VIP Asymmetric Catalysis

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Highly Enantioselective Hydrophosphonylation of Aldehydes: Base-Enhanced Aluminum–salalen Catalysis**

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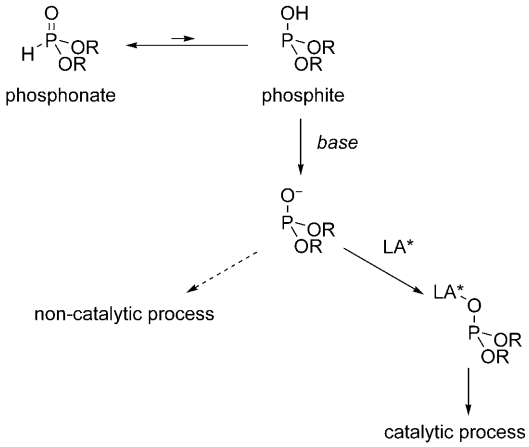
α-Hydroxy phosphonates and α-hydroxy phosphonic acids are an important class of molecules that are widely used in biological applications.[1] The asymmetric hydrophosphonylation of aldehydes with phosphonates is a powerful and direct method for synthesizing enantioenriched α-hydroxy phosphonates.[2–4] Thus, intense research has been devoted to developing highly enantioselective catalysts for this reaction, and it is now becoming an emerging area in organic chemistry. A variety of chiral Lewis acid and heterobimetallic catalysts have been reported and high enantioselectivities have been achieved. However, most of these methods require relatively high catalyst loading and a longer reaction time to obtain the products in acceptable yields.

Dialkyl phosphonates exist in equilibrium between their phosphite and phosphonate forms. The phosphite form is thought to be the active species; however, under neutral conditions the equilibrium lies predominantly toward the phosphonate form, which leads to sluggish reactivity.[5] Consequently, the facilitation of phosphite–phosphonate tautomerization is essential for achieving hydrophosphonylation with low catalyst loading. For example, Abell and Yamamoto utilized the reactive reagent $(CF_3CH_2)_2PO(OH)$ to achieve a highly enantioselective hydrophosphonylation with only 1 mol% of catalyst.[6] Ooi and co-workers applied chiral triaminoiminophosphoranes as organic base catalysts and achieved high yield and enantioselectivity with low catalyst loading at −98 °C.[7,8] These results further highlighted the importance of rapid phosphite-phosphonate tautomerization.

A simple technique for accelerating the phosphite–phosphonate tautomerization is the deprotonation of phosphonates using a base. However, the hydrophosphonylation of aldehydes is a well-known base-mediated process,[9] and the participation of the base-mediated pathway is a critical problem for the enantioselective reaction. Nevertheless, we believed that a judicial choice of base and catalyst would facilitate the Lewis acid catalyzed asymmetric hydrophosphonylation reaction without eroding the enantioselectivity, presuming that the trapping of the phosphite anion by the catalyst and release of the hydrophosphonylation product could proceed rapidly enough for the catalytic process to exclusively occur before the non-catalytic process (Scheme 1). Herein, we report that inorganic bases significantly enhance the rate of reaction of the Al(salalen)-catalyzed asymmetric hydrophosphonylation of aldehydes, in which high enantioselectivities ranging from 93 to 98% *ee* were achieved for the reactions of both conjugated and non-conjugated aldehydes.



Scheme 1. Predicted asymmetric hydrophosphonylation in the presence of a base.

We have previously reported that Al(salalen) complex **1** effectively promotes the asymmetric hydrophosphonylation of aldehydes with dimethyl phosphonate to give the α-hydroxy phosphonates in good to high enantioselectivities (Scheme 2).[10] However, the reaction proceeded quite slowly, and a high catalyst loading of 10 mol% and longer reaction time were required to obtain acceptable yields of the α-hydroxy phosphonates.

We expected that inorganic bases, such as alkaline metal carbonates, which have a relatively weak basicity and low solubility in tetrahydrofuran, would generate an active phosphite anion at an appropriate rate and enhance the hydrophosphonylation without reducing the enantioselectivity. Indeed, the addition of 1.0 equivalent of lithium carbonate significantly accelerated the asymmetric hydrophosphonylation of benzaldehyde using catalyst **1** with no erosion of the enantioselectivity (Table 1, entries 1 and 2).[11] Sodium carbonate and potassium carbonate each increased the reaction rate, but the addition of cesium carbonate resulted in significantly diminished enantioselectivity (11% *ee*; Table 1,

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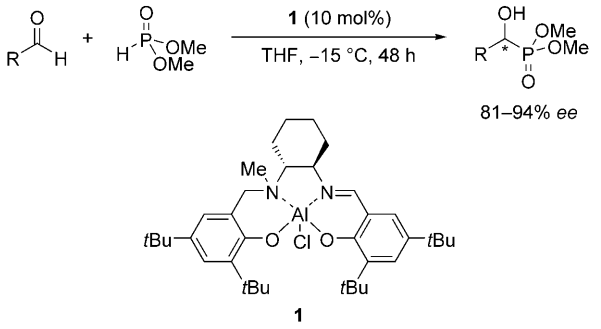
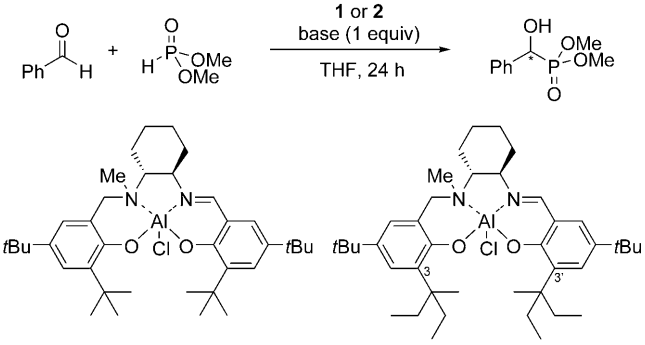


Scheme 2. Asymmetric hydrophosphonylation of aldehydes with Al(salalen) complex **1** in the absence of base.

Table 1: Al(salalen)-catalyzed hydrophosphonylation of benzaldehyde with dimethyl phosphonate in the presence of metal carbonates.



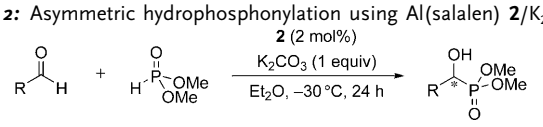
Entry	Catalyst	[mol%]	Base	*T* [°C]	Yield [%][a]	*ee* [%][b]
1[c]	**1**	10	–	−15	87	90
2	**1**	10	Li_2CO_3	−15	>99	90
3	**1**	10	Na_2CO_3	−15	>99	90
4	**1**	10	K_2CO_3	−15	>99	90
5	**1**	10	Cs_2CO_3	−15	84	11
6	**1**	10	Li_2CO_3	−30	53	93
7	**1**	10	Na_2CO_3	−30	65	91
8	**1**	10	K_2CO_3	−30	91	92
9[d]	**1**	10	K_2CO_3	−30	>99	92
10[d]	**2**	10	K_2CO_3	−30	>99	97
11[d]	**2**	1	K_2CO_3	−30	>99 (99)[e]	97
12	–	–	K_2CO_3	−30	89	–

[a] Determined by ^{1}H NMR analysis (400 MHz). [b] Determined by chiral HPLC analysis. [c] Reaction time: 48 h (taken from Ref. [9a]). [d] Et_2O was used instead of THF. [e] Yield of isolated product.

entries 3–5). Alkaline earth metal carbonates, such as calcium, strontium, and barium carbonate, had no positive effect. Of the metal carbonates that were examined, potassium carbonate gave the most enhanced reaction rate, even at a lower temperature (Table 1, entries 6–8). Changing the solvent to diethyl ether led to improved yield (Table 1, entry 9). The employment of Al(salalen) **2**, which has more sterically demanding *tert*-hexyl groups (rather than *tert*-butyl groups) at the C3 and C3' positions, further improved the enantioselectivity to 97% *ee* (Table 1, entry 10).[12] The catalyst loading of **2** was successfully reduced to only 1 mol% without deterioration of the enantioselectivity (Table 1, entry 11). In the control experiment, without catalyst, potassium carbonate promoted the racemic hydrophosphonylation reaction to give the product in 89% yield, even at −30°C (Table 1, entry 12). This result indicates that the phosphite anion is immediately trapped by the aluminum catalyst and undergoes asymmetric hydrophosphonylation, which is followed by rapid product release. Therefore, the enantioselectivity of the hydrophosphonylation reaction could be successfully maintained in the presence of different bases.

The system **2**/K_2CO_3 was then extended to other aldehydes (Table 2). Although other conjugated- and non-conjugated aldehydes required a higher catalyst loading of 2

Table 2: Asymmetric hydrophosphonylation using Al(salalen) **2**/K_2CO_3.



Entry	R	Yield [%][a]	*ee* [%][b]
1	*p*-$MeOC_6H_4$	98	93
2	*p*-$O_2NC_6H_4$	98	98
3[c,d,e]	*p*-ClC_6H_4	95	98
4	*o*-ClC_6H_4	94	97
5	(*E*)-PhCH=CH	97	95
6[e]	$PhCH_2CH_2$	93	97
7	nC_7H_{15}	90	96[f]
8[d]	*i*Pr	96	96[f]

[a] Yield of isolated product. [b] *ee* determined by chiral HPLC analysis unless otherwise mentioned. [c] 4 mol% of **2**. [d] 0.1 equiv of K_2CO_3. [e] Reaction time was 48 h. [f] Determined by chiral HPLC analysis after conversion of the product into the corresponding benzoate.

mol%, the enantioselectivities were remarkably improved compared with those under the previous conditions.[10a] Aromatic aldehydes with methoxy or nitro substituents at the *para* position afforded their corresponding hydrophosphonylation products in high yields and enantiomeric excesses (Table 2, entries 1 and 2). During the reaction of *para*-chlorobenzaldehyde, addition of 1 equivalent of potassium carbonate lowered the enantioselectivity owing to a base-mediated non-catalytic process; a high enantiomeric excess (98% *ee*) could be obtained by reducing the amount of base to 0.1 equivalent with 4 mol% of **2** (Table 2, entry 3). An *ortho*-substituted benzaldehyde also successfully underwent the reaction (Table 2, entry 4). The reaction of (*E*)-cinnamaldehyde, which was a difficult substrate under the previous conditions, also proceeded almost quantitatively in 95% *ee* (Table 2, entry 5). Moreover, high enantioselectivity was observed in the reaction of both α-branched and non-branched aliphatic aldehydes (Table 2, entries 6–8).

In conclusion, we found that the addition of potassium carbonate significantly enhanced the reaction rate of the Al(salalen)-catalyzed asymmetric hydrophosphonylation of aldehydes with dimethyl phosphonate, such that the catalyst loading could be reduced from 10 mol% to 1–4 mol% without eroding the enantioselectivity. Although the non-catalytic hydrophosphonylation process mediated by additional base is to be expected, an appropriate choice of base and solvent allows for highly enantioselective hydrophosphonylation using an ordinary dialkylphosphate under basic

conditions. Both conjugated and non-conjugated aldehydes underwent the hydrophosphonylation with high enantioselectivities of 93–98% *ee*.

Experimental Section

General procedure: Complex **2** (3.4 mg, 1 mol%) and potassium carbonate (69.1 mg, 0.5 mmol) were added to an oven-dried Schlenk tube. The tube was cooled to −30 °C, before diethyl ether (5.0 mL), aldehyde (0.5 mmol), and dimethyl phosphonate (48.1 μL, 0.525 mmol) were added successively. After stirring for 24 h at −30 °C, the reaction was quenched with 0.5M HCl, and the mixture was extracted with ethyl acetate. The organic phase was washed with water and brine and then dried over anhydrous sodium sulfate. The crude product was purified by silica gel chromatography (hexanes/acetone) to give the desired α-hydroxy phosphonates. The enantiomeric excesses were determined by chiral HPLC analysis.

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