Enantioselective Hydrophosphonylation of Aldehydes Using an Aluminum Binaphthyl Schiff Base Complex as a Catalyst

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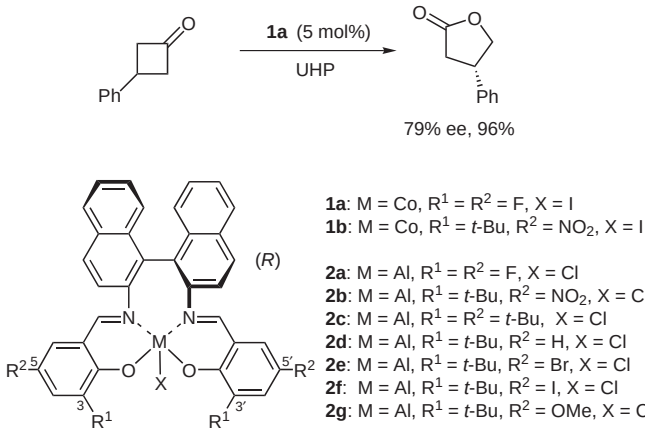
Abstract: An aluminum binaphthyl Schiff base complex was found to be an efficient catalyst for enantioselective hydrophosphonylation of aldehydes. High enantioselectivities were obtained in reactions of both aromatic and aliphatic aldehydes (up to 84% and 86% ee, respectively).

Key words: aluminum, asymmetric catalysis, binaphthyl Schiff bases, hydrophosphonylation, α-hydroxy phosphonate

Optically active α-hydroxy phosphonic acids and phosphonates are useful compounds with wide pharmaceutical application,[1] and there have been multiple efforts to develop a practical synthesis method. Of these methods, the enantioselective addition of phosphite to aldehydes (asymmetric Pudovik reaction) is the most straightforward one.[2] However, successful enantioselective addition has been limited thus far. Shibuya et al.[2a,b] reported enantioselective hydrophosphonylation using the La–Li–BINOL (LLB) complex as a catalyst and obtained good enantioselectivity up to 82% ee in the reaction of some aromatic aldehydes.[2b] On the other hand, Shibasaki et al.[2d,f] achieved widely applicable, highly enantioselective hydrophosphonylation by complementarily using Al–Li–BINOL (ALB) and LLB complexes as catalysts. These unique catalysts are multifunctional and control the hydrophosphonylation between aldehyde and phosphite. Recently, Kee et al. reported the hydrophosphonylation of aromatic aldehydes using Al(salen)[3a,c] and Al(salan) complexes[3b] bearing a cyclohexanediamine unit, which showed moderate enantioselectivity up to 61% ee.[3b] The X-ray analysis of the Al(salan) complex revealed that it possesses a di-μ-hydroxo structure and the salan ligand adopts a *cis*-β-conformation.[3d] These results also suggested that a chiral complex possessing two coordination sites in a *cis*-relation could be a catalyst for asymmetric hydrophosphonylation. Moreover, we reported that the chiral Al(*N*-methylsalalen) complex that takes a trigonal bipyramidal configuration and possesses a chiral nitrogen atom close to the metal center was an excellent catalyst for enantioselective hydrophosphonylation of various types of aldehydes and imines.[4] On the other hand, we have reported that the chiral cobalt binaphthyl–Schiff base complex **1** that has a *cis*-β-configuration[5] serves as an effective catalyst for enantioselective Baeyer–Villiger oxidation, in which a Criegee intermediate chelates with a cobalt ion (Scheme 1).[6] Since the binaphthyl group is a potent chiral auxiliary, we predicted that cobalt and aluminum binaphthyl Schiff base complexes would also exert asymmetric catalysis for hydrophosphonylation as efficiently as the Al(*N*-methylsalalen) complex. Moreover, metal binaphthyl Schiff base complexes have the advantage of high availability and modifiability.



Scheme 1

We first examined hydrophosphonylation of *p*-chlorobenzaldehyde with dimethyl phosphite in THF at room temperature in the presence of **1a** or **1b**, however, the desired reaction did not occur. Thus, we next examined the more oxygenophilic Al(chloro) complex **2a**, bearing the same ligand as **1a**, as a catalyst[7] and **2a** was found to catalyze the desired reaction, albeit slowly and with low enantioselectivity (Table 1, entry 1). Encouraged by this result, we examined the catalysis of several other Al(chloro) complexes and found that the use of complexes (**2b**–**g**)[8] that possess a *tert*-butyl group at C3 and C3′ remarkably improved chemical yield and enantioselectivity (entries 2–7). The substituents at C5 and C5′ also affected yield and enantioselectivity to a lesser extent. Complex **2e** bearing a bromo substituent was found to be the catalyst of choice in terms of enantioselectivity (84% ee, entry 5).[9] Complex **2f** bearing an electron-donating methoxy group also showed high enantioselectivity, but the chemical yield was diminished (entry 7). Other solvents were examined with complex **2e** but did not improve the

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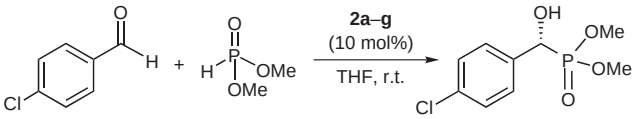
Table 1 Enantioselective Hydrophosphonylation of *p*-Chlorobenzaldehyde Using Aluminum Binaphthyl Schiff Base Complexes as Catalysts[a]



Entry	Cat.	Time (d)	Yield (%)	ee (%)[b]	Config.[c]
1	**2a**	4	29	11	*R*
2	**2b**	4	86	76	*R*
3	**2c**	3	100	65	*R*
4	**2d**	5	83	68	*R*
5	**2e**	3	78	84	*R*
6	**2f**	3	69	78	*R*
7	**2g**	3	68	83	*R*

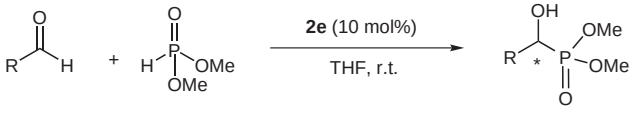
[a] All reactions were carried out at r.t. with a 1:1.1:0.1 molar ratio of *p*-chlorobenzaldehyde:dimethyl phosphite:**2**.
[b] Determined by HPLC analysis using chiral stationary phase column (Daicel Chiralpak AS-H; hexane–*i*-PrOH = 4:1).
[c] Absolute configuration was determined by chiroptical comparison with the published value (ref. 2d).

enantioselectivity (toluene, 81% ee; CH_2Cl_2, 74% ee; *N*,*N*-dimethylformamide, 73% ee). The reaction with **2e** was examined at several reaction temperatures and room temperature was found to be optimal (0 °C: 44% yield, 83% ee; 30 °C: 79% yield, 80% ee; 40 °C: 90% yield, 78% ee).

With **2e** as a catalyst, we next examined the reactions of various aromatic aldehydes under the optimized conditions (Table 2, entries 1–6). Irrespective of the electronic nature of the aryl substituent and their location, the reactions of aromatic aldehydes showed high enantioselectivities (ca. 80% ee), except for the reaction of *o*-tolualdehyde that showed a slightly reduced 75% ee (entries 1–6). To our delight, the reaction of linear and α-substituted aliphatic aldehydes proceeded smoothly with good enantioselectivities greater than 80% ee (entries 7–9). The reaction of cinnamaldehyde, however, showed moderate enantioselectivity (64% ee, entry 10).

Although the reaction mechanism of this reaction is unclear, the electronic nature of the C5(5′) substituents does not greatly affect the enantioselectivity and the presence of a *tert*-butyl group at C3(3′) is essential for achieving good enantioselectivity and acceptable yield. These results suggest that the *tert*-butyl group may play an important role in the regulation of the transition-state structure of this reaction. On the other hand, aliphatic aldehydes are better substrates than aromatic aldehydes in terms of enantioselectivity, but further study is required to fully understand the mechanism of asymmetric induction.

Table 2 Enantioselective Hydrophosphonylation of Various Aldehydes Using the Aluminum Binaphthyl Schiff Base Complex **2e** as Catalyst[a]



Entry	R in RCHO	Time (d)	Yield (%)	ee (%)	Config.[b]
1	Ph	5	62	79[c]	*R*
2	*p*-FC_6H_4	5	69	82[c]	
3	*p*-$MeOC_6H_4$	2	55	79[c]	*R*
4	*p*-MeC_6H_4	2	82	80[c]	*R*
5	*o*-FC_6H_4	2	69	80[c]	
6	*o*-MeC_6H_4	2	79	75[c]	
7	$PhCH_2CH_2$	1	71	83[c]	
8	*c*-Hex	1	86	86[d]	
9	*n*-Hex	2	79	86[d]	
10	(*E*)-PhCH=CH	2	82	64[c]	*R*

[a] All reactions were carried out at r.t. with a 1:1.1:0.1 molar ratio of aldehyde:dimethyl phosphite:**2e**.
[b] Absolute configuration was determined by chiroptical comparison with the published value (ref. 2d).
[c] Determined by HPLC analysis using chiral stationary phase column (Daicel Chiralpak AS-H; hexane–*i*-PrOH = 4:1).
[d] Determined by HPLC analysis using chiral stationary phase column (Daicel Chiralpak AS-H; hexane–*i*-PrOH = 9:1) after benzoylation of the product.

In conclusion, we have demonstrated that a suitably substituted aluminum binaphthyl Schiff base complex is a promising catalyst for enantioselective hydrophosphonylation of both aromatic and aliphatic aldehydes, though these are preliminary results. Further studies on the optimization of the ligand and the reaction mechanism are in progress in our laboratory.

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(7) Complexes **2** were prepared according to the reported procedure (ref. 4).

(8) The cationic complex of **2c** has been reported to be an efficient catalyst for enantioselective aldol reactions of aldehydes and 5-alkoxyoxazoles. See: Evans, D. A.; Janey, J. M.; Magomedov, N.; Tedrow, J. S. *Angew. Chem. Int. Ed.* **2001**, *40*, 1884.

(9) **Typical Procedure: Hydrophosphonylation of *p*-Chlorobenzaldehyde**

Complex **2e** (8.2 mg, 10 μmol) was placed in a flask under nitrogen and THF (0.5 mL) and dimethyl phosphite (10.1 μL, 0.11 mmol) were added. After stirring for 10 min at r.t., *p*-chlorobenzaldehyde (14.1 mg, 0.1 mmol) was added. After stirring for another 3 d, the reaction was quenched with 1 N HCl and extracted with EtOAc. The organic extract was dried over anhyd $MgSO_4$ and concentrated. Silica gel chromatography of the residue (hexane–EtOAc, 7:3 to 1:1) gave the desired product (19.5 mg, 78%) as an oil. The ee of the product was determined to be 84% by HPLC using chiral stationary phase column as described in the footnote to Table 1.