Asymmetric Catalysis

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Highly Enantioselective Hydrophosphonylation of Aldehydes Catalyzed by Tridentate Schiff Base Aluminum(III) Complexes**

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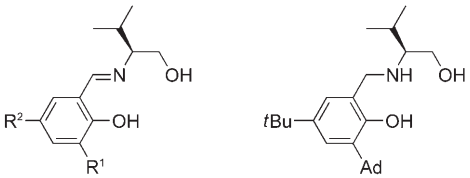
Chiral α-hydroxy phosphonates and phosphonic acids are widely applied in the pharmaceutical industry owing to their biological activity,[1] and intense efforts have been made on the asymmetric hydrophosphonylation of aldehydes. To our knowledge, the first highly enantioselective hydrophosphonylation was realized by the Shibasaki group using heterobimetallic complexes ([$LaLi_3$(binaphthoxide)$_3$], [AlLi(binaphthoxide)$_2$]) as tailor-made catalysts.[2] Recently, Kee and co-workers studied the catalytic performance of chiral [Al(salcyen)] and [Al(salcyan)] complexes.[3] Subsequently, the Katsuki group developed an interesting and highly efficient C_1-symmetric [Al(salalen)] complex for the reaction.[4] An aluminum–binaphthyl Schiff base complex was also found to be effective for the reaction.[5] Although a number of works have appeared on the synthesis of chiral α-hydroxy phosphonates,[6] searching for a catalyst system that could achieve high reactivity and enantioselectivity is still challenging and interesting. As excellent chiral scaffolds, tridentate Schiff base metal complexes, especially those of vanadium, chromium, and iron, have successfully been applied in many asymmetric reactions.[7] Herein, we present a highly efficient asymmetric hydrophosphonylation of various aldehydes catalyzed by chiral tridentate Schiff base Al^{III} complexes.

Initially, tridentate Schiff base **1a** (Scheme 1), derived from L-valinol and 3,5-di-tert-butylsalicylaldehyde, reacted in situ with various aluminum(III) reagents to form complexes that catalyze the asymmetric hydrophosphonylation (Table 1, entries 1–3). The counterions of **1a**–Al^{III} complexes showed a decisive effect on the enantioselectivity.[3a,8] Complex **1a**–Et_2AlCl catalyzed the reaction smoothly, giving the desired products with 86% *ee*, while only a racemate product was obtained in the presence of **1a**–$AlEt_3$ (Table 1, entry 1 vs. 3). It was interesting that catalyst **1a**–Al(O*i*Pr)$_3$ showed an opposite absolute sense of stereoinduction (Table 1, entry 2). The disparate results were probably caused by the different steric and electronic properties of the counterions (Cl, Et, and O*i*Pr), which each exhibited a different action in the catalytic cycle.[9b,d]

To further improve the enantioselectivity of the reaction,[9a] the steric and electronic effects based on **1** were examined (Table 1, entries 1 and 4–8). As shown in Table 1, electron-donating groups at the position *para* to the OH



1a: R^1 = *t*Bu, R^2 = *t*Bu
1b: R^1 = H, R^2 = H
1c: R^1 = H, R^2 = *t*Bu
1d: R^1 = H, R^2 = NO^2
1e: R^1 = Ad, R^2 = *t*Bu

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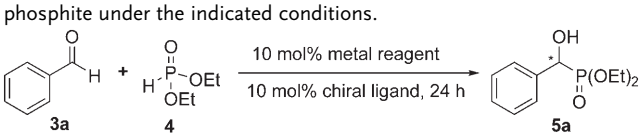
Scheme 1. Chiral ligands used in the study. Ad = adamantyl.

Table 1: Asymmetric hydrophosphonylation of benzaldehyde with diethyl phosphite under the indicated conditions.



3a **4** **5a**

Entry[a]	Al source	L	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	Et_2AlCl	**1a**	THF	0	88	86 (*S*)
2	Al(O*i*Pr)$_3$	**1a**	THF	0	50	30 (*R*)
3	$AlEt_3$	**1a**	THF	0	60	0
4	Et_2AlCl	**1b**	THF	0	68	60 (*S*)
5	Et_2AlCl	**1c**	THF	0	71	73 (*S*)
6	Et_2AlCl	**1d**	THF	0	48	43 (*S*)
7	Et_2AlCl	**1e**	THF	0	81	86 (*S*)
8	Et_2AlCl	**2**	THF	0	30	35 (*R*)
9	Et_2AlCl	**1a**	CH_2Cl_2	0	59	92 (*S*)
10	Et_2AlCl	**1e**	CH_2Cl_2	0	53	94 (*S*)
11	Et_2AlCl	**1e**	CH_2Cl_2	−20	36	97 (*S*)
12[d]	Et_2AlCl	**1e**	CH_2Cl_2/THF	−15	80	96 (*S*)[e]

[a] All reactions were carried out under nitrogen: diethyl phosphite (0.3 mmol), benzaldehyde (0.25 mmol) in 1.0 mL solvent. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] The catalyst was prepared in situ in 0.4 mL CH_2Cl_2. [e] The *R* product with the same *ee* value could be obtained by changing the absolute configuration of **1e** to *R*.

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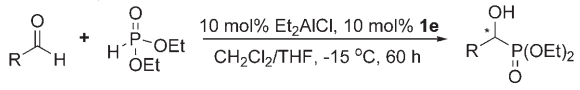
group increased the enantioselectivities and the reactivities (Table 1, entries 4–6). Furthermore, ligands with bulkier *ortho* groups, such as *tert*-butyl and adamantyl, could achieve higher enantioselectivities (up to 86% *ee*; Table 1, entry 5 vs. entries 1 and 7). Although ligands **1e** and **2** have the same absolute backbone configuration, the hydrogenated Schiff base **2** afforded an opposite configuration of product with a poor *ee* value (Table 1, entry 8 vs. 7).

A survey of various solvents revealed that THF provided the product with good reactivity and enantioselectivity (Table 1, entry 1).[9e] However, CH_2Cl_2 showed a strong solvent effect in which a higher *ee* value was obtained (Table 1, entry 9). Furthermore, discrimination on the stereoinducing capability between **1a**–Et_2AlCl and **1e**–Et_2AlCl was also exhibited by using CH_2Cl_2 as the solvent (Table 1, entry 9 vs. 10), and **1e**–Et_2AlCl showed better enantioselectivity (up to 94% *ee*). When the temperature of the reaction was lowered, the enantioselectivity further improved, but the yield was rather poor (Table 1, entry 11 vs. 10). Fortunately, using THF as a cosolvent dramatically improved the reactivity while the enantioselectivity was maintained (96% *ee*; Table 1, entry 12 vs. 11).

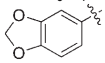
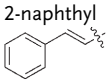
Under the optimized conditions, a series of aldehydes were examined, and the corresponding products were given in high yields with good to excellent enantioselectivities (Table 2). It is interesting to note that not only the electronic properties of the substitution at the aromatic ring, but also the steric hindrance, had no obvious effect on the enantioselectivity (Table 2, entries 1–18). While the condensed-ring aldehydes (1-naphthaldehyde and 2-naphthaldehyde) reacted smoothly with diethyl phosphite, giving the products with 96% *ee* (Table 2, entries 19 and 20),[6g] the α,β-unsaturated aldehyde (cinnamaldehyde) showed a slightly reduced reactivity and enantioselectivity (Table 2, entry 21). Though both nonbranched and branched aliphatic aldehydes gave high enantioselectivities, aldehydes with more steric hindrance generally gave the corresponding α-hydroxy phosphonates with higher *ee* values (up to 91% *ee*; Table 2, entries 24–27). It is noteworthy that excellent enantioselectivities have been achieved for the first time in the asymmetric hydrophosphonylation of heteroaromatic aldehydes (up to 94% *ee*; Table 2, entries 22 and 23).[6f]

To gain insight into the origin of the enantioselectivity, the relationship between the enantiomeric excess of Schiff base **1e** and the product **5a** was tested (Figure 1).[10] The results indicate a strong positive nonlinear effect, which implies that the reaction occurs in the presence of a polymeric aluminum active species. Direct evidence of the dimeric species was observed by HRMS analyses and deduced from experimental observations.[9b,c] The strong positive nonlinear effect makes it possible that the high enantioselectivity of the reacton can be achieved using a moderate *ee* value of **1e**. HRMS analyses show that the two Cl^- ions of dimeric **1e**–Et_2AlCl are substituted by phosphite ions,[9b] which suggests that the counterion Cl^- does not function as the bridge of dimeric **1e**–Et_2AlCl. On the basis of previous reports,[11] we propose that the oxygen atom of the flexible alcohol group acts as a bridge in the dimeric aluminum species, while it seems impossible that the oxygen atom of the phenol group could act as a bridge

Table 2: Substrate scope for the catalytic asymmetric hydrophosphonylation of aldehydes.



3 4 5

Entry[a]	R	Product	Yield [%][b]	*ee* [%][c]
1	Ph	**5a**	96	95 (*S*)[d]
2	2-MeC_6H_4	**5b**	93	96
3	3-MeC_6H_4	**5c**	95	96
4	4-MeC_6H_4	**5d**	89	97 (*S*)[d]
5	2-$NO_2C_6H_4$	**5e**	79	94
6	3-$NO_2C_6H_4$	**5f**	88	94
7	4-$NO_2C_6H_4$	**5g**	81	92
8	2-$MeOC_6H_4$	**5h**	87	95
9	3-$MeOC_6H_4$	**5i**	87	93
10	4-$MeOC_6H_4$	**5j**	94	97 (*S*)[d]
11	4-FC_6H_4	**5k**	87	97
12	2-ClC_6H_4	**5l**	85	95
13	3-ClC_6H_4	**5m**	86	92
14	4-ClC_6H_4	**5n**	82	95 (*S*)[d]
15	4-BrC_6H_4	**5o**	83	97
16	4-CNC_6H_4	**5p**	88	89
17	4-PhC_6H_4	**5q**	83	95
18		**5r**	82	97
19	1-naphthyl	**5s**	87	96
20	2-naphthyl	**5t**	89	96
21		**5u**	73	85
22	2-thienyl	**5v**	90	93 (*S*)[d]
23	2-furyl	**5w**	89	94 (*S*)[d]
24	$PhCH_2CH_2$	**5x**	93	87
25	*n*Bu	**5y**	92	85[e]
26	*i*Pr	**5z**	87	90[e]
27	*t*Bu	**5aa**	73	91[e]

[a] All reactions were carried out under nitrogen: aldehyde (0.25 mmol), diethyl phosphite (0.3 mmol), a mixture of 0.4 mL CH_2Cl_2 and 0.6 mL THF; the catalyst was prepared in situ in 0.4 mL CH_2Cl_2. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] The absolute configurations were determined by comparison with literature data.[6f,g] [e] Determined by HPLC analysis after conversion of the product into the corresponding benzoate.

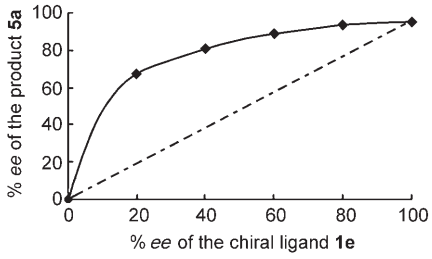


Figure 1. Nonlinear effect in the enantioselective hydrophosphonylation of aldehyde **3a**.

owing to the sterically demanding adamantyl group. Though the exact transition state for the reaction is unclear, it is believed that dimeric **1e**–Et_2AlCl possesses an excellent chiral environment which tolerates a wide range of substrates.

In conclusion, we have developed a new chiral tridentate Schiff base Al^{III} complex for the asymmetric hydrophosphonylation of aldehydes. Significant progress has been obtained with an extremely broad substrate scope, giving chiral α-hydroxy phosphonates in good yields with excellent enantioselectivities (up to 97% *ee*). Further studies of the reaction mechanism and the application of this catalyst to other reactions are underway.

Experimental Section

Typical experimental procedure: Et_2AlCl (0.025 mmol) was added to a solution of **1e** (0.025 mmol) in CH_2Cl_2 (0.4 mL) under nitrogen. After stirring at 30 °C for 30 min, the aldehyde (0.25 mmol) in THF (0.3 mL) was added and stirred for a further 30 min. The diethyl phosphite (0.3 mmol) in THF (0.3 mL) was added at −15 °C, and the reaction was stirred for 60 h. The pure α-hydroxy phosphonate was afforded by column chromatography on silica gel (ethyl acetate/petroleum ether 1:1→9:1)

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[9] a) Other phosphites were also examined; see the Supporting Information. b) The HRMS analyses of the reaction solution showed a high level at 1119.6494, which was relative to the diphosphite-substituted dimeric **1e**–Et_2AlCl; ESI-HRMS calcd for $[C_{60}H_{94}Al_2N_2O_{10}P_2+H]^+$: 1119.6093. c) Using enantiopure **1e** as the chiral ligand, the catalyst **1e**–Et_2AlCl, prepared in situ in CH_2Cl_2, was soluble; using chiral ligand **1e** which was not enantiomerically pure, a large amount of deposition was observed when preparing the catalyst in situ in CH_2Cl_2; d) ^{13}C NMR spectra (100 MHz, $CDCl_3$) showed signals of Et ($\delta = 16.4$ and 9.8 ppm) and O*i*Pr (77.9, 27.9, and 27.7 ppm) on the catalysts that were unchanged both during the catalysts generation in the absence of diethyl phosphite and during the reaction period, which indicated that the counterions Et and O*i*Pr had not been substituted by phosphite. e) Other solvents such as toluene, $CHCl_3$, and Et_2O were examined; see the Supporting Information.

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