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[A0093]

Lewis Acid Catalyzed Enantioselective Reactions Using Highly Coordinating Nucleophiles. Conjugate Additions of Thiols, Thiocarboxylic acids, and *O*-Benzylhydroxylamine

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Abstract

Studies of chiral Lewis acid catalyzed enantioselective reactions using strongly coordinating nucleophiles, as a rather unexplored categoly of catalyzed enantioselective reactions, are described. Selection of a proper chiral catalyst should be essential. The author has employed complexes of two chiral ligands, (*R,R*)-4,6-dibenzofurandiyl-2,2'-bis(4-phenyloxazoline) and (*R,R*)-isopropylidene-2,2'-bis[4-(*o*-hydroxybenzyl)oxazoline)], designated *R,R*-DBFOX/Ph and *R,R*-BOX/*o*-HOBn, respectively. The complex catalyst derived from *R,R*-DBFOX/Ph and $Ni(ClO_4)_2 \cdot 3H_2O$ works as a powerful catalyst in the enantioselective thiol conjugate additions to 3-(2-alkenoyl)-2-oxazolines, and the complex derived from *R,R*-BOX/*o*-HOBn and $Cu(OTf)_2$ catalyzes the reactions of *O*-benzylhydroxylamine to 1-alkyl-3-(2-alkenoyl)-2-imidazolidinones. Internal delivery of nucleophiles to the activated acceptors is proposed as a powerful principle for the development of the titled reactions.

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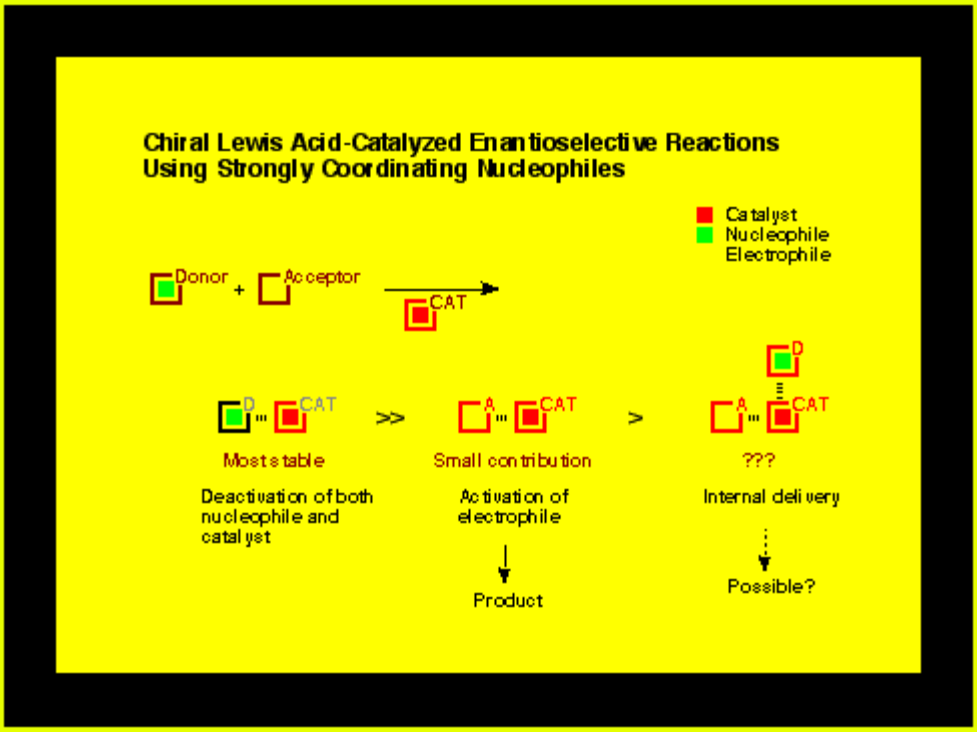
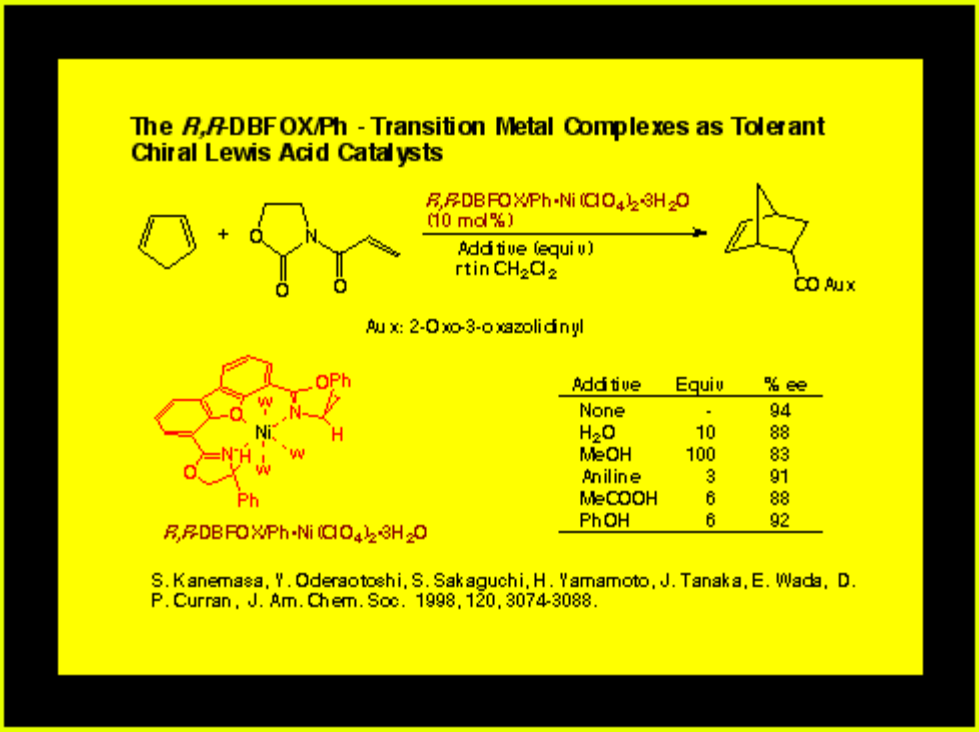
Introduction

Conjugate addition of heteronucleophiles to electron-deficient carbon-carbon double bonds is a fundamentally important reaction.*1* Lewis acid-catalyzed enantioselective conjugate additions of *alpha,beta*-unsaturated carbonyls are attractive as a direct access to enantiomers of beta-heterosubstituted carbonyl compounds.*2,3* Ready availability of the starting *alpha,beta*-unsaturated carbonyl acceptors is an advantage. However, a serious problem exists: Lewis acid catalysts should interact strongly with heteronucleophiles to inactivate the catalyst. Therefore, this promising enantioselective methodology is difficult to exploit in practice. Success depends upon the correct choice of chiral Lewis acid catalyst (Scheme 01).



Scheme 01

The cationic aqua complex*4* prepared between (*R,R*)-4,6-dibenzofuradiyl-2,2'-bis(4-phenyloxazoline) ligand (designated hereafter *R,R*-DBFOX/Ph) and nickel(II) perchlorate hexahydrate is an effective chiral Lewis acid catalyst in the Diels-Alder reactions of cyclopentadiene, even in the presence of a variety of coordinating reagents (Scheme 02).*4b* The high tolerance and catalytic activity observed depend upon the aqua complex structure, and we believe that the strongly coordinating reagents undergo rapid ligand exchange on the metallic center of the complex. Based on this high synthetic potential of the *R,R*-DBFOX/Ph - transition metal aqua complexes, enantioselective nitrone 1,3-dipolar cycloadditions*5* were already reported from this laboratory.



Scheme 02

In this lecture, we present enantioselective conjugate addition reactions of thiols and *O*-benzylhydroxylamine*3a,b* catalyzed by a new chiral copper(II) catalyst, the complex prepared from (*R,R*)-isopropylidene-2,2'-bis[4-(*o*-hydroxybenzyl)oxazoline)] (hereafter designated *R,R*-BOX/*o*-HOBn) and copper(II) trifluoromethanesulfonate.*6*

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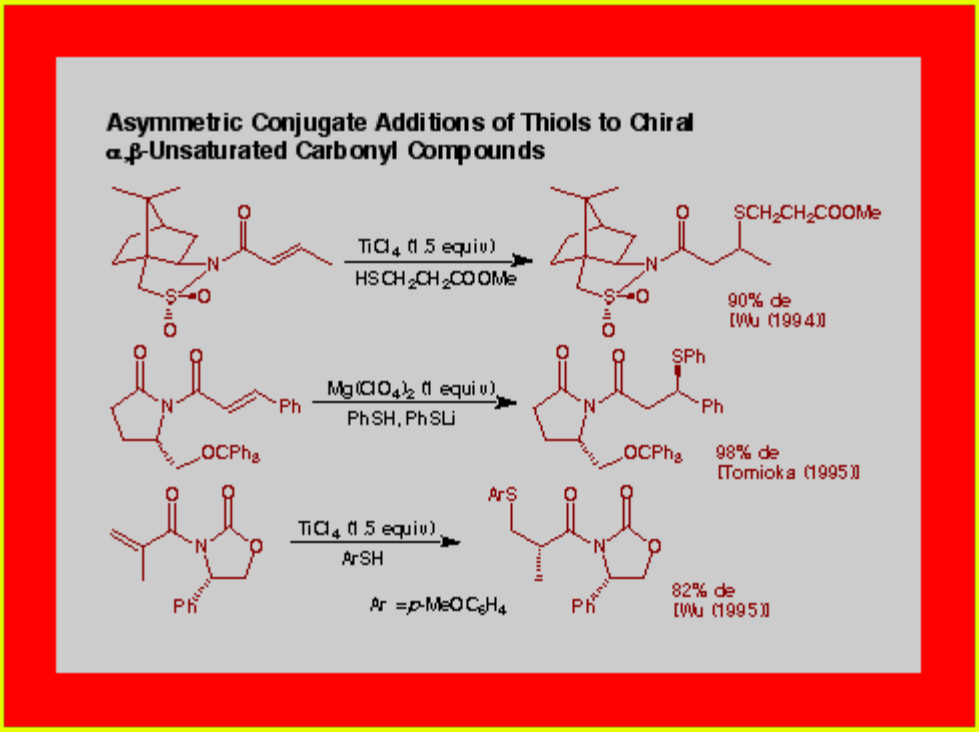
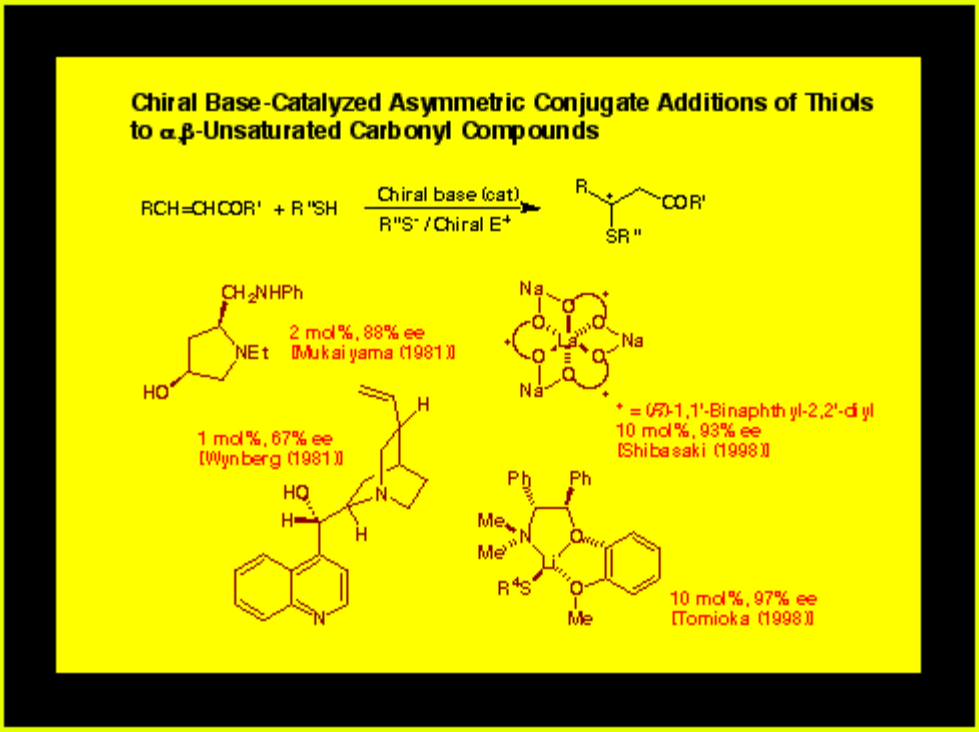
Thiol Conjugate Additions

Thiols have been studied as nucleophiles in the conjugate addition reactions to 3-(2-alkenoyl)-2-oxazolidinones. Stereoselective thiol conjugate additions catalyzed by a Lewis acid are interesting not only from the standpoint of biological and synthetic importance but also from the difficulty encountered in the catalyzed reactions using thiols in industry.*7* Quite a number of asymmetric thiol conjugate addition reactions are known (Scheme 03),*8* but previous examples of enantioselective thiol conjugate additions have all been based on the activation of thiol nucleophiles by use of chiral base catalysts such as amino alcohols,*2a-c* the lithium thiolate complex of amino bisether,*2d* and a lantanoid tris(binaphthoxide) (Scheme 04).*2e* To the best of our knowledge, there are no examples reported for the enantioselective thiol conjugate additions through the activation of acceptors by the aid of chiral Lewis acid catalysts. In the first section of my lecture, I would like to describe the first examples of enantioselective thiol conjugate additions catalyzed by a chiral Lewis acid.



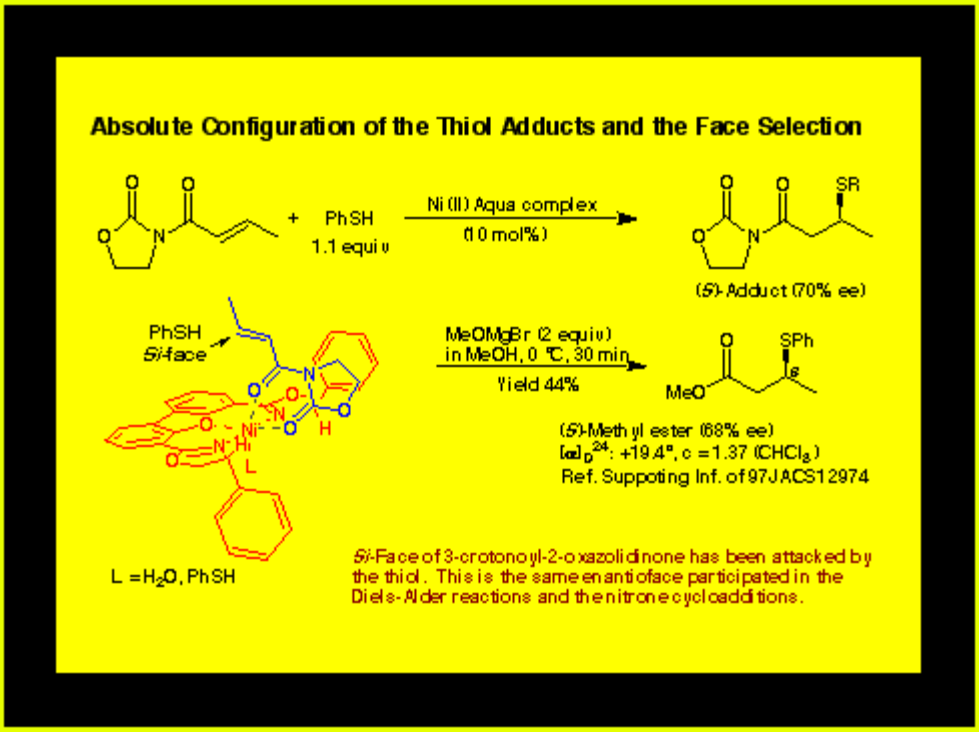
Scheme 03



Scheme 04

The nickel(II) aqua complex *R,R*-DBFOX/Ph · $Ni(ClO_4)_2 \cdot 3H_2O$ was prepared in situ by treatment of equimolar amounts (10 mol%) of *R,R*-DBFOX/Ph ligand with nickel(II) perchlorate hexahydrate in tetrahydrofuran (THF) by stirring at room temperature for 30 min. Reaction of benzenethiol (1.1 equiv) with 3-crotonoyl-2-oxazolidinone (1 equiv) was quite slow and it took about 24 h at room temperature until the oxazolidinone acceptor was all

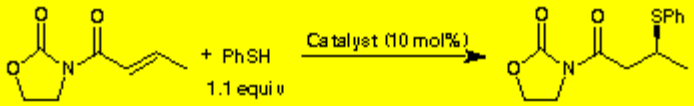
consumed (checked by tlc). After aqueous workup, the mixture was purified through silica gel column chromatography to give the conjugate adduct, whose enantiopurity was determined by chiral hplc.*9* Based on the absolute configuration of adduct,*10* it was found that the thiol conjugate addition took place on the Si-face of the oxazolidinone acceptor (Scheme 05).



Scheme 05

Among a variety of DBFOX/Ph complexes examined as chiral catalysts, the nickel(II) aqua complex was exceptionally effective (Scheme 06). Although the magnesium and zinc complexes prepared from *R,R*-DBFOX/Ph ligand by treatment with $Mg(ClO_4)_2$, $Zn(ClO_4)_2 \cdot 6H_2O$, $Zn(OTf)_2$, or ZnI_2 showed satisfactory catalytic activity, the enantioselectivities observed in the catalyzed thiol conjugate additions were relatively poor. On the other hand, metal complexes prepared from the perchlorates of copper(II), iron(II), and manganese(II) ions showed only a low catalytic activity.

A Variety of *R,R*-DBFOX/Ph - Metal Salt Complex Catalysts (Part 1)



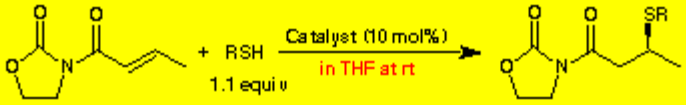
Entry	Metal Salt	Solvent	Time/h	Yield/%	ee%[a]
1	$Mg(ClO_4)_2$	CH_2Cl_2	24	quant	52
2[b]	$Mn(ClO_4)_2 6H_2O$	THF	24	quant	25
3	$FeCl_2+2AgClO_4$	THF	24	7	0
4	$Cu(ClO_4)_2 6H_2O$	THF	24	49	-11
5	$Zn(ClO_4)_2 6H_2O$	THF	24	62	0
6	$Ni(ClO_4)_2 6H_2O$	THF	48	quant	80

[a] Determined by HPLC (Daicel Chiral Cel OD-H). [b] DBFOX was added to a mixture of $Ni(ClO_4)_2 6H_2O$, thiophenol, and 3-crotonoyl-2-oxazolidinone.

Scheme 06

Reactions of a variety of thiols were catalyzed by the nickel(II) aqua complex *R,R*-DBFOX/Ph · $Ni(ClO_4)_2 \cdot 3H_2O$ to give the corresponding adducts. Satisfactorily high enantioselectivities as well as high chemical yields were observed with some exceptions when the reactions were performed in THF at room temperature (Scheme 07).

Enantioselective Conjugate Additions of Thiols Catalyzed by *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$



1. *R,R*-DBFOX/Ph + $Ni(ClO_4)_2 6H_2O$ (0.1 equiv each) in THF at rt 2 h
2. 3-Crotonoyl-2-oxazolidinone (1 equiv)
3. Thiol (1.1 equiv) then stir at rt under nitrogen

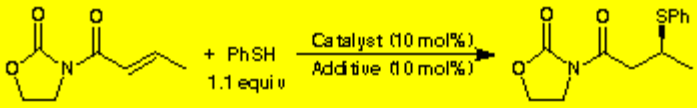
Entry	R	Time/h	Yield/%	ee%
1	Phenyl	24	quant	80
2	*o*-Tolyl	24	82	89
3	*p*-Tolyl	24	82	84
4	Mesityl	24	84	95
5	*o*-Isopropylphenyl	24	96	80
6	*o*-*tert*-Butylphenyl	24	quant	93
7	*p*-*tert*-Butylphenyl	24	74	86
8	1-Naphthyl	24	73	87
9	2-Naphthyl	24	94	87
10	Benzyl	48	26	89
11	*o*-Methoxyphenyl	48	69	11
12	*p*-Methoxyphenyl	72	30	78

Scheme 07

Enantioselectivities were found to change sharply depending upon the reaction conditions including catalyst structure, reaction temperature, solvent, and additives (Scheme 08). Some representative examples of such selectivity dependence are listed in the table for the reaction between benzenethiol and 3-crotonoyl-2-oxazolidinone. The adduct was formed with 79% ee (81% yield) when the reaction was catalyzed by the nickel(II) aqua complex at room temperature in dichloromethane. However, reactions either by use of the anhydrous complex*11* or the aqua complex together with MS 4A gave racemic adduct, indicating that the aqua complex should be more favored than the anhydrous complex in thiol conjugate additions. Slow addition of the thiol to the dichloromethane solution of 3-crotonoyl-2-oxazolidinone was ineffective for enantioselectivity. Enantioselectivity was dramatically lowered and reversed to -17% ee in the reaction at -78°C. A similar tendency was observed in the reactions in diethyl ether and THF. For example, a satisfactory enantioselectivity (80% ee) was observed in the reaction in THF at room temperature, while the selectivity almost disappeared (7% ee) at 0°C.

To examine such high sensitivity of enantioselectivity to the reaction conditions, the reactions of benzenethiol with 3-crotonoyl-2-oxazolidinone were performed in dichloromethane at room temperature in the presence of a variety of additives. Although addition of methanol (CH_2Cl_2/MeOH = 10: 1 v/v) did not affect either the chemical yield or enantioselectivity of the adduct (quant, 82% ee), addition of acetonitrile or *N,N*-dimethylformamide (both 1:1 v/v ratios) slowed the reactions (13, 15% yields) and provided products with lower enantioselectivities (19, 30% ees). The presence of acetic acid, even in a small amount (CH_2Cl_2/AcOH = 10:1 v/v), gave the racemic product, while saturated aqueous ammonium chloride provided a reversed enantioselectivity (CH_2Cl_2/sat. NH_4Cl aq. = 10: 1 v/v, 99% yield, -27% ee).

Effect of Catalysts, Solvents, and Additives (Part 2)

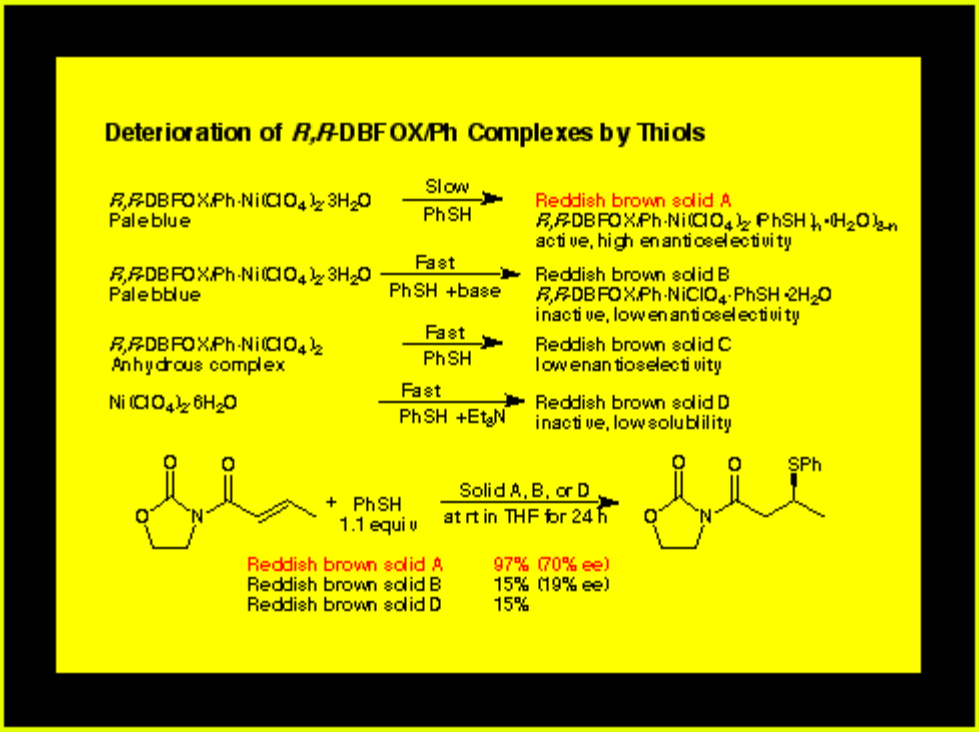


Entry	Metal Salt	Solvent	Additive	Temp/°C	Yield/%	ee%[a]
1[b]	$Ni(ClO_4)_2 6H_2O$	CH_2Cl_2	-	rt	81	79
2[c]	$Ni(ClO_4)_2 6H_2O$	CH_2Cl_2	-	rt	91	20
3	$NiBr_2$+2 $AgClO_4$	CH_2Cl_2	-	rt	50	0
4	$Ni(ClO_4)_2 6H_2O$	CH_2Cl_2	-	-78	33	-17
5	$Ni(ClO_4)_2 6H_2O$	Et_2O	Pyridine	rt	42	73
6[c]	$NiBr_2$+2 $AgClO_4$	Et_2O	Pyridine	rt	53	-10
7	$Ni(ClO_4)_2 6H_2O$	THF	-	rt	quant	80
8	$Ni(ClO_4)_2 6H_2O$	THF	-	0	62	7
9	$Ni(ClO_4)_2 6H_2O$	MeOH	-	rt	72	77
10	$Ni(ClO_4)_2 6H_2O$	CH_2Cl_2	MeOH (1/1 v/v)	rt	quant	82
11	$Ni(ClO_4)_2 6H_2O$	CH_2Cl_2	AcOH (10/1 v/v)	rt	99	0
12	$Ni(ClO_4)_2 6H_2O$	CH_2Cl_2	NH_4Cl aq (10/1 v/v)	rt	99	-27

[a] Determined by HPLC (Daicel Chiral Cel OD-H). [b] DBFOX was added to the mixture of $Ni(ClO_4)_2 6H_2O$, thiophenol and 3-crotonoyl-2-oxazolidinone. [c] Thiophenol was added slowly to a mixture of the catalyst and 3-crotonol-2-oxazolidinone in a period of 3 h.

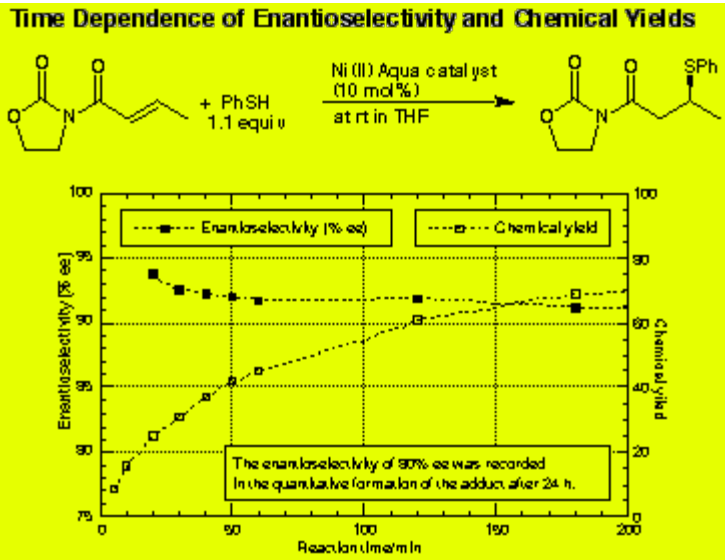
Scheme 08

We suspected at the beginning of this work that thiol would strongly coordinate to the Lewis acid catalyst *R,R*-DBFOX/Ph · $Ni(ClO_4)_2 \cdot 3H_2O$ to poison its catalytic activity. We therefore examined the interaction between benzenethiol and the catalyst to learn about the catalytic activity of the thiol-coordinating complex (Scheme 09). When the thiol was added to a solution of the catalyst in THF, the original pale blue color of the catalyst gradually faded to reddish brown. This color change was rapid in dichloromethane,[*12*] probably arising from the coordination of thiol to the catalyst. A brown colored solid was isolated as precipitate on treatment with a mixture of isopropyl alcohol and hexane,[*13*] and this showed sufficient catalytic activity in the reaction of benzenethiol with 3-crotonoyl-2-oxazolidinone in THF leading to a high enantioselectivity (97% yield, 70% ee).



Scheme 09

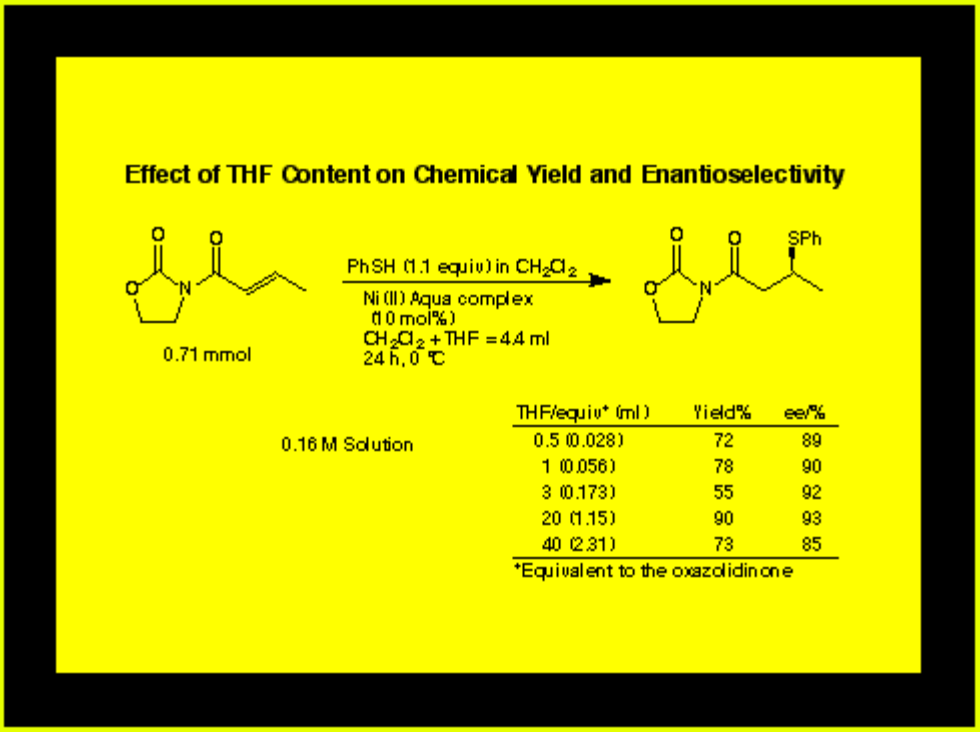
Accordingly, it is apparent that the thiol certainly binds with the catalyst, but the binding is not so strong that the thiol ligand may be easily replaced with the acceptor molecule in the reaction. This ligand exchange should be more favored in a coordinating media such as THF. However at the same time, THF competes with the acceptor molecule in coordination to the catalyst to deactive the reaction. In the presence of an amine base such as pyridine or triethylamine, a totally inert reddish brown complex immediately precipitated.[*14*] Since the resulting brown solid is totally insoluble in the reaction medium and free from perchlorate ions (according to analysis for chloride), we assume that the perchlorate counterions have been replaced with the highly nucleophilic thiolate ions.



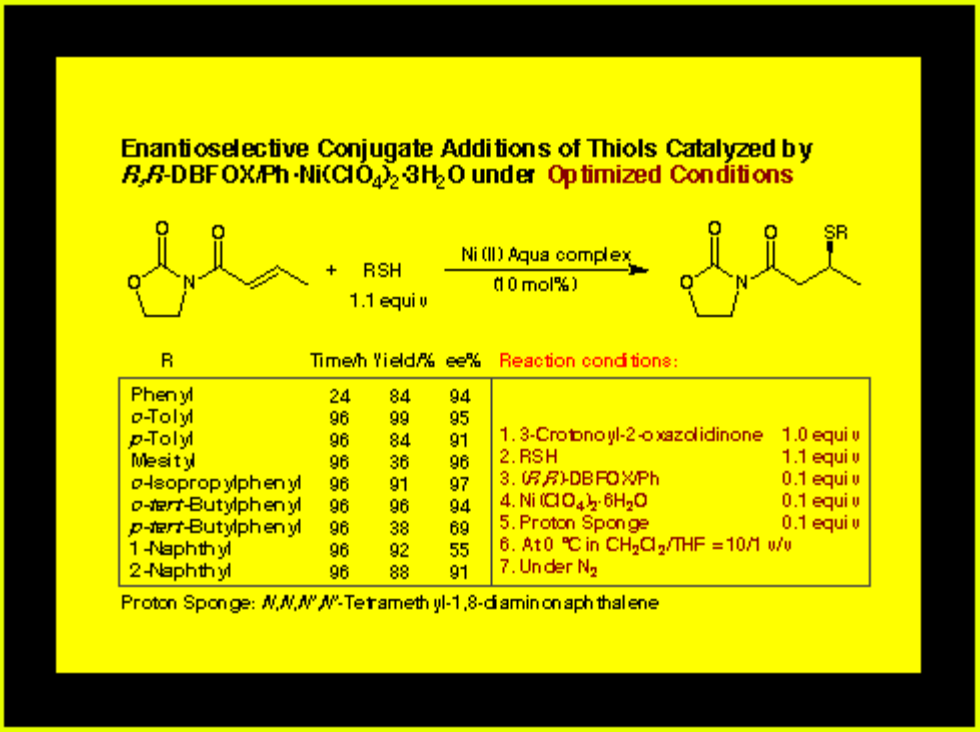
Scheme 10

The time dependence of enantioselectivity in the reaction between benzenethiol with 3-crotonoyl-2-oxazolidinone catalyzed by *R,R*-DBFOX/Ph · $Ni(ClO_4)_2 \cdot 3H_2O$ at room temperature in THF is shown in Scheme 10. After 3 h, yield of the adduct is 70% with the enantioselectivity of 91% ee, but the enantioselectivity was 80% ee at the completion of reaction after 24 h (yield: 100%). Although the catalyst maintains a high catalytic activity, and hence a satisfactory enantioselectivity, at the early stage of reaction, the deterioration of catalyst cannot be neglected thereafter even under neutral conditions.

However, to our delight, the reaction in a mixed solvent of CH_2Cl_2/THF = 10: 1 v/v (Scheme 11) catalyzed by the nickel(II) aqua complex at 0°C in the presence of *N,N,N',N'*-tetramethyl-1,8-diaminonaphthalene (proton sponge, 10 mol%) gave the best result (84% yield, 94% ee, Scheme 12). Some other thiols provided excellent enantioselectivities under similar reaction conditions (condition B) with 97% ee for a bulky thiol such as *o*-isopropylbenzenethiol.



Scheme 11

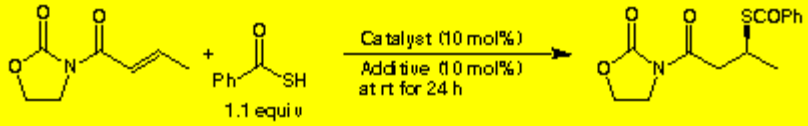


Scheme 12

It is found that thiobenzoic acid is also a good nucleophile in enantioselective conjugate additions to 3-crotonoyl-2-oxazolidinone in the presence of the magnesium and transition metal complexes of *R,R*-DBFOX/Ph ligand (Scheme 13). Thus, reaction of thiobenzoic acid with 3-crotonoyl-2-oxazolidinone gave the corresponding adduct. Again the nickel(II) aqua complex provided the best result albeit in a moderate enantioselectivities (up to 80% ee). Acceptors

having a variety of *beta*-substituents can be successfully employed (Scheme 14).

Enantioselective Conjugate Additions of Thiobenzoic Acid
- Effect of Solvents and Additives -

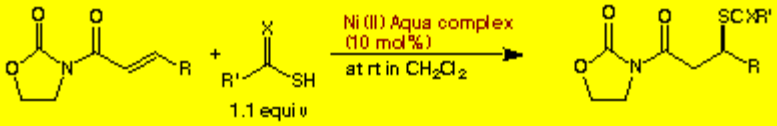


Entry	Metal Salt and Additive	Solvent	Yield/%	ee%[a]
1	$Mg(ClO_4)_2$	CH_2Cl_2	quant	63
2	$Mn(ClO_4)_2 6H_2O$	CH_2Cl_2	quant	33
3	$FeCl_2$+2 $AgClO_4$	CH_2Cl_2	87	0
4	$Co(ClO_4)_2 6H_2O$	CH_2Cl_2	quant	56
5	$Ni(ClO_4)_2 6H_2O$	CH_2Cl_2	quant	80
6	$Cu(ClO_4)_2 6H_2O$	CH_2Cl_2	quant	25
7	$Zn(ClO_4)_2 6H_2O$	CH_2Cl_2	quant	6
8	$Ni(ClO_4)_2 6H_2O$	THF	quant	70
9	$Ni(ClO_4)_2 6H_2O$	$CHCl_3$	quant	77
10	$Ni(ClO_4)_2 6H_2O$	MeOH	79	21
11	$Ni(ClO_4)_2 6H_2O$, Pyridine	CH_2Cl_2	quant	76
12	$Ni(ClO_4)_2 6H_2O$, PS[b]	CH_2Cl_2	quant	58
13	$Ni(ClO_4)_2 6H_2O$, $MgSO_4$	CH_2Cl_2	93	64

[a] Determined by HPLC (Daicel Chiral Cel OD-H). [b] PS: *N,N,N',N'*-Tetramethyl-1,8-diaminonaphthalene

Scheme 13

Asymmetric Conjugate Additions of Thiocarboxylic Acid with β-Substituted 3-Alkenoyl-2-oxazolidinone



Entry	R	R'	X	Time/h	Yield/%	ee%[a]
1	Me	Me	O	24	quant	86
2	Me	Ph	O	24	quant	80
3	^{n}Pr	Ph	O	24	77	70
4	^{i}Pr	Ph	O	24	67	68
5	Ph	Ph	O	48	67	80
6	-CH=CHMe	Ph	O	48	trace	-
7	Me	Ph	S	72	nr	-

[a] Determined by HPLC (Daicel Chiral Cel OD-H).

Scheme 14

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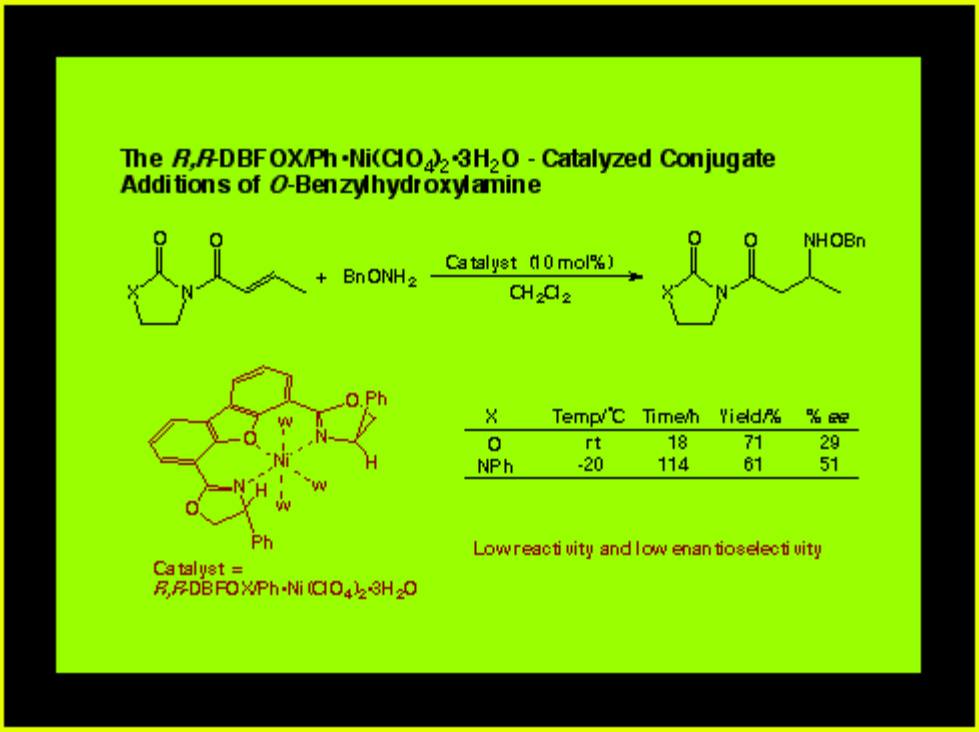
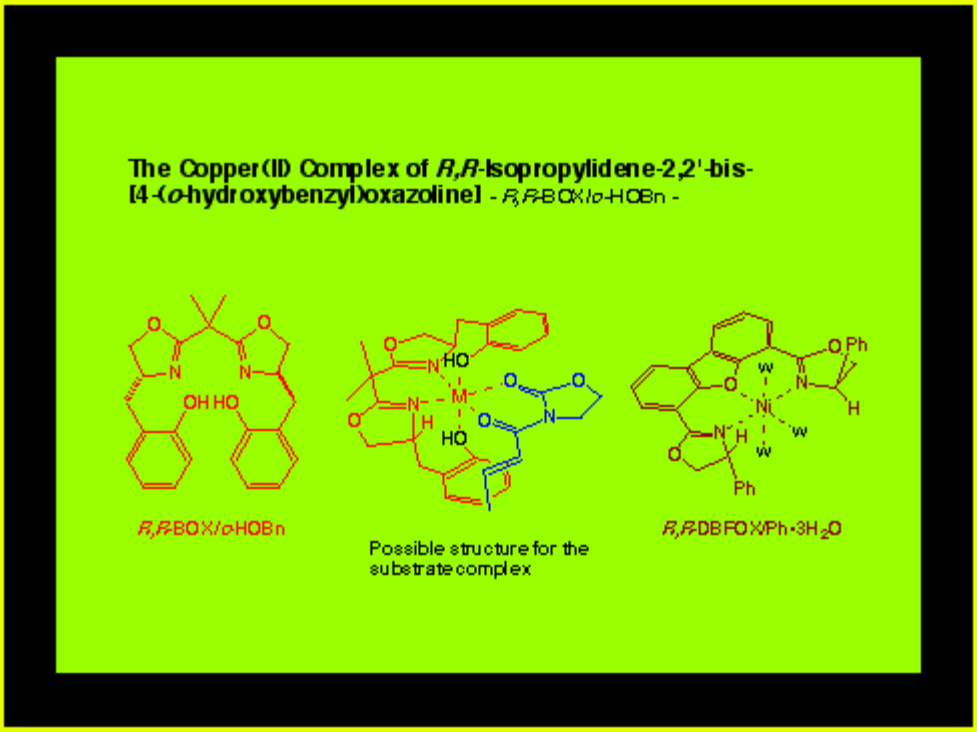
Our next topic deals with the chiral Lewis acid catalyzed enantioselective conjugate addition reactions of *O*-benzylhydroxylamine. There is the only one successful example known for the enantioselective amine conjugate addition reactions catalyzed by the magnesium complex of chiral bisoxazoline ligand.*3* Sibi and coworkers have achieved the maximum enantioselectivity up to 97% ee in the reactions of *O*-benzylhydroxylamine with 1-(2-alkenoyl)-3,5-dimethylpyrazoles when the reaction was performed in the presence of an equimolar amount of the catalyst. Lower selectivities have been observed when a catalytic loading of the catalyst is used. It is proposed that enantioselective destruction of the minor enantiomer of product is responsible for the high enantioselectivities observed.*3b*

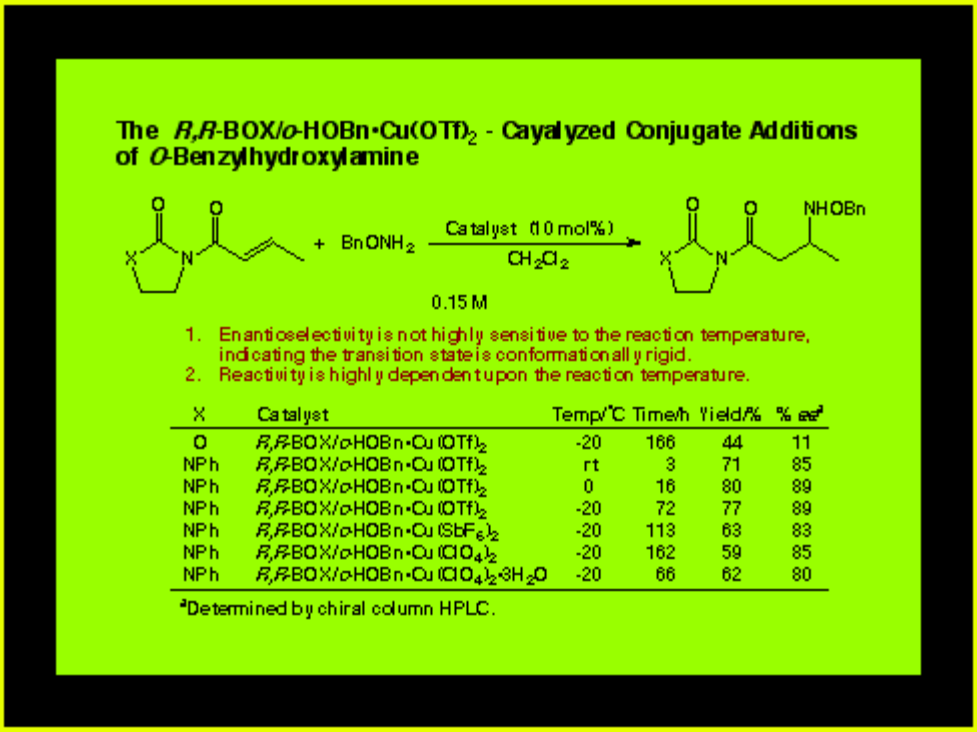


Scheme 15



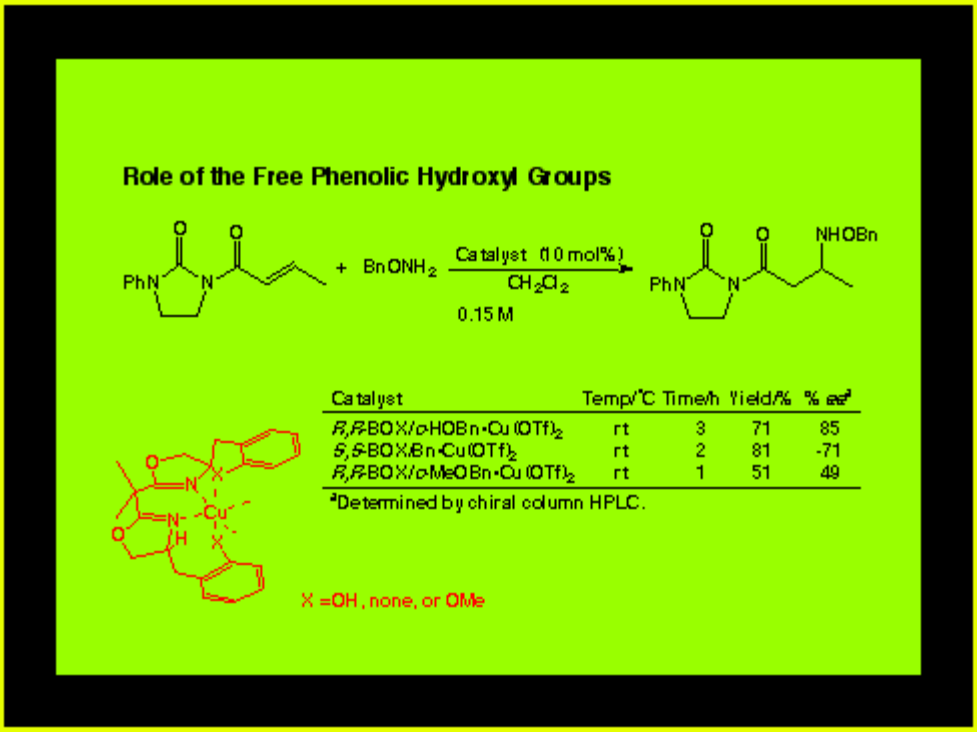
Scheme 16

We have applied a new chiral copper(II) catalyst, the complex prepared from (*R,R*)-isopropylidene-2,2'-bis[4-(*o*-hydroxybenzyl)oxazoline)] (hereafter designated *R,R*-BOX/*o*-HOBn) and copper(II) trifluoromethanesulfonate (Scheme 16).*15* The chiral copper(II) complex catalyst (10 mol%) was prepared in situ from *R,R*-BOX/*o*-HOBn and $Cu(OTf)_2$ in dichloromethane by stirring at room temperature for a few hours. After addition of 1-crotonoyl-3-phenyl-2-imidazolidinone and *O*-benzylhydroxylamine, the reaction (0.15 M) was continued at -20°C for 72 h to give 1-[3-(benzyloxyamino)butanoyl]-3-phenyl-2-imidazolidinone in 77% yield (Scheme 17). Enantioselectivity of the adduct was 89% ee. Among other copper(II) complexes derived from $Cu(SbF_6)_2$, $Cu(ClO_4)_2$, $Cu(ClO_4)_2 \cdot nH_2O$, the complex prepared from $Cu(OTf)_2$ was the best catalyst both for chemical yields and enantioselectivities.



Scheme 17

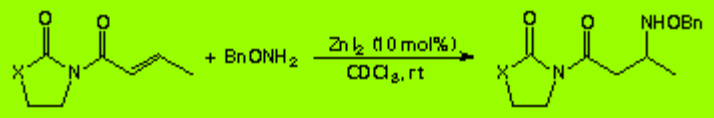
Importance of the *o*-hydroxyl group involved in the 4-benzyl shielding group of the complex catalyst was confirmed when enantioselectivities were compared among the following reactions. Thus, enantioselectivity observed in the reaction of *O*-benzylhydroxylamine with 1-crotonoyl-3-phenyl-2-imidazolidinone catalyzed by the *R,R*-BOX/*o*-HOBn · $Cu(OTf)_2$ complex at room temperature was 85% ee, while the enantioselectivity was only 49% ee when the hydroxyl group is methylated (Scheme 18). Use of the catalyst having no hydroxyl group on the benzyl phenyl group provided 71% ee. The same absolute configurations were induced in these three reactions. We believe that the free hydroxyl groups of *R,R*-BOX/*o*-HOBn · $Cu(OTf)_2$ weakly coordinate to the copper(II) ion to hinder to a certain extent the free rotation of the benzyl shielding substituent across the C(4) - CH_2 bond. This conformational restriction either facilitates the coordination of the acceptor molecule to the metallic center of complex catalyst easy or increases the efficiency of chiral shielding. However, the catalytic activities of all three catalysts were about the same.



Scheme 18

Acceptors having *N*-alkyl-2-imidazolidinone chelating auxiliaries are more electron rich than those having *N*-phenyl-2-imidazolidinone and 2-oxazolidinone auxiliaries so that the *N*-alkyl acceptors should be less reactive under the uncatalyzed conditions than the later two, but coordination to the catalyst should be stronger. Accordingly, the reaction rate difference between the catalyzed and uncatalyzed reactions should be greater for *N*-alkyl-2-imidazolidinone acceptors. Competitive coordination of the substrate *O*-benzylhydroxylamine and acceptors affects the total reaction rate in the Lewis acid-catalyzed reactions using coordinating nucleophiles so that *N*-alkyl-2-imidazolidinone acceptors are anticipated to be much more effective in reactivities and enantioselectivities (Scheme 19).

Effect of Chelating Auxiliary on Reaction Rates under Catalyzed and Uncatalyzed Conditions



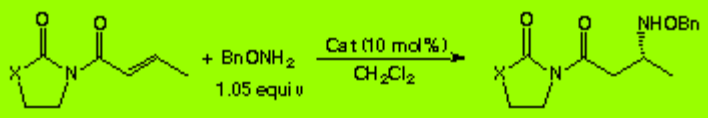
X	Catalyst	Time/h	Yield/%
O	-	24	7
O	ZnI_2	24	16
NPh	-	26	2
NPh	ZnI_2	26	70
NMe	-	20	-
NMe	ZnI_2	20	61
NPr-*i*	-	21	-
NPr-*i*	ZnI_2	21	91

N-Alkyl-2-imidazolidinones are the choice of chelating auxiliaries.

Scheme 19

To our delight, this anticipation was correct. The imidazolidinone chelating auxiliary having *N*-isopropyl group showed especially satisfactory features. The reaction of 1-crotonoyl-3-isopropyl-2-imidazolidinone with *O*-benzylhydroxylamine was completed in 5 h at -20°C to provide 92% ee for the adduct (Scheme 20). Several other derivatives of 1-(2-alkenoyl)-3-isopropyl-2-imidazolidinones having ethyl, isopropyl, and *t*-butyl substituents at the *beta*-position were successfully applied to give satisfactory enantioselectivities (Scheme 21).

Use of *N*-Alkyl-2-imidazolidinone Chelating Auxiliary

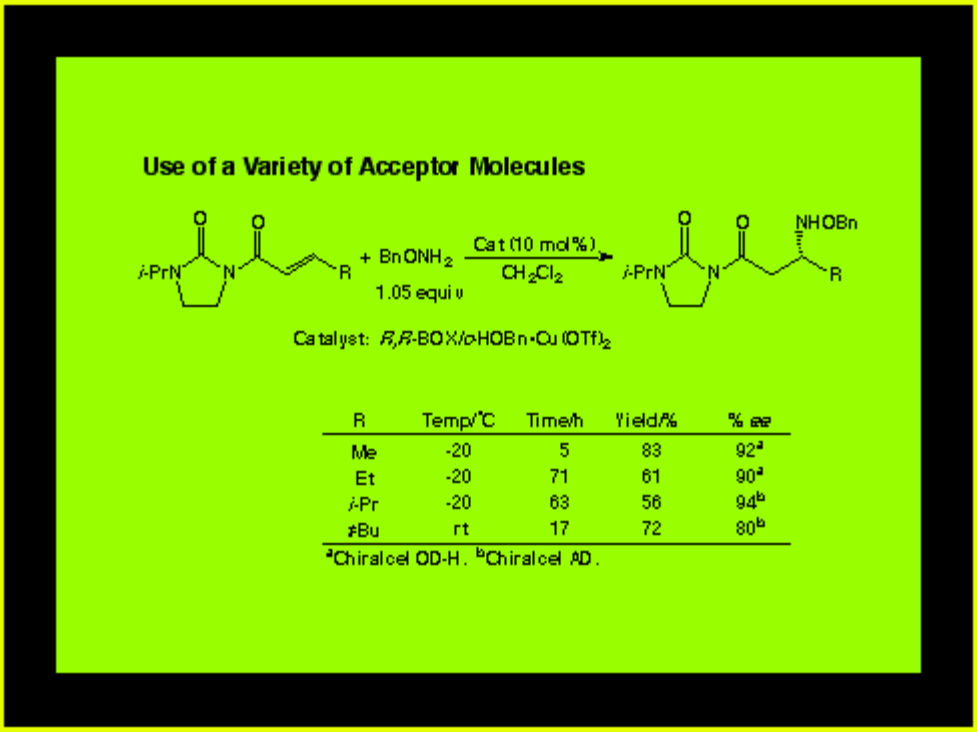


Catalyst: *R,R*-BOX/*c*-HOBn•Cu(OTf)$_2$

X	Temp/°C	Time/h	Yield/%	% ee[a]
NMe	rt	1	77	89
NMe	0	7	48	88
NMe	-20	28	25	92
NPr-*i*	0	7	80	88
NPr-*i*	-20	5	83	92
NPr-*i*	-40	43	71	93

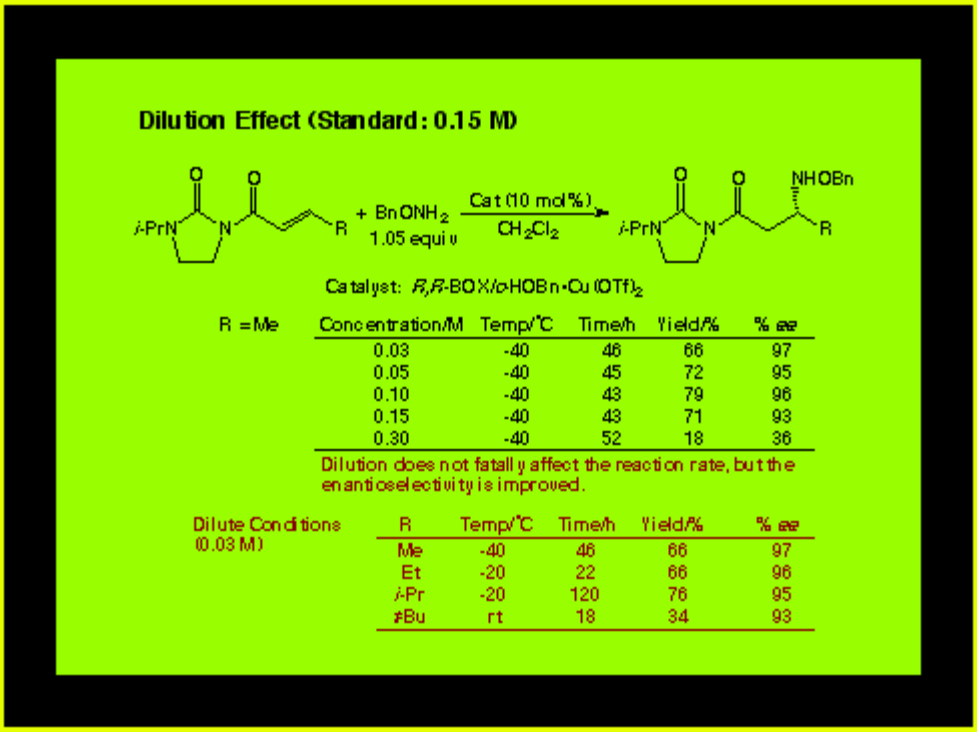
[a]Determined by chiral column HPLC (Chiralcel OD-H).

Scheme 20



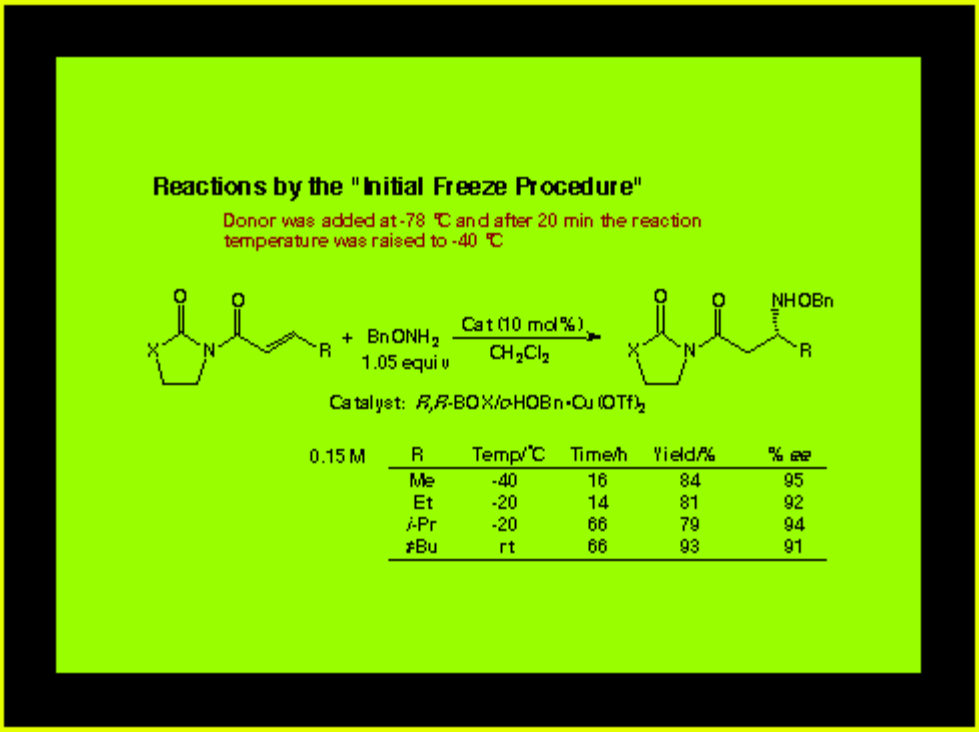
Scheme 21

When the same reaction was diluted five-fold with dichloromethane (0.03 M), the reaction rate was not so fatally decreased as expected for the second-order reaction,*16* and the enantioselectivity (97% ee) was improved (0.15M: 93% ee at -40°C). Accordingly the reactions using other acceptors were examined under dilute conditions (0.03 M) to find that the enantioselectivities were much improved regardless of the *beta*-substituents of the acceptors (Scheme 22). This probably indicates that both the acceptor and nucleophile are condensed on the copper catalyst and the nucleophile is delivered internally to the activated acceptor. This internal delivery mechanism should guarantee high enantioselectivity since the transition structure becomes much more rigid by coordination. Dilution should be favored for the inhibition of both competing external delivery of nucleophile and competing uncatalyzed background process.



Scheme 22

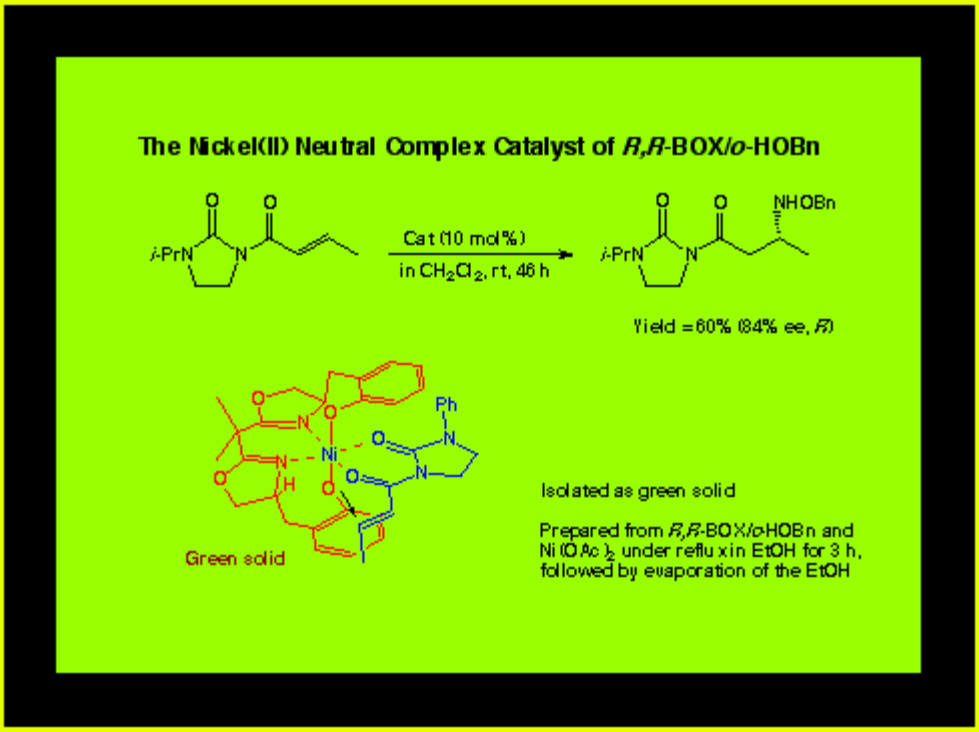
Dependence of enantioselectivities on reaction temperature was only small as shown in Schemes 17 and 20, while the reaction rates were highly temperature-dependent. This temperature insensitivity on the enenatioselectivity indicates that the transition structure has a rigid structure. Addition of *O*-benzylhydroxylamine to the bluish green-colored solution of *R,R*-BOX/*o*-HOBn · Cu(OTf)2 and 1-crotonoyl-3-isopropyl-2-imidazolidinone in dichloromethane induced the immediate color change to dark-green, indicating that coordination of amine to the catalyst is very rapid. The above observations are likely to support the internal delivery mechanism.



Scheme 23

In a preliminary experiment for the reaction between 1-crotonoyl-3-isopropyl-2-imidazolidinone and *O*-benzylhydroxylamine we have found that the enantioselectivity of the adduct changes depending upon the conversion of reaction; a low enantioselectivity results at the early stage of reaction and this is gradually recovered with the progress of reaction. Probably the intermolecular conjugate addition reaction providing a lower selectivity competes at the initial stage as mentioned above. The dilution method has offered an efficient solution. As an alternative, we tried to freeze the competing intermolecular reaction by applying "initial freeze procedure". The amine nucleophile was added to a 0.15 M solution of 1-crotonoyl-3-isopropyl-2-imidazolidinone and *R,R*-BOX/*o*-HOBn · $Cu(OTf)_2$ at -78°C and, after a while (20 min) at this temperature, the mixture was warmed up to the reaction temperature. By this "initial freeze procedure" the reaction was accelerated and the enantioselectivity was improved (Scheme 23).

We are happy to find that the neutral nickel(II) complex catalyst*17* derived from *R,R*-BOX/*o*-HOBn and nickel(II) acetate shows a high catalytic activity in the reaction of 1-crotonoyl-3-isopropyl-2-imidazolidinone with *O*-benzylhydroxylamine. With the catalytic loading of 10 mol% of the isolated catalyst, the reaction done at room temperature gave an enantioselectivity of 84% ee for the adduct (Scheme 24).



Scheme 24

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Conclusion

We have succeeded in the establishment of highly effective enantioselective conjugate additions of thiols to 3-(2-alkenoyl)-2-oxazolidinones in the presence of the nickel(II) aqua complex derived from *R,R*-DBFOX/Ph and $Ni(ClO_4)_2 \cdot 6H_2O$, as well as the reactions of *O*-benzylhydroxylamine to 1-(2-alkenoyl)-3-isopropyl-2-imidazolidinones in the presence of the copper(II) complex catalyst prepared from *R,R*-BOX/*o*-HOBn and $Cu(OTf)_2$. These reactions provide rare examples of "*Lewis acid catalyzed enantioselective reactions using strongly coordinating nucleophiles*". We believe these two reactions will pioneer a conceptually new methodology in the field of synthetic organic chemistry. Use of tolerant chiral Lewis acid catalysts such as the complexes derived from *R,R*-DBFOX/Ph and *R,R*-BOX/*o*-HOBn ligands is no doubt highly responsible for the success. The author sincerely hopes the present lecture stimulates not only the field of synthetic organic chemistry but also the field of molecular catalyst chemistry.

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Acknowledgment

This work has been achieved by three dear graduate students. Dr. Yoji Oderaotoshi is the pioneer of this chemistry.*4a,b* He has synthesized the *R,R*-DBFOX/Ph ligand and prepared a variety of complex catalysts from transition metal complexes. He has found that the aqua complexes derived from *R,R*-DBFOX/Ph and a variety of

transition metals show high tolerance to highly coordinating nucleophiles to make a great contribution to this work. Nitrone cycloadditions*5* as well as thiol conjugate additions*18* catalyzed by the *R,R*-DBFOX/Ph complexes have been achieved by him. The *R,R*-BOX/*o*-HOBn ligand has been prepared by Mr. Takanori Kai. Miss Asami Miura has established the amine conjugate addition methodology. The author is very satisfied with their great contribution. He would like to express his sincere thanks to these coworkers.

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5 Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* 1998, *120*, 12355-12356.

6 The *R,R*-DBFOX/Ph - transition metal aqua complex catalysts were totally ineffective in the reactions of *O*-

benzylhydroxylamine and N-benzylhydroxylamine with 3-(2-alkenoyl)-2-oxazolidinones (Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S. Unpublished results). Both rate acceleration and enantioselectivities were disappointingly poor.

7 (a) "The Chemistry of the Thiol Group", ed. by Patai, S., Wiley, New York, 1974. (b) Ohno, A.; Oae, S. in "Organic Chemistry of Sulfur", ed. by Oae, S., Plenum, New York, 1976. (c) "Comprehensive Organic Chemistry, The Synthesis and Reactions of Organic Compounds", Sir Barton, D.; Ollis, W. D., "Sulphur, Selenium, Silicon, Boron, Organometallic Compounds" as Volume 3, ed. by Jones, D. N. pp. 3-20, Pergamon Press, Oxford, 1979.

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9 Chiral hplc was performed on a column packed with Daicel chiralcel OD-H with hexane - 2-PrOH (9:1 v/v).

10 The thiol adduct was converted into the methyl ester without racemization by treatment with methoxymagnesium bromide in methanol at 0°C. Optical rotaion of the resulting methyl ester was compared with the authentic sample to determine the absolute configuration to be 3*S*.

11 The anhydrous complex was in situ prepared by consequtive treatment of *R,R*-DBFOX/Ph, $NiBr_2$ (10 mole% each), and $AgClO_4$ (20 mol%).

12 Treatment of benzenethiol with *R,R*-DBFOX/Ph · $Ni(ClO_4)_2 \cdot 3H_2O$ in dichloromethane or diethyl ether immediately precipitated a brown solid which was an active catalyst. Because of less solubility of this thiol complex, the reaction in dichloromethane or diethyl ether is less effective leading to low yields and enantioselectivities.

13 The solid slowly liberates thiol at room temperature.

14 This complex was negative and positive in the halogen and sulfer tests, respectively, and no liberation of thiol was detected. Although it is soluble in acetone, THF, and dichloromethane, no catalytic activity was observed in the thiol conjugate addition.

15 The *R,R*-DBFOX/Ph - transition metal aqua complex catalysts were totally ineffective in the reactions of *O*-benzylhydroxylamine and *N*-benzylhydroxylamine with 3-(2-alkenoyl)-2-oxazolidinones (Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S. Unpublished results). Both rate acceleration and enantioselectivities were

disappointingly poor (Scheme 15).

16 We expect that the reaction would be second order against 1-crotonoyl-3-isopropyl-2-imidazolidinone and the complex of *O*-benzylhydroxylamine to *R,R*-BOX/*o*-HOBn · $Cu(OTf)_2$.

17 The catalyst can be prepared as follows: A mixture of equimolar amounts of *R,R*-BOX/*o*-HOBn and $Ni(OAc)_2$ was heated under reflux in ethanol for 3 h. The ethanol was evaporated in vacuo to give a green colored solid of the complex catalyst.

18 Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* 1999, *121*, 8675-8676.

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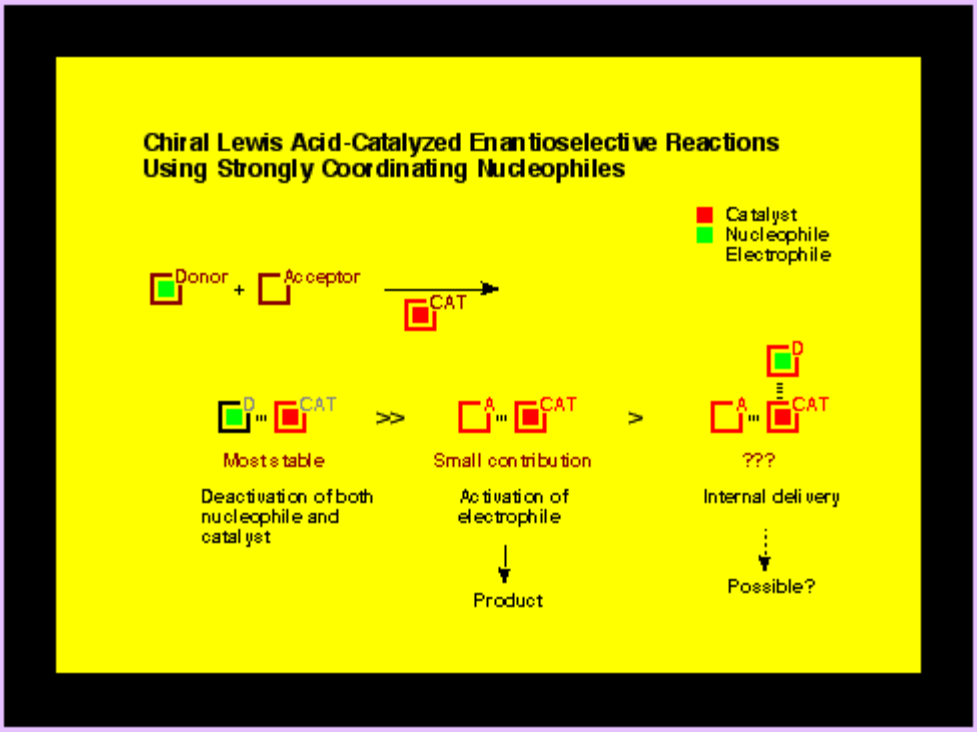
Scheme 01



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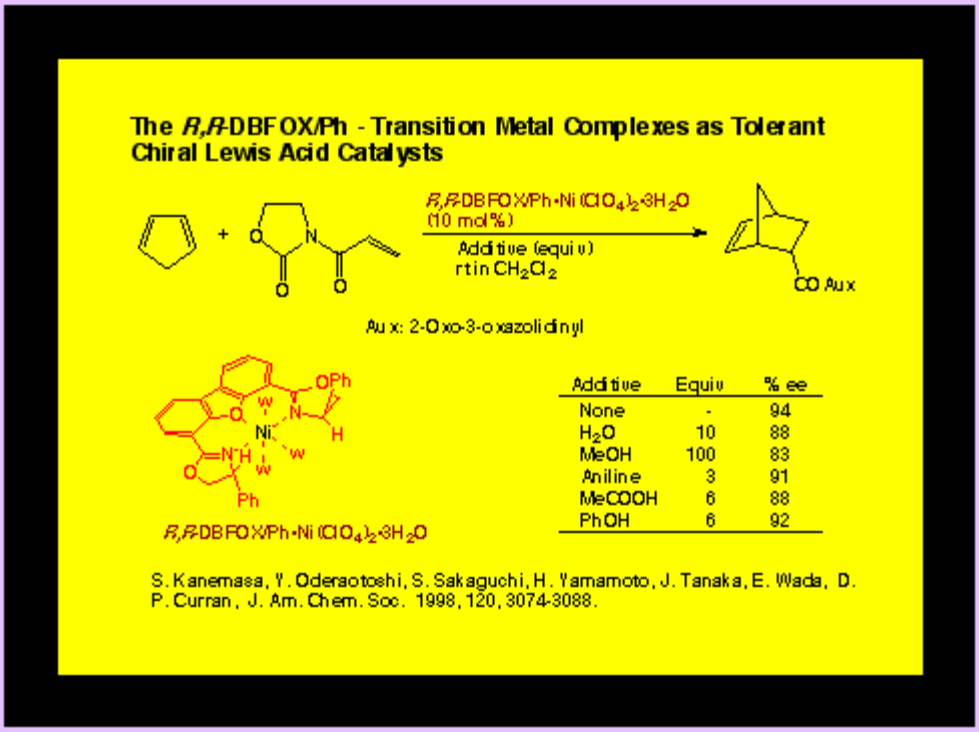
Scheme 02



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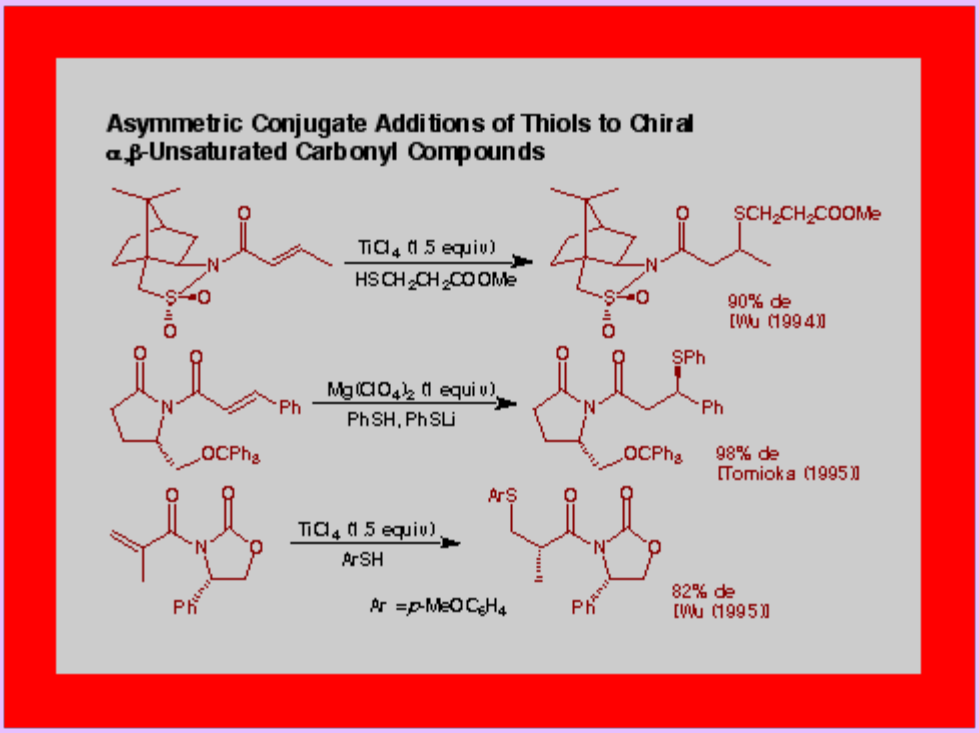
Scheme 03



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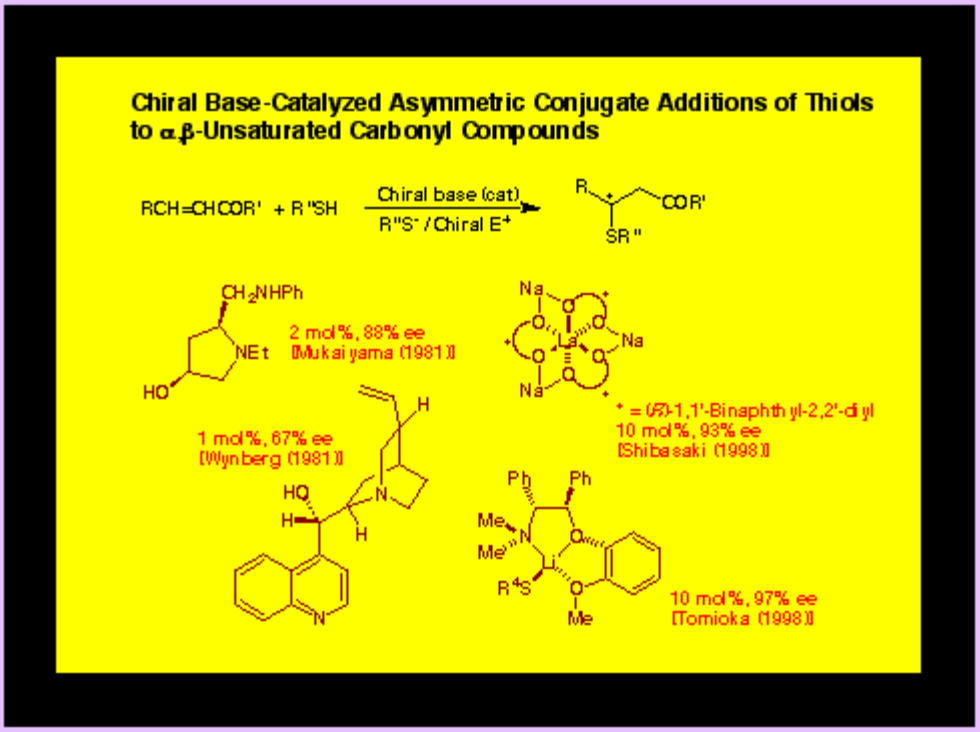
Scheme 04



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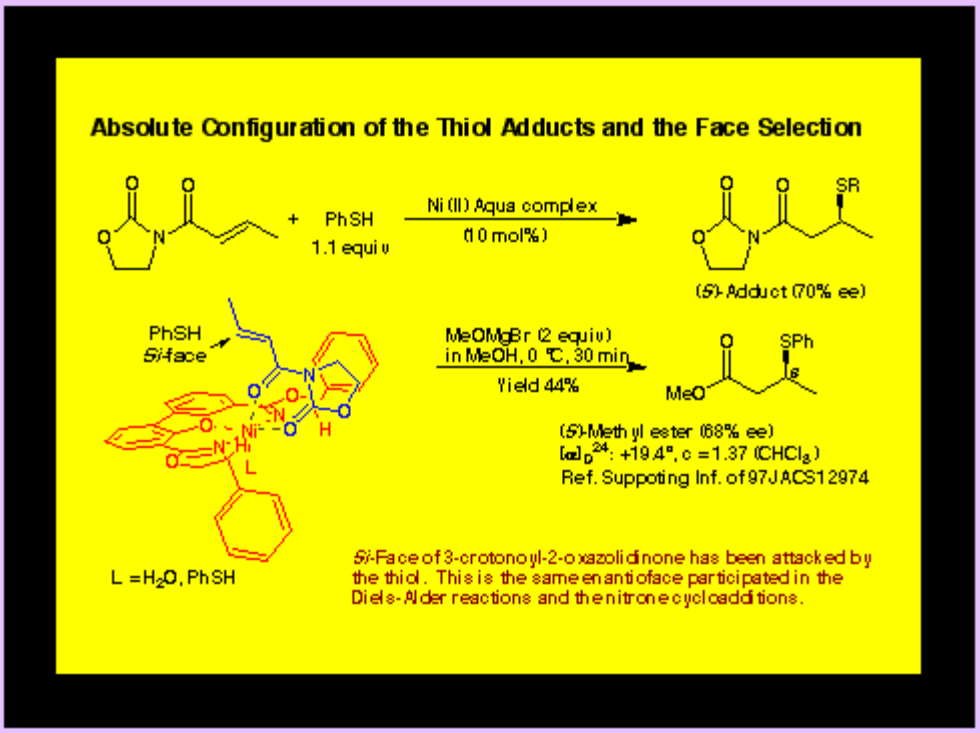
Scheme 05



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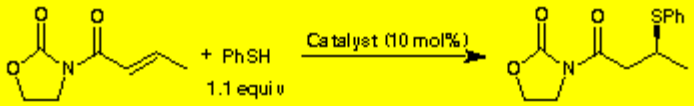
Scheme 06

A Variety of *R,R*-DBFOX/Ph - Metal Salt Complex Catalysts (Part 1)



Entry	Metal Salt	Solvent	Time/h	Yield/%	ee%[a]
1	$Mg(ClO_4)_2$	CH_2Cl_2	24	quant	52
2[b]	$Mn(ClO_4)_2 6H_2O$	THF	24	quant	25
3	$FeCl_2$+2 $AgClO_4$	THF	24	7	0
4	$Cu(ClO_4)_2 6H_2O$	THF	24	49	-11
5	$Zn(ClO_4)_2 6H_2O$	THF	24	62	0
6	$Ni(ClO_4)_2 6H_2O$	THF	48	quant	80

[a] Determined by HPLC (Daicel Chiral Cel OD-H). [b] DBFOX was added to a mixture of $Ni(ClO_4)_2 6H_2O$, thiophenol, and 3-crotonoyl-2-oxazolidinone.

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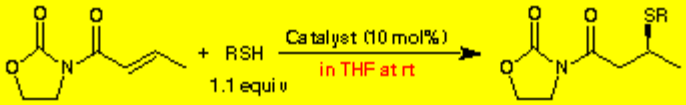
Scheme 07

Enantioselective Conjugate Additions of Thiols Catalyzed by *R,R*-DBFOX/Ph·$Ni(ClO_4)_2 \cdot 3H_2O$



1. *R,R*-DBFOX/Ph + $Ni(ClO_4)_2 6H_2O$ (0.1 equiv each) in THF at rt 2 h
2. 3-Crotonoyl-2-oxazolidinone (1 equiv)
3. Thiol (1.1 equiv) then stir at rt under nitrogen

Entry	R	Time/h	Yield/%	ee%
1	Phenyl	24	quant	80
2	*o*-Tolyl	24	82	89
3	*p*-Tolyl	24	82	84
4	Mesityl	24	84	95
5	*o*-Isopropylphenyl	24	96	80
6	*o*-*tert*-Butylphenyl	24	quant	93
7	*p*-*tert*-Butylphenyl	24	74	86
8	1-Naphthyl	24	73	87
9	2-Naphthyl	24	94	87
10	Benzyl	48	26	89
11	*o*-Methoxyphenyl	48	69	11
12	*p*-Methoxyphenyl	72	30	78

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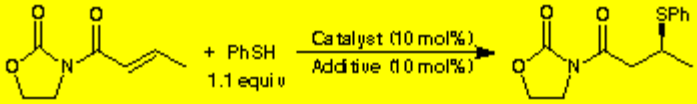
Scheme 08

Effect of Catalysts, Solvents, and Additives (Part 2)



Entry	Metal Salt	Solvent	Additive	Temp/°C	Yield/%	ee%[a]
1[b]	$Ni(ClO_4)_2·6H_2O$	CH_2Cl_2	-	rt	81	79
2[c]	$Ni(ClO_4)_2·6H_2O$	CH_2Cl_2	-	rt	91	20
3	$NiBr_2$+2 $AgClO_4$	CH_2Cl_2	-	rt	50	0
4	$Ni(ClO_4)_2·6H_2O$	CH_2Cl_2	-	-78	33	-17
5	$Ni(ClO_4)_2·6H_2O$	Et_2O	Pyridine	rt	42	73
6[c]	$NiBr_2$+2 $AgClO_4$	Et_2O	Pyridine	rt	53	-10
7	$Ni(ClO_4)_2·6H_2O$	THF	-	rt	quant	80
8	$Ni(ClO_4)_2·6H_2O$	THF	-	0	62	7
9	$Ni(ClO_4)_2·6H_2O$	MeOH	-	rt	72	77
10	$Ni(ClO_4)_2·6H_2O$	CH_2Cl_2	MeOH (1/1 v/v)	rt	quant	82
11	$Ni(ClO_4)_2·6H_2O$	CH_2Cl_2	AcOH (10/1 v/v)	rt	99	0
12	$Ni(ClO_4)_2·6H_2O$	CH_2Cl_2	NH_4Cl aq (10/1 v/v)	rt	99	-27

[a] Determined by HPLC (Daicel Chiral Cel OD-H). [b] DBFOX was added to the mixture of $Ni(ClO_4)_2·6H_2O$, thiophenol, and 3-crotonoyl-2-oxazolidinone. [c] Thiophenol was added slowly to a mixture of the catalyst and 3-crotonol-2-oxazolidinone in a period of 3 h.

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Scheme 09

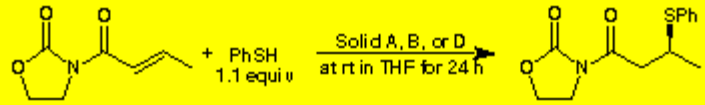
Deterioration of *R,R*-DBFOX/Ph Complexes by Thiols

R,R-DBFOX/Ph·$Ni(ClO_4)_2·3H_2O$ (Pale blue) —Slow, PhSH→ Reddish brown solid A
R,R-DBFOX/Ph·$Ni(ClO_4)_2$·(PhSH)$_n$·$(H_2O)_{3-n}$
active, high enantioselectivity

R,R-DBFOX/Ph·$Ni(ClO_4)_2·3H_2O$ (Pale bblue) —Fast, PhSH +base→ Reddish brown solid B
R,R-DBFOX/Ph·$NiClO_4$·PhSH·$2H_2O$
inactive, low enanticoselectivity

R,R-DBFOX/Ph·$Ni(ClO_4)_2$ (Anhydrous complex) —Fast, PhSH→ Reddish brown solid C
low enantioselectivity

$Ni(ClO_4)_2·6H_2O$ —Fast, PhSH +Et_3N→ Reddish brown solid D
inactive, low solubility



Reddish brown solid A 97% (70% ee)
Reddish brown solid B 15% (19% ee)
Reddish brown solid D 15%

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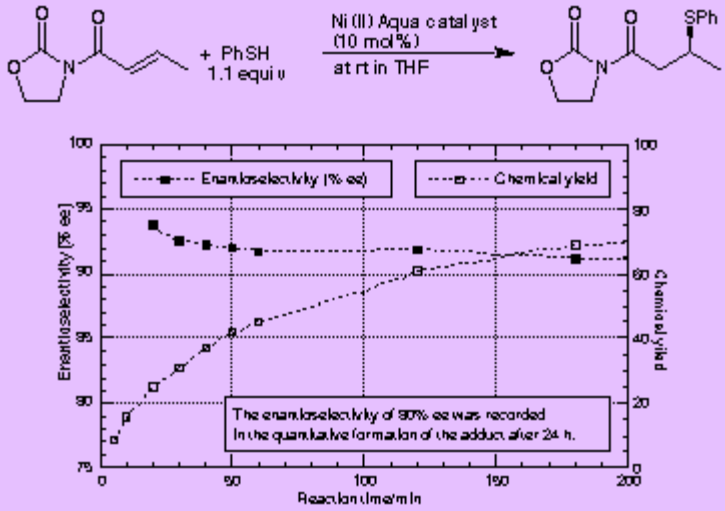
Scheme 10

Time Dependence of Enantioselectivity and Chemical Yields



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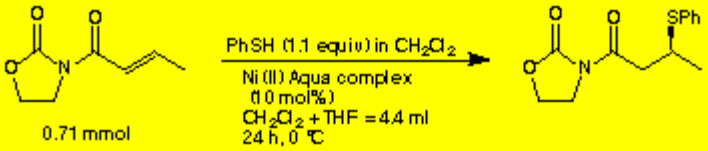
Scheme 11

Effect of THF Content on Chemical Yield and Enantioselectivity



0.71 mmol

0.16 M Solution

THF/equiv* (ml)	Yield%	ee/%
0.5 (0.028)	72	89
1 (0.056)	78	90
3 (0.173)	55	92
20 (1.15)	90	93
40 (2.31)	73	85

*Equivalent to the oxazolidinone

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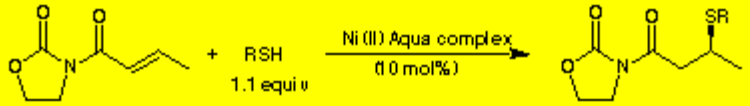
Scheme 12

Enantioselective Conjugate Additions of Thiols Catalyzed by *R,R*-DBFOX/Ph·Ni(ClO$_4$)$_2$·3H$_2$O under Optimized Conditions



R	Time/h	Yield/%	ee%
Phenyl	24	84	94
o-Tolyl	96	99	95
p-Tolyl	96	84	91
Mesityl	96	36	96
o-Isopropylphenyl	96	91	97
o-*tert*-Butylphenyl	96	96	94
p-*tert*-Butylphenyl	96	38	69
1-Naphthyl	96	92	55
2-Naphthyl	96	88	91

Reaction conditions:

1. 3-Crotonoyl-2-oxazolidinone 1.0 equiv
2. RSH 1.1 equiv
3. (*R,R*)-DBFOX/Ph 0.1 equiv
4. Ni(ClO$_4$)$_2$·6H$_2$O 0.1 equiv
5. Proton Sponge 0.1 equiv
6. At 0 °C in CH_2Cl_2/THF = 10/1 v/v
7. Under N_2

Proton Sponge: *N,N,N',N'*-Tetramethyl-1,8-diaminonaphthalene

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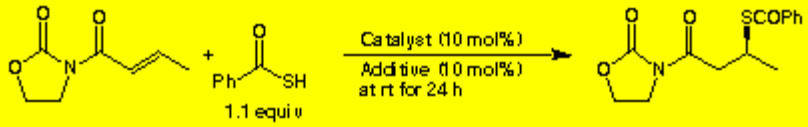
Scheme 13

Enantioselective Conjugate Additions of Thiobenzoic Acid
- Effect of Solvents and Additives -



Entry	Metal Salt and Additive	Solvent	Yield/%	ee%[a]
1	Mg(ClO$_4$)$_2$	CH_2Cl_2	quant	63
2	Mn(ClO$_4$)$_2$·6H$_2$O	CH_2Cl_2	quant	33
3	FeCl$_2$+2AgClO$_4$	CH_2Cl_2	87	0
4	Co(ClO$_4$)$_2$·6H$_2$O	CH_2Cl_2	quant	56
5	Ni(ClO$_4$)$_2$·6H$_2$O	CH_2Cl_2	quant	80
6	Cu(ClO$_4$)$_2$·6H$_2$O	CH_2Cl_2	quant	25
7	Zn(ClO$_4$)$_2$·6H$_2$O	CH_2Cl_2	quant	6
8	Ni(ClO$_4$)$_2$·6H$_2$O	THF	quant	70
9	Ni(ClO$_4$)$_2$·6H$_2$O	$CHCl_3$	quant	77
10	Ni(ClO$_4$)$_2$·6H$_2$O	MeOH	79	21
11	Ni(ClO$_4$)$_2$·6H$_2$O, Pyridine	CH_2Cl_2	quant	76
12	Ni(ClO$_4$)$_2$·6H$_2$O, PS[b]	CH_2Cl_2	quant	58
13	Ni(ClO$_4$)$_2$·6H$_2$O, MgSO$_4$	CH_2Cl_2	93	64

[a] Determined by HPLC (Daicel Chiral Cel OD-H). [b] PS: *N,N,N',N'*-Tetramethyl-1,8-diaminonaphthalene

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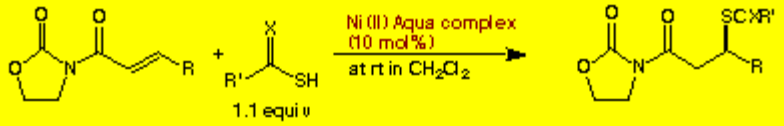
Scheme 14

Asymmetric Conjugate Additions of Thiocarboxylic Acid with β-Substituted 3-Alkenoyl-2-oxazolidinone



Entry	R	R'	X	Time/h	Yield/%	ee%[a]
1	Me	Me	O	24	quant	86
2	Me	Ph	O	24	quant	80
3	^{n}Pr	Ph	O	24	77	70
4	^{i}Pr	Ph	O	24	67	68
5	Ph	Ph	O	48	67	80
6	-CH=CHMe	Ph	O	48	trace	-
7	Me	Ph	S	72	nr	-

[a] Determined by HPLC (Daicel Chiral Cel OD-H).

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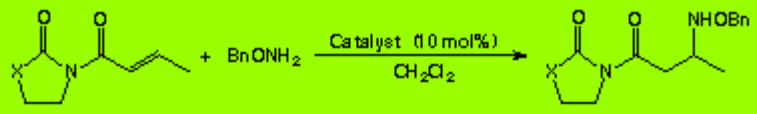
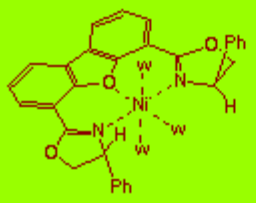
Scheme 15

The *R,R*-DBFOX/Ph·Ni(ClO$_4$)$_2$·3H$_2$O - Catalyzed Conjugate Additions of *O*-Benzylhydroxylamine





Catalyst =
R,R-DBFOX/Ph·Ni(ClO$_4$)$_2$·3H$_2$O

X	Temp/°C	Time/h	Yield/%	% ee
O	rt	18	71	29
NPh	-20	114	61	51

Low reactivity and low enantioselectivity

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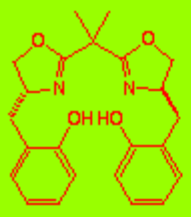
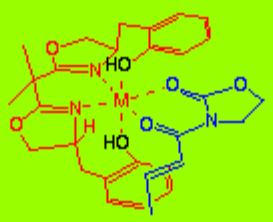
Scheme 16

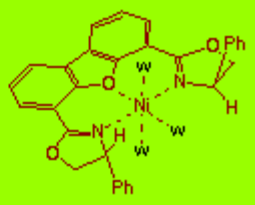
The Copper(II) Complex of *R,R*-Isopropylidene-2,2'-bis-[4-(*o*-hydroxybenzyl)oxazoline] - *R,R*-BOX/*o*-HOBn -



R,R-BOX/*o*-HOBn



Possible structure for the substrate complex



R,R-DBFOX/Ph·3H$_2$O

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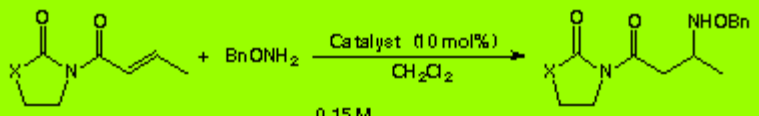
Scheme 17

The *R,R*-BOX/*o*-HOBn·Cu(OTf)$_2$ - Cayalyzed Conjugate Additions of *O*-Benzylhydroxylamine



0.15 M

1. Enanticoselectivity is not highly sensitive to the reaction temperature, indicating the transition state is conformationally rigid.
2. Reactivity is highly dependent upon the reaction temperature.

X	Catalyst	Temp/°C	Time/h	Yield/%	% ee[a]
O	*R,R*-BOX/*o*-HOBn·Cu(OTf)$_2$	-20	166	44	11
NPh	*R,R*-BOX/*o*-HOBn·Cu(OTf)$_2$	rt	3	71	85
NPh	*R,R*-BOX/*o*-HOBn·Cu(OTf)$_2$	0	16	80	89
NPh	*R,R*-BOX/*o*-HOBn·Cu(OTf)$_2$	-20	72	77	89
NPh	*R,R*-BOX/*o*-HOBn·Cu(SbF$_6$)$_2$	-20	113	63	83
NPh	*R,R*-BOX/*o*-HOBn·Cu(ClO$_4$)$_2$	-20	162	59	85
NPh	*R,R*-BOX/*o*-HOBn·Cu(ClO$_4$)$_2$·3H$_2$O	-20	66	62	80

[a]Determined by chiral column HPLC.

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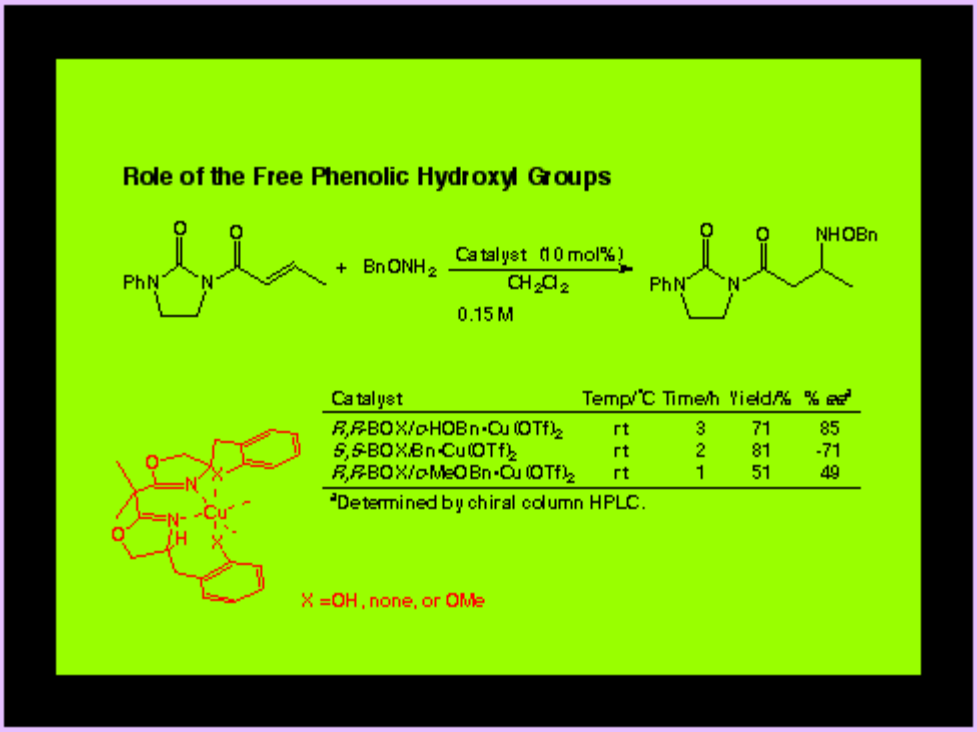
Scheme 18



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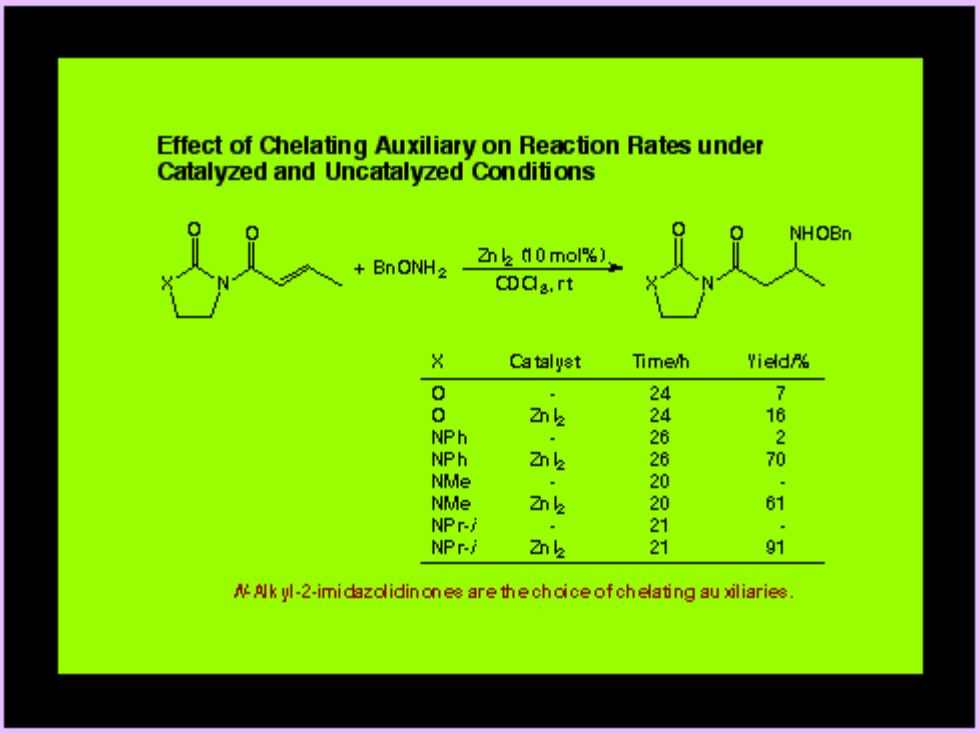
Scheme 19



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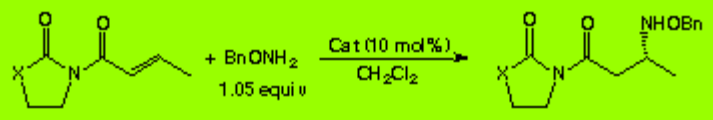
Scheme 20

Use of *N*-Alkyl-2-imidazolidinone Chelating Auxiliary



Catalyst: *R,R*-BOX/*c*-HOBn•Cu(OTf)$_2$

X	Temp/°C	Time/h	Yield/%	% ee[a]
NMe	rt	1	77	89
NMe	0	7	48	88
NMe	-20	28	25	92
NPr-*i*	0	7	80	88
NPr-*i*	-20	5	83	92
NPr-*i*	-40	43	71	93

[a]Determined by chiral column HPLC (Chiralcel OD-H).

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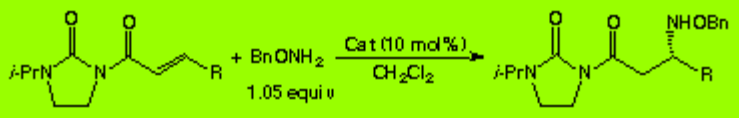
Scheme 21

Use of a Variety of Acceptor Molecules



Catalyst: *R,R*-BOX/*c*-HOBn•Cu(OTf)$_2$

R	Temp/°C	Time/h	Yield/%	% ee
Me	-20	5	83	92[a]
Et	-20	71	61	90[a]
i-Pr	-20	63	56	94[b]
t-Bu	rt	17	72	80[b]

[a]Chiralcel OD-H. [b]Chiralcel AD.

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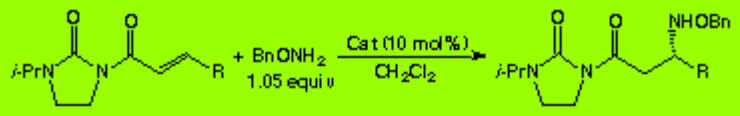
Scheme 22

Dilution Effect (Standard: 0.15 M)



Catalyst: *R,R*-BOX/*o*-HOBn•Cu(OTf)$_2$

R = Me

Concentration/M	Temp/°C	Time/h	Yield/%	% ee
0.03	-40	46	66	97
0.05	-40	45	72	95
0.10	-40	43	79	96
0.15	-40	43	71	93
0.30	-40	52	18	36

Dilution does not fatally affect the reaction rate, but the enantioselectivity is improved.

Dilute Conditions (0.03 M)

R	Temp/°C	Time/h	Yield/%	% ee
Me	-40	46	66	97
Et	-20	22	66	96
i-Pr	-20	120	76	95
≠Bu	rt	18	34	93

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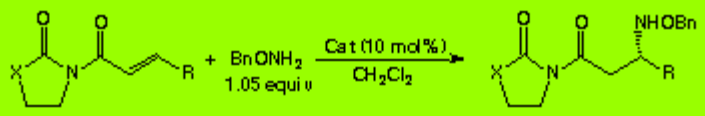
Scheme 23

Reactions by the "Initial Freeze Procedure"

Donor was added at -78 °C and after 20 min the reaction temperature was raised to -40 °C



Catalyst: *R,R*-BOX/*o*-HOBn•Cu(OTf)$_2$

0.15 M

R	Temp/°C	Time/h	Yield/%	% ee
Me	-40	16	84	95
Et	-20	14	81	92
i-Pr	-20	66	79	94
≠Bu	rt	66	93	91

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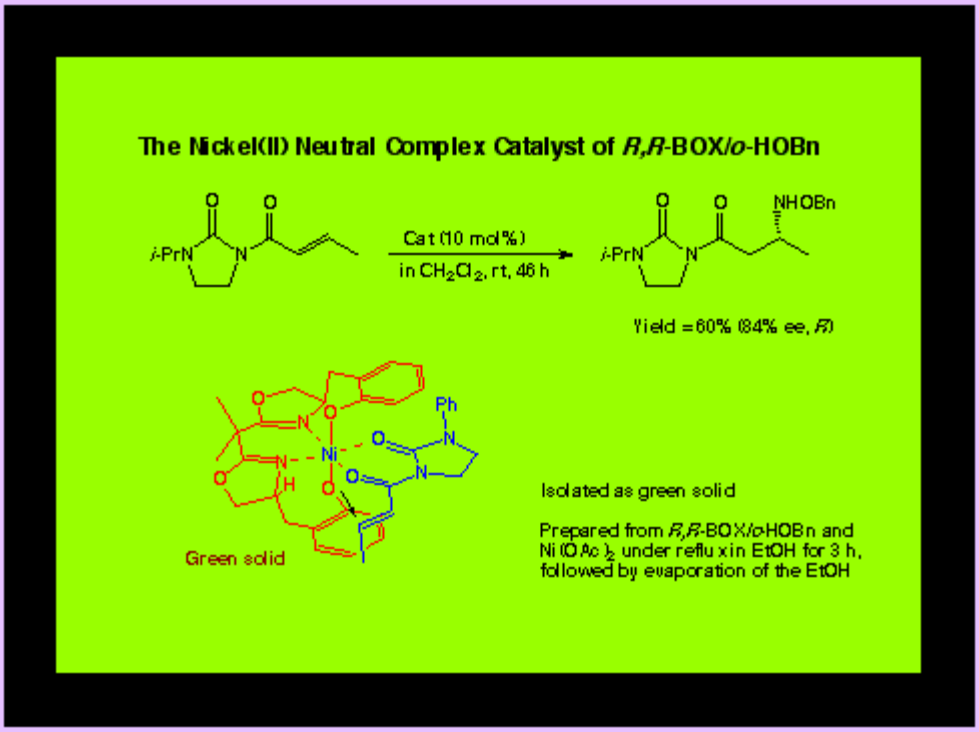
Scheme 24



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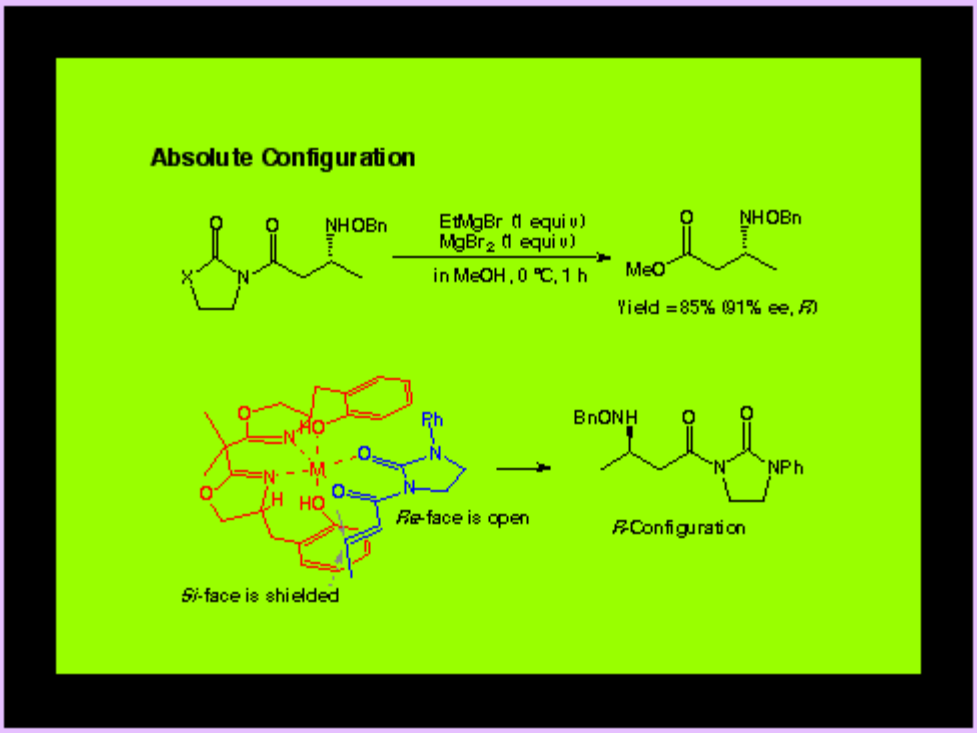
Scheme 25



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