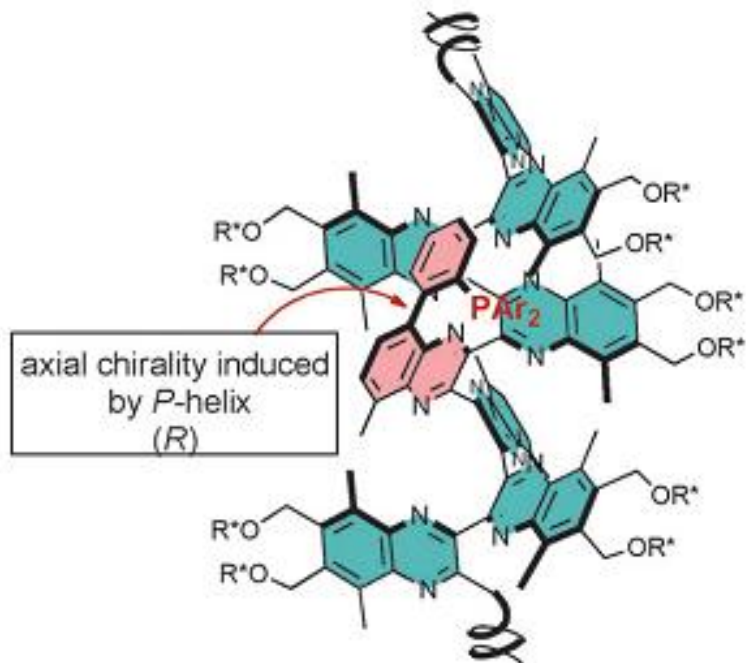


y. 95% ee 86%
(+)-(R)-product

Angew. Chem. Int. Ed. **2011**, 50, 8844-8847

Catalytic Asymmetric Suzuki-Miyaura Coupling

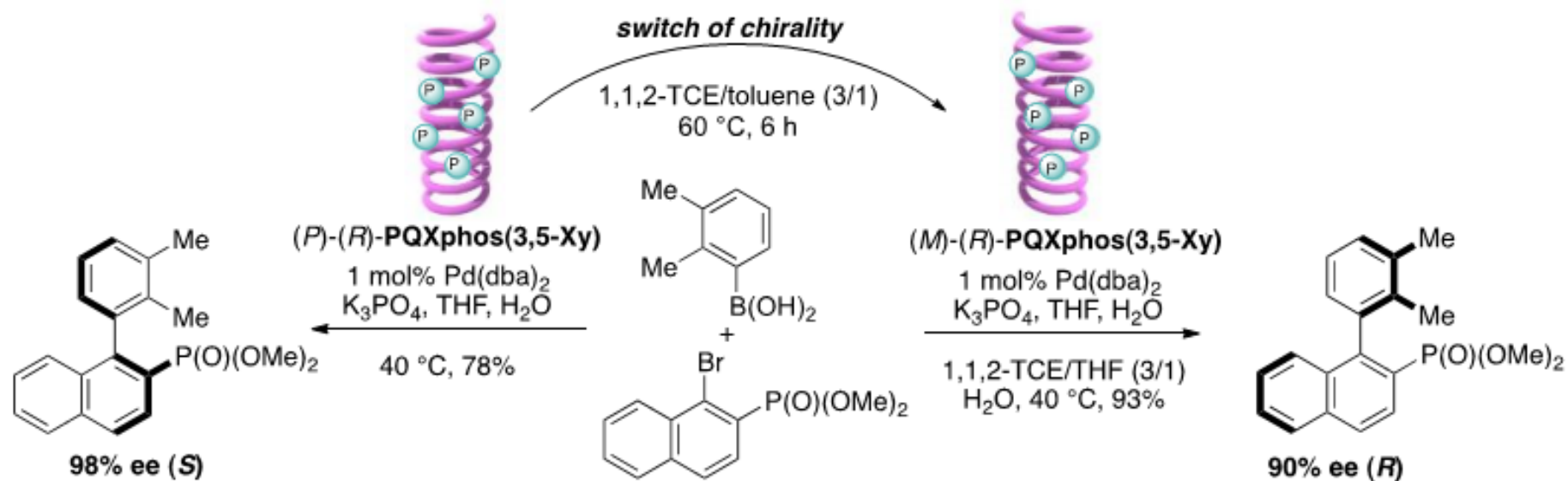
(*P*)-(*R*)-PQXphos ligand afforded (-)-(*S*)-compound (94% *ee*),
whereas (*S*)-KenPhos gave its enantiomer (+)-(*R*)-compound (86% *ee*).



(*P*)-helical PQXphos bearing *R*-configured side chains
[(*P*)-(*R*)-PQXphos]

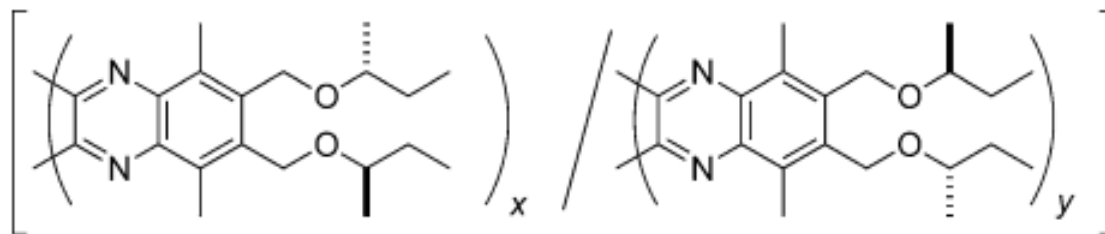
Because of the absence of the dimethylamino group

Catalytic Asymmetric Suzuki-Miyaura Coupling



Chirality-Amplification System

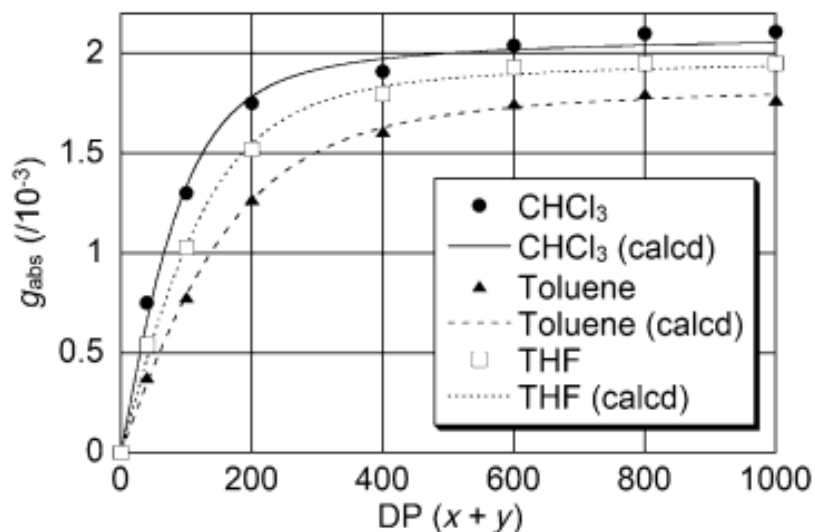
Chirality-Amplification System



2(x/y) (random copolymer)

$$[(x-y)/(x+y) \times 100] = 10\% \text{ ee (55:45)}$$

$x+y = 40, 100, 200, 400, 600, 800, \text{ and } 1000$

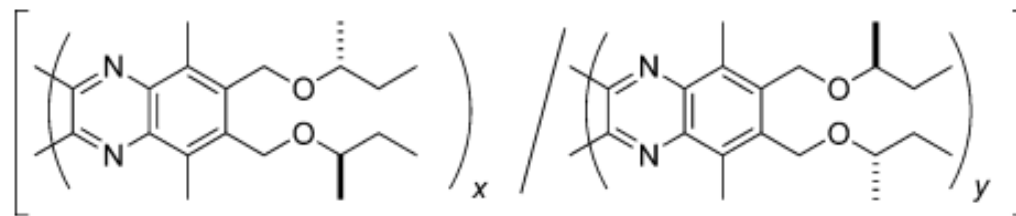


Solvent	ΔG_h [kJ mol ⁻¹]
CHCl ₃	-0.41
toluene	-0.22
THF	-0.30

※ $\Delta G_h = E_h$

ΔG_h value suggests that the use of monomers with 10% ee is inefficient for the induction of absolute screw senses.

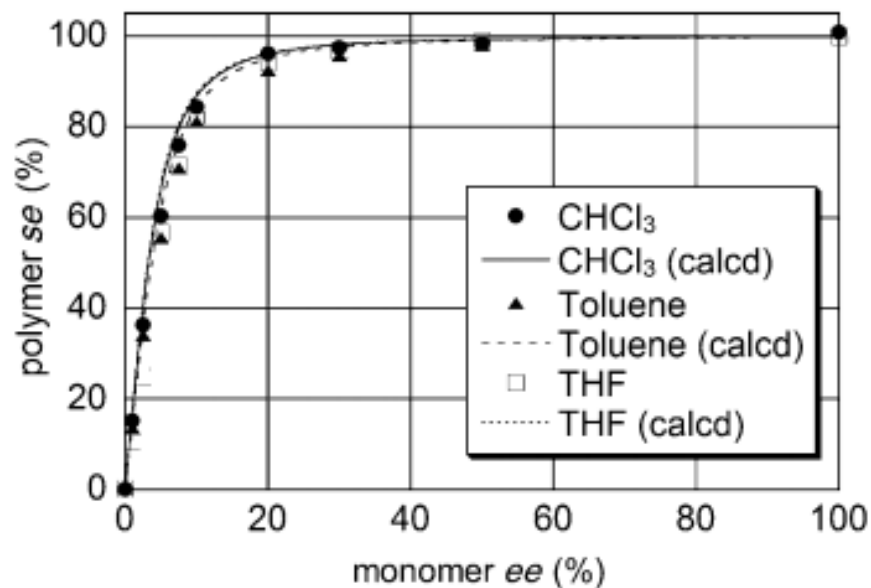
Chirality-Amplification System



$$2(x/y)$$

$$x+y = 1000$$

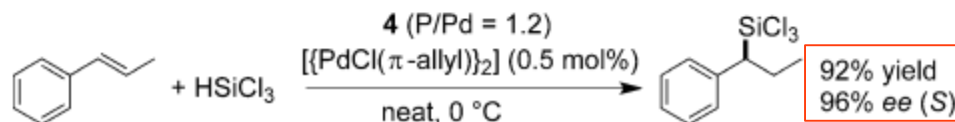
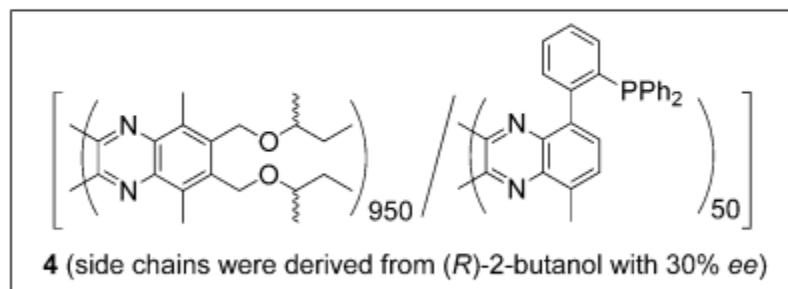
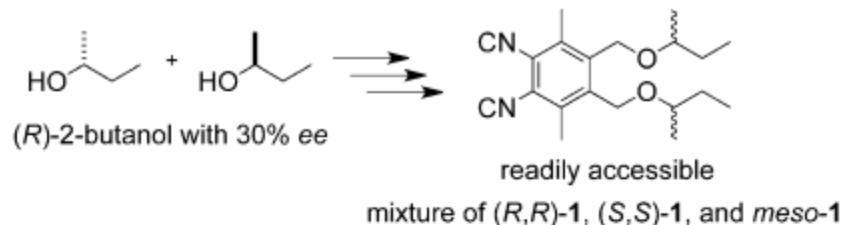
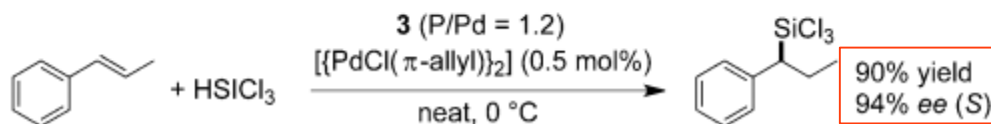
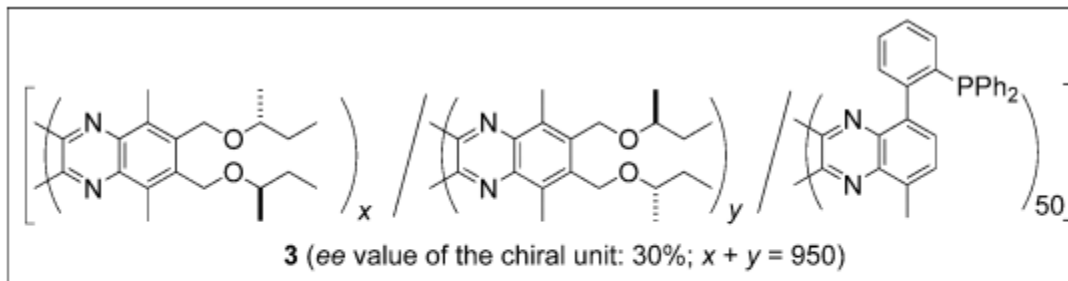
$$[(x-y)/(x+y) \times 100] = 0.0, 1.0, 2.5, 5.0, 7.5, 10, 20, 30, 50, \text{ and } 100\% \text{ ee}$$



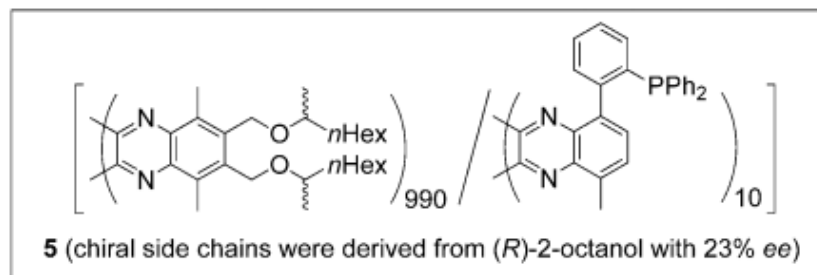
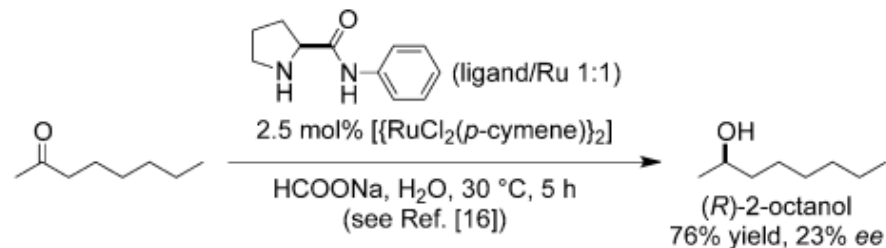
Monomers with 30% ee were able to induce > 97% se in the polymer backbone.

Chirality-Amplification System

Polymer ligand 3 and 4 exhibited an almost absolute *P*-helical conformation.

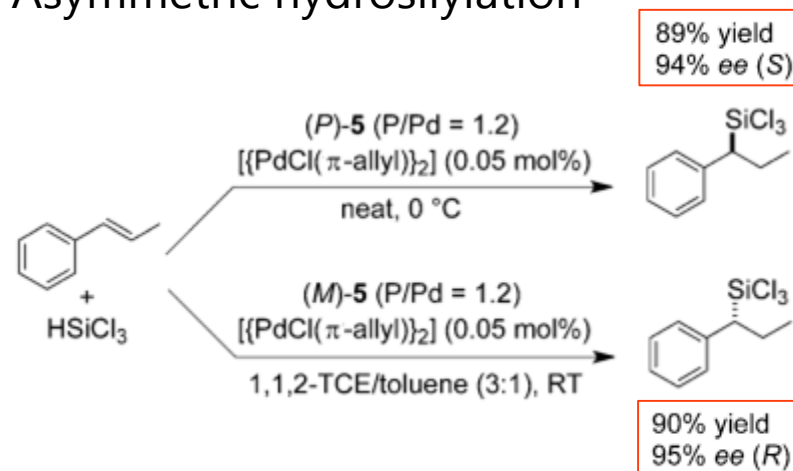


Chirality-Amplification System

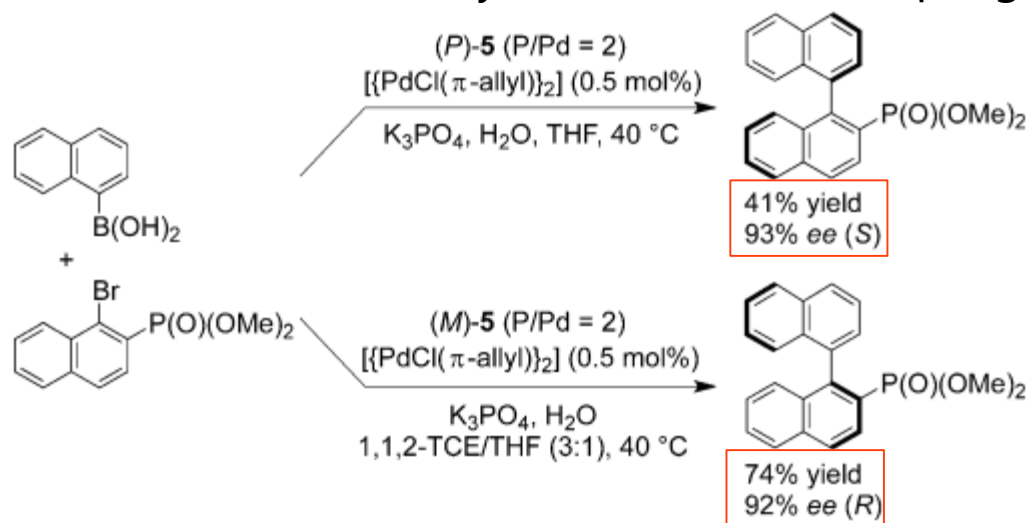


Purely right handed helical structure

Asymmetric hydrosilylation



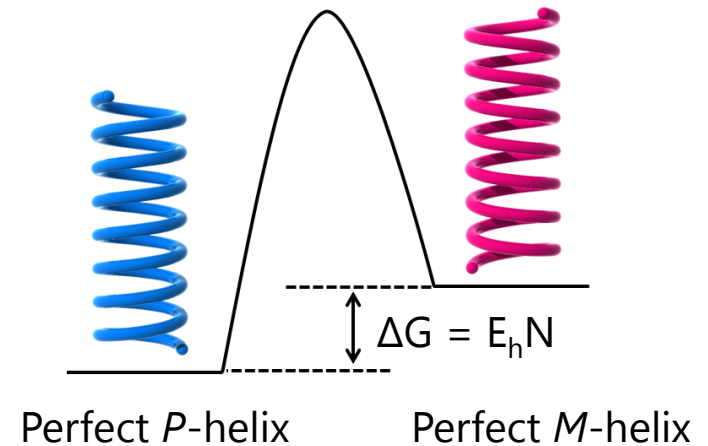
Asymmetric Suzuki coupling



Summary

Summary 1

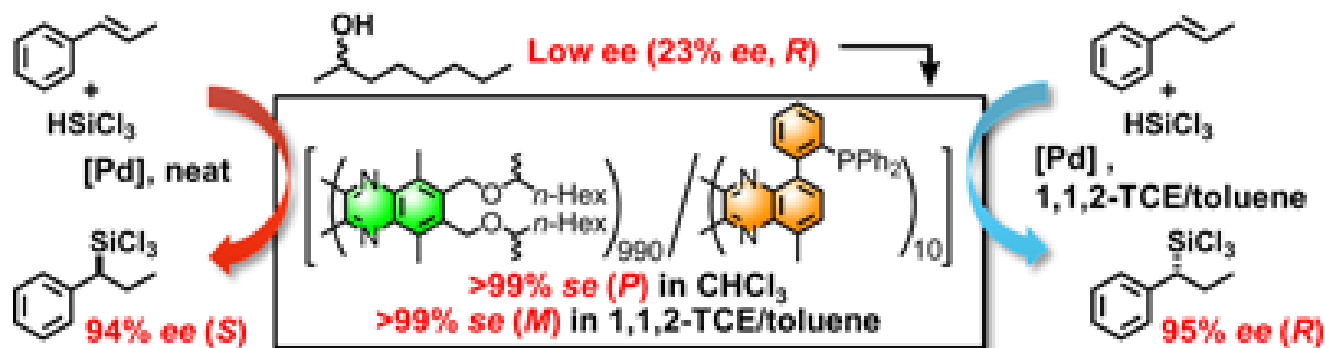
- ✓ PQX exhibits pure right- or left-handed helical sense because of large E_h value.



- ✓ PQX shows an efficient solvent dependent helix inversion.
- ✓ Studies for establishing the origin of conformational change are currently being undertaken in Suginome Lab..

Summary 2

- ✓ PQXphos ligand can induce high enantioselectivities that are comparable to those obtained by low-molecular-weight catalyst system.
- ✓ PQXphos ligand is easily separable, reusable.
- ✓ Reversible conformational change of the polymer backbone can be applied to switch the enantioinduction.
- ✓ The highly enantioselective generation of both enantiomers of a catalyst from a single chiral source with a low ee value has not been reported previously.



Appendix



Calculation of the value of E_h and g_{\max}

The total energy difference between P and M helical polymers is expressed as

$$\Delta G = -RT \ln([P]/[M]) \dots (1)$$

Where R , T , $[P]$, $[M]$ are the gas constant ($8.314 \text{ J K}^{-1} \text{ mol}^{-1}$), operating temperature (293.15 K), and molar concentration of P and M helical polymers ($[P]/[M]$). In the case where the polymer has no conformations containing helical reversal, ΔG is proportional to the number of chiral units N and E_h , i.e., the gained energy difference between P and M helical per a chiral unit.

$$\Delta G = E_h N \dots (2)$$

The screw-sense excess (se) is defined as

$$se = ([p] - [M])/([P] + [M]) \dots (3)$$

Here, se is represent using E_h , N , R , and T as

$$\begin{aligned} se &= \{\exp(-E_h N/RT) - 1\}/\{\exp(-E_h N/RT) + 1\} \\ &= \tanh(-E_h N/2RT) \dots (4) \end{aligned}$$

where hyperbolic tangent function (\tanh) is involved. The observed dissymmetry factor g_{abs} is proportional to the screw-sense excess, namely

$$se = g_{\text{abs}}/g_{\text{max}} \dots (5)$$

where g_{max} is the g value for the purely single-handed poly(quinoxaline-2, 3-diyl)s.

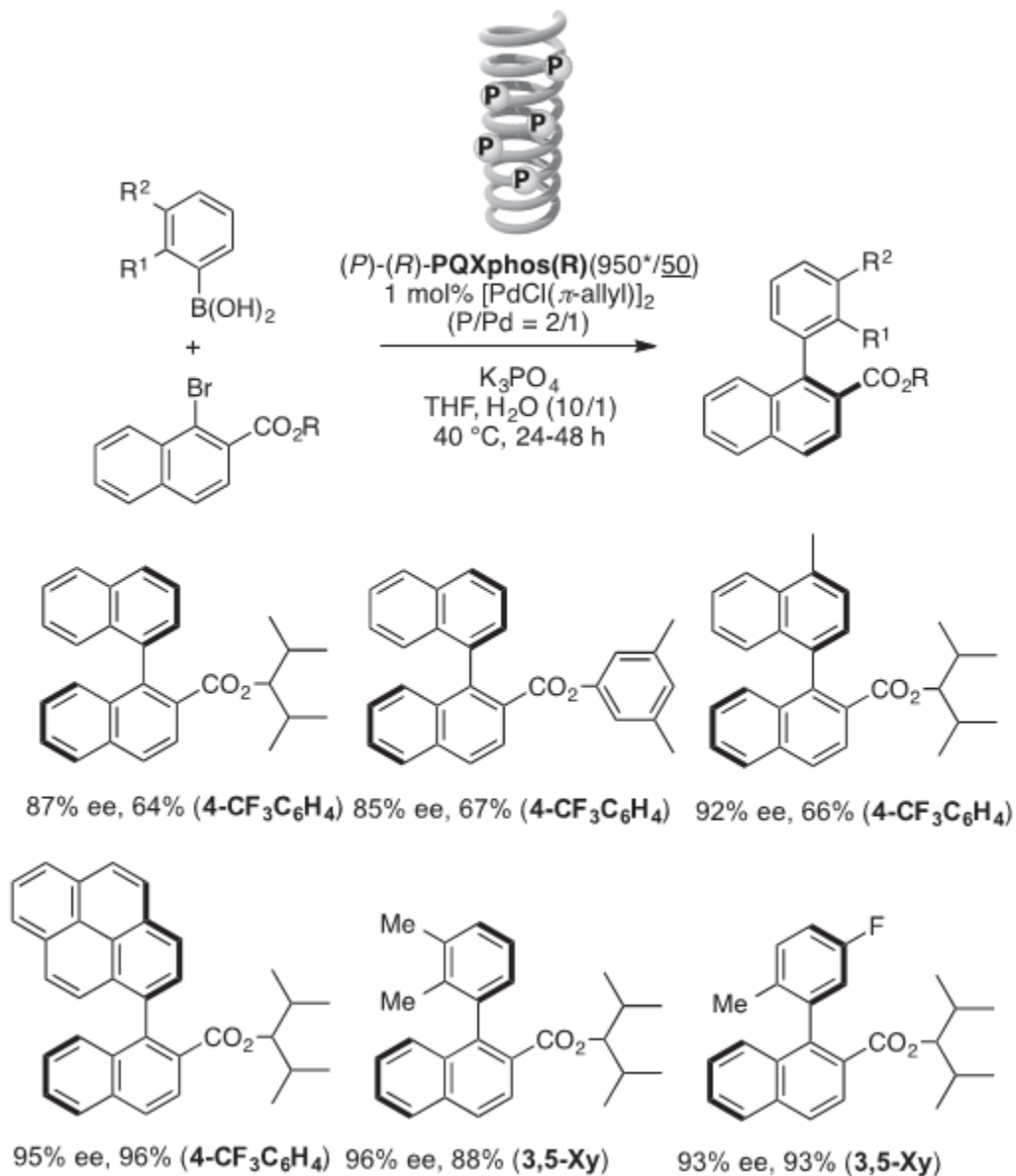
Equation 4 can be expressed using g_{abs} and g_{max} as

$$g_{\text{abs}} = \tanh(-E_h N/2RT) \times g_{\text{max}} \dots (6)$$

Nonlinear least-square fitting of g_{abs} versus N was performed by using the Solver Function in Microsoft Office Excel 2007. Sums of the squares of the deviation were minimized by varying two parameters, g_{max} and E_h (7)

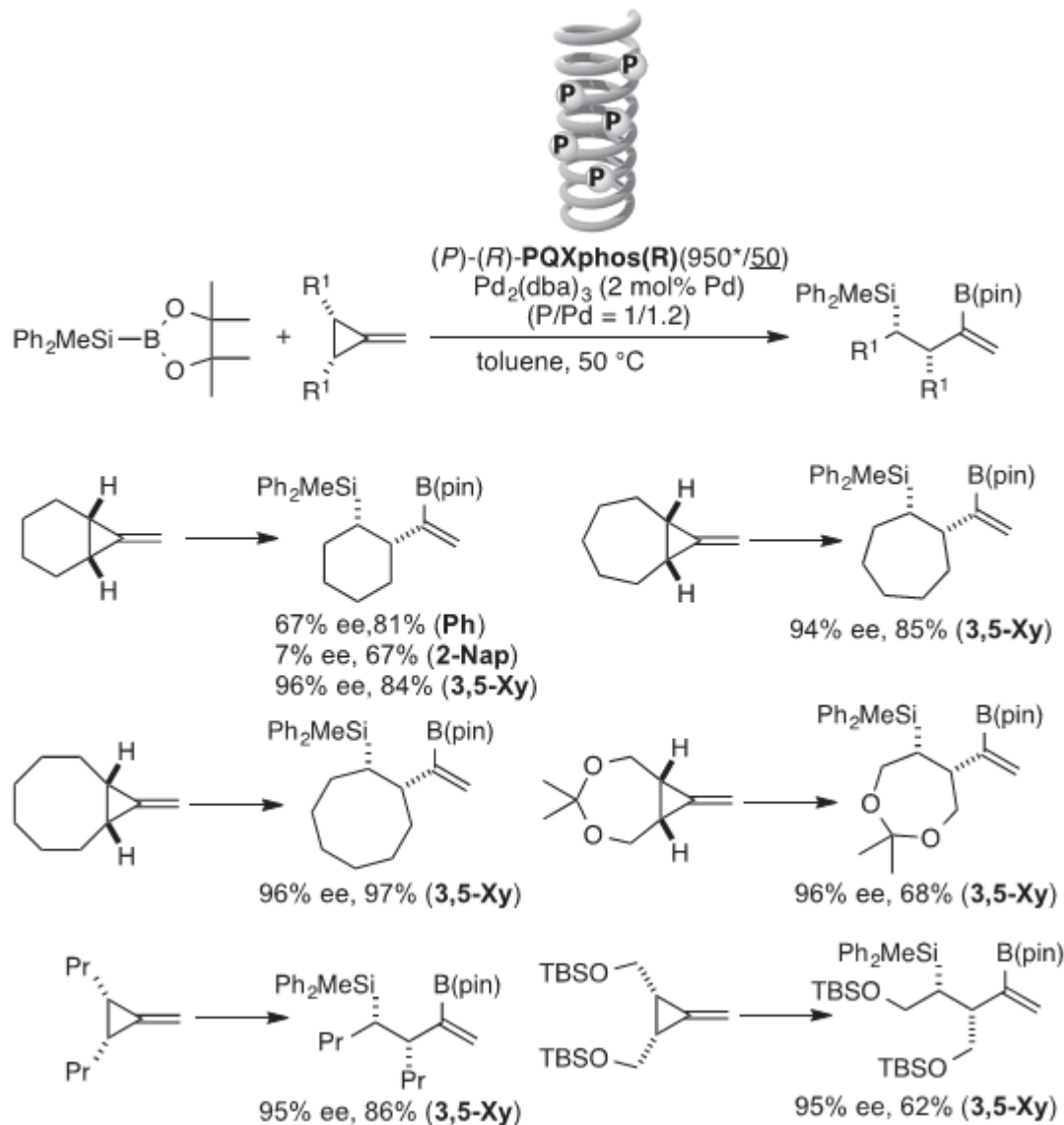


Asymmetric Suzuki-Miyaura cross-coupling of 1-bromo-2-naphthoates



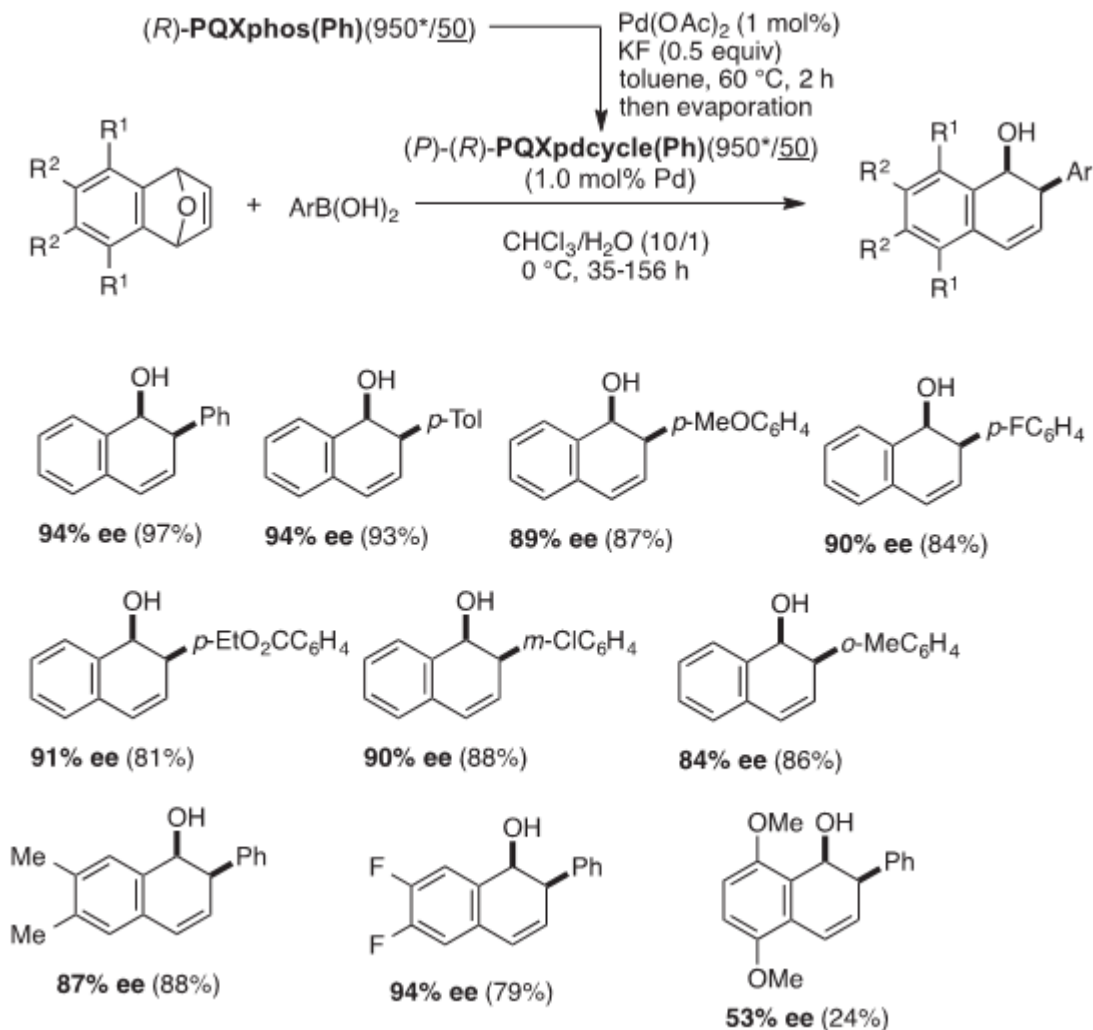


Asymmetric Silaborative Cleavage of meso-Methylenecyclopropanes





Asymmetric desymmetrization through arylative ring opening of 1,4-dihydro-1,4-epoxynaphthalenes with arylboronic acids



Q&A

Q. 高温でも適用可能か?

- A. 関連論文を見る限り高くても50°C程度での反応となっています。
らせん反転は60°Cで起こるので、それ以上の温度で反応をかけると生成物の ee の低下などが生じるのかもしれませんが。

J. Am. Chem. Soc. **2012**, *134*, 11092-11095

Q. ランダムポリマーの三連子構造のマイクロ構造はどうなっているのか?

- A. ランダム共重合で合成されるため完全にランダムになっているはずですが
キラル側鎖を持つモノマーユニットが高分子末端に来ると se が低下する傾向にあるため
40mer 程度の重合度の場合にはブロック共重合などでキラルモノマーが末端に来ないように
制御する必要がありますが、重合度が上がるほどキラルモノマーが末端に来る確率が
下がるためランダム共重合での合成が可能になります。

J. Am. Chem. Soc. **2013**, *135*, 10104-10113

Q. ホスフィンが入る位置による反応への影響は?

- A. ホスフィンユニットが末端に来るとエナンチオ選択性を失うようです。
ただし、ホスフィンユニットが連続してしまっても生成物の選択性に影響はないようです。

Angew. Chem. **2009**, *121*, 547-550

Q. 何merくらいが反応効率が最大になる?

A. 重合度と反応収率の関係について記述された論文は見つけれませんでした。らせんのselは重合度が高いほど高くなるため、1000mer程度のPQXphosを使う場合が多いように感じます。

また40mer程度の重合度で配位子として使う場合には、キラルモノマーがポリマー末端にこないように制御する必要があるため、低重合度で効率よく反応を進行させたい場合には、ポリマーの重合段階で手間が増えてしまいます。

Angew. Chem. **2009**, 121, 547-550

Q. P, M, selはどうやって決めているのか?

A. らせんの回転方向は、5mer程度のオリゴマーについてX線構造解析を行い、CDスペクトルの結果と対応させたようです。

selはスライド内で述べたように、実測値の g_{abs} と計算値の g_{max} との比によって算出されます。

J. Synth. Org. Chem., Jpn. **2015** 73, 1141-1155