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Construction of a new asymmetric reaction site: asymmetric 1,4-addition of thiol using pentagonal bipyramidal Hf(salen) complex as catalyst

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Abstract—Pentagonal bipyramidal Hf(salen) complex **1** was found to serve as a catalyst for 1,4-addition reaction of thiol to *N*-(2-alkenoyl)-2-oxazolidinones.

Optically active quadridentate salen ligands have been widely used as chiral auxiliaries for asymmetric synthesis, and various types of salen ligands have been synthesized. Complexes of these salen ligands usually take octahedral configuration and the ligands adopt square planar (*trans*) geometry, placing ancillary ligands (X and Y) at their apical positions (Fig. 1),[1] but Hf- and Zr-(salen) complexes have been reported to adopt pentagonal bipyramidal configuration (**A**), in which an additional neutral ligand (S) such as THF is coordinated to the central metal ion in its equatorial position.[2] These octahedral and pentagonal bipyramidal salen complexes are expected to show different asymmetric catalysis. Different from the former complexes widely used as asymmetric catalysts, the latter complexes have not drawn the attention of synthetic chemists and have not been used as catalyst. On the other hand, Hf- and Zr-complexes have been reported to adopt *cis*-β octahedral configuration with loss of the neutral ligand upon their heating,[2] and we have disclosed that a chiral Zr(salen) complex is an efficient catalyst for asymmetric Baeyer–Villiger (B–V) oxidation, in which the Zr complex is considered to adopt a *cis*-β octahedral configuration upon complexation of the Criegee intermediate, a dianionic bidentate ligand, with the zirconium ion.[3] These results suggest that coordination of a dianionic ligand accelerates dissociation of the apical ligand and urges the complex to take *cis*-β configuration. This

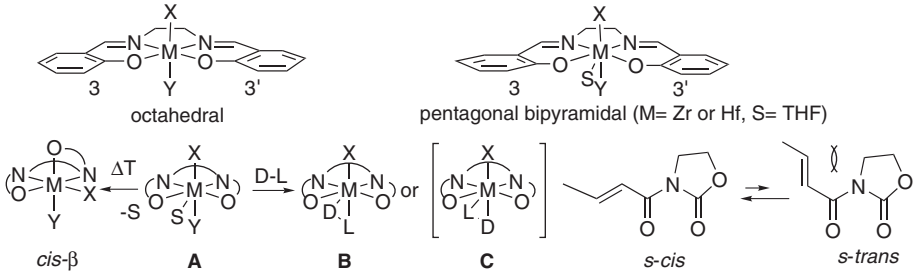

Figure 1.

Keywords: Hf(salen) complex; Asymmetric catalysis; Michael addition; Thiol; Baeyer–Villiger oxidation.
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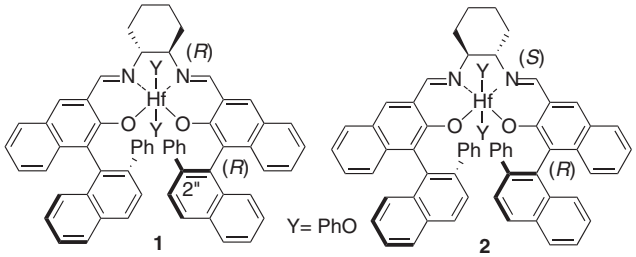
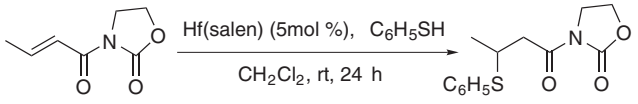
complicates the use of pentagonal bipyramidal Hf- and Zr-(salen) complexes as catalyst. However, the pentagonal bipyramidal configuration was expected to be retained during a reaction, if the bidentate substrate is of neutral or monoanionic nature. Thus, we examined 1,4-addition of thiol to *N*-(2-alkenoyl)-2-oxazolidinone, a neutral bidentate ligand, in the presence of a Hf(salen) complex in order to expand metallosalen chemistry.[4,5] Although two isomeric chelates (**B** and **C**) can be formed by coordination of a bidentate substrate (D–L), we expected that one of them would be prepared preferentially, if the Hf(salen) complex possesses a bulky chiral substituent at C3 and C3′ and replacement of the neutral ligand is slowed (Fig. 1). *N*-(2-Alkenoyl)-2-oxazolidinone can exist as an equilibrium of *s-cis* and *s-trans* conformers, but the former should be more stable than the latter due to the steric reason. The sterically less crowded oxazolidinone-carbonyl group was expected to first coordinate with the hafnium ion at the apical site and then make a chelate, positioning the alkenoyl group at the space between the chiral substituents. In addition, the hafnium ion of the Hf(salen)$(OR)_2$ complex serves as a Lewis acid[5] and the alkoxide as a mild base. Thus, the Hf(salen)$(OR)_2$ complex was expected to catalyze the desired 1,4-addition under mild conditions.

Addition of benzenethiol to *N*-crotonoyl-2-oxazolidinone was first examined in dichloromethane with Hf(salen) complex **1** or **2** as the catalyst in the presence of molecular sieves 4 Å (Table 1). Both complexes catalyzed the desired reaction smoothly, but complex **1** showed much better enantioselectivity than complex **2**, though the ee values were somewhat scattered (entries 1 and 2, Method A). During this study, molecular sieves were found to catalyze the addition of thiol, albeit slowly. Thus, we examined the reaction in the absence of molecular sieves but the enantioselectivity was reduced considerably (entry 3, Method B). Therefore, we carried out the reaction using the substrates and the solvent dried with molecular sieves immediately before use (entry 4, Method C). Under the conditions, however, the enantioselectivity was poorly reproducible and was found to be dependent on the catalyst used. This strongly indicated that the complex **1** including some ingredient(s) suffered diminished enantioselectivity.



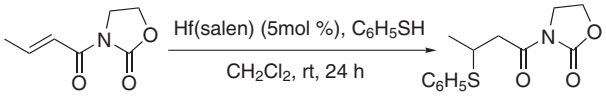
All the complexes **1** were prepared from the corresponding Hf(salen)Cl_2 by its treatment with lithium phenoxide in tetrahydrofuran and purified by recrystallization from hexane–dichloromethane. We submitted all the complexes **1** used for the above experiments to elementary analysis and found that the complex giving the satisfactory analysis (Found: C, 71.58; H, 4.76; N, 2.33. Calcd for $C_{72}H_{54}Hf_1N_2O_4{\cdot}H_2O$: C, 71.60; H, 4.67; N, 2.32) showed the best enantioselectivity (92–93% ee, entry 5). This enantioselectivity was reproducible, as long as the complex giving the satisfactory analysis was used as the catalyst.[6,7] In general, as the analytical value of the complex became less satisfactory, enantioselectivity became lower. This indicated contamination of a metal salt that promotes non-enantioselective 1,4-addition. From the synthetic procedure of **1**, contamination of some lithium salt(s) was most suspicious.[8] Thus, we examined the 1,4-addition with the complex inducing an inferior enantioselectivity, in the presence of 12-crown-4 ether that can trap the lithium ion, and found that the addition of the crown ether improved enantioselectivity, though the chemical yield of the 1,4-adduct was reduced (Scheme 1).

Table 1. 1,4-Addition of benzenethiol to *N*-crotonoyl-2-oxazolidinone using Hf(salen) **1** or **2** as catalyst



Entry	Catalyst	Method	Yield (%)	% Ee[a]	Config[b]
1	**1**	A[c]	72–81	80–88	*S*
2	**2**	A[c]	66–90	5–10	*S*
3	**1**	B[d]	36	58	*S*
4	**1**	C[e]	72–90	27–93	*S*
5	**1**	C[e,f]	75–81	92–93	*S*

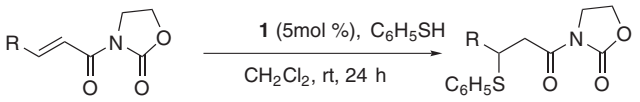
[a] Determined by chiral HPLC using Daicel Chiralcel OD-H (hexane/*i*-PrOH = 8/2 v/v).
[b] Absolute configuration was determined by chiroptical comparison.[4d]
[c] Reaction was carried out in the presence of MS 4 Å.
[d] Reaction was carried out in the absence of MS 4 Å.
[e] Solutions of *N*-crotonoyl-2-oxazolidinone and benzenethiol in dichloromethane were dried with MS 4 Å immediately before use, respectively.
[f] Reaction was carried out with complex **1** that gave the satisfactory elementary analysis.



Elementary analysis of the used Hf(salen) complex, found: C, 71.06; H, 4.76; N, 2.25.

Scheme 1.

Table 2. Effect of the β-substituent (R) on enantioselectivity[a]



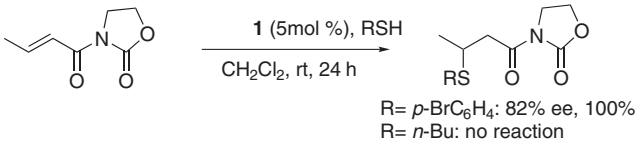
Entry	R	Yield (%)	% Ee[b]
1	Et	77	87
2	*n*-C_5H_{11}	73	84
3	*i*-C_3H_7	31	59
4	Ph	10	59
5	*t*-Bu	N.R.[c]	

[a] Solutions of *N*-crotonoyl-2-oxazolidinone and benzenethiol in dichloromethane were dried with MS before use, respectively.
[b] Determined by chiral HPLC using Daicel Chiralcel OD-H (hexane/*i*-PrOH = 8/2 v/v).
[c] No reaction occurred.

With the pure complex **1**, we next examined the reactions of other *N*-[(*E*)-2-alkenoyl]-2-oxazolidinones (Table 2). When the β-substituent was a primary alkyl group, the enantioselectivity of the reaction was greater than 80% ee (entries 1 and 2). However, as the β-substituent became bulkier, the reaction rate and the enantioselectivity were reduced (entries 3 and 4), and no reaction occurred, when the substituent was a *tert*-butyl group (entry 5). These results suggested that the β-substituent was placed in a sterically crowded space.

The reactions with other thiols were also examined by using **1** as the catalyst (Scheme 2). The addition of *p*-bromobenzenethiol proceeded smoothly with slightly diminished enantioselectivity, while the addition of butanethiol did not occur.

Recrystallization of **1** from CH_2Cl_2–heptane gave a single crystal. Its X-ray diffraction analysis determined the structure of **1** unambiguously (Fig. 2).[9] In analogy with the report by Floriani and co-workers,[2a] complex **1** adopted a slightly distorted pentagonal bipyramidal



Scheme 2.

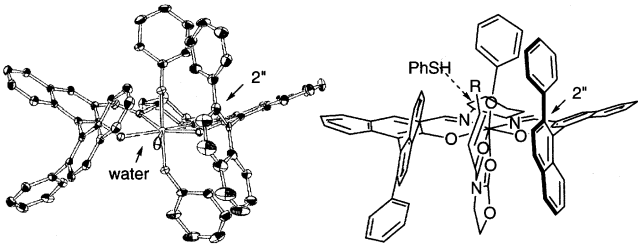
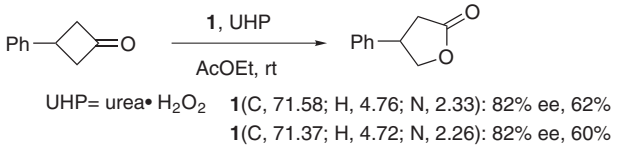


Figure 2. X-ray structure of complex **1** and the proposed **1**-*N*-(2-alkenoyl)-2-oxazolidinone adduct.



Scheme 3.

structure, in which two phenoxy ligands occupied its axial positions and one water molecule was equatorially coordinated. However, the salen ligand took an unusual umbrella structure, and the five-membered chelate ring between the hafnium ion and the cyclohexanediamine unit adopted an envelope conformation: the hafnium ion, two nitrogen atoms and one of the methine carbons existed in the same plane and the other methine carbon existed below the plane. The OH-π interaction between the water molecule and its left-side naphthalene ring and the CH-π interaction between the 2″-phenyl group and the phenyl group in the axial ligand seems to be responsible for this unique structure. The space above the hafnium ion is sterically crowded and highly asymmetric, but the space below the ion is much less crowded. Thus, it was expected that the bottom axial ligand would be replaced with a donor ligand, the carbonyl group of the oxazolidinone unit (vide supra), delivering the alkenyl moiety to the asymmetric but sterically crowded space by chelate formation with the coordination of the carbonyl group of the alkenoyl moiety. Although the replacement of the water ligand eliminates the OH-π interaction, the CH-π interaction should remain and the right-side face of the alkenyl group is blocked by the 2″-phenyl group. Thus, thiol attacks the *si*-face of the β-carbon of the alkenoyl group to give the (*S*)-adduct. This model also explains why good substrates are limited to *N*-(2-alkenoyl)-2-oxazolidinones bearing a primary *E*-substituent.

Considering the similarity in nature of the Zr and Hf ions,[2a] complex **1** was expected to be an efficient catalyst for B–V oxidation. Indeed, the oxidation of 3-phenylcyclobutanone with **1** proceeded with high enantioselectivity (Scheme 3), though the corresponding Zr(salen) complex showed slightly better enantioselectivity (87% ee). This oxidation is also considered to proceed via a Criegee intermediate *cis*-β **1** adduct (vide supra). It is noteworthy that enantioselectivity of the oxidation was not much affected by the purity of **1**, probably because the lithium ion does not promote B–V oxidation.

In conclusion, we were able to demonstrate that a pentagonal bipyramidal metallosalen complex can be used as an asymmetric catalyst.

References and notes

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5. For hafnium-mediated asymmetric thiol 1,4-addition, see Ref. 4f.
6. The complex used was recrystallized from CH_2Cl_2–heptane until it gave a satisfactory elementary analysis, and dried at 70 °C in vacuum.
7. Typical experimental procedure was as follows: a CH_2Cl_2 (1 mL) solution of *N*-crotonoyl-2-oxazolidinone (31.0 mg, 0.20 mmol) and a CH_2Cl_2 (1 mL) solution of benzenethiol (26.4 mg, 0.24 mmol) were dried with MS 4 Å, respectively. Both the solutions (0.5 mL each) were placed in a flask. To the solution, was added complex **1** (5.9 mg, 5 mol%) and the whole solution was stirred at room temperature for 24 h. The mixture was directly passed through a short silica gel column (hexane/AcOEt = 4/1 v/v) and subjected to silica gel TLC (neat CH_2Cl_2) to give the addition product (21.5 mg, 81%). The enantiomeric excess of the product was determined to be 92% as described in the footnote of Table 1.
8. Although lithium chloride did not catalyze addition of benzenethiol to *N*-crotonoyl-2-oxazolidinone, addition of lithium chloride to the present reaction medium reduced the enantioselectivity.
9. Crystallographic data for complex **1** have been deposited with the Cambridge Crystallographic Data Centre, UK as supplementary publication number CCDC 222762.