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Enantioselective Acylphosphonylation—Dual Lewis Acid–Lewis Base Activation of Aldehyde and Acylphosphonate

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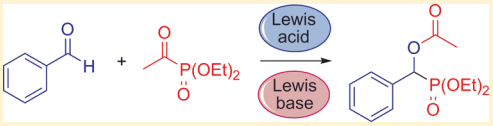
Supporting Information

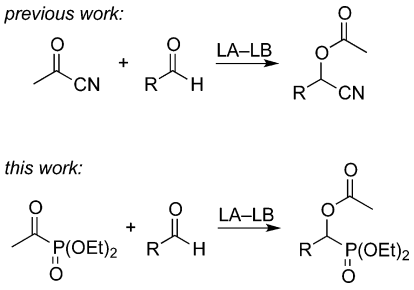
ABSTRACT: Acetoxyphosphonates were obtained by a one-step procedure consisting of reaction of diethyl acetylphosphonate with prochiral aldehydes in the presence of a catalytic system comprising a chiral Lewis acid, an achiral Lewis base, and a Brønstedt base. Best results were obtained using a tridentate Schiff base aluminum(III) Lewis acidic complex, 1*H*-1,2,3-benzotriazole, and a tertiary amine such as DBU. The target compounds were in most cases obtained in high yields, but with moderate enantiomeric ratios (up to 78:22).



INTRODUCTION

Synergistic catalysis whereby several reaction components are simultaneously activated may allow otherwise unreactive species to undergo a desired reaction.[1] Activation of both electrophiles and nucleophiles by combined use of Lewis acids (electron-pair acceptors) and Lewis bases (electron-pair donors) is an attractive way to enhance chemical reactivity.[2] Whereas Lewis acids have the ability to activate electrophiles, Lewis bases[3] may enhance the reactivity of both nucleophiles and electrophiles. We have previously demonstrated that Lewis acid–Lewis base catalysis allows enantioselective acylcyanation of prochiral aldehydes.[4] Although the reaction occurs in the presence of only base,[5] a chiral Lewis acid is required in order to obtain enantioenriched products. We assumed that acylphosphonates may exhibit a reactivity similar to that of acyl cyanides and thus react with aldehydes to form acetoxyphosphonates (Scheme 1); low-valent

Scheme 1. Analogy between Acylcyanation and Acylphosphonylation of Aldehydes



achiral samarium compounds have indeed been shown to catalyze this reaction, which however under the conditions used was limited to racemic benzoyloxyphosphonates.[6] Racemic α-acetoxyphosphonates have also been obtained by a one-step reaction of diethylphosphite with certain aldehydes in the presence of acetic anhydride employing metal oxides or carbonates as solid phase catalysts,[7] and, along with 1,4-addition products, from reaction of a dialkyl acylphosphite with α,β-unsaturated aldehydes.[8]

Whereas hydroxyphosphonates are accessible in enantioenriched form by reaction of aldehydes with dialkylphosphites in the presence of a variety of different catalysts (the Pudovik reaction[9]),[10] no direct enantioselective methods have been reported for the preparation of acylated derivatives.[11] Enantioenriched acetoxyphosphonates are instead normally prepared either from hydroxyphosphonates by acetylation[12] or reaction with ketene,[13] or by lipase-catalyzed kinetic resolution of racemic acetoxyphoshonates[14] or hydroxyphosphonates.[15] Both types of compounds have interesting biological properties and therefore constitute attractive synthetic targets. Acylated derivatives have, for example, found use as herbicides,[16] and direct methods for the preparation of both types of compounds are therefore desirable.

Since acylphosphonates are conveniently accessible by Arbuzov reaction between a phosphite and an acid chloride, we thought that a direct synthetic process employing acylphosphonates would constitute an attractive method for the preparation of α-acyloxyphosphonates. For this purpose, conditions resulting in cleavage of the carbon–phosphorus bond of less reactive phosphonates were required. The proximity of two electrophilic groups in acylphosphonates results in enhanced reactivity of both functional groups, at the same time as the carbon–phosphorus bond linking the two groups is weakened.[17] Most nucleophiles attack the carbonyl group while the dialkylphosphoryl group serves as leaving group. Reaction with primary or secondary amines indeed results in cleavage of the carbon–phosphorus bond and formation of amides.[18] The order of reactivities of the amines parallels their basicities, and primary amines react more rapidly than secondary. Aromatic amines do not react under these conditions. For our purpose, use of a tertiary amine was required in order to obtain a reactive acylating agent.

With these known reactivities in mind, we decided to explore whether acylphosphonates might serve as suitable starting materials

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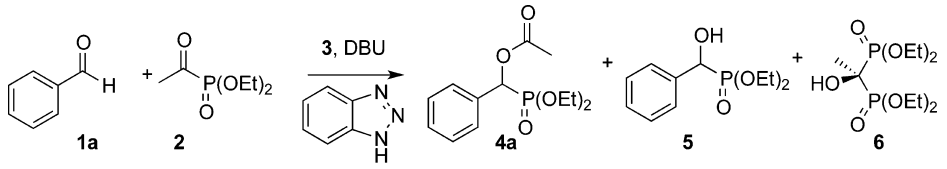
Scheme 2. Reaction in the Presence of Titanium Salen Complex 3



for a more general direct preparation of acetoxyphosphonates from aldehydes. The results are presented here.

RESULTS AND DISCUSSION

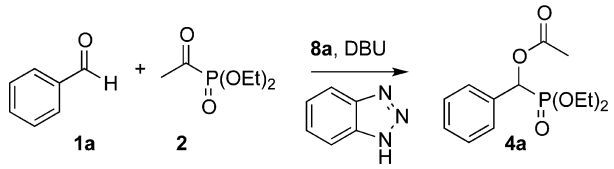
In contrast to reactions with acetyl cyanide, a Lewis acid catalyst is required for reaction of benzaldehyde (**1a**) with acylphosphonate **2** to occur. Attempted reaction in the presence of only tertiary amine (TEA, DABCO, DMAP) led, according to ^{1}H NMR, to reversible formation of a tetrahedral intermediate,[19] or, with the more basic DBU, also to enolate formation.[20] Considering the weak acidity of dialkylphosphites,[21] the observation that reaction with a tertiary amine does not lead to cleavage of the carbon−phosphorus bond is hardly surprising. Use of a tertiary amine (DBU, TEA, DABCO, or DMAP) in combination with (*S*,*S*)-[(4,6-bis(*tert*-butyl)salen)Ti(μ-O)]$_2$ (**3**), a catalyst system which provided excellent reactivity and selectivity in the cyanation of aldehydes with acyl cyanides,[4] resulted in only trace amounts of product. Replacement of the tertiary amine by 1*H*-1,2,3-benzotriazole, which is less nucleophilic than DABCO, DBU, and DMAP,[22] required the presence of an additional base in order to react with the acetylphosphonate. The *N*-acylated benzotriazole expected to form is known to be an efficient *O*-acylating agent.[23] Full conversion of an independently prepared hydroxyphosphonate to acylated product was indeed observed in toluene in the presence of DBU; in the absence of DBU, the reaction was exceedingly slow.

Reaction of benzaldehyde (**1a**) with **2** in the presence of 10 mol % of each 1*H*-benzotriazole and DBU and 10 mol % of titanium complex **3** (Scheme 2) afforded, however, after 24 h at room temperature neither the desired product **4a**, nor non-acylated **5**, but only **6**, resulting from attack of the phosphite anion on unreacted **2**.[24] In order to suppress this undesired reaction, acylphosphonate **2** was added to the reaction mixture over 20 h, thereby maintaining a low concentration of **2**. This procedure did indeed result in the formation of the desired product **4a**, but along with hydroxyphosponate **5** and appreciable amounts of **6**.

Exchange of titanium complex **3** for aluminum salen complex **7** resulted, under otherwise identical conditions, in only trace amounts of product **4a** and compound **6**. Superior results were obtained when aluminum complex **8a**, containing a tridentate Shiff base derived from L-valinol and 3,5-di-*tert*-butylsalicylaldehyde, was used as Lewis acid catalyst (Table 1). This complex, prepared in situ, has previously been used for hydrophosphonylation of aldehydes, and has been shown to be a dimer.[25] The dimeric structure was shown by DFT calculations to be favored over the monomer during the catalytic reaction,[26] a result supported by the observation of a nonlinear effect.[25] The corresponding bromide has been shown by X-ray crystallography to be a dimer with the two bromine atoms positioned on the same side of the molecular plane.[27,28]

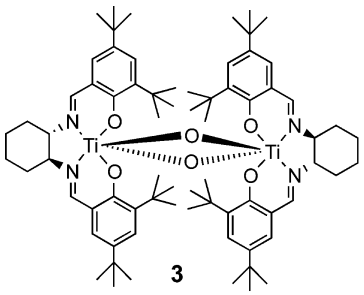
In order to optimize the reaction conditions, the amounts of benzotriazole and Brønstedt base were varied (Table 1).

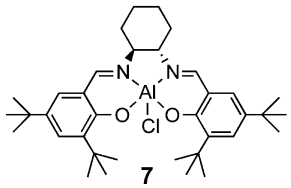
Table 1. Optimization of Catalyst Composition[a]

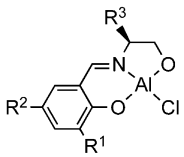


entry	1*H*-benzotriazole (mol %)	Brønstedt base (mol %)	**4a**:**5** (mol ratio)	Yield of **4a** (%)[b]	*R*:*S* **4a**[c]
1	0	DBU (15)	1:0.13	37	64:36
2	0	DBU (50)	1:0.16	38	59:41
3	10	DBU (15)	1:0.13	53	64:36
4	20	DBU (15)	1:0.05	79	69:31
5	50	DBU (15)	1:0	100	65:35
6	20	DBU (30)	1:0	36	66:34
7	20	DBU (50)	1:0	32	63:37
8	20	DMAP (15)	1:0.04	63	67:33
9	20	DABCO (15)	1:0.09	61	69:31
10	20	DIPEA (15)	1:1.7	16	46:54

[a]Reaction conditions: benzaldehyde (0.25 mmol), **8a** (10 mol %), toluene (1 mL), room temperature; acetyl phosphonate **2** (3 equiv) diluted to 200 μL with toluene was added over 20 h using a syringe pump. [b]Determined by ^{1}H NMR with 1-methoxynaphthalene as internal standard. [c]Determined by HPLC using chiral IA column.







8a: R^1=R^2=^{t}Bu, R^3=^{i}Pr
8b: R^1=R^2=^{t}Bu, R^3=Bn
8c: R^1=R^2=R^3=^{t}Bu
8d: R^1=adam, R^2=^{t}Bu, R^3=^{i}Pr
8e: R^1=adam, R^2=R^3=^{t}Bu
8f: R^1=H, R^2=^{t}Bu, R^3=^{i}Pr
8g: R^1=^{t}Bu, R^2=OMe, R^3=^{i}Pr
8h: R^1=^{t}Bu, R^2=NO_2, R^3=^{i}Pr

Reactions without benzotriazole led to poor yields of **4a**, even in the presence of a large amount of DBU (entries 1 and 2). Successive increase of the amount of benzotriazole resulted in increasing yields (entries 3−5), whereas lower yields were observed with increasing amounts of DBU (entries 4, 6, and 7): the latter effect may be a result of extensive enolate formation. A quantitative yield of **4a**, with no trace of hydroxyphosphonate **5**, was obtained using 50 mol % of benzotriazole and 15 mol % of DBU (entry 5), but the highest enantiomeric ratio (69:31) was observed with merely 20 mol % benzotriazole (entry 4).

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Somewhat inferior yields were obtained when DBU was replaced by DMAP or DABCO (entries 8 and 9). With DIPEA, hydroxyphosphonate **5** was the main product, obtained together with essentially racemic **4a** (entry 10). Minor effects on the enantiomeric ratios were observed by use of chiral bases; cinchonidine and cinchonine gave **4a** with 66:34 and 63:37 er, respectively, demonstrating that the chirality originates from the chiral Lewis acid.

Although a quantitative yield could be obtained with the optimal catalyst system, the enantiomeric ratios were unsatisfactory. Attempts were therefore made to improve the enantioselectivity by using ligands with different steric and electronic properties (Table 2). Unfortunately, neither variation of the steric properties of the substituent on the amino alcohol part of the ligand (entries 1–3) and/or in the 3-position of the aromatic ring (entries 4–6), nor the electronic properties of the ligand (entries 7–8), led to any improvement of the enantioselectivity.

Table 2. Variation of Ligand Structure[a]

entry	L (10 mol %)	**4a:5** (mol ratio)	yield of **4a** (%)[b]	er **4a**[c)]
1	**8a**	1:0.05	79	69:31 (*R*)
2	**8b**	1:0.04	48	51:49 (*R*)
3	**8c**	1:0.25	35	64:36 (*R*)
4	**8d**	1:0.31	38	56:44 (*R*)
5	**8e**	1:0.51	23	48:52 (*S*)
6	**8f**	1:0.28	13	45:55 (*S*)
7	**8g**	1:0	61	60:40 (*R*)
8	**8h**	1:0	46	66:34 (*R*)

[a]Reaction conditions: benzaldehyde (0.25 mmol), 1*H*-benzotriazole (20 mol %), DBU (15 mol %) in toluene (1 mL), room temperature, acetyl phosphonate **2** (3 equiv) diluted to 200 μL with toluene was added over 20 h using a syringe pump. [b]Determined by ^{1}H NMR with 1-methoxynaphthalene as internal standard. [c)]Determined by HPLC using chiral IA column.

Further optimization studies showed that the amount of **2** could be decreased by increasing the time of addition to 30 h. As shown in Table 3, a quantitative yield of **4a** was obtained when merely 1.5 equiv of **2** were used (entry 3), but under these conditions the enantiomeric ratio was lower.

Table 3. Amount Acylphosphonate[a]

entry	**2** (equiv)	**4a:5** (mol ratio)	yield of **4a** (%)[b]	*R*:*S* **4a**[c]
1	3	1:0	98	68:32
2	2	1:0	99	64:36
3	1.5	1:0	100	63:37
4	1.2	1:0.06	89	62:38

[a]Reaction conditions: benzaldehyde (0.25 mmol), 1*H*-benzotriazole (20 mol %), DBU (15 mol %), **8a** (10 mol %) in toluene (1 mL) at room temperature, acetyl phosphonate **2** diluted to 300 μL with toluene was added over 30 h using a syringe pump. [b]Determined by ^{1}H NMR with 1-methoxynaphthalene as internal standard. [c]Determined by HPLC using chiral IA column.

In order to attempt to increase the enantioselectivity, reactions were run at lower temperatures (Table 4). The reagents had insufficient solubility in toluene below room temperature, and therefore dichloromethane was used as solvent; this solvent led to somewhat decreased enantiomeric ratios at room temperature. On the other hand, formation of **6** was somewhat suppressed in dichloromethane: at room temperature instantaneous addition of **2** resulted in 35% yield after 47 h, as compared to ca. 5% in toluene. Although 1.5 equiv of acylphosphonate proved sufficient at room temperature, a larger excess was used in order to ascertain acceptable conversions. 50 mol % of 1*H*-benzotriazole and more base were required in order to achieve a quantitative yield at 0 °C (entries 1 and 2). At −10 °C no further increase of the selectivity was observed, and the yield was lower.

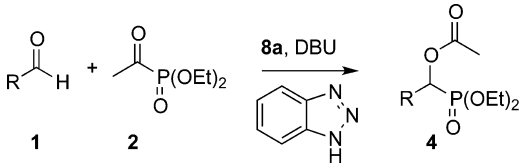
Table 4. Effect of Temperature[a]

entry	temp (°C)	1*H*-benzotriazole (mol %)	DBU (mol %)	**4a:5** (mol ratio)	yield of **4a** (%)[b]	*R*:*S* **4a**[c]
1	0	20	15	1:07	60	78:22
2	0	50	20	1:0	100	76:24

[a]Reaction conditions: benzaldehyde (0.25 mmol) and **8a** (10 mol %) in dichloromethane (1 mL). Acetyl phosphonate **2** (3 equiv) diluted to 300 μL with dichloromethane was added over 45 h using a syringe pump. [b]Determined by ^{1}H NMR with 1-methoxynaphthalene as internal standard. [c]Determined by HPLC using chiral IA column.

The optimized reaction conditions were applied to a range of different aldehydes (Table 5). We were pleased to see that high yields were obtained with most of the aldehydes tested, although enantiomeric ratios were moderate. No hydroxyphosphonate **5** was obtained in any of the reactions. The reaction was successful with both electron-rich (entries 3–5) and electron-poor aromatic aldehydes (entries 6–7), and substituents in the 2,3- or 4-positions were tolerated (entries 2–7). The aliphatic substrate propanal reacted more sluggishly and it was necessary to perform the reaction at room temperature due to low conversion at 0 °C (entries 8–9). Attempted reaction with (*E*)-2-butenal gave an impure product in low yield, even after several attempts to improve the results.

Table 5. Application to Different Aldehydes[a]



1 **2** **4**

entry	R	product	yield of **4** (%)[b]	isolated yield of **4** (%)	*R*:*S* **4**[c]
1	C_6H_5	**4a**	98	84	75:25
2	2-naphthyl	**4b**	96	83	73:27
3	4-MeO-C_6H_4	**4c**	93	83	69:31
4	3-MeO-C_6H_4	**4d**	92	83	75:25
5	4-Me-C_6H_4	**4e**	100	89	75:25
6	4−Cl-C_6H_4	**4f**	84	72	77:23
7	2−Cl-C_6H_4	**4g**	61	60	78:22
8	C_2H_5	**4h**	16	15	79:21
9	C_2H_5[d]	**4h**	61	53	66:34

[a]Reaction conditions: aldehyde (0.25 mmol), 1*H*-benzotriazole (50 mol %), DBU (20 mol %), **8a** (10 mol %) in dichlormethane (1 mL) at 0 °C. Acetyl phosphonate **2** (3 equiv) diluted to 300 μL with dichlormethane and added over 45 h using a syringe pump. [b]Determined by ^{1}H NMR with 1-methoxynaphthalene as internal standard. [c]Determined by HPLC or GC with chiral columns. [d]Reaction at rt.

Absolute Configuration. The products were shown to have *R* absolute configuration by comparison of the sign of optical rotation of the hydroxyphosphonates obtained by hydrolysis (*p*-toluene sulfonic acid/ethanol/water) of **4a**, **4e**, and **4f** with literature data.[25] The remaining compounds (**4b**, **4c**, **4d**, **4g**, and **4h**) were assumed to have the same absolute configuration.

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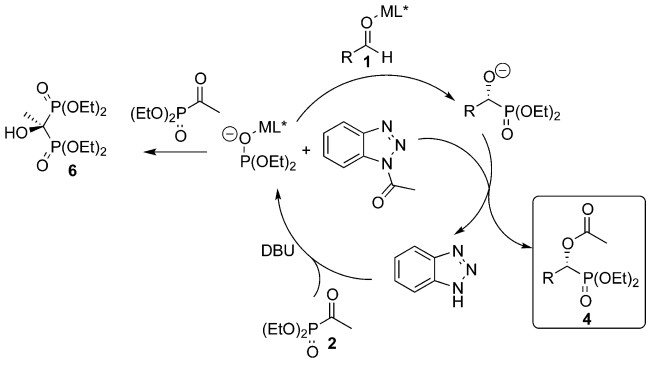
This is opposite to the configuration of products obtained by hydrophosphonylation using the same ligand (**8a**).[25]

Mechanistic Aspects. In line with the known reactivity of acylphosphonates as well as the present results, we propose the following mechanism (Scheme 3): The first step is suggested to

Scheme 3. Suggested Mechanism



involve deprotonation of 1*H*-benzotriazole by DBU; in contrast to DABCO and DMAP, DBU is expected to be able to achieve complete deprotonation. This is followed by attack of the anion on acetyl phosphonate to give 1-acetylbenzotriazole and phosphonate ion which, like in hydrophosphonylation,[26] probably binds to an aluminum center. Nucleophilic addition of the anion to the Lewis acid-activated aldehyde and subsequent acetylation afford the final α-acetoxyphosphonate. Support for this suggestion comes from ^{1}H NMR of the crude reaction mixture, which showed the presence of 1-acetylbenzotriazole, assumed to be an intermediate of the catalytic reaction. Acetylation probably does not occur within the same molecular complex as P−C bond formation, as shown by the formation of mixed products from reaction of benzaldehyde with 0.5 equiv each of diisopropyl acetylphosphonate and diethyl propanoylphosphonate (analyzed by GC-MS).

The hydrophosphonylation employing the same Al(III) complex (**8a**), reported by Feng and co-workers, was shown by DFT calculations to be catalyzed by the dimeric metal complex,[26] a situation that gave rise to a pronounced positive linear effect.[25] In our case, a very weak negative nonlinear effect was observed (Figure 1). This result does, however, not allow any conclusions whether dimeric species are involved in the catalytic reaction.

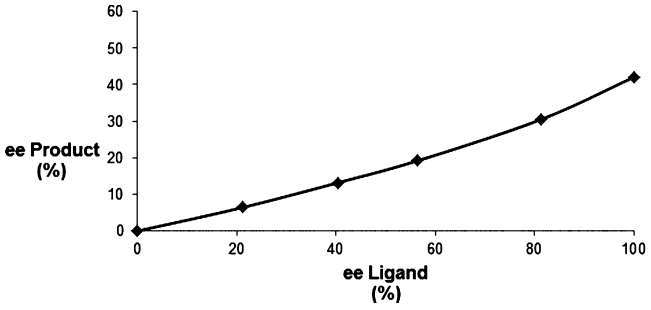


Figure 1. Relation between product er and catalyst precursor er.

CONCLUSION

A three-component catalyst system for a one-step synthesis of enantioenriched α-acetoxyphosphonates from aldehydes and an acetyl phosphonate was developed. The combination of tridentate Shiff base aluminum complex **8a**, DBU, and 1*H*-benzotriazole provided an efficient catalyst system for the reaction. Although moderate enantioselectivities were observed, high yields of products from aldehydes with different substitution patterns were obtained.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR spectra were recorded at 500 or 400 MHz, ^{13}C NMR spectra at 126 or 100 MHz, and ^{31}P NMR spectra at 202 MHz. Chemical shifts are reported in ppm with reference to residual $CHCl_3$ in $CDCl_3$. Multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), and multiplet (m). Broad signals are reported as (br). Enantiomeric ratios (er) were determined by HPLC analyses with a UV-detector and a chiral column (Daicel Chiralpak IA, 0.46 cm × 25 cm), or by gas chromatography using a chiral column (30 m × 0.250 mm × 0.25 μm) containing Cyclosil-B as the stationary phase. All aldehydes were purified using known procedures. Triethyl phosphite was distilled prior to use. Dry solvents were taken from a Glass Contour solvent dispensing system. Complexes **3**[29] and **7**,[30] and ligands used for the preparation of **8a**−**f**,[31,32] **8g**,[32,33] and **8h**[32−34] were synthesized according to published procedures. Complexes **8a**−**h** were prepared in dichloromethane and used directly after evaporation of the solvent, and complexes **8g**−**h** were prepared in situ in toluene.

Complex 8a. *S*-Valinol (0.52 g, 5.0 mmol) was added to a solution of 3,5-di-*tert*-butyl salicylaldehyde (1.17 g, 5.0 mmol) in EtOH (60 mL). The resulting yellow solution was stirred for 5 h at rt, and then the solvent was evaporated under reduced pressure. The residue was purified by column chromatography using hexanes/ethyl acetate (5:1) as eluent to give the ligand[32] as a yellow solid (1.49 g, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.49 (brs, 1H), 8.38 (s, 1H), 7.43 (d, J = 2.4 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 3.83 (A-part of ABX, J = 3.5, 11.3 Hz, 1H), 3.78 (B-part of ABX, J = 8.5, 11.3 Hz, 1H), 3.05 (ddd, J = 3.8, 6.0, 8.5 Hz, 1H), 1.96 (dsept, J_{HH} = J_{HP} = 6.6 Hz, 1H), 1.66 (brs, 1H), 1.45 (s, 9H), 1.31 (s, 9H), 0.97 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.1, 158.1, 140.2, 136.8, 127.2, 126.2, 117.7, 77.9, 64.7, 35.1, 34.2, 31.5, 30.1, 29.5, 19.8, 18.8.

Et_2AlCl (1 M hexane solution, 1.26 mL, 1.26 mmol) was added to a solution of the ligand (0.38 g, 1.2 mmol) in dry CH_2Cl_2 (10 mL) in a glovebox. The solution was stirred for 2 h before removing the solvent under vacuum. The resulting pale yellow solid was used as the catalyst without further purification.

Diethyl Acetyl Phosphonate (2). Compound **2** was synthesized by an Arbuzov reaction using a slightly modified literature procedure.[35] Triethyl phosphite (3.0 mL, 18.0 mmol) was slowly added to a solution of acetyl chloride (1.4 mL, 19.8 mmol) in CH_2Cl_2 (25 mL) at 0 °C under N_2. Then the mixture was stirred overnight at room temperature before the solvent was removed under vacuum. The residue was purified by column chromatography using hexanes/ethyl acetate (2:1) as eluent to give **2** as a colorless liquid (2.7 g, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 (dq, J = 7.1, J_{HP} = 7.1 Hz, 4H), 2.48 (d, J = 5.0 Hz, 3H), 1.37 (t, J = 7.1 Hz, 6H); ^{31}P NMR (202 MHz, $CDCl_3$) δ −2.87.

General Procedure for Synthesis of Racemic Acetoxyphosphonates.[36] Aldehyde (20 mmol) and diethyl phosphite (2.58 mL, 20 mmol) were dissolved in dry THF (20 mL) under N_2, and the solution was cooled to 0 °C before DBU (1.62 mL, 20 mmol) was added. The resulting solution was stirred for 5 min at 0 °C, then allowed to warm to room temperature and kept at that temperature for 15−60 min, during which time the aldehyde was consumed (TLC). After removal of the solvent, CH_2Cl_2 (50 mL) was added, and the solution was washed successively with 1 M HCl and brine, and dried over $MgSO_4$. After removal of the solvent, hydroxyphosphonates were obtained.

α-Acetoxyphosphonates could be obtained by any of the following methods: Method A:[12a] $Cu(OTf)_2$ (22 mg, 0.06 mmol) was added to a mixture of hydroxyphosphonate (3 mmol) and Ac_2O (1.4 mL, 15 mmol) at room temperature. The resulting mixture was stirred and the reaction was monitored by TLC. After 1−2 h, diethyl ether was

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added and the mixture was washed sequentially, with H_2O, sat. aq. $NaHCO_3$, and brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure to give the crude product. Further purification by column chromatography using hexanes/ethyl acetate (1:1) as eluent gave the racemic α-acetoxyphosphonates. This method was used for benzaldehyde, 4-chlorobenzaldehyde, and 3-methoxybenzaldehyde.

Method B:[37] To a solution of hydroxyphosphonate (1 mmol) in ethyl acetate (20 mL), K_2CO_3 (276 mg, 2.0 mmol), *N*,*N*-dimethylaminopyridine (6.1 mg, 0.05 mmol), and acetic anhydride (0.14 mL, 1.5 mmol) were added. The mixture was stirred at room temperature until the starting materials disappeared by TLC. Then the mixture was filtered to remove K_2CO_3 and the filtrate was washed with H_2O. The aqueous phase was extracted with ethyl acetate, the combined organic phases were dried over $MgSO_4$, and the solvent evaporated. The crude product was purified by column chromatography using petroleum ether/ethyl acetate (1:1 or 1:4) as eluent to get the product. This method was used for 4-methoxybenzaldehyde, 4-methylbenzaldehyde, 2-chlorobenzaldehyde, 2-naphthaldehyde, and propionaldehyde.

General Procedure for Asymmetric Synthesis of α-Acetoxyphosphonates. In a glovebox, the aldehyde (0.25 mmol), DBU (7.5 μL, 0.050 mmol), and 1-methoxynaphthalene as internal standard (10 μL) were added to a vial containing a solution of aluminum complex **8a** (9.5 mg, 0.025 mmol) and 1*H*-benzotriazole (14.9 mg, 0.125 mmol) in dichloromethane (1 mL). Then the vial was capped and taken out of the glovebox, and the solution was cooled to the indicated temperature. Acetyl phosphonate (122 μL, 0.750 mmol) diluted to 300 μL with dichloromethane was added to the mixture over the indicated time using a syringe pump. After the addition was finished, a sample was taken and filtered through a plug of silica, which was rinsed with ethyl acetate, the solvent evaporated, and the yield determined by ^{1}H NMR. The reaction was quenched by the addition of a sat. aq. $NaHCO_3$ solution, followed by diethyl ether. The mixture was washed with sat. aq. $NaHCO_3$ to remove diethyl phosphite which had been formed by hydrolysis of remaining acetyl phosphonate. Further purification by column chromatography gave the desired product.

Diethyl 1-Acetoxyphenylmethylphosphonate (4a).[12b] This compound was prepared from benzaldehyde (25.5 μL, 0.25 mmol). Chromatography: hexanes/ethyl acetate (1:1). Colorless oil, 60.1 mg, 84% yield (98% yield by ^{1}H NMR), (*R*:*S*) = 75:25. Chiral HPLC conditions (wavelength 220 nm): hexanes/isopropanol = 97:3, rate = 0.7 mL/min, t_R (minor) = 20.6 min, t_R (major) = 25.3 min. $[\alpha]_D^{20}$ +23.4 (*c* 0.99 in $CHCl_3$, for the compound with 75:25 er). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d (broad), J = 7.8 Hz, 2H), 7.31−7.38 (m, 3H), 6.14 (d, J_{HP} = 13.6 Hz, 1H), 4.01−4.12 (m, 3H), 3.89−3.97 (m, 1H), 2.17 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3 (d, J_{CP} = 8.9 Hz), 133.5 (d, J_{CP} = 2.0 Hz), 128.7 (d, J_{CP} = 2.8 Hz), 128.5 (d, J_{CP} = 2.2 Hz), 127.9 (d, J_{CP} = 5.8 Hz), 70.5 (d, J_{CP} = 170.1 Hz), 63.4 (d, J_{CP} = 2.3 Hz), 63.3 (d, J_{CP} = 1.8 Hz), 20.9, 16.4 (d, J_{CP} = 5.7 Hz), 16.3 (d, J_{CP} = 5.8 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 17.78.

Diethyl 1-Acetoxy-(2-naphthyl)methylphosphonate (4b).[12b] This compound was prepared from 2-naphthylaldehyde (39.0 mg, 0.25 mmol). Chromatography: hexanes/ethyl acetate (1:2). Colorless oil, 70.1 mg, 83% yield (96% yield by ^{1}H NMR), (*R*:*S*) = 73:27. Chiral HPLC conditions (wavelength 220 nm): hexanes/isopropanol = 98:2, rate = 0.7 mL/min, t_R (minor) = 63.6 min, t_R (major) = 67.7 min. $[\alpha]_D^{20}$ +33.4 (*c* 1.3 in $CHCl_3$, for the compound with 73:27 er). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.82−7.87 (m, 3H), 7.62 (d, J = 8.5 Hz. 1H), 7.47−7.52 (m, 2H), 6.30 (d, J_{HP} = 13.7 Hz, 1H), 4.02−4.15 (m, 3H), 3.89−3.98 (m, 1H), 2.21 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5 (d, J_{CP} = 9.3 Hz), 133.5 (d, J_{CP} = 1.7 Hz), 133.2 (d, J_{CP} = 2.3 Hz), 131.1 (d, J_{CP} = 2.2 Hz), 128.4 (d, J_{CP} = 1.6 Hz), 128.3, 127.9, 127.6 (d, J_{CP} = 7.5 Hz), 126.7, 126.5, 125.5 (d, J_{CP} = 4.4 Hz), 70.8 (d, J_{CP} = 170.3 Hz), 63.53 (d, J_{CP} = 4.5 Hz), 63.48 (d, J_{CP} = 4.0 Hz), 21.1, 16.6 (d, J_{CP} = 5.6 Hz), 16.5 (d, J_{CP} = 5.8 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 17.74.

Diethyl 1-Acetoxy-(4-methoxyphenyl)methylphosphonate (4c).[12b] This compound was prepared from 4-methoxybenzaldehyde (30.4 μL, 0.25 mmol). Chromatography: hexanes/ethyl acetate (1:1). Colorless oil, 65.4 mg, 83% yield (93% yield by ^{1}H NMR), (*R*:*S*) = 69:31. Chiral HPLC conditions (wavelength 220 nm): hexanes/isopropanol = 97:3, rate = 0.7 mL/min, t_R (minor) = 37.5 min, t_R (major) = 45.3 min. $[\alpha]_D^{20}$ +16.6 (*c* 0.98 in $CHCl_3$, for the compound with 69:31 er). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, J = 1.7, 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.07 (d, J_{HP} = 13.1 Hz, 1H), 4.00−4.15 (m, 3H), 3.87−3.95 (m, 1H), 3.80 (s, 3H), 2.15 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4 (d, J_{CP} = 9.1 Hz), 160.0 (d, J_{CP} = 2.5 Hz), 129.6 (d, J_{CP} = 6.2 Hz), 125.4 (d, J_{CP} = 1.8 Hz), 113.9 (d, J_{CP} = 1.7 Hz), 70.1 (d, J_{CP} = 172.7 Hz), 63.3 (d, J_{CP} = 5.4 Hz), 63.2 (d, J_{CP} = 6.0 Hz), 55.3, 20.9, 16.5 (d, J_{CP} = 5.7 Hz), 16.3 (d, J_{CP} = 5.7 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 18.13.

Diethyl 1-Acetoxy-(3-methoxyphenyl)methylphosphonate (4d).[7b] This compound was prepared from 3-methoxybenzaldehyde (30.5 μL, 0.25 mmol). Chromatography: hexanes/ethyl acetate (1:1). Colorless oil, 65.2 mg, 83% yield (92% yield by ^{1}H NMR), (*R*:*S*) = 75:25. Chiral HPLC conditions (wavelength 220 nm): hexanes/isopropanol = 97:3, rate = 0.7 mL/min, t_R (minor) = 23.9 min, t_R (major) = 36.5 min. $[\alpha]_D^{20}$ +16.4 (*c* 0.73 in $CHCl_3$, for the compound with 75:25 er). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, J = 7.9, 7.9 Hz, 1H, partly hidden by $CHCl_3$), 7.06 (d (broad), J = 7.6 Hz, 1H), 7.03 (brs, 1H), 6.87 (d (broad), J = 8.3 Hz, 1H), 6.11 (d, J_{HP} = 13.6 Hz, 1H), 4.03−4.12 (m, 3H), 3.92−3.99 (m, 1H), 3.81 (s, 3H), 2.18 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3 (d, J_{CP} = 8.9 Hz), 159.6 (d, J_{CP} = 2.2 Hz), 134.9 (d, J_{CP} = 1.9 Hz), 129.5 (d, J_{CP} = 2.1 Hz), 120.2 (d, J_{CP} = 5.9 Hz), 114.4 (d, J_{CP} = 2.8 Hz), 113.3 (d, J_{CP} = 5.6 Hz), 70.4 (d, J_{CP} = 169.9 Hz), 63.4 (d, J_{CP} = 2.6 Hz), 63.3 (d, J_{CP} = 2.1 Hz), 55.3, 20.9, 16.4 (d, J_{CP} = 5.8 Hz), 16.3 (d, J_{CP} = 5.8 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 17.68.

Diethyl 1-Acetoxy(4-methylphenyl)methylphosphonate (4e).[12b] This compound was prepared from 4-methylbenzaldehyde (29.6 μL, 0.25 mmol). Chromatography: hexanes/ethyl acetate (1:2). Colorless oil, 66.4 mg, 89% yield (100% yield by ^{1}H NMR), (*R*:*S*) = 75:25. Chiral HPLC conditions (wavelength 220 nm): hexanes/isopropanol = 97:3, rate = 0.7 mL/min, t_R (minor) = 24.7 min, t_R (major) = 31.6 min. $[\alpha]_D^{20}$ +23.9 (*c* 0.80 in $CHCl_3$, for the compound with 75:25 er). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, J = 1.6, 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 6.10 (d, J_{HP} = 13.3 Hz, 1H), 4.01−4.13 (m, 3H), 3.89−3.97 (m, 1H), 2.34 (s, 3H), 2.16 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4 (d, J_{CP} = 9.1 Hz), 138.7 (d, J_{CP} = 2.9 Hz), 130.4 (d, J_{CP} = 1.9 Hz), 129.2 (d, J_{CP} = 2.0 Hz), 128.0 (d, J_{CP} = 5.9 Hz), 70.4 (d, J_{CP} = 171.0 Hz), 63.3 and 63.2 (2C), 21.2, 20.9, 16.4 (d, J_{CP} = 5.6 Hz), 16.3 (d, J_{CP} = 5.8 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 18.00.

Diethyl 1-Acetoxy (4-chlorophenyl)methylphosphonate (4f).[12b] This compound was prepared from 4-chlorobenzaldehyde (35.1 mg, 0.25 mmol). Chromatography: hexanes/ethyl acetate (1:1). Colorless oil, 57.8 mg, 72% yield (84% yield by ^{1}H NMR), (*R*:*S*) = 77:23. Chiral HPLC conditions (wavelength 220 nm): hexanes/isopropanol = 97:3, rate = 0.7 mL/min, t_R (minor) = 27.0 min, t_R (major) = 33.7 min. $[\alpha]_D^{20}$ +27.1 (*c* 0.79 in $CHCl_3$, for the compound with 77:23 er). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, J = 1.8, 8.5 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 6.08 (d, J_{HP} = 13.8 Hz, 1H), 4.03−4.13 (m, 3H), 3.93−4.01 (m, 1H), 2.17 (s, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.23 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2 (d, J_{CP} = 9.0 Hz), 134.7 (d, J_{CP} = 3.4 Hz), 132.1 (d, J_{CP} = 2.0 Hz), 129.3 (d, J_{CP} = 5.8 Hz), 128.7 (d, J_{CP} = 2.1 Hz), 69.8 (d, J_{CP} = 170.8 Hz), 63.5 (d, J_{CP} = 6.6 Hz), 63.4 (d, J_{CP} = 6.2 Hz), 20.8, 16.4 (d, J_{CP} = 5.6 Hz), 16.3 (d, J_{CP} = 5.6 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 17.25.

Diethyl 1-Acetoxy-(2-chlorophenyl)methylphosphonate (4g).[12b] This compound was prepared from 2-chlorobenzaldehyde (28.2 μL, 0.25 mmol). Chromatography: hexanes/ethyl acetate (1:2). Colorless oil, 48.3 mg, 60% yield (61% yield by ^{1}H NMR), (*R*:*S*) = 78:22. Chiral HPLC conditions (wavelength 220 nm): hexanes/isopropanol = 97:3, rate = 0.7 mL/min, t_R (minor) = 35.4 min, t_R (major) = 37.6 min. $[\alpha]_D^{20}$ +13.1 (*c* 0.83 in $CHCl_3$, for the compound with 78:22 er). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dt, J = 1.8, 7.5 Hz, 1H),

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7.38 (d, J = 7.7 Hz, 1H), 7.27−7.32 (m, 2H), 6.62 (d, J_{HP} = 13.7 Hz, 1H), 4.17 (dq, J_{HH} = 7.1 Hz, J_{HP} = 7.7 Hz, 2H), 4.00−4.06 (m, 1H), 3.89−3.97 (m, 1H), 2.16 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0 (d, J_{CP} = 9.6 Hz), 133.7 (d, J_{CP} = 7.9 Hz), 132.0 (d, J_{CP} = 1.0 Hz), 129.8 (d, J_{CP} = 2.8 Hz), 129.7 (d, J_{CP} = 3.9 Hz), 129.5 (d, J_{CP} = 1.9 Hz), 127.1 (d, J_{CP} = 2.7 Hz), 66.9 (d, J_{CP} = 173.0 Hz), 63.5 (d, J_{CP} = 3.4 Hz), 63.4 (d, J_{CP} = 3.6 Hz), 20.8, 16.4 (d, J_{CP} = 5.8 Hz), 16.2 (d, J_{CP} = 5.7 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 17.20.

Diethyl 1-Acetoxypropanephosphonate (4h).[38] This compound was prepared from propanal (18.0 μL, 0.25 mmol). Chromatography: hexanes/ethyl acetate (1:1). Colorless oil, 9.0 mg, 15% yield (16% yield by ^{1}H NMR), (*R*:*S*) = 79:21. Chiral GC conditions: flow 1 mL/min, 50 °C for 10 min, 2 °C/min to 100 °C, hold for 20 min, 1 °C/min to 135 °C, 10 °C/min to 180 °C, t_R (major) = 86.1 min, t_R (minor) = 86.5 min. $[\alpha]_D^{20}$ −32.1 (*c* 0.14 in $CHCl_3$, for the compound with 79:21 er). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (ddd, J = 4.2, 8.7, 9.6 Hz, 1H), 4.11−4.19 (m, 4H), 2.13 (s, 3H), 1.89−1.97 (m, 1H), 1.77−1.86 (m, 1H), 1.33 (t, J = 7.2 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (d, J_{CP} = 5.3 Hz), 69.2 (d, J_{CP} = 167.7 Hz), 62.7 (d, J_{CP} = 7.0 Hz), 62.6 (d, J_{CP} = 6.3 Hz), 22.9, 20.7, 16.5 (d, J_{CP} = 5.7 Hz), 16.4 (d, J_{CP} = 5.9 Hz), 10.3 (d, J_{CP} = 12.6 Hz); ^{31}P NMR (202 MHz, $CDCl_3$) δ 20.88.

General Procedure for Hydrolysis of Acetoxyphosphonates 4a, 4e, and 4f. *p*-TsOH·H_2O (27 mg, 0.14 mmol) was added to the solution of acetoxyphosphonate (0.10 mmol) in EtOH (2 mL) at room temperature. The resulting mixture was stirred for 3 d. Then the solvent was evaporated and the crude product was purified by column chromatography using hexanes/ethyl acetate (1:2) as eluent gave the hydroxyphosphonates.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectra of compounds **2**, **4a**−**h**, ligand for complex **8a**, ^{31}P NMR spectrum of compound **2**, and HPLC and GC of compounds **4a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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