Asymmetric Catalysis

Synthesis of an Optically Active C_1-Symmetric Al(salalen) Complex and Its Application to the Catalytic Hydrophosphonylation of Aldehydes**

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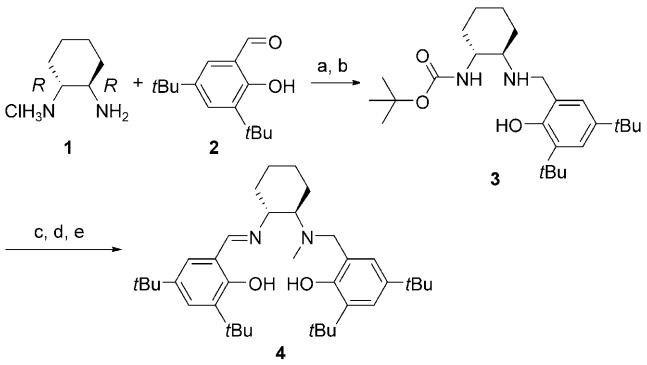
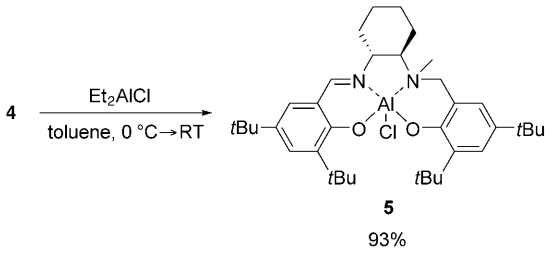
For the last few decades asymmetric catalysis of optically active complexes has been a major topic in synthetic chemistry, and various types of chiral ligands have been introduced.[1] Among these, tetradentate ligands have been widely used because of their good ability to form complexes. In particular, chiral salen ligands have received a great deal of attention owing to their high asymmetry-inducing ability and ready availability. Chiral metallosalen complexes show potent and diverse asymmetric catalytic activities and have been used as catalysts for a wide range of enantioselective reactions, including epoxidation, aziridination, sulfoxidation, Michael reaction, epoxide opening, etc.[2] Salen complexes adopt mostly an octahedral configuration in which two ancillary ligands are *trans*-oriented. However, recent studies have disclosed that *cis*-β isomers show unique catalytic behavior.[2c] For example, a di-μ-oxo Ti(salen) complex that bears chiral *cis*-β-salen ligands catalyzes asymmetric cyanation with high enantioselectivity.[3] Furthermore, a di-μ-oxo Ti(salen) complex has been found to be an excellent pre-catalyst for asymmetric sulfoxidation, in which a monomeric *cis*-β-peroxo complex has been proven to be the active species.[4] Kol and co-workers reported quite recently that treatment of an achiral hybrid salan/salen tetradentate [ONN(Me)O]-type ligand (hereafter referred to as salalen) with titanium and zirconium tetraethoxides yielded the corresponding octahedral Ti- and Zr(salalen)$(OEt)_2$ complexes, in which the two diastereotopic ethoxy groups are *cis*-oriented and the coordinated amino nitrogen atom that is closer to the metal ion by one C–C bond than the ethylene carbon is chiral.[5] Thus, we expected that the chiral salalen ligand would establish a unique asymmetric reaction site that induces a high extent of asymmetry. Herein, we describe the synthesis of a chiral aluminum salalen complex and its application to the asymmetric hydrophosphonylation of aldehydes to give optically active α-hydroxy phosphonates.

We initially attempted the synthesis of an optically active salalen ligand according to Kol's procedure, but the attempt ended in failure because the key Mannich condensation of 2,4-di(*tert*-butyl)phenol and chiral secondary amines derived from cyclohexane-1,2-diamine and 1,2-diphenylethylenediamine did not proceed. Thus, the salalen ligand **4** was synthesized in a stepwise manner (Scheme 1). Reductive



Scheme 1. Synthesis of the optically active salalen ligand **4**: a) **1** and **2**, MeOH, room temperature, then $NaBH_4$ (2.5 equiv), 0 °C → RT; b) $(Boc)_2O$, EtOH, room temperature (67%, 2 steps); c) aq. CH_2O, Pd/C, H_2, MeOH, room temperature; d) 3 M HCl, MeOH, room temperature; e) **2**, MeOH, room temperature (76%, 3 steps). Boc = *tert*-butoxycarbonyl.

amination of aldehyde **2** with monoammonium salts of diamine **1**[6] in the presence of sodium borohydride, followed by *N*-protection with the *tert*-butoxycarbonyl (Boc) group, gave the corresponding amine **3** in 67% yield. The *N*-methylation of amine **3**, deprotection of the Boc group with aqueous HCl, and condensation of the resulting primary amine with aldehyde **2** afforded the desired ligand **4** in 76% yield. The salalen ligand **4** was then treated with Et_2AlCl to give the corresponding Al(salalen) complex **5** in high yield (Scheme 2). Recrystallization of **5** from heptane and



Scheme 2. Synthesis of Al(salalen) complex **5**.

dichloromethane gave single crystals, one of which was submitted for X-ray diffraction analysis (Figure 1).[7] This analysis demonstrated that complex **5** has a unique structure that is different from that of Al(salen) complexes:[8] it adopts a distorted trigonal-bipyramidal configuration, and the absolute configuration of the coordinated tertiary amine is *S*. As the chiral ligand adopts a unique *cis*-β-like structure and as the methyl group on the nitrogen atom is located in the middle of the chiral ligand and close to the chloro ligand that should be replaceable by a substrate such as an aldehyde, we expected that the orientation of the substrate ligated to the

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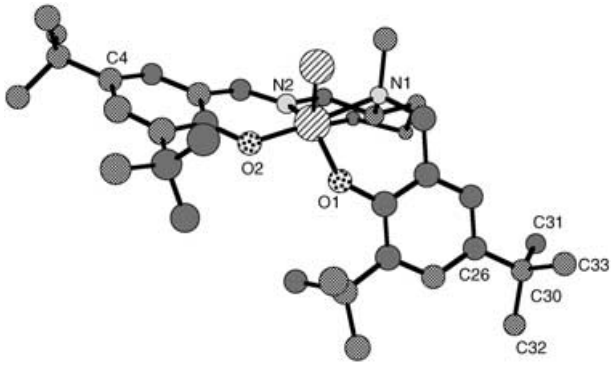


Figure 1. X-ray crystal structure of **5**. Hydrogen atoms have been omitted for clarity. The *tert*-butyl group (C30–C33) attached to C26 is disordered (disorder omitted for clarity).

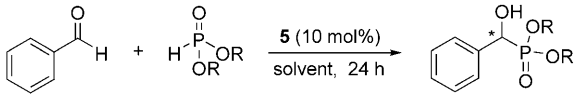
aluminum ion should be efficiently regulated by the ligand. Thus, we considered that **5** should be a highly efficient chiral Lewis acid catalyst. To explore the catalytic behavior of **5**, we first examined the asymmetric hydrophosphonylation of aldehydes.

Optically active α-hydroxy phosphonates and phosphonic acids are biologically active compounds that are widely used in pharmaceutical applications, and much effort has been directed toward the development of asymmetric hydrophosphonylation of carbonyl compounds (the Pudovik reaction).[9,10] To the best of our knowledge, LLB ($LaLi_3$tris(binaphthoxide)) and ALB (AlLibis(binaphthoxide)) reported by Shibasaki and co-workers are the most efficient catalysts for this reaction and have been complementarily used as catalysts for the reaction of various aldehydes.[10d,f] Recently, Kee and co-workers reported that chiral Al(salen) complexes serve as catalysts for asymmetric hydrophosphonylation; however, the enantioselectivities obtained were modest (up to 49% *ee*).[11] The introduction of a novel catalyst that can show wide applicability for various aldehydes, especially aliphatic ones, is therefore still required to achieve a highly efficient Pudovik reaction.

With the Al(salalen) complex **5** in hand, we first examined the asymmetric hydrophosphonylation of benzaldehyde with dimethyl phosphite at room temperature under various conditions (Table 1, entries 1–5). All the reactions proceeded smoothly to give the desired product in acceptable yields and the best enantioselectivity was observed in the reaction with diisopropyl ether as solvent. The reactions with dialkyl phosphites, especially dimethyl phosphite, showed better enantioselectivities than those with diphenyl phosphite (see entries 1–3). Lowering the temperature of the reaction in diisopropyl ether to 0°C improved the enantioselectivity to 89% *ee* (entry 7), whereas a further reduction of the temperature affected the reproducibility of the enantioselectivity (entry 9).[12] The enantioselectivity of the reaction in THF was inferior to that in diisopropyl ether at room temperature, but the reaction at −15°C showed the best and most reproducible enantioselectivity of 90% *ee*, albeit with some reduction of the chemical yield (entry 8).

Thus, we examined the asymmetric hydrophosphonylation of various aldehydes with complex **5** as catalyst at −15°C in THF (Table 2). The electronic effect on enantioselectivity was investigated with *para*-substituted benzaldehyde derivatives, and we found that an electron-withdrawing group increases the enantioselectivity (entries 1–3); the highest enantioselectivity of 94% *ee* was observed in the reaction with *p*-nitrobenzaldehyde (entry 1), although the reaction of *o*-chlorobenzaldehyde also proceeded with high enantioselectivity (entry 4). The reaction of an α,β-unsaturated aldehyde (cinnamaldehyde) was a little slow and showed a slightly reduced enantioselectivity of 83% *ee* (entry 5). To our delight, high enantioselectivity was also observed in the reactions of aliphatic aldehydes. Both nonbranched (entries 6 and 8) and branched (entry 7) aliphatic aldehydes gave the corresponding α-hydroxy phosphonates with high enantioselectivities and in good yields. To the best of our knowledge, this is the first example where a molecular catalyst can be

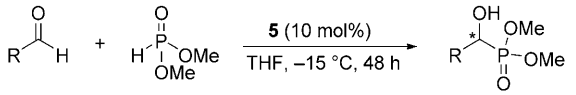
Table 1: Asymmetric hydrophosphonylation of benzaldehyde.



Entry	R	Solvent	*T* [°C]	Yield [%][a]	*ee* [%][b]	Config.[c]
1	Me	THF	RT	92	73	*S*
2	Et	THF	RT	96	70	
3	Ph	THF	RT	87	17	
4	Me	Et_2O	RT	97	68	*S*
5	Me	iPr_2O	RT	94	79	*S*
6	Me	THF	0	91	87	*S*
7	Me	iPr_2O	0	94	89	*S*
8[d]	Me	THF	−15	87	90	*S*
9[d]	Me	iPr_2O	−15	80	81–90	*S*

[a] Yield of isolated product. [b] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AS-H; hexane/*i*PrOH 4:1). [c] Determined by chiroptical comparison (ref. [10d]). [d] The reaction was carried out for 48 h.

Table 2: Asymmetric hydrophosphonylation of various aldehydes.



Entry	R	Yield [%][a]	*ee* [%]	Config.
1	*p*-$O_2NC_6H_4$	95	94[b]	*S*[c]
2	*p*-ClC_6H_4	88	88[b]	*S*[c]
3	*p*-$MeOC_6H_4$	87	81[b]	*S*[c]
4	*o*-ClC_6H_4	96	91[b]	
5	(*E*)-PhCH=CH	77	83[b]	*S*[c]
6	$PhCH_2CH_2$	94	91[b]	
7	$(CH_3)_2CH$	89	89[d]	
8	CH_3CH_2	61	89[d]	*S*[e]

[a] Yield of isolated product. [b] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AS-H; hexane/*i*PrOH 7:3). [c] Determined by chiroptical comparison (ref. [10d]). [d] Determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AS-H; hexane/*i*PrOH 9:1) after conversion of the product into the corresponding benzoate. [e] Determined by chiroptical comparison (ref. [13]).

applied to the reactions of both aromatic and aliphatic aldehydes with enantioselectivities greater than 80% *ee*.

In conclusion, we have synthesized a chiral, trigonal-bipyramidal aluminum(salalen) complex **5** that provides a unique asymmetric reaction site in which an asymmetric nitrogen atom is bound to the metal ion and the *N*-methyl group is *cis* to the chloro ligand. Moreover, complex **5** is an efficient catalyst for the enantioselective hydrophosphonylation of various aldehydes with dimethyl phosphite. Further application of this novel aluminum complex to other asymmetric reactions is under investigation.

Experimental Section

Complex **5** (12.5 mg, 0.02 mol) and dimethyl phosphite (10.1 μL, 0.21 mmol) were dissolved in THF (1.0 mL) under nitrogen, and the solution was stirred for 10 min at room temperature. After cooling to −15 °C, aldehyde (0.20 mmol) was added to the solution and the solution was stirred for 48 h. The reaction was quenched with 1 M HCl and extracted with AcOEt (3 × ca. 1 mL), and the combined organic phase was passed through a pad of Celite and Na_2SO_4. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (hexane/acetone, 7:3–3:7) to give the corresponding α-hydroxy phosphonate. The *ee* values were determined by HPLC on a chiral stationary phase under the conditions described in the footnotes to Table 1 and Table 2.

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