

# Nickel-based Lewis Acid Asymmetric Catalysis

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An Evans Group Afternoon Seminar

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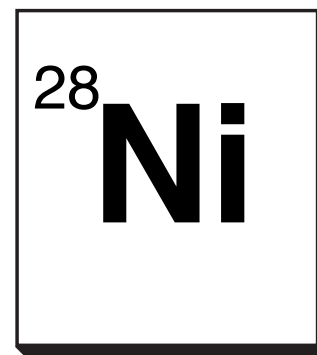
- I      General Introduction to Nickel**
- II     Ni(II) Catalyzed Diels-Alder Reactions**
- III    Ni(II) Catalyzed 1,3-Dipolar Cycloadditions**
- IV    Ni(II) Catalyzed Conjugate Additions**
- V     Conclusions**

## ***Introduction***

Nickel (*German*, Satan, or 'Old Nick')

Atomic Weight: 58.71

mp. 1453° C bp. 2732° C



Discovered in 1752 by Cronstedt in *kupfernickel* (or niccolite)

Found as a constituent in most meteorites

Most important deposits commercially are *garnierite* - a Mg-Ni-silicate

Important industrial uses include *Raney Nickel* for hydrogenation

Ni-based olefin polymerization catalysts

# Oxidation States and Co-ordination Geometry

General trend across periodic table -

Decreasing stability of higher oxidation states, Ni<sup>0</sup>, Ni<sup>I</sup> and Ni<sup>II</sup> most common

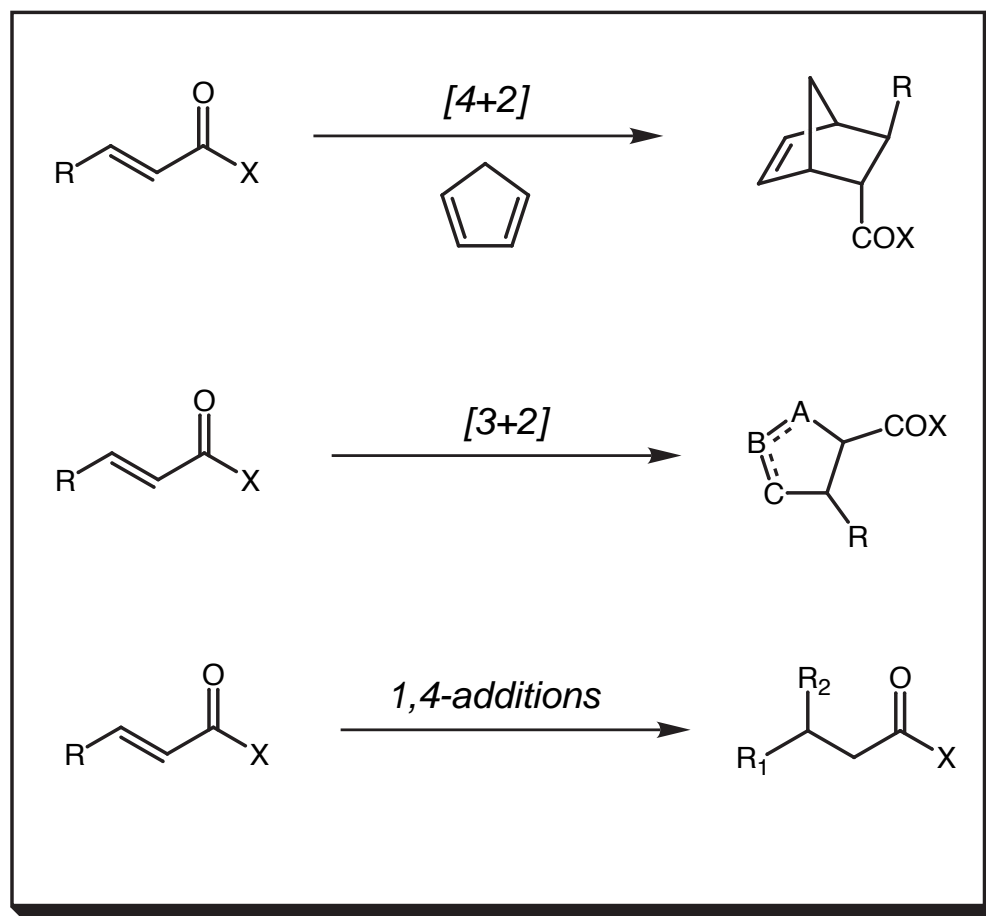
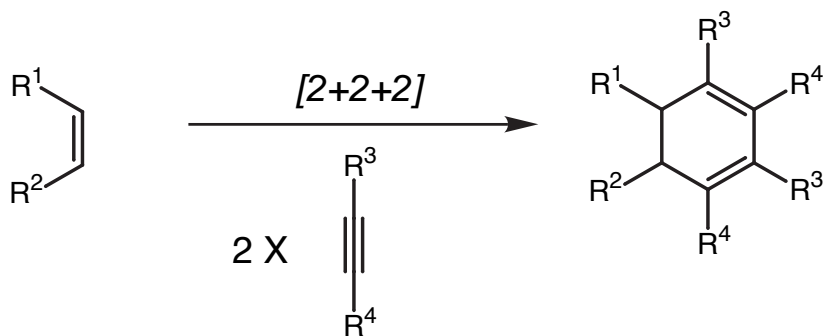
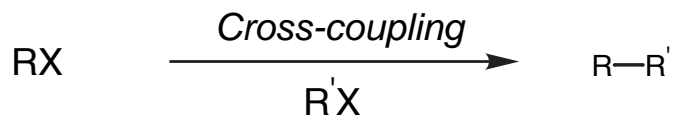
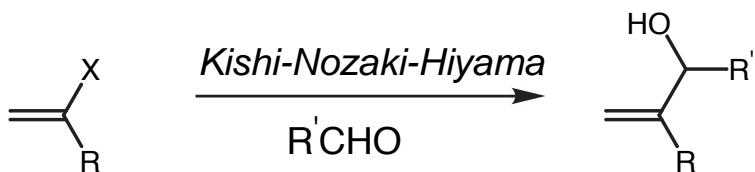
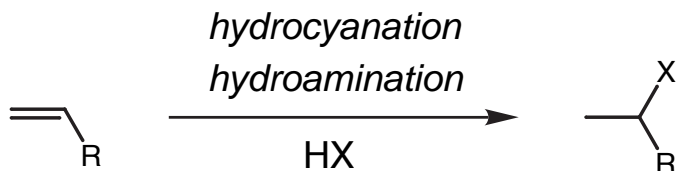
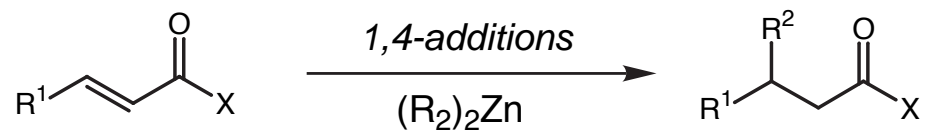
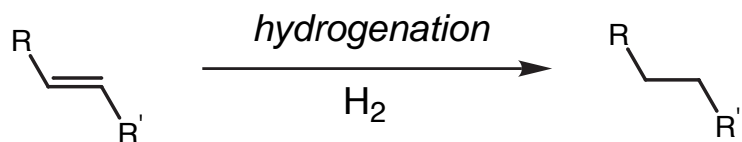
Oxidation State	Co-ordination number	Geometry	Examples
Ni <sup>0</sup>	4	Tetrahedral	Ni(CO) <sub>4</sub> , [Ni(CN) <sub>4</sub> ] <sup>4-</sup>
Ni <sup>I</sup> , d <sup>9</sup>	4	Tetrahedral	Ni(PPh <sub>3</sub> ) <sub>3</sub> Br
Ni <sup>II</sup> , d <sup>8</sup>	3	Trigonal planar	[Ni(NR <sub>2</sub> ) <sub>3</sub> ] <sup>-</sup>
	4	Square planar	[Ni(CN) <sub>4</sub> ] <sup>2-</sup> , Ni(PPh <sub>3</sub> ) <sub>2</sub> Br <sub>2</sub>
	4	Tetrahedral	[NiCl <sub>4</sub> ] <sup>2-</sup> , NiCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>
	5	Square pyramidal	[Ni((S,S)- <i>t</i> -BuBox)]OTf <sub>2</sub> <sup>*</sup>
	6	Octahedral	[Ni(NH <sub>3</sub> ) <sub>6</sub> ] <sup>2+</sup> , [Ni(bipy) <sub>3</sub> ] <sup>2+</sup> [Ni((R,R)-PhDBFOX)](ClO <sub>4</sub> ) <sub>2</sub> · 3H <sub>2</sub> O <sup>†</sup>

Taken from *Advanced Inorganic Chemistry*, Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochmann, M., John Wiley and Sons, Inc.: New York, **1999**.

\* Evans, D. A.; Downey, C. W. Downey; Hubbs, J. L. *J. Am. Chem. Soc.* submitted

† Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074.

# Important Nickel Catalyzed Reactions



# Key Players in the Field

## **Professor Shuji Kanemasa - Kyushu University**

- 1997** - Developed the DBFOX/Ph ligand for  $\text{Ni}(\text{ClO}_4)_2$  catalyzed enantioselective Diels-Alder reactions - in collaboration with *Prof. Dennis Curran*
- 1998** -  $^1\text{H}$  NMR spectroscopic study of DBFOX/Ph- $\text{Zn}(\text{ClO}_4)_2$ , as a model for Ni based catalyst
  - Enantioselective LA catalyzed 1,3-dipolar cycloaddition of nitrones
- 1999** - Enantioselective conjugate radical additions, in collaboration with *Prof. Dennis Curran*
  - First enantioselective LA catalyzed thiol conjugate additions
- 2000** - First enantioselective LA catalyzed 1,3-dipolar cycloaddition of diazoalkane
- 2002** - Enantioselective conjugate additions of nitromethane using chiral LA and achiral amine base
- 2003** - Ni catalyzed enol lactone synthesis by tandem 1,4-addition/cyclization sequence
  - Enantioselective LA catalyzed conjugate additions of aldoximes and malononitrile

## **Professor Seiji Iwasa - Toyohashi University of Technology**

- 2001** - Enantioselective 1,3-dipolar cycloadditions using Ni(II) and pybox ligands
- 2002** - Developed *tunable* pybox-*hm* ligand for enantioselective 1,3-dipolar cycloadditions

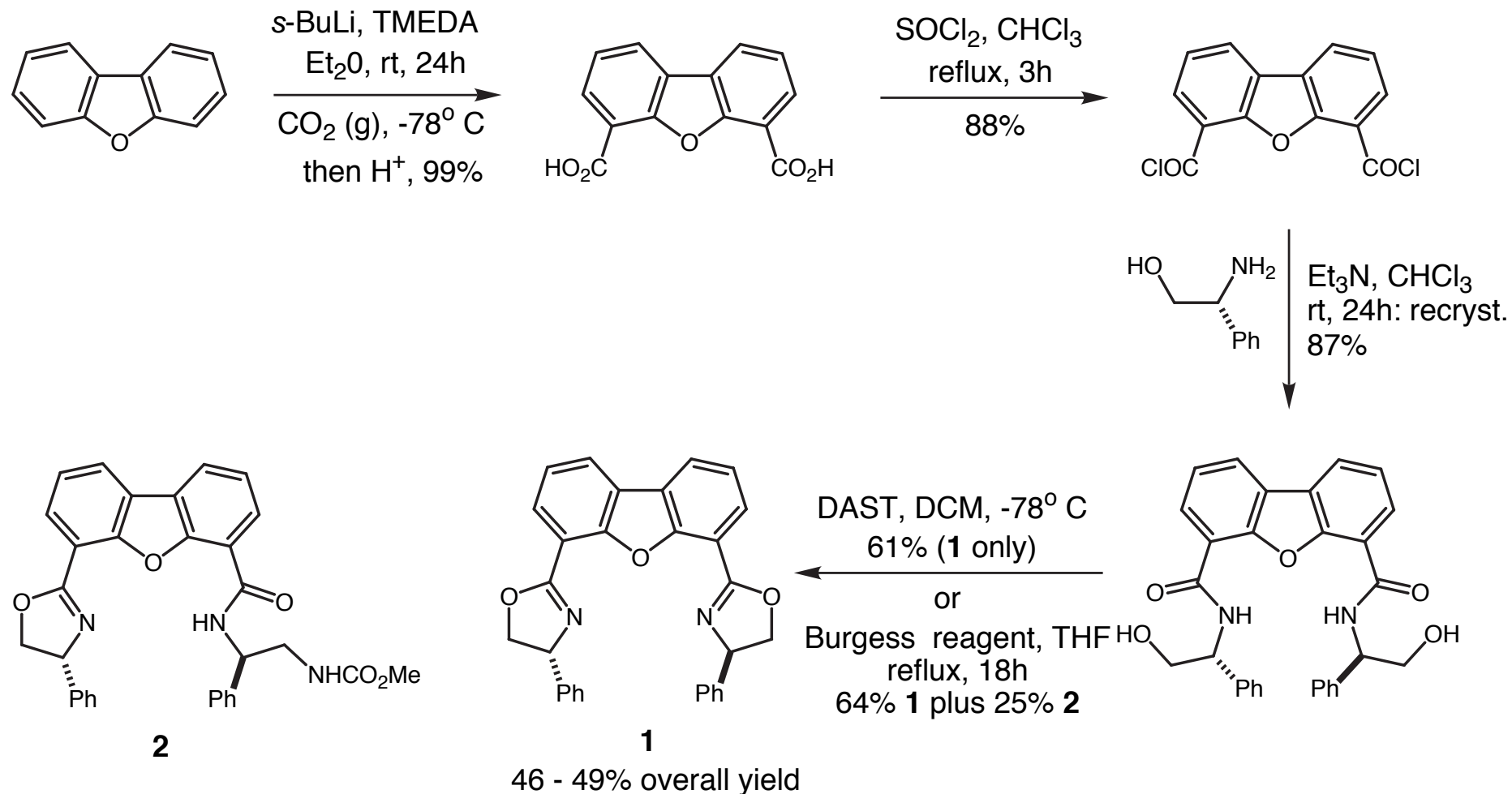
## **Professor Hiroyuki Suga - Shinshu University**

- 2002** - Developed Ni(II)-BINIM catalysts for 1,3-dipolar cycloadditions and Diels-Alder reactions

# DBFOX/Ph

*(R,R)*-4,6-Dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) - A C<sub>2</sub>-Symmetric trans-Chelating Ligand

Optimized Ligand Synthesis:



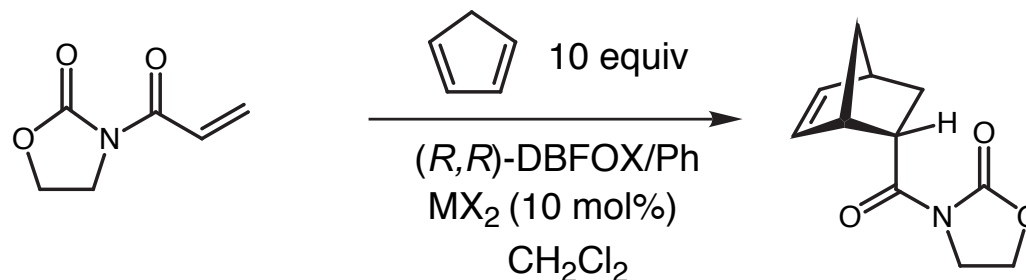
Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron Asymmetry* **1999**, *10*, 2417

Initial prep, 28% overall yield: Kanemasa et al. *J. Am. Chem. Soc.* **1998**, *120*, 3074

For the formation of methyl urethanes from 1° alcohols using Burgess rgt, see: Burgess et al. *Organic Syntheses, Coll. Vol. 6* **1998**, 788

# Diels-Alder Reactions

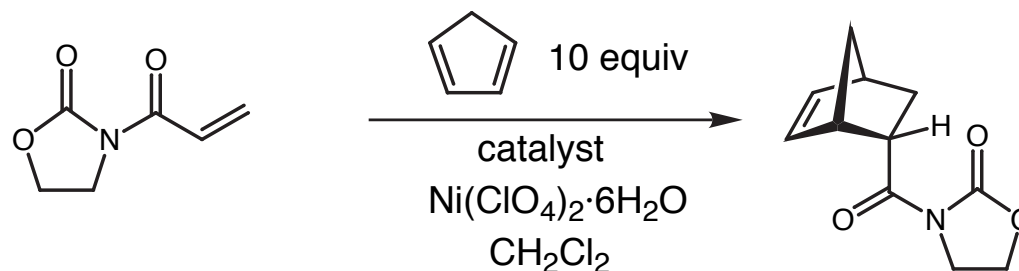
Kanemasa's initial report: A Survey of metals



$MX_2$	temp/ $^{\circ}$ C	time/h	yield/%	endo:exo	% ee (endo)
$Mg(OTf)_2$	rt	1	93	88:12	25
$Mg(ClO_4)_2$	-40	10	100	97:3	91
$Mn(ClO_4)_2$	rt	2	91	89:11	64
$Fe(ClO_4)_2$	-40	48	90	99:1	98
$Co(ClO_4)_2 \cdot 6H_2O$	-40	48	97	97:3	99
$Ni(ClO_4)_2 \cdot 6H_2O$	-40	14	96	97:3	>99
$Ni(ClO_4)_2$	-40	24	100	95:5	96
$Cu(ClO_4)_2 + 3H_2O$	-40	15	99	97:3	96
$Zn(ClO_4)_2 + 3H_2O$	-40	15	99	96:4	97

Kanemasa et al. *J. Org. Chem.* **1997**, 62, 6454; *J. Am. Chem. Soc.* **1998**, 120, 3077.

**Kanemasa's initial report: Temperature and catalyst loading**

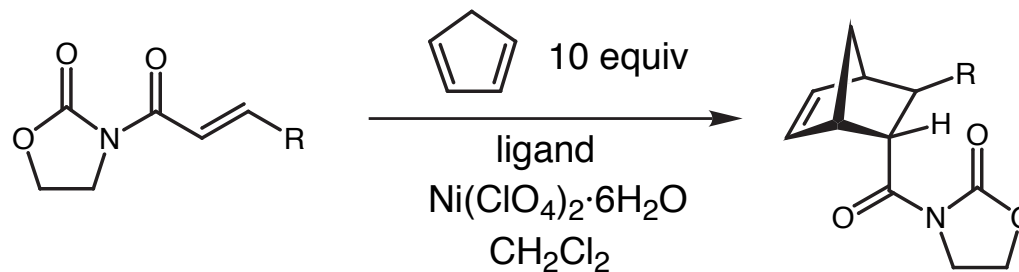


catalyst	mol%	temp/ <sup>o</sup> C	time/h	yield/%	endo:exo	% ee (endo)
DBFOX/Ph	10	rt	2	95	92:8	89
DBFOX/Ph	10	-20	24	97	97:3	95
DBFOX/Ph	10	-40	14	96	97:3	>99
DBFOX/Ph	10	-78	96	100	98:2	>99
DBFOX/Ph	2	-40	21	95	98:2	96
DBFOX/Ph	2	0	4	96	95:5	89
DBFOX/Ph	1	rt	1	95	92:8	78
<sup>*</sup> DBFOX/Ph	10	-40	72	98	98:2	>99

\* Crystallized DBFOX/Ph- $\text{Ni}(\text{ClO}_4)_2 \cdot 3\text{H}_2\text{O}$  complex, from  $\text{CH}_2\text{Cl}_2$ /Acetone

Kanemasa et al. *J. Org. Chem.* **1997**, 62, 6454; *J. Am. Chem. Soc.* **1998**, 120, 3077.

**Kanemasa's initial report: 3-substituted dienophiles**



R	catalyst	temp/ <sup>o</sup> C	time/h	yield/%	endo:exo	% ee (endo)
H	DBFOX/Ph	rt	2	95	92:8	89
Me	DBFOX/Ph	rt	20	90	92:8	93
<i>n</i> -Pr	DBFOX/Ph	rt	72	100	93:7	94
Ph	DBFOX/Ph	rt	48	54	nd <sup>*</sup>	74
H	( <i>R,R</i> )-Ph-BOX	-40	72	97	88:12	-52

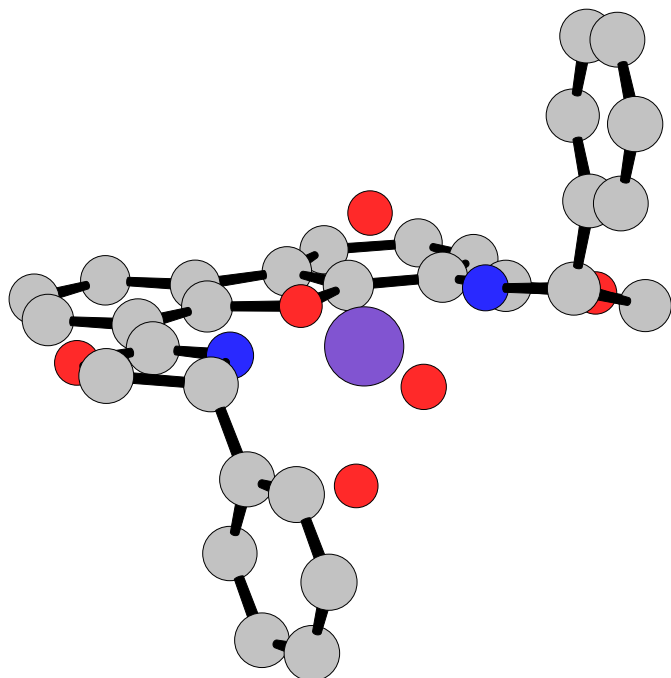
\* not determined

- 3-Substituted dienophiles much less reactive
- Ph-Box gives product in moderate ee but of *opposite absolute stereochemistry*

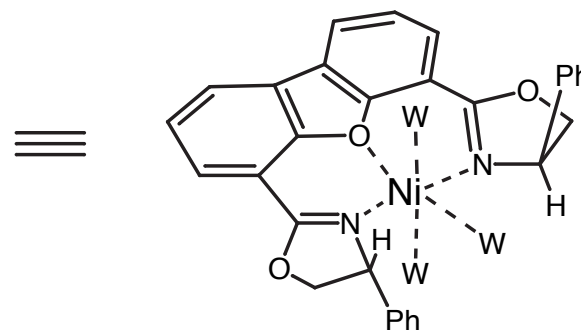
Kanemasa et al. *J. Org. Chem.* **1997**, 62, 6454; *J. Am. Chem. Soc.* **1998**, 120, 3077.

# The Catalyst

Kanemasa's initial report: Crystal structure of DBFOX/Ph-3H<sub>2</sub>O



Octahedral co-ordination geometry



W = H<sub>2</sub>O

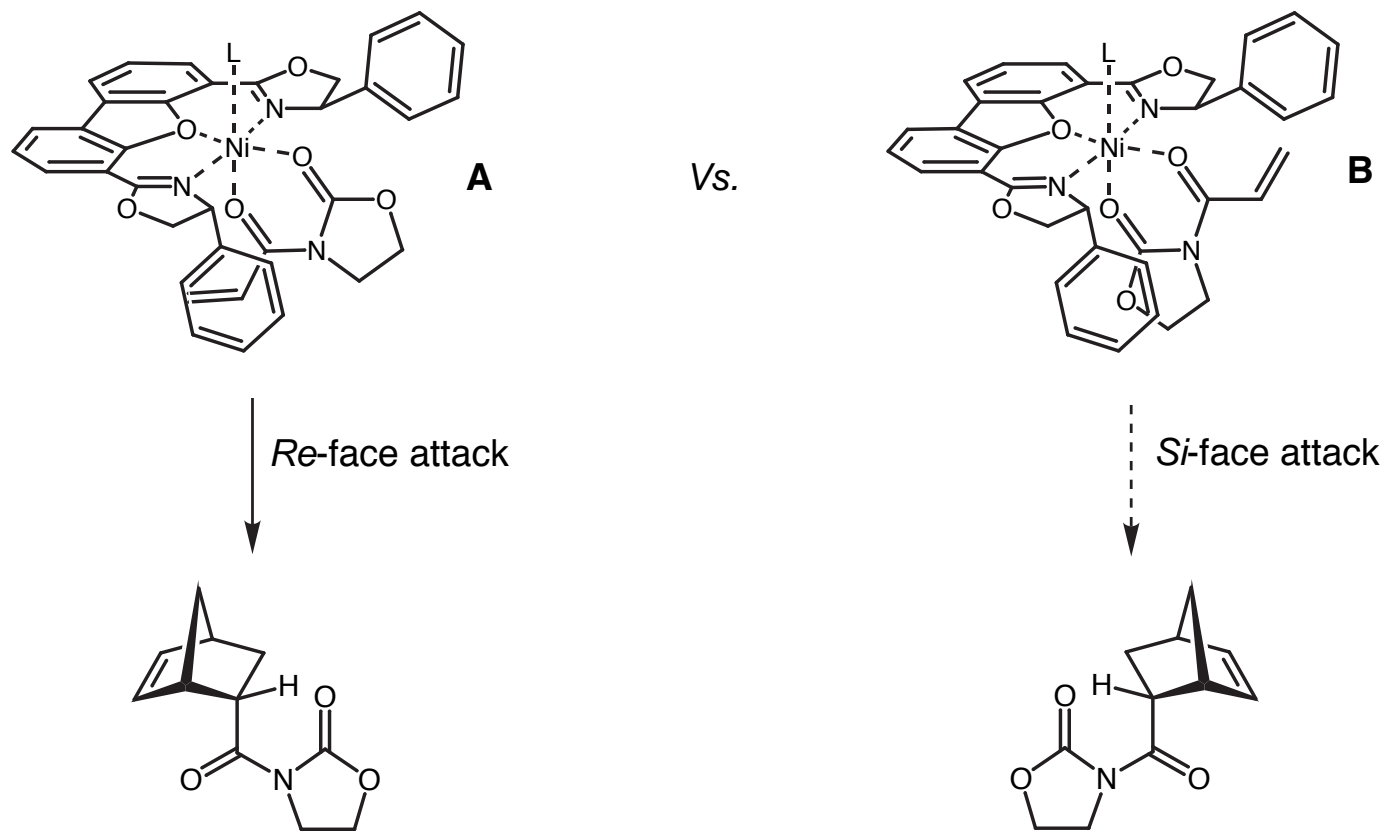
Bond lengths (Angstroms) about Nickel:

Ni-O (benzofuran)	- 2.133
Ni-O ( <i>trans</i> -H <sub>2</sub> O)	- 2.037
Ni-O (apical-H <sub>2</sub> O)	- 2.071, 2.052
Ni-N	- 2.067, 2.150

N-Ni-N bond angle: 174.2°

# The Catalyst

Kanemasa's initial report: Stereochemical rationale

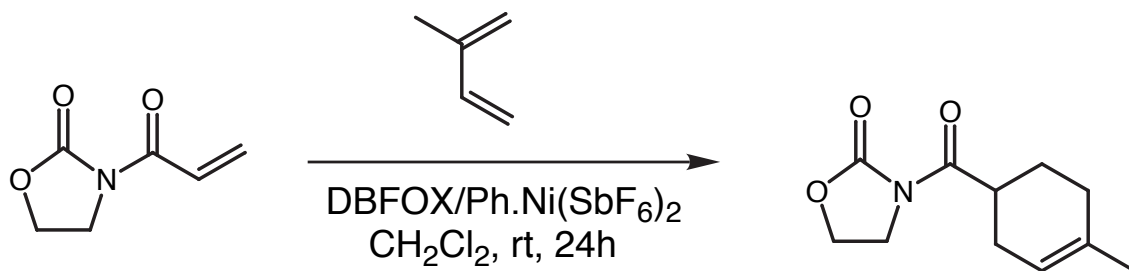


- Author's reasoning: The sterically more hindered or  $\pi$ -stacking **B** should be less reactive than **A**
- What about an electronic effect?
- Carbonyl group of acryloyl moiety in **B** deactivated relative to **A** ie. *trans* to donating furan oxygen

Kanemasa et al. *J. Am. Chem. Soc.* **1998**, *120*, 3077.

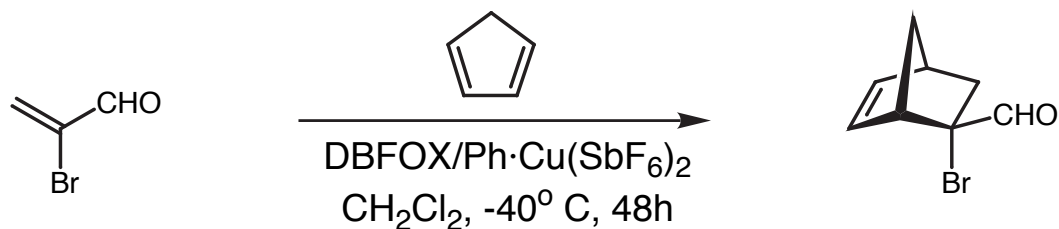
# Other Reactions

## Kanemasa's initial report: Effect of diene and dienophile



10 equiv Isoprene: 99% (62% ee)  
5 equiv Isoprene: 61% (86% ee)

Author's comments: "the selectivity is not satisfactory"  
No details on regioselectivity, or absolute stereochemistry. Expt section:  $[\alpha]_D = -71.29$ , 56% ee



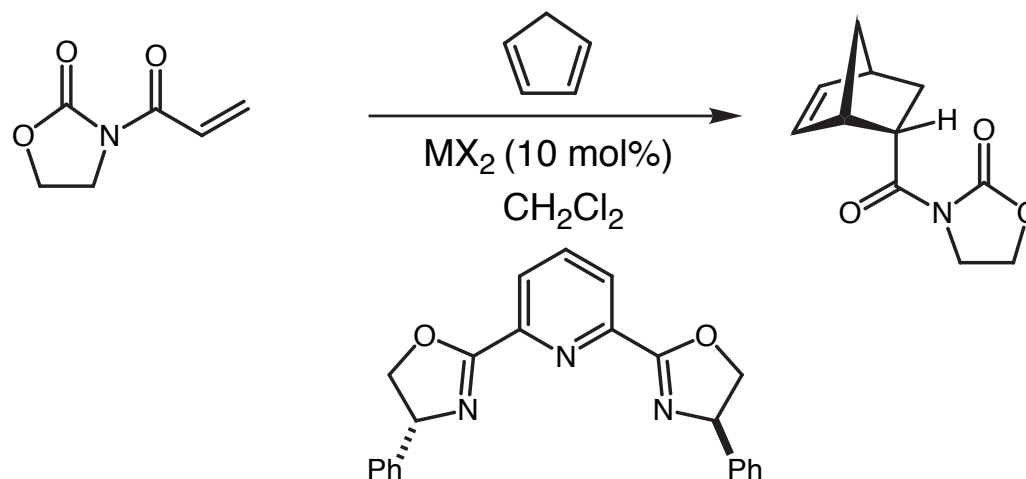
93% (*endo:exo* = 3:97)  
86% ee

In a footnote:

The reaction catalyzed by Ni(ClO<sub>4</sub>)<sub>2</sub> prepared from NiBr<sub>2</sub> and AgClO<sub>4</sub>, at rt, 24h gave:  
91% (*endo:exo* = 6:94), 53% ee

# Other Reactions

## Kanemasa's initial report: Ph-PyBox



$\text{MX}_2$	temp/ $^{\circ}$ C	time/h	yield/%	endo:exo	% ee (endo)
$\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	-40	144	79	95:5	2
$\text{Ni}(\text{ClO}_4)_2$	-40	48	95	87:13	38

Author's comments: "We suspect, on the basis of the observed low catalytic activity as well as the disappointingly low enantioselectivity, that the pybox ligand could not form a stable metal complex like the DBFOX/Ph ligand. The reason is not clear."

# Diels-Alder Reactions - Bisoxazoline Ligands

- Well known ligands for Lewis Acid catalyzed Diels-Alder reactions:
- For examples see below, and references cited therein:

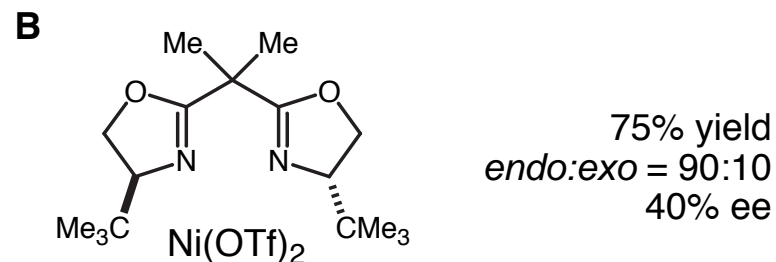
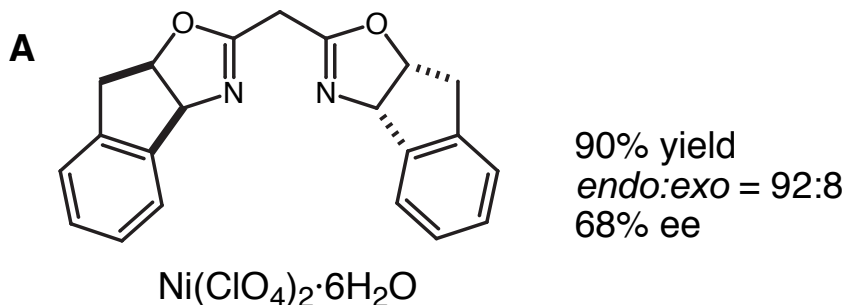
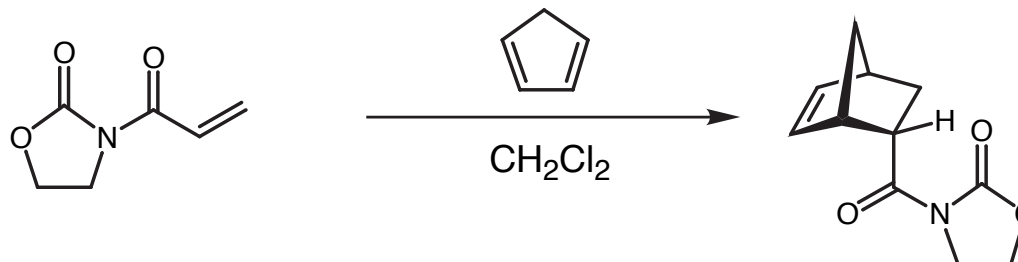
Fe(III): Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, 113, 728.

Mg(II): Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, 33, 6807.

Zn(II): Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron* **1996**, 37, 7481.

Cu(II): Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, 121, 7559.

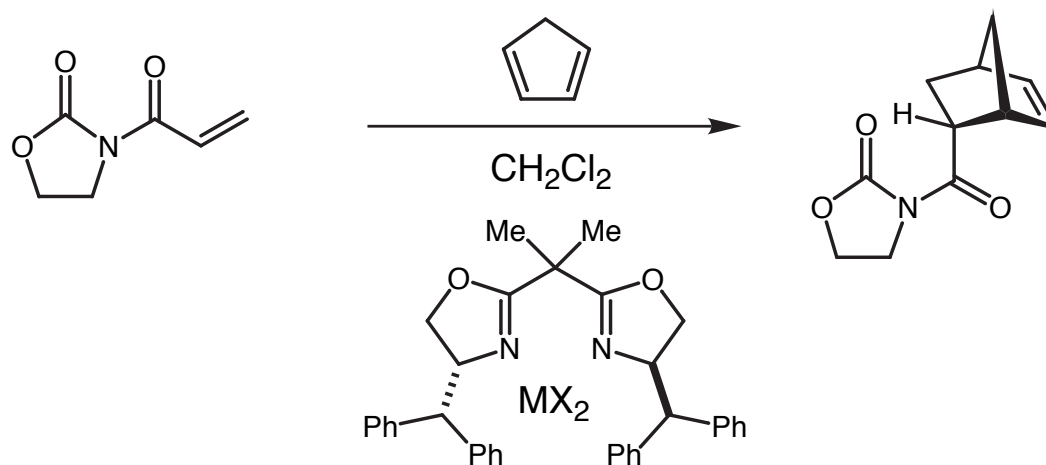
- Nickel based systems?
- Early examples from metal screens:



**A:** Ghosh, A. K.; Cho, H.; Cappiello, J. *Tetrahedron Asymmetry* **1998**, 9, 3687.

**B:** Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, 121, 7559.

## Kanemasa: Diphenylmethyl-Bisoxazoline Ligands



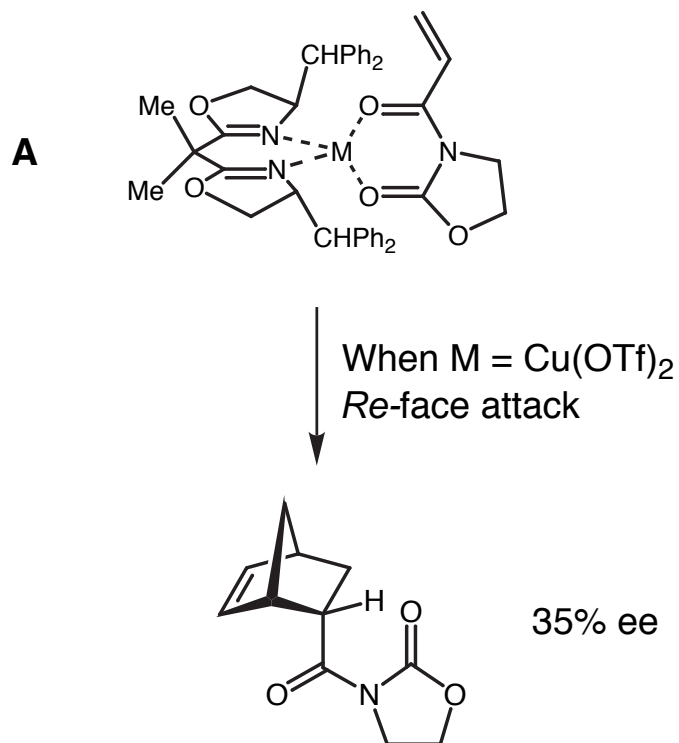
MX <sub>2</sub>	temp/ <sup>o</sup> C	time/h	yield/%	endo:exo	% ee ( <i>endo</i> )
Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	rt	0.5	nr	76:23	21
Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	-40	nr*	nr	93:7	78
Ni(ClO <sub>4</sub> ) <sub>2</sub> <sup>a</sup>	-40	nr	93	85:15	75

\* not reported <sup>a</sup> Refers to anhydrous Ni(ClO<sub>4</sub>)<sub>2</sub> prepared from NiBr<sub>2</sub> and AgClO<sub>4</sub>

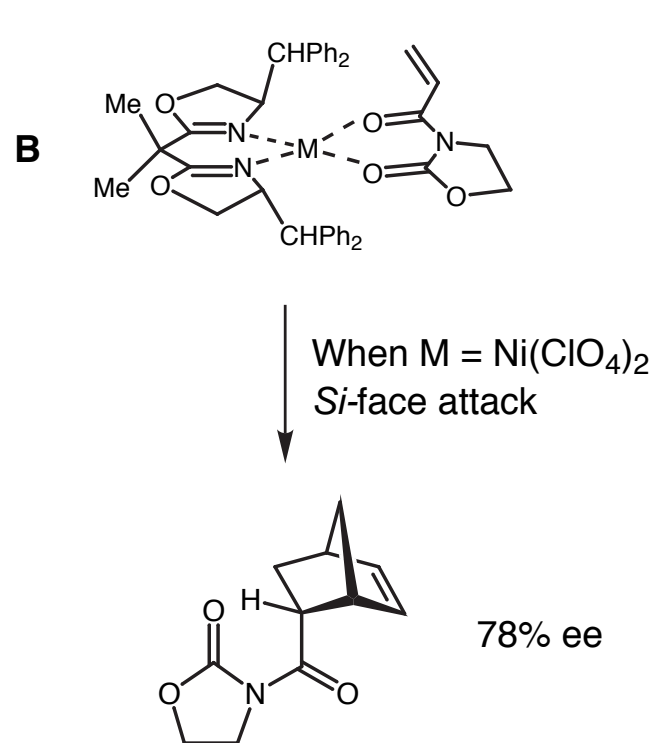
- The Ni complexes display high catalytic ability - although no reaction times given for low temp. expts.
- Other Box ligands were not reported.
- Use of Cu(OTf)<sub>2</sub> gives *opposite* sense of induction to Ni(ClO<sub>4</sub>)<sub>2</sub>

## Kanemasa: Stereochemical rationale

Tetrahedral



'Square Planar'



- Authors suggest a tetrahedral copper(II) complex to account for observed stereochemistry
- The major product obtained using Cu(OTf)<sub>2</sub> and (*R,R*)-diphenylmethyl-Box has the same absolute stereochemistry as that obtained using (*S,S*)-*t*-Bu-Box and other (*S,S*)-box ligands - see Evans and Co-workers, *J. Am. Chem. Soc.* **1999**, 121, 7559.
- Absolute stereochemistry with Ni(II) complex correlates well to a 'square planar' geometry. Although, it seems more likely that this would, in fact, be octahedral, with two apically bound counter ions.

## Kanemasa: A Key Insight

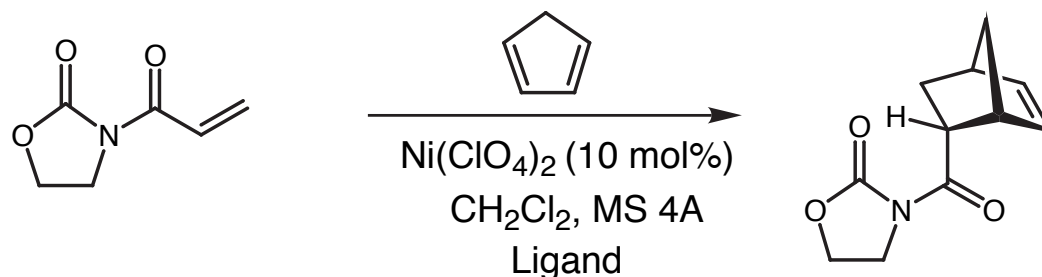
- Authors speculated on the addition of an amine base to act as an axial ligand (or ligands) to enforce the in-plane co-ordination of dienophile in the case of Ni catalyst.
- Addition of Et<sub>3</sub>N retarded the reaction rate significantly.
- Two mol. equivs of pyridine (relative to catalyst) to aqua complex gave an active catalyst (79% yield, 24h, -40 °C) but with lowered ee (54%). Anhydrous complex lost all activity.
- The addition of phenylisocyanide to Ni(II) complex did not decrease catalytic activity for either aqua or anhydrous complex. Although ee's were lowered to 29% and 35%, respectively.

Although the addition of an amine to act as a ligand was ineffective in improving the ee of these reactions it demonstrates the ability of Ni(II) based catalysts to remain catalytically active in the presence of highly co-ordinating additives.

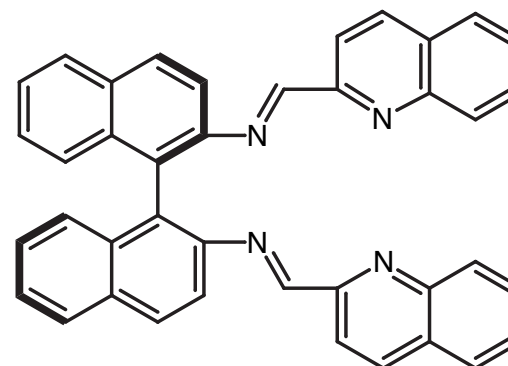
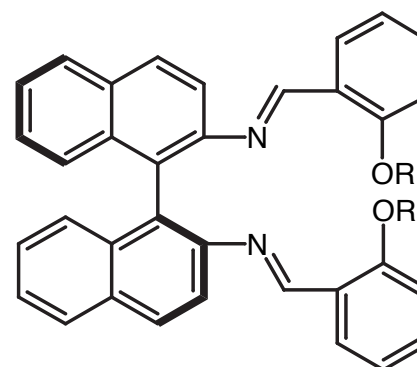
Kanemasa, S.; Adachi, K.; Yamamoto, H.; Wada, E. *Bull. Chem. Soc. Jpn* **2000**, 73, 681.

# Binaphthyldiimine (BINIM) derived Ni(II) Catalysts

## Suga's Enantioselective Diels-Alder Reaction

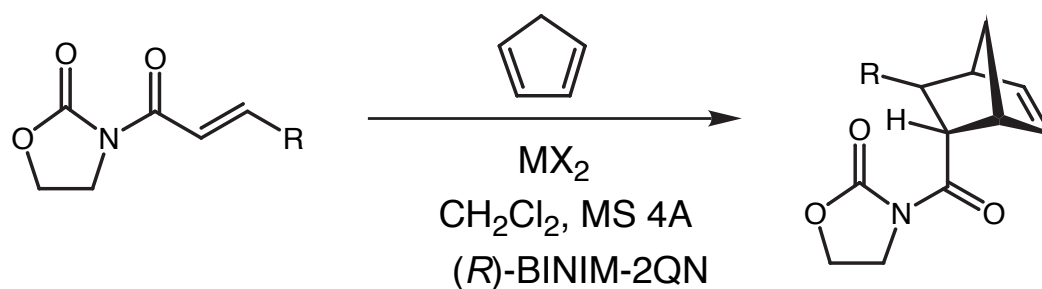


- A diverse range of BINIM ligands synthesized
- Ligands with co-ordinating functionality near diimine portion (ie **A**, R = H) gave increased ee over typical dichloro imines.
- Conversion of the hydroxyl group into a benzyl ether gave large decrease in ee.
- (*R*)-BINIM-2QN (**B**) gave the best results



Suga, H.; Kakehi, A.; Mitsuda, M. *Chem. Lett.* **2002**, 900

## Suga's Enantioselective Diels-Alder Reaction



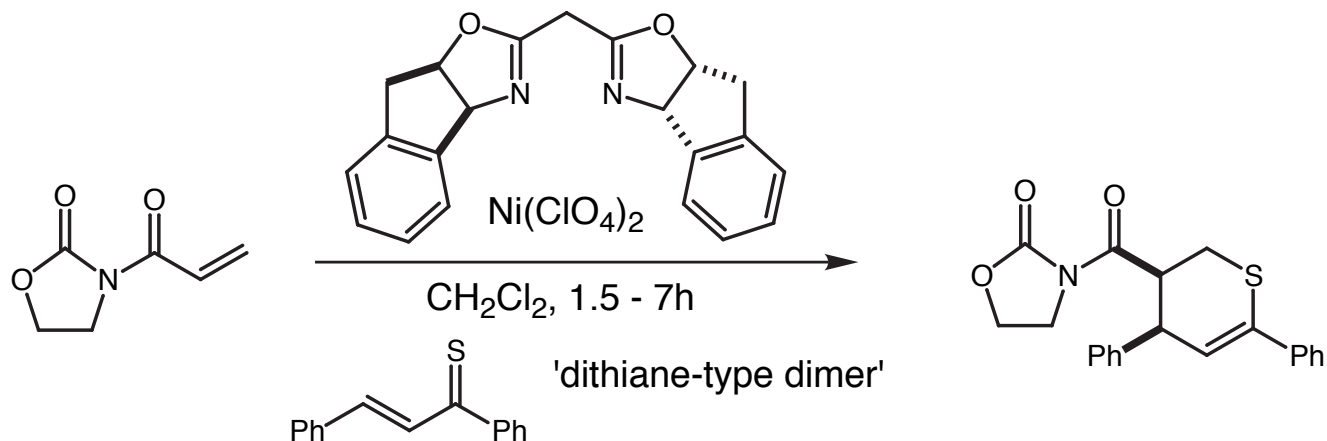
R	$\text{MX}_2$	mol%	temp/ $^\circ\text{C}$	time/h	yield/%	endo:exo	% ee (endo)
H	$\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	10	-40	17	94	>99:1	94
H	$\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	10	-40	17	98	95:5	90
H	$\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	10	-40	17	97	95:5	84
H	$\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	10	-40	13	89	92:8	93
H	$\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	5	-40	33	87	93:7	92
H	$\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	2	-40	38	85	93:7	90
Me	$\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	1	rt	13	85	80:20	92
Ph	$\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	10	rt	48	96	73:27	90

Author's model for observed stereochemistry is not clear

Suga, H.; Kakehi, A.; Mitsuda, M. *Chem. Lett.* **2002**, 900.

# Hetero-Diels-Alder Reaction of Thiabutadienes

Saito



temp/ $^{\circ}\text{C}$	yield (%)	endo:exo	% ee (endo)
-65	49 <sup>*</sup>	79:21	1
0	90	78:22	85
rt	99	76:24	96
rt	80	78:22	80

\* Reaction incomplete after 3h

- Only results using Ni(II) are shown. Ee's >99% were obtained using Cu(OTf)<sub>2</sub> under optimized conditions

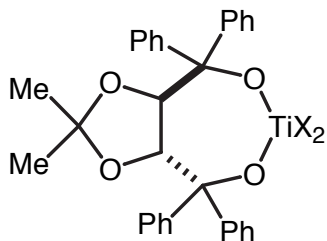
Saito, T.; Takekawa, K.; Takahashi, T. *Chem. Commun.* **1999**, 1001.

# ***Conclusions for Ni(II) Catalyzed Diels-Alder Reactions***

- DBFOX/Ph ligands with Ni(ClO<sub>4</sub>)<sub>2</sub> provide high levels of diastereo- and enantioselectivity  
A limited range of dienes and dienophiles have been investigated
- Py-Box ligands have been briefly investigated, and provide low levels of asymmetric induction
- Box ligands have been used with Ni(II) with moderate results, a detailed study has not been carried out
- The Diels-Alder reaction using Ni(II) was shown to be tolerant to highly co-ordinating additives, such as pyridine
- Napthyldiimine ligands with Ni(ClO<sub>4</sub>)<sub>2</sub> provide high levels of diastereo- and enantioselectivity  
A limited range of dienes and dienophiles have been investigated
- All the studies presented focused almost solely on oxazolidinones and cyclopentadiene as the reacting partners, except for one hetero-Diels-Alder reaction utilizing butadienes.

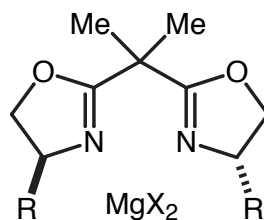
# Ni(II) Catalyzed 1,3-Dipolar Cycloadditions

Other metals have been utilized



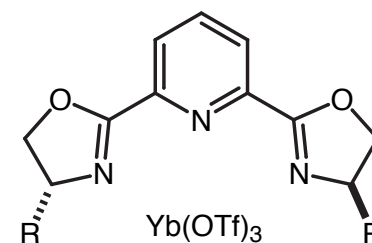
up to 60% ee

Jørgensen, *J. Org. Chem.* **1994**, 59, 5687.



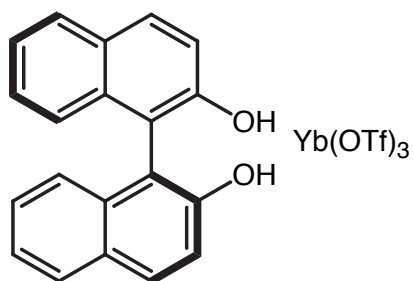
70-80% ee

Jørgensen, *J. Org. Chem.* **1996**, 61, 346.

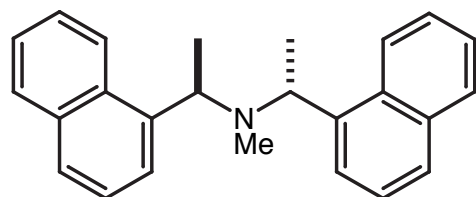


up to 73% ee

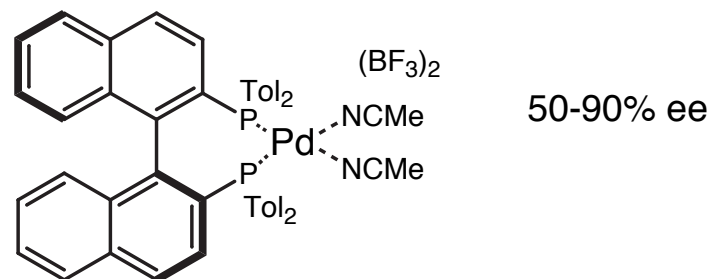
Jørgensen, *J. Am. Chem. Soc.* **1999**, 120, 5840.



80-96% ee



Kobayashi, *J. Am. Chem. Soc.* **1998**, 119, 5840.

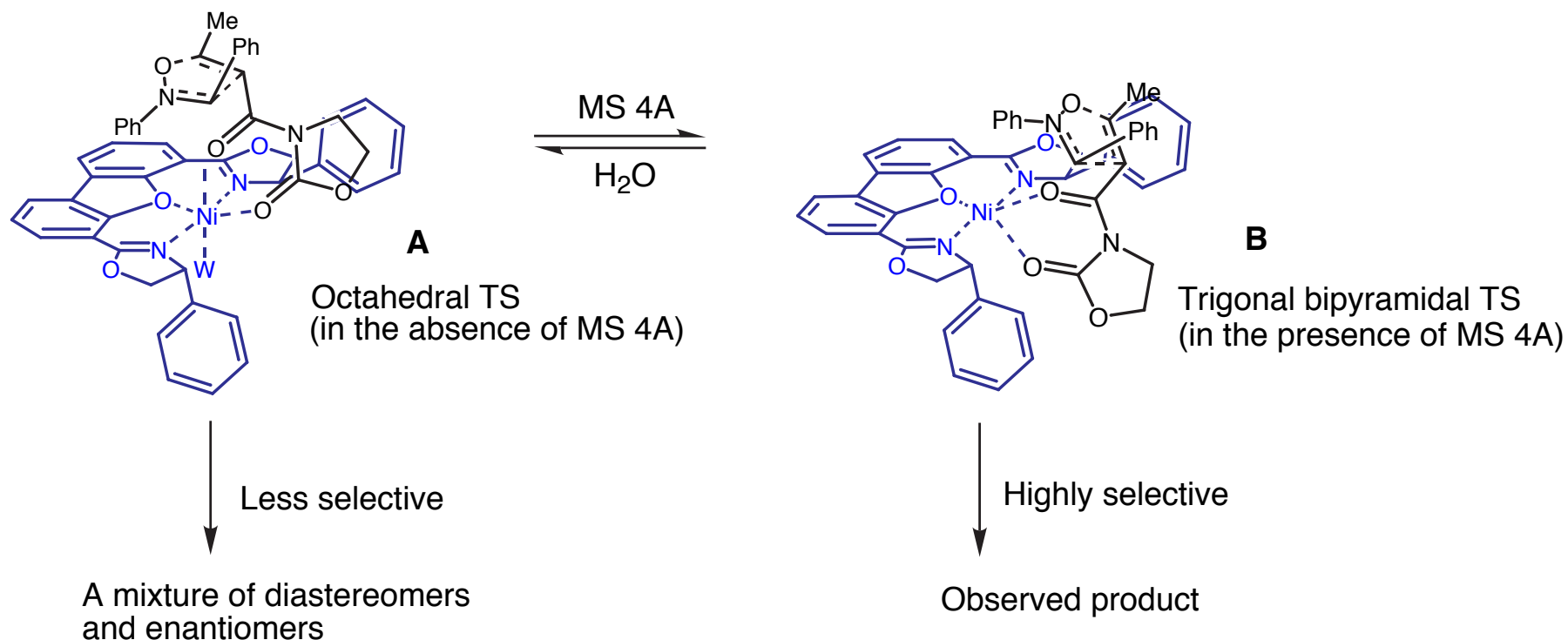


50-90% ee

Furakawa, *J. Org. Chem.* **1999**, 64, 5017.

# The Catalyst

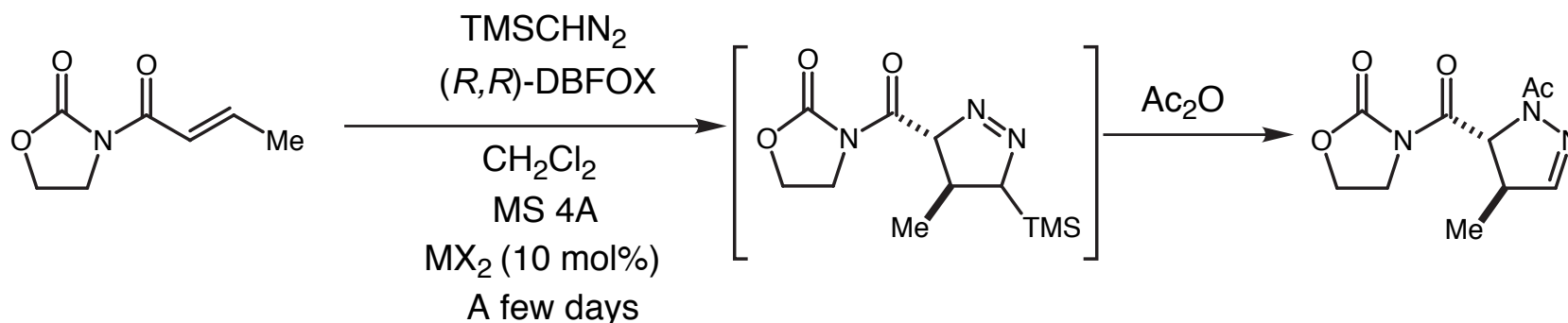
## Kanemasa: Stereochemical rationale



- Trigonal bipyramidal TS **B** predicted on the basis of NMR spectroscopic studies of a DBFOX/Ph-Zn(ClO<sub>4</sub>)<sub>2</sub> complex with 3-acetyl-2-oxazolidinone, see, Kanemasa et al. *Tetrahedron Lett.* **1998**, 39, 7521.
- Reaction in the absence of MS 4A gives poor diastereo- and enantioselectivity
- Similar observations made by Jørgensen, *J. Org. Chem.* **1996**, 61, 346
- Explains the role of MS 4A in the reaction

Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, 120, 12355

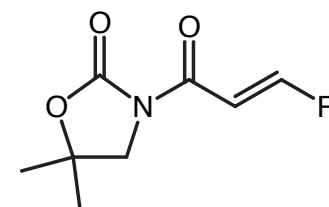
## Kanemasa - 1,3-Dipolar Cycloadditions of TMSdiazomethane



$\text{MX}_2$	temp/ $^\circ\text{C}$	yield/%	% ee
$\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	rt	49	40
$\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	-40	85	96
$\text{Zn}(\text{ClO}_4)_2$	-40	81	97
$\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	-40	79	93
$\text{Mg}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	-20	64	82

- Stereochemical rationale with unsubstituted oxazolidinone is the same as DBFOX/Ph nitrene reactions.
- The dimethyl oxazolidinone selects for the opposite face of the olefin.

- When Me is replaced with other R groups ee's lowered (40-70% ee for Zn complex)



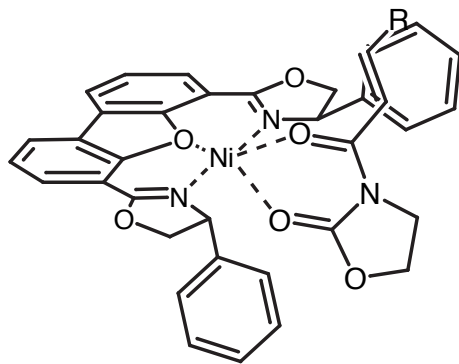
- The dimethyl-oxazolidinone proved effective for other R groups (80-98% ee, R = Me, *n*-Pr, *i*-Pr)
- Only Mg complex was active.

Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710.

# The Catalyst

## A Possible Explanation?

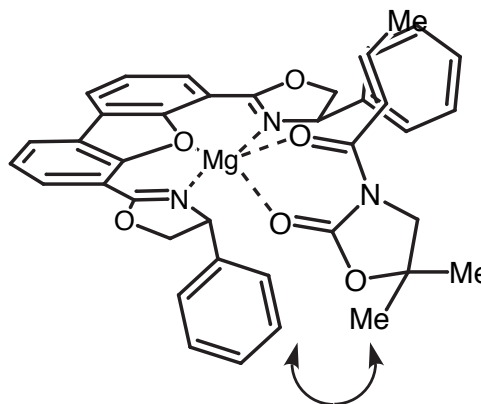
unsubstituted oxazolidinone



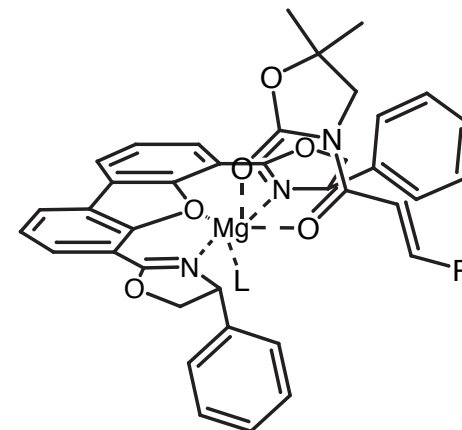
Observed product

Trigonal bipyramidal TS  
(in the presence of MS 4A)

disubstituted oxazolidinone



Vs.

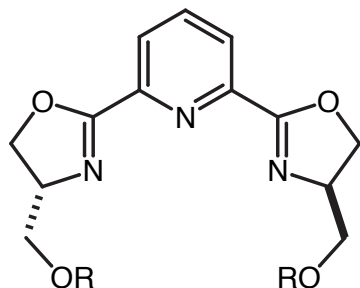


Observed product

- For unsubstituted oxazolidinone trigonal pyramidal geometry favored.
- Steric effects force dimethyl oxazolidinone into a different geometry, possibly an octahedral complex. This would explain the reversal of absolute stereochemistry.

# Trialkylsiloxyethyl-Py-Box Ligands

Iwasa: 'Tunable' ligands



R = H (pybox-*hm*)

R = TBDMS (pybox-*tbdmsom*)

R = TIPS (pybox-*tipsom*)

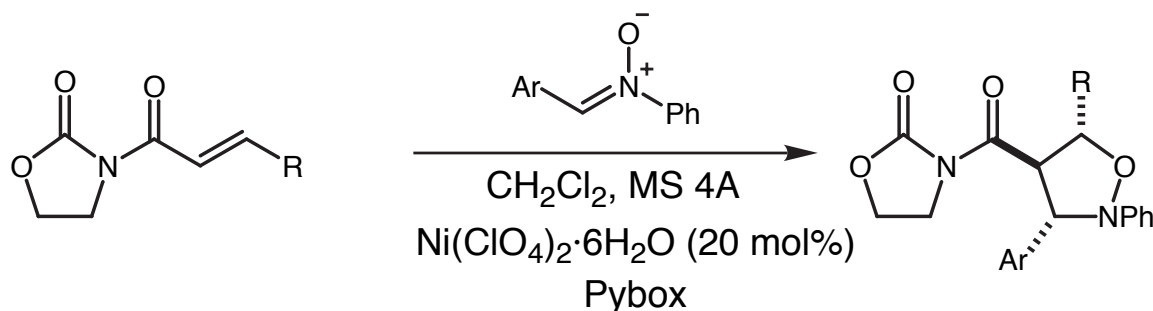
R = TBDPS (pybox-*tbdpsom*)

- Alteration of the protecting group facilitates the *steric tuning* of the chiral environment of the pybox
- The large silyl groups probably enhance the solubility of the ligand-metal complexes

For ligand synthesis, see: a) Iwasa, S.; Nakamura, H.; Nishiyama, H. *Heterocycles* **2000**, *52*, 939. b) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227.

# Iwasa's 1,3-Dipolar Cycloaddition Study

## Iwasa: The Classical Pybox system



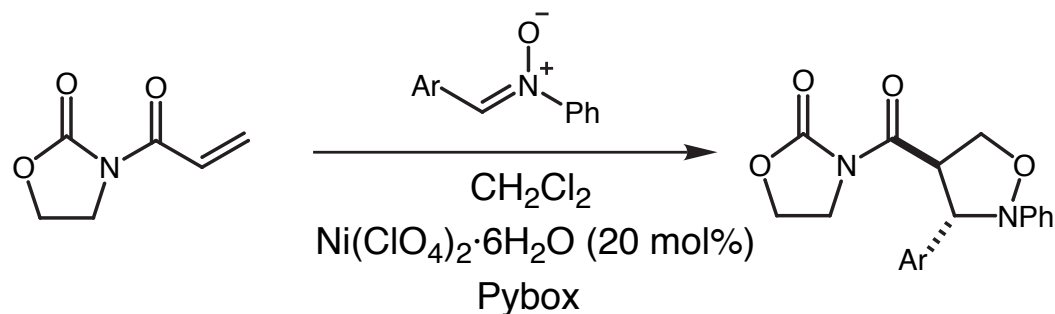
R	Ar	Pybox	temp/ <sup>o</sup> C	time/h	yield/%	endo:exo	% ee (endo)
H	Ph	<i>t</i> -Bu	0	72	97	92:8	90
H	4-MePh	<i>t</i> -Bu	0	72	99	96:4	86
Me	Ph	<i>t</i> -Bu	rt	72	98	97:3	86
Me	4-MePh	<i>t</i> -Bu	rt	72	99	99:1	82
Me	Ph	<i>i</i> -Pr	rt	72	89	97:3	66

- *i*-Pr-pybox also used with Co(ClO<sub>4</sub>)<sub>2</sub> (*endo:exo* = 96:4, 63% ee); Mn(ClO<sub>4</sub>)<sub>2</sub> (96:4, 71% ee); Fe(ClO<sub>4</sub>)<sub>2</sub> (52:48, 24% ee)
- *t*-Bu-pybox provides higher asymmetric induction than *i*-Pr-pybox. Steric 'tuning' of the pybox-*hm* ligand was next attempted in order to improve ee

Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227

For initial communication, see: Iwasa, S.; Shimada, S.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 6715

## Iwasa: Siloxymethyl-Pybox Ligands



Pybox	MS 4A	temp/ <sup>o</sup> C	time/h	yield/%	endo:exo	% ee (endo)
<i>hm</i> *	no	25	24	0	-	-
<i>tbdmsom</i>	no	25	24	83	93:7	93
<i>tbdmsom</i>	no	0	24	96	94:6	95
<i>tbdmsom</i>	no	-15	24	94	95:5	98
<i>tipsom</i>	yes	0	4	99	>99:1	>99
<i>tbdpsom</i>	no	0	1.5	99	97:3	>99

\* Solvent: IPA:DCM:water, 3:3:1

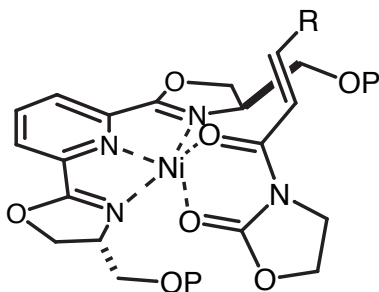
Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227

For initial communication, see: Iwasa, S.; Shimada, S.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 6715

## Iwasa: Siloxymethyl-Pybox Ligands

- The reaction also works well for crotonyl-oxazolidinone (>99:1 *endo:exo*, 92-98%ee)
- Catalyst loadings as low as 1 mol% were possible with little loss of selectivity
- Linear correlation observed between ee of *tipsom*-pybox ligand and product - only a singly-coordinated Ni-pybox species in solution *cf.* DBFOX/Ph Kanemasa, *J. Am. Chem. Soc.* **1998**, *120*, 3074.
- Reactions can be performed in alcoholic media *ie.* *t*-BuOH with increased reaction rates. Obviates the need for chlorinated solvents, see: Iwasa and co-workers, *Tetrahedron*, **2002**, *58*, 8281.

### Stereochemical rationale

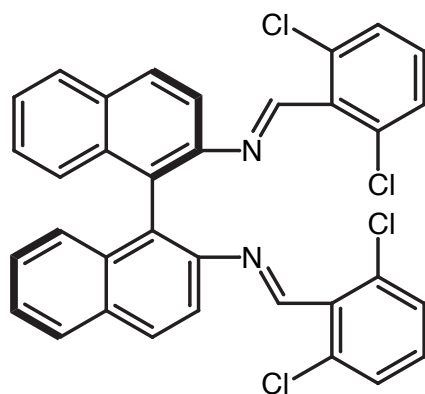
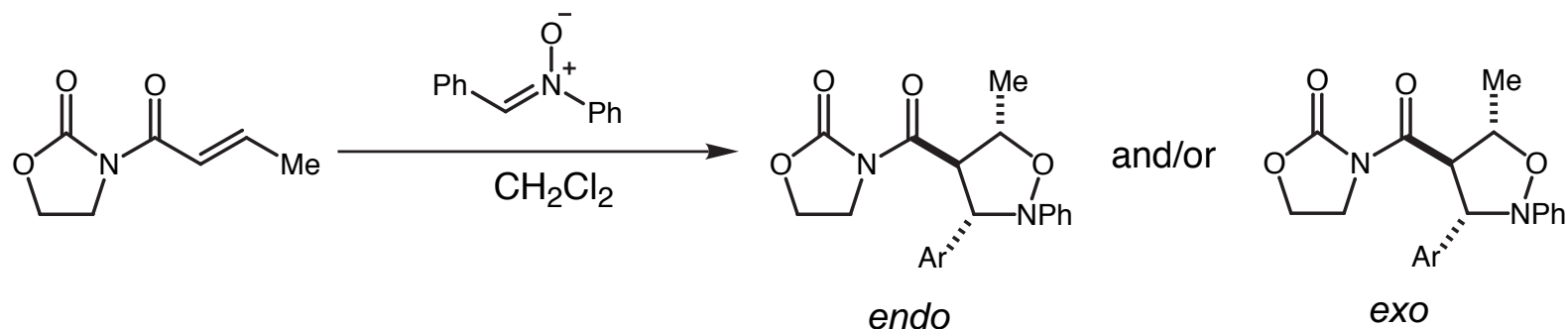


—————> observed products

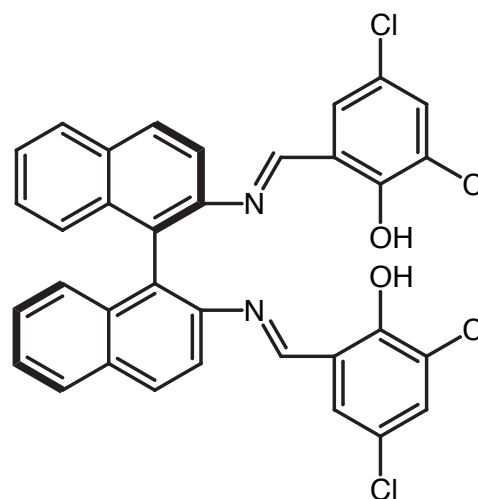
- Trigonal bipyramidal with MS 4A, *cf.* Kanemasa, *J. Am. Chem. Soc.* **1998**, *120*, 12355

Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227

# Suga's Ni(II)-Binaphthyldiimine Catalysts



$\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ , MS 4A  
86% yield  
*endo:exo* = 96:4  
66% ee

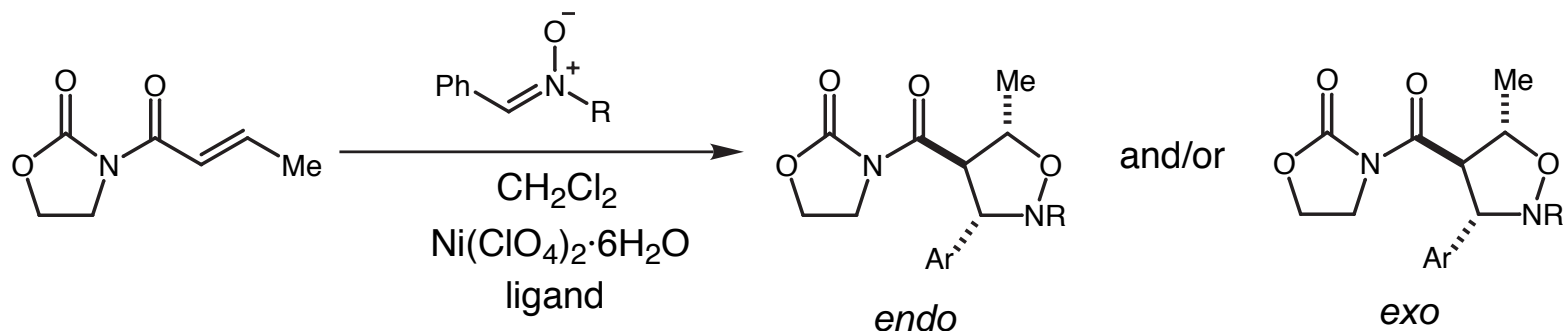


$\text{Ni}(\text{SbF}_6)_2 \cdot 6\text{H}_2\text{O}$   
63% yield  
*endo:exo* = 42:58  
82% ee *endo*, 24% ee *exo*

- Alcoholic additives gave increased ee's for BINIM-DC. Hence, BINIM-DCOH ligands explored.
- BINIM-DC affords high de with lower ee. BINIM-DCOH affords higher ee with lowered de!

Suga, H.; Kakehi, A.; Ito, S.; Sugimoto, H. *Bull. Chim. Soc. Jpn.* **2003**, 76, 327.

## An Interesting Result - Exo-selectivity



ligand	R	time/h	yield/%	<i>endo:exo</i>	% ee ( <i>major</i> )
BINIM-DC	Ph	46	92	82:18	80
BINIM-DCOH	Ph	95	86	8:92	63
BINIM-DC	Bn	66	51	95:5	32
BINIM-DCOH	Bn	287	55	12:88	52
BINIM-DC	Me	215	77	91:9	59
BINIM-DCOH	Me	425	66	15:85	31

(BINIM-DC used with 100 mol% PhOH as additive)

- In contrast to other reported 1,3-dipolar cycloadditions of nitrones with oxazolidinones the  $\text{Ni}(\text{ClO}_4)_2$ -BINIMDCOH catalyst affords *exo* products in high diastereoselectivity
- Unfortunately the reaction suffers from low ee at this stage

Suga, H.; Kakehi, A.; Ito, S.; Sugimoto, H. *Bull. Chim. Soc. Jpn.* **2003**, 76, 327.

## ***Conclusions - Ni(II) catalyzed 1,3-dipolar cycloadditions***

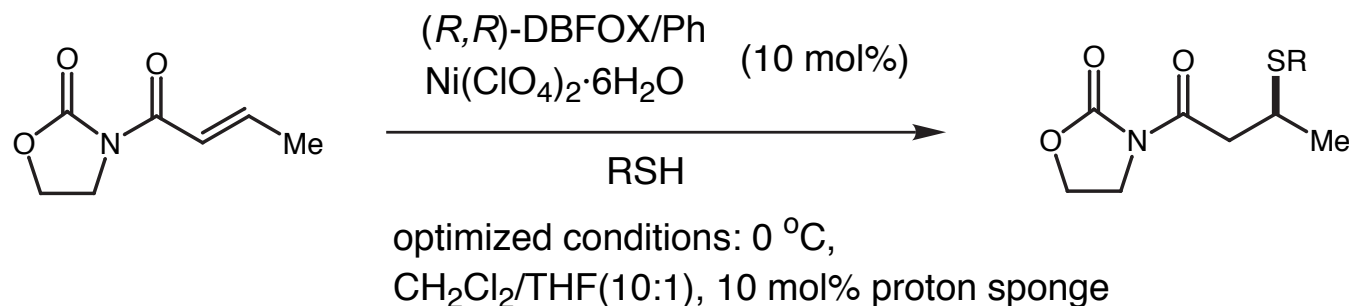
- Kanemasa has successfully utilized his Ni(II)-DBFOX/Ph catalyst for highly *endo*-selective asymmetric 1,3-dipolar cycloadditions of a limited number of nitrones and oxazolidinones.
- The importance of MS 4A in the reaction was observed and rationalized in terms of catalyst/substrate co-ordination geometries.
- Iwasa has demonstrated the use of classical pybox ligands in conjunction with Ni(II) salts.
- Iwasa's pybox-*hm* ligand provides a useful scaffold for *steric tuning* of the pybox ligands. On this basis highly *endo*- and enantioselective 1,3-dipolar cycloadditions were developed.
- The effectiveness of these catalysts lies, to some extent, in their increased solubility relative to classical pybox ligands.
- Suga's Ni(II)-Binaphthyldiimine catalysts provide moderate levels of enantioselectivity, but more importantly, an *exo*-selective catalyst was uncovered.

# ***Ni(II) Catalyzed Conjugate Additions***

***Kanemasa has published several Ni(II) catalyzed conjugate additions***

- Conjugate additions of thiols to oxazolidinones, *J. Am. Chem. Soc.* **1999**, 121, 8675.
- Conjugate additions of nitromethane to acylpyrazoles, *J. Am. Chem. Soc.* **2002**, 124, 13394.
- Conjugate additions of malononitrile to oxazolidinones, *Tetrahedron: Asymmetry* **2003**, 14, 635.
- Enol lactone synthesis by conjugate addition of 5,5-dimethyl-1,3-cyclohexanedione to acylpyrazoles, followed by *in situ* cyclization (not enantioselective, yet), *Tetrahedron Lett.* **2003**, 44, 1799.
- Although Zn(II) was chosen for optimization, Ni(II) was effective in catalyzing the conjugate addition of benzaldoxime to an oxazolidinone, *Tetrahedron Lett.* **2002**, 43, 829.

# Ni(II) Catalyzed Conjugate Additions of Thiols



<i>selected entries</i>	RSH	time/h	yield/%	% ee
	Ph	24	84	94
	<i>o</i> -Tolyl	96	99	95
	<i>p</i> -Tolyl	96	91	91
	Mesityl	96	96	96
	<i>p-t</i> -BuPh	96	38	69
	1-Naphthyl	96	92	55

- No examples of aliphatic thiols
- Absolute stereochemistry fits with octahedral model for DA reaction, see: Kanemasa, *J. Am. Chem. Soc.* **1998**, *120*, 3074.

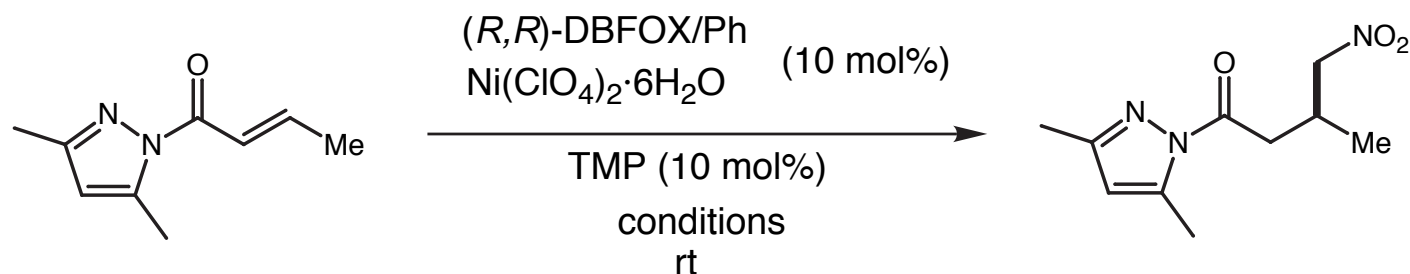
Kanemasa, S.; Oderatoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675

# ***Ni(II) Catalyzed Conjugate Additions of Thiols***

- Use of anhydrous Ni(II) catalyst, or aqua catalyst with MS 4A gave racemic products
- Addition of PhSH to DBFOX/Ph-Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O in THF gives a gradual color change from pale blue to reddish brown. This color change is rapid in CH<sub>2</sub>Cl<sub>2</sub>. Thiol co-ordination is rapid in non-coordinating solvent.
- Isolation of a brown ppt. using IPA and hexanes. Slowly liberated thiol at room temperature.
- Ppt. showed reasonable catalytic activity in THF (97% yield, 70% ee).
- Clearly, thiol binds to Ni catalyst, but this process is reversible in the presence of oxazolidinone and co-ordinating solvent.
- Hence, the anhydrous complex probably binds thiol irreversibly to give inactive catalyst. The presence of water allows for effective ligand exchange.
- The presence of an amine base such as Et<sub>3</sub>N or pyridine gives a totally inert, reddish brown solid which is insoluble in the reaction medium. Analysis showed no perchlorate counterions. Replaced by the highly coordinating thiolate ions.

Kanemasa, S.; Odatoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675

# Ni(II) Catalyzed Conjugate Additions of Nitromethane



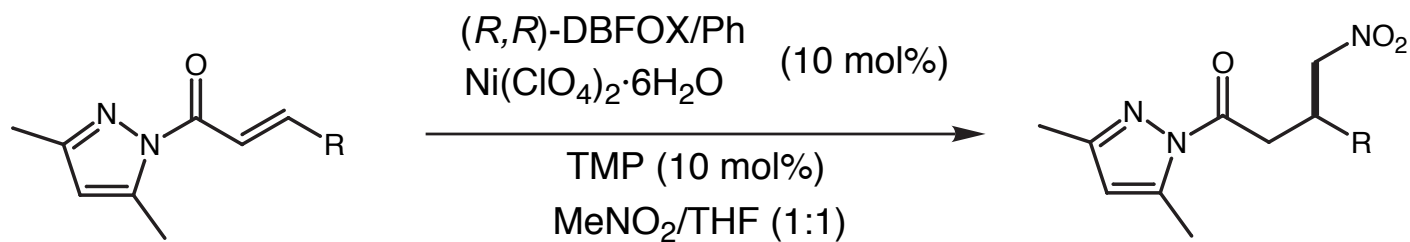
*initial development*

conditions	time/h	yield/%	% ee
MeNO <sub>2</sub> (1 equiv) in THF	168	trace	-
MeNO <sub>2</sub> as solvent	5	95	77
MeNO <sub>2</sub> /THF (1:1)	5	97	84
MeNO <sub>2</sub> /THF (1:1) with MS 4A	5	84	67

- The equivalent reaction with an oxazolidinone acceptor, using MeNO<sub>2</sub> as solvent was very slow. After 144h, 30% yield, 39% ee.
- Although TMP itself catalyzes the reaction (10 mol%, rt, 72h, 89%), DBFOX/Ph/Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O does not.
- Use of the anhydrous complex results in lowered ee (rt, 48h, 19% yield, 31% ee).
- The tolerance of Ni(II) towards amine bases once again demonstrated.

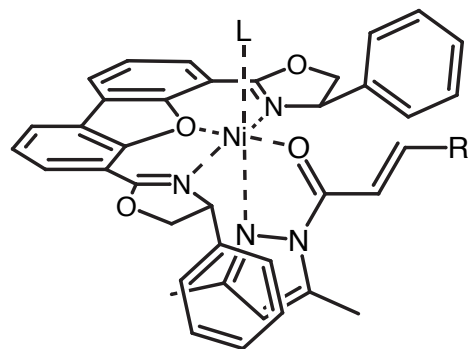
Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394.

# Substrate Scope

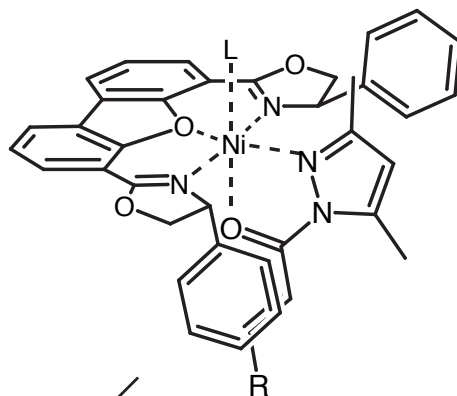


R	temp/ $^{\circ}\text{C}$	time/h	yield/%	% ee
Me	rt	5	97	84
Me	0	48	91	90
Me	-20	96	85	94
Et	-20	24	93	95
<i>i</i> -Pr	-20	96	74	94
<i>t</i> -Bu	0	168	39	95
$\text{CO}_2\text{Me}$	rt	168	91	83
	-20	3	49	77
Ph	-20	96	90	93
2-Thienyl	-20	168	83	97

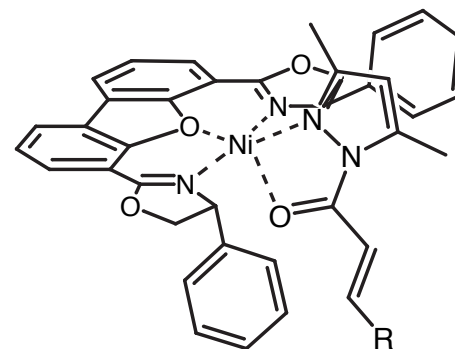
# A Possible Model?



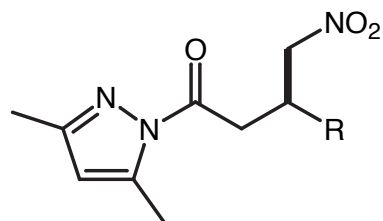
Vs.



Vs.

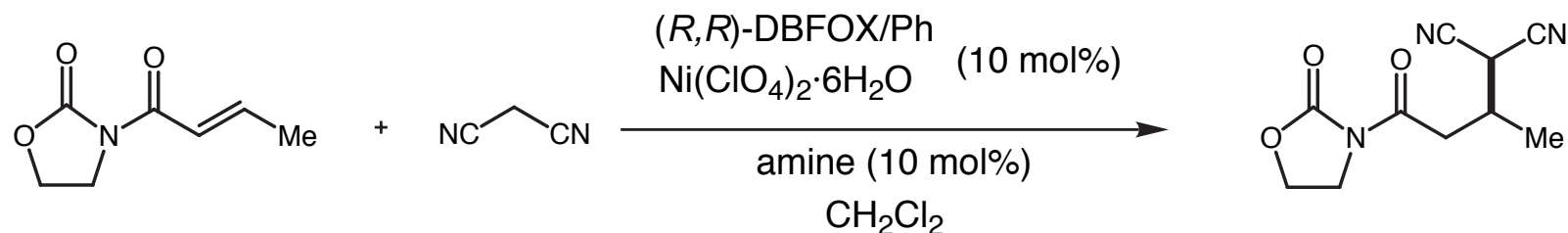


Trigonal pyramid less effective at shielding one face of double bond?



- Assuming an octahedral co-ordination geometry the two orientations of the acylpyrazole seem to both lead to the observed absolute stereochemistry.
- Trigonal pyramidal co-ordination implicated in reactions involving MS 4A and anhydrous Ni-DBFOX complexes, *cf.* Kanemasa, *J. Am. Chem. Soc.* **1998**, 120, 12355.
- This analysis would fit with the observation that anhydrous complex and the use of MS 4A gave lower ee for the conjugate addition of nitromethane.

# Conjugate Additions of Malononitrile

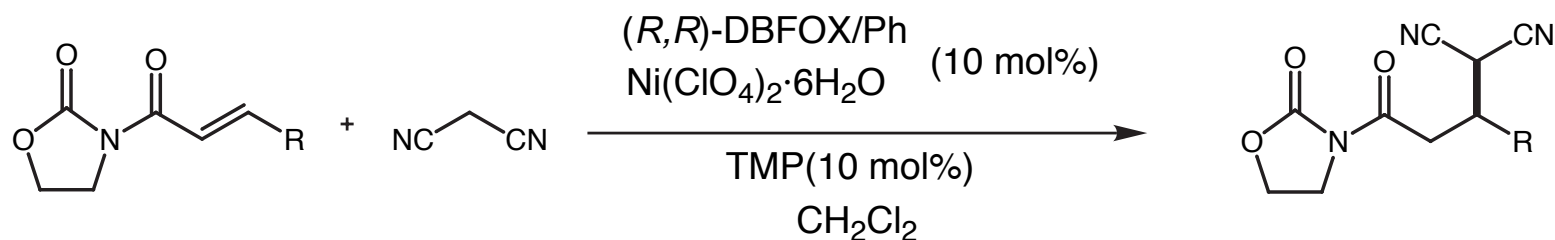


## The Effect of Amine Additives

amine	temp/ $^{\circ}\text{C}$	time/h	yield/%	% ee
none	rt	72	40	5
proton sponge	-20	18	92	85
DIPEA	-20	24	100	87
DBU	-20	96	70	87
<i>N,N</i> -dibenzylamine	-20	32	100	82
<i>N,N</i> -dicyclohexylamine	-20	8	85	82
TMP	-20	6	90	85

- Ni(II) DBFOX/Ph catalyst remains highly active in the presence of amines.
- DBFOX/Ph- $\text{Mg}(\text{ClO}_4)_2$  displayed the highest catalytic activity in the absence of an amine. The addition of  $\text{Et}_3\text{N}$  to the reaction led to heavy deactivation (rt, 96h, 26% yield, 26% ee).

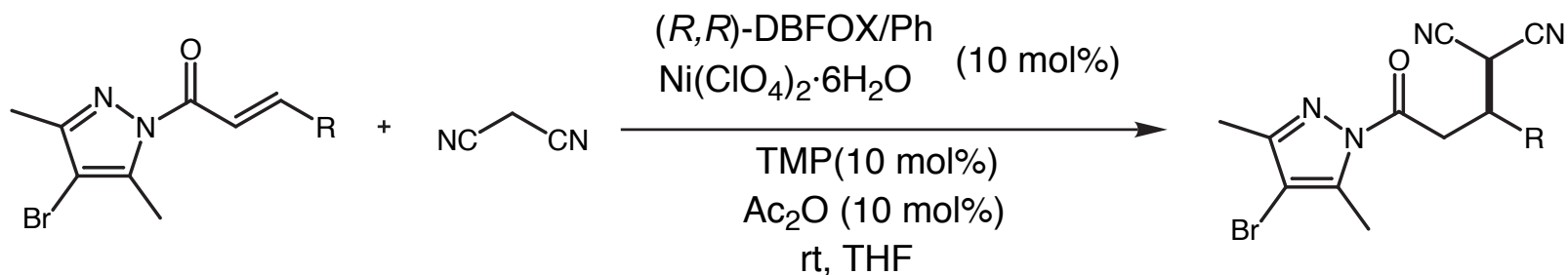
# Conjugate Additions of Malononitrile



R	temp/ $^{\circ}\text{C}$	time/h	yield/%	% ee
Me	-20	6	90	85
<i>n</i> -Pr	-20	96	100	90
<i>i</i> -Pr	-20	48	90	87
<i>t</i> -Bu	0	168	58	90
<i>t</i> -Bu	-20	168	38	94
Ph	-20	96	95	75

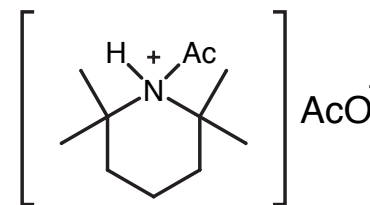
- In some cases reactions at  $-40^{\circ}\text{C}$  and  $-78^{\circ}\text{C}$  give lower selectivities.
- Some polar solvents could also be utilized: ACN (rt, 69% ee;  $-20^{\circ}\text{C}$ , 74% ee), ACN/THF (1:1, rt, 75% ee);  $\text{CH}_2\text{Cl}_2$ /THF (10:1,  $0^{\circ}\text{C}$ , 81% ee);  $\text{CH}_2\text{Cl}_2$ /MeOH (10:3,  $-20^{\circ}\text{C}$ , 84% ee).
- Polar co-ordinating solvents decrease reaction rate by competitive coordination to metal. This also suppresses the undesired coordination of the amine base. These reactions are a delicate balance.

# Conjugate Additions of Malononitrile



R	time/h	yield/%	% ee
Me	5	94	88
<i>i</i> -Pr	7	94	93
<i>c</i> -Hex	24	88	90
<i>t</i> -Bu	120	82	91
Ph	12	87	88
<i>p</i> -BrPh	12	94	85
<i>p</i> -MePh	24	91	78
2-Furyl	48	78	55

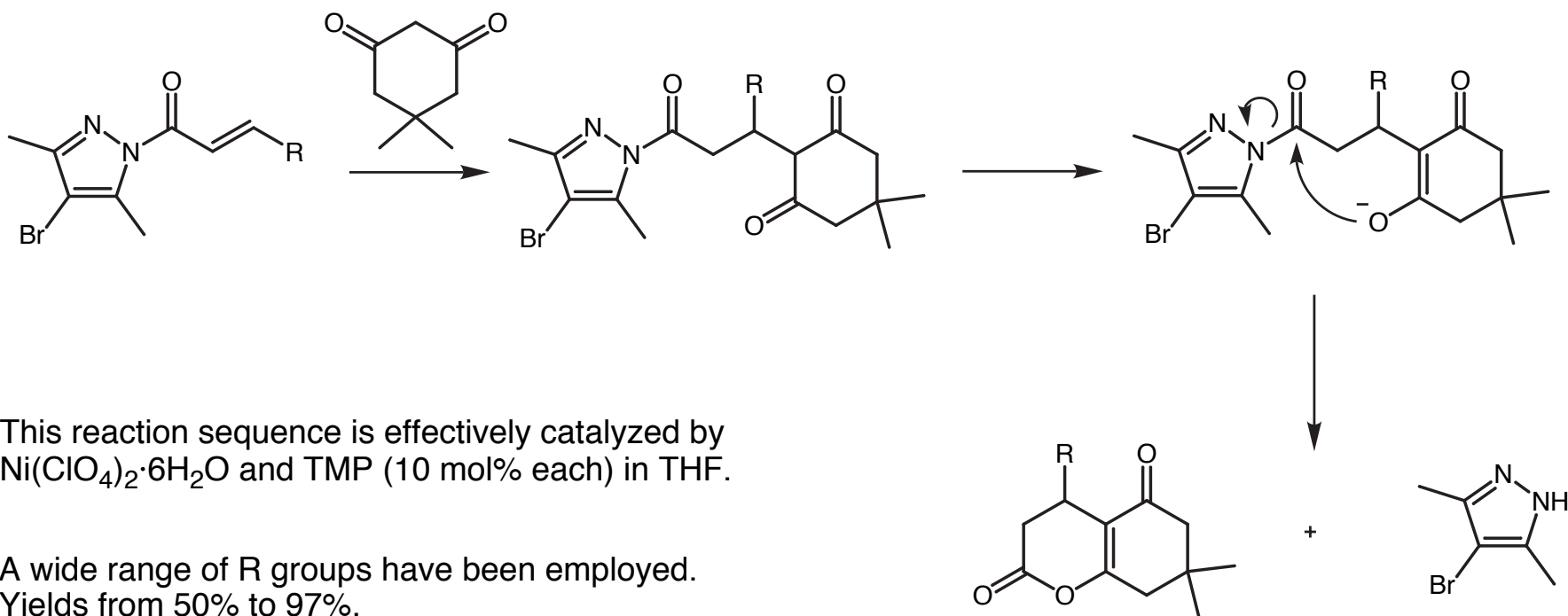
- The des-bromo pyrazole gave lower ee. For R = Me, 81%
- Without  $\text{Ac}_2\text{O}$  the reaction gives only 23% ee.
- No explanation given.



- Is acetate the base?
- Could  $\text{Ni}(\text{OAc})_2$  be effective?

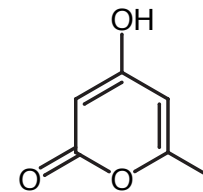
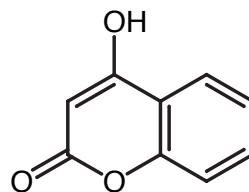
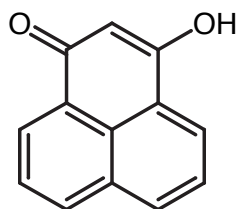
Itoh, K.; Oderaotoshi, Y.; Kanemasa, S. *Tetrahedron Asymmetry* **2003**, *14*, 635.

# Kanemasa's Enol Lactone Synthesis



- This reaction sequence is effectively catalyzed by  $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$  and TMP (10 mol% each) in THF.
- A wide range of R groups have been employed. Yields from 50% to 97%.

- Other diketones have also been employed.



- At the present time Kanemasa has not reported an enantioselective variant of this transformation.

Itoh, K.; Kanemasa, S. *Tetrahedron Lett.* **2003**, *44*, 1799.

## ***Conclusions - Conjugate Additions***

- Several useful Ni(II) catalyzed asymmetric conjugate additions have been reported by Kanemasa.
- The successful conjugate addition of thiols demonstrated the catalytic fidelity of Ni(II) based systems in the presence of strongly co-ordinating substances.
- The use of amine bases in conjunction with Ni(II) Lewis acids has been further demonstrated.

## ***Overall Conclusions***

- Ni(II) has proven a useful metal in asymmetric Diels-Alder reactions and 1,3-dipolar cycloadditions.
- Ni(II) based catalysts have been utilized in the presence of amine bases in asymmetric conjugate additions.
- In many of these reactions control over Ni co-ordination geometry - Octahedral vs. Trigonal Pyramidal - has proven necessary for absolute stereocontrol.
- Anhydrous Ni complexes appear to proceed through trigonal pyramidal co-ordination geometries, while aqua Ni complexes appear to go through octahedral geometries.
- Ni complexes appear to be excellent candidates for the development of asymmetric aza-Diels-Alder reactions, aza-ene reactions and amine conjugate additions, amongst others.