Asymmetric Conjugate Addition of Thiols to a 3-(2-Alkenoyl)-2-oxazolidinone Catalyzed by the DBFOX/Ph Aqua Complex of Nickel(II) Perchlorate

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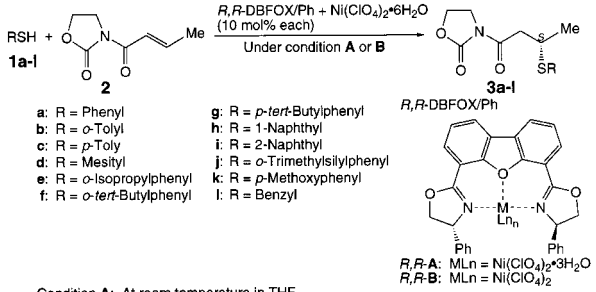
The trans-chelating tridentate chiral ligand, 4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline), designated as DBFOX/Ph, has been developed by our group. Its aqua complexes of transition metal perchlorates act as excellent Lewis acid catalysts in Diels−Alder reactions[1] and nitrone dipolar cycloadditions.[2] Noteworthy features of the Ni(II) aqua complex of DBFOX/Ph are its high catalytic activity and tolerance to a variety of nucleophilic reagents. This catalyst is isolable and can be stored for months in open air without loss of catalytic activity. It shows sufficient catalytic activity in the presence of coordinating additives such as ethers, water, alcohols, acids, and even amines. Therefore, we expected that these catalysts would be successfully applied to the catalyzed asymmetric reactions using strongly coordinating or nucleophilic reagents.

Thiols have been studied as nucleophiles in the conjugate addition reactions with 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.[3] Quite a number of asymmetric thiol conjugate addition reactions are known,[4] 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,[5] the lithium thiolate complex of amino bisether,[6] and a lanthanoid tris(binaphthoxide).[7] 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 present communication, we describe the first examples of enantioselective thiol conjugate additions catalyzed by a chiral Lewis acid.

Scheme 1



		Condition **A**			Condition **B**		
Entry	Thiol **1**	Time/h	Yield/% (**3**)	ee%	Time/h	Yield/% (**3**)	ee%
1	**a**	24	quant	80	24	84	94
2	**b**	24	82	89	96	99	95
3	**c**	24	82	84	96	84	91
4	**d**	24	84	95	96	36	96
5	**e**	24	96	80	96	91	97
6	**f**	24	quant	93	96	96	94
7	**g**	24	74	86	96	38	69
8	**h**	24	73	87	96	92	55
9	**i**	24	94	87	96	88	91
10	**j**	24	84	87[a]	-	-	-
11	**k**	72	30	78	-	-	-
12	**l**	48	26	89	-	-	-

[a] The product isolated was **4a** together with **4j** (16%, 87% ee).

The aqua complex of *R,R*-DBFOX/Ph−nickel(II) perchlorate (*R,R*-**A**) 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 (**1a**, 1.1 equiv) with 3-crotonoyl-2-oxazolidinone (**2**, 1 equiv) was quite slow, and it took about 24 h at room temperature until oxazolidinone **2** was consumed (checked by TLC). After aqueous workup, the mixture was purified through silica gel column chromatography to give the conjugate adduct **3a**, whose enantiopurity was determined by chiral HPLC.[8] Based on the absolute configuration of adduct **3a**,[9] it was found that the thiol conjugate addition took place on the *Si* face of the acceptor oxazolidinone **2**.

Among a variety of DBFOX/Ph complexes examined as chiral catalysts, the nickel aqua complex *R,R*-**A** was exceptionally effective. Although the magnesium and zinc complexes prepared from 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. Reactions of a variety of thiols **1b**−**l** were catalyzed by the aqua nickel complex *R,R*-**A** to give the corresponding adducts **3b**−**l** (Scheme 1). Satisfactorily high enantioselectivities as well as high chemical yields were observed with some exceptions when the reactions were performed in THF at room temperature (under conditions **A**, see the table in Scheme 1).

Enantioselectivities were found to change sharply depending upon the reaction conditions, including catalyst structure, reaction temperature, solvent, and additives. Some representative examples of such selectivity dependence are listed in Table 1. The adduct **3a** was formed with 79% ee (81% yield) when the reaction was catalyzed by the aqua nickel complex *R,R*-**A** at room temperature in dichloromethane. However, reactions using either the anhydrous complex *R,R*-**B**[10] or the aqua complex *R,R*-**A** together with 4-Å molecular sieves gave racemic adduct *rac*-**3a**, indicating that the

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

(9) The thiol adduct **3a** 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 that of the authentic sample to determine the absolute configuration of **3a** to be 3*S*.[8]

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Table 1. Effect of Reaction Conditions in the Reaction of Thiophenol (**1a**) with 3-Crotonoyl-2-oxazolidinone (**2**) Catalyzed by DBFOX/Ph·$Ni(ClO_4)_2$·Ln (Ln = $3H_2O$ or None)

entry	metal salt[a]	solvent	temp (°C)	time (h)	yield of **3a** (%)[b]	ee (%)[c]
1[d]	$Ni(ClO_4)_2·6H_2O$	CH_2Cl_2	rt	48	81	79
2	$NiBr_2 + AgClO_4$ (2 equiv)	CH_2Cl_2	rt	72	50	0
3[e]	$Ni(ClO_4)_2·6H_2O$	CH_2Cl_2	rt	24	91	20
4[d]	$Ni(ClO_4)_2·6H_2O$	CH_2Cl_2	−78	48	33	−17
5	$NiBr_2 + AgClO_4$ (2 equiv)	Et_2O	rt	48	50	−10
6	$Ni(ClO_4)_2·6H_2O$	Et_2O	rt	24	42	73
7	$Ni(ClO_4)_2·6H_2O$	THF	rt	24	quant	80
8	$Ni(ClO_4)_2·6H_2O$	THF	0	72	62	7
9	$Ni(ClO_4)_2·6H_2O$	CH_2Cl_2/MeOH (1:1 v/v)	rt	24	quant	82
10	$Ni(ClO_4)_2·6H_2O$	CH_2Cl_2/AcOH (10:1 v/v)	rt	48	99	0
11	$Ni(ClO_4)_2·6H_2O$	CH_2Cl_2/sat'd aq NH_4Cl (10:1 v/v)	rt	48	99	−27

[a] Catalyst was prepared in situ from equimolar amounts of DBFOX/Ph and metal salt in CH_2Cl_2. [b] Isolated yield. [c] Determined by chiral HPLC (Daicel Chiral Cel OD-H), ee = %*S* − %*R*. [d] DBFOX/Ph was added to a mixture of $Ni(ClO_4)_2·6H_2O$, **1a**, and **2**. [e] Thiophenol (**1a**) was added slowly to a mixture of DBFOX/Ph and **2** in a period of 3 h.

aqua complex should be more favored than the anhydrous complex in thiol conjugate additions (Scheme 1). Slow addition of thiol **1a** to the dichloromethane solution of **2** 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 (**1a**) with 3-crotonoyl-2-oxazolidinone (**2**) 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 the enantioselectivity of **3a** (quantitative, 82% ee), addition of acetonitrile or *N*,*N*-dimethylformamide (both 1:1 v/v ratios) slowed the reactions (13, 15% yields of **3a**) and provided products with lower enantioselectivities (19, 30% ee's). 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/saturated aqueous NH_4Cl = 10:1 v/v, 99% yield, −27% ee). However, to our delight, the reaction in a mixed solvent of CH_2Cl_2/THF = 10:1 v/v catalyzed by the aqua nickel complex *R*,*R*-**A** at 0 °C in the presence of *N*,*N*,*N*′,*N*′-tetramethyl-1,8-diaminonaphthalene (proton sponge, 10 mol %) gave the best result (**3a**: 84% yield, 94% ee). Some other thiols provided excellent enantioselectivities under similar reaction conditions, with 97% ee for a bulky thiol such as *o*-isopropylbenzenethiol (**1e**, Scheme 1).

We suspected at the beginning of this work that thiol **1a** would strongly coordinate to the Lewis acid catalyst *R*,*R*-**A** to poison its catalytic activity. We therefore examined the interaction between thiol **1a** and the catalyst *R*,*R*-**A** to learn about the catalytic activity of the thiol-coordinating complex. When **1a** was added to the solution of *R*,*R*-**A** in THF, the original pale blue color of the catalyst gradually faded to reddish brown. This color change was rapid in dichloromethane,[11] probably arising from the coordination of thiol **1a** to the catalyst. A brown solid was isolated as precipitate on treatment with a mixture of isopropyl alcohol and hexane,[12] and this showed sufficient catalytic activity in the reaction of **1a** with **2** in THF, leading to a high enantioselectivity (97% yield, 70% ee). Accordingly, it is apparent that the thiol certainly binds with the catalyst **A**, but the binding is not so strong that the thiol ligand may be easily replaced with the acceptor molecule **2** in the reaction. This ligand exchange should be more favored in a coordinating medium 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.[13] 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.

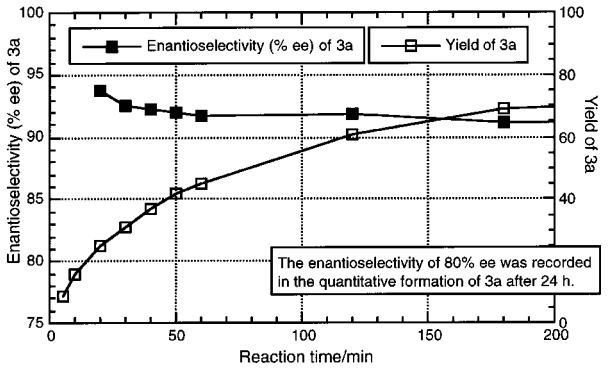

Figure 1. Time dependence of yield and enantioselectivity in the reaction of **1a** with **2** catalyzed by *R*,*R*-**A** at room temperature in THF.

The time dependence of enantioselectivity in the reaction between **1a** and **2** catalyzed by *R*,*R*-**A** at room temperature in THF is shown in Figure 1. After 3 h, the yield of **3a** is 70%, with an enantioselectivity of 91% ee, but the enantioselectivity was 80% ee at the completion of reaction after 24 h (100% yield of **3a**). 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.

In conclusion, thiol conjugate addition reactions to 3-crotonoyl-2-oxazolidinones have been effectively catalyzed by the aqua nickel(II) complex of *R*,*R*-DBFOX/Ph to produce conjugate adducts in high chemical yields and enantioselectivities. This provides the first example of enantioselective thiol conjugate additions catalyzed by a chiral Lewis acid catalyst. Irreversible coordination of thiols to the catalyst takes place slowly under neutral conditions, but the catalytic activity is maintained for several hours from the beginning of reaction. Under the optimized conditions (in dichloromethane/THF = 10:1 v/v) at −20 °C in the presence of *N*,*N*,*N*′,*N*′-tetramethyl-1,8-diaminonaphthalene (10 mol %)), enantioselectivity as high as 97% ee has been attained with the catalytic loading of 10 mol % of *R*,*R*-DBFOX/Ph·$Ni(ClO_4)_2·3H_2O$ catalyst.

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Supporting Information Available: Experimental details and characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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

(11) Treatment of thiol **1a** with the catalyst *R*,*R*-**A** in dichloromethane or diethyl ether immediately precipitated a brown solid which was an active catalyst (see ref 12). Because of the lower solubility of this thiol complex, the reaction in dichloromethane or diethyl ether is less effective, leading to low yields and enantioselectivities.

(12) The solid slowly liberates thiol at room temperature.

(13) This complex was negative and positive in the halogen and sulfer tests, respectively, and no liberation of thiol **1a** was detected. Although it is soluble in acetone, THF, and dichloromethane, no catalytic activity was observed in the thiol conjugate addition.