

Nickel-based Lewis Acid Asymmetric Catalysis

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An Evans Group Afternoon Seminar

18 April 2003

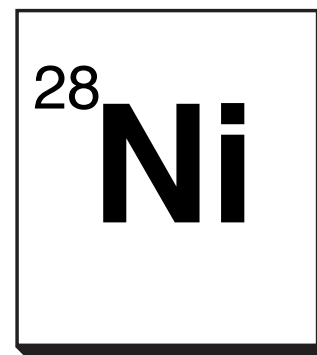
- I General Introduction to Nickel**
- II Ni(II) Catalyzed Diels-Alder Reactions**
- III Ni(II) Catalyzed 1,3-Dipolar Cycloadditions**
- IV Ni(II) Catalyzed Conjugate Additions**
- V Conclusions**

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, Ni⁰, Ni^I and Ni^{II} most common

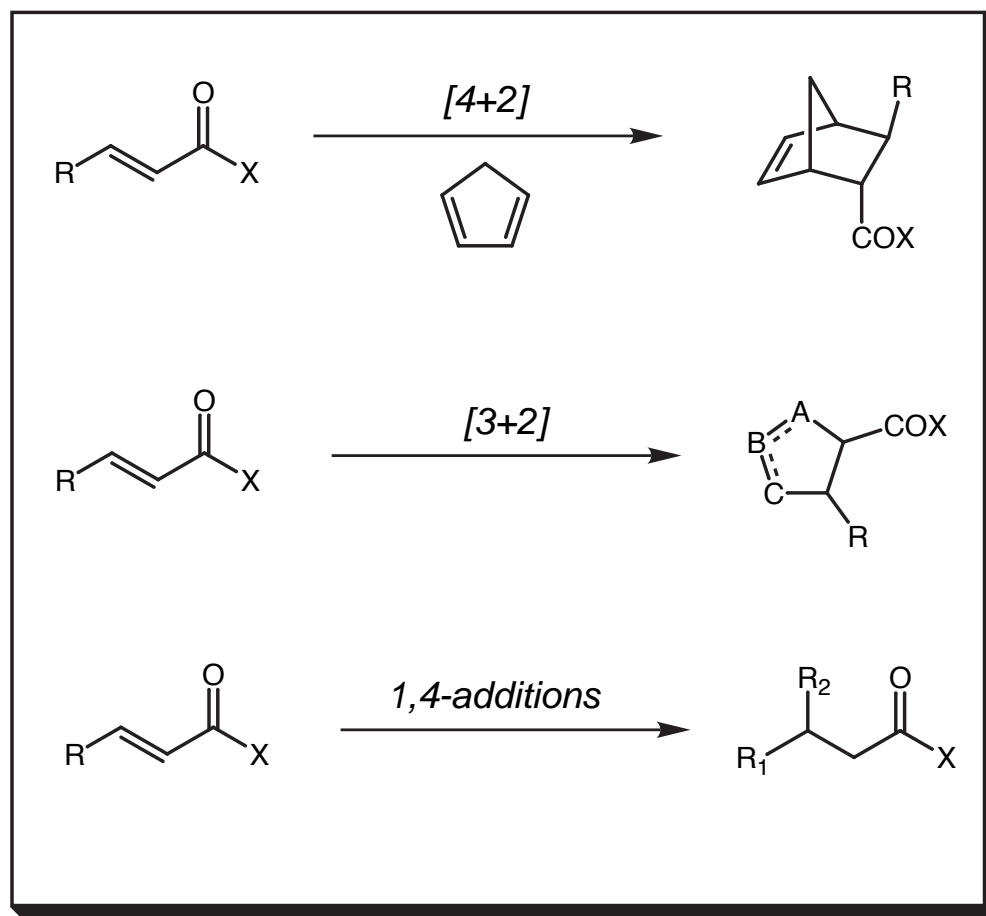
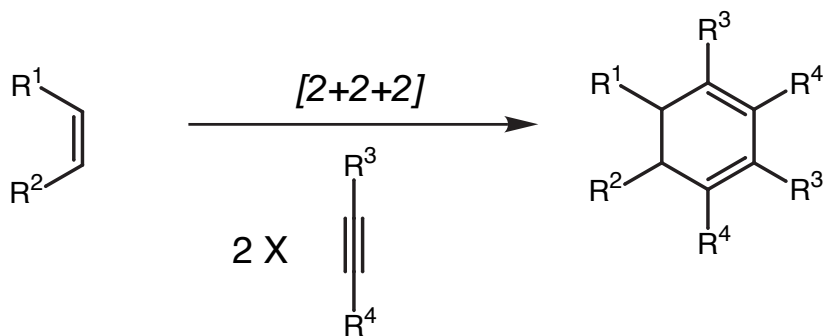
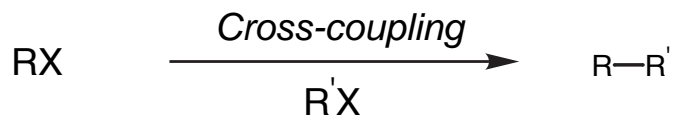
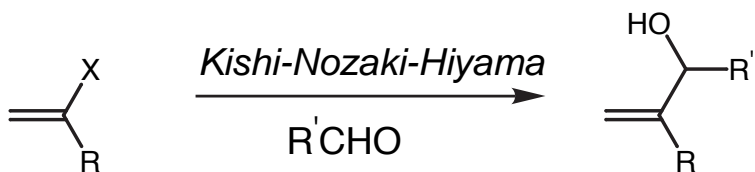
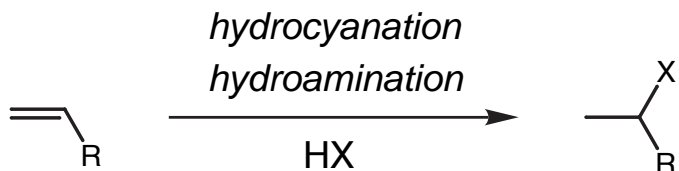
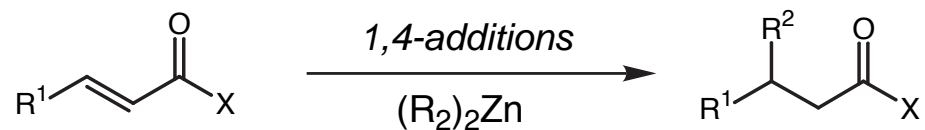
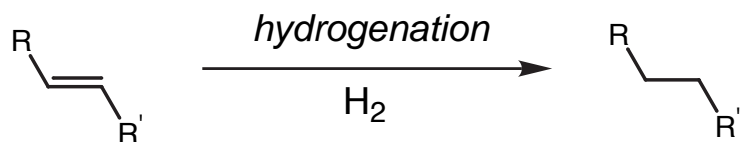
Oxidation State	Co-ordination number	Geometry	Examples
Ni ⁰	4	Tetrahedral	Ni(CO) ₄ , [Ni(CN) ₄] ⁴⁻
Ni ^I , d ⁹	4	Tetrahedral	Ni(PPh ₃) ₃ Br
Ni ^{II} , d ⁸	3	Trigonal planar	[Ni(NR ₂) ₃] ⁻
	4	Square planar	[Ni(CN) ₄] ²⁻ , Ni(PPh ₃) ₂ Br ₂
	4	Tetrahedral	[NiCl ₄] ²⁻ , NiCl ₂ (PPh ₃) ₂
	5	Square pyramidal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

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 Ni(ClO₄)₂ catalyzed enantioselective Diels-Alder reactions - in collaboration with *Prof. Dennis Curran*
- 1998** - ¹H NMR spectroscopic study of DBFOX/Ph-Zn(ClO₄)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

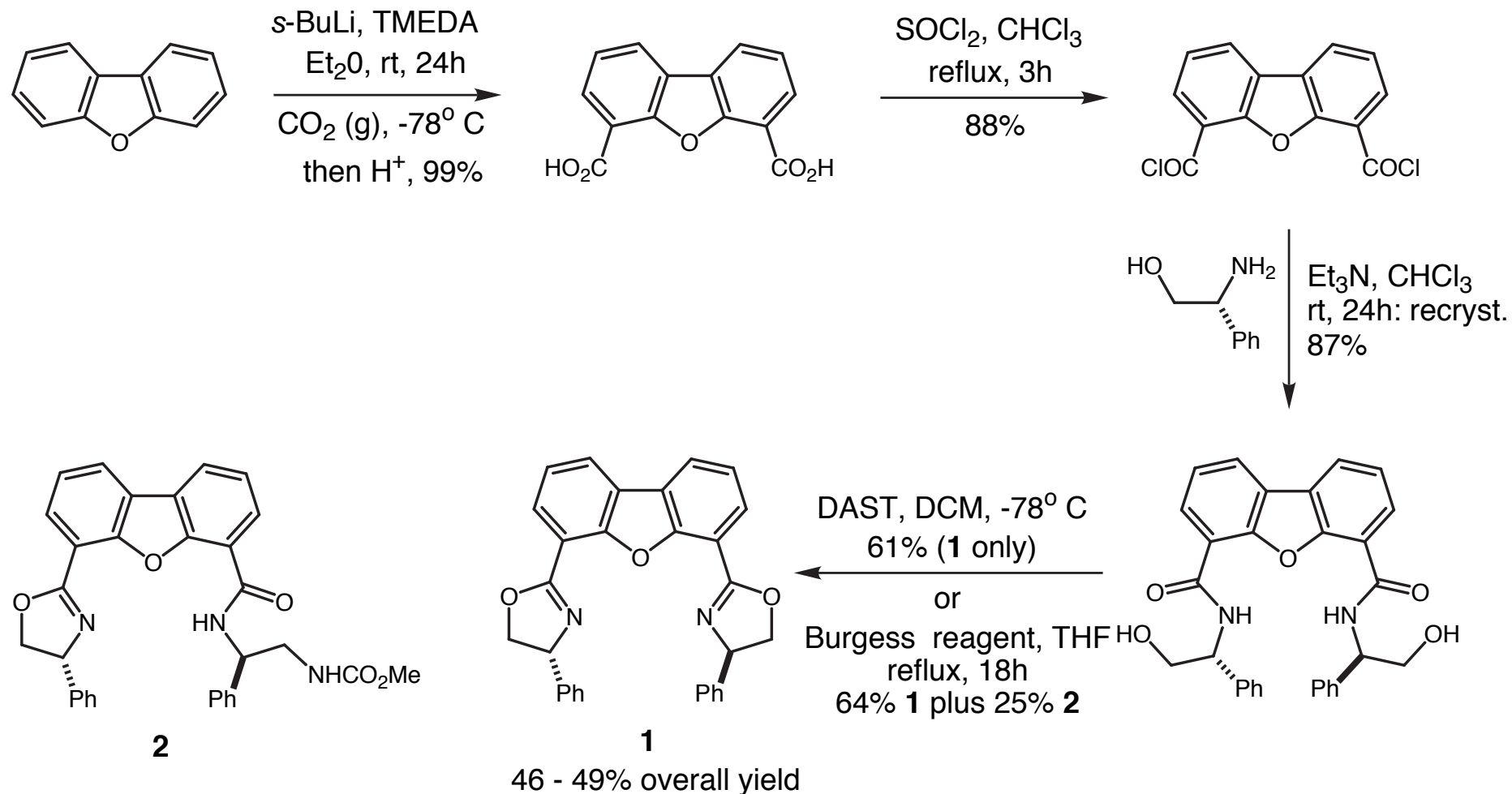
Professor Hiroyuki Suga - Shinshu University

- 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 C₂-Symmetric trans-Chelating Ligand

Optimized Ligand Synthesis:



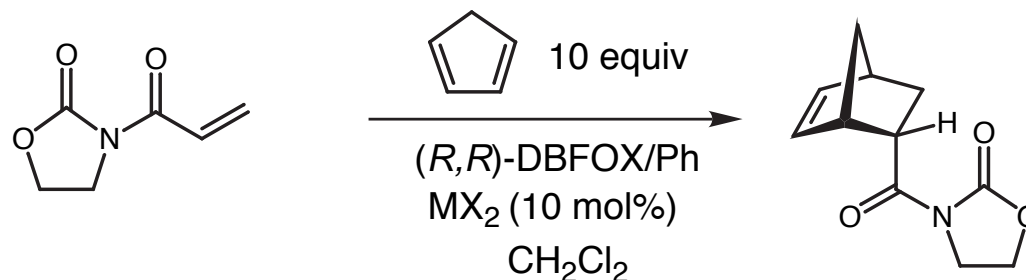
Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron Asymmetry* **1999**, *10*, 2417

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

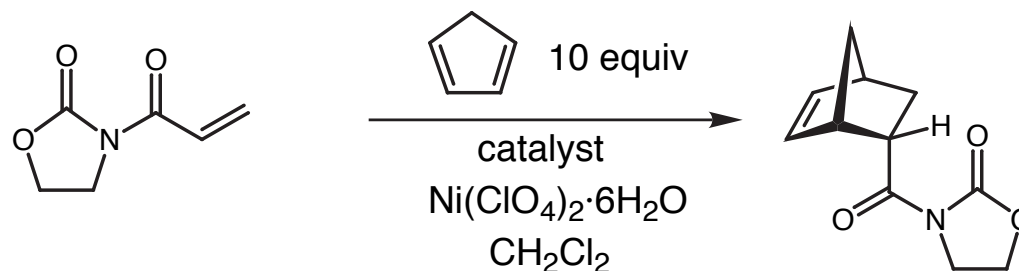
Kanemasa's initial report: A Survey of metals



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

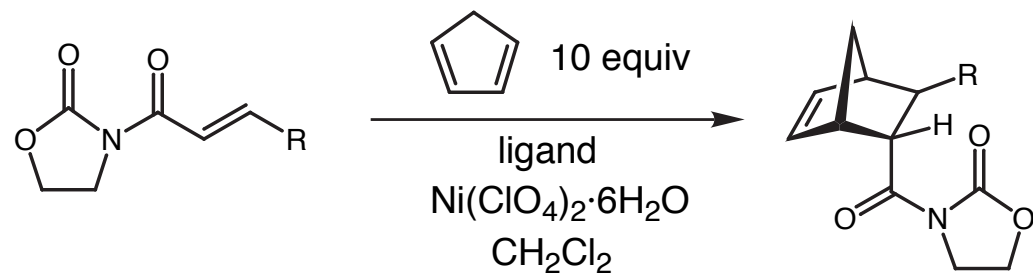


catalyst	mol%	temp/ ^o C	time/h	yield/%	endo:exo	% ee (endo)
DBFOX/Ph	10	rt	2	95	92:8	89
DBFOX/Ph	10	-20	24	97	97:3	95
DBFOX/Ph	10	-40	14	96	97:3	>99
DBFOX/Ph	10	-78	96	100	98:2	>99
DBFOX/Ph	2	-40	21	95	98:2	96
DBFOX/Ph	2	0	4	96	95:5	89
DBFOX/Ph	1	rt	1	95	92:8	78
[*] DBFOX/Ph	10	-40	72	98	98:2	>99

* Crystallized DBFOX/Ph- $\text{Ni}(\text{ClO}_4)_2 \cdot 3\text{H}_2\text{O}$ complex, from CH_2Cl_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/ ^o 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 [*]	74
H	(<i>R,R</i>)-Ph-BOX	-40	72	97	88:12	-52

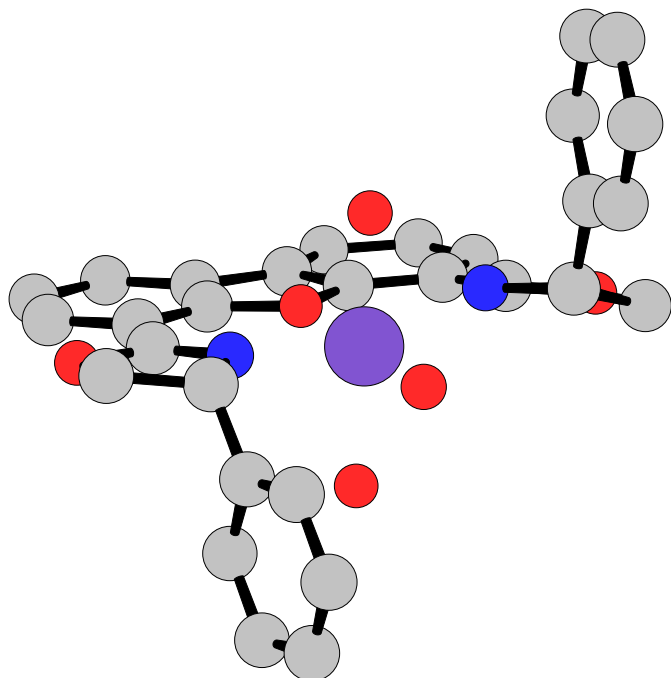
* not determined

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

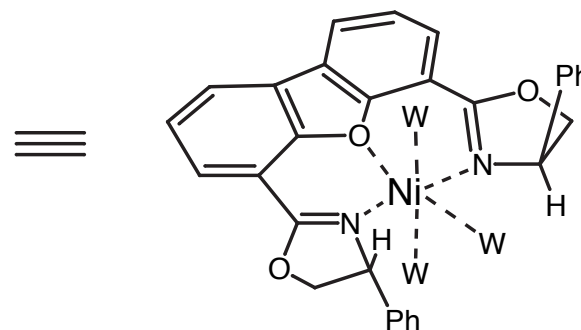
Kanemasa et al. *J. Org. Chem.* **1997**, 62, 6454; *J. Am. Chem. Soc.* **1998**, 120, 3077.

The Catalyst

Kanemasa's initial report: Crystal structure of DBFOX/Ph-3H₂O



Octahedral co-ordination geometry



W = H₂O

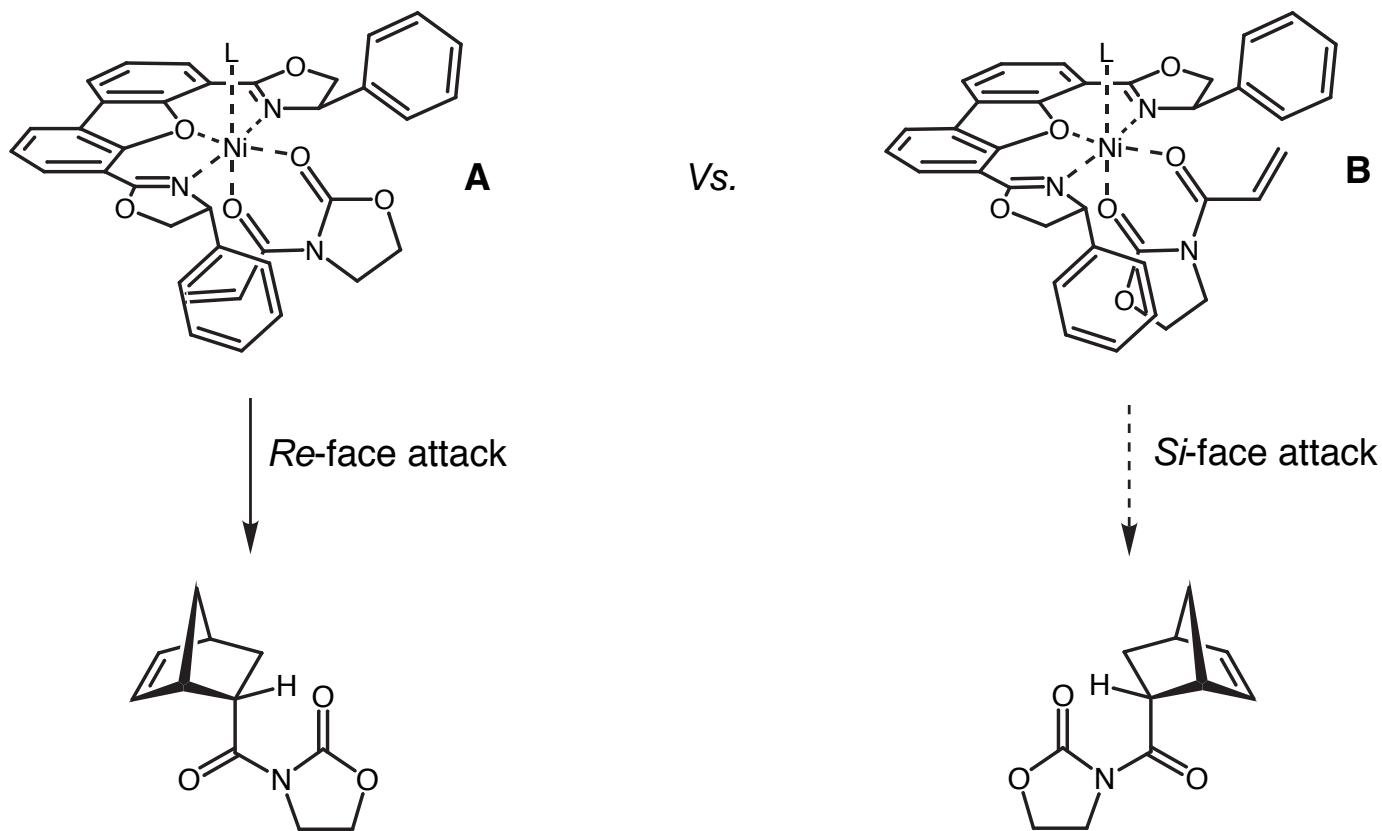
Bond lengths (Angstroms) about Nickel:

Ni-O (benzofuran)	- 2.133
Ni-O (<i>trans</i> -H ₂ O)	- 2.037
Ni-O (apical-H ₂ 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

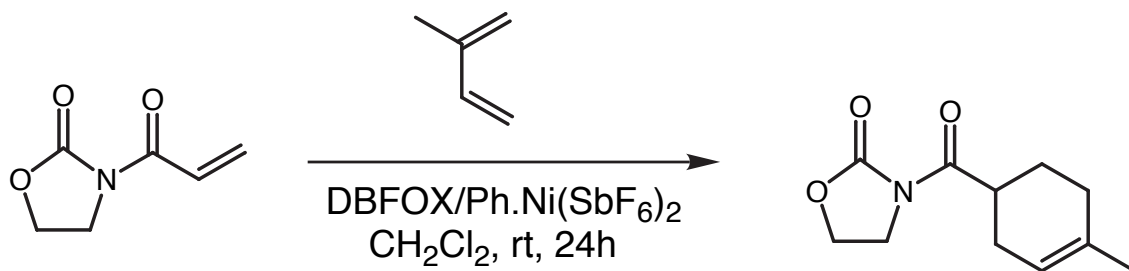


- Author's reasoning: The sterically more hindered or π -stacking **B** should be less reactive than **A**
- What about an electronic effect?
- Carbonyl group of acryloyl moiety in **B** deactivated relative to **A** ie. *trans* to donating furan oxygen

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

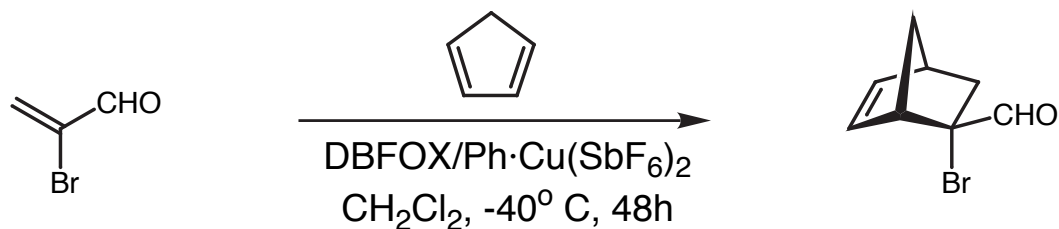
Other Reactions

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



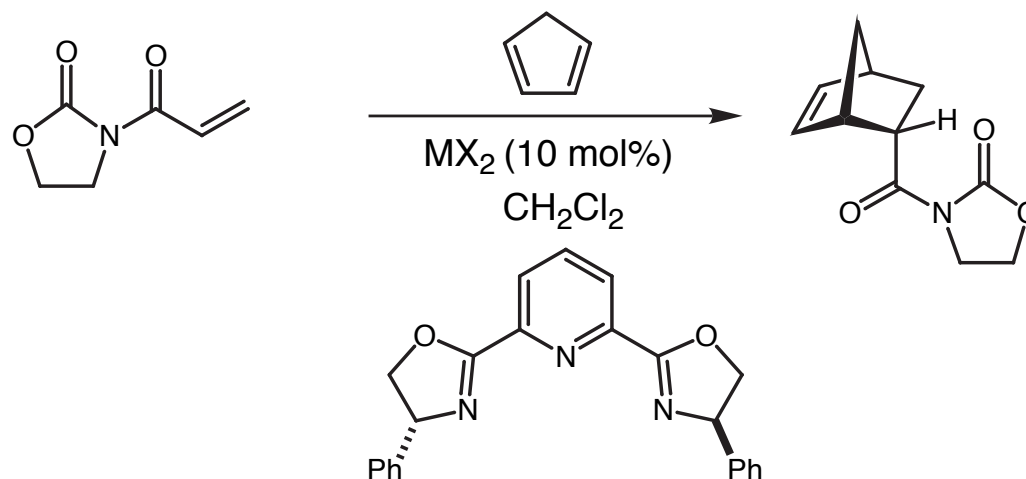
93% (*endo:exo* = 3:97)
86% ee

In a footnote:

The reaction catalyzed by Ni(ClO₄)₂ prepared from NiBr₂ and AgClO₄, at rt, 24h gave:
91% (*endo:exo* = 6:94), 53% ee

Other Reactions

Kanemasa's initial report: Ph-PyBox



MX_2	temp/ $^\circ\text{C}$	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:

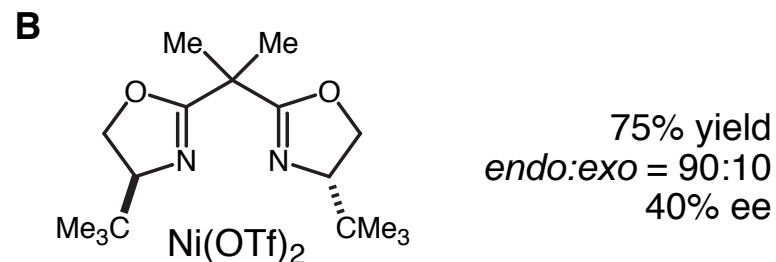
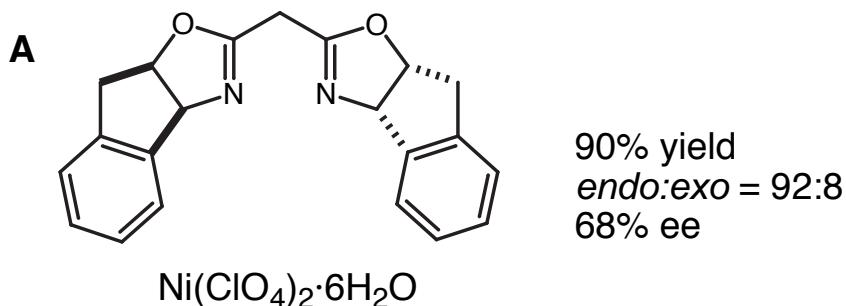
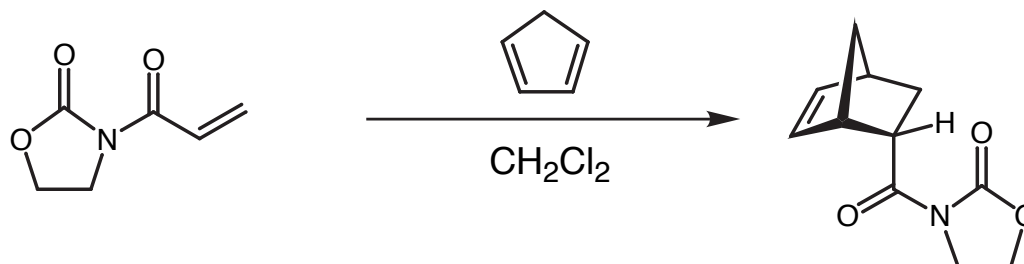
Fe(III): Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, 113, 728.

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.

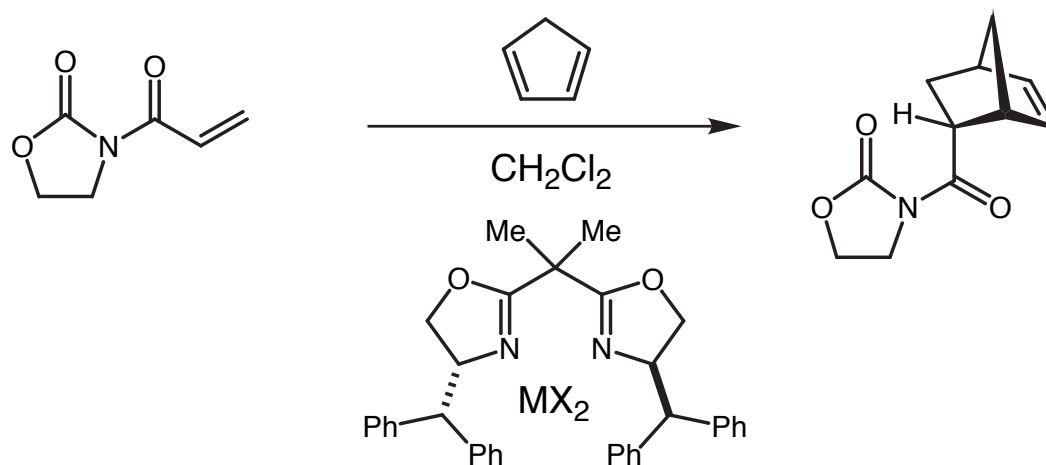
- Nickel based systems?
- Early examples from metal screens:



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



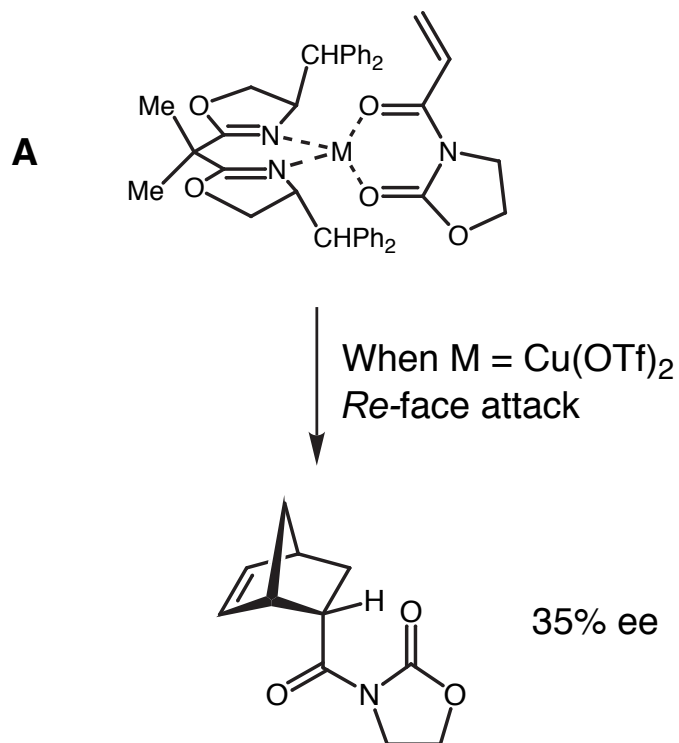
MX_2	temp/ $^\circ\text{C}$	time/h	yield/%	endo:exo	% ee (endo)
$\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	rt	0.5	nr	76:23	21
$\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	-40	nr*	nr	93:7	78
$\text{Ni}(\text{ClO}_4)_2^{\text{a}}$	-40	nr	93	85:15	75

* not reported ^a Refers to anhydrous $\text{Ni}(\text{ClO}_4)_2$ prepared from NiBr_2 and AgClO_4

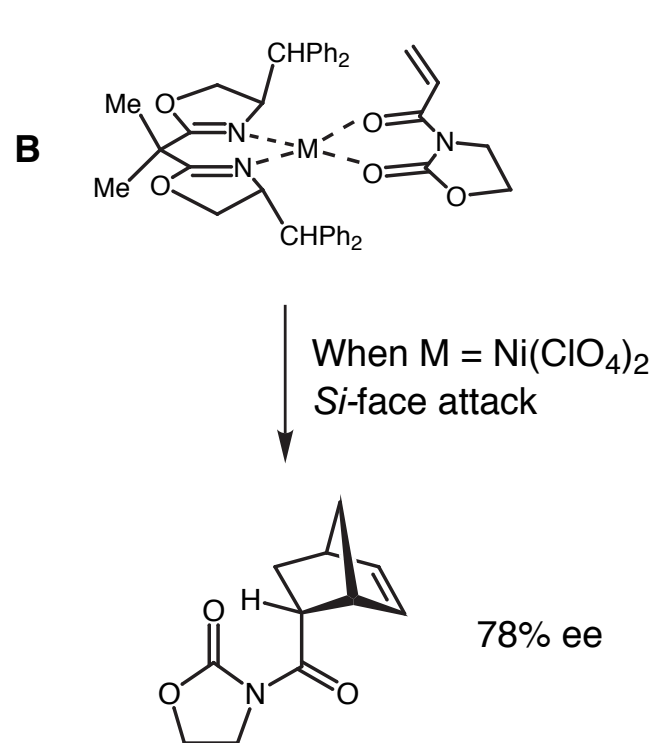
- The Ni complexes display high catalytic ability - although no reaction times given for low temp. expts.
- Other Box ligands were not reported.
- Use of $\text{Cu}(\text{OTf})_2$ gives *opposite* sense of induction to $\text{Ni}(\text{ClO}_4)_2$

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)₂ 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

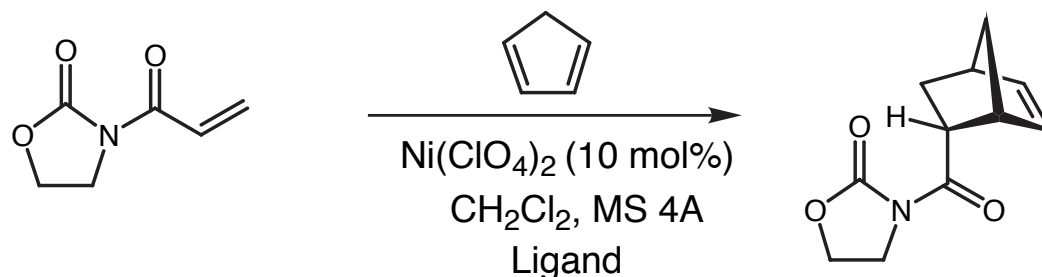
- Authors speculated on the addition of an amine base to act as an axial ligand (or ligands) to enforce the in-plane co-ordination of dienophile in the case of Ni catalyst.
- Addition of Et₃N retarded the reaction rate significantly.
- Two mol. equivs of pyridine (relative to catalyst) to aqua complex 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.

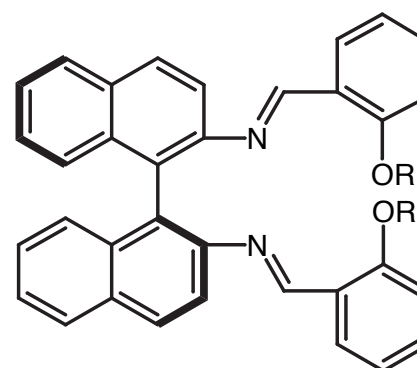
Kanemasa, S.; Adachi, K.; Yamamoto, H.; Wada, E. *Bull. Chem. Soc. Jpn* **2000**, 73, 681.

Binaphthyldiimine (BINIM) derived Ni(II) Catalysts

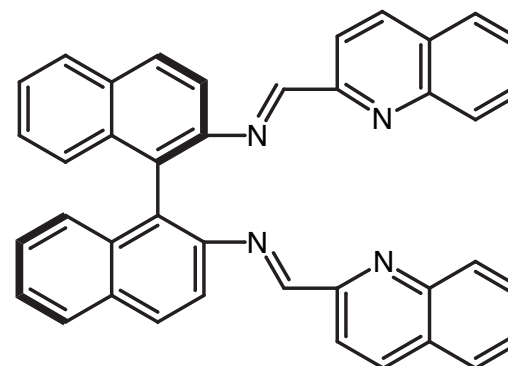
Suga's Enantioselective Diels-Alder Reaction



- 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



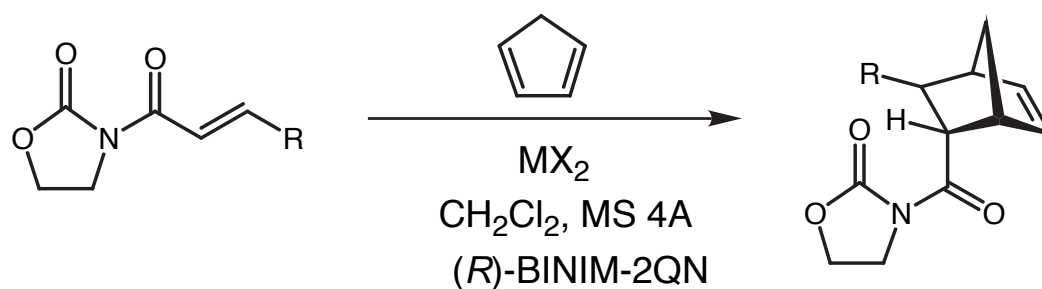
A
R = H or Bn



B
(*R*)-BINIM-2QN

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

Suga's Enantioselective Diels-Alder Reaction



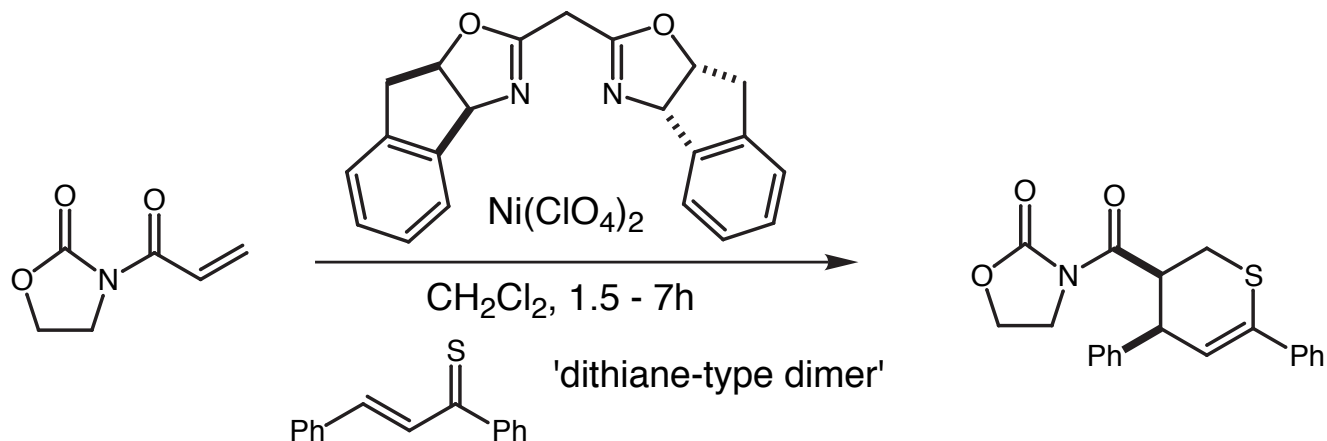
R	MX_2	mol%	temp/ $^\circ\text{C}$	time/h	yield/%	endo:exo	% ee (endo)
H	$\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	10	-40	17	94	>99:1	94
H	$\text{Co}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	10	-40	17	98	95:5	90
H	$\text{Zn}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	10	-40	17	97	95:5	84
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 [*]	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)₂ under optimized conditions

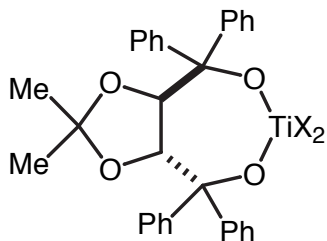
Saito, T.; Takekawa, K.; Takahashi, T. *Chem. Commun.* **1999**, 1001.

Conclusions for Ni(II) Catalyzed Diels-Alder Reactions

- DBFOX/Ph ligands with Ni(ClO₄)₂ 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(ClO₄)₂ 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.

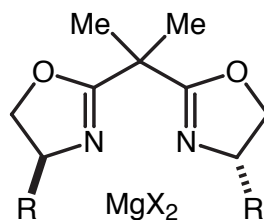
Ni(II) Catalyzed 1,3-Dipolar Cycloadditions

Other metals have been utilized



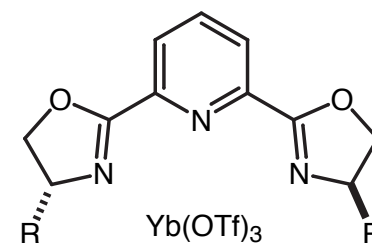
up to 60% ee

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



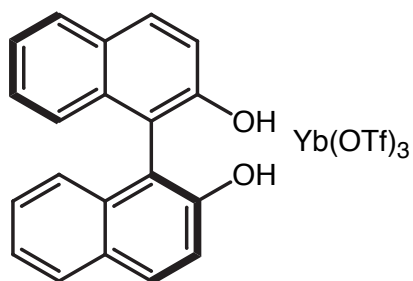
70-80% ee

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

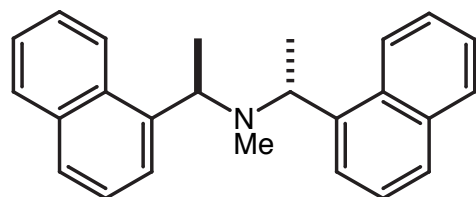


up to 73% ee

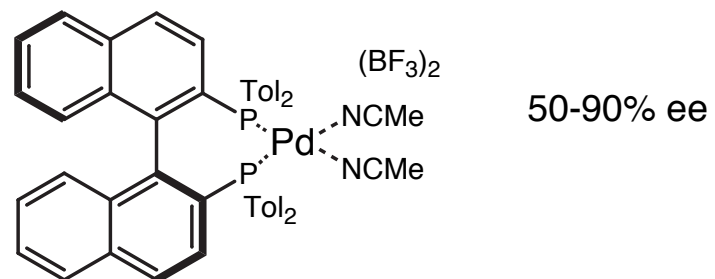
Jørgensen, *J. Am. Chem. Soc.* **1999**, 120, 5840.



80-96% ee



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

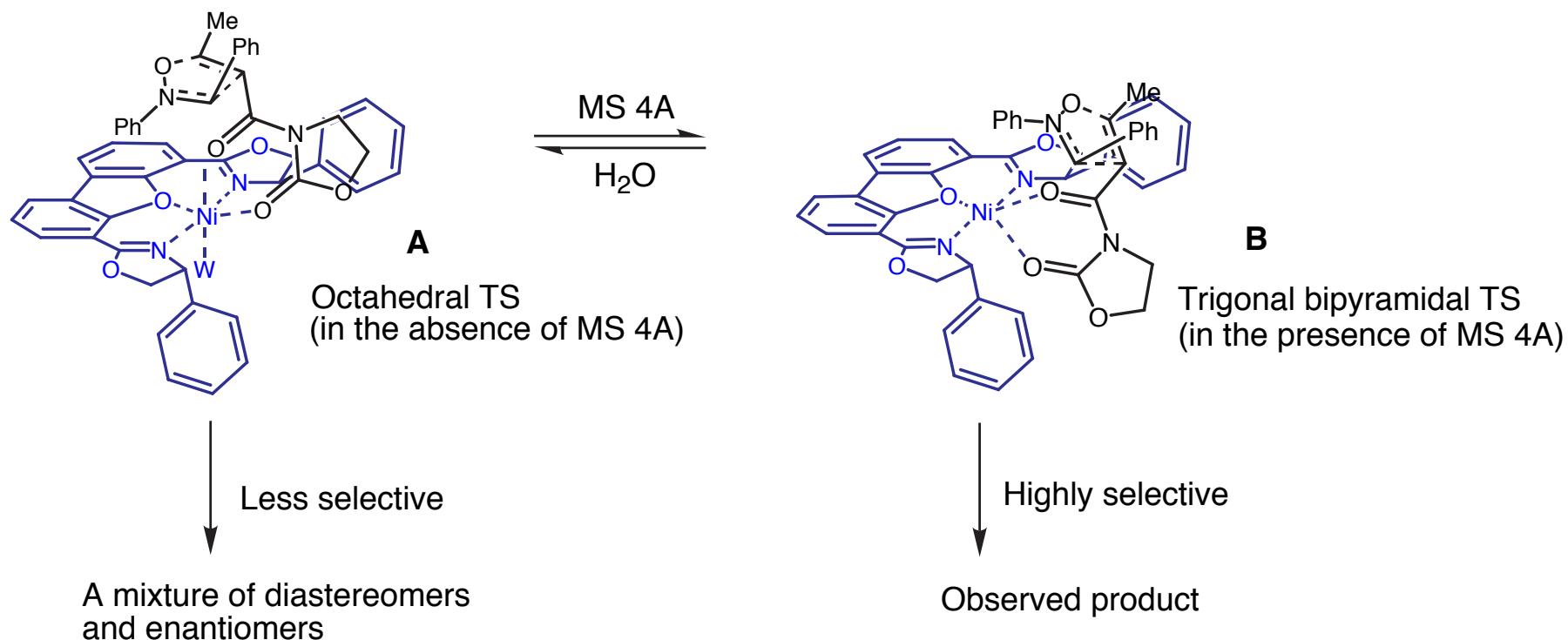


50-90% ee

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

The Catalyst

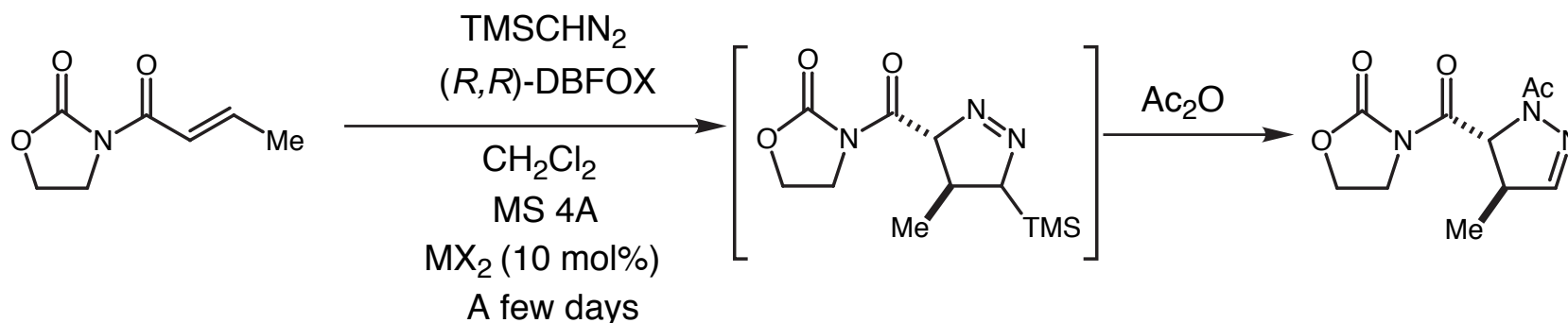
Kanemasa: Stereochemical rationale



- Trigonal bipyramidal TS **B** predicted on the basis of NMR spectroscopic studies of a DBFOX/Ph-Zn(ClO₄)₂ 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

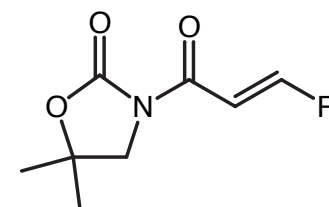
Kanemasa - 1,3-Dipolar Cycloadditions of TMSdiazomethane



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 nitron 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)



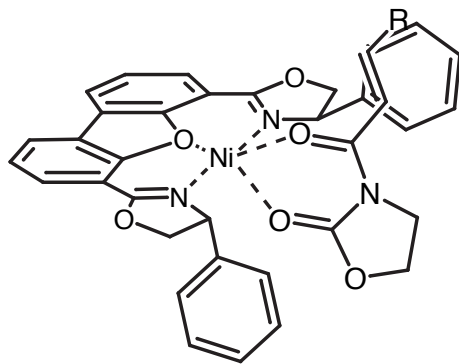
- The dimethyl-oxazolidinone proved effective for other R groups (80-98% ee, R = Me, *n*-Pr, *i*-Pr)
- Only Mg complex was active.

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

The Catalyst

A Possible Explanation?

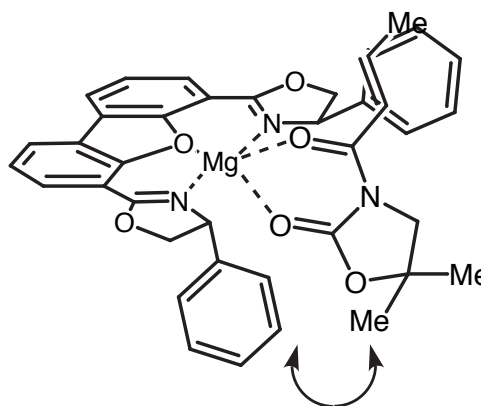
unsubstituted oxazolidinone



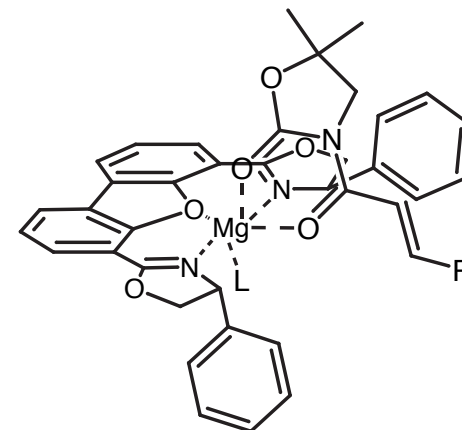
Observed product

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

disubstituted oxazolidinone



Vs.

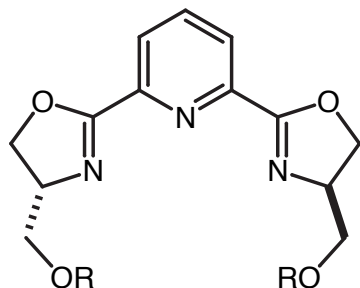


Observed product

- 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*)

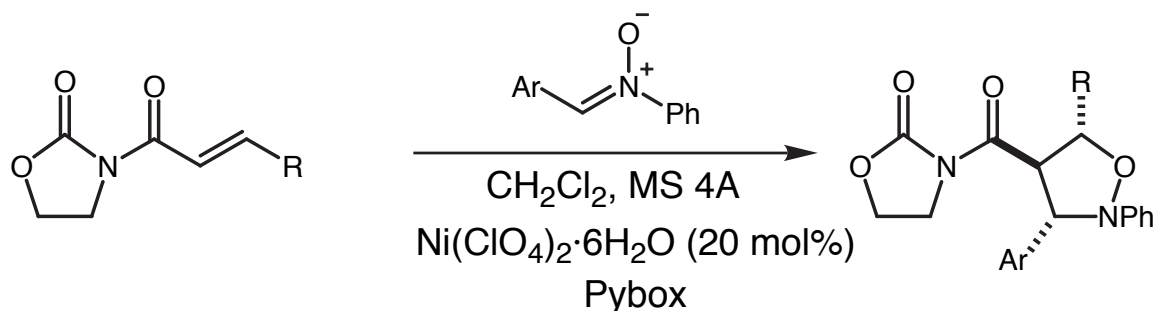
R = TBDPS (pybox-*tbdpsom*)

- 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



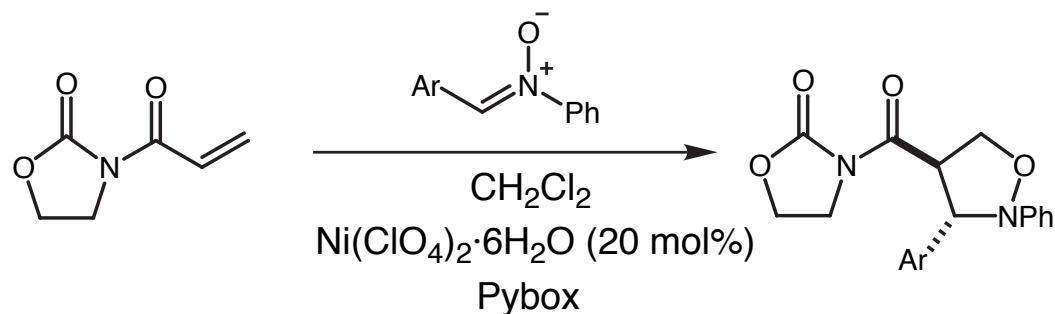
R	Ar	Pybox	temp/ ^o C	time/h	yield/%	endo:exo	% ee (endo)
H	Ph	<i>t</i> -Bu	0	72	97	92:8	90
H	4-MePh	<i>t</i> -Bu	0	72	99	96:4	86
Me	Ph	<i>t</i> -Bu	rt	72	98	97:3	86
Me	4-MePh	<i>t</i> -Bu	rt	72	99	99:1	82
Me	Ph	<i>i</i> -Pr	rt	72	89	97:3	66

- *i*-Pr-pybox also used with Co(ClO₄)₂ (*endo:exo* = 96:4, 63% ee); Mn(ClO₄)₂ (96:4, 71% ee); Fe(ClO₄)₂ (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



Ar = Ph, but 4-substituted Ar also work (not shown)

Pybox	MS 4A	temp/ ^o C	time/h	yield/%	endo:exo	% ee (<i>endo</i>)
<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

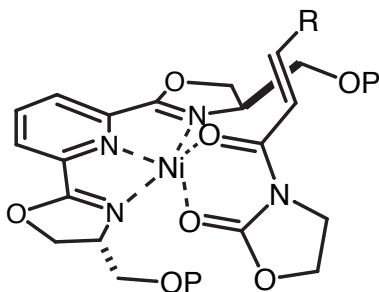
Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227

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

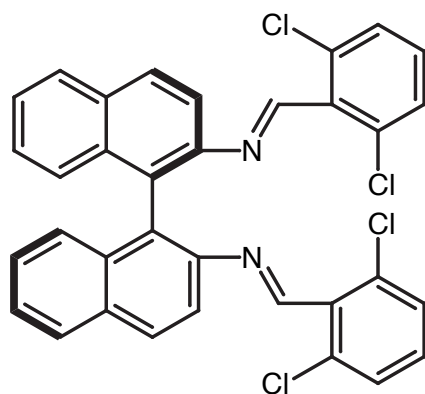
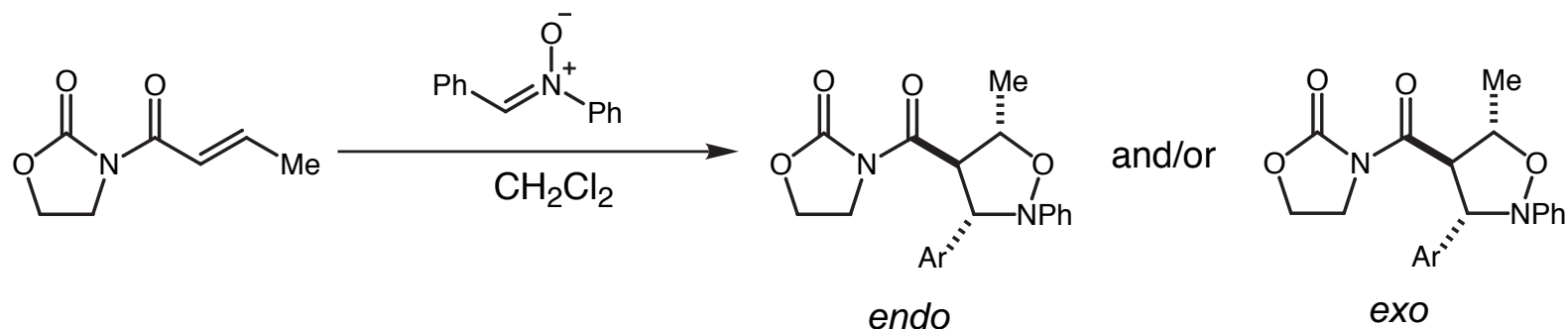


—————> observed products

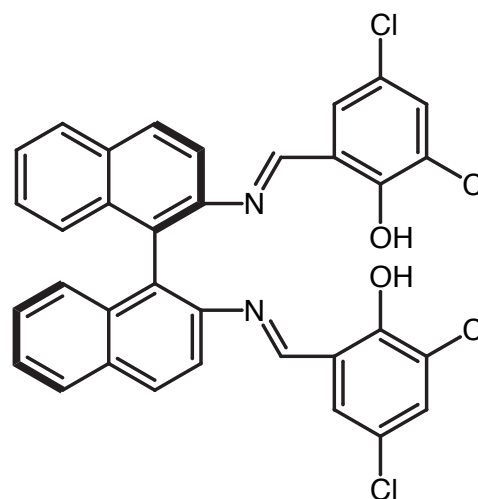
- Trigonal bipyramidal with MS 4A, *cf.* Kanemasa, *J. Am. Chem. Soc.* **1998**, *120*, 12355

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

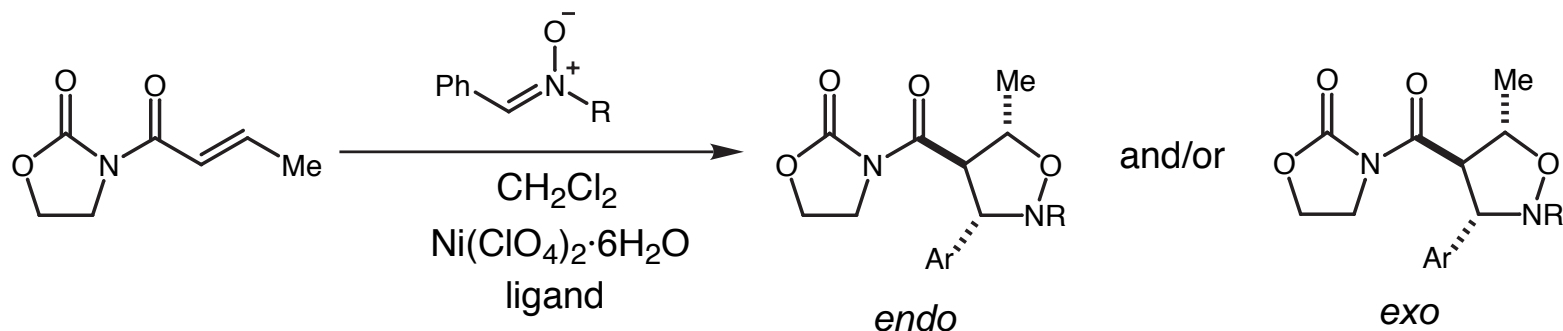


$\text{Ni}(\text{SbF}_6)_2 \cdot 6\text{H}_2\text{O}$
63% yield
endo:exo = 42:58
82% ee *endo*, 24% ee *exo*

- 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

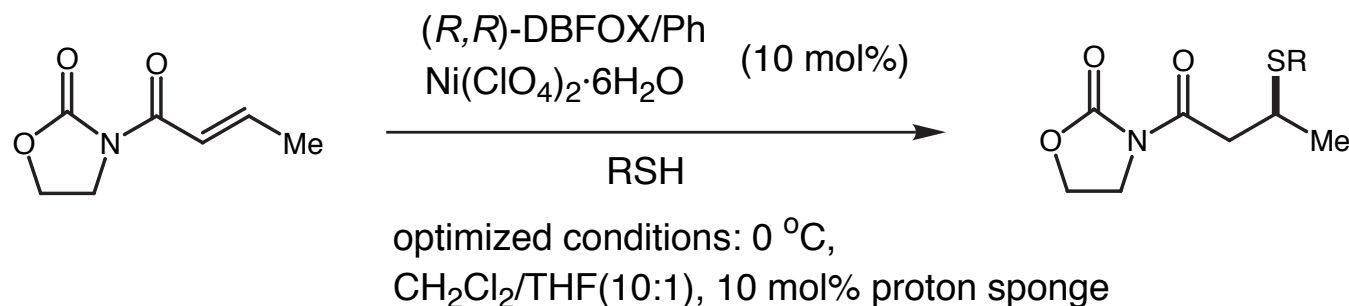
- Kanemasa has successfully utilized his Ni(II)-DBFOX/Ph catalyst for highly *endo*-selective asymmetric 1,3-dipolar cycloadditions of a limited number of nitrones and oxazolidinones.
- The importance of MS 4A in the reaction was observed and rationalized in terms of catalyst/substrate co-ordination 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</i> - <i>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.

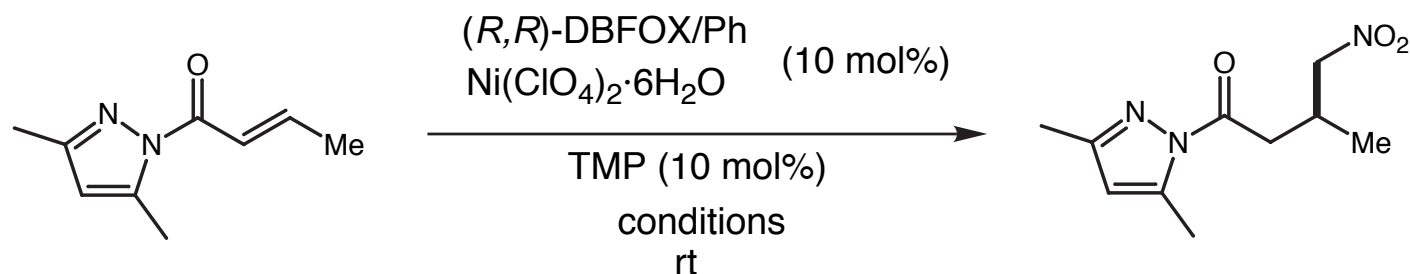
Kanemasa, S.; Oderatoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675

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(ClO₄)₂·6H₂O in THF gives a gradual color change from pale blue to reddish brown. This color change is rapid in CH₂Cl₂. 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 Et₃N 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



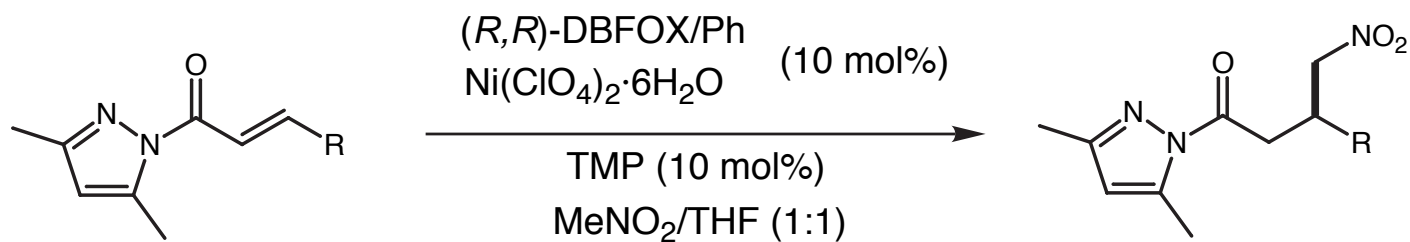
initial development

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

- The equivalent reaction with an oxazolidinone acceptor, using MeNO₂ 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(ClO₄)₂·6H₂O 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.

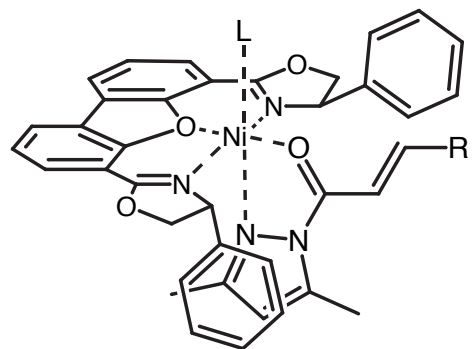
Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394.

Substrate Scope

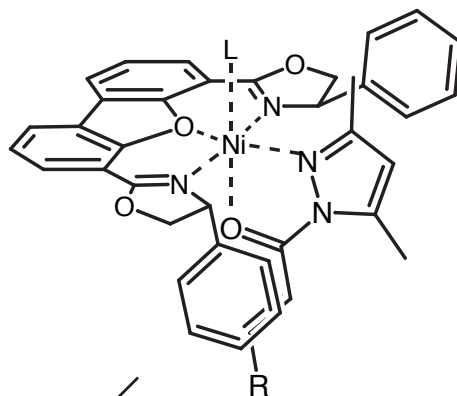


R	temp/ $^{\circ}\text{C}$	time/h	yield/%	% ee
Me	rt	5	97	84
Me	0	48	91	90
Me	-20	96	85	94
Et	-20	24	93	95
<i>i</i> -Pr	-20	96	74	94
<i>t</i> -Bu	0	168	39	95
CO ₂ Me	rt	168	91	83
	-20	3	49	77
Ph	-20	96	90	93
2-Thienyl	-20	168	83	97

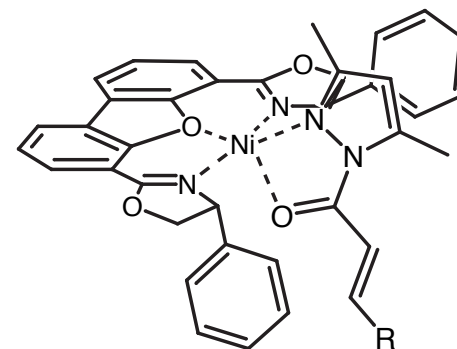
A Possible Model?



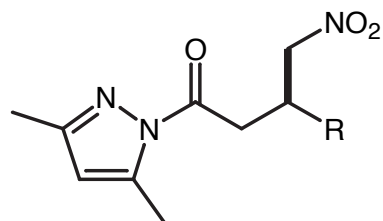
Vs.



Vs.

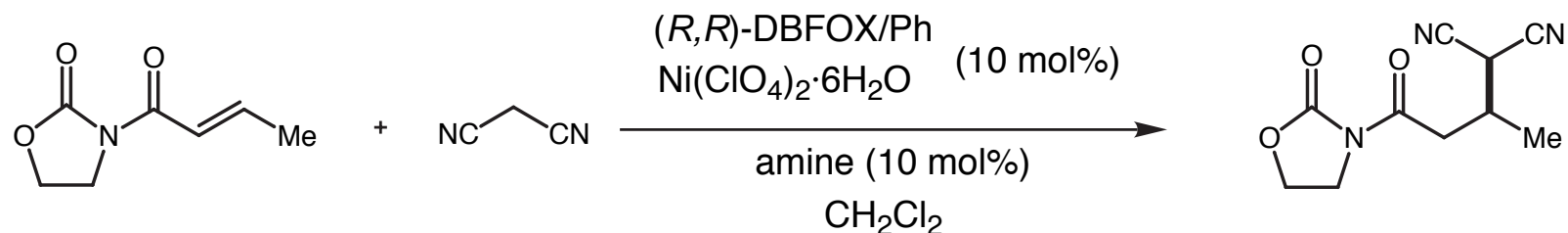


Trigonal pyramid less effective at shielding one face of double bond?



- 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

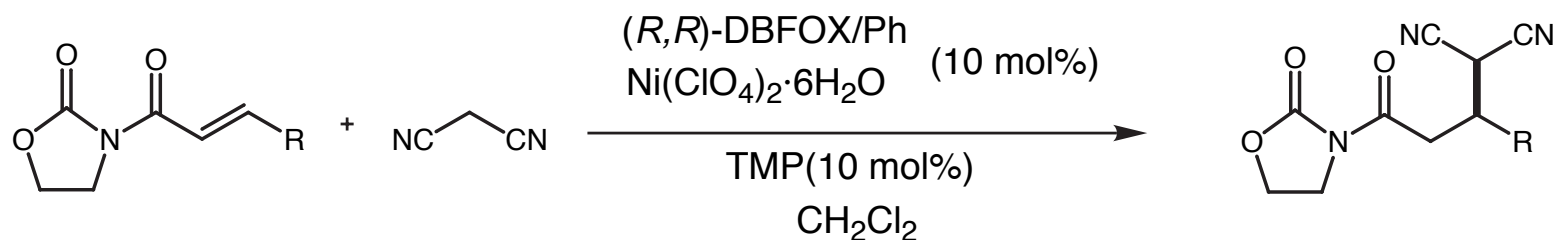


The Effect of Amine Additives

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 Et_3N to the reaction led to heavy deactivation (rt, 96h, 26% yield, 26% ee).

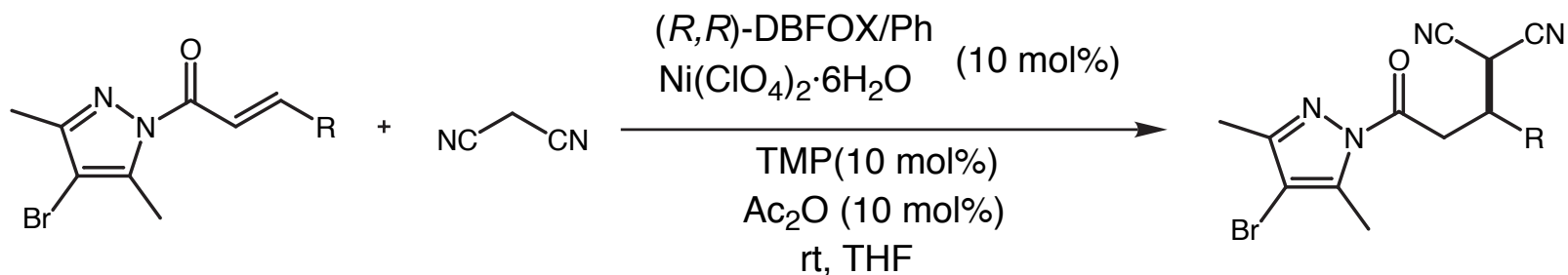
Conjugate Additions of Malononitrile



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

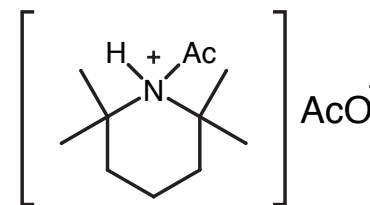
- In some cases reactions at -40°C and -78°C give lower selectivities.
- Some polar solvents could also be utilized: ACN (rt, 69% ee; -20°C , 74% ee), ACN/THF (1:1, rt, 75% ee); CH_2Cl_2 /THF (10:1, 0°C , 81% ee); CH_2Cl_2 /MeOH (10:3, -20°C , 84% ee).
- Polar co-ordinating solvents decrease reaction 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

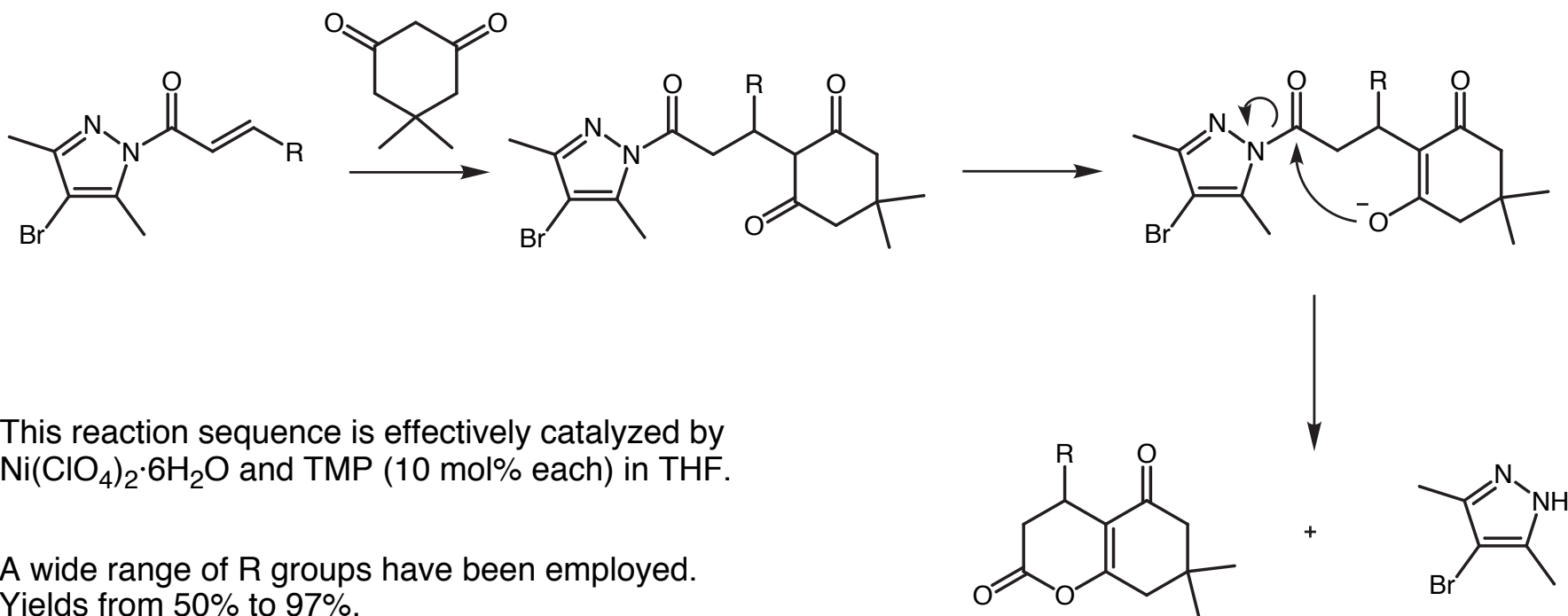
- The des-bromo pyrazole gave lower ee. For R = Me, 81%
- Without Ac_2O the reaction gives only 23% ee.
- No explanation given.



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

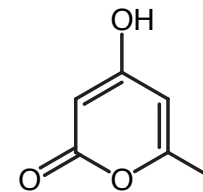
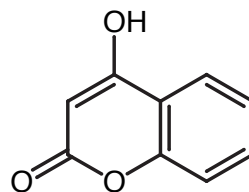
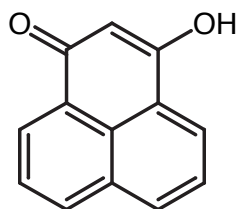
Itoh, K.; Oderaotoshi, Y.; Kanemasa, S. *Tetrahedron Asymmetry* **2003**, 14, 635.

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.