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Dynamic Kinetic Resolution Based Asymmetric Transfer Hydrogenation of α-Alkoxy-β-Ketophosphonates. Diastereo- and Enantioselective Synthesis of Monoprotected 1,2-Dihydroxyphosphonates

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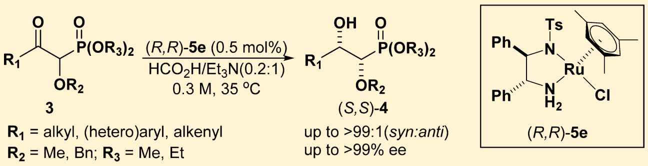
Ⓢ *Supporting Information*

ABSTRACT: Dynamic kinetic resolution driven, asymmetric transfer hydrogenation reactions of a wide range of 2-substituted α-alkoxy-β-ketophosphonates **3** were observed to proceed efficiently to give the corresponding 2-substituted α-alkoxy-β-hydroxy phosphonates **4** with excellent levels of diastereo- and enantioselectivity. These processes are promoted by using well-defined, commercially available, chiral transition metal catalysts and a 0.2:1 mixture of formic acid and triethylamine as the hydrogen source and solvent.



■ INTRODUCTION

Enantiomerically enriched α-substituted-β-hydroxy phosphonates have attracted considerable interests because of their wide range of biological activities as well as their abilities to serve as surrogates of the corresponding β-hydroxy carboxylates.[1−6] These substances are also key intermediates in the synthesis of potentially important peptide analogues, enzyme inhibitors, phosphonic acid-based antibiotics, and drug candidates.[2,7−12] Although a number of methods have been described for the preparation of enantiomerically enriched β-hydroxy phosphonates, including enzymatic[13−19] and nonenzymatic resolutions of racemic mixtures,[20−22] most suffer from either low levels of stereoselectivitiy or poor efficiencies. Enantiomerically enriched α-substituted-β-hydroxy phosphonates have also been prepared by utilizing asymmetric C−P bond-forming reactions of chiral α-hydroxy aldehydes with phosphonates.[23,24] However, these approaches require the use of stoichiometric amounts of chiral starting materials and the observed stereoselectivities of the formed chiral 1,2-dihydroxy phosphonates are not high.[25,26] In some cases, Sharpless asymmetric dihydroxylation of α,β-unsaturated phosphonates was used to generate 1,2-dihydroxy phosphonates with high levels of stereoselectivity.[27−29] However, in this case the need exists to discriminate between the hydroxyl groups in the 1,2-dihydroxy phosphonate moiety when selective transformations to produce α-substituted-β-hydroxy phosphonates are desired.

In 1995, Noyori and co-workers described asymmetric hydrogenation (AH) reactions of β-ketophosphonates using a BINAP-based Ru catalyst system, which generate β-hydroxy phosphonates, and applied this method to the synthesis of the antibiotic, fosfomycin.[10] Later, Genet and co-workers also explored AH reactions of β-ketophosphonates and β-ketothiophosphonates using similar chiral Ru-catalyst systems.[30] Recently, Zhang and co-workers uncovered a stereoselective AH reactions of α-alkyl-β-ketophosphonates[2] and α-acylamindo-β-ketophosphonates employing Ru-SunPhos as the catalyst system,[1] which generate the corresponding α-alkyl-β-hydroxy phosphonates and α-acylamido-β-hydroxy phosphonates. In addition, enantioselective syntheses of β-hydroxy-α-aminophosphonate derivatives were reported via organocatalytic asymmetric 1,2-addition reactions of α-isothiocyanato phosphonates to aldehydes.[31,32] However, until now, no reports exist describing the efficient synthesis of enantiomerically enriched α-alkoxy-β-hydroxy phosphonates.

Asymmetric transfer hydrogenation (ATH) reactions, which employ hydrogen sources other than molecular hydrogen, have proven to be among the most powerful methods for asymmetric reductions of ketones to produce chiral alcohols.[33−39] Major reasons for the superior nature of these reactions lie in their operational simplicity, excellent stereoselectivities, the availability of various hydrogen sources, and the ability to use readily accessible and less sensitive catalysts. In addition, transition metal-catalyzed asymmetric transfer hydrogenation of configurationally labile carbonyl compounds via dynamic kinetic resolution (DKR) has emerged as an efficient and powerful technique for controlling the stereochemistry at two contiguous stereogenic centers formed in the process. Examples of reactions of this type include ATH of α-substituted β-ketoesters,[40−42] β-ketoamides,[43] cyclic α-oxy-β-ketoamides (e.g., 2-benzoylmorpholin-3-ones),[44] β-ketosulfones,[45] 2-substituted-cycloalkanones,[46−48] 1,3-diketones,[49−51] 1,2-diketones,[52,53] α-ketoesters,[54] and α-ketophosphonates.[55]

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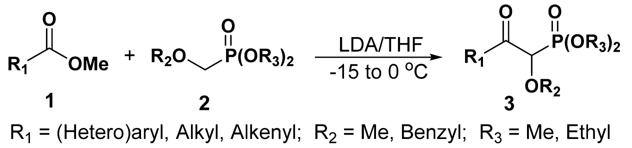
Interestingly, ATH-DKR of *α*-ketophosphonates, forming the corresponding *α*-hydroxy phosphonates,[55] proceeds by addition of hydrogen to the carbonyl diastereotopic face that is opposite to that observed in the analogous reduction of *α*-ketoesters. Recently, stereoselective ATH-DKR reactions of *α*-alkoxy-*β*-keto esters have been reported to form the corresponding *α*-alkoxy-*β*-hydroxy esters.[40] However, no previous reports exist describing asymmetric hydrogenation (AH) or asymmetric transfer hydrogenation (ATH) of *α*-alkoxy-*β*-ketophosphonates using chiral transition metal-catalysts.

In the studies described below, we have developed a highly efficient and stereoselective method for the synthesis of *α*-alkoxy-*β*-hydroxy phosphonates **4** (monohydroxy-protected 1,2-dihydroxy phosphonates) starting from the corresponding racemic *α*-alkoxy-*β*-ketophosphonates **3** (Scheme 2). The process, which enables simultaneous stereochemical control of two contiguous stereogenic centers in a single step, involves DKR driven, chiral transition metal catalyzed, asymmetric transfer hydrogenation (ATH).

RESULTS AND DISCUSSION

The racemic *α*-alkoxy-*β*-ketophosphonates **3**, used in this effort to explore the ATH-DKR process, were readily prepared through LDA promoted condensation reactions of the corresponding carboxylate esters **1** with dialkyl *α*-alkoxymethylphosphonates **2**[56,57] (Scheme 1).[58,59] In initial studies, diethyl *α*-benzoyl-*α*-benzyloxymethylphosphonate (**3a**) was subjected to ATH reaction (methylene chloride at 35 °C for 23 h) using the known chiral transition metal catalysts **5a**−**5e** (0.5 mol %) and a 5:2 mixture of formic acid and triethylamine as the hydrogen source (Scheme 2, Table 1).

Scheme 1. Synthesis of *α*-Alkoxy-*β*-ketophosphonates 3



Scheme 2. ATH-DKR Reactions of *α*-Alkoxy-*β*-ketophosphonates 3

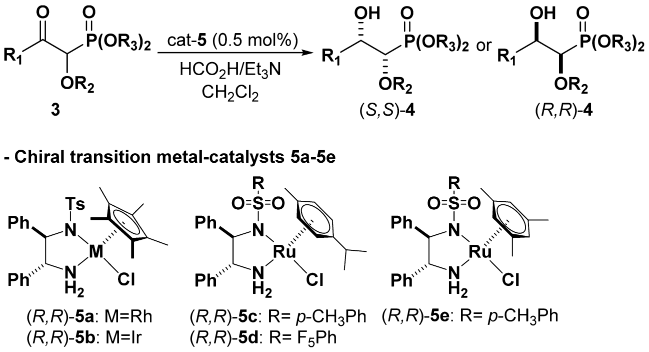
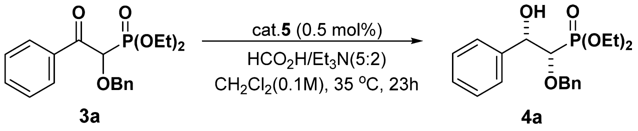


Table 1. Optimization of Chiral Catalysts 5 in ATH-DKR Reactions of 3a[a]



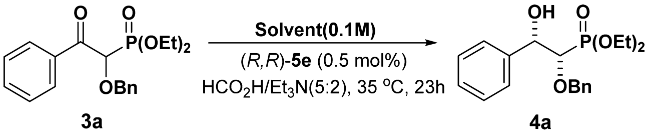
entry	5	conv (%)[b]	dr[c] (*syn*:*anti*)	ee(*syn*) (%)[d]	config[e]
1	(*R*,*R*)-**5a**	56	98:2	98	*S*,*S*
2	(*R*,*R*)-**5b**	74	97:3	98	*S*,*S*
3	(*R*,*R*)-**5c**	93	93:7	98	*S*,*S*
4	(*R*,*R*)-**5d**	44	90:10	>99	*S*,*S*
5	(*R*,*R*)-**5e**	>99	99:1	>99	*S*,*S*

[a] Reaction conditions: **3a** (1 mmol), **5** (0.5 mol %), F/T (1 mL), CH_2Cl_2 (10 mL), at 35 °C. [b] Determined by using ^1H NMR analysis. [c] *syn*-**4a**:*anti*-**4a**, determined by using ^1H NMR or chiral HPLC analysis of the crude reaction mixture. [d] Determined by using chiral HPLC analysis. [e] Determined by comparison of the optical rotation of debenzylation product **6** (see Scheme 4 below) with those reported in the literature.

ATH reactions of **3a** using the rhodium (*R*,*R*)-**5a**[60] or iridium catalyst (*R*,*R*)-**5b**[61] were observed to yield the *syn*-diastereomer (*S*,*S*)-**4a** as the major product with high levels of diastereo- and enantioselectivity. However, the reactions do not proceed to completion as reflected in the respective conversions of 56% and 74% for processes (23 h at 35 °C) promoted by (*R*,*R*)-**5a** and (*R*,*R*)-**5b** (Table 1, entries 1 and 2). When Noyori's Ru-catalyst, (*R*,*R*)-**5c**, is employed,[38] the conversion of the ATH reaction is improved to 93% (Table 1, entry 3). In contrast, use of the Ru-catalyst (*R*,*R*)-**5d**,[43] which contains an electron-deficient pentafluorophenylsulfonyl group on the chiral ligand, results in an inefficient (44% conversion) ATH reaction and a decreased level of diastereoselectivity (90:10 dr) (Table 1, entry 4). The results of further studies revealed that ATH reaction of **3a** using the Ru catalyst (*R*,*R*)-**5e**,[39,40] which possesses an η^6-arene = mesitylene ligand, produces (*S*,*S*)-**4a** in the highest conversion (>99%) and levels of stereoselectivity (99:1 dr, 99% ee) (Table 1, entry 5).

The influence of solvents on ATH-DKR reaction of **3a** promoted by (*R*,*R*)-**5e** was investigated next (Table 2). In most of the solvents tested (CH_2Cl_2, $Cl(CH_2)_2Cl$, $CHCl_3$, EtOAc, Toluene, DMF, MeOH, THF, IPA), reactions (23 h at 35 °C) of diethyl (1-benzoyl-1-benzyloxy)methylphosphonate (**3a**, 0.1 M) take place completely to form (*S*,*S*)-**4a** with high levels of stereoselectivity (dr =97:3−99:1, ee =92−99%). Reaction in THF is

Table 2. Optimization of the ATH-DKR of 3a in Various Solvents[a]



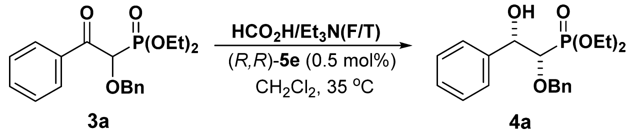
entry	solvent	convn (%)[b]	dr[c] (*syn*:*anti*)	ee (*syn*) (%)[d]
1	CH_2Cl_2	>99	99:1	>99
2	$Cl(CH_2)_2Cl$	>99	98:2	99
3	EtOAc	99	98:2	>99
4	$CHCl_3$	98	98:2	99
5	toluene	97	98:2	>99
6	DMF	96	97:3	99
7	MeOH	92	97:3	>99
8	THF	86	97:3	92
9	2-propanol	99	99:1	99

[a] Reaction conditions: **3a** (0.1 mmol), (*R*,*R*)-**5e** (0.5 mol %), and HCO_2H/Et_3N (*F*/*T* = 5:2) (0.1 mL) in 1.0 mL of solvent at 35 °C for 23 h. [b] Determined by ^1H NMR. [c] dr was determined by ^1H NMR or chiral HPLC. [d] ee was determined by chiral HPLC.

the exception to this trend in that it takes place more slowly than those in other solvents (86% conversion, 92% ee, 23 h).

Transition metal catalyzed-ATH reactions of ketones are most often performed in 2-propanol (IPA) or a 5:2 mixture of formic acid and triethylamine, with the latter being preferred because in this case reactions are nearly irreversible. Recently it has been shown that ratio of formic acid and triethylamine has a significant effect on both the rates and enantioselectivities of ATH reactions of ketones.[44,62] In the current effort, we also observed that the formic acid and triethylamine ratio dramatically affects the time required for completion of the ATH reaction of **3a** catalyzed by **5e** (Table 3). Specifically, reduction of the ratio of formic acid and triethylamine from 5:2 to 1:1 and to 0.2:1 affects a dramatic reduction in the time required for completion of the ATH reaction from 24 to 6 and to 2 h without causing a deterioration of the dr or % ee. In addition, we observed that slow addition of formic acid (4 equiv) to a Et_3N (20 equiv) solution of **3a** and (*R*,*R*)-**5e** (0.5 mol %) promoted the most efficient process in terms of stereoselectivity and reaction time (2 h). Moreover, the amount of catalyst loading can be reduced to 0.1 mol % (S/C = 1000) with longer reaction time to complete the reaction without loss of the optical purity (Table 3, entry 6).

Table 3. ATH-DKR Reaction of 3a with Varying HCO_2H/Et_3N (F/T) Ratio[a]



entry	F/T ratio	FA (equiv)	time (h)	conv. (%)[b]	dr[c] (*syn*:*anti*)	ee (*syn*) (%)[d]
1	5:2	10.7	24	>99 (97)	99:1	>99
2	1:1	5.6	6	>99	99:1	>99
3	0.2:1[e]	13.6	5	>99	99:1	>99
4	0.2:1[f]	13.6	2	>99	99:1	>99
5	0.2:1[g]	4.1	2	>99	99:1	>99
6[h]	0.2:1[g,h]	4.1	7	>99	99:1	>99

[a] Reaction conditions: **3a** (0.1 mmol), (*R*,*R*)-**5e** (0.5 mol %), and HCO_2H/Et_3N (F/T = 5:2 or 1:1) (0.1 mL) in 1.0 mL of CH_2Cl_2. [b] Determined by using ^1H NMR analysis of the crude reaction mixture (isolated yields in parentheses). [c] dr was determined by using ^1H NMR or chiral HPLC. [d] ee was determined by using chiral HPLC. [e] HCO_2H/Et_3N (F/T = 0.2:1, 1 mL) was used as hydrogen source and solvent with addition of small amount of CH_2Cl_2 (~0.2 mL) to make the solution a single phase. [f] Only HCO_2H/Et_3N (F/T = 0.2:1, 1 mL) was used (0.1 M) with no added solvent. [g] Amount of HCO_2H/Et_3N (F/T = 0.2:1) was reduced to 0.3 mL (0.3 M). [h] 0.1 mol % (S/C = 1000) of (*R*,*R*)-**5e** was used. FA (equiv): equivalent amount of formic acid to **3a**.

The scope and limitations of AHT-DKR process were explored next using a variety of *α*-alkoxy-*β*-ketophosphonates (**3**, 0.3 M) and the optimized reaction conditions (35 °C) involving **5e** (0.5 mol %) as the catalyst and a 0.2:1 molar ratio of formic acid and triethylamine as both the hydrogen source and solvent. The results of this survey are summarized in Table 4.

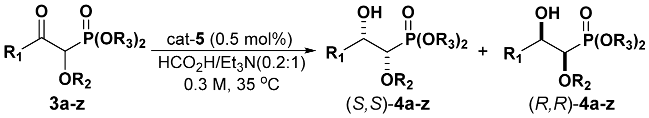
The results show that ATH reactions of both the *α*-benzyloxy- and *α*-methyloxy-substituted phosphonates **3a** and **3b** produce the corresponding products **4a** and **4b** with excellent efficiencies and stereoselectivities (Table 4, entries 1 and 2). In a similar manner, ATH reactions of both the diethyl (**3b**) and dimethyl (**3c**) esters of ketophosphonate take place to generate the corresponding products **4b** and **4c** with excellent levels of stereoselectivity (Table 4, entries 2 and 3). The benzyl ether group in **3a** tolerates the reductive reaction conditions, but it can be removed using Pd/C-H_2 in EtOH/AcOH (Scheme 4). Various *α*-benzyloxy-*β*-ketophosphonates **3** bearing *meta*- or *para*-electron-donating and electron-withdrawing substituted aryl moieties are smoothly converted to the corresponding monobenzyl protected 2-aryl-1,2-dihydroxy phosphonates **4** in uniformly excellent yields (94−99%) and stereoselectivities (98:2−99:1 dr, 98−99% ee) and in short reaction time periods (2−5 h). The results also show that substrates with electron-withdrawing aryl groups react slightly faster (2−3 h) than those containing electron-donating groups such as methyl or methoxy (4−5 h). However, ATH reaction of the *α*-benzyloxy-*β*-ketophosphonate **3d** containing an *ortho*-Cl substituted aryl group produces the corresponding reduction product **4d** in high yield (97%) but with poor stereoselectivities (60:40 dr, 82/47% ee) (Table 4, entry 4). In addition, the *ortho*-Me aryl substituted substrate **3g** is inert under the reaction conditions even after 24 h (quantitative recovery of **3g**) (Table 4, entry 7). Although ATH reaction of **3o**, possessing a 2′-naphthyl group, proceeds smoothly in 4 h to produce **4o** with an excellent yield and stereoselectivities, the 1′-naphthyl analogue **3p** reacts only reluctantly to generate **4p** in 19% yield in 4 h, and although a >90% conversion is attained in 30 h, the diastereoselectivity of the process is extremely low (dr = 43:57) (Table 4, entries 15 and 16). These observations suggest that both the steric and electronic natures of *ortho*-substituents have an effect on the ATH process, perhaps by inhibiting formation of the catalyst−substrate complex.

Importantly, ATH reaction of **3a** under the same conditions, except employing (*S*,*S*)-**5e** instead of (*R*,*R*)-**5e** as catalyst, produces (*R*,*R*)-**4a** as the major product with excellent levels of stereoselectivity (99:1 dr, 99% ee) (Table 4, entry 30). This observation demonstrates that the source of dynamic kinetic resolution in this process is the configurational lability of the stereogenic center in **3a**, which causes rapid racemization of the substrate under the reaction conditions (Scheme 3). As a result, the absolute stereochemistry of the major reduction product depends on the chirality of the Ru-catalysts in a manner such that (*S*)-**3a** is preferentially reduced with (*R*,*R*)-**5e** to afford alcohol (*S*,*S*)-**4a** and (*R*)-**3a** is preferentially reduced with (*S*,*S*)-**5e** to give alcohol (*R*,*R*)-**4a**.

α-Benzyloxy-*β*-ketophosphonates containing heteroaromatic moieties such as 2-furyl (**3q**) and 2-thienyl (**3r**) are also suitable substrates for the ATH-DKR reaction. These processes produce the respective reduction products **4q** and **4r** with excellent levels of stereoselectivity (Table 4, entries 17 and 18). Similarly, ATH reactions of *β*-ketophosphonates bearing nitrogen-containing heteroaromatic substituents such as 3′-pyridyl (**3t**) and 4′-pyridyl (**3u**) react to form the corresponding products **4t** and **4u** with excellent stereoselectivities (Table 4, entries 20 and 21). In the cases of ATH of the pyridyl containing *β*-ketophosphonates **3t** and **3u**, excess amounts of formic acid (16 equiv) are need to promote complete reactions in 3.5 h. In contrast, the 2′-pyridyl substituted substrate **3s** *β*-ketophosphonate undergoes the ATH reaction only slowly (31% conversion to **4s** in 3.5 h, Table 4, entry 19).

The results of continuing studies revealed that Rh-containing **5a** is a better catalyst than Ru-**5e** for the ATH reaction of 2′-pyridyl *β*-ketophosphonates **3s**. Specifically, **3s** reacts in the presence of **5a** in 1:1 formic acid and triethylamine in 6 h to produce **4s** completely but with a low level of stereoselectivity (96:4 dr, 44% ee, Table 4, entry 22). In addition, ATH

Table 4. ATH-DKR Reactions of 2-Substituted α-Alkoxy-β-ketophosphonates 3[a]



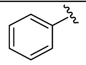
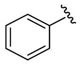
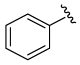
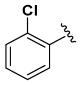
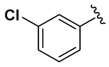
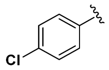
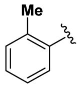
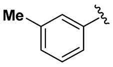
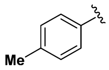
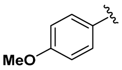
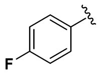
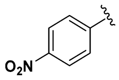
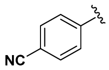
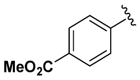
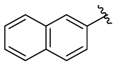
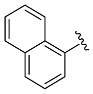
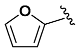
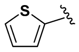
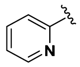
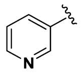
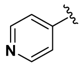
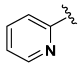
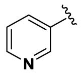
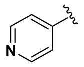
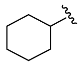
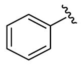
entry	3,4	substrate			cat-5	time (h)	conv[b] (%)	dr[c] (*syn*:*anti*)	ee(*syn*)[d] (%)	config[e]
		R_1	R_2	R_3						
1	**a**		Bn	Et	(*R*,*R*)-**5e**	2	>99(99)	99:1	>99	*S*,*S*[f]
2	**b**		Me	Et	(*R*,*R*)-**5e**	3	>99(98)	99:1	99	*S*,*S*
3	**c**		Me	Me	(*R*,*R*)-**5e**	3	>99(98)	99:1	>99	*S*,*S*
4	**d**		Bn	Et	(*R*,*R*)-**5e**	2	>99(97)	60:40	82/47	-
5	**e**		Bn	Et	(*R*,*R*)-**5e**	2	>99(96)	99:1	>99	*S*,*S*
6	**f**		Bn	Et	(*R*,*R*)-**5e**	2	>99(99)	99:1	>99	*S*,*S*
7	**g**		Bn	Et	(*R*,*R*)-**5e**	24	NR[g]	-	-	-
8	**h**		Bn	Et	(*R*,*R*)-**5e**	4	>99(98)	99:1	>99	*S*,*S*
9	**i**		Bn	Et	(*R*,*R*)-**5e**	4	>99(99)	99:1	>99	*S*,*S*
10	**j**		Bn	Et	(*R*,*R*)-**5e**	5	>99(95)	99:1	99	*S*,*S*
11	**k**		Bn	Et	(*R*,*R*)-**5e**	3	>99(95)	99:1	>99	*S*,*S*
12	**l**		Bn	Et	(*R*,*R*)-**5e**	3	>99(98)	98:2	98	*S*,*S*
13	**m**		Bn	Et	(*R*,*R*)-**5e**	2	>99(99)	99:1	99	*S*,*S*
14	**n**		Bn	Et	(*R*,*R*)-**5e**	3	>99(99)	99:1	>99	*S*,*S*[h]
15	**o**		Bn	Et	(*R*,*R*)-**5e**	4	>99(99)	99:1	>99	*S*,*S*
16	**p**		Bn	Et	(*R*,*R*)-**5e**	30	92	43:57	92/53	-

Table 4. continued

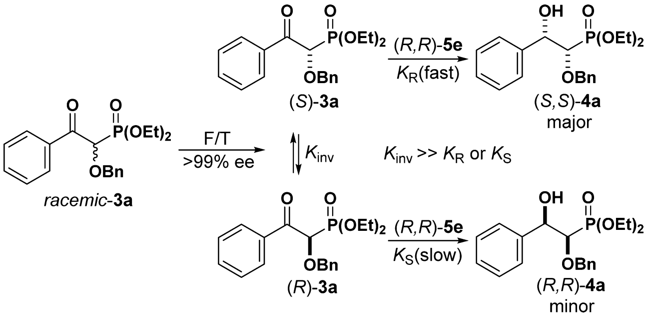
entry	3,4	substrate			cat-5	time (h)	conv[b] (%)	dr[c] (*syn*:*anti*)	ee(*syn*)[d] (%)	config[e]
		R_1	R_2	R_3						
17	**q**		Bn	Et	(*R*,*R*)-**5e**	3	>99(98)	99:1	>99	*S*,*S*
18	**r**		Bn	Et	(*R*,*R*)-**5e**	3	>99(97)	99:1	>99	*S*,*S*
19	**s**		Bn	Et	(*R*,*R*)-**5e**[i]	3.5	31	92:8	82	-
20	**t**		Bn	Et	(*R*,*R*)-**5e**[i]	3.5	>99	99:1	>99	*S*,*S*
21	**u**		Bn	Et	(*R*,*R*)-**5e**[i]	3.5	>99	98:2	>99	*S*,*S*[h]
22	**s**		Bn	Et	(*R*,*R*)-**5a**[j]	6	>99(98)	96:4	44	-
23	**t**		Bn	Et	(*R*,*R*)-**5a**[j]	6	>99(96)	99:1	91	*S*,*S*
24	**u**		Bn	Et	(*R*,*R*)-**5a**[j]	6	>99(97)	98:2	98	*S*,*S*[h]
25	**v**	Me	Bn	Et	(*R*,*R*)-**5e**	3	>99(99)	96:4	98	*S*,*S*[f]
26	**w**	Et	Bn	Et	(*R*,*R*)-**5e**	4	>99	83:17	97	*S*,*S*
27	**x**		Bn	Et	(*R*,*R*)-**5e**	24	NR[g]	-	-	-
28	**y**	$Ph(CH_2)_2$	Bn	Et	(*R*,*R*)-**5e**	5	>99(96)	85:15	95/99	*S*,*S*[f]
29	**z**	$Ph(CH_2)_2$	Me	Me	(*R*,*R*)-**5e**	4	>99	88:12	95/98	*S*,*S*
30	**a**		Bn	Et	(*S*,*S*)-**5e**	2	>99(98)	99:1	>99	*R*,*R*

[a] Reaction conditions: **3** (1 mmol) and (*R*,*R*)-**5** (0.5 mol %) in Et_3N (2.85 mL, 20 equiv) with slow addition of formic acid (0.15 mL, 4 equiv) at 35 °C. [b] Conversion was determined by using ^1H NMR analysis of the crude reaction mixture (isolated yields in the parentheses) [c] dr was determined by using ^1H NMR or chiral HPLC. [d] ee was determined by using chiral HPLC. [e] Determined by analogy to **4a**, **4n**, **4u**, **4v**, or **4y**. [f] Determined by comparison of the optical rotation of debenzylation product with that reported in the literature (see Scheme 4). [g] No reaction. [h] Determined by using X-ray crystallography. [i] Reaction conditions for entries 19−21: **3** (1 mmol) and Ru-catalyst (*R*,*R*)-**5e** (0.5 mol %) in Et_3N (80 equiv) with slow addition of formic acid (16 equiv) at 35 °C. [j] Same reaction conditions for entries 19−21 (Table 4) except that **Rh**-catalyst (*R*,*R*)-**5a** instead of **Ru**-catalyst (*R*,*R*)-**5e** in 1:1 mixture of formic acid and triethylamine was employed.

reactions of the 3′-pyridyl- and 4′-pyridyl-phosphonates **3t** and **3u** using Rh-catalyst **5a** in 1:1 formic acid and triethylamine form the corresponding products **4t** (99:1 dr, 91% ee) and **4u** (98:2 dr, 98% ee) with varying degrees of stereoselectivity (Table 4, entries 23 and 24).

The application of the ATH reaction to stereoselective reductions of 2-alkyl substituted α-alkoxy-β-ketophosphonates was explored next. The results demonstrate that ATH reactions of 2-methyl or 2-ethyl substituted α-benzyloxy-β-ketophosphonates **3v** and **3w** using Ru-catalyst **5e** occur to produce the

Scheme 3. Dynamic Kinetic Resolution in ATH Reaction of *Racemic*-3a Catalyzed by (*R,R*)-5e

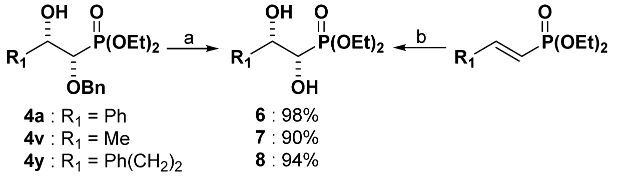


corresponding products **4v** and **4w** in high yields but with slightly lower diastereoselectivities than those that attend ATH of 2-(hetero)aryl substituted β-ketophosphonates (Table 4, entries 25 and 26). ATH of 2-phenethyl substituted β-ketophosphonates bearing α-benzyloxy (**3y**) and α-methoxy (**3z**) groups also proceed to completion in 4−5 h and also take place with slightly lower levels of diastereoselectivity (Table 4, entries 28 and 29). However, the efficiencies of ATH reactions of 2-alkyl substituted α-benzyloxy-β-ketophosphonates are sensitive to the steric bulkiness of the 2-alkyl group, as is exemplified by the 2-cyclohexyl analogue **3x**, which is inert under the reaction conditions even over an extended time period of 24 h (Table 4, entry 27).

Finally, the scope of the process was explored employing the 2-cinnamoyl substituted α-benzyloxy-β-ketophosphonate **3ab** (Table 5). Reaction of this substrate promoted by the Ru-catalyst **5e** takes place to generate **4ab** as the expected major product (66%) with good stereoselectivities (99:1 dr, 98% ee) (Table 5, entry 3) along with the C═C reduction products **3y** (22%) and **4y** (12%). Because it is well-known that transfer hydrogenations promoted by Noyori-type diamine−transition metal (Ru, Rh, Ir) complexes are highly chemoselective, with C═O reduction being favored over C═C reduction,[39,63] the present result is interesting. However, it was reported recently that the use of Ru- or Rh-amido catalysts causes reversal of the typical C═O over C═C selectivities in ATH reactions of α,β-unsaturated carbonyl compounds when the C═C double bond is activated by electron-withdrawing substituents or the reaction is performed in an aqueous medium.[64,65] In line with this finding, we observed that the chemoselectivity of reaction of **3ab** can be changed to favor C═C reduction by replacing catalyst **5e** with Rh(III)-**5a** or Ir(III)-**5b** (Table 5, entries 3−5).

In order to determine the absolute and relative stereochemistries of the ATH-DKR reaction products, **4a**, **4v**, and **4y** were converted to the respective 1,2-dihydroxy-substituted phosphonates **6**,[27,28] **7**,[28,66] and **8** by using Pd/C-catalyzed hydrogenolysis (Scheme 4). The absolute stereochemistries of **6**, **7**, and **8** were then determined on the basis of comparisons of their properties with those of known (**6** and **7**) or independently synthesized phosphonate **8** using Sharpless asymmetric dihydroxylation of the corresponding α,β-unsaturated phosphonate[67] employing AD-mix-α. Additionally, the absolute stereochemistries of **4n** and **4u** were unambiguously assigned by using single-crystal X-ray crystallographic analysis (deposited, CCDC-982444 for (*S,S*)-**4n** and CCDC-982443 for (*S,S*)-**4u**, see Supporting Information).

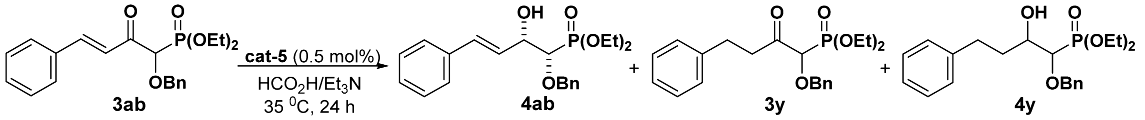
Scheme 4. Determination of the Absolute Stereochemistry of ATH-DKR Product 4[a]



[a](a) Pd/C, H_2, EtOH/AcOH (100:1), rt; (b) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C.

In summary, the investigation described above has led to the development of a convenient and general protocol for asymmetric transfer hydrogenation (ATH) reactions of readily available, racemic 2-substituted α-alkoxy-β-ketophosphonates **3** that generate 2-substituted α-alkoxy-β-hydroxyphosphonates **4**. This process, which employs a 0.2:1 molar ratio mixture of HCO_2H and Et_3N as the hydrogen source and solvent, along with the well-defined chiral RuCl(TsDPEN)mesitylene catalysts (*S,S*)- and (*R,R*)-**5e**, efficiently produces the corresponding monobenzyl protected 2-aryl-, 2-heteroaryl-, 2-alkyl-, and 2-alkenyl-substituted 1,2-dihydroxy phosphonates with excellent levels of diastereo- and enantioselectivity in short reaction times. ATH reactions, carried out under the conditions outlined above, are accompanied by dynamic kinetic resolution (DKR) which leads to simultaneous control of the stereochemistry at two contiguous stereogenic centers. Finally, the observations show that the chemoselectivity of the ATH reaction of 1-cinnamoyl-1-benzyloxy-methylphosphonate (**3ab**) can be switched from favoring C═O reduction to favoring C═C

Table 5. ATH-DKR Reactions of 1-Cinnamoyl-1-benzyloxy-methylphosphonate (3ab)[a]



3ab **4ab** **3y** **4y**

entry	cat-5	solvent	F/T ratio	conv (%)[b]	4ab[c]	3y[c]	4y[c]
1	(*R,R*)-**5e** (Ru)	CH_2Cl_2	5:2	>99	56(>99:1)	13	31(64:36)
2	(*R,R*)-**5e** (Ru)	CH_2Cl_2	1:1	>99	63(>99:1)	–	37(57:43)
3	(*R,R*)-**5e** (Ru)	neat[d]	0.2:1	>99	66(99:1, 98%ee)	22	12
4	(*R,R*)-**5a** (Rh)	neat[d]	0.2:1	>99	4	87	9
5	(*R,R*)-**5b** (Ir)	neat[d]	0.2:1	>99	14	76	10

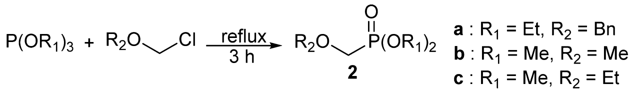
[a]Reaction conditions: **3** (0.1 mmol) in 1.0 mL of solvent with 0.1 mL of HCO_2H/Et_3N (*F/T* = 5:2 or 1:1), cat-**5** (0.5 mol %) at 35 °C for 24 h. [b]Determined by using ^1H NMR. [c]Ratio by ^1H NMR, dr and ee (in parentheses) by chiral HPLC. [d]HCO_2H/Et_3N (0.2:1) was used (0.1 M) as the hydrogen source and solvent.

reduction by changing the catalyst from Ru(II)-**5e** to Rh(III)-**5a** or Ir(III)-**5b**.

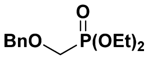
■ EXPERIMENTAL SECTION

General Methods. All commercial reagents were used as obtained unless otherwise noted. Reactions were performed using oven-dried glassware under an atmosphere of nitrogen. Dichloromethane (DCM), ether, THF were dried and purified using a solvent purification system. Flash column chromatography was carried out using silica gel (38−75 μm). Analytical thin layer chromatography (TLC) was performed using silica gel 60 F_{254} plates. Preparative thin layer chromatography (PLC) was performed using silica gel 60 F_{254} 2 mm plates. Visualization of the developed chromatograms was accomplished with UV light and by staining with ethanolic phosphomolybdic acid (PMA) solution or ninhydrin solution followed by heating. Nuclear magnetic resonance (NMR) spectra were recorded using a 500 MHz (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz) or 300 MHz instrument (^{1}H NMR at 300 MHz and ^{13}C NMR at 75 MHz). ^{1}H NMR data are reported as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constants (Hz). ^{13}C NMR data are reported in terms of chemical shifts (δ, ppm). High performance liquid chromatography (HPLC) was carried out on a system equipped with a Chiralpak IA, Chiralpak IB, Chiralpak IC, Chiralpak ID, or Chiralpak AD-H column. HR-MS were measured using electron impact (EI) ionization via double focusing mass analyzer (magnetic and electric fields) or electrospray ionization (ESI) via a time of flight (TOF) analyzer. Formic acid/triethylamine mixtures (molar ratio = 5:2 or 1:1) are commercially available. The formic acid/triethylamine mixture (molar ratio = 0.2:1) was prepared by slow addition of formic acid to triethylamine with stirring at room temperature according to the literature procedure.[62] Chiral catalysts, (*R*,*R*)-**5c**, (*R*,*R*)-**5d**, and (*R*,*R*)-**5e** are commercially available. (*R*,*R*)-**5a**[60] and (*R*,*R*)-**5b**[61] were prepared according to the literature procedures.

*1. Synthesis of 1-Alkyloxymethylphosphonate Dialkyl Ester (**2**).*[56,57] A mixture of triethyl phosphite (0.1 mmol) and benzyl chloromethyl ether (0.11 mmol) was heated to 130 °C with stirring for 3 h. After completion of reaction, the reaction mixture was cooled to room temperature and purified by flash chromatograph (SiO_2, hexane/EtOAc 1:2) to give diethyl benzyloxymethylphosphonate (**2a**, 23.6 g, 87%) as a pale-yellow oil.

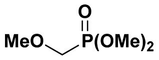


*1.1. Diethyl Benzyloxymethylphosphonate (**2a**):* yield: 87% (23.6 g as a pale-yellow oil); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40−7.29 (m, 5H), 4.67 (s, 1H), 4.22−4.17 (m, 4H), 3.78 (d, 1H, *J* = 8.7 Hz), 1.37 (t, 6H, *J* = 7.0 Hz).



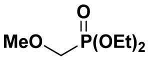
2a

*1.2. Dimethyl methyloxymethylphosphonate (**2b**):* yield: 72% (5.6 g as a colorless oil); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.83 (d, 6H, *J* = 10.6 Hz), 3.79 (d, 2H, *J* = 8.6 Hz), 3.49 (s, 3H).



2b

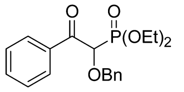
*1.3. Diethyl methyloxymethylphosphonate (**2c**):* yield: 57% (5.7 g as a colorless oil); bp 69−73 °C/2 mmHg; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.23−4.17 (m, 4H), 3.76 (d, 2H, *J* = 8.4 Hz), 3.50 (s, 3H), 1.38 (t, 6H, *J* = 7.0 Hz).



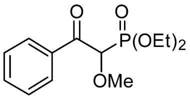
2c

*2. General Procedure for the Synthesis of α-Benzyloxy β-Ketophosphonates (**3**).* To the ester (1.15 equiv) and diethyl benzyloxymethylphosphonate (**2a**, 1 equiv) in THF at −5 °C was added dropwise with stirring a 1.5 M solution of LDA (2.1 equiv) maintaining the internal temperature below 0 °C. The reaction mixture was stirred at 0 °C until complete consumption of diethyl benzyloxymethylphosphonate (**2a**) as determined by TLC (typically less than 45 min.). The reaction mixture was then carefully quenched with 5 N HCl to adjust the pH to ∼4 and diluted with EtOAc. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to yield α-benzyloxy β-ketophosphonate **3**. Purification by column chromatography afforded pure **3**.

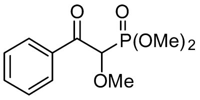
*2.1. Diethyl (1-benzyloxy-2-oxo-2-phenylethyl)phosphonate, **3a**:* yield: 95.6% (4.8 g as a coloress oil); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, 2H, *J* = 8.2 Hz), 7.60−7.58 (m, 1H), 7.47−7.44 (m, 2H), 7.32−7.29 (m, 5H), 5.14 (d, 1H, J_{cp} = 20 Hz), 4.78 (d, 1H, *J* = 11.8 Hz), 4.56 (d, 1H, *J* = 11.8 Hz), 4.21−4.10 (m, 4H), 1.29 (t, 3H, *J* = 7.0 Hz), 1.21 (t, 3H, *J* = 7.0 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0, 136.2, 135.7, 133.7, 129.5, 128.6, 128.6, 128.5, 128.4, 80.0 (d, J_{cp} = 151.1 Hz), 74.0 (d, J_{cp} = 12.6 Hz), 63.8 (d, J_{cp} = 6.8 Hz), 63.6 (d, J_{cp} = 6.8 Hz), 16.4 (d, J_{cp} = 6.5 Hz), 16.3 (d, J_{cp} = 6.5 Hz).; HRMS (EI): *m*/*z* calcd for $C_{19}H_{23}O_5P$ 362.1283, found 362.1279.



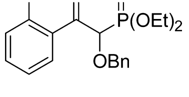
*2.2. Diethyl (1-methoxy-2-oxo-2-phenylethyl)phosphonate, **3b**.* yield: 73.0% (1.6 g as a coloress oil); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, 2H, *J* = 7.7 Hz), 7.61 (t, 1H, *J* = 7.5 Hz), 7.49 (t, 2H, *J* = 7.6 Hz), 5.01 (d, 1H, J_{cp} = 19.4 Hz), 4.24−4.13 (m, 4H), 3.51 (s, 3H), 1.32 (t, 3H, *J* = 7.1 Hz), 1.23 (t, 3H, *J* = 7.1 Hz).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.6, 135.5, 133.7, 129.3, 128.4, 83.4 (d, J_{cp} = 151.1 Hz), 63.8 (d, J_{cp} = 7.0 Hz), 63.5 (d, J_{cp} = 7.0 Hz), 60.4 (d, J_{cp} = 12.9 Hz), 16.3 (d, J_{cp} = 5.9 Hz), 16.1 (d, J_{cp} = 6.1 Hz).; HRMS (EI): *m*/*z* calcd for $C_{13}H_{19}O_5P$ 286.0970, found 286.0960.



*2.3. Dimethyl (1-methoxy-2-oxo-2-phenylethyl)phosphonate, **3c**:* yield: 76.0% (1.7 g as a coloress oil); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, 2H, *J* = 7.7 Hz), 7.63 (t, 1H, *J* = 7.4 Hz), 7.51 (t, 2H, *J* = 7.6 Hz), 5.04 (d, 1H, J_{cp} = 19.4 Hz), 3.85 (d, 3H, *J* = 10.9 Hz), 3.78 (d, 3H, *J* = 10.9 Hz), 3.51 (s, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5, 135.3, 133.9, 129.3, 128.5, 83.0 (d, J_{cp} = 151.5 Hz), 60.4 (d, J_{cp} = 13.2 Hz), 54.2 (d, J_{cp} = 6.6 Hz), 54.0 (d, J_{cp} = 6.6 Hz).; HRMS (EI): *m*/*z* calcd for $C_{11}H_{15}O_5P$ 258.0657, found 258.0654.

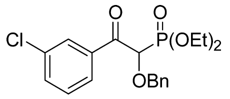


*2.4. Diethyl [1-benzyloxy-2-(2-chloro-phenyl)-2-oxo-ethyl]-phosphonate, **3d**:* yield: 86.7% (1.4 g as a pale-yellow oil); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, 1H, *J* = 7.6 Hz), 7.41−7.40 (m, 2H), 7.36−7.29 (m, 6H), 5.24 (d, 1H, J_{cp} = 21.4 Hz), 4.87 (d, 1H, *J* = 11.8 Hz), 4.72 (d, 1H, *J* = 11.8 Hz), 4.21−4.11 (m, 4H), 1.29 (t, 3H, *J* = 7.1 Hz), 1.18 (t, 3H, *J* = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3 (d, J_{cp} = 1.9 Hz), 137.4, 136.5, 132.1, 131.2, 130.3, 130.3, 128.6, 128.5, 128.4, 126.7, 81.3 (d, J_{cp} = 151.7 Hz), 74.1 (d, J_{cp} = 10.5 Hz), 63.8 (d, J_{cp} = 6.7 Hz), 63.5 (d, J_{cp} = 6.7 Hz), 16.4 (d, J_{cp} = 5.9 Hz), 16.2

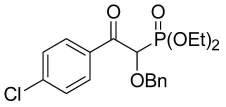


(d, J_{cp} = 6.2 Hz).; HRMS (EI): *m*/*z* calcd for $C_{19}H_{22}ClO_5P$ 396.0893, found 396.0892.

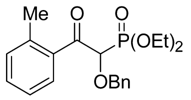
2.5. Diethyl [1-benzyloxy-2-(3-chloro-phenyl)-2-oxo-ethyl]-phosphonate, ***3e:*** yield: 93.0% (2.5 g as a pale-yellow oil); ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (s,1H), 7.95 (d, 1H, J = 7.9 Hz), 7.56−7.54 (m, 1H), 7.41−7.38 (m, 1H), 7.33−7.28 (m, 5H), 5.03 (d, 1H, J_{cp} = 20.3 Hz), 4.74 (d, 1H, J = 11.8 Hz), 4.59 (d, 1H, J = 11.8 Hz), 4.21−4.14 (m, 4H), 1.30 (t, 3H, J = 7.0 Hz), 1.24 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2 (d, J_{cp} = 1.0 Hz) 137.1, 136.0, 134.8, 133.7, 129.8, 129.5, 128.8, 128.7, 128.6, 127.9, 80.7(d, J_{cp} = 151.1 Hz), 74.4 (d, J_{cp} = 12.4 Hz), 64.0 (d, J_{cp} = 6.8 Hz), 63.8 (d, J_{cp} = 6.8 Hz), 16.5 (d, J_{cp} = 5.6 Hz), 16.4 (d, J_{cp} = 5.1 Hz).; HRMS (EI): *m*/*z* calcd for $C_{19}H_{22}ClO_5P$ 396.0893, found 396.0896.



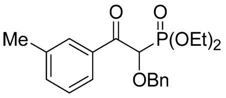
2.6. Diethyl [1-benzyloxy-2-(4-chloro-phenyl)-2-oxo-ethyl]-phosphonate, ***3f:*** yield: 88.5% (1.3 g as a pale-yellow oil); ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, 2H, J = 8.6 Hz), 7.43 (d, 2H, J = 8.6 Hz), 7.34−7.27 (m, 5H), 5.02 (d, 1H, J_{cp} = 20.2 Hz), 4.74 (d, 1H, J = 11.8 Hz), 4.56 (d, 1H, J = 11.8 Hz), 4.21−4.12 (m, 4H), 1.30 (t, 3H, J = 7.1 Hz), 1.25 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.0, 140.3, 136.0, 133.8, 131.1, 128.8, 128.7, 128.7, 128.6, 80.7 (d, J_{cp} = 151.0 Hz), 74.3 (d, J_{cp} = 12.6 Hz), 63.9 (d, J_{cp} = 6.8 Hz), 63.8 (d, J_{cp} = 6.8 Hz), 16.4 (d, J_{cp} = 5.9 Hz).; HRMS (EI): *m*/*z* calcd for $C_{19}H_{22}ClO_5P$ 396.0893, found 396.0898.



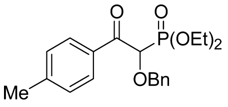
2.7. Diethyl [1-benzyloxy-2-oxo-2-(o-tolyl)-ethyl]phosphonate, ***3g:*** Yield: 89.7% (930 mg as a pale-yellow oil); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, 1H, J = 7.8 Hz), 7.37−7.29 (m, 6H), 7.23 (d, 1H, J = 7.5 Hz), 7.18 (t, 1H, J = 7.5 Hz), 5.06 (d, 1H, J_{cp} = 21.0 Hz), 4.80 (d, 1H, J = 12.0 Hz), 4.65 (d, 1H, J = 11.9 Hz), 4.19−4.00 (m, 4H), 2.43 (s, 3H), 1.26 (t, 3H, J = 7.1 Hz), 1.12 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9 (d, J_{cp} = 1.3 Hz), 138.4, 136.7, 136.3, 131.6, 131.6, 128.9, 128.6, 128.5, 128.4, 125.3, 80.8 (d, J_{cp} = 151.6 Hz), 73.7 (d, J_{cp} = 11.6 Hz), 63.6 (d, J_{cp} = 6.6 Hz), 63.3 (d, J_{cp} = 6.9 Hz), 20.4, 16.3 (2, J_{cp} = 6.0 Hz), 16.1 (d, J_{cp} = 6.3 Hz).; HRMS (EI): *m*/*z* calcd for $C_{20}H_{25}O_5P$ 376.1440, found 376.1442.



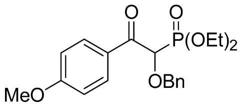
2.8. Diethyl [1-benzyloxy-2-oxo-2-(m-tolyl)-ethyl]phosphonate, ***3h:*** Yield: 93.5% (1.3 g as a pale-yellow oil); ^1H NMR (500 MHz, $CDCl_3$) δ 7.83−7.81 (d, 2H, J = 8.6 Hz), 7.39−7.29 (m, 7H), 5.14 (d, 1H, J_{cp} = 19.9 Hz), 4.76 (d, 1H, J = 11.8 Hz), 4.55 (d, 1H, J = 11.8 Hz), 4.22−4.08 (m, 4H), 2.39 (s, 3H), 1.28 (t, 3H, J = 7.1 Hz), 1.20 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0 (d, J_{cp} = 0.9 Hz) 138.2, 136.3, 135.8, 134.5, 129.7, 128.5, 128.5, 128.3, 128.3, 126.7, 79.8 (d, J_{cp} = 151.1 Hz), 73.8 (d, J_{cp} = 12.6 Hz), 63.7 (d, J_{cp} = 6.8 Hz), 63.5 (d, J_{cp} = 6.8 Hz), 21.3, 16.3 (d, J_{cp} = 6.3 Hz), 16.2 (d, J_{cp} = 7.5 Hz).; HRMS (EI): *m*/*z* calcd for $C_{20}H_{25}O_5P$ 376.1440, found 376.1439.



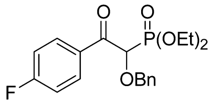
2.9. Diethyl [1-benzyloxy-2-oxo-2-(p-tolyl)-ethyl]phosphonate, ***3i:*** Yield; 92.5% (1.0 g as a pale-yellow oil); ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, 2H, J = 8.2 Hz), 7.34−7.29 (m, 5H), 7.25 (d, 2H, J = 8.1 Hz), 5.12 (d, 1H, J_{cp} = 19.8 Hz), 4.78 (d, 1H, J = 11.9 Hz), 4.54 (d, 1H, J = 11.9 Hz), 4.22−4.09 (m, 4H), 2.42 (s, 3H), 1.29 (t, 3H, J = 7.1 Hz), 1.22 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 144.8, 136.3, 133.2, 129.6, 129.2, 128.6, 128.5, 128.4, 79.9 (d, J_{cp} = 150.9 Hz), 73.8 (d, J_{cp} = 12.7 Hz), 63.8 (d, J_{cp} = 6.7 Hz), 63.6 (d, J_{cp} = 6.8 Hz), 21.8, 16.4 (d, J_{cp} = 5.6 Hz), 16.3 (d, J_{cp} = 5.6 Hz).; HRMS (EI): *m*/*z* calcd for $C_{20}H_{25}O_5P$ 376.1440, found 376.1441.



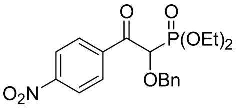
2.10. Diethyl [1-benzyloxy-2-(4-methoxy-phenyl)-2-oxo-ethyl]-phosphonate, ***3j:*** yield: 92.8% (2.3 g as a pale-yellow oil); ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, 2H, J = 9.0 Hz), 7.33−7.29 (m, 5H), 6.93 (d, 2H, J = 9.0 Hz), 5.06 (d, 1H, J_{cp} = 19.8 Hz), 4.77 (d, 1H, J = 11.8 Hz), 4.53 (d, 1H, J = 11.8 Hz), 4.22−4.11 (m, 4H), 3.88 (s, 3H), 1.29 (t, 3H, J = 7.1 Hz), 1.24 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0 (d, J_{cp} = 1.2 Hz), 164.1, 136.4, 132.1, 128.6, 128.6, 128.6, 128.4, 113.7, 80.2 (d, J_{cp} = 150.8 Hz), 73.9 (d, J_{cp} = 13.0 Hz), 63.7 (d, J_{cp} = 7.2 Hz), 63.7 (d, 1H, J_{cp} = 7.4 Hz), 55.6, 16.4 (d, J_{cp} = 6.0 Hz), 16.3 (d, J_{cp} = 5.9 Hz).; HRMS (EI): *m*/*z* calcd for $C_{20}H_{25}O_6P$ 392.1389, found 392.1386.



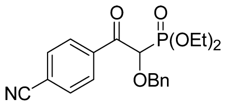
2.11. Diethyl [1-benzyloxy-2-(4-fluoro-phenyl)-2-oxo-ethyl]-phosphonate, ***3k:*** yield: 96.7% (1.3 g as a pale-yellow oil); ^1H NMR (500 MHz, $CDCl_3$) δ 8.16−8.13 (m, 2H), 7.33−7.28 (m, 5H), 7.14−7.11 (m, 2H), 5.02 (d, 1H, J_{cp} = 20.2 Hz), 4.74 (d, 1H, J = 11.8 Hz), 4.56 (d, 1H, J = 11.8 Hz), 4.22−4.11 (m, 4H), 1.30 (t, 3H, J = 7.0 Hz), 1.25 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6 (d, J_{cp} = 1.4 Hz), 166.2 (d, J_{cf} = 254.4 Hz), 136.1, 132.5 (d, J_{cf} = 9.4 Hz), 131.9 (d, J_{cf} = 2.9 Hz), 128.7, 128.6, 128.5, 115.6 (d, J_{cf} = 21.7 Hz), 80.7 (d, J_{cp} = 150.9 Hz), 74.2 (d, J_{cp} = 12.6 Hz), 63.9 (d, J_{cp} = 5.4 Hz), 63.8 (d, J_{cp} = 6.6 Hz), 16.4 (d, J_{cp} = 5.4 Hz).; HRMS (EI): *m*/*z* calcd for $C_{19}H_{22}FO_5P$ 380.1189, found 380.1184.



2.12. Diethyl[1-benzyloxy-2-(4-nitro-phenyl)-2-oxo-ethyl]-phosphonate, ***3l:*** yield: 26.6% (330 mg as a pale-yellow oil); ^1H NMR (500 MHz, $CDCl_3$) δ 8.32−8.21 (m, 5H), 7.32−7.24 (m, 4H), 5.04 (d, 1H, J_{cp} = 20.8 Hz), 4.71 (d, 1H, J = 11.8 Hz), 4.63 (d, 1H, J = 11.8 Hz), 4.23−4.17 (m, 4H), 1.31 (t, 3H, J = 7.0 Hz), 1.28 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.5 (d, J_{cp} = 1.6 Hz), 150.5, 139.9, 135.6, 130.8, 128.8, 128.8, 123.5, 81.3 (d, J_{cp} = 151.0 Hz), 74.7 (d, J_{cp} = 12.0 Hz), 64.1 (d, J_{cp} = 7.1 Hz), 16.4 (d, J_{cp} = 5.9 Hz).; HRMS (EI): *m*/*z* calcd for $C_{19}H_{22}$ NO_7P 407.1134, found 407.1130.

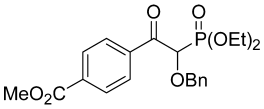


2.13. Diethyl [1-benzyloxy-2-(4-cyano-phenyl)-2-oxo-ethyl]-phosphonate, ***3m:*** yield: 86.1% (1.3 g as a pale-yellow oil); ^1H NMR (500 MHz, $CDCl_3$) δ 8.15(d, 2H, J = 8.3 Hz), 7.74 (d, 2H, J = 8.3 Hz), 7.32−7.23 (m, 5H), 4.98 (d, 1H, J_{cp} = 20.6 Hz), 4.70 (d, 1H, J = 11.8 Hz), 4.61 (d, 1H, J = 11.8 Hz), 4.22−4.12 (m, 4H), 1.30 (t, 3H, J = 7.1 Hz), 1.27 (t, 3H, J = 7.0 Hz).; ^{13}C NMR (75 MHz,

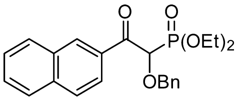


CDCl$_3$) δ 194.5 (d, J_{cp} = 1.6 Hz), 138.4, 135.7, 132.1, 130.1, 128.7, 118.0, 116.7, 81.2 (d, J_{cp} = 150.9 Hz), 74.6 (d, J_{cp} = 12.1 Hz), 64.0 (d, J_{cp} = 6.9 Hz), 16.4 (d, J_{cp} = 5.9 Hz).; HRMS (EI): *m/z* calcd for $C_{20}H_{22}NO_5P$ 387.1236, found 387.1237.

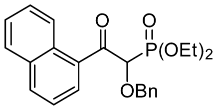
*2.14. Diethyl [1-benzyloxy-2-(4-carbomethoxy-phenyl)-2-oxo-ethyl]phosphonate, **3n**:* yield: 90.7% (2.8 g as a pale-yellow oil); ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.12−8.10 (m, 4H), 7.33−7.27 (m, 5H), 5.09 (d, 1H, J_{cp} = 20.3 Hz), 4.75 (d, 1H, J = 11.8 Hz), 4.60 (d, 1H, J = 11.8 Hz), 4.23−4.16 (m, 4H), 3.97 (s, 1H), 1.28 (t, 3H, J = 7.1 Hz), 1.23 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, CDCl$_3$) δ 194.9, 166.2, 138.8, 135.9, 134.1, 129.5, 129.3, 128.6, 128.6, 128.5, 80.5 (d, J_{cp} = 151.1 Hz), 74.2 (d, J_{cp} = 12.3 Hz), 63.9 (d, J_{cp} = 6.8 Hz), 63.6 (d, J_{cp} = 6.9 Hz), 52.5, 16.3 (d, J_{cp} = 5.4 Hz), 16.2 (d, J_{cp} = 5.3 Hz).; HRMS (EI): *m/z* calcd for $C_{21}H_{25}O_7P$ 420.1338, found 420.1333.



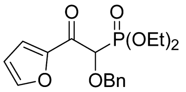
*2.15. Diethyl [1-benzyloxy-2-(naphthalen-2-yl)-2-oxo-ethyl]phosphonate, **3o**:* yield: 94.0% (1.1 g as a pale-yellow oil); ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.66 (s, 1H), 8.08 (d, 1H, J = 8.6 Hz), 7.97 (d, 1H, J = 8.1 Hz), 7.91−7.89 (m, 2H), 7.64 (t, 1H, J = 7.6 Hz), 7.59 (t, 1H, J = 7.6 Hz), 7.33 (s, 5H), 5.26 (d, 1H, J_{cp} = 19.9 Hz), 4.83 (d, 1H, J_{cp} = 11.9 Hz), 4.62 (d, 1H, J_{cp} = 11.9 Hz), 4.22−4.13 (m, 4H), 1.30 (t, 3H, J = 7.1 Hz), 1.20 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, CDCl$_3$) δ 194.7, 136.2, 135.8, 132.9, 132.3, 131.8, 130.0, 128.8, 128.5, 128.4, 128.2, 127.7, 126.7, 124.6, 80.2 (d, J_{cp} = 151.3 Hz), 74.0 (d, J_{cp} = 12.5 Hz), 63.8(d, J_{cp} = 7.0 Hz), 63.5 (d, J_{cp} = 7.1 Hz), 16.3 (d, J_{cp} = 6.1 Hz), 16.2 (d, J_{cp} = 6.1 Hz).; HRMS (EI): *m/z* calcd for $C_{23}H_{25}O_5P$ 412.1440, found 412.1430.



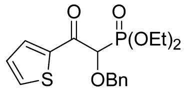
*2.16. Diethyl [1-benzyloxy-2-(naphthalen-1-yl)-2-oxo-ethyl]phosphonate, **3p**:* yield: 81.0% (930 mg as a pale-yellow solid); mp: 76−79 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.39 (d, 1H, J = 8.4 Hz), 8.01 (d, 1H, J = 8.2 Hz), 7.88 (d, 1H, J = 8.0 Hz), 7.76 (d, 1H, J = 7.2 Hz), 7.59−7.55 (m, 2H), 7.48 (t, 1H, J = 7.8 Hz), 7.35 (s, 5H), 5.22 (d, 1H, J_{cp} = 21.2 Hz), 4.87 (d, 1H, J_{cp} = 12.0 Hz), 4.73 (d, 1H, J_{cp} = 12.0 Hz), 4.18−4.15 (m, 2H), 4.01−3.98 (m, 2H), 1.26 (t, 3H, J = 7.0 Hz), 0.99 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, CDCl$_3$) δ 197.7, 136.3, 134.4, 133.8, 132.9, 130.3, 128.6, 128.6, 128.4, 128.4, 128.3, 128.0, 126.5, 125.4, 124.1, 80.9 (d, J_{cp} = 151.9 Hz), 73.8 (d, J_{cp} = 11.7 Hz), 63.8 (d, J_{cp} = 6.6 Hz), 63.2 (d, J_{cp} = 7.2 Hz), 16.3 (d, J_{cp} = 5.7 Hz), 15.9 (d, J_{cp} = 6.2 Hz).; HRMS (EI): *m/z* calcd for $C_{23}H_{25}O_5P$ 412.1440, found 412.1427.



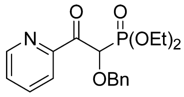
*2.17. Diethyl [1-benzyloxy-2-(furan-2-yl)-2-oxo-ethyl]phosphonate, **3q**:* yield: 76.2% (2.5 g as a light-pink oil); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.66 (s, 1H), 7.51 (d, 1H, J = 3.5 Hz), 7.35−7.29 (m, 5H), 6.58 (d, 1H, J = 2.0 Hz), 4.96 (d, 1H, J_{cp} = 19.2 Hz), 4.81 (d, 1H, J = 11.8 Hz), 4.61 (d, 1H, J = 11.8 Hz), 4.22−4.15 (m, 4H), 1.31 (t, 3H, J = 7.0 Hz), 1.27 (t, 3H, J = 7.0 Hz).; ^{13}C NMR (75 MHz, CDCl$_3$) δ 182.7, 151.1, 147.5, 136.2, 128.6, 128.6, 128.5, 121.0, 112.7, 79.6 (d, J_{cp} = 152.1 Hz), 74.2 (d, J_{cp} = 12.2 Hz), 63.9 (d, J_{cp} = 6.7 Hz), 63.7 (d, J_{cp} = 6.8 Hz), 16.5 (d, J_{cp} = 5.9 Hz) 16.4 (d, J_{cp} = 6.1 Hz).; HRMS (EI): *m/z* calcd for $C_{17}H_{21}O_6P$ 352.1076, found 352.1074.



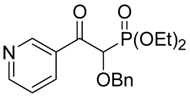
*2.18. Diethyl [1-benzyloxy-2-oxo-2-(thiophen-2-yl)-ethyl]phosphonate, **3r**:* yield: 90.9% (2.5 g as a light-green oil); ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.11 (d, 1H, J = 3.4 Hz), 7.73 (d, 1H, J = 4.4 Hz), 7.35−7.33 (m, 5H), 7.17−7.15 (m, 1H), 4.86 (d, 1H, J_{cp} = 19.2 Hz), 4.83 (d, 1H, J = 11.4 Hz), 4.60 (d, 1H, J = 11.8 Hz), 4.23−4.13 (m, 4H), 1.30 (t, 3H, J = 7.3 Hz), 1.27 (t, 3H, J = 7.3 Hz).; ^{13}C NMR (75 MHz, CDCl$_3$) δ 187.5, 141.4, 136.1, 135.3, 135.3, 128.7, 128.6, 128.5, 128.3, 81.2 (d, J_{cp} = 151.5 Hz), 74.4 (d, J_{cp} = 12.7 Hz), 63.9 (d, J_{cp} = 6.7 Hz), 63.8 (d, J_{cp} = 6.8 Hz), 16.4 (d, J_{cp} = 6.2 Hz).; HRMS (EI): *m/z* calcd for $C_{17}H_{21}O_5PS$ 368.0847, found 368.0842.



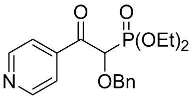
*2.19. Diethyl [1-benzyloxy-2-oxo-2-(pyridin-2-yl)-ethyl]phosphonate, **3s**:* yield: 89.0% (1.3 g as a pale-yellow oil); ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.67 (d, 1H, J = 3.8 Hz), 8.04 (d, 1H, J = 8.1 Hz), 7.87−7.84 (m, 1H), 7.51−7.49 (m, 1H), 7.42−7.40 (m, 2H), 7.35−7.31 (m, 1H), 6.40 (d, 1H, J_{cp} = 19.7 Hz), 4.81 (d, 1H, J = 11.6 Hz), 4.71 (d, 1H, J = 11.9 Hz), 4.25−4.19 (m, 2H), 4.11−4.07 (m, 2H), 1.30 (t, 3H, J = 7.1 Hz), 1.10 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, CDCl$_3$) δ 195.5, 153.0, 148.8, 137.0, 128.5, 128.2, 127.6, 122.5, 76.9 (d, J_{cp} = 149.7 Hz), 74.2 (d, J_{cp} = 11.0 Hz), 63.8 (d, J_{cp} = 6.7 Hz), 63.3 (d, J_{cp} = 6.5 Hz), 16.4 (d, J_{cp} = 6.1 Hz), 16.2 (d, J_{cp} = 6.4 Hz).; HRMS (EI): *m/z* calcd for $C_{18}H_{22}NO_5P$ 363.1236, found 363.1234.



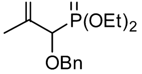
*2.20. Diethyl [1-benzyloxy-2-oxo-2-(pyridin-3-yl)-ethyl]phosphonate, **3t**:* yield: 95.9% (1.1 g as a pale-yellow oil); ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.19 (d, 1H, J = 1.4 Hz), 8.79 (dd, 1H, J = 1.8 Hz, J = 8.0 Hz), 7.41−7.39 (m, 1H), 7.32−7.27 (m, 5H), 4.99 (d, 1H, J_{cp} = 20.4 Hz), 4.74 (d, 1H, J = 11.8 Hz), 4.64 (d, 1H, J = 11.8 Hz), 4.22−4.15 (m, 4H), 1.31 (t, 3H, J = 7.1 Hz), 1.27 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, CDCl$_3$) δ 194.6 (d, J_{cp} = 1.4 Hz), 153.7, 150.7, 137.1, 135.8, 131.0, 128.7, 128.7, 123.3, 81.2 (d, J_{cp} = 150.9 Hz), 74.5 (d, J_{cp} = 12.0 Hz), 64.0 (d, J_{cp} = 6.8 Hz), 63.9 (d, J_{cp} = 6.9 Hz), 16.4 (d, J_{cp} = 5.9 Hz), 16.3 (d, J_{cp} = 6.0 Hz).; HRMS (EI): *m/z* calcd for $C_{18}H_{22}NO_5P$ 363.1236, found 363.1236.



*2.21. Diethyl [1-benzyloxy-2-oxo-2-(pyridin-4-yl)-ethyl]phosphonate, **3u**:* yield: 93.6% (1.2 g as a pale yellow oil); ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.80 (d, 2H, J = 6.0 Hz), 7.81 (dd, 2H, J = 1.5 Hz, J = 4.5 Hz), 7.34−7.26 (m, 5H), 5.00 (d, 1H, J_{cp} = 20.5 Hz), 4.72 (d, 1H, J = 11.8 Hz), 4.63 (d, 1H, J = 11.8 Hz), 4.22−4.14 (m, 4H), 1.31 (t, 3H, J = 7.1 Hz), 1.26 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, CDCl$_3$) δ 195.4 (d, J_{cp} = 1.1 Hz), 150.7, 141.4, 135.7, 128.7, 122.2, 80.8 (d, J_{cp} = 151.1 Hz), 74.5 (d, J_{cp} = 11.8 Hz), 64.0 (d, J_{cp} = 7.1 Hz), 63.9 (d, J_{cp} = 8.2 Hz), 16.4 (d, J_{cp} = 5.8 Hz), 16.3 (d, J_{cp} = 5.9 Hz).; HRMS (EI): *m/z* calcd for $C_{18}H_{22}NO_5P$ 363.1236, found 363.1236.

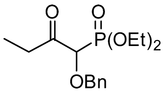


*2.22. Diethyl [1-(benzyloxy)-2-oxopropyl]phosphonate, **3v**:* yield: 78.0% (1.6 g as a coloress oil); ^{1}H NMR (500 MHz, CDCl$_3$) δ

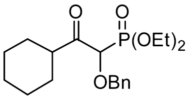


7.40–7.29 (m, 5H), 4.76 (d, 1H, J = 11.8 Hz), 4.67 (d, 1H, J = 11.8 Hz), 4.32 (d, 1H, J_{cp} = 19.4 Hz), 4.24–4.17 (m, 4H), 1.35 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (125 MHz, CDCl$_3$) δ 203.1, 135.8, 128.1, 127.8, 127.8, 81.6 (d, J_{cp} = 150.0 Hz), 73.7 (d, J_{cp} = 10.0 Hz), 63.0 (d, J_{cp} = 6.3 Hz), 27.0, 15.8 (d, J_{cp} = 5.0 Hz).; HRMS (EI): m/z calcd for $C_{14}H_{21}O_5P$ 300.1127, found 300.1103.

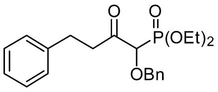
*2.23. Diethyl [1-(benzyloxy)-2-oxobutyl]phosphonate, **3w**:* yield: 54.0% (1.1 g as a coloress oil); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.40–7.33 (m, 5H), 4.74 (d, 1H, J = 11.8 Hz), 4.66 (d, 1H, J = 11.8 Hz), 4.35 (d, 1H, J_{cp} = 19.3 Hz), 4.25–4.18 (m, 4H), 2.79–2.71 (m, 1H), 2.66–2.58 (m, 1H), 1.35 (t, 6H, J = 7.0 Hz), 1.06 (t, 3H, J = 7.2 Hz).; ^{13}C NMR (125 MHz, CDCl$_3$) δ 206.2 (d, J_{cp} = 3.8 Hz), 136.0, 128.3 (d, J_{cp} = 1.3 Hz), 128.1, 128.1 (d, J_{cp} = 1.3 Hz), 81.4 (d, J_{cp} = 150.0 Hz), 63.3 (d, J_{cp} = 3.8 Hz), 63.3 (d, J_{cp} = 1.3 Hz), 33.1 (d, J_{cp} = 16.3 Hz), 33.0 (d, J_{cp} = 1.3 Hz), 16.1 (d, J_{cp} = 6.3 Hz), 6.98.; HRMS (EI): m/z calcd for $C_{15}H_{23}O_5P$ 314.1283, found 314.1277.



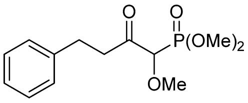
*2.24. Diethyl [1-(benzyloxy)-2-cyclohexyl-2-oxo-ethyl]-phosphonate, **3x**:* yield: 94.1% (1.1 g as a coloress oil); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.38–7.34 (m, 5H), 4.76 (d, 1H, J = 12.0 Hz), 4.59 (d, 1H, J = 12.0 Hz), 4.51 (d, 1H, J_{cp} = 20.1 Hz), 4.24–4.15 (m, 4H), 2.89–2.85 (m, 1H), 1.80–1.73 (m, 4H), 1.69–1.65 (m, 1H), 1.50–1.45 (m, 1H), 1.34 (q, 6H, J = 7.1 Hz), 1.30–1.19 (m, 4H).; ^{13}C NMR (125 MHz, CDCl$_3$) δ 208.1 (d, J_{cp} = 1.7 Hz), 136.4, 128.5, 128.3, 80.3 (d, J_{cp} = 149.0 Hz), 73.8 (d, J_{cp} = 10.2 Hz), 63.5 (d, J_{cp} = 6.7 Hz), 63.4 (d, J_{cp} =6.9 Hz), 47.7, 29.2, 27.5, 25.8, 25.7, 25.1, 16.4 (d, J_{cp} = 4.3 Hz).; HRMS (EI): m/z calcd for $C_{19}H_{29}O_5P$ 368.1753, found 368.1754.



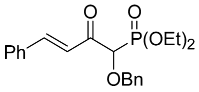
*2.25. Diethyl (1-benzyloxy-2-oxo-4-phenyl-butyl)phosphonate, **3y**:* yield: 92.3% (2.5 g as a pale yellow oil); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.36–7.28 (m, 7H), 7.22–7.19 (m, 3H), 4.67 (d, 1H, J = 11.9 Hz), 4.57 (d, 1H, J = 11.9 Hz), 4.30 (d, 1H, J_{cp} = 19.4 Hz), 4.22–4.11 (m, 4H), 3.09–3.03 (m, 1H), 2.97–2.90 (m, 3H), 1.32 (t, 6H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, CDCl$_3$) δ 205.0, 140.8, 136.2, 128.6, 128.5, 128.4, 128.4, 126.1, 81.9 (d, J_{cp} = 149.0 Hz), 74.2 (d, J_{cp} = 10.0 Hz), 63.6 (d, J_{cp} = 6.7 Hz), 63.5 (d, J_{cp} = 6.7 Hz), 41.3, 29.2, 16.4(d, J_{cp} = 5.8 Hz).; HRMS (EI): m/z calcd for $C_{21}H_{27}O_5P$ 390.1596, found 390.1601.



*2.-26. Dimethyl (1-methoxy-2-oxo-4-phenyl-butyl)phosphonate, **3z**:* yield: 54.0% (1.2 g as a pale yellow oil); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.31–7.29 (m, 2H), 7.24–7.19 (m, 3H), 4.15 (d, 1H, J = 19.4 Hz), 3.82 (d, 3H, J = 11.1 Hz), 3.80 (d, 3H, J_{cp} = 11.1 Hz), 3.46 (s, 3H), 3.08–2.95 (m, 4H).; ^{13}C NMR (125 MHz, CDCl$_3$) δ 205.0, 140.7, 128.5, 128.5, 126.2, 85.0 (d, J_{cp} = 149.5 Hz), 60.7 (d, J_{cp} = 10.6 Hz), 54.0 (d, J_{cp} = 6.6 Hz), 63.8 (d, J_{cp}= 7.1 Hz), 41.1, 29.2.; HRMS (EI): m/z calcd for $C_{13}H_{19}O_5P$ 286.0970, found 286.0963.

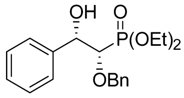


*2.27. Diethyl (1-benzyloxy-2-oxo-4-phenyl-but-3-enyl)-phosphonate, **3ab**:* Yield: 75.3% (1.1 g as a pale yellow oil); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.78 (d, 1H, J = 16.0 Hz), 7.62–7.61 (m, 2H), 7.44–7.33 (m, 8H), 7.26 (d, 1H, J = 16.0 Hz), 4.82 (d, 1H, J = 11.9 Hz), 4.66 (d, 1H, J = 11.8 Hz), 4.52 (d, 1H, J_{cp} = 19.4 Hz), 4.25–4.18 (m, 4H), 1.35 (m, 6H).; ^{13}C NMR (75 MHz, CDCl$_3$) δ 194.1, 144.3, 136.2, 134.4, 130.9, 128.9, 128.8, 128.6, 128.5, 128.4, 121.6, 81.8 (d, J_{cp} = 150.0 Hz), 74.2 (d, J_{cp} = 11.9 Hz), 63.6 (d, J_{cp} = 6.6 Hz), 63.5 (d, J_{cp} = 6.6 Hz), 16.4 (d, J_{cp} = 5.9 Hz).; HRMS (EI): m/z calcd for $C_{21}H_{25}O_5P$ 388.1440, found 388.1419.

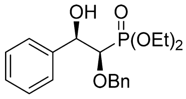


*3. General Procedure for the ATH-DKR of α-Alkoxy β-Ketophosphonates (**3**) to the α-Alkoxy β-Hydroxy Phosphonates (**4**).* The solution of α-alkoxy-β-ketophosphonate (**3**, 1 mmol, 1 equiv) and (*R*,*R*)-**5e** catalyst (3.1 mg, 0.005 mmol, 0.005 equiv) in Et$_3$N (2.85 mL, 20 equiv) was stirred for 10 min at room temperature. The formic acid (0.15 mL, 4 equiv) was slowly added by syringe and the resulting mixture was then purged with nitrogen. The mixture was allowed to react at 35 °C. After complete consumption of β-ketophosphonate, the reaction mixture was diluted with EtOAc (50 mL) and washed with water (10 mL), saturated aqueous NaHCO$_3$ and brine. The solution was dried over anhydrous MgSO$_4$, and concentrated under reduced pressure to afford the product. The product was subjected to short path column of SiO$_2$ to remove colored impurity.

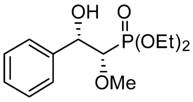
*3.1. Diethyl (1S,2S)-(1-benzyloxy-2-hydroxy-2-phenyl-ethyl)-phosphonate, (1S,2S)-**4a**:* yield: 99.5% (362 mg as coloress oil); dr = >99:1; >99% ee: Chiralpak AD-H, 10% isopropanol/*n*-hexane, 1.5 mL/min, 254 nm t_R (minor) = 7.9 min, t_R (major) = 10.9 min.); $[\alpha]^{24}_D$ = +67.1 (*c* 1.0, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.43 (d, 2H, J = 7.3 Hz), 7.37–7.28 (m, 6H), 7.18–7.15 (m, 2H), 5.11 (dd, 1H, J = 4.4 Hz, J = 10.4 Hz), 4.70 (d, 1H, J = 11.1 Hz), 4.37 (d, 1H, J = 11.1 Hz), 4.21–4.02 (m, 4H), 3.91 (dd, 1H, J = 7.9 Hz, J = 3.8 Hz), 1.33 (t, 3H, J = 7.1 Hz), 1.26 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (125 MHz, CDCl$_3$) δ 140.4, 140.3, 136.7, 128.4, 128.4, 128.2, 128.1, 127.8, 126.7, 79.1 (d, J_{cp} = 160.2 Hz), 75.1 (d, J_{cp} = 12.5 Hz), 72.4 (d, J_{cp} = 4.0 Hz), 62.9 (d, J_{cp} = 7.1 Hz), 62.4 (d, J_{cp} = 6.8 Hz), 16.5 (d, J_{cp} = 6.0 Hz), 16.3 (d, J_{cp} = 5.6 Hz).; HRMS (ESI-TOF): m/z $[M + Na]^+$ calcd for $C_{19}H_{25}O_5NaP$ 387.1337, found 387.1336.



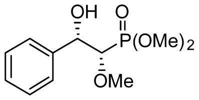
*3.2. Diethyl (1R,2R)-(1-benzyloxy-2-hydroxy-2-phenyl-ethyl)-phosphonate, (1R,2R)-**4a**:* yield: 98.4% (359 mg as coloress oil); dr = >99:1; >99% ee: Chiralpak AD-H, 10% isopropanol/*n*-hexane, 1.5 mL/min, 254 nm t_R (major) = 7.9 min, t_R (minor) = 10.9 min.); $[\alpha]^{23}_D$ = −66.6 (*c* 1.0, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.43 (d, 2H, J = 7.4 Hz), 7.38–7.29 (m, 6H), 7.17 (bs, 2H), 5.11 (bs, 1H), 4.70 (d, 1H, J = 11.1 Hz), 4.37 (d, 1H, J = 11.1 Hz), 4.12–4.04 (m, 4H), 3.92–3.90 (m, 1H), 1.34 (t, 3H, J = 7.0 Hz), 1.27 (t, 3H, J = 7.2 Hz).



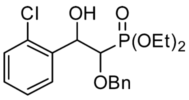
*3.3. Diethyl (1S,2S)-(1-methoxy-2-hydroxy-2-phenyl-ethyl)-phosphonate, (1S,2S)-**4b**:* yield: 98.2% (383 mg as coloress oil); dr = >99:1; 99.4% ee: Chiralpak IC, 30% isopropanol/*n*-hexane, 1.0 mL/min, 215 nm t_R (major) = 15.9 min, t_R (minor) = 17.9 min.); $[\alpha]^{24}_D$ = +40.5 (*c* 0.4, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.47 (d, 2H, J = 7.6 Hz), 7.38 (t, 2H, J = 7.4 Hz), 7.33–7.32 (m, 1H), 5.07 (d, 1H, J = 4.3 Hz), 4.18–4.07 (m, 4H), 3.65 (dd, 1H, J = 3.8 Hz, J = 8.4 Hz), 3.52 (d, 1H, J = 4.1 Hz), 3.41 (s, 3H), 1.34 (t, 3H, J = 7.1 Hz), 1.28 (t, 3H, J = 7.0 Hz).; ^{13}C NMR (125 MHz, CDCl$_3$) δ 140.2 (d, J_{cp} = 10.0 Hz), 128.2, 127.8, 126.7, 81.9 (d, J_{cp} = 160.9 Hz), 72.4 (d, J_{cp} = 5.1 Hz), 63.0 (d, J_{cp} = 6.6 Hz), 62.3 (d, J_{cp} = 7.3 Hz), 61.7 (d, J_{cp} = 3.6 Hz),



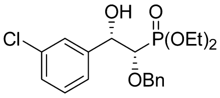
16.4 (d, J_{cp} = 5.3 Hz), 16.4 (d, J_{cp} = 5.4 Hz).; HRMS (EI): m/z calcd for $C_{13}H_{21}O_5P$ 288.1127, found 288.1119.



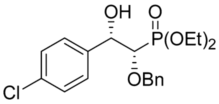
*3.4. Dimethyl (1S,2S)-(1-methoxy-2-hydroxy-2-phenyl-methyl)phosphonate, (1S,2S)-**4c**:* yield: 98.0% (255 mg as coloress oil); dr = >99:1; 99.5% ee: Chiralpak IC, 30% isopropanol/n-hexane, 1.0 mL/min, 215 nm t_R (major) = 16.9 min, t_R (minor) = 20.5 min; $[\alpha]^{24}_{D}$ = +42.8 (c 0.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, 2H, J = 7.6 Hz), 7.39 (t, 2H, J = 7.4 Hz), 7.34−7.32 (m, 1H), 5.09 (bs, 1H), 3.76 (d, 6H, J = 10.6 Hz), 3.69 (dd, 1H, J = 3.3 Hz, J = 8.5 Hz), 3.42 (bs, 1H), 3.39 (s, 3H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.1 (d, J_{cp} = 10.4 Hz), 128.3, 127.9, 126.6, 81.9 (d, J_{cp} = 160.7 Hz), 72.3 (d, J_{cp} = 4.9 Hz), 61.6 (d, J_{cp} = 6.5 Hz), 53.5 (d, J_{cp} = 6.5 Hz), 52.6 (d, J_{cp} = 7.3 Hz).; HRMS (EI): m/z calcd for $C_{11}H_{17}O_5P$ 260.0814, found 260.0834.



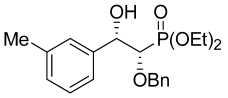
*3.5. Diethyl [1-benzyloxy-2-(2-chloro-phenyl)-2-hydroxy-ethyl]phosphonate, **4d**:* yield: 97.0% (387 mg as white solid); dr = 60:40; diastereomers are inseparable by silica gel chromatography. **major isomer (60%)**; 82% ee: Chiralpak AD-H, 30% isopropanol/n-hexane, 0.5 mL/min, 254 nm, t_R (minor) = 10.5 min, t_R (major) = 13.2 min; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (dd, 1H, J = 1.6 Hz, J = 7.7 Hz), 7.34−7.19 (m, 8H), 5,48 (br s, 1H), 4.63 (d, 1H, J = 11.5 Hz), 4.50 (d, 1H, J = 11.5 Hz), 4.44 (d, 1H, J = 4.2 Hz), 4.32−4.21 (m, 2H), 4.05−3.94 (m, 3H), 1.35 (t, 3H, J = 7.0 Hz), 1.16 (d, 3H, J = 7.0 Hz). **minor isomer (40%)**; 47% ee: Chiralpak AD-H, 30% isopropanol/n-hexane, 0.5 mL/min, 254 nm, t_R (minor) = 9.6 min, t_R (major) = 14.2 min; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, 1H, J = 7.7 Hz), 7.34−7.19 (m, 6H), 6.98 (d, 2H, J = 6.6 Hz), 5,51 (br s, 1H), 4.53 (d, 1H, J = 11.1 Hz), 4.32−4.21 (m, 4H), 4.17 (d, 1H, J = 11.1 Hz), 4.12 (dd, 1H, J = 1.8 Hz, J = 9.4 Hz), 3.84 (br s, 1H), 1.43−1.33 (m, 6H).; HRMS (EI): m/z calcd for $C_{19}H_{24}ClO_5P$ 398.1050, found 398.1036.



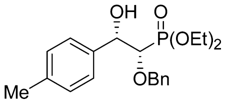
*3.6. Diethyl (1S,2S)-[1-benzyloxy-2-(3-chloro-phenyl)-2-hydroxy-ethyl]phosphonate, (1S,2S)-**4e**:* yield: 96.4% (384 mg as a pale-yellow oil); dr = 99:1; >99% ee: Chiralpak AD-H, 10%isopropanol/n-hexane, 1.5 mL/min, 254 nm, t_R (minor) = 6.9 min, t_R (major) = 8.5 min; $[\alpha]^{24}_{D}$ = +61.3 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.29−7.26 (m, 6H), 5.06 (br, 1H), 4.71 (d, 1H, J = 11.1 Hz), 4.36 (d, 1H, J = 11.1 Hz), 4.21−4.10 (m, 4H), 3.84 (dd, 1H, J = 3.4 Hz, J = 7.7 Hz), 3.74 (br, 1H), 1.35 (t, 3H, J = 7.1 Hz), 1.29 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6 (d, J_{cp} = 10.9 Hz), 136.4, 134.2, 129.5, 128.6, 128.5, 128.3, 127.9, 127.1, 124.9, 78.5 (d, J_{cp} = 166.9 Hz), 75.1 (d, J_{cp} = 2.8 Hz), 72.0 (d, J_{cp} = 3.8 Hz), 63.2 (d, J_{cp} = 6.8 Hz), 62.6 (d, J_{cp} = 7.1 Hz), 16.6 (d, J_{cp} = 5.7 Hz), 16.5 (d, J_{cp} = 5.6 Hz).; HRMS (EI): m/z calcd for $C_{19}H_{24}ClO_5P$ 398.1050, found 398.1043.



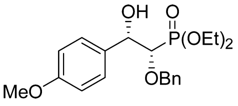
*3.7. Diethyl (1S,2S)-[1-benzyloxy-2-(4-chloro-phenyl)-2-hydroxy-ethyl]phosphonate, (1S,2S)-**4f**:* yield: 99.5% (397 mg as a pale-yellow oil); dr = 99:1; 99.6% ee: Chiralpak AD-H, 10% isopropanol/n-hexane, 1.5 mL/min, 254 nm, t_R (minor) = 8.4 min, t_R (major) = 10.6 min; $[\alpha]^{26}_{D}$ = +78.6 (c 1.0, $CHCl_3$).; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.28 (m, 7H), 7.14−7.13 (m, 2H), 5.07−5.05 (m, 1H), 4.72 (d, 1H, J = 11.2 Hz), 4.39 (d, 1H, J = 11.3 Hz), 4.19−4.07 (m, 4H), 3.84 (dd, 1H, J = 3.6 Hz, J = 7.5 Hz), 3.66 (t, 1H, J = 4.4 Hz), 1.35 (t, 3H, J = 7.0 Hz), 1.28 (t, 3H, J = 7.0 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9 (d, J_{cp} = 10.5 Hz), 136.5, 133.6, 128.6, 128.5, 128.4, 128.3, 128.2, 78.6 (d, J_{cp} = 158.5 Hz), 75.0 (d, J_{cp} = 2.7 Hz), 72.0 (d, J_{cp} = 4.0 Hz), 63.2 (d, J_{cp} = 7.0 Hz), 62.6 (d, J_{cp} = 7.1 Hz), 16.6 (d, J_{cp} = 5.6 Hz), 16.5 (d, J_{cp} = 5.6 Hz).; HRMS (EI): m/z calcd for $C_{19}H_{24}ClO_5P$ 398.1050, found 398.1053.



*3.8. Diethyl (1S,2S)-[1-benzyloxy-2-hydroxy-2-(m-tolyl)-ethyl]phosphonate, (1S,2S)-**4h**:* yield: 98.2% (372 mg as a pale-yellow oil); dr =99:1; >99% ee: Chiralpak AD-H, 10% isopropanol/n-hexane, 1.5 mL/min, 254 nm, t_R (minor) = 6.9 min, t_R (major) = 8.5 min; $[\alpha]^{25}_{D}$ = +67.4 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.12 (m, 9H), 5.09−5.07 (m, 1H), 4.70 (d, 1H, J = 11.1 Hz), 4.35 (d, 1H, J = 11.1 Hz), 4.21−4.07 (m, 4H), 3.91−3.89 (m, 1H), 3.48 (d, 1H, J = 4.7 Hz), 2.36 (s, 1H), 1.35 (t, 3H, J = 7.1 Hz), 1.29 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 140.3, 137.9, 136.9, 128.6, 128.4, 128.2, 128.2, 127.5, 123.8, 79.2 (d, J_{cp} = 160.2 Hz), 75.3 (d, J_{cp} = 3.2 Hz), 72.5 (d, J_{cp} = 4.0 Hz), 63.1 (d, J_{cp} = 6.8 Hz), 62.5 (d, J_{cp} = 7.1 Hz), 21.6, 16.7 (d, J_{cp} = 2.4 Hz), 16.5 (d, J_{cp} = 3.2 Hz).; HRMS (EI): m/z calcd for $C_{20}H_{27}O_5P$ 378.1596, found 378.1602.

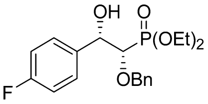


*3.9. Diethyl (1S,2S)-[1-benzyloxy-2-hydroxy-2-(p-tolyl)-ethyl]phosphonate, (1S,2S)-**4i**:* yield: 98.6% (373 mg as a pale-yellow oil); dr = 99:1; 99.5% ee: Chiralpak AD-H, 10% isopropanol/n-hexane, 1.5 mL/min, 254 nm, t_R (minor) = 8.9 min, t_R (major) = 12.3 min; $[\alpha]^{23}_{D}$ = +68.0 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.29 (m, 5H), 7.18−7.15 (m, 4H), 5.08 (br, 1H), 4.70 (d, 1H, J = 11.1 Hz), 4.38 (d, 1H, J = 11.1 Hz), 4.18−4.04 (m, 4H), 3.90−3.88 (m, 1H), 3.49 (br, 1H), 2.37 (s, 1H), 1.33 (t, 3H, J = 7.0 Hz), 1.26 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 137.3, 136.9, 128.9, 128.5, 128.4, 128.1, 126.7, 79.3 (d, J_{cp} = 159.9 Hz), 75.2 (d, J_{cp} = 3.2 Hz), 72.4 (d, J_{cp} = 4.3 Hz), 63.0 (d, J_{cp} = 6.9 Hz), 62.4 (d, J_{cp} = 7.1 Hz), 21.2, 16.6 (d, J_{cp} = 5.7 Hz), 16.5 (d, J_{cp} = 5.7 Hz).; HRMS (EI): m/z calcd for $C_{20}H_{27}O_5P$ 378.1596, found 378.1592.



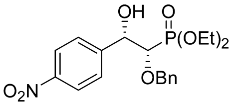
*3.10. Diethyl (1S,2S)-[1-benzyloxy-2-hydroxy-2-(4-methoxy-phenyl)-ethyl]phosphonate, (1S,2S)-**4j**:* yield: 94.6% (373 mg as a pale-yellow oil); dr = 99:1; 98.7% ee: Chiralpak AD-H, 10% isopropanol/n-hexane, 1.5 mL/min, 254 nm, t_R (minor) = 14.5 min, t_R (major) = 17.2 min; $[\alpha]^{25}_{D}$ = +73.6 (c 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, 2H, J = 8.6 Hz), 7.30−7.29 (m, 3H), 7.21−7.20 (m, 2H), 6.88 (d, 2H, J = 8.6 Hz), 5.06−5.03 (m, 1H), 4.72 (d, 1H, J = 11.1 Hz), 4.40 (d, 1H, J = 11.1 Hz), 4.17−4.03 (m, 4H), 3.87−3.84 (m, 1H), 3.83 (s, 1H), 3.51−3.50 (m, 1H), 1.32 (t, 3H, J = 7.1 Hz), 1.26 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 136.9, 132.4 (d, J_{cp} = 9.7 Hz), 128.5, 128.4, 128.1, 128.0, 113.7, 79.3 (d, J_{cp} = 159.5 Hz), 75.2 (d, J_{cp} = 3.1 Hz), 72.2 (d, J_{cp} = 4.6 Hz), 63.0 (d, J_{cp} = 6.8 Hz), 62.4 (d, J_{cp} = 7.0 Hz), 55.4, 16.6 (d, J_{cp} = 5.7 Hz), 16.5 (d, J_{cp} = 5.7 Hz).; HRMS (EI): m/z calcd for $C_{20}H_{27}O_6P$ 394.1545, found 394.1547.

*3.11. Diethyl (1S,2S)-[1-benzyloxy-2-(4-fluoro-phenyl)-2-hydroxy-ethyl]phosphonate, (1S,2S)-**4k**:* yield: 94.1% (360 mg as a pale-yellow oil); dr = 99:1; 99.5% ee: Chiralpak AD-H, 10% isopropanol/n-hexane,

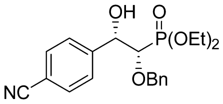


1.5 mL/min, 254 nm, t_{R} (minor) = 6.8 min, t_{R} (major) = 9.8 min; $[\alpha]^{26}_{\mathrm{D}}$= +86.5 ($c$ 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.37 (d, 2H), 7.31–7.29 (m, 3H), 7.18–7.17 (m, 2H), 7.03 (t, 2H, J = 8.7 Hz), 5.09–5.06 (m, 1H), 4.75 (d, 1H, J = 11.2 Hz), 4.40 (d, 1H, J = 11.2 Hz), 4.21–4.05 (m, 4H), 3.86–3.83 (m, 1H), 3.60 (d, 1H, J = 4.4 Hz), 1.35 (t, 3H, J = 7.1 Hz), 1.28 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.5 (d, J_{cf} = 244.1 Hz), 136.7, 136.0, 128.5 (d, J_{cf} = 8.0 Hz), 128.5, 128.5, 128.3, 115.1 (d, J_{cf} = 21.3 Hz), 78.9 (d, J_{cp} = 159.8 Hz), 75.1 (d, J_{cp} = 2.7 Hz), 72.1 (d, J_{cp} = 4.4 Hz), 63.1 (d, J_{cp} = 7.0 Hz), 62.6 (d, J_{cp} = 7.3 Hz), 16.6 (d, J_{cp} = 5.6 Hz), 16.6 (d, J_{cp} = 5.6 Hz).; HRMS (EI): m/z calcd for $C_{19}H_{24}FO_5P$ 382.1345, found 382.1347.

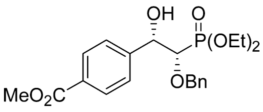
*3.12. Diethyl (1S,2S)-[1-benzyloxy-2-hydroxy-2-(4-nitro-phenyl)-ethyl]phosphonate, (1S,2S)-**4l**:* yield: 97.8% (400 mg as a pale-yellow oil); dr =98:2; 98.0% ee: Chiralpak AD-H, 20% isopropanol/n-hexane, 1.5 mL/min, 254 nm, t_{R} (minor) = 6.8 min, t_{R} (major) = 8.8 min; $[\alpha]^{25}_{\mathrm{D}}$ = +71.6 (c 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.13(d, 2H, J = 8.5 Hz), 7.52 (d, 2H, J = 8.5 Hz), 7.29–7.22 (m, 3H), 7.06 (d, 2H, J = 7.0 Hz), 5.18–5.16 (m, 1H), 4.72 (d, 1H, J = 11.0 Hz), 4.36 (d, 1H, J = 11.0 Hz), 4.24–4.14 (m, 4H), 3.92 (d, 1H, J = 4.5 Hz), 3.89 (dd, 1H, J = 3.0 Hz, J = 7.5 Hz), 1.39 (t, 3H, J = 7.0 Hz), 1.31 (t, 3H, J = 7.0 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 147.4, 135.9, 128.6, 128.4, 128.3, 127.4, 123.2, 77.7 (d, J_{cp} = 159.4 Hz), 74.7 (d, J_{cp} = 2.3 Hz), 71.9 (d, J_{cp} = 3.4 Hz), 63.4 (d, J_{cp} = 6.9 Hz), 62.7 (d, J_{cp} = 7.1 Hz), 16.5 (d, J_{cp} = 5.5 Hz), 16.5 (d, J_{cp} = 5.5 Hz).; HRMS (ESI): m/z calcd for $C_{19}H_{24}NO_7NaP$ 432.1188, found 432.1183.



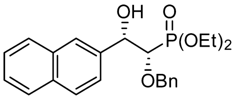
*3.13. Diethyl (1S,2S)-[1-benzyloxy-2-(4-cyano-phenyl)-2-hydroxy-ethyl]phosphonate, (1S,2S)-**4m**:* yield: 99.8% (389 mg as a pale-yellow oil); dr = 99:1; 99.3% ee: Chiralpak AD-H, 0.8% isopropanol/n-hexane, 1.6 mL/min, 254 nm, t_{R} (minor) = 14.7 min, t_{R} (major) = 17.7 min; $[\alpha]^{27}_{\mathrm{D}}$ = +63.3 (c 0.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, 2H, J = 7.6 Hz), 7.48 (d, 2H, J = 8.1 Hz), 7.31–7.26 (m, 4H), 7.08 (d, 2H, J = 6.9 Hz), 5.13–5.10 (m, 1H), 4.72 (d, 1H, J = 11.3 Hz), 4.37 (d, 1H, J = 11.4 Hz), 4.24–4.10 (m, 4H), 3.87 (dd, 1H, J = 7.4 Hz, J = 3.2 Hz), 3.81 (d, 1H, J = 4.8 Hz), 1.38 (t, 3H, J = 7.1 Hz), 1.30 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0, 136.1, 132.0, 128.6, 128.6, 128.4, 127.5, 119.0, 111.5, 77.9 (d, J_{cp} = 167.9 Hz), 74.9, 72.1 (d, J_{cp} = 3.4 Hz), 63.4 (d, J_{cp} = 7.0 Hz), 62.8 (d, J_{cp} = 7.4 Hz), 16.6 (d, J_{cp} = 3.1 Hz).; HRMS (EI): m/z calcd for $C_{20}H_{24}NO_5P$ 389.1392, found 389.1376.



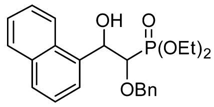
*3.14. Diethyl (1S,2S)-[1-benzyloxy-2-(4-carbomethoxy-phenyl)-2-hydroxy-ethyl]phosphonate, (1S,2S)-**4n**:* yield: 98.6% (416 mg as a pale-yellow oil); dr = 99:1; >99% ee: Chiralpak IB, 10% isopropanol/n-hexane, 1.5 mL/min, 254 nm, t_{R} (major) = 13.5 min, t_{R} (minor) = 18.3 min; $[\alpha]^{21}_{\mathrm{D}}$ = +72.5 (c 0.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, 2H, J = 8.4 Hz), 7.48 (d, 2H, J = 8.3 Hz), 7.29–7.24 (m, 3H), 7.10 (dd, 2H, J = 1.4 Hz, J = 7.4 Hz), 5.16–5.14 (m, 1H), 4.67 (d, 1H, J = 11.2 Hz), 4.33 (d, 1H, J = 11.2 Hz), 4.21–4.07 (m, 4H), 3.95 (s, 3H), 3.90 (dd, 1H, J = 3.4 Hz, J = 8.0 Hz), 3.74 (d, 1H, J = 4.6 Hz), 1.36 (t, 3H, J = 7.1 Hz), 1.28 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 145.6 (d, J_{cp} = 11.0 Hz), 136.3, 129.5, 129.4, 128.4, 128.2, 126.6, 78.4 (d, J_{cp} = 160.6 Hz), 75.0 (d, J_{cp} = 3.0 Hz), 72.2 (d, J_{cp} = 3.7 Hz), 63.2 (d, J_{cp} = 6.8 Hz), 62.6 (d, J_{cp} = 7.1 Hz), 52.1, 16.5 (d, J_{cp} = 5.6 Hz), 16.5 (d, J_{cp} = 5.6 Hz).; HRMS (EI): m/z calcd for $C_{21}H_{27}O_7P$ 422.1494, found 422.1478.



*3.15. Diethyl (1S,2S)-[1-benzyloxy-2-(naphthalen-2-yl)-2-hydroxy-ethyl]phosphonate, (1S,2S)-**4o**:* yield: 99.5% (412 mg as a pale-yellow solid); mp: 68–72 °C; dr = 99:1; >99% ee: Chiralpak AD-H, 10% isopropanol/n-hexane, 1.0 mL/min, 254 nm, t_{R} (minor) = 19.0 min, t_{R} (major) = 23.4 min; $[\alpha]^{21}_{\mathrm{D}}$ = +23.9 (c 0.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.86–7.80 (m, 3H), 7.51–7.48 (m, 3H), 7.23–7.20 (m, 1H), 7.16 (t, 2H, J = 7.3 Hz), 7.06 (d, 2H, J = 7.4 Hz), 5.28 (d, 1H, J = 3.0 Hz), 4.67 (d, 1H, J = 11.1 Hz), 4.33 (d, 1H, J = 11.1 Hz), 4.20–4.09 (m, 4H), 4.00 (dd, 1H, J = 6.0 Hz, J = 1.8 Hz), 3.70 (br, 1H), 1.34 (t, 3H, J = 7.1 Hz), 1.24 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.8 (d, J_{cp} = 11.2 Hz), 136.5, 133.2, 133.1, 128.5 128.2, 128.1, 128.0, 127.8, 127.6, 126.1, 125.9, 125.7, 124.5, 78.8 (d, J_{cp} = 160.4 Hz), 75.1 (d, J_{cp} = 3.0 Hz), 72.5 (d, J_{cp} = 4.0 Hz), 63.1 (d, J_{cp} = 6.6 Hz), 62.5 (d, J_{cp} = 7.1 Hz), 16.5 (d, J_{cp} = 5.9 Hz), 16.4 (d, J_{cp} = 6.0 Hz).; HRMS (EI): m/z calcd for $C_{23}H_{27}O_5P$ 414.1596, found 414.1591.

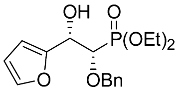


*3.16. Diethyl [1-benzyloxy-2-hydroxy-2-(naphthalen-1-yl)-ethyl)-phosphonate, **4p**:* dr = 57:43; diastereomers are inseparable by silica gel chromatography.

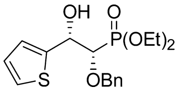


major isomer (57%); 53% ee: Chiralpak IC, 20% isopropanol/n-hexane, 1.5 mL/min, 254 nm, t_{R} (minor) = 18.0 min, t_{R} (major) = 20.0 min. **minor isomer (43%)**; 47% ee: Chiralpak IC, 20% isopropanol/n-hexane, 1.5 mL/min, 254 nm, t_{R} (minor) = 11.8 min, t_{R} (major) = 14.9 min. HRMS (EI): m/z calcd for $C_{23}H_{27}O_5P$ 414.1596, found 414.1583.

*3.17. Diethyl (1S,2S)-[1-benzyloxy-2-(furan-2-yl)-2-hydroxy-ethyl]phosphonate, (1S,2S)-**4q**:* yield: 98.4% (349 mg as a pale-yellow oil); dr = 99:1; >99% ee: Chiralpak AD-H, 20% isopropanol/n-hexane, 1.0 mL/min, 254 nm, t_{R} (minor) = 6.9 min, t_{R} (major) = 8.1 min; $[\alpha]^{21}_{\mathrm{D}}$ = +48.5 (c 0.4 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 6H), 6.42–6.39 (m, 2H), 5.12–5.10 (m, 1H), 4.77 (d, 1H, J = 11.1 Hz), 4.52 (d, 1H, J = 11.1 Hz), 4.22–4.13 (m, 5H), 3.35 (d, 1H, J = 5.9 Hz), 1.35 (t, 3H, J = 6.6 Hz), 1.31 (t, 3H, J = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0 (d, J_{cp} = 11.0 Hz), 153.0, 142.1, 137.0, 128.6, 128.3, 110.7, 108.0, 76.8 (d, J_{cp} = 162.8 Hz), 75.1 (d, J_{cp} = 3.5 Hz), 67.5 (d, J_{cp} = 4.6 Hz), 63.1 (d, J_{cp} = 7.1 Hz), 62.7 (d, J_{cp} = 6.9 Hz), 16.6 (d, J_{cp} = 4.1 Hz).; HRMS (EI): m/z calcd for $C_{17}H_{23}O_6P$ 354.1232, found 354.1229.



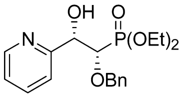
*3.18. Diethyl (1S,2S)-[1-benzyloxy-2-hydroxy-2-(thiophen-2-yl)-ethyl]-phosphonate, (1S,2S)-**4r**:* yield: 97.1% (360 mg as a pale-yellow oil);



dr = 99:1; >99% ee: Chiralpak AD-H, 10% isopropanol/n-hexane, 1.5 mL/min, 254 nm, t_{R} (minor) = 8.0 min, t_{R} (major) = 12.2 min;

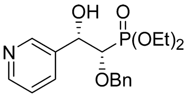
$[\alpha]^{25}_{D}$ = +47.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.29 (m, 6H), 7.07 (d, 2H, *J* = 3.4 Hz), 7.00–6.99 (m, 1H), 5.39–5.35 (m, 1H), 4.83 (d, 1H, *J* = 11.0 Hz), 4.56 (d, 1H, *J* = 11.0 Hz), 4.21–4.07 (m, 3H), 4.05–3.96 (m, 1H), 3.69 (d, 1H, *J* = 6.0 Hz), 1.35 (t, 3H, *J* = 7.1 Hz), 1.28 (t, 3H, *J* = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1 (d, J_{cp} = 11.7 Hz), 136.9, 128.5, 128.5, 128.3, 126.6, 125.3, 124.9, 79.1 (d, J_{cp} = 159.9 Hz), 75.2 (d, J_{cp} = 3.0 Hz), 69.4 (d, J_{cp} = 4.3 Hz), 63.1 (d, J_{cp} = 6.8 Hz), 62.6 (d, J_{cp} = 7.0 Hz), 16.6 (d, J_{cp} = 5.7 Hz), 16.6 (d, J_{cp} = 5.7 Hz).; HRMS (EI): *m/z* calcd for $C_{17}H_{23}O_5PS$ 370.1004, found 370.1003.

*3-19. Diethyl [1-benzyloxy-2-hydroxy-2-(pyridin-2-yl)-ethyl]-phosphonate, **4s**:* With (*R,R*)-**5e** catalyst and HCO_2H/Et_3N (0.2:1): 31% conversion after 3.5 h; dr = 92:8; 81.7% ee; Chiralpak IC, Hx/EtOH/DEA= 90:10:0.1, 1.5 mL/min, 215 nm, t_R (minor) = 22.8 min, t_R (major) = 26.0 min.



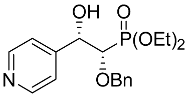
With (*R,R*)-**5a** catalyst and HCO_2H/Et_3N (1:1): yield: 98.0% (358 mg as a white solid); mp 59–65 °C; dr = 96:4; 44% ee; Chiralpak IC, Hx/EtOH/DEA = 90:10:0.1, 1.5 mL/min, 254 nm, t_R (minor) = 20.1 min, t_R (major) = 22.7 min; $[\alpha]^{16}_{D}$ = +87.0 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, 1H, *J* = 4.6 Hz), 7.68 (td, 1H, *J* = 7.7 Hz, *J* = 1.7 Hz), 7.52 (d, 1H, *J* = 7.9 Hz), 7.23–7.18 (m, 4H), 6.97 (d, 2H, *J* = 6.6 Hz), 5.20–5.17 (m, 1H), 4.60 (d, 1H, *J* = 11.3 Hz), 4.36 (dd, 1H, *J* = 2.2 Hz, *J* = 8.3 Hz), 4.31–4.21 (m, 6H), 1.39 (t, 3H, *J* = 7.1 Hz), 1.36 (t, 3H, *J* = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3 (d, J_{cp} = 14.0 Hz), 148.4, 136.8, 136.5, 128.3, 128.2, 127.8, 122.4, 121.3, 77.5 (d, J_{cp} = 162.6 Hz), 74.7 (d, J_{cp} = 3.0 Hz), 72.9, 63.1 (d, J_{cp} = 6.6 Hz), 62.4 (d, J_{cp} = 7.0 Hz), 16.6 (d, J_{cp} = 5.9 Hz).; HRMS (EI): *m/z* calcd for $C_{18}H_{24}NO_5P$ 365.1392, found 365.1395.

*3.20. Diethyl (1S,2S)-[1-benzyloxy-2-hydroxy-2-(pyridin-3-yl)-ethyl]phosphonate, (1S,2S)-**4t**:* With (*R,R*)-**5e** catalyst and HCO_2H/Et_3N (0.2:1): >99% conversion after 3.5 h; dr = >99:1; >99% ee; Chiralpak IC, 20% EtOH/*n*-hexane, 1.5 mL/min, 215 nm, t_R (minor) = 11.5 min, t_R (major) = 18.3 min.



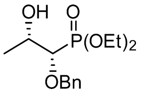
With (*R,R*)-**5a** catalyst and HCO_2H/Et_3N (1:1): Yield: 96.2% (343 mg as a pale-yellow oil); dr = 99:1; >99% ee: Chiralpak IC, 20% EtOH/n-hexane, 1.5 mL/min, 254 nm, t_R(minor) = 10.9 min, t_R(major) = 17.3 min; $[\alpha]^{15}_{D}$ = +75.1 (*c* 0.6, $CHCl_3$).; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, 1H, *J* = 1.5 Hz), 8.55 (dd, 1H, *J* = 1.5 Hz, *J* = 4.8 Hz), 7.75 (td, 1H, *J* = 1.5 Hz, *J* = 7.5 Hz), 7.31–7.25 (m, 4H), 7.18–7.16 (m, 2H), 5.12–5.10 (m, 1H), 4.78 (d, 1H, *J* = 11.0 Hz), 4.42 (d, 1H, *J* = 11.0 Hz), 4.23–4.05 (m, 4H), 3.87–3.84 (m, 2H), 1.36 (t, 3H, *J* = 7.0 Hz), 1.25 (t, 3H, *J* = 7.0 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 148.5, 136.3, 135.7 (d, J_{cp} = 9.8 Hz), 134.6, 128.5, 128.5, 128.3, 123.0, 78.3 (d, J_{cp} = 160.2 Hz), 74.9 (d, J_{cp} = 2.3 Hz), 70.8 (d, J_{cp} = 4.1 Hz), 63.1 (d, J_{cp} = 7.0 Hz), 62.6 (d, J_{cp} = 7.1 Hz), 16.5 (d, J_{cp} = 5.9 Hz), 16.4 (d, J_{cp} = 7.1 Hz).; HRMS (EI): *m/z* calcd for $C_{18}H_{24}NO_5P$ 365.1392, found 365.1389.

*3.21. Diethyl (1S,2S)-[1-benzyloxy-2-hydroxy-2-(pyridin-4-yl)-ethyl]-phosphonate, (1S,2S)-**4u**:* With (*R,R*)-**5e** catalyst and HCO_2H/Et_3N (0.2:1): >99% conversion after 3.5 h; dr = 98:2; 99.6% ee; Chiralpak ID, 30% isopropanol/n-hexane, 1.0 mL/min, 215 nm, t_R (minor) = 9.0 min, t_R (major) = 10.5 min.



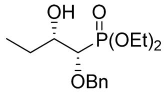
With (*R,R*)-**5a** catalyst and HCO_2H/Et_3N (1:1): Yield: 96.9% (354 mg as a white solid); mp: 64–66 °C dr = 98:2; 97.8% ee, Chiralpak ID, 30% isopropanol/*n*-hexane, 1.0 mL/min, 254 nm, t_R (minor) = 8.6 min, t_R(major) = 10.1 min; $[\alpha]^{17}_{D}$ = +74.8 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (d, 2H, *J* = 6.0 Hz), 7.30–7.25 (m, 5H), 7.07–7.06 (m, 2H), 5.07 (dd, 1H, *J* = 3.0 Hz, *J* = 7.8 Hz), 4.70 (d, 1H, *J* = 11.4 Hz), 4.37 (d, 1H, *J* = 11.3 Hz), 4.23–4.09 (m, 5H), 3.91 (dd, 1H, *J* = 3.0 Hz, *J* = 7.7 Hz), 1.37 (t, 3H, *J* = 7.1 Hz), 1.30 (t, 3H, *J* = 7.1 Hz).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6(d, J_{cp} = 14.0 Hz), 149.5, 136.0, 128.5, 128.4, 128.3, 121.5, 77.6 (d, J_{cp} = 161.1 Hz), 74.7 (d, J_{cp} = 2.6 Hz), 71.3 (d, J_{cp} = 3.1 Hz), 63.3 (d, $J_{c\,p}$= 6.8 Hz), 62.6 (d, J_{cp} = 7.0 Hz), 16.5 (d, J_{cp} = 5.5 Hz), 16.4 (d, J_{cp} = 4.1 Hz).; HRMS (EI): *m/z* calcd for $C_{18}H_{24}NO_5P$ 365.1392, found 365.1382.

*3.22. Diethyl (1S,2S)-(1-benzyloxy-2-hydroxy-propyl)-phosphonate, (1S,2S)-**4v**:* yield: 99.3% (300 mg as a coloress oil);

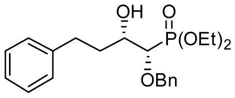


dr =96:4; 97.8% ee: Chiralpak IC, 20% isopropanol/n-hexane, 1.5 mL/min, 215 nm, t_R(minor) = 10.1 min, t_R(major) = 13.2 min.); $[\alpha]^{17}_{D}$ = +53.3 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.36 (m, 5H), 4.96 (d, 1H, *J* = 11.4 Hz), 4.63 (d, 1H, *J* = 11.3 Hz), 4.26–4.19 (m, 4H), 4.10 (bs, 1H), 3.59 (t, 1H, *J* = 5.2 Hz), 2.94 (d, 1H, *J* = 3.6 Hz), 1.38 (t, 6H, *J* = 7.1 Hz), 1.29 (d, 3H, *J* = 6.4 Hz).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 128.5, 128.5, 128.2, 79.0 (d, J_{cp} = 158.6 Hz), 74.8, 66.8 (d, J_{cp} = 4.4 Hz), 62.8 (d, *J* = 7.2 Hz), 62.4 (d, *J* = 7.1 Hz), 19.3 (d, *J* = 7.3 Hz), 16.5 (d, J_{cp} = 6.7 Hz).; HRMS (EI): *m/z* calcd for $C_{14}H_{23}O_5P$ 302.1283, found 302.1263.

*3.23. Diethyl (1-benzyloxy-2-hydroxy-butyl)phosphonate, **4w**:* yield: 98% (310 mg as a coloress oil); dr of crude product = 83:17 (diastereomers are difficult to separate by silica gel chromatography); dr of purified product = 90:10; **major isomer (90%)**; 97% ee: Chiralpak ID, 20% isopropanol/n-hexane, 1.0 mL/min, 215 nm, t_R(minor) = 8.7 min, t_R(major) = 9.6 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.29 (m, 5H), 4.93 (d, 1H, *J* = 11.3 Hz), 4.63 (d, 1H, *J* = 11.2 Hz), 4.28–4.19 (m, 4H), 3.83 (bs, 1H), 3.69 (t, 1H, *J* = 4.6 Hz), 2.81 (d, 1H, *J* = 5.9 Hz), 1.64–1.59 (m, 2H), 1.39–1.37 (m, 6H), 0.91 (t, 3H, *J* = 7.4 Hz). **minor isomer (10%)**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.29 (m, 5H), 4.83 (d, 1H, *J* = 11.3 Hz), 4.60 (d, 1H, *J* = 11.3 Hz), 4.28–4.19 (m, 4H), 3.82 (bs, 1H), 3.63 (t, 1H, *J* = 5.8 Hz), 3.34 (bs, 1H), 1.54–1.48 (m, 2H), 1.39–1.37 (m, 6H), 0.98 (t, 3H, *J* = 7.4 Hz).

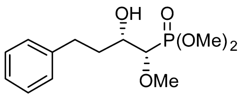


*3.24. Diethyl (1S,2S)-(1-benzyloxy-2-hydroxy-4-phenyl-butyl)-phosphonate, (1S,2S)-**4y**:* yield: 96.0% (377 mg as a coloress oil);



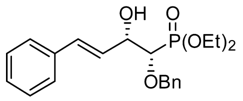
dr = 85:15; major = 97.8% ee, minor = 99% ee: Chiralpak IC, 10% ethanol/*n*-hexane, 0.5 mL/min, 215 nm, t_R(major) = 27.4 min, t_R(minor) = 30.2 min; **major isomer**; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.28 (m, 7H), 7.21–7.18 (m, 3H), 4.91 (d, 1H, *J* = 11.3 Hz), 4.61 (d, 1H, *J* = 11.3 Hz), 4.26–4.17 (m, 4H), 3.92 (bs, 1H), 3.68 (t, 1H, *J* = 5.2 Hz), 2.94 (bs, 1H), 2.83–2.78 (m, 1H), 2.67–2.60 (m, 1H), 1.96–1.87 (m, 2H), 1.35 (t, 3H, *J* = 7.2 Hz).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 137.0, 128.5, 128.5, 128.3, 128.3, 125.8, 77.4 (d, J_{cp} = 156.0 Hz), 74.6 (d, J_{cp} = 1.7 Hz), 69.8 (d, J_{cp} = 3.3 Hz), 62.8 (d, *J* = 7.1 Hz), 62.4 (d, *J* = 6.9 Hz), 34.9 (d, J_{cp} = 8.3 Hz), 31.8, 16.5 (d, *J* = 5.3 Hz), 16.5 (d, J_{cp} = 5.4 Hz).; HRMS (EI): *m/z* calcd for $C_{21}H_{29}O_5P$ 392.1753, found 392.1747.

*3.25. Dmiethyl (1S,2S)-(2-hydroxy-1-methoxy-4-phenyl-butyl)-phosphonate, (1S,2S)-**4z**:* dr = 88:12 by chiral HPLC (diastereomers are inseparable by silica gel chromatography) **major isomer (88%)**; 95% ee: Chiralpak IA, 5% isopropanol/*n*-hexane, 1.0 mL/min, 215 nm,



t_R (major) = 22.7 min, t_R (minor) = 25.0 min; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.19 (m, 5H), 3.94 (br s, 1H), 3.84 (t, 6H, J = 9.9 Hz), 3.58 (s, 3H), 3.45 (t, 1H, J = 5.6 Hz), 2.94–2.88 (m, 2H), 2.75–2.69 (m, 1H), 2.01–1.90 (m, 1H), 1.90–1.82 (br s, 1H).; ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 128.5, 128.4, 125.9, 80.6 (d, J_{cp} = 158.9 Hz), 69.8 (d, J_{cp} = 3.5 Hz), 61.3 (d, J_{cp} = 2.4 Hz), 53.4 (d, J_{cp} = 6.7 Hz), 52.6 (d, J_{cp} = 7.2 Hz), 35.0 (d, J_{cp} = 8.6 Hz), 32.0.; HRMS (EI): m/z calcd for $C_{13}H_{21}O_5P$ 288.1127, found 288.1125. **minor isomer (12%)**; 98% ee: Chiralpak AD-H, 5% isopropanol/n-hexane, 1.5 mL/min, 215 nm, t_R (major) = 9.6 min, t_R (minor) = 10.5 min

*3.26. Diethyl (1S,2S,E)-(1-benzyloxy-2-hydroxy-4-phenylbut-3-en-1-yl)-phosphonate, (1S,2S)-**4ab**:* With (R,R)-**5e** catalyst and HCO_2H/Et_3N



(F/T = 5:2) at 35 °C for 24 h. **4ab**:**3y**:**4y** = 56(>99:1 dr):13:31 (64:36 dr); ratio was determined by using ^1H NMR, dr and ee (in parentheses) were determined by using chiral HPLC; Chiralpak ID, 30% isopropanol/n-hexane, 0.8 mL/min, 254 nm, t_R(major) = 16.8 min, t_R(minor) = 24.4 min. (Stereoisomers are inseparable by silica gel chromatography.)

With (R,R)-**5e**(Ru) catalyst and HCO_2H/Et_3N (F/T = 1:1) at 35 °C for 24 h. **4ab**:**3y**:**4y** = 63 (>99:1 dr):0:37(57:43 dr).

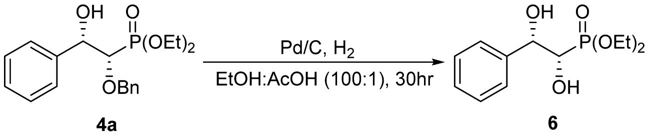
With (R,R)-**5e**(Ru) and HCO_2H/Et_3N (F/T=0.2:1) at 35 °C for 24 h. **4ab**:**3y**:**4y** = 66(>99:1 dr, 98% ee):22:37(57:43 dr).

With (R,R)-**5a**(Rh) and HCO_2H/Et_3N (F/T=0.2:1) at 35 °C for 24 h. **4ab**:**3y**:**4y** = 4:87:9.

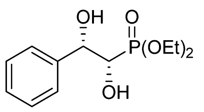
With (R,R)-**5b**(Ir) and HCO_2H/Et_3N (F/T=0.2:1) at 35 °C for 24 h. **4ab**:**3y**:**4y** = 14:76:10.

4ab: ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.25 (m, 10H), 6.74 (d, 1H, J = 16.0 Hz), 6.26(dd, 1H, J = 10.0 Hz, J = 5.6 Hz), 4.91 (d, 1H, J = 11.5 Hz), 4.69 (d, 1H, J = 11.5 Hz), 4.68–4.64 (m, 1H), 4.27–4.16 (m, 4H), 3.84 (dd, 1H, J = 6.5 Hz, J = 4.4 Hz), 3.35 (br s, 1H), 1.39–1.29 (m, 6H).

*4. Determination of the Absolute Configuration of **4a**, **4v**, **4y** by Comparing with the Known Compound **6**, **7**, and **8** respectively.*



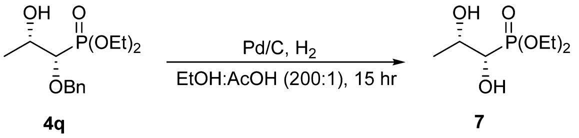
*4.1. Debenzylation of **4a** to 1,2-Dihydroxy Phosphonate **6**.* (S,S)-**4a** (120 mg, 0.33 mmol, 99% ee), which was obtained from the ATH-DKR of **3a** with (R,R)-**5e** catalyst, was dissolved in a mixed solvent of EtOH/AcOH (20:0.2) (20.2 mL), and 10% Pd/C (12 mg) was added. The suspension was stirred under hydrogen atmosphere (balloon) for 30 h. After completion of the reaction the catalyst was removed by filtration through a layer of Celite, the solution was concentrated, and the residue was purified by a silica gel column chromatography to give diol **6** (88 mg, 97.5%) as a colorless oil. The sense and magnitude of optical rotation of the debenzylated product **6** were matched with the known diol compound (S,S)-**6**[27,28] which was prepared from Sharpless asymmetric dihydroxylation of diethyl (E)-styrylphosphonate with AD-mix-α.



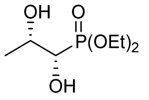
(S,S)-**6**

yield: 97.5%; $[\alpha]^{30}_D$ = +30.7 (c 0.4, $CHCl_3$), $[\alpha]^{30}_D$ = +34.3 (c 0.3, MeOH), lit.[27] $[\alpha]^{20}_D$ = +24.7 (c 1.0, $CHCl_3$) for a material of 100% ee, lit.[28] $[\alpha]^{20}_D$ = +33.7 (c 1.0, MeOH) for a material of 91% ee; ^1H NMR (500 MHz, $CDCl_3$); δ 7.46–7.29 (m, 5H), 5.14 (br s, 1H), 4.22–4.18 (m, 4H), 4.06 (d, 1H, J = 8.0 Hz), 1.37 (t, 3H, J = 7.1 Hz), 1.31 (t, 3H, J = 7.0 Hz).; ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.2 (d, J_{cp} = 10.8 Hz), 128.2, 127.8, 126.6, 72.7 (d, J_{cp} = 158.2 Hz), 72.5 (d, J_{cp} = 4.1 Hz), 63.4 (d, J_{cp} = 7.1 Hz), 62.8 (d, J_{cp} = 7.3 Hz), 16.4 (d, J_{cp} = 5.9 Hz), 16.3 (d, J_{cp} = 5.9 Hz).

*4.2. Debenzylation of **4v** to 1,2-Dihydroxy Phosphonate **7**.* (S,S)-**4v** (150 mg, 0.50 mmol, 98% ee), which was obtained from the



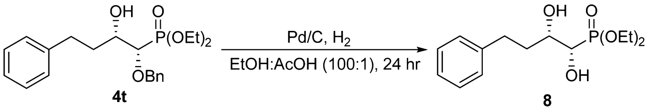
ATH-DKR of **3v** with (R,R)-**5e** catalyst, was dissolved in a mixed solvent of EtOH/AcOH (20:0.1) (20.1 mL), and 10% Pd/C (15 mg) was added. The suspension was stirred under hydrogen atmosphere (balloon) for 15 h. After completion of the reaction the catalyst was removed by filtration through a layer of Celite, the solution was concentrated, and the residue was purified by a silica gel column chromatography to give diol **7** (95 mg, 90.4%) as a colorless oil. The sense and magnitude of optical rotation of the debenzylated product **7** were matched with the known diol compound (S,S)-**7**.[66,28]



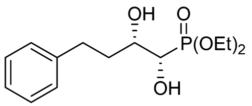
(S,S)-**7**

yield: 90.4%; $[\alpha]^{29}_D$ = +9.1 (c 0.7, $CHCl_3$), $[\alpha]^{29}_D$ = +11.5 (c 2.0, MeOH), lit.[66] $[\alpha]^{20}_D$ = +10.3 (c 1.4, $CHCl_3$), lit.[28] $[\alpha]^{20}_D$ = +3.7 (c 1.0, MeOH) for a material of 33% ee; ^1H NMR (500 MHz, $CDCl_3$); δ 4.26–4.16 (m, 5H), 4.07 (br s, 1H), 3.70 (td, 1H, J = 8.2 Hz, J = 3.0 Hz), 3.64 (br s, 1H), 1.38–1.34 (m, 6H), 1.32 (d, 3H, J = 6.5 Hz).; ^{13}C NMR (125 MHz, $CDCl_3$): δ 72.1 (d, J_{cp} = 158.2 Hz), 66.7 (d, J_{cp} = 3.3 Hz), 63.1 (d, J_{cp} = 6.6 Hz), 62.6 (d, J_{cp} = 7.4 Hz), 19.2 (d, J_{cp} = 9.5 Hz), 16.4 (d, J_{cp} = 5.4 Hz), 16.3 (d, J_{cp} = 5.2 Hz).

*4.3. Debenzylation of **4y** to 1,2-Dihydroxy Phosphonate **8**.* (S,S)-**4y** (100 mg, 0.25 mmol, syn:$anti$ = 85(95% ee):15(99% ee), which was

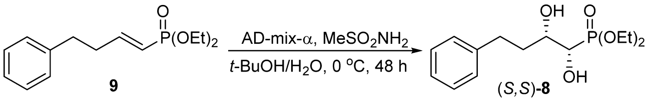


obtained from the ATH-DKR of **3y** with (R,R)-**5e** catalyst, was dissolved in a mixed solvent of EtOH/AcOH (10:0.1) (10.1 mL), and 10% Pd/C (10 mg) was added. The suspension was stirred under hydrogen atmosphere (balloon) for 24 h. After completion of the reaction the catalyst was removed by filtration through a layer of Celite, and the solution was concentrated to give **8** (72 mg, 93.5%). The residue was cautiously separated by silica gel column chromatography to give syn-diol **8** as colorless oil. The sense and magnitude of optical rotation of the debenzylated product syn-diol **8** were matched with the syn-diol compound (S,S)-**8** which was independently prepared from Sharpless asymmetric dihydroxylation of diethyl (E)-(4-phenylbut-1-en-1-yl)phosphonate (**9**)[67] with AD-mix-α[68] (see, exp. 4.4 below and chiral HPLC analysis in Supporting Information for comparison).

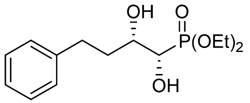


(S,S)-**8**

96.7% ee: Chiralpak IC, 10% ethanol/n-hexane, 0.8 mL/min, 215 nm, t_R (major) = 17.4 min, t_R (minor) = 21.9 min; $[\alpha]^{21}_D$ = −6.9 (c 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 7.32–7.20 (m, 5H), 4.26−4.15 (m, 4H), 4.00 (br s, 1H), 3.79 (t, 1H, *J* = 9.0 Hz), 3.41 (d, 1H, *J* = 3.4 Hz, OH), 3.33 (d, 1H, *J* = 9.4 Hz, OH), 2.86−2.81 (m, 1H), 2.77−2.70 (m, 1H), 2.09−2.05 (m, 1H), 1.91−1.88 (m, 1H), 1.38 (t, 3H, *J* = 7.1 Hz), 1.33 (t, 3H, *J* = 7.1 Hz).; ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.8, 128.4, 128.2, 125.7, 71.0 (d, J_{cp} =158.7 Hz), 69.8 (d, J_{cp} = 1.6 Hz), 63.0 (d, J_{cp} = 6.8 Hz), 62.8 (d, J_{cp} = 7.2 Hz), 34.7 (d, J_{cp} = 10.7 Hz), 31.8, 16.3 (d, J_{cp} = 5.6 Hz), 16.3 (d, J_{cp} = 5.6 Hz).; HRMS (EI): *m*/*z* calcd for $C_{14}H_{23}O_5P$ 302.1283, found 302.1270.



*4.4. Synthesis of (S,S)-**8** from Diethyl (E)-(4-phenylbut-1-en-1-yl)-phosphonate (**9**) by Sharpless Asymmetric Dihydroxylation with AD-mix-α.* To a stirred solution of *tert*-butyl alcohol (18 mL) and water (18 mL) were added AD-mix-*α* (5.0 g) and methanesulfonamide (0.34 g, 3.54 mmol) at room temperature. The mixture was vigorously stirred at room temperature until both phases were clear and then was cooled to 0 °C. A solution of the diethyl (*E*)-(4-phenylbut-1-enyl)phosphonate (**9**)[67] (0.95 g, 3.54 mmol) in *tert*-butyl alcohol (5 mL) was added at 0 °C. The reaction mixture was stirred at the same temperature for 48 h. The reaction was quenched at 0 °C by the addition of sodium sulfite (5.1 g), warmed to room temperature, and further stirred for 1 h. The reaction mixture was then extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with aqueous 2 N KOH (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered, and then concentrated under reduced pessure. Purification of the crude product by silica gel column chromatography afforded (*S*,*S*)-**8** (925 mg, 86.4%) as a colorless oil.



(*S*,*S*)-**8**

yield: 86.4%; 84.2% ee: Chiralpak IC, 10% ethanol/*n*-hexane, 0.8 mL/min, 215 nm, t_R (major) = 17.4 min, t_R (minor) = 21.9 min; $[\alpha]^{21}{}_D = -6.0$ (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31−7.19 (m, 5H), 4.25−4.16 (m, 4H), 3.99 (s, 1H), 3.80 (d, 1H, *J* = 8.6 Hz), 3.69 (br s, 1H), 2.86−2.81 (m, 1H), 2.77−2.71 (m, 1H), 2.10−2.03 (m, 1H), 1.93−1.86 (m, 1H), 1.74 (br s, 1H), 1.37 (t, 3H, *J* = 7.0 Hz), 1.33 (t, 3H, *J* = 7.1 Hz).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H-, ^{13}C NMR spectra, chiral HPLC chromatograms of all new chiral compounds and X-ray crystallography data of (*S*,*S*)-**4n** and (*S*,*S*)-**4u** in CIF format (CCDC-982444 for (*S*,*S*)-**4n** and CCDC-982443 for (*S*,*S*)-**4u**). 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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