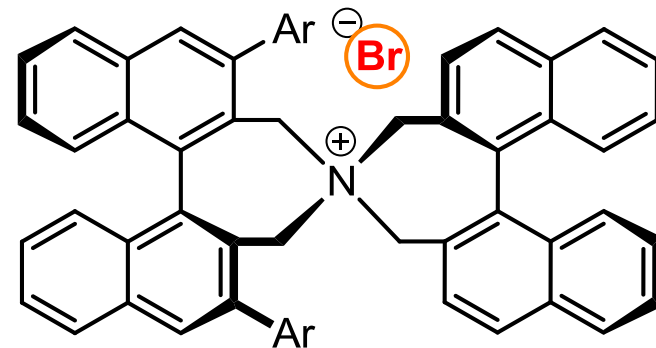
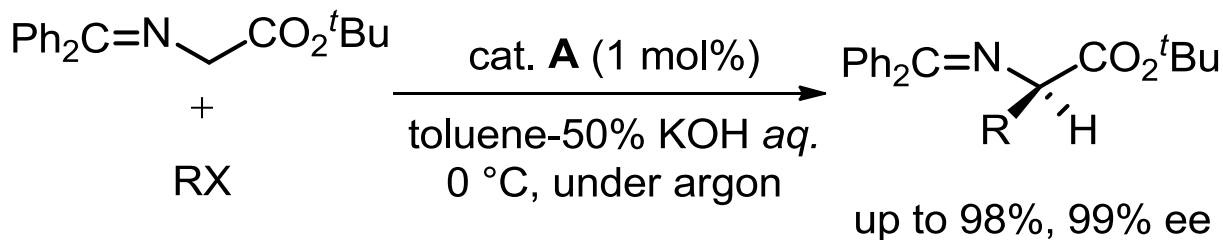


**Development of Ion-Pair Cooperative Asymmetric  
Catalyses of Chiral Tetraaminophosphonium Salts  
Possessing Functional Organic Anions**

**Yusuke Ueki**

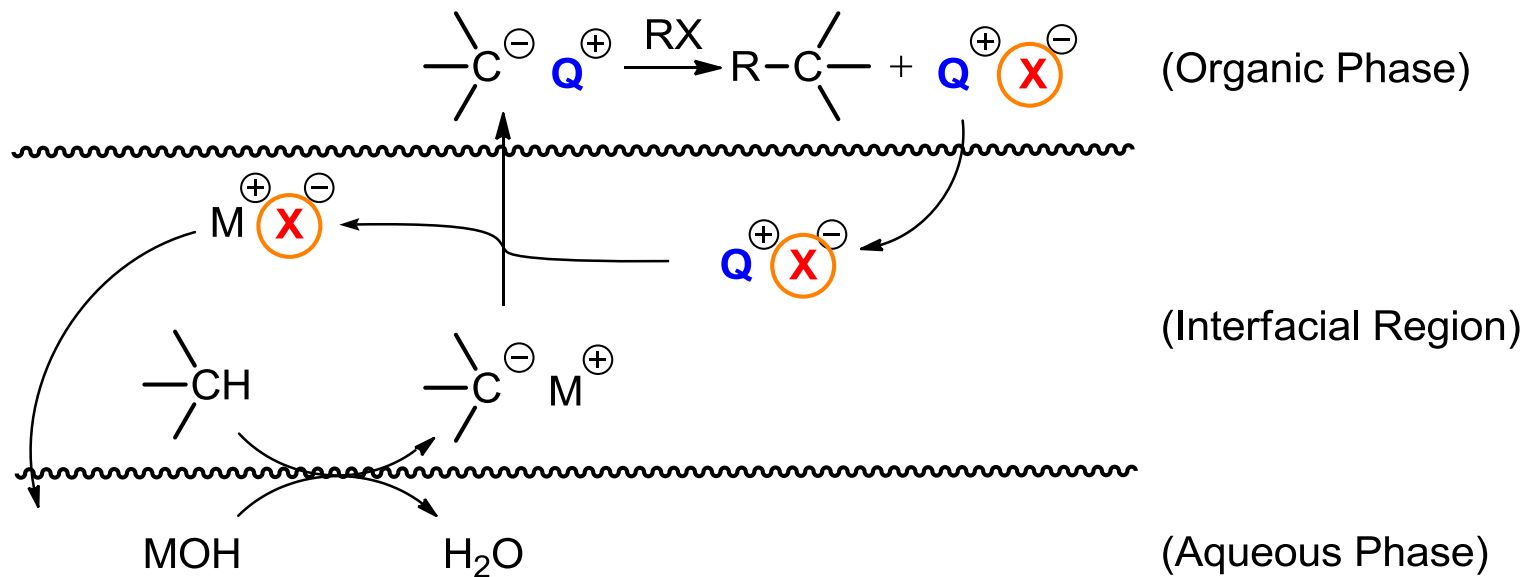
# Onium Salts for Phase-Transfer Catalyst



cat. **A**  
 (Ar = 3,4,5-F<sub>3</sub>-C<sub>6</sub>H<sub>2</sub>)

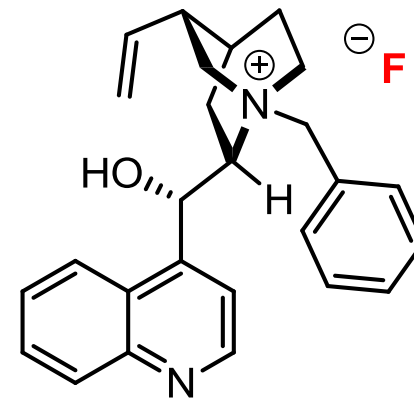
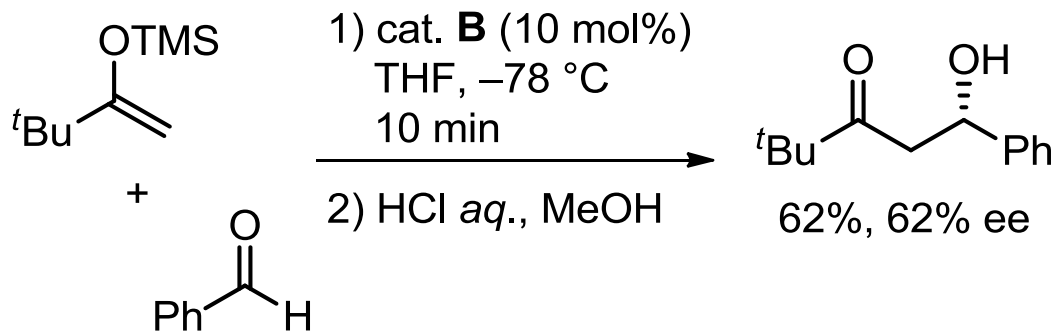
Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, 125, 5139.

## Plausible Mechanism



$\text{Q}^+$  : quaternary ammonium cation     $\text{M}^+$  : alkaline metal ion

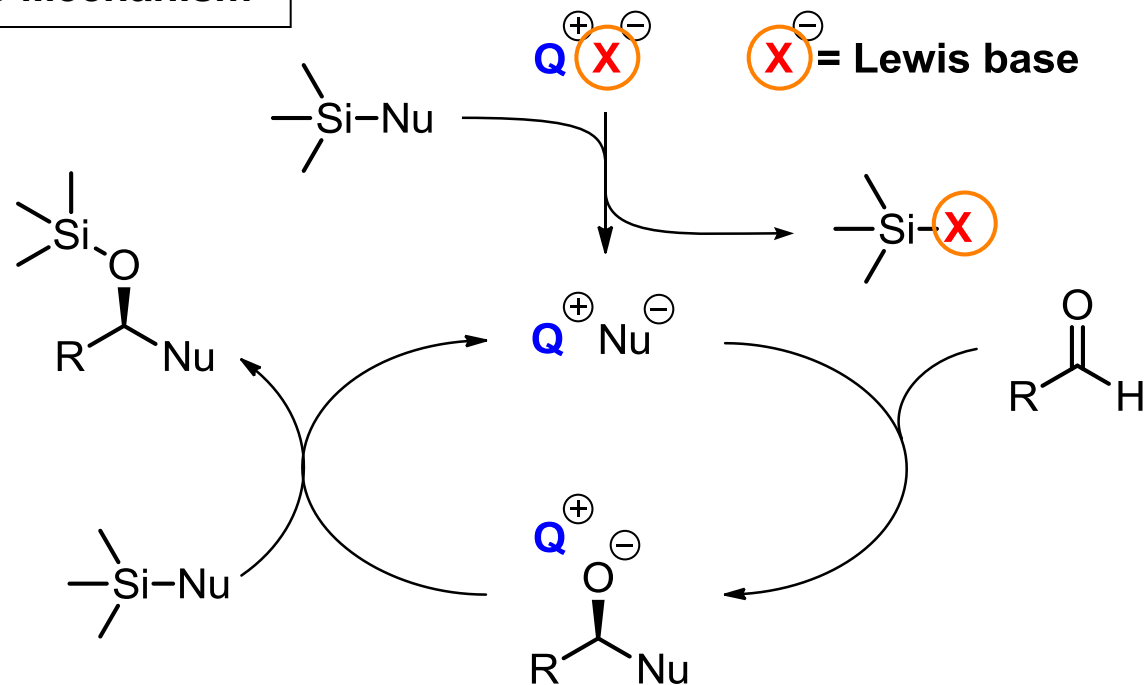
# Example of Homogeneous Onium Salt Catalysis



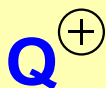
cat. **B**

Ando, A.; Miura, T.; Tatematsu, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, 34, 1507.

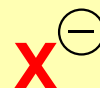
## Plausible Mechanism



# Example of Homogeneous Onium Salt Catalysis



controlling the reactivity  
and selectivity



neutralizing the charge  
initiation of the reaction

*continuous participation  
in the catalytic cycle*

controlling the reactivity  
and selectivity

*a new cooperative catalysis of chiral onium salts  
possessing an appropriate organic anion*

# Characteristic Features of Catalyst

Amino Acid Derived Alkyl Substituent

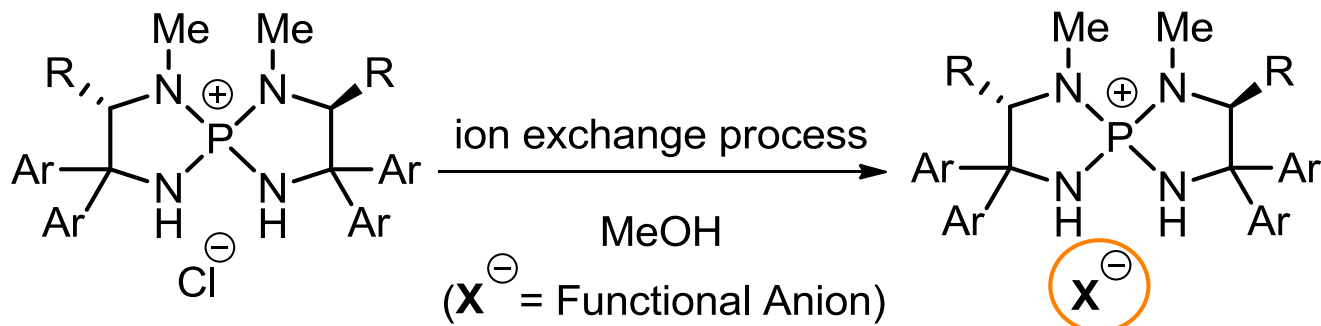
Selective Alkylation

[5,5]-P-spirocyclic Core

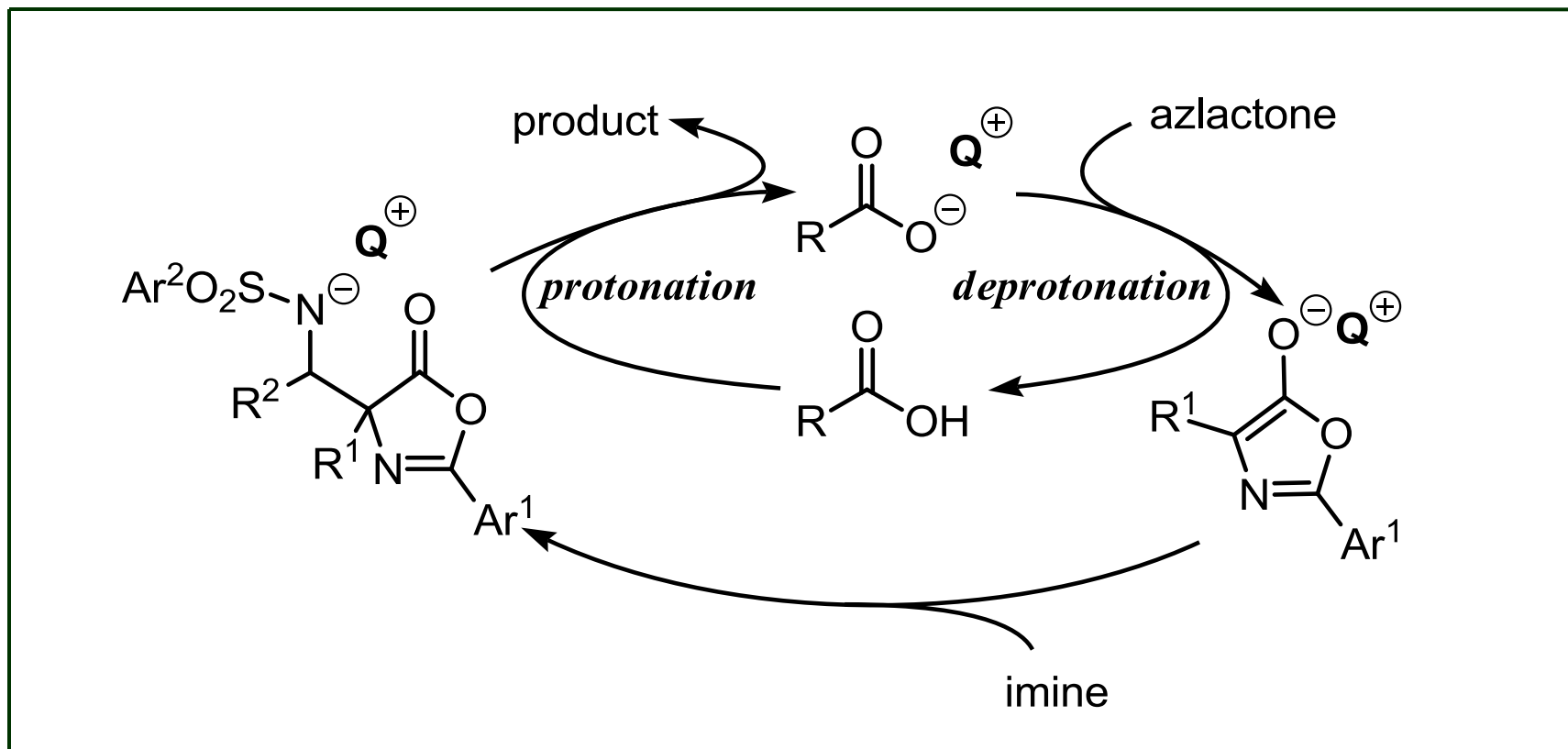
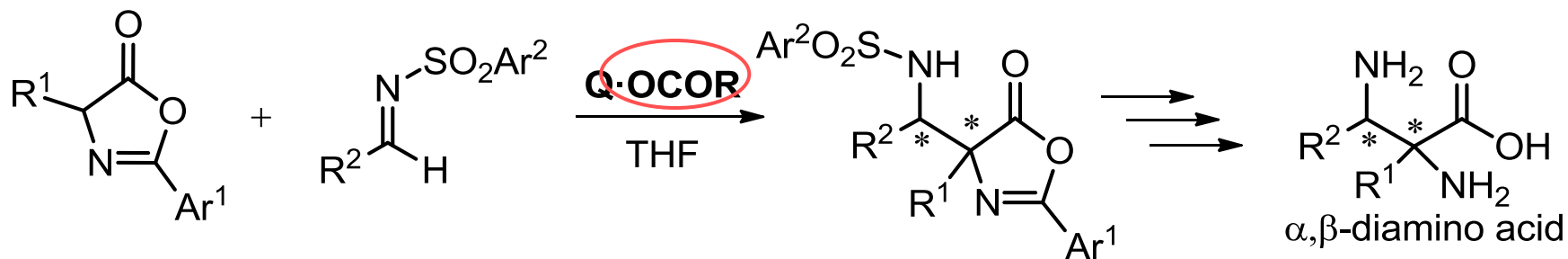
Variable Ar Substituents

Anion Recognition via Double Hydrogen-Bonding

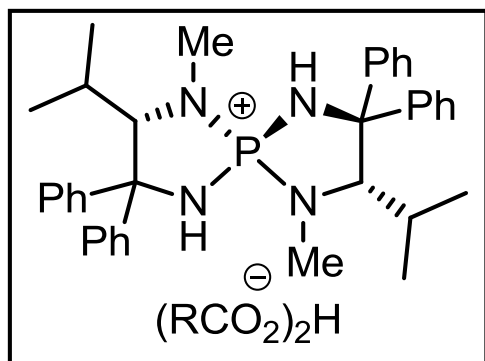
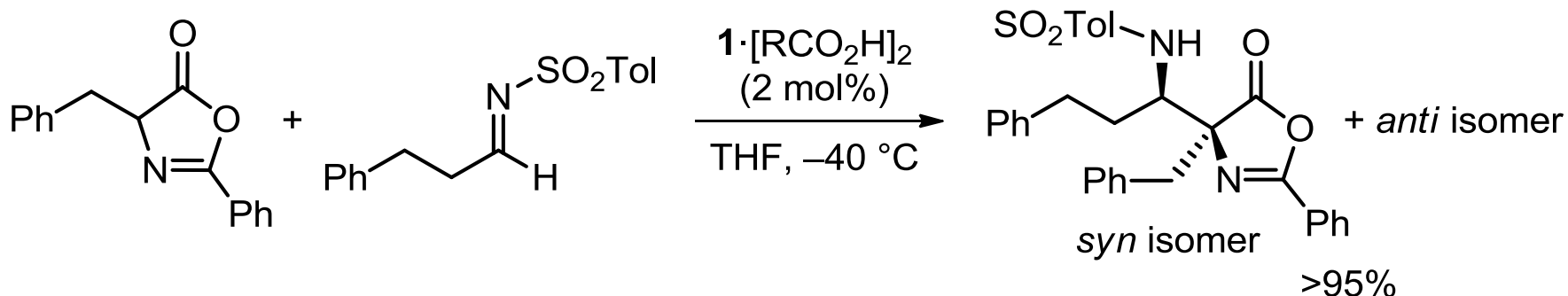
Catalyst Preparation: Ion Exchange



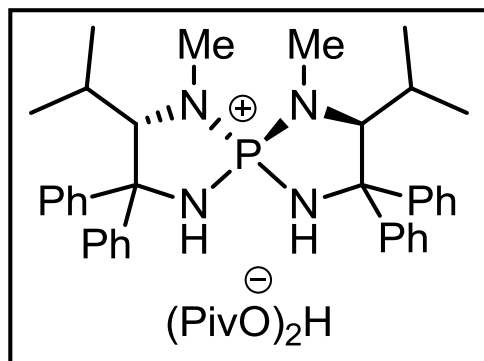
# Working Hypothesis



# Effect of Catalyst on Reactivity and Selectivity



$1\mathbf{a}_M \cdot [\text{RCO}_2\text{H}]_2$



$1\mathbf{a}_P \cdot [\text{PivOH}]_2$

$1\mathbf{a}_M = (M,S)$ ,  $1\mathbf{a}_P = (P,S)$

$1\mathbf{a}_M \cdot [\text{HCO}_2\text{H}]_2$  : 3.5 h, *syn/anti* = 1.3:1  
6% ee, (*syn isomer*)

$1\mathbf{a}_M \cdot [\text{AcOH}]_2$  : 2 h, 1.2:1, 5% ee

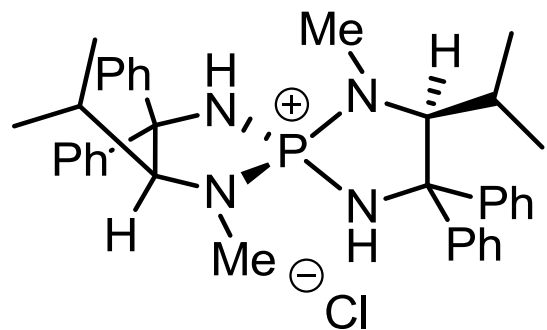
$1\mathbf{a}_M \cdot [\text{PivOH}]_2$  : 0.5 h, 1.3:1, 6% ee

$1\mathbf{a}_P \cdot [\text{PivOH}]_2$  : 1 h, 1.6:1, 60% ee

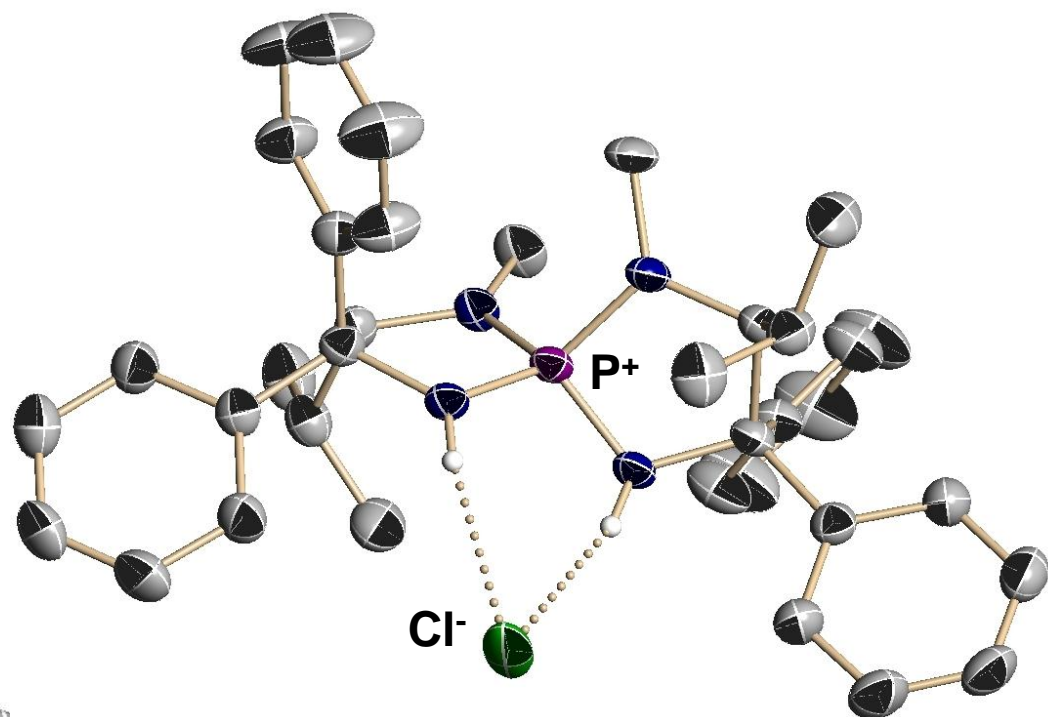
## $\text{pK}_a$ of carboxylic acid in $\text{H}_2\text{O}$

$\text{HCO}_2\text{H}$	3.77
$\text{AcOH}$	4.76 (12.6 in DMSO)
$\text{PivOH}$	5.03

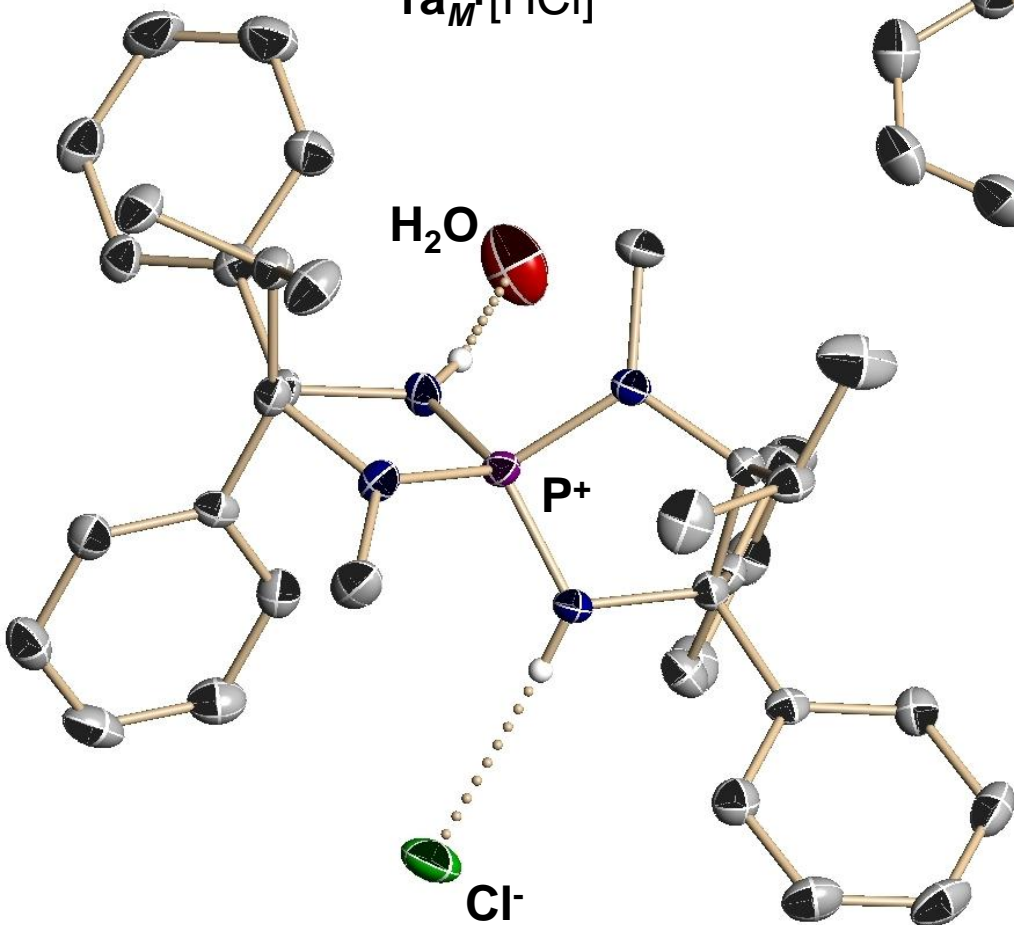
# Hydrogen-Bonding Mode of Phosphonium Salts



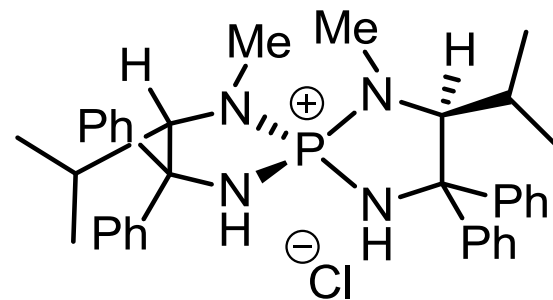
$1a_M$  [HCl]



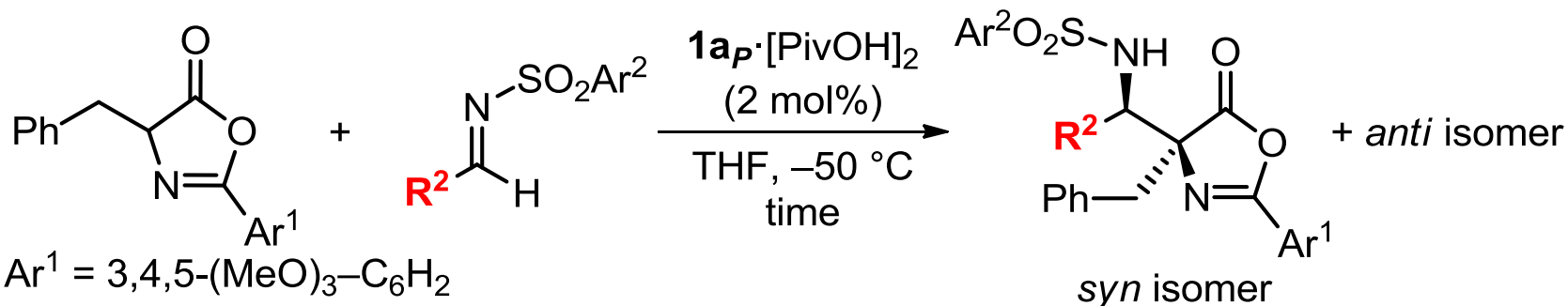
$1a_P$  [HCl]



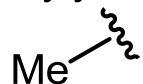
Cl<sup>-</sup>



# Scope of Imines



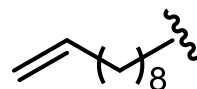
$R^2 =$



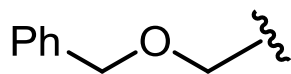
12 h, 91%  
*syn/anti* = 4.5:1  
 92% ee



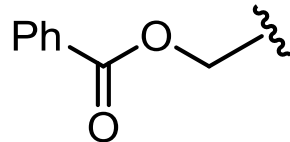
20 h, 92%  
 6.6:1, 96% ee



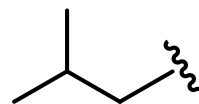
21 h, 99%  
 7.6:1, 96% ee



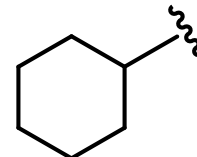
14 h, 98%  
 5.3:1, 95% ee



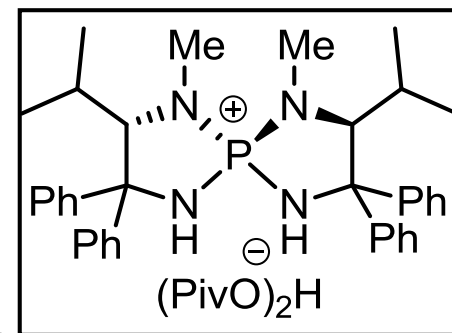
24 h, 88%  
 12:1, 92% ee



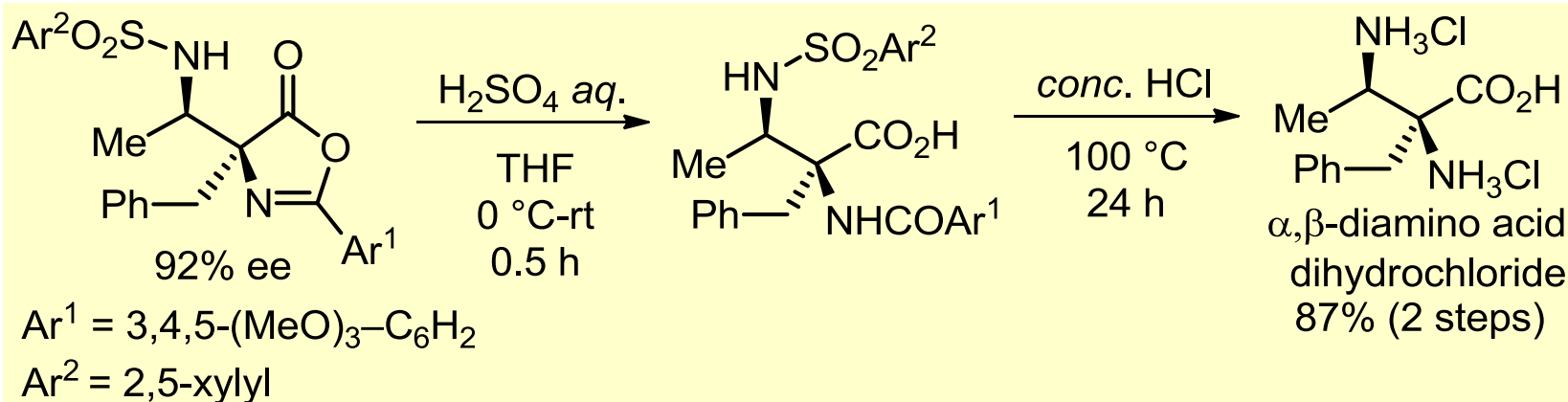
17 h, 94%  
 4.4:1, 95% ee



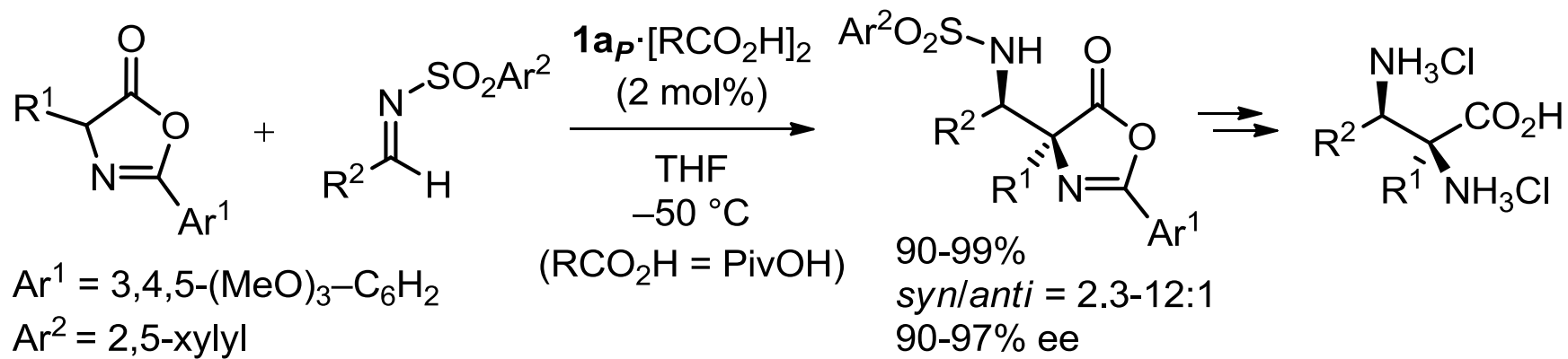
37 h, 98%  
 2.3:1, 90% ee



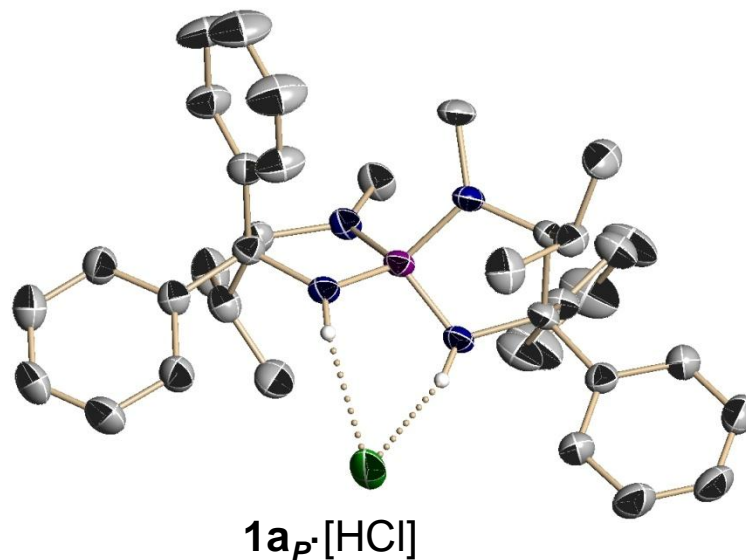
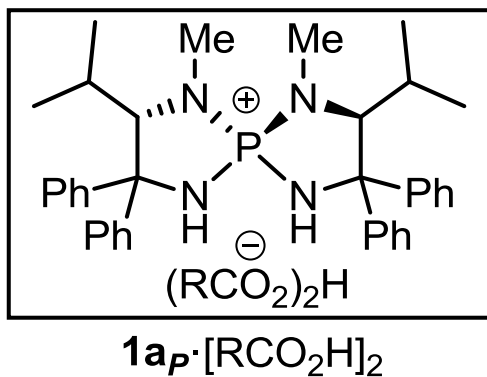
$1a_P \cdot [PivOH]_3$



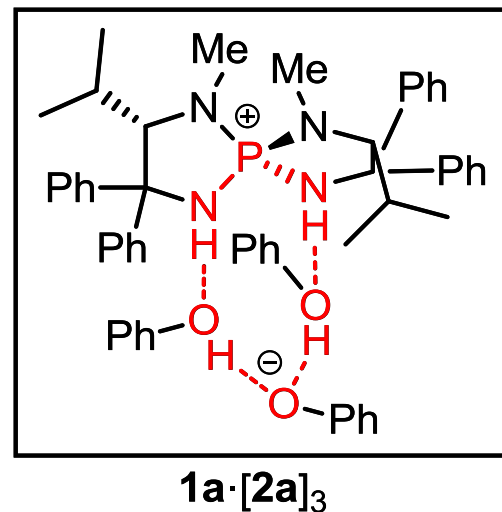
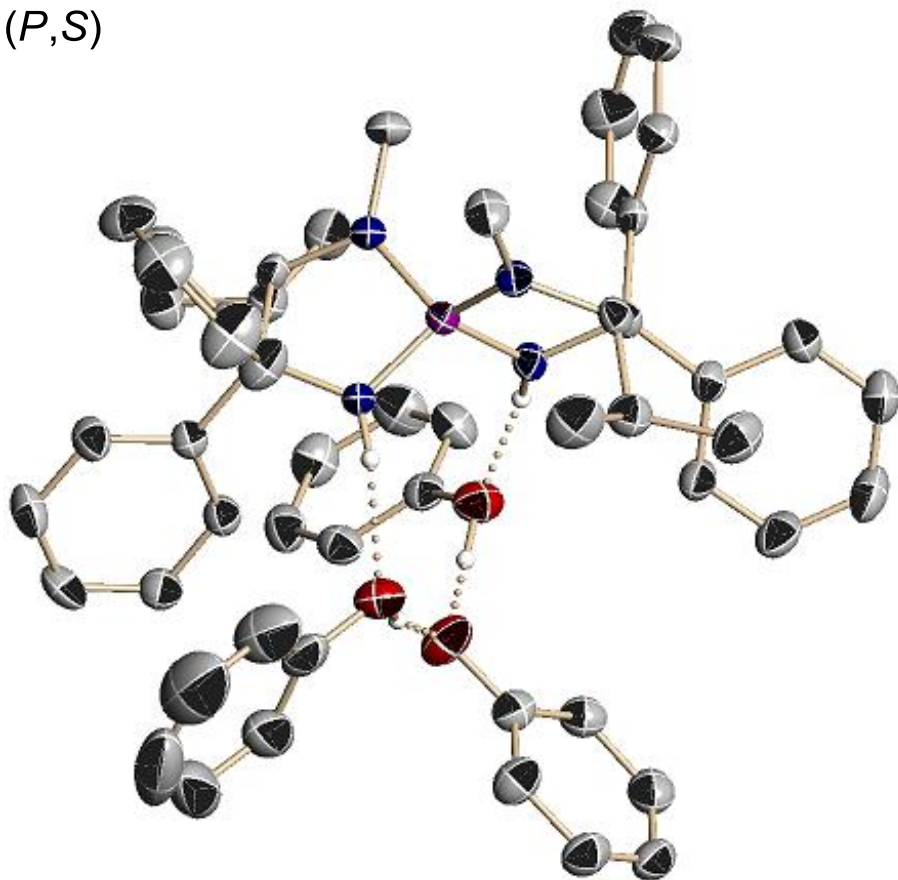
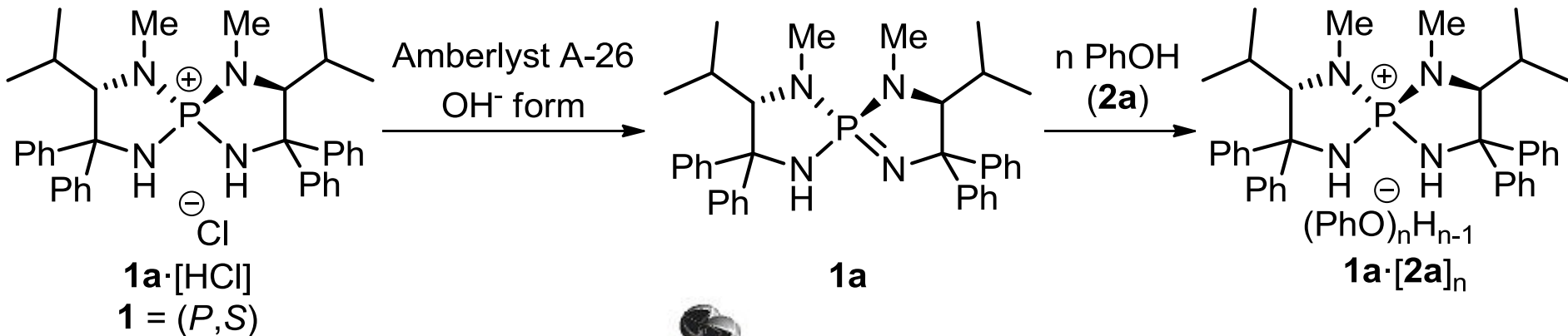
# Summary 1



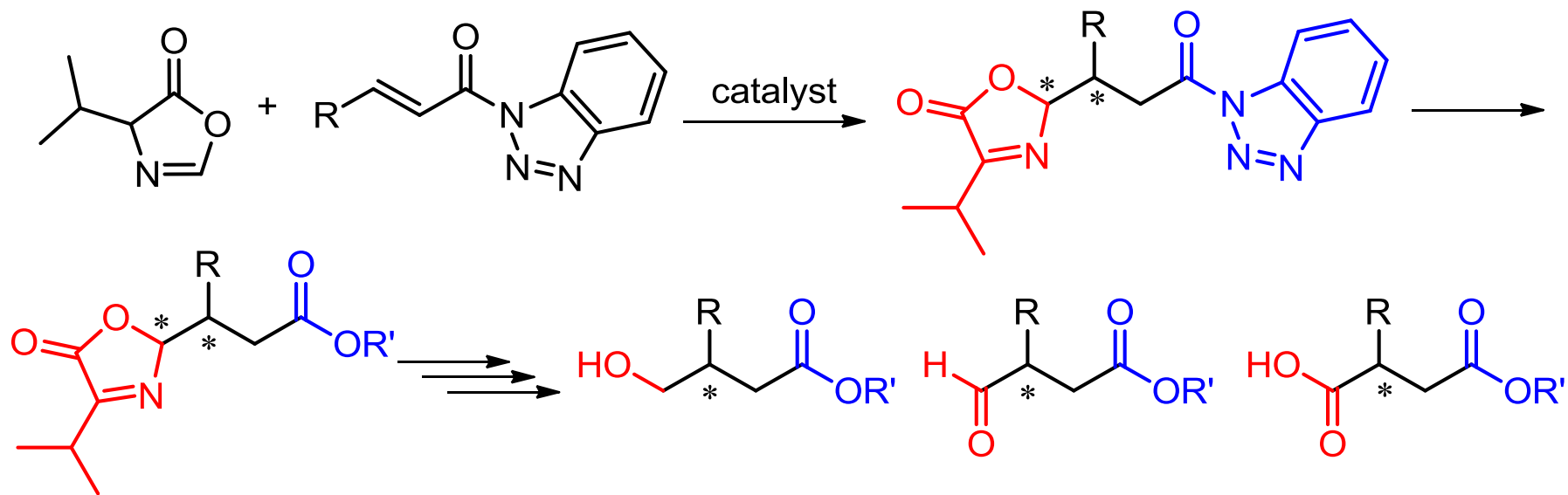
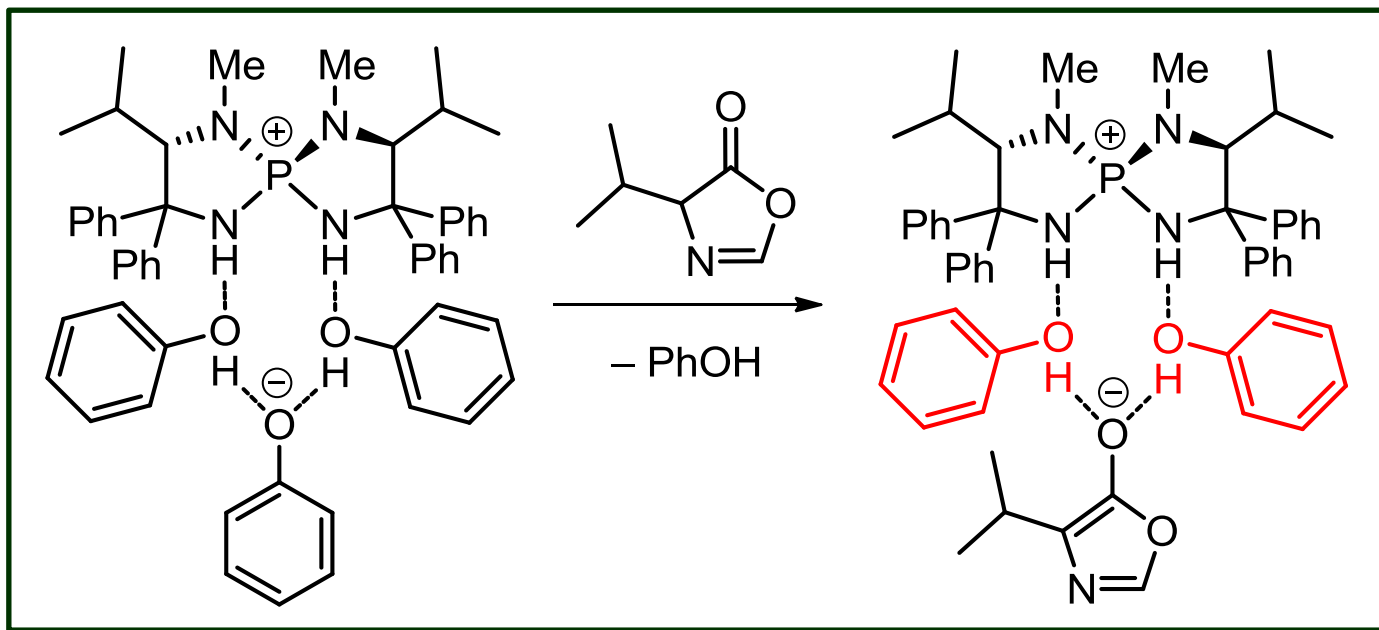
Uraguchi, D.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 14088.



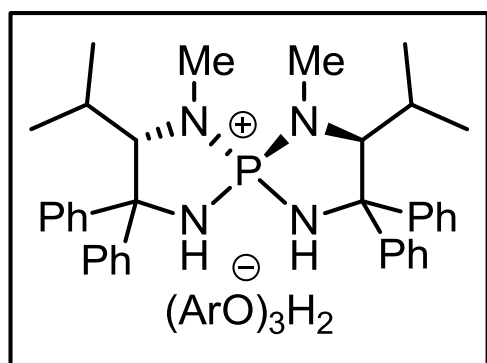
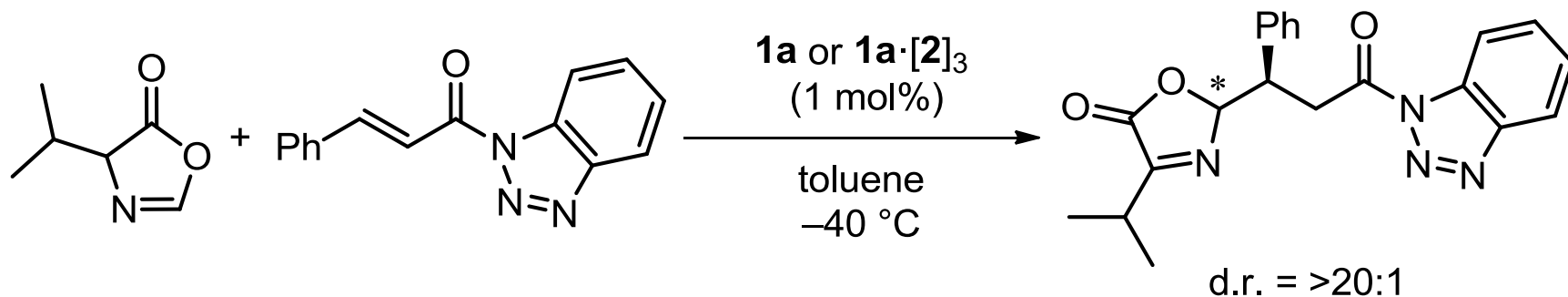
# Preparation and Structure of Phosphonium Phenoxide



# Conjugate Addition of Acyl Anion Equivalent

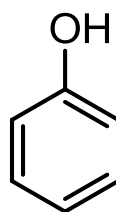


# Effect of Counter Anion Structure on the Selectivity

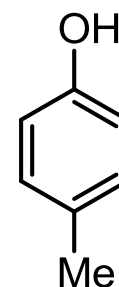


**1a·[2]<sub>3</sub>**

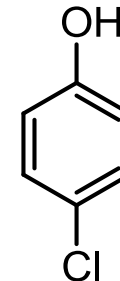
2 =



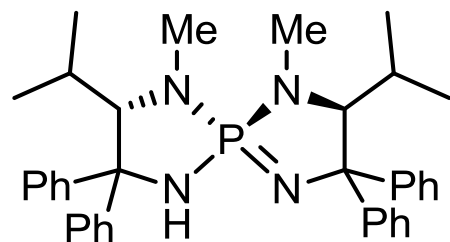
6 h, 99%  
60% ee



4 h, 96%  
58% ee

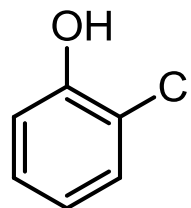


10 h, 97%  
75% ee

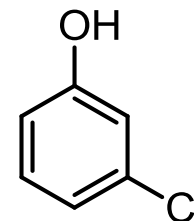


**1a**

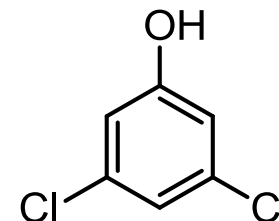
2 h, 99%  
34% ee



12 h, 94%  
63% ee

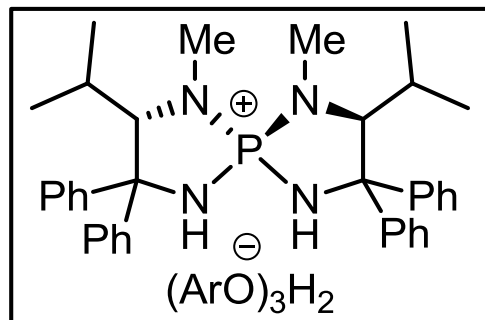
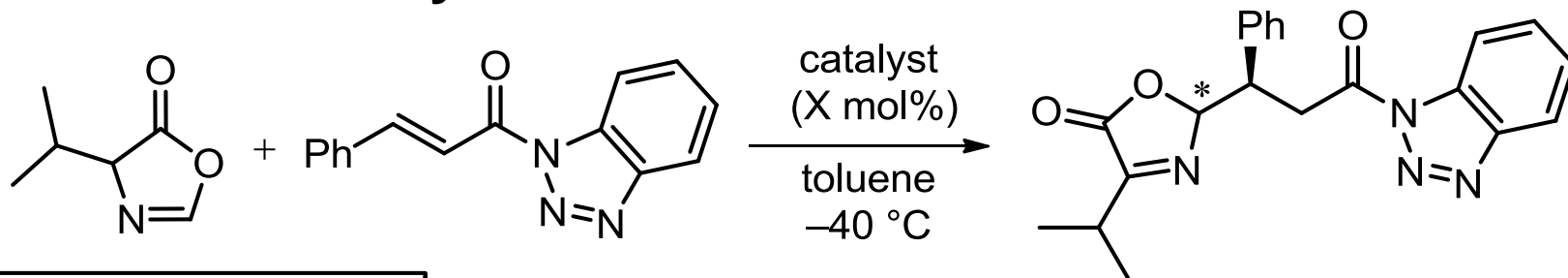


6 h, 93%  
70% ee



16 h, 92%  
80% ee

# Effect of Catalyst Concentration and Cation Structure

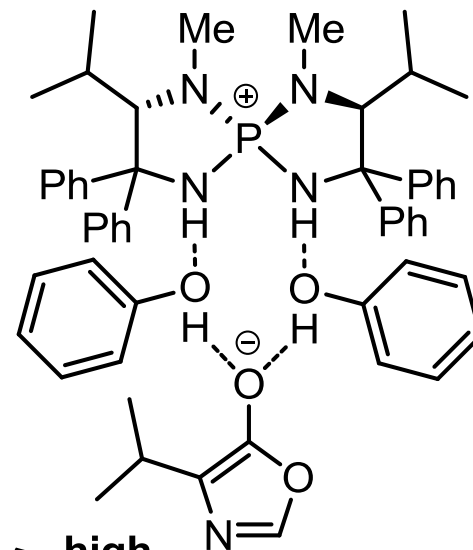
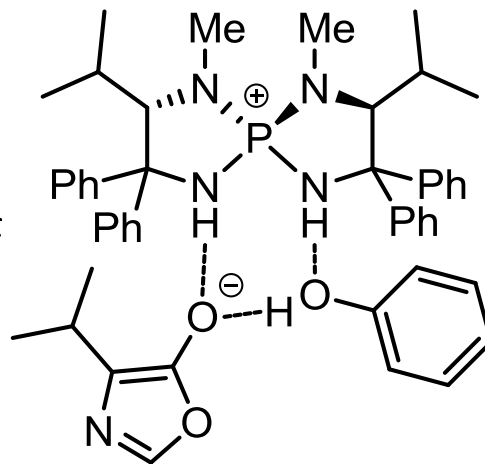
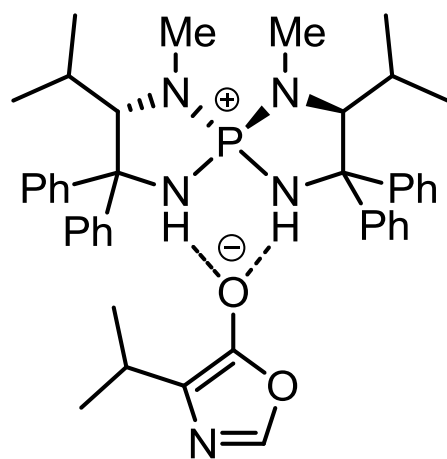


**1a·[2b]<sub>3</sub>**  
(Ar = 3,5-Cl<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>)  
dilute

X	Conc. (Catalyst)	Conc. (Substrate)	ee (%)
1 mol%	1 mM	0.1 M	80% ee
1 mol%	10 mM	1.0 M	87% ee
10 mol%	10 mM	0.1 M	89% ee

concentration

concentrate

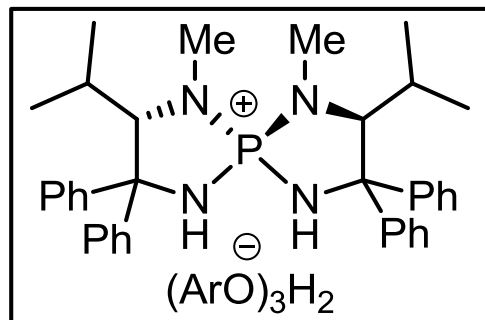
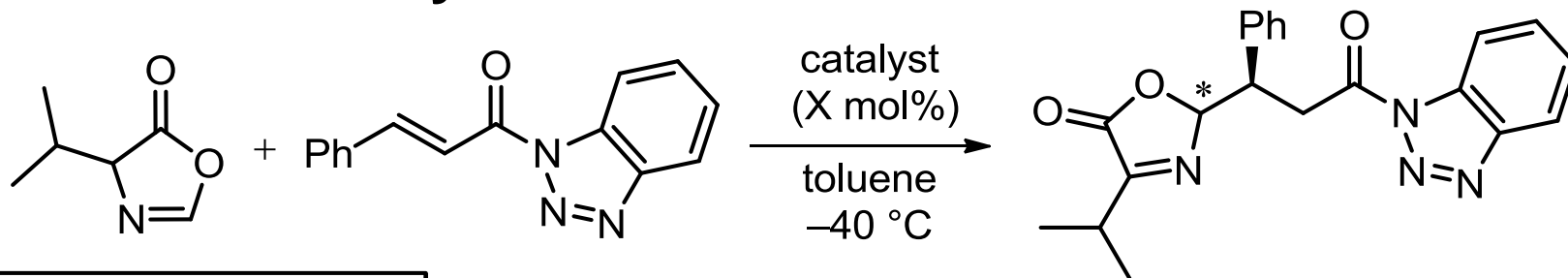


low

enantioselectivity

high

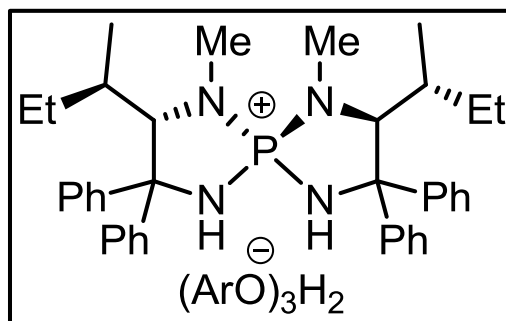
# Effect of Catalyst Concentration and Cation Structure



**1a**·[**2b**]<sub>3</sub>

(Ar = 3,5-Cl<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>)

X	Conc. (Catalyst)	Conc. (Substrate)	ee (%)
1 mol%	1 mM	0.1 M	80% ee
1 mol%	10 mM	1.0 M	87% ee
10 mol%	10 mM	0.1 M	89% ee



**1b**·[**2b**]<sub>3</sub>

(Ar = 3,5-Cl<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>)

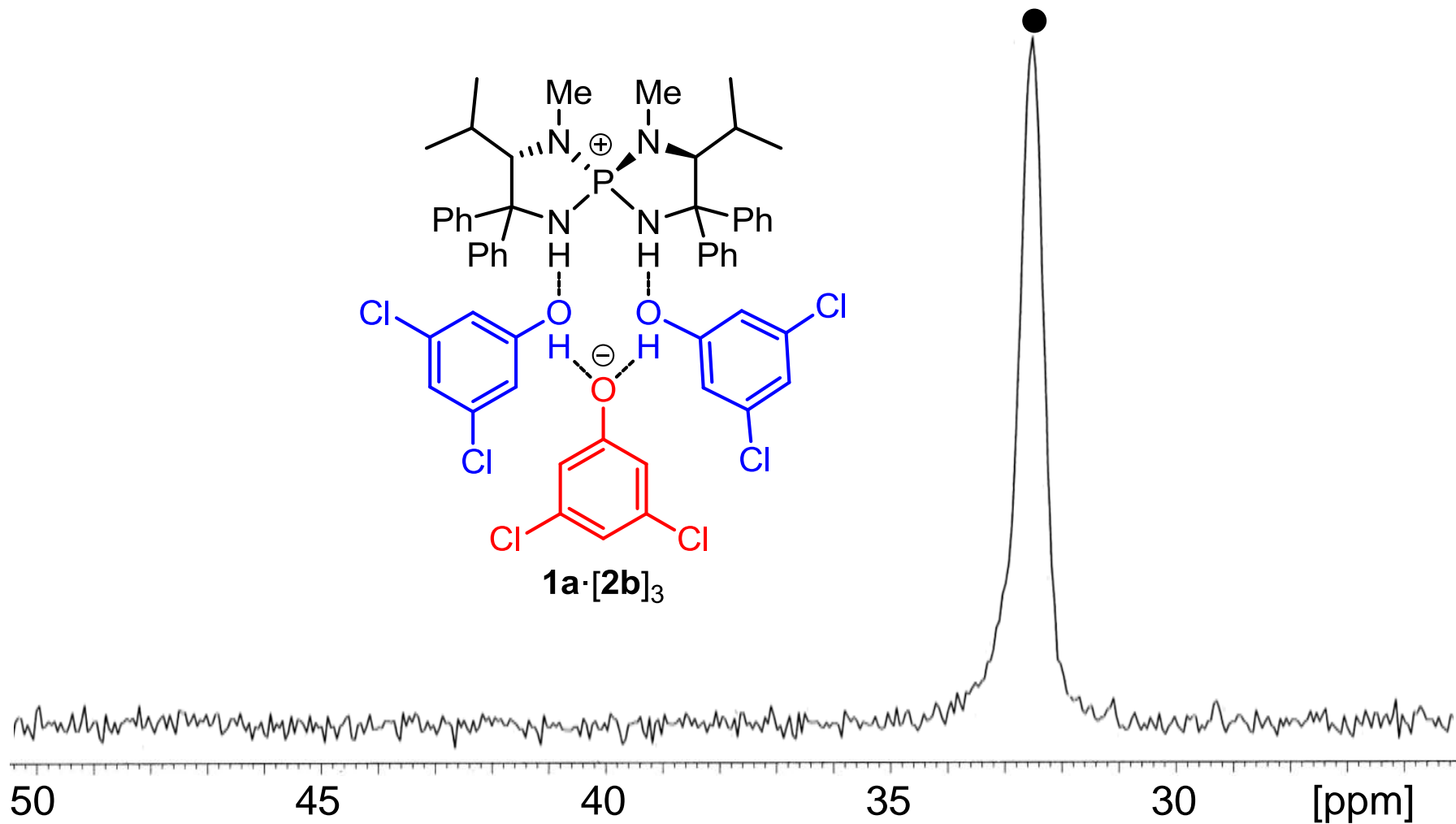
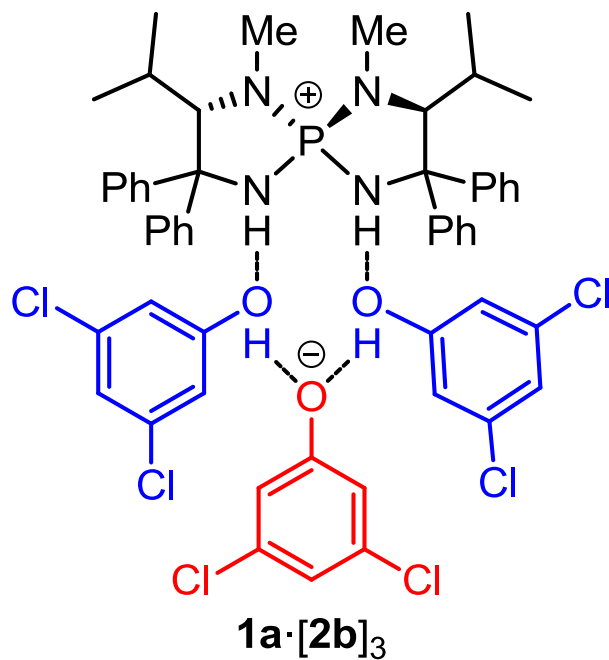
1 mol%, 10 mM\*

4 h, 95%

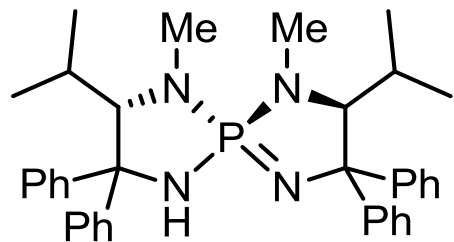
95% ee

\* Concentration was calculated based on the amount of catalyst.

# $^{31}\text{P}$ NMR Study 1: **toluene**, $-98\text{ }^\circ\text{C}$

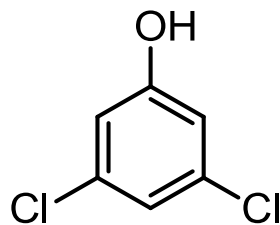


# $^{31}\text{P}$ NMR Study 1: **toluene**, $-98\text{ }^\circ\text{C}$



**1a**

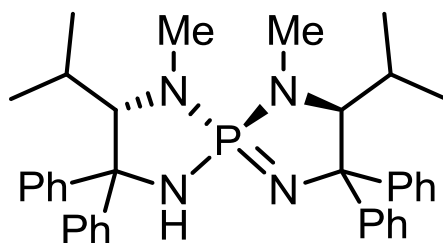
+



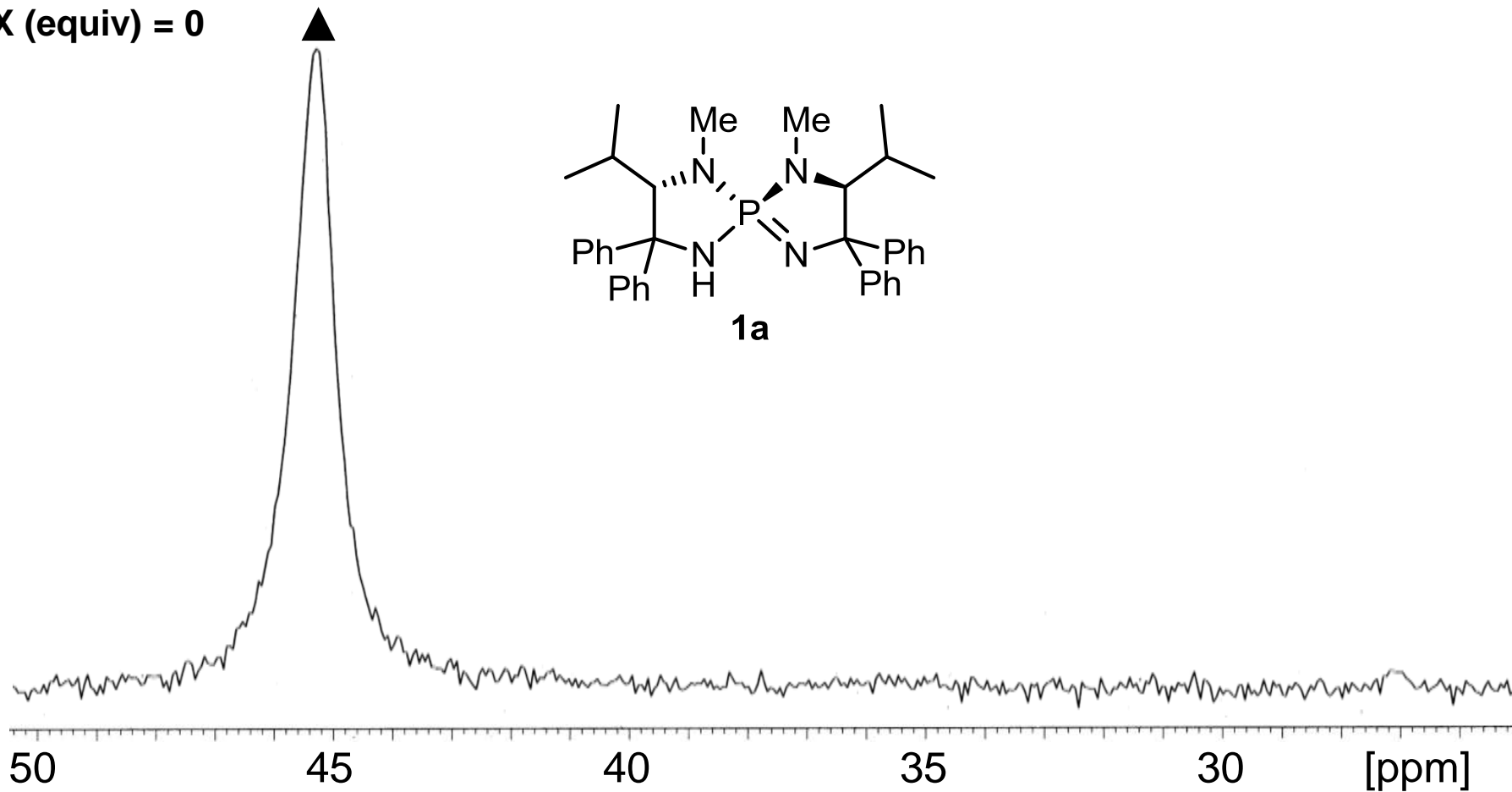
(X equiv)

**2b**

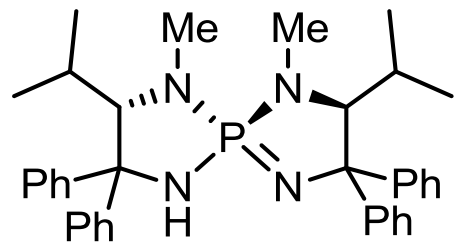
X (equiv) = 0



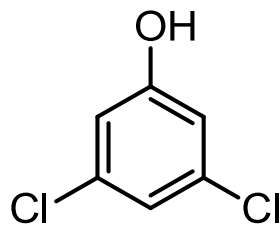
**1a**



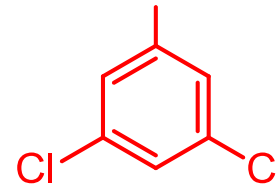
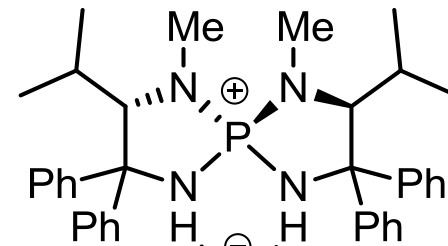
# $^{31}\text{P}$ NMR Study 1: **toluene**, $-98\text{ }^\circ\text{C}$



+

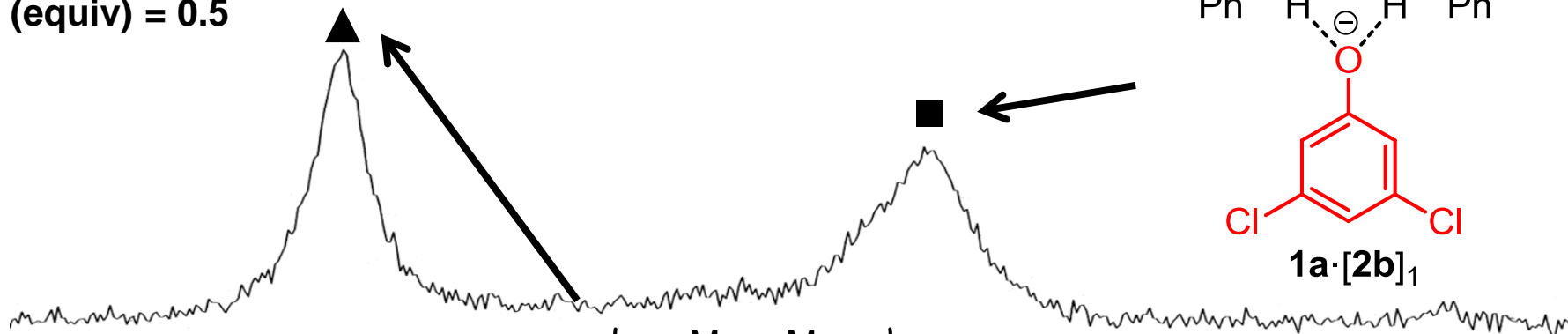


(X equiv)

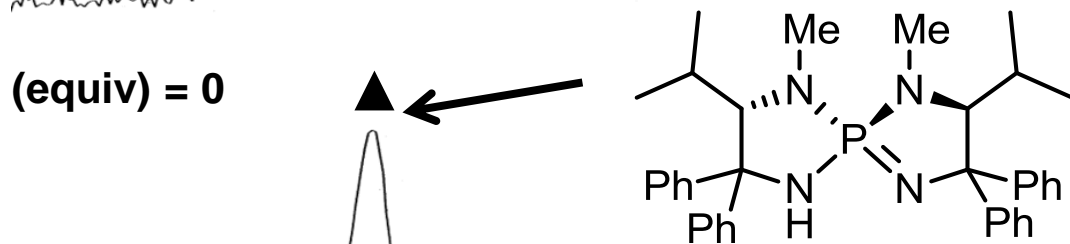


**1a·[2b]<sub>1</sub>**

**X (equiv) = 0.5**

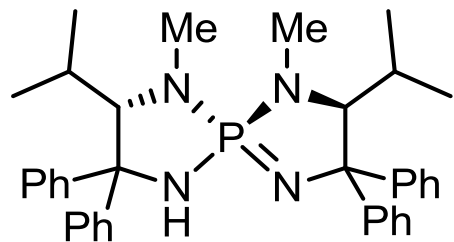


**X (equiv) = 0**

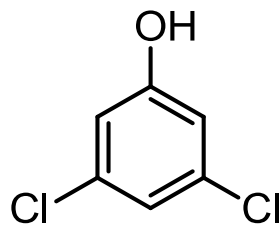


50 45 40 35 30 [ppm]

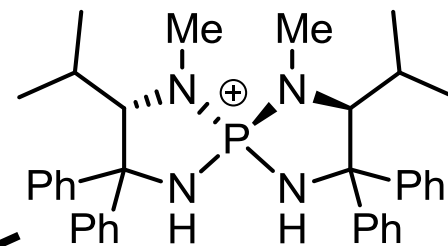
# $^{31}\text{P}$ NMR Study 1: **toluene**, $-98\text{ }^\circ\text{C}$



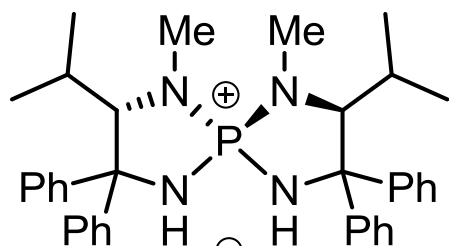
+



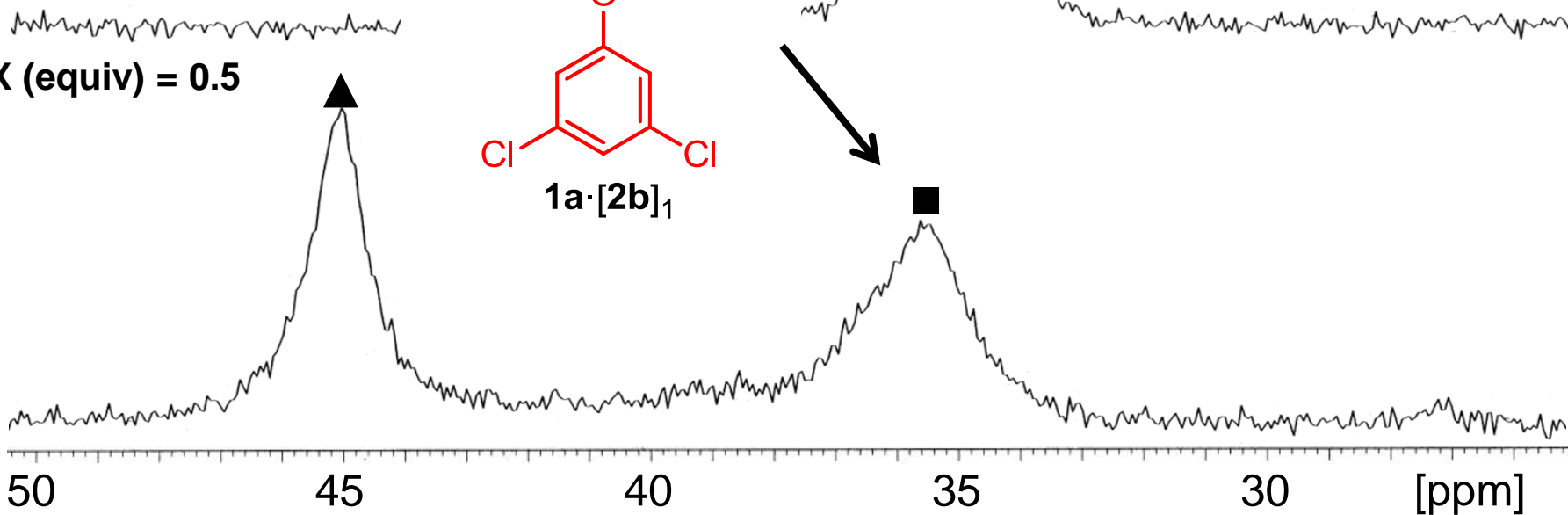
(X equiv)



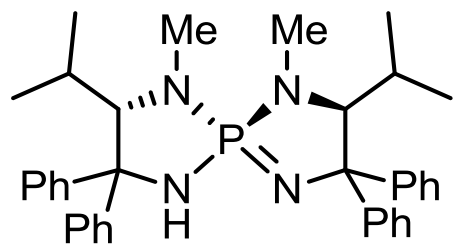
**X (equiv) = 1.5**



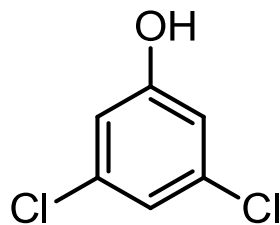
**X (equiv) = 0.5**



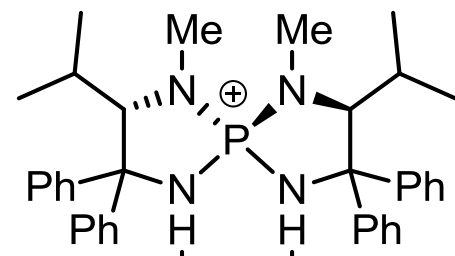
# $^{31}\text{P}$ NMR Study 1: **toluene**, $-98\text{ }^\circ\text{C}$



+



(X equiv)



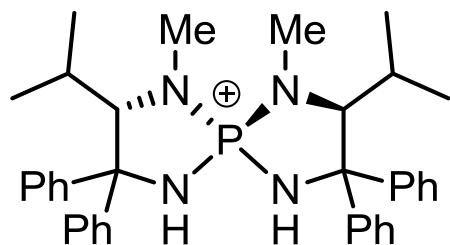
1a

2b

1a·[2b]<sub>3</sub>

X (equiv) = 3

X (equiv) = 2.5



X (equiv) = 1.5

1a·[2b]<sub>2</sub>

50

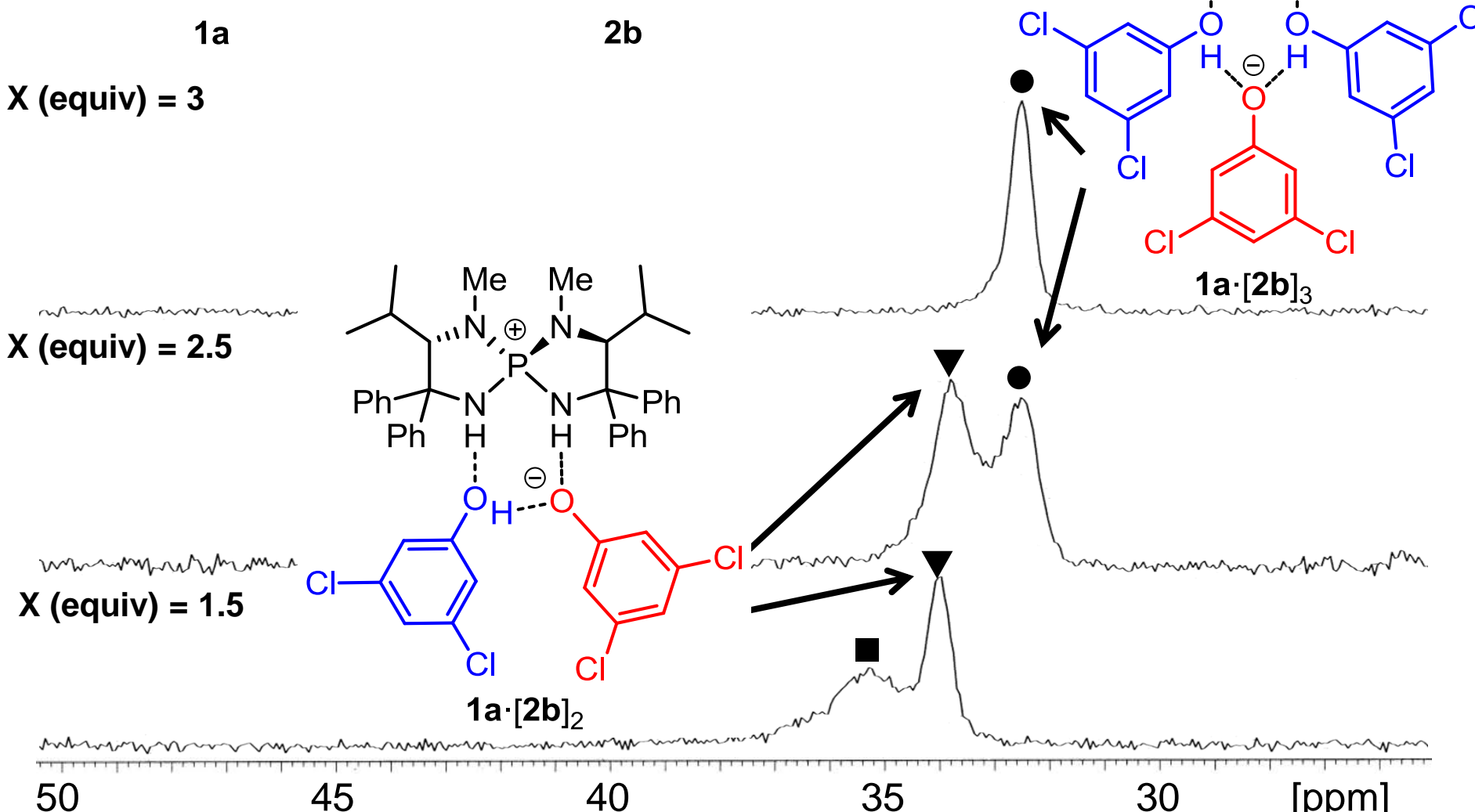
45

40

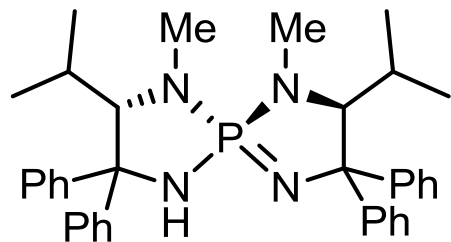
35

30

[ppm]



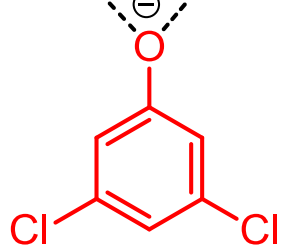
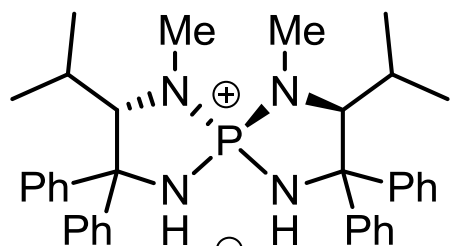
# X-ray Diffraction Analysis



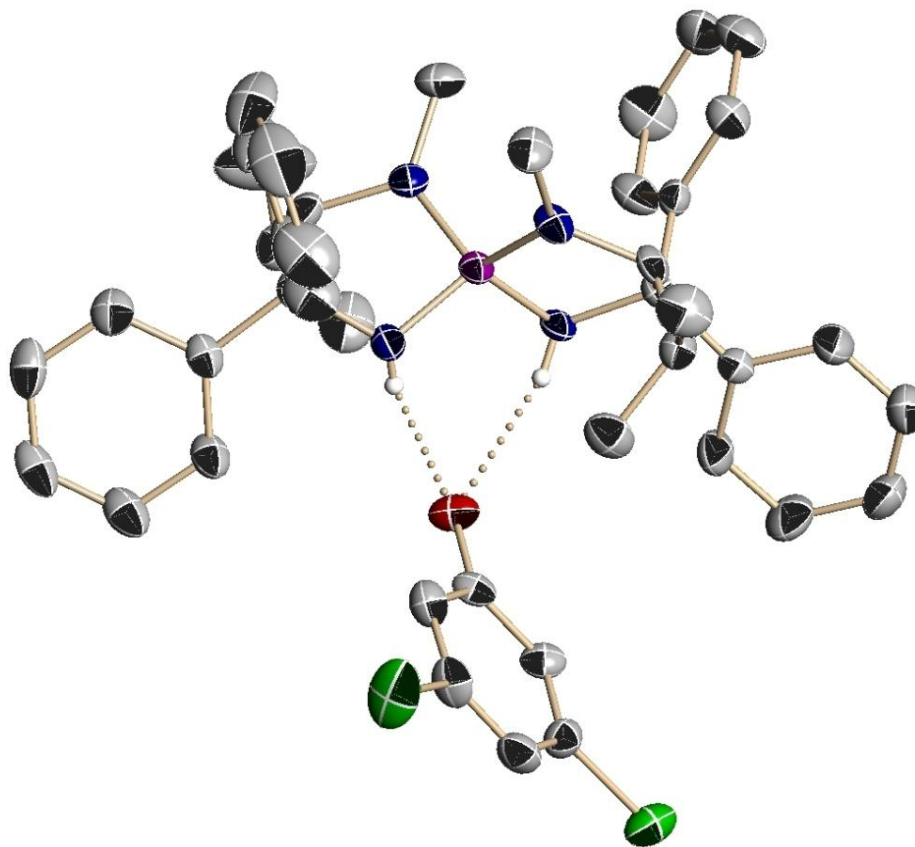
**1a**



1 equiv  
3,5-Cl<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>OH

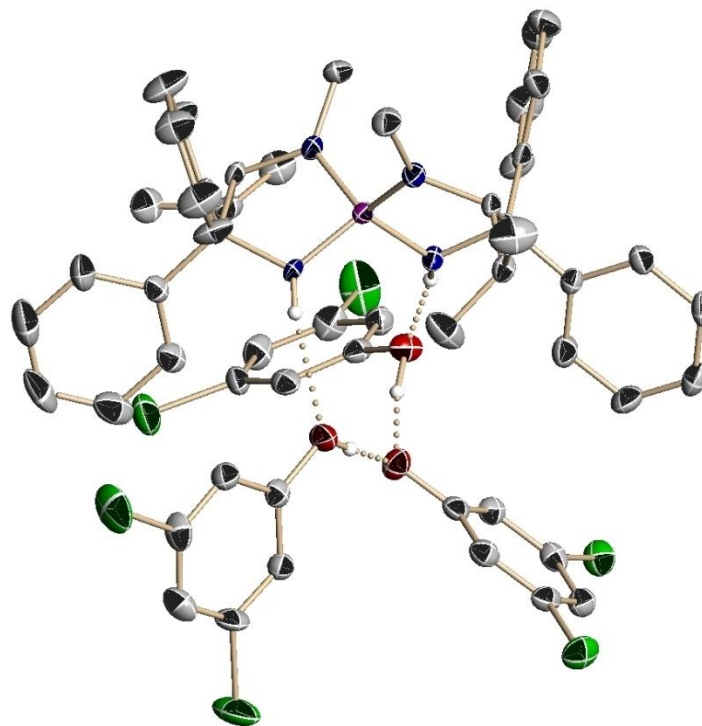
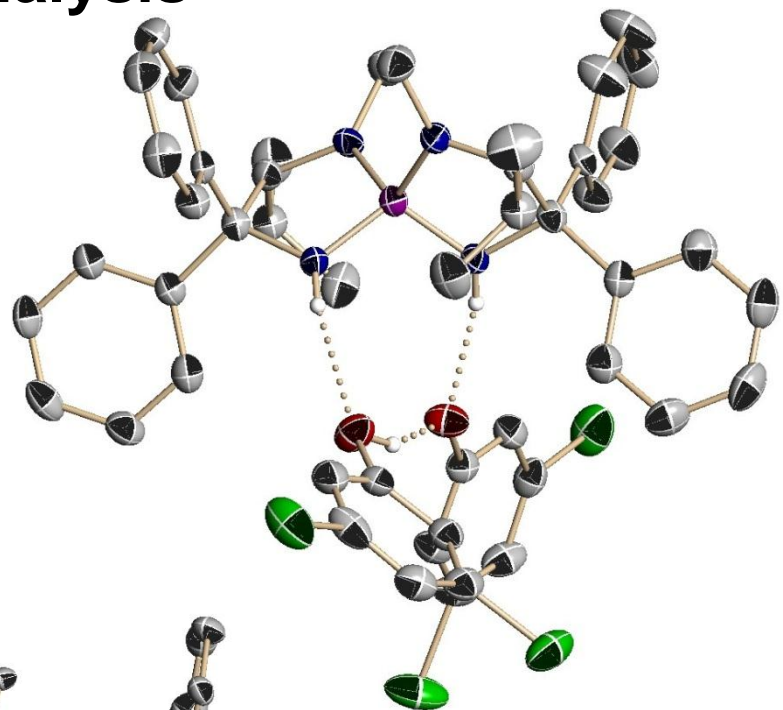
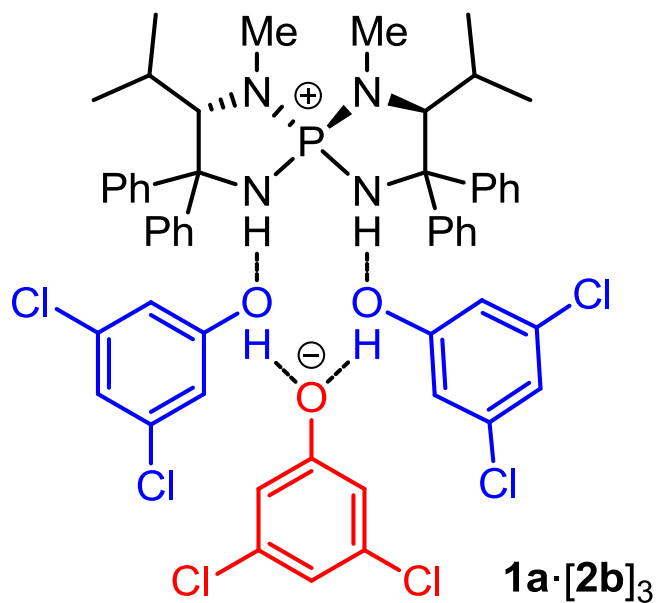
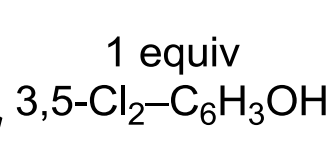
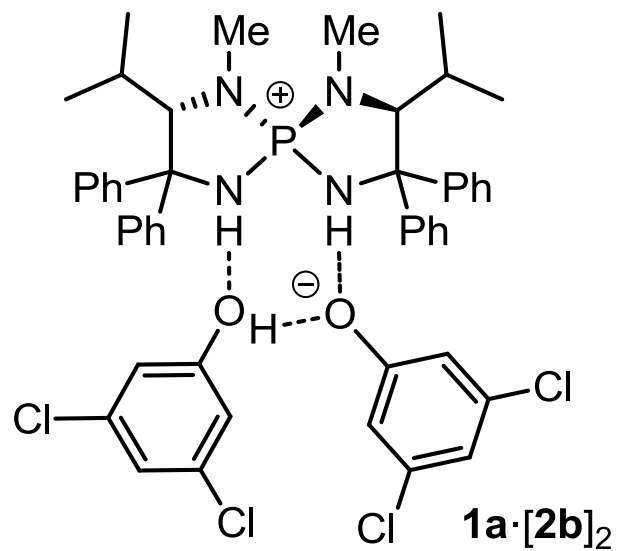


**1a·[2b]<sub>1</sub>**

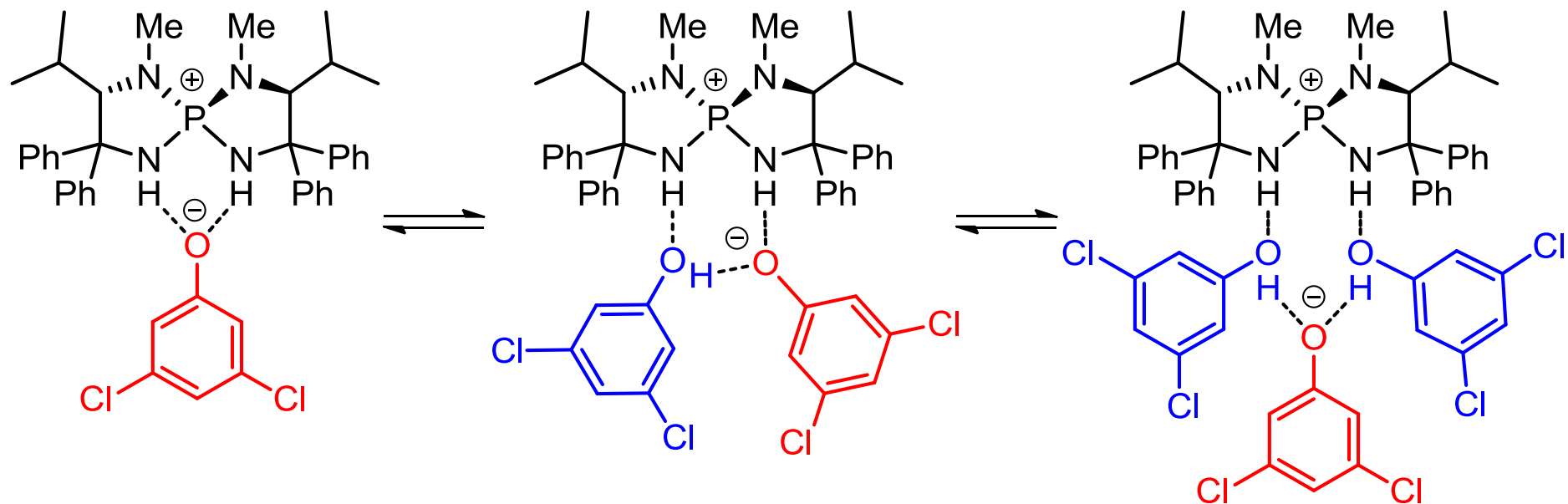




# X-ray Diffraction Analysis



# X-ray Diffraction Analysis



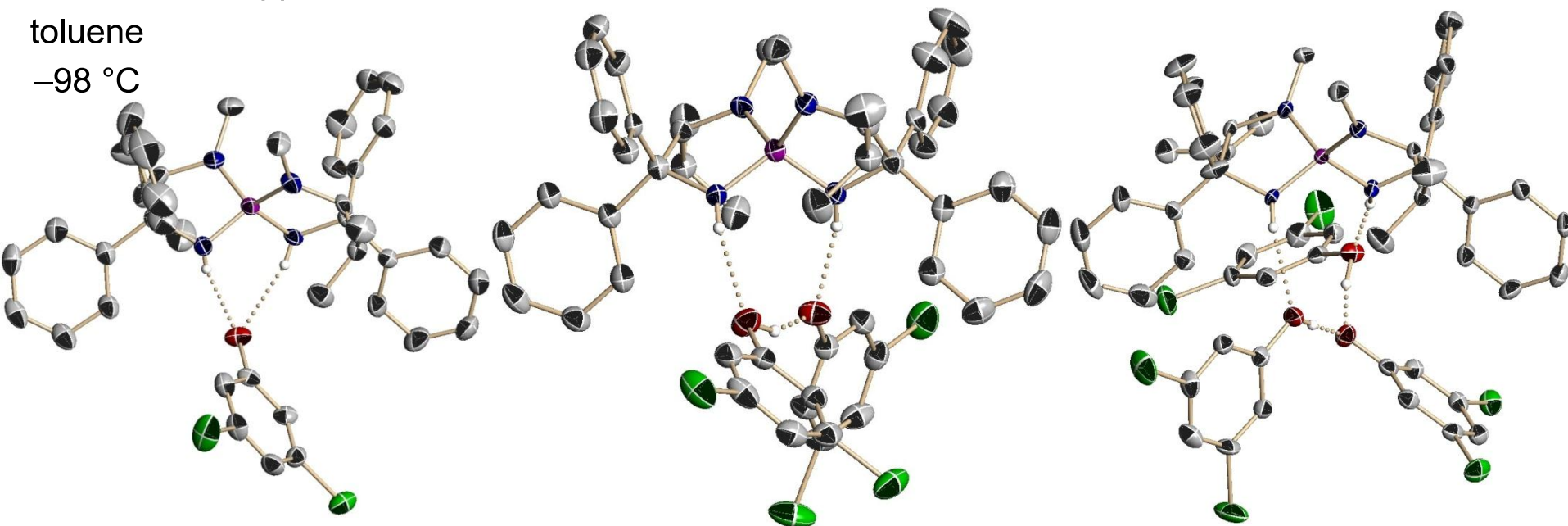
$^{31}\text{P}$  NMR : 34.9 ppm

33.9 ppm

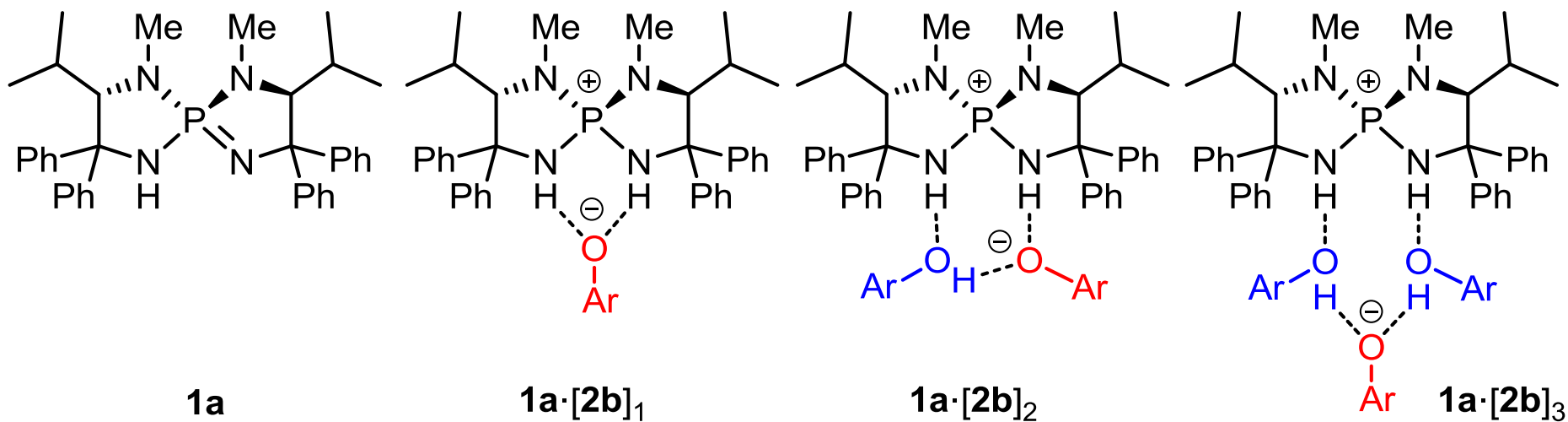
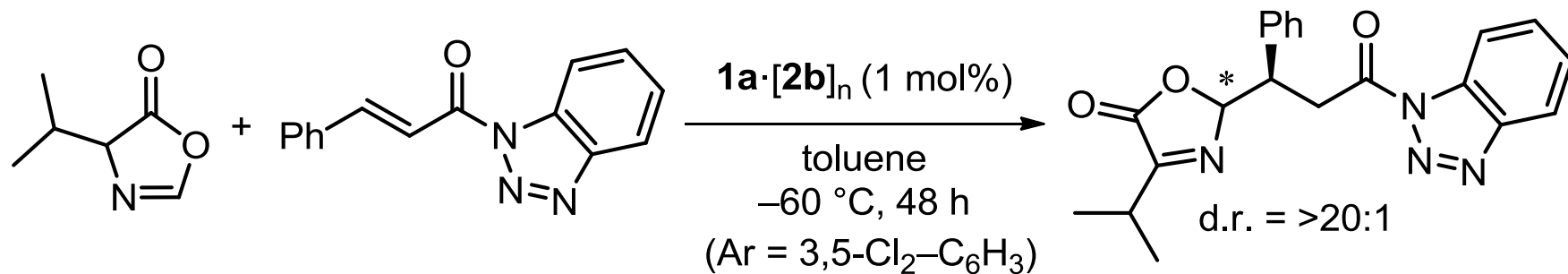
32.4 ppm

toluene

-98 °C



# Effect of the Mode of Self-Assembly



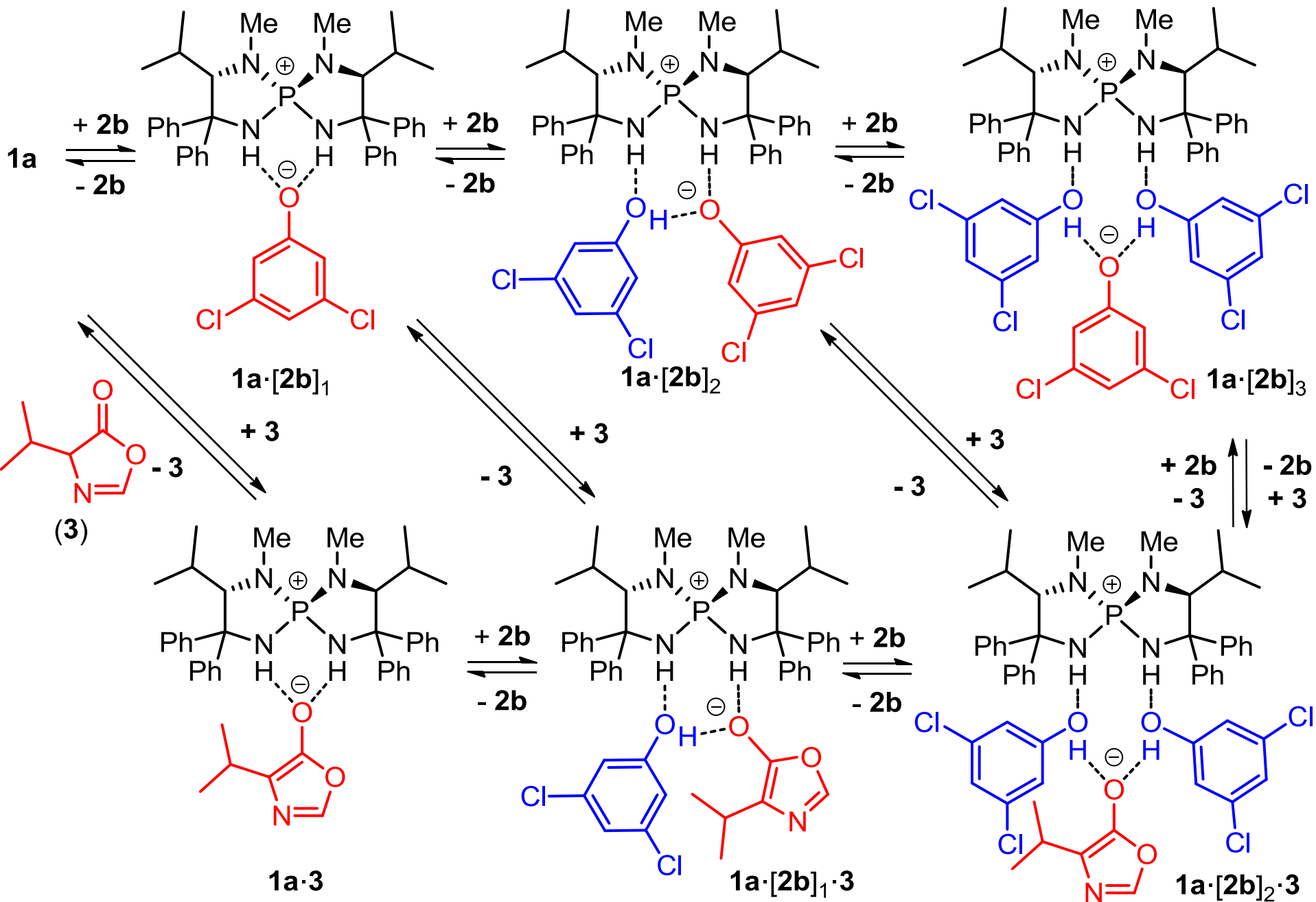
85%, 51% ee

81%, 67% ee

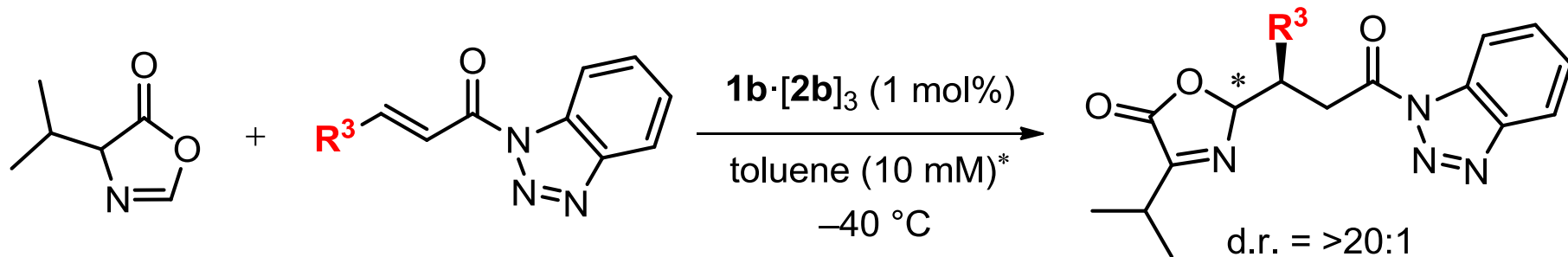
82%, 89% ee

89%, 90% ee

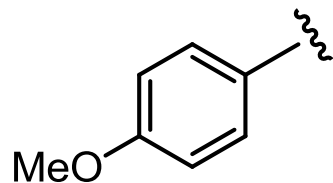
# Plausible Molecular Assemblies



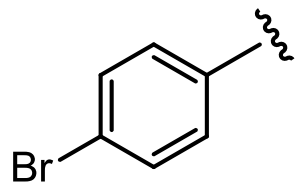
# Substrate Scope of $\alpha,\beta$ -unsaturated Acylbenzotriazole



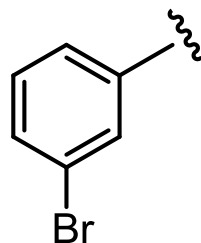
**R**<sup>3</sup> =



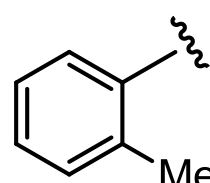
24 h, 98%  
97% ee



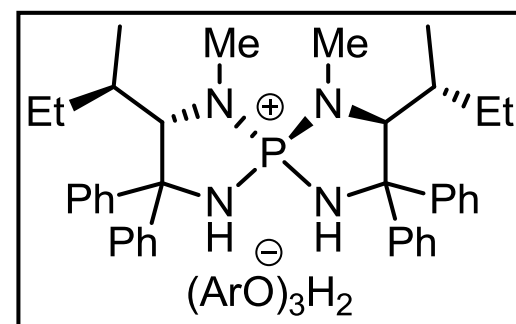
21 h, 98%  
98% ee



4 h, 96%  
95% ee

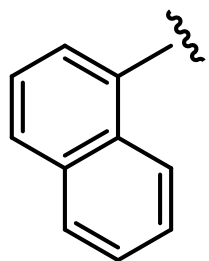


8 h, 90%  
93% ee

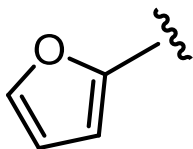


**1b**·**[2b]**<sub>3</sub>

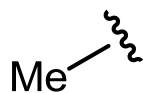
(Ar = 3,5-Cl<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>)



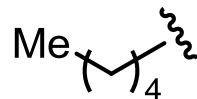
12 h, 91%  
95% ee



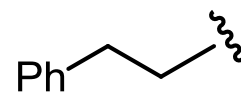
22 h, 91%  
96% ee



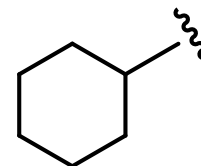
2 h, 97%  
96% ee



1 h, 96%  
95% ee



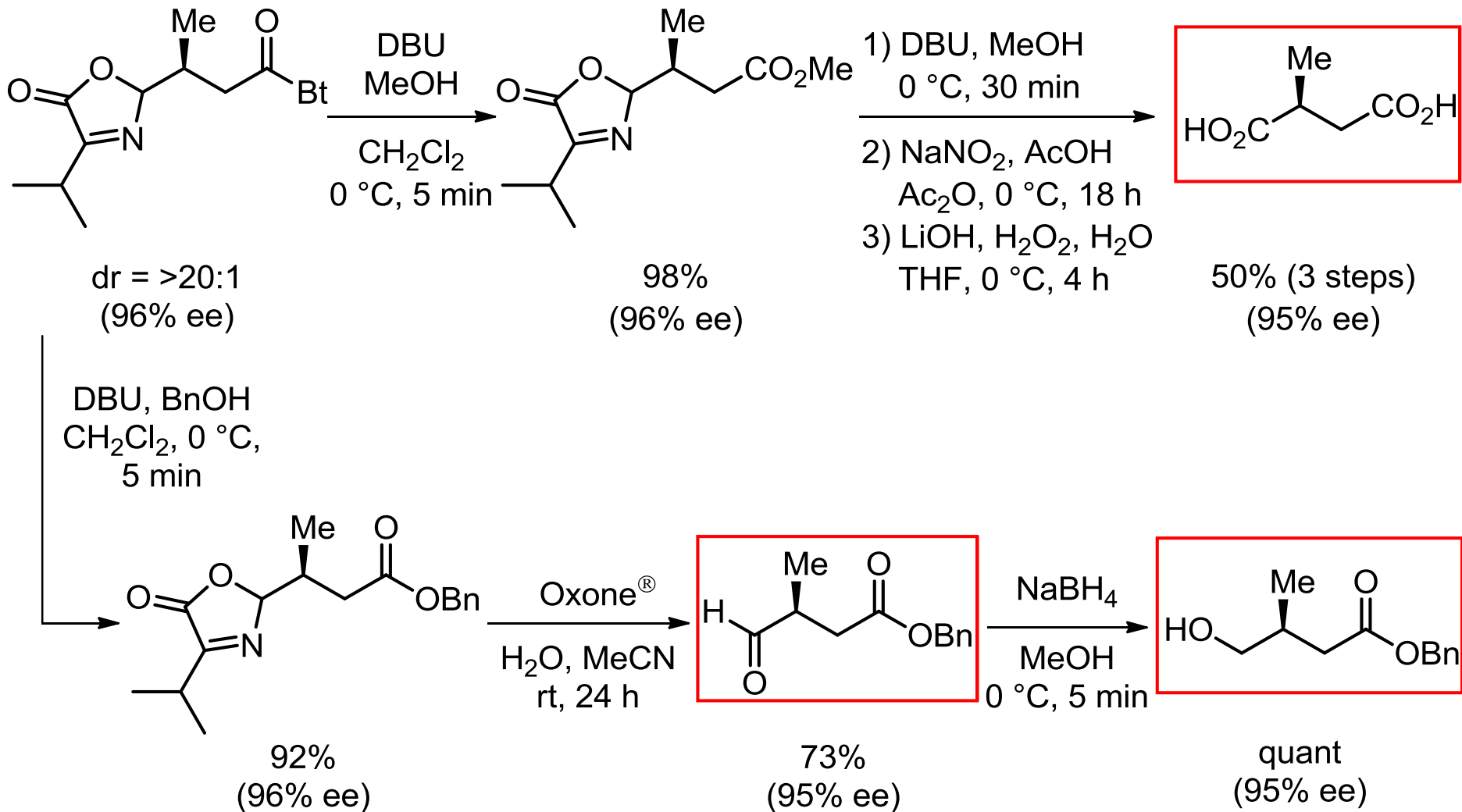
2 h, 92%  
96% ee



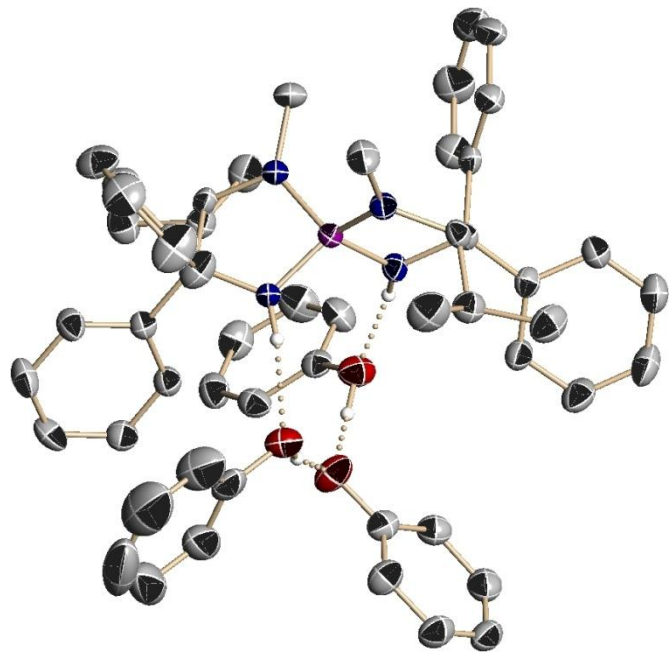
4 h, 93%  
98% ee

\* Concentration was calculated based on the amount of catalyst.

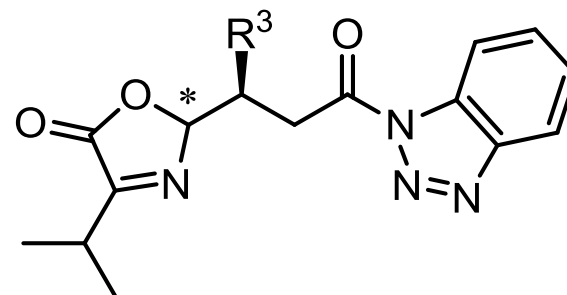
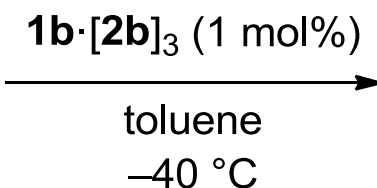
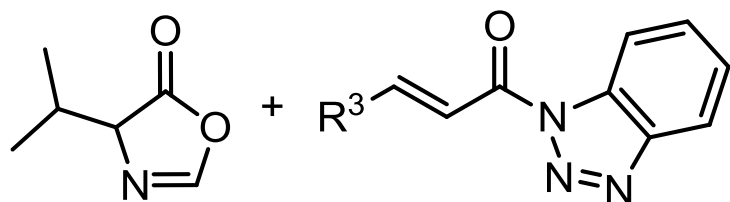
# Derivatization of the Product



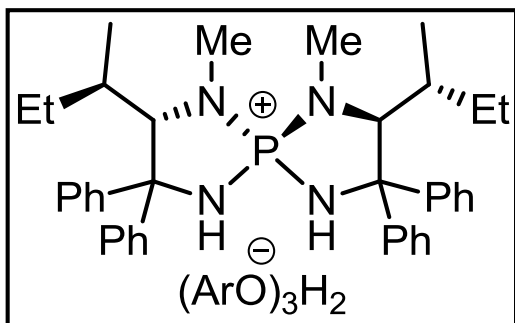
## Summary 2



- **All the structural components of catalyst cooperatively participate in the stereocontrolling event.**
- **Increase catalyst loading and decreased solvent volume further improved the enantioselectivity.**



90-98%, d.r. = >20:1  
93-98% ee for major isomer



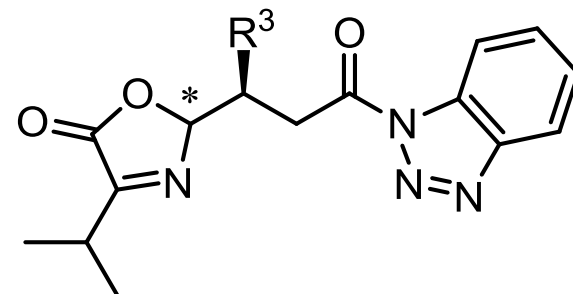
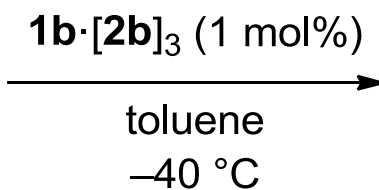
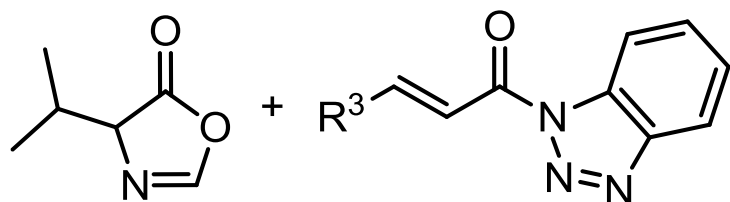
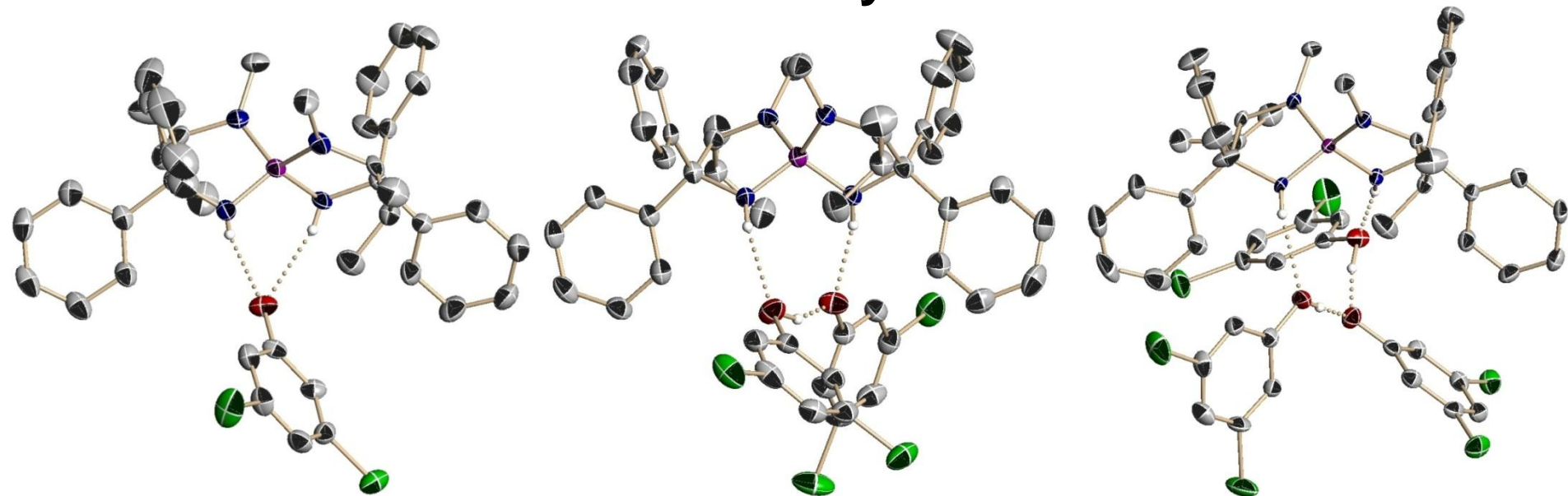
**1b·[2b]<sub>3</sub>**

(Ar = 3,5-Cl<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>)

Uraguchi, D.; Ueki, Y.; Ooi, T. *Science* **2009**, 326, 120.

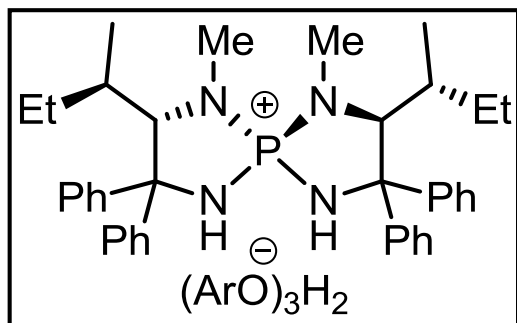
Uraguchi, D.; Ueki, Y.; Ooi, T. *Angew. Chem. Int. Ed.* **2011**, 50, 3681.

## Summary 2



90-98%, d.r. = >20:1

93-98% ee for major isomer



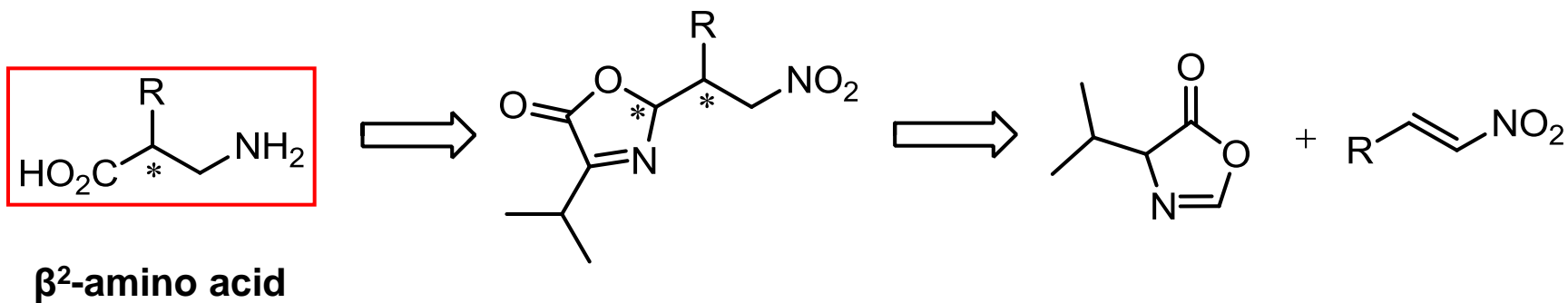
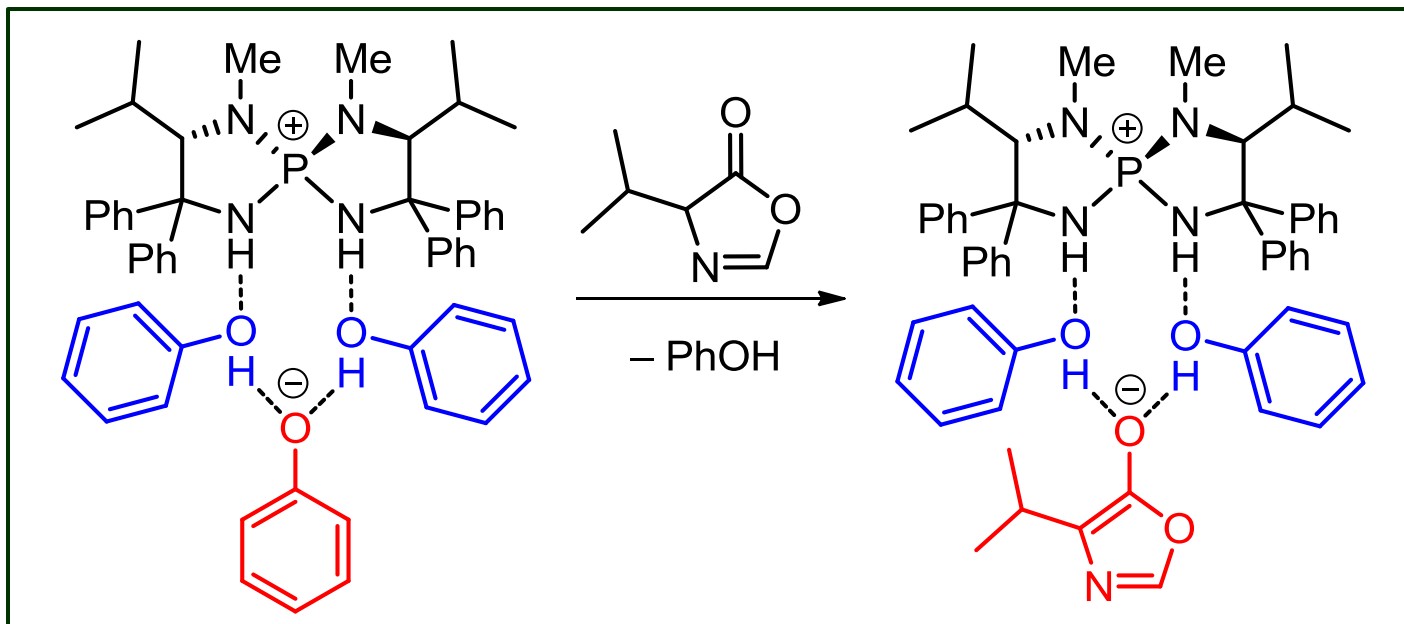
**1b·[2b]<sub>3</sub>**

(Ar = 3,5-Cl<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>)

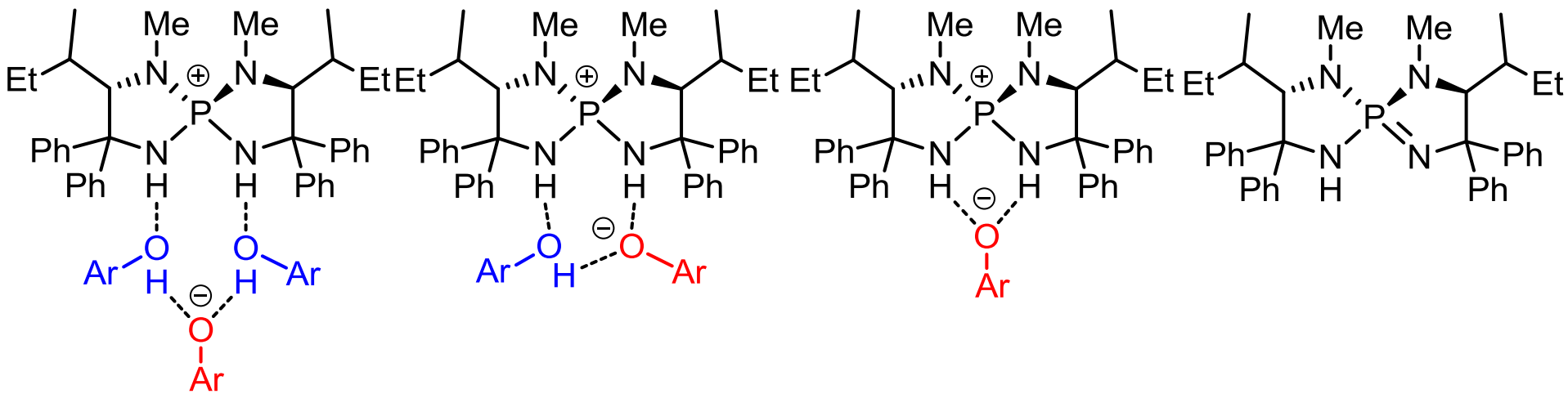
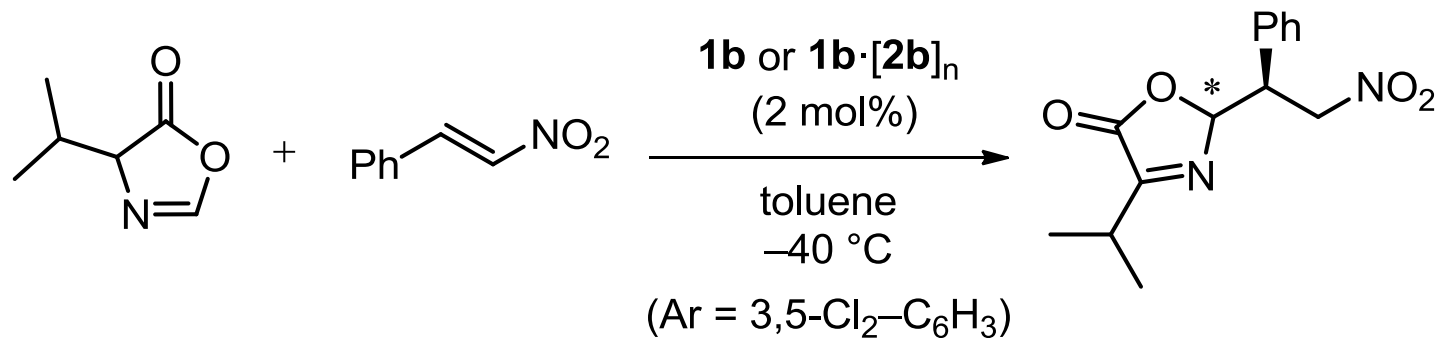
Uraguchi, D.; Ueki, Y.; Ooi, T. *Science* **2009**, 326, 120.

Uraguchi, D.; Ueki, Y.; Ooi, T. *Angew. Chem. Int. Ed.* **2011**, 50, 3681.

# Conjugate Addition to Nitroolefin

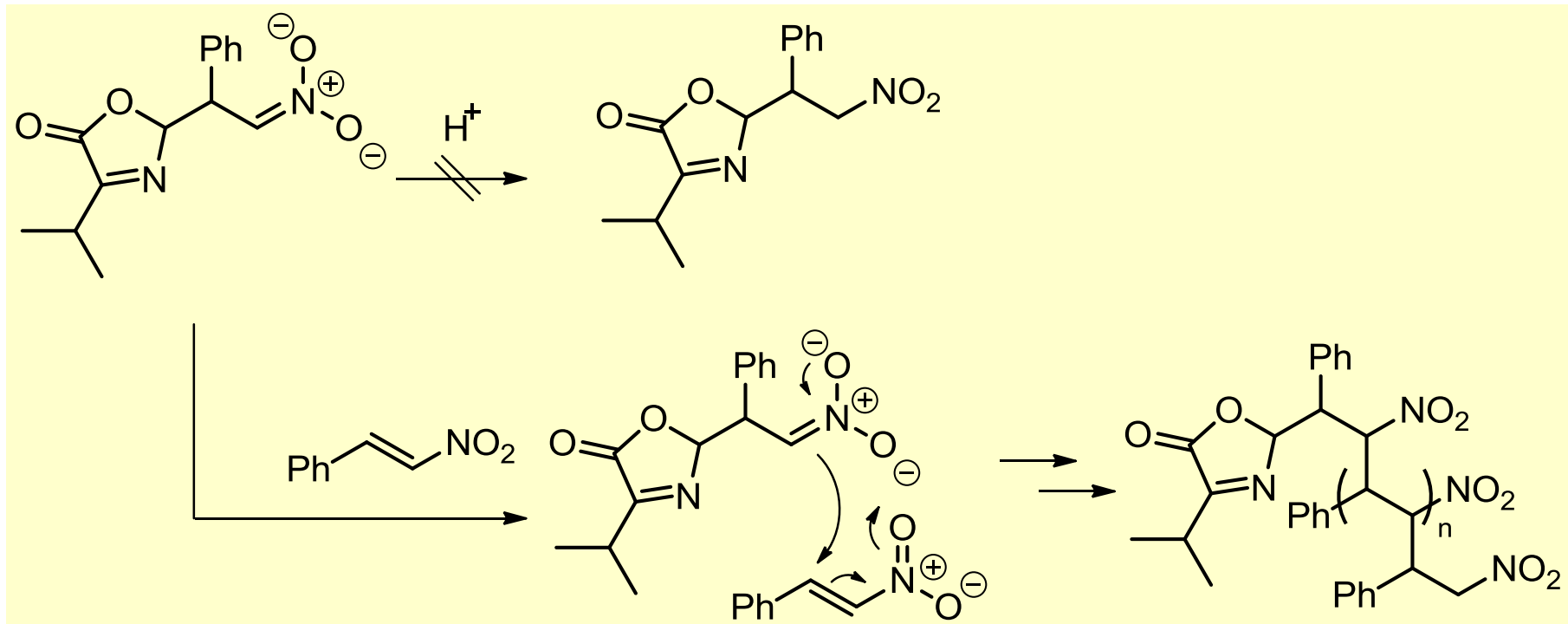


# Effect of the Mode of Self-Assembly

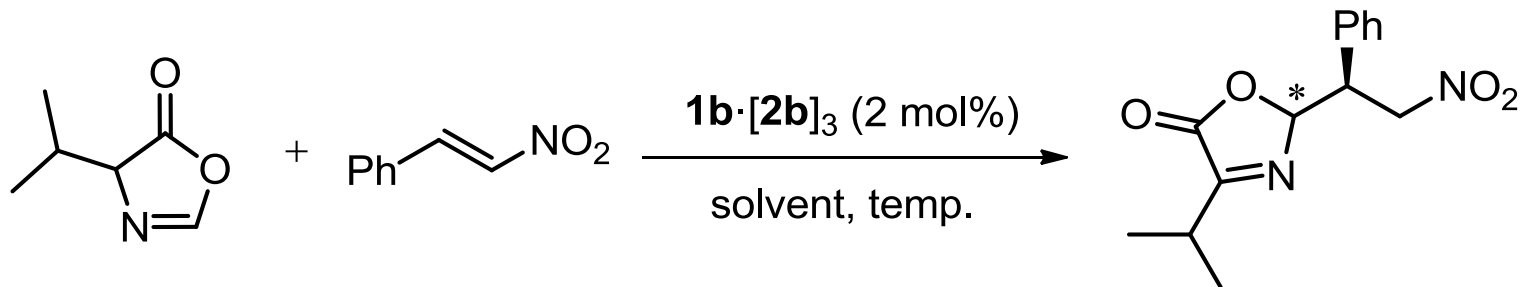


<b>1b·[2b]<sub>3</sub></b>	<b>1b·[2b]<sub>2</sub></b>	<b>1b·[2b]<sub>1</sub></b>	<b>1b</b>
8 h, 90%	4 h, <77%	4 h, <61%	16 h, <10%
d.r. = 1:1.3	d.r. = 1:1.3	d.r. = 1:1	d.r. = 1:2.4
82, 13% ee	89, 10% ee	90, <5% ee	72, 69% ee

# Effect of the Mode of Self-Assembly



# Modification of Reaction Conditions



toluene, -40 °C

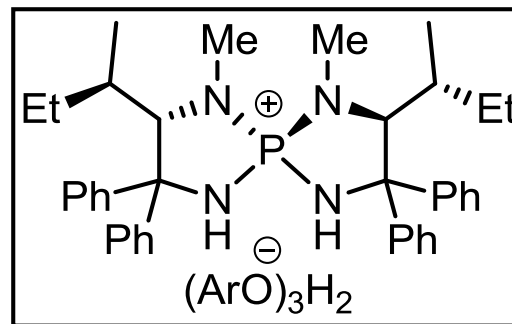
8 h, 90%  
d.r. = 1:1.3  
82, 13% ee

THF, -40 °C

3 h, 99%  
d.r. = 5.9:1  
90, <5% ee

THF, -60 °C

12 h, 96%  
d.r. = 13:1  
94, <5% ee

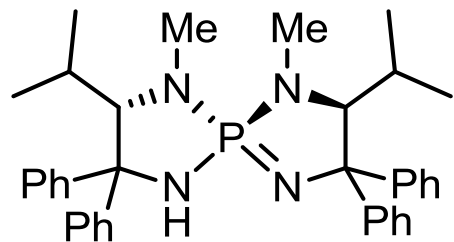


**1b·[2b]<sub>3</sub>**  
(Ar = 3,5-Cl<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>)

THF/DMF (5%), -60 °C

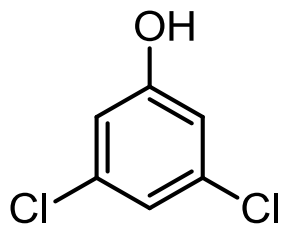
12 h, 90%  
d.r. = >20:1  
97, 11% ee

# $^{31}\text{P}$ NMR Study 2: **THF**, $-98\text{ }^\circ\text{C}$



**1a**

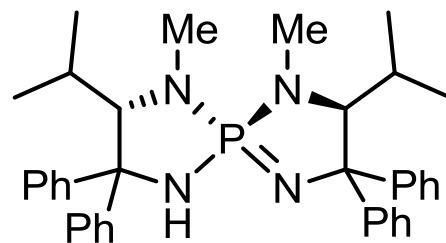
+



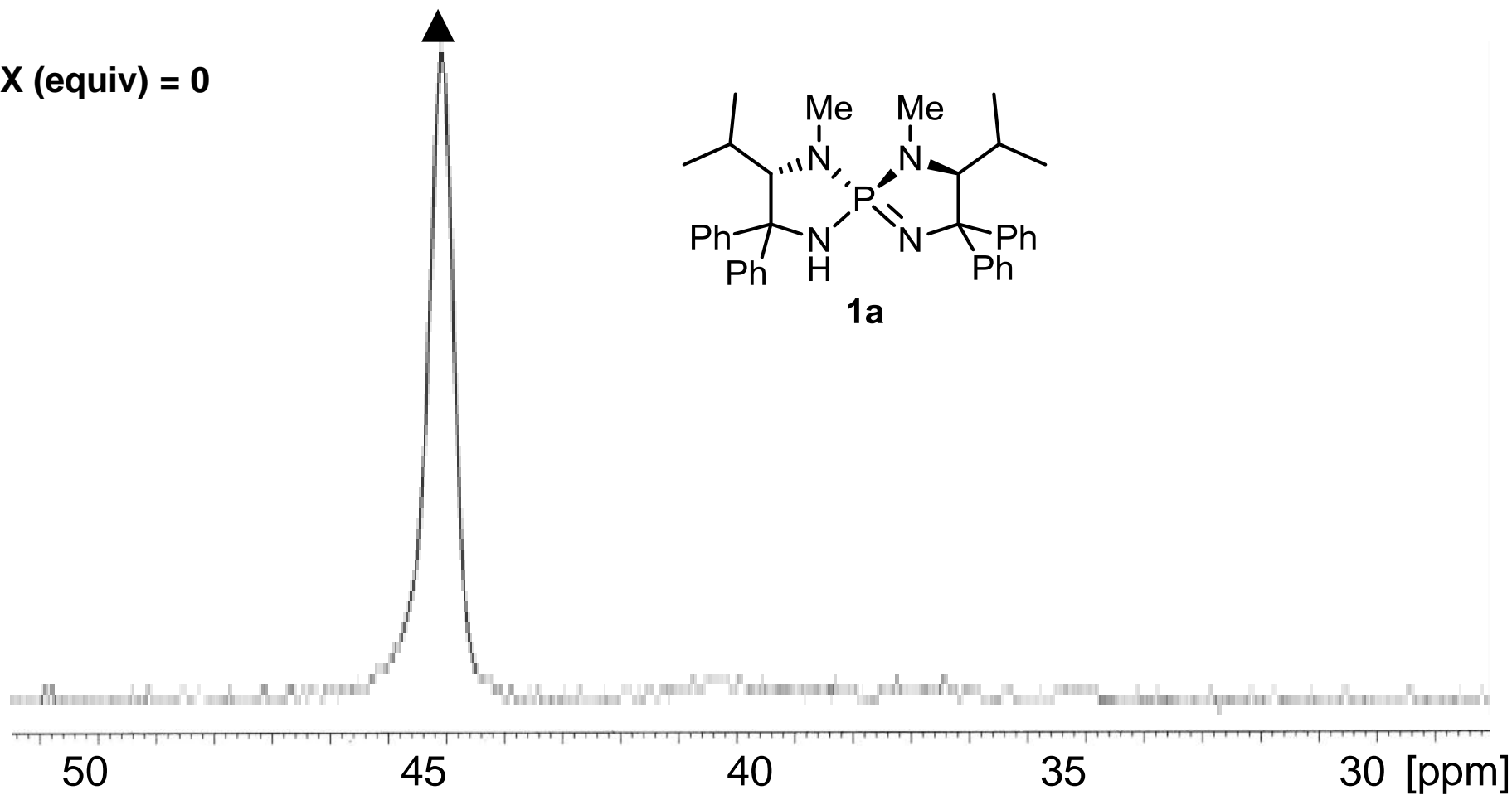
(X equiv)

**2b**

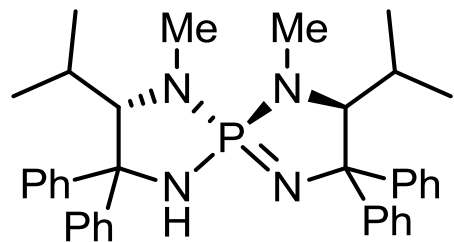
X (equiv) = 0



**1a**

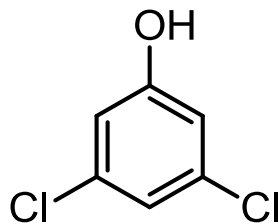


# $^{31}\text{P}$ NMR Study 2: **THF**, $-98\text{ }^\circ\text{C}$



**1a**

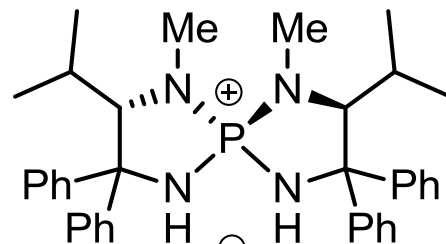
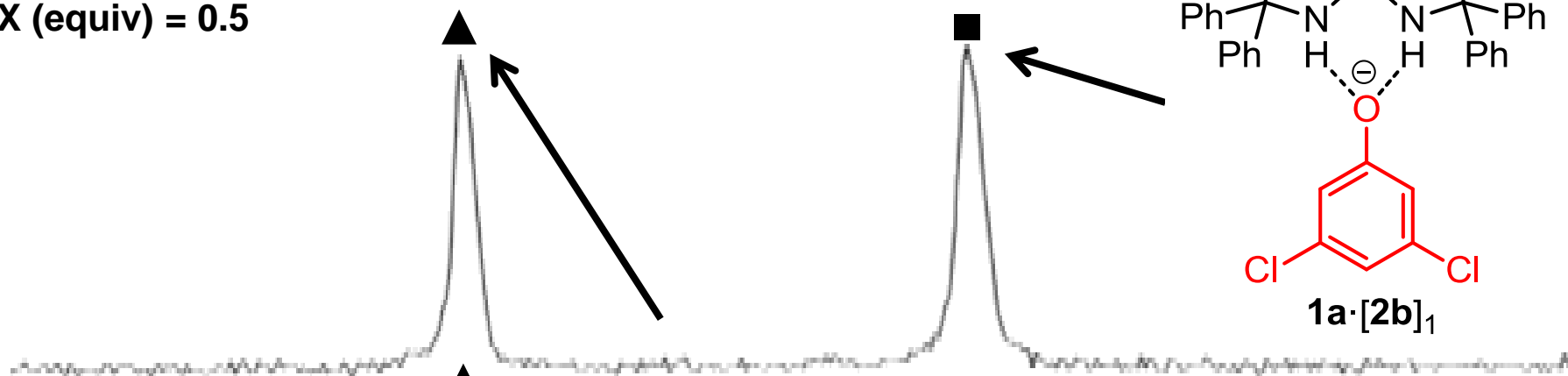
+



**2b**

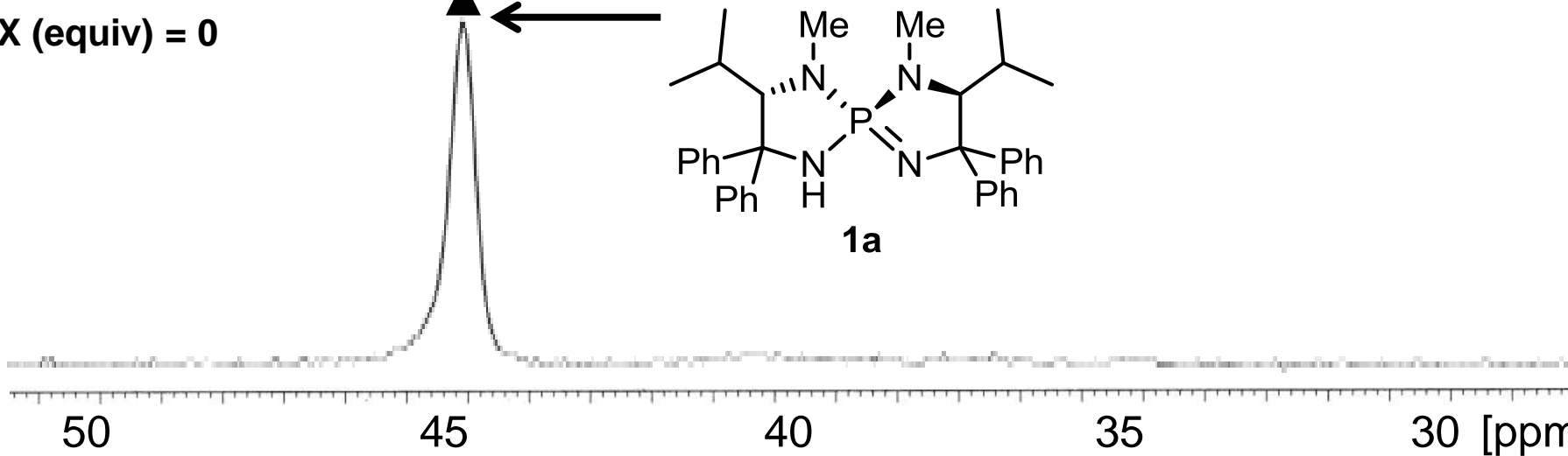
(X equiv)

X (equiv) = 0.5



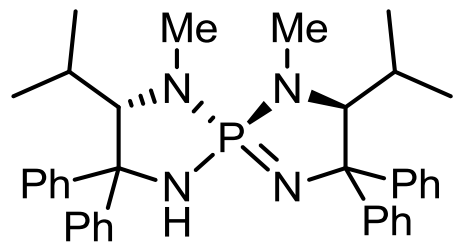
**1a**·[**2b**]<sub>1</sub>

X (equiv) = 0



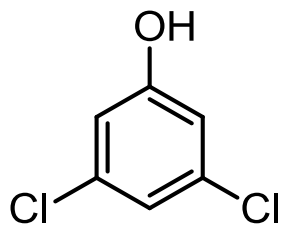
**1a**

# $^{31}\text{P}$ NMR Study 2: THF, $-98\text{ }^\circ\text{C}$



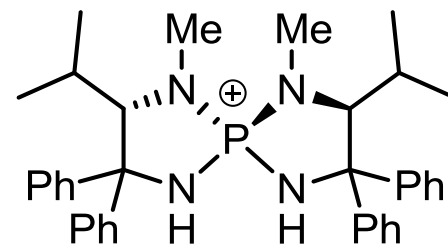
**1a**

+



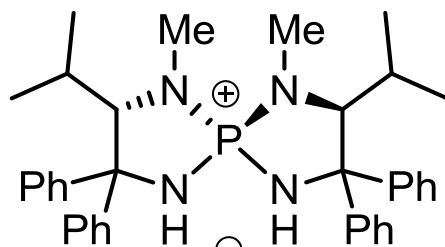
(X equiv)

**2b**



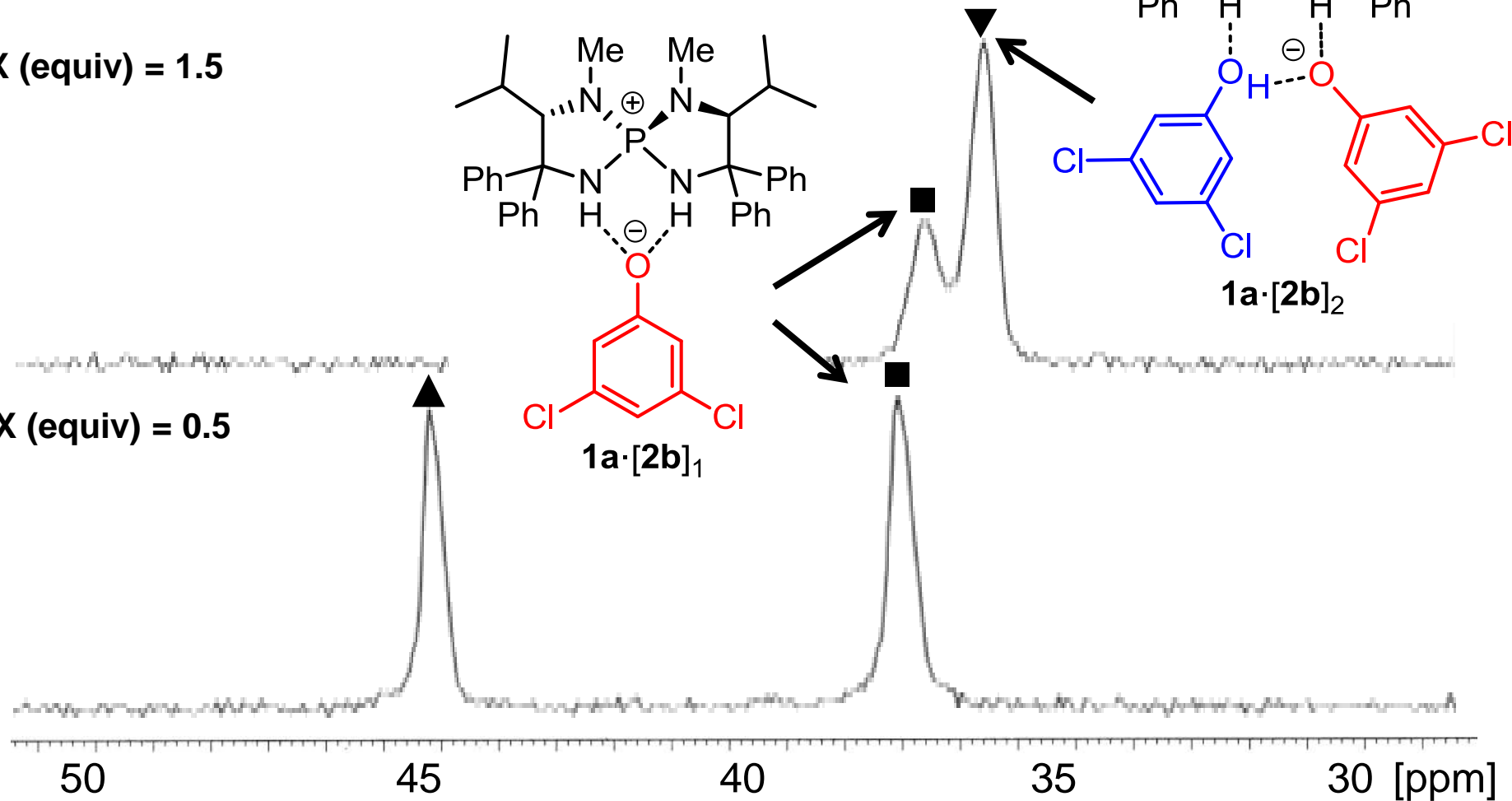
**1a·[2b]<sub>2</sub>**

**X (equiv) = 1.5**

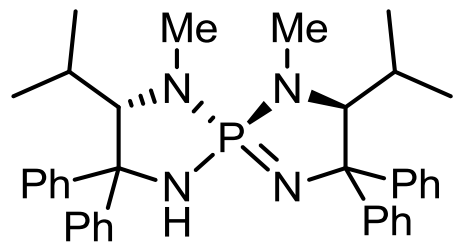


**1a·[2b]<sub>1</sub>**

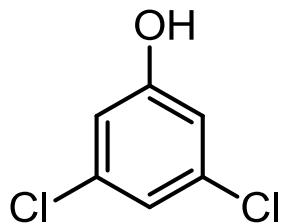
**X (equiv) = 0.5**



# $^{31}\text{P}$ NMR Study 2: THF, $-98\text{ }^\circ\text{C}$



+

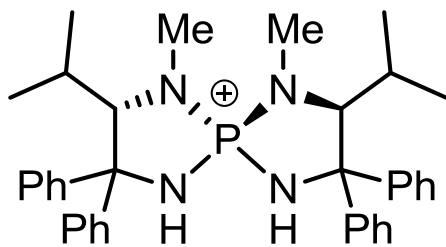


(X equiv)

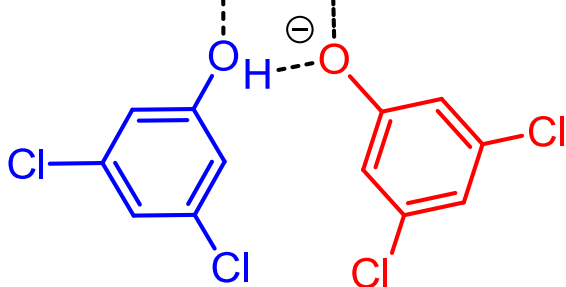
**1a**

**2b**

**X (equiv) = 10**



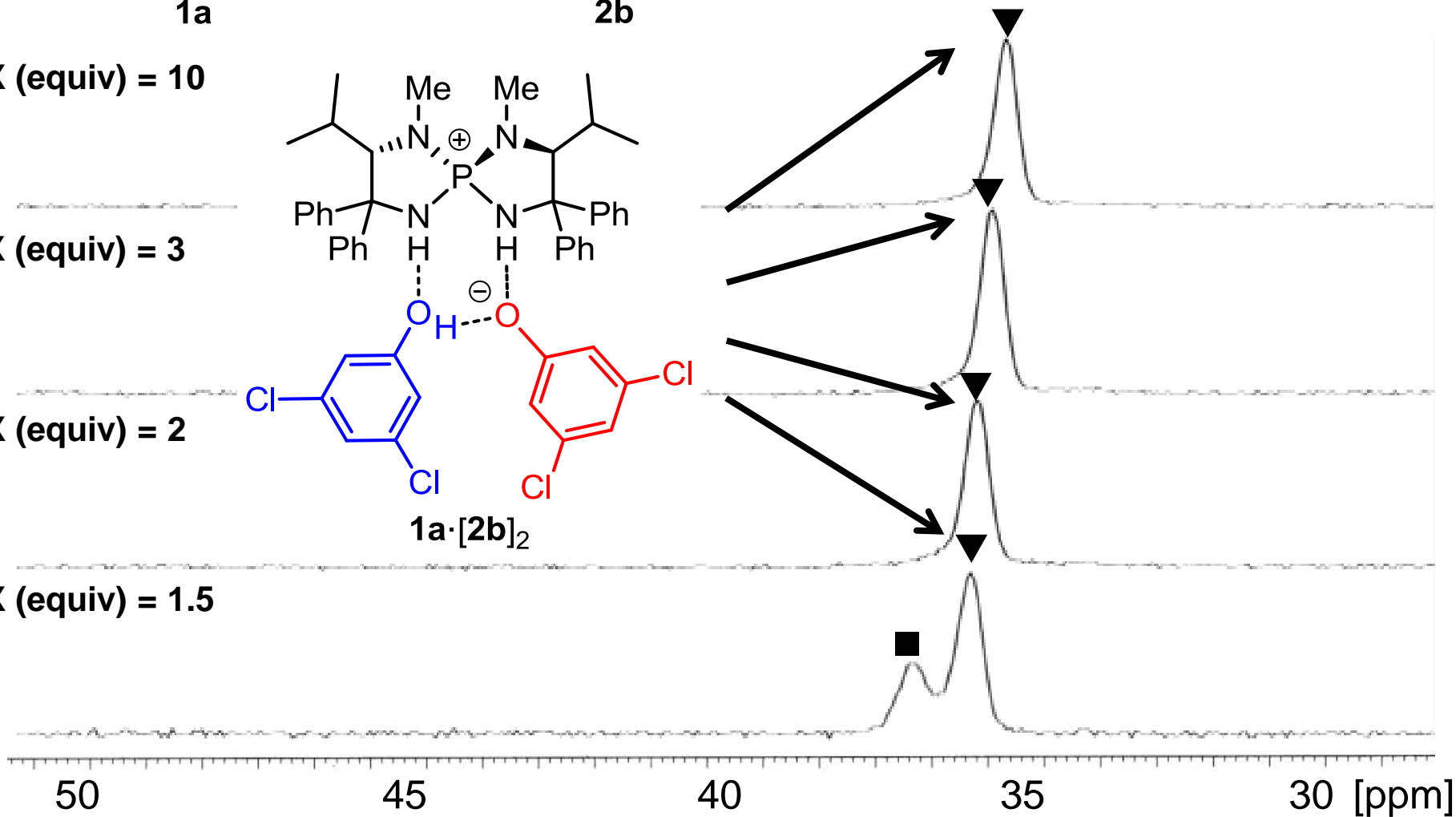
**X (equiv) = 3**



**X (equiv) = 2**

**1a·[2b]<sub>2</sub>**

**X (equiv) = 1.5**

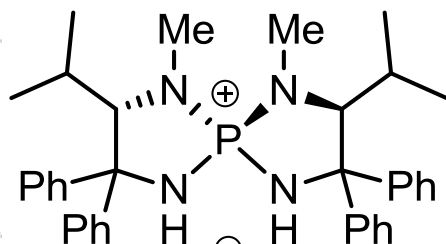


# $^{31}\text{P}$ NMR Study 2: THF, $-98\text{ }^\circ\text{C}$

X (equiv) = 10

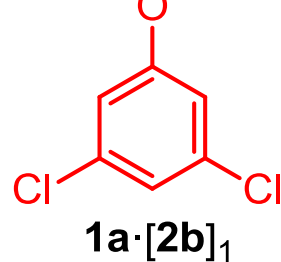
$1\text{a}\cdot[2\text{b}]_3$  was not detected

X (equiv) = 3

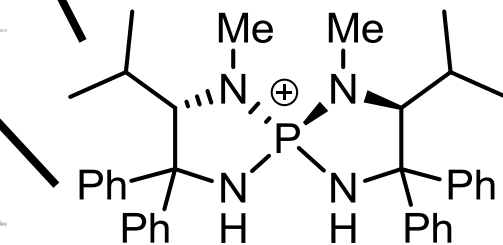


X (equiv) = 1.5

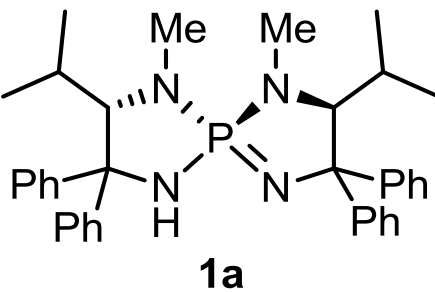
X (equiv) = 1.25



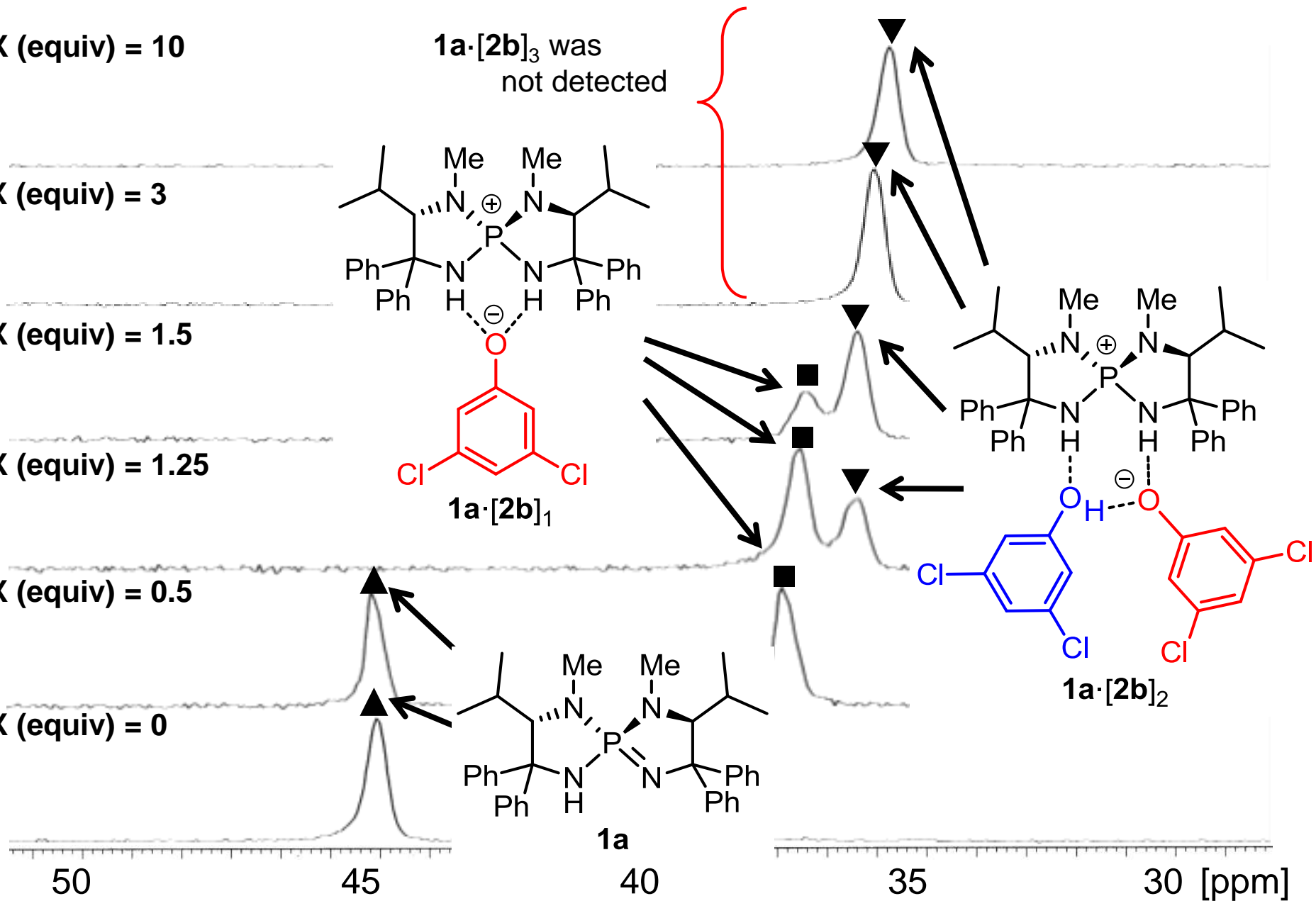
X (equiv) = 0.5



X (equiv) = 0



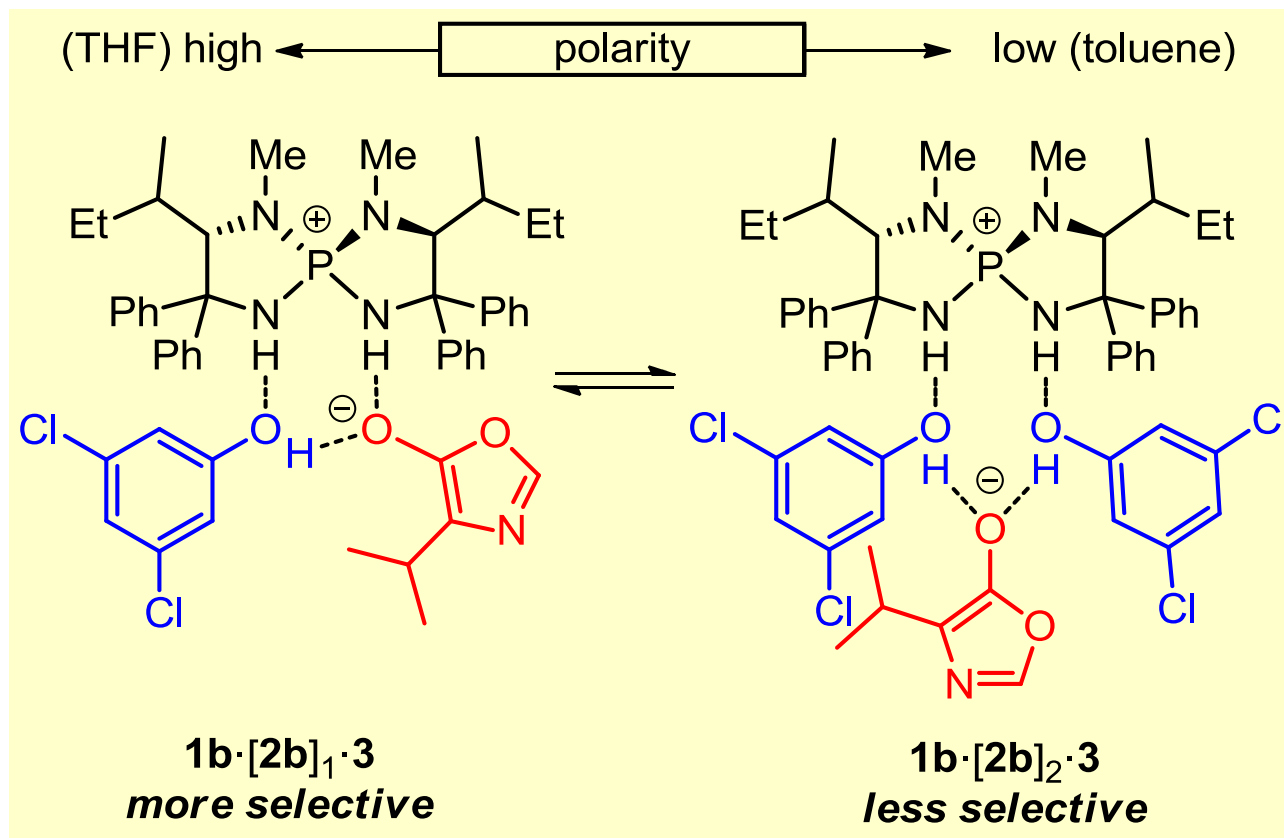
50 45 40 35 30 [ppm]



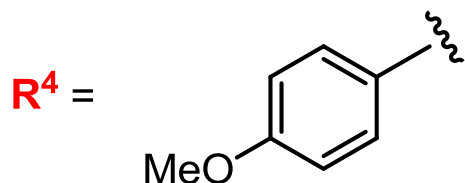
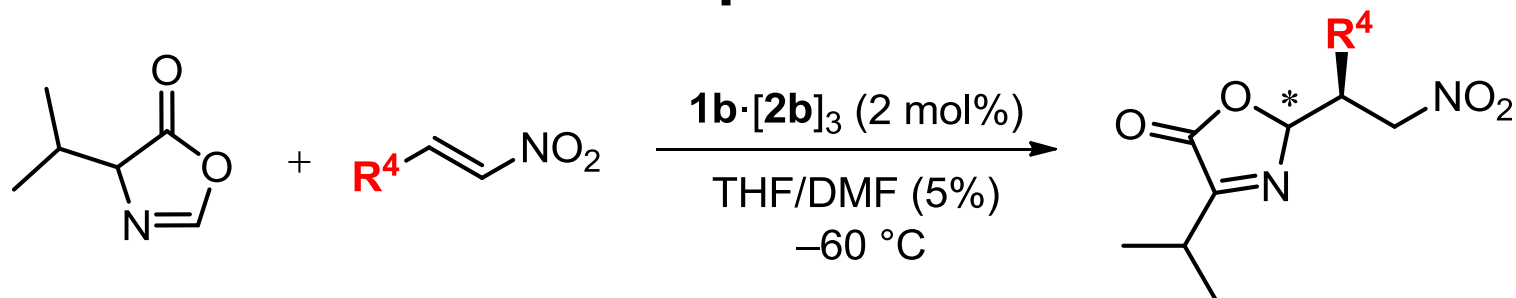




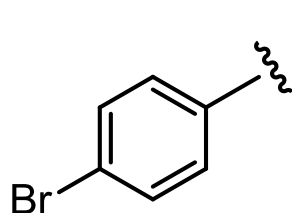
# Consideration of the Self-Assembled Catalyst Structure



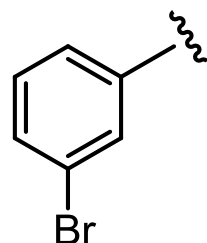
# Substrate Scope of Nitroolefin



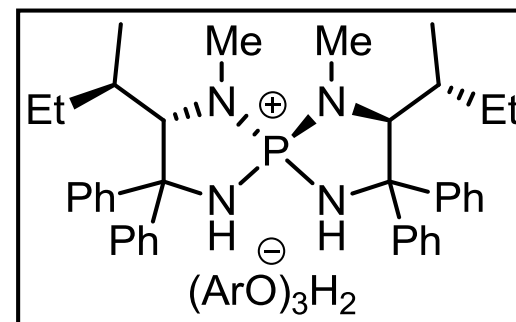
24 h, 93%  
d.r. = >20:1  
96% ee



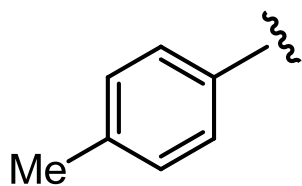
18 h, 91%  
d.r. = >20:1  
98% ee



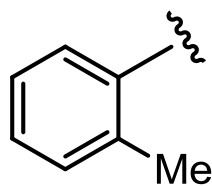
20 h, 99%  
d.r. = >20:1  
95% ee



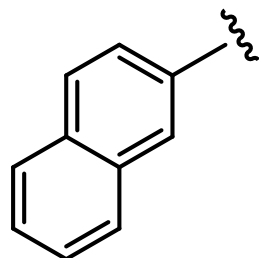
$1b \cdot [2b]_3$   
(Ar = 3,5-Cl<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>)



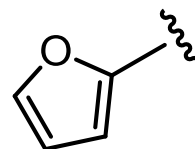
12 h, 88%  
d.r. = >20:1  
97% ee



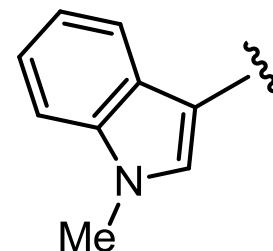
12 h, 90%  
d.r. = >20:1  
96% ee



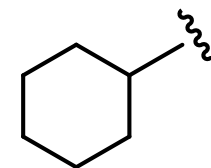
12 h, 99%  
d.r. = >20:1  
96% ee



12 h, 92%  
d.r. = 20:1  
91% ee



24 h, 75%  
d.r. = >20:1  
98% ee



24 h, 82%  
d.r. = 4:1  
94% ee

# Derivatization of the Product

