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Kinetic resolution of 2-hydroxy-2-aryl-ethylphosphonates by a non-enzymatic acylation catalyst

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ABSTRACT

Optically pure hydroxyphosphonates are widely used as derivatizable compounds that can be incorporated into a variety of synthetic strategies for the preparation of other high value organic products. A non-enzymatic kinetic resolution procedure to obtain chiral 2-hydroxy-2-arylethylphosphonates from the easily available racemic counterparts is described. A range of 2-hydroxy-2-arylethylphosphonates was efficiently resolved employing a planar-chiral DMAP derived catalyst with good selectivities (up to S=68). The chiral hydroxyphosphonates were isolated in good yields and high enantiomeric excess (>94% *ee*).

1. Introduction

The synthesis of enantiomerically pure compounds has emerged as one of the most important fields of organic chemistry.[1] Chiral secondary alcohols are undoubtedly one of the most important broad classes of building blocks available for the synthesis of pharmaceuticals and other fine chemicals.[2] In addition, hydroxyphosphonic acids and their esters are important precursors for biologically active compounds, such as aminophosphonic esters, which have received significant attention due to their ability to mimic their carboxylic counterparts.[3] Particularly, 2-amino-2-arylethylphosphonates analogues have attracted considerable attention due to their wide range of potential applications, such as enzyme inhibitors[4] or pharmacologic agents.[5] For instance, 2-amino-2-arylethylphosphonic acids are reported to be potential $GABA_B$ receptor antagonists,[5a,c] and therefore, the development of asymmetric synthesis of these compounds is important. Current stereoselective approaches to 2-amino-2-aryl-ethylphosphonates involve the synthesis of chiral 2-hydroxy-2-arylethylphosphonates by enzymatic catalysis,[4b,6] followed by the substitution of the hydroxyl by an azide group with inversion of configuration under Mitsunobu reaction conditions, and subsequent reduction of the azide to the amine.

Several synthetic routes for the preparation of enantioenriched 2-hydroxy-2-arylethylphosphonates have been developed (Scheme 1),[7] which involve the asymmetric reduction of the corresponding 2-ketophosphonates[3,8] and kinetic resolution.[6,9] The asymmetric reduction of 2-ketophosphonates can occur via chiral metal complexes,[3,8a–c] chirally modified metal hydrides,[8d,e] chiral reagents[8d,e] or by biotransformation.[8f,g] Several studies of kinetic resolution by lipase-catalyzed hydrolysis of the corresponding acetates[6,9a,b] have been reported. Although many lipases were explored for acylative kinetic resolution of 2-hydroxy-2-arylethylphosphonates, none proved to be fruitful, probably due to the bulkiness of the phosphonate group.[9a,b] So far, the only example of acylative kinetic resolution is described by Onomura and co-workers,[9d] who reported a method for the kinetic resolution of 2-hydroxyalkane-phosphonates by 2-fluorobenzylation in the presence of a copper (II) triflate/(*R*,*R*)-Ph-BOX catalyst system with good selectivities (up to S=21) (Scheme 1).

During the last two decades, a variety of organic small-molecule catalysts for the acylative kinetic resolution of secondary alcohols have been developed.[10] Schreiner and Müller[10d] classified these organocatalysts into six distinct groups: phosphines and phosphinites, *N*-alkylimidazoles, amidines, vicinal diamines, *N*-heterocyclic carbenes, and 4-aminopyridines derivates (DMAP analogues). The first member of the 'chiral DMAP' family[11] was introduced by Vedejs and Chen in 1996[12] and they demonstrated its efficiency in the kinetic resolution of secondary benzylic alcohols[12] using stoichiometric amounts of their chiral DMAP analogue in the presence of 2 equiv of a Lewis acid. In the same year, Fu and coworkers developed the synthesis of planar-chiral ferrocenyl DMAP derivates.[13] The DMAP analogue (−)-**1** catalysed the kinetic resolution of secondary aryl alkyl alcohols.[14] This catalytic system

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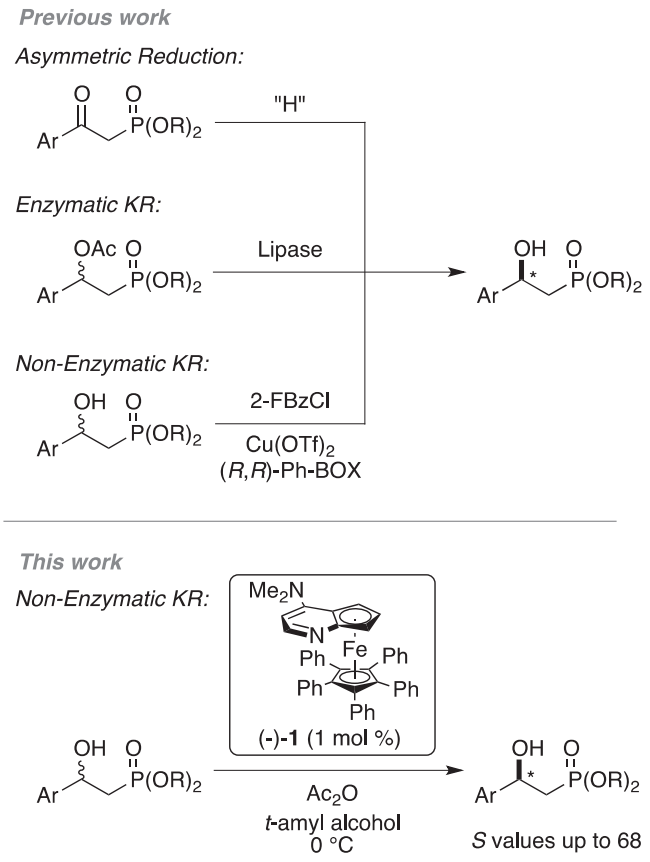


Scheme 1. Synthetic routes to enantiopure 2-hydroxy-2-arylethylphosphonates.

was also very efficient in the kinetic resolution of propargylic[15] and allylic[16] alkyl alcohols. Recently, Fu and co-workers reported the first non-enzymatic dynamic kinetic resolution of secondary alcohols and demonstrated the compatibility of (−)-**1** with a ruthenium-based racemization catalyst.[17]

In our effort to expand the applicability of the planar chiral DMAP catalyst (−)-**1**, we have previously studied the kinetic resolution of *sec*-alcohols that contain an additional heteroatom-containing functional group in the alkyl moiety. Recently, we demonstrated that the catalyst (−)-**1** promotes the kinetic resolution for a range of aromatic 1,2-azidoalcohols with good selectivity factors (up to S=45) and high enantiomeric excess (up to 99% *ee*) of the remaining alcohol.[18] Herein, we wish to present the non-enzymatic kinetic resolution of a variety of 2-hydroxy-2-arylethylphosphonates using the planar-chiral ferrocenyl DMAP derivate (−)-**1** as a catalyst with excellent selectivities (up to S=68) (Scheme 1, bottom).

2. Results and discussion

Previous work has shown that the bulky base, triethylamine, catalyses the acetylation of some *sec*-alcohols,[15] and therefore, we studied how the presence or the absence of this base affects the selectivity of the system under study.

The enantiomeric excess (*ee*) and the conversion were determined by ^{31}P NMR spectroscopy using quinine as a chiral solvating agent. ^{31}P NMR spectroscopy is a convenient tool for the determination of the enantiomeric excess of phosphorus-containing compounds due to the large chemical shift dispersion and the simplicity of the ^{31}P NMR spectra.[19] In order to obtain undistorted ^{31}P signal intensities for an accurate integration, long relaxation times (30 s) were used without irradiation during this period to avoid Nuclear Overhauser Effect (NOE) enhancements (see Experimental section for more details). Upon addition of quinine (molar ratio quinine-hydroxy phosphonate 5:1),[20] the chemical shift differences of the (*R*)- and (*S*)-alcohols were relatively large ($\Delta\delta$=0.30−0.44 ppm, in $CDCl_3$) for all the substrates (**2a**–**j**) (Fig. 1a and b).[21]

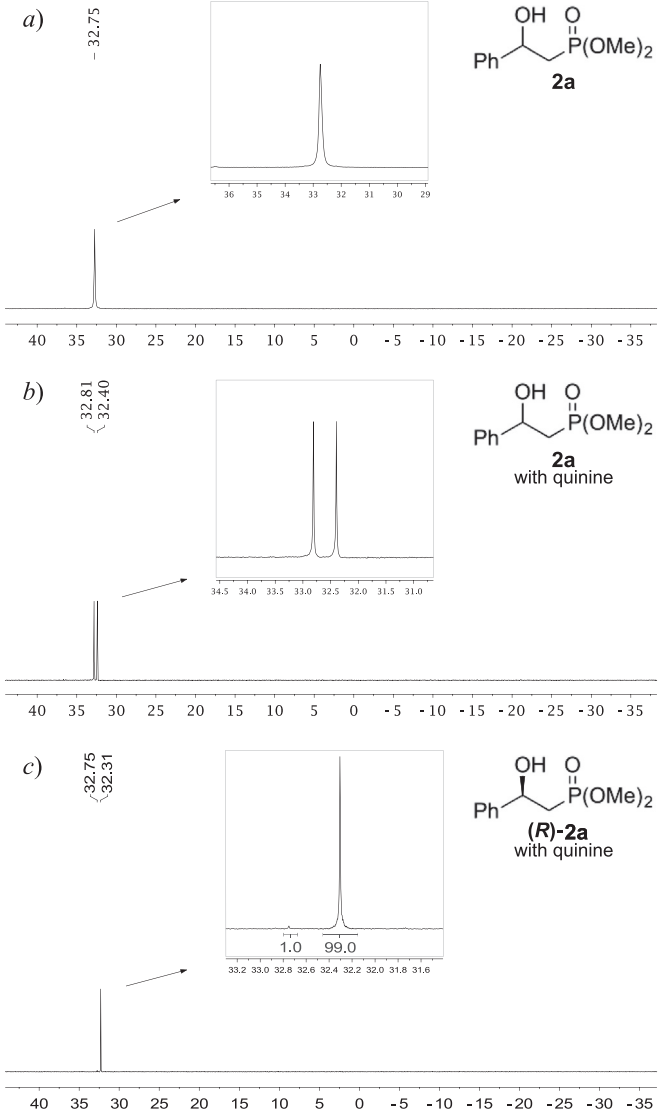


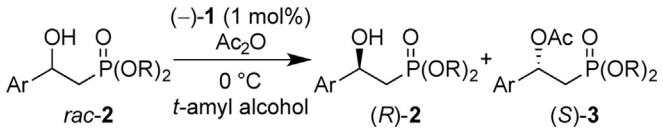
Fig. 1. ^{31}P NMR spectra of racemic dimethyl (2-hydroxy-2-phenylethyl)phosphonate, *rac*-**2a** (a) in the absence, (b) in the presence of 5 equiv of quinine, and (c) enantiopure dimethyl (*R*)-(2-hydroxy-2-phenylethyl)phosphonate, (*R*)-**2a**, in the presence of quinine.

The kinetic resolution of diethyl (2-hydroxy-2-phenylethyl) phosphonate (**2d**) was performed following the conditions previously reported[14b,18] using the racemic alcohol **2d** (0.25 mmol), acetic anhydride (0.75 equiv), triethylamine (0.75 equiv), and (−)-**1** (0.0025 mmol, 1 mol %) in *tert*-amyl alcohol (1.0 mL) at 0 °C. After 24 h, the conversion was 53% and the selectivity factor (S) was 20. When the reaction was performed in the absence of base, the selectivity improved significantly (S=37), but the reaction slowed down. We finally decided to compromise the speed of the reaction in favour of the selectivity, excluding triethylamine in the successive experiments.

In the first stage of the study, the selectivity factor of the kinetic resolution of *rac*-**2a**–**j** was determined after 4 h of reaction in order to easily compare the efficiency of the kinetic resolution

methodology of the different substrates. The reaction was carried out using racemic alcohol (0.25 mmol), acetic anhydride (0.75 equiv), and (−)-**1** (0.0025 mmol, 1 mol %) in *tert*-amyl alcohol (1.0 mL) at 0 °C (Table 1). Initially, the effect of the size of the phosphonate ester substituents was evaluated using either the dimethyl- or diethylhydroxyphosphonates.

Table 1
Selectivity factor of kinetic resolution of 2-hydroxy-2-arylethylphosphonates by (−)-**1**[a]



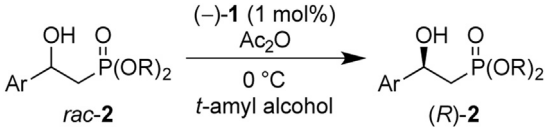
Entry	Ar	R	ee_{ROH} (%)[b]	Conv. (%)[b]	S[c]
1	Ph (**2a**)	Me	38	31	24
2	4-NO_2-Ph (**2b**)	Me	23	16	5
3	3-MeO-Ph (**2c**)	Me	36	31	16
4	Ph (**2d**)	Et	32	25	43
5	4-NO_2-Ph (**2e**)	Et	31	25	62
6	3-MeO-Ph (**2f**)	Et	22	20	19
7	2-Naphthyl (**2g**)	Et	55	37	68
8	2,4-diCl-Ph (**2h**)	Et	35	28	35
9	4-Me-Ph (**2i**)	Et	15	14	25
10	4-F-Ph (**2j**)	Et	43	38	11

[a] Reaction conditions: **2** (0.25 mmol), Ac_2O (0.75 equiv), (−)-**1** (0.0025 mmol, 1 mol %) in *tert*-amyl alcohol (1.0 mL) at 0 °C for 4 h.
[b] Determined by ^{31}P NMR spectroscopy using quinine as the chiral solvating agent. The value given is an average of two runs.
[c] The best selectivity of two runs.

The compounds investigated included the parent compounds **2a** and **2d** (entries 1 and 4), compounds **2b** and **2e** with the electron withdrawing nitro group in the 4-position (entries 2 and 5), and compounds **2c** and **2f** with the electron donating methoxy group in the 4-position (entries 3 and 6). The substrates bearing the larger ethyl group in the phosphonate ester, **2d**–**f** (entries 4–6), show significantly higher selectivity than the dimethyl hydroxyphosphonates **2a**–**c** (entries 1–3). These results are in accordance with the previous result reported by Fu for secondary benzylic alcohols with a bulky aliphatic substituent.[14b] The significantly lower selectivity (ten times lower) obtained for dimethyl (2-hydroxy-2-(4-nitrophenyl)ethyl)-phosphonate **2b** (S=5, entry 2) could also be a consequence of its poor solubility in *t*-amyl alcohol. With these results in hand, we continued with the study of the effect of different substituents in the aromatic ring among diethyl phosphonates. The larger 2-naphthyl derivate **2g** gave better results in terms of both selectivity and reactivity (S=68, 37% conv.). The electron withdrawing nitro group in the 4-position also increases the selectivity (S=62) compared to the parent compound **2d** (S=43). The presence of an electron donating group in the phenyl ring, such as a methyl or methoxy group (entries 6 and 9) decreases the selectivity compared to the parent compound **2d**, and it can also be observed that the reactivity decreases for substrate **2i** (entry 8). In the case of the alcohol **2h**, having two chloro substituents in the 2- and 4-position of the aromatic ring, the selectivity obtained was slightly lower (S=35) compared to the corresponding parent compound **2d**. The decrease in the selectivity is even larger in the case of the 4-fluoro derivate (S=11). In general, it could be observed that substrates having electron withdrawing substituents show a higher selectivity than the substrates having electron donating substituents. Previously, π–π-stacking between the catalysts and the aromatic group of the substrates is suggested to be involved in the rate-determining step of these acylation reactions, which could also be the case for the Fu catalyst.[22]

In the second stage of the study, the kinetic resolutions of the different substrates (*rac*-**2a** and *rac*-**2c**–**j**) were performed with longer reaction times, under the general conditions, in order to isolate the enantiomerically pure hydroxyarylphosphonates and to demonstrate the practical use of this methodology (Table 2). As previously mentioned, the enantioselectivity of the reaction was determined by ^{31}P NMR spectroscopy using quinine as the solvating agent. Integral ratios ranging from 1:99 to 0:100 were judged as >95% *ee*, even in cases where only one peak was observed. In general, all the substrates were obtained with very high enantiomeric excess (>95% *ee*) and good yields (29–49%). For instance, the larger 2-naphthyl derivate **2g** was isolated enantiomerically pure (>95% *ee*) in 32% yield after only 24 h (entry 6). For the less reactive parent compound (*R*)-**2d**, longer reaction times were necessary (96 h) in order to obtain the product in high *ee* (>95%) (Table 2, entry 3). On the contrary, substrates having halogens in the aromatic ring ((*R*)-**2h** and (*R*)-**2j**) show a lower selectivity compared to the parent compound, but are more reactive and could be isolated with high *ee* after shorter reaction time (48 h) (Table 2, entries 7 and 9).

Table 2
Synthesis of (*R*)-2-hydroxy-2-arylethylphosphonates by means of kinetic resolution[a,b]



Entry	R	R	Time/h	Integral ratio[c,d]	ee_{ROH} (%)[d]	Yield (%)[e]
1	Ph (**2a**)	Me	72	1:99	>95	30 (60)
2	3-MeO-Ph (**2c**)	Me	68	0:100	>95	35 (70)
3	Ph (**2d**)	Et	96	0:100	>95	41 (82)
4	4-NO_2-Ph (**2e**)	Et	45	0:100	>95	33 (66)
5	3-MeO-Ph (**2f**)	Et	70	0:100	>95	31 (62)
6	2-Naphthyl (**2g**)	Et	24	0:100	>95	32 (64)
7	2,4-diCl-Ph (**2h**)	Et	51	0:100	>95	29 (58)
8	4-Me-Ph (**2i**)	Et	96	3:97	94	49 (98)
9	4-F-Ph (**2j**)	Et	48	0:100	>95	44 (88)

[a] Reaction conditions: **2** (0.25 mmol), Ac_2O (0.75 equiv), (−)-**1** (0.0025 mmol, 1 mol %) in *tert*-amyl alcohol (1.0 mL) at 0 °C.
[b] The absolute configuration was assigned by comparison of the optical rotation sign of (*R*)-**2a** and (*R*)-**2d** with literature.
[c] Integral ratio.
[d] Determined by ^{31}P NMR spectroscopy using quinine as the solvating agent; integral ratios between 1:99 to 0:100 were judged as >95% *ee*.
[e] Isolated yields based on *rac*-2-hydroxy-2-arylethanephosphonate. In parenthesis: % recovered (*R*)-isomer.

Finally, in order to demonstrate the applicability of the current method for synthetic purposes, the reaction was scaled up. The kinetic resolution of the hydroxyphosphonate *rac*-**2d** (using 3 mmol scale) was performed following the general procedure, obtaining compound (*R*)-**2d** in good yield (258 mg, 1.0 mmol, 33% yield) with high enantiomeric excess (>95% *ee*) after 96 h.

3. Conclusion

In summary, we have demonstrated that the chiral DMAP derivative catalyst (−)-**1** catalysed the kinetic resolution of a range of aromatic 2-hydroxyphosphonates with good selectivities (selectivity factor up to 68) and high enantiomeric excess (>95% *ee*) of the remaining alcohol. The 2-hydroxy-2-aryl-phosphonates with the more bulky ethyl substituent in the phosphonate ester show in general a higher selectivity than the less bulky methylsubstituted phosphonate ester. To the best of our knowledge, these results represent the first example of kinetic resolution of 2-hydroxy-2-arylethylphosphonates using a non-enzymatic nucleophilic chiral catalyst.

4. Experimental section

4.1. General

Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Thin Layer Chromatography (TLC) was performed on ALUGRAM® SIL G/UV_{254} plates (0.2 mm), using UV-light (254 nm) for visualization. Flash chromatography was performed using Merck silica gel (0.04–0.06 mm). ^{1}H, and ^{13}C spectra were recorded on a Varian Mercury 300 MHz, Varian Unity 400 MHz or Varian Unity 500 MHz. ^{31}P NMR spectra were recorded on a Varian Mercury 300 MHz. The chemical shifts values (δ) are given in parts per million (ppm) relative to TMS and referred to and internally referenced to the residual undeuterated peak of solvent used ($CHCl_3$: δ_H=7.26 ppm, δ_C=77.16 ppm) or externally to H_3PO_4 (85%). *J* values are given in Hertz. Abbreviations used are s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). IR spectra were recorded on a Perkin–Elmer Spectrum One (ATR Technique). High-resolution mass spectra were recorded by Dr. Aleh Yahorau, Department of Pharmaceutical Biosciences, Uppsala University, Sweden.

The enantiomeric excesses of **2a**–**j** were determined by ^{31}P NMR spectroscopy with quinine as the chiral solvating agent. In order to obtain undistorted ^{31}P signal intensities for an accurate integration, an inverse gated decoupling pulse sequence was always used to obtain proton-decoupled spectra with no NOE enhancement. The decoupler is switched off before the excitation pulse so that the NOE enhancement is not allowed to develop. Proton decoupling is provided since the decoupler is switched on during the excitation pulse and the acquisition time. Spectra were collected using 128 transients with long relaxation time (30 s). Integral ratios between 1:99 and 0:100 were judged as >95% *ee*. The selectivity (*S*) values were calculated with the equation: $S=\ln[(1-c)(1-ee_{ROH})]/\ln[(1-c)(1+ee_{ROH})]$.[23]

4.2. General procedure for the kinetic resolution of racemic 2-aryl-2-hydroxyethylphosphonates *rac*-2a–j

Catalyst (−)-**1** (1.65 mg, 0.0025 mmol), racemic 2-aryl-2-hydroxyethylphosphonates *rac*-**2a**–**j** (0.25 mmol), and *tert*-amyl alcohol (1.0 mL) were sequentially added to a vial. The vial was capped and stirred at room temperature in order to dissolve the catalyst. The reaction mixture was cooled to 0 °C, and then acetic anhydride (18 μL, 0.19 mmol) was added. After an appropriate amount of time, the reaction mixture was quenched by the addition of a large excess of methanol. The resulting solution was concentrated, and the unreactive alcohol, the acetate, and the catalyst were separated by flash chromatography using DCM (1% EtOH) as eluent. All the previously described compounds were confirmed by NMR spectroscopy. All new compounds and for those compounds where no NMR data was reported, were also confirmed by IR and HRMS spectroscopy. Characterization data for these compounds are as follows (copies of the ^{1}H, ^{13}C, and ^{31}P NMR spectra are included in Supplementary data).

*4.2.1. Dimethyl (R)-(2-hydroxy-2-phenylethyl)phosphonate ((R)-**2a**).*[3,9d] Colourless oil (17.3 mg, 30% yield, >95% *ee*); $[\alpha]_D^{20}$ −10.0 (*c* 0.5, $CDCl_3$), lit. $[\alpha]_D^{25}$ −21.1 (CH_3OH, *c* 1.26, 95% *ee*).[3] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ=7.42–7.28 (m, 5H, Ar*H*), 5.17–5.09 (m, 1H, C*H*OH), 3.78 (d, *J*=10.9 Hz, 3H, OCH_3), 3.73 (d, *J*=11.0 Hz 3H, OCH_3), 2.28–2.18 (m, 2H, CH_2). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 25 °C) δ=143.6 (d, *J*=15.9 Hz), 128.7, 128.0, 125.6, 68.9 (d, *J*=4.8 Hz), 52.8 (d, *J*=6.3 Hz), 52.6 (d, *J*=6.6 Hz), 35.2 (d, *J*=136.4 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C) δ=32.8.

*4.2.2. (Dimethyl (R)-(2-hydroxy-2-(3-methoxyphenyl)ethyl)phosphonate ((R)-**2c**)).* Yellowish oil; (22.8 mg, 35% yield, >95% *ee*); $[\alpha]_D^{20}$ −30.7 (*c* 1.6, $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ=7.28–7.25 (m, 1H, Ar*H*), 6.97–6.94 (m, 2H, Ar*H*), 6.83–6.81 (m, 1H, Ar*H*), 5.12–5.07 (m, 1H, C*H*OH), 3.81 (s, 3H, ArOCH_3), 3.78 (d, *J*=10.8 Hz, 3H, OCH_3), 3.74 (d, *J*=10.9 Hz, 3H, OCH_3), 2.29–2.15 (m, 2H, CH_2). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 25 °C) δ=160.0, 145.2 (d, *J*=16.6 Hz), 129.8, 117.8, 113.6, 111.0, 68.8, 55.4, 52.8 (d, *J*=5.6 Hz), 52.6 (d, *J*=5.6 Hz), 35.2 (d, *J*=136.1 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C) δ=32.8. IR (neat): ν(cm^{-1})=3340, 2958, 1588, 1213, 1020. HRMS (ESI) Calcd for $C_{11}H_{18}O_5P^+$ [M+H$^+$]:[25] 261.0892, found: 261.0894.

*4.2.3. (Diethyl (R)-(2-hydroxy-2-phenylethyl)phosphonate ((R)-**2d**)).*[9d] Colourless oil (26.5 mg, 41% yield, >95.0% *ee*); $[\alpha]_D^{20}$ −40.0 (*c* 1.4, $CDCl_3$); $[\alpha]_D^{20}$ −10.8 (*c* 1.1, acetone, 41% *ee*).[9d] ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ=7.41–7.26 (m, 5H, Ar*H*), 5.14–5.07 (m, 1H, C*H*OH), 4.17–4.02 (m, 4H, 2OCH_2CH$_3$), 2.25–2.16 (m, 2H, CH_2), 1.34 (d, *J*=7.1 Hz, 3H, OCH$_2$CH_3), 1.29 (t, *J*=7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 25 °C) δ=143.6 (d, *J*=16.2 Hz), 128.6, 127.8, 125.6, 68.9 (d, *J*=4.6 Hz), 62.2 (d, *J*=6.4 Hz), 62.1 (d, *J*=6.7 Hz), 36.0 (d, *J*=136.0 Hz), 16.6 (d, *J*=2.7 Hz), 16.5 (d, *J*=2.9 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C) δ=30.2.

*4.2.4. Diethyl (R)-(2-hydroxy-2-(4-nitrophenyl)ethyl)-phosphonate ((R)-**2e**).*[24] Yellowish oil (25.9 mg, 33% yield, >95% *ee*); $[\alpha]_D^{20}$ −36.8 (*c* 1.4, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ=8.22 (d, *J*=8.7 Hz, 2H, Ar*H*), 7.59 (d, *J*=8.7 Hz, 2H, Ar*H*), 5.25–5.16 (m, 1H, C*H*OH), 4.20–4.07 (m, 4H, 2OCH_2CH$_3$), 2.22–2.11 (m, 2H, CH_2), 1.38 (t, *J*=7.0 Hz, 3H, OCH$_2$CH_3), 1.31 (t, *J*=7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 25 °C) δ=150.6, 126.5, 123.9, 100.3, 69.8–66.8 (m), 62.5 (dt, *J*=7.6, 4.5 Hz), 35.9 (d, *J*=137.1 Hz), 16.6 (d, *J*=5.9 Hz), 16.5 (d, *J*=5.9 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C) δ=29.3.

*4.2.5. Diethyl (R)-(2-hydroxy-2-(3-methoxyphenyl)ethyl)-phosphonate ((R)-**2f**).* Colourless oil (22.3 mg, 31% yield, >95% *ee*); $[\alpha]_D^{20}$ −25.5 (*c* 2.3, $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ=7.37–7.23 (m, 1H, Ar*H*), 7.08–6.92 (m, 2H, Ar*H*), 6.91–6.78 (m, 1H, Ar*H*), 5.25–5.01 (m, 1H, C*H*OH), 4.30–3.99 (m, 4H, 2OCH_2CH$_3$), 3.86 (s, 3H, ArOCH_3), 2.39–2.06 (m, 2H, CH_2), 1.40 (t, *J*=7.1 Hz, 3H, OCH$_2$CH_3), 1.35 (t, *J*=7.0 Hz, 3H, OCH$_2$CH_3). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 25 °C) δ=159.9, 145.3 (d, *J*=16.5 Hz), 129.7, 117.9, 113.5, 111.0, 68.8 (dd, *J*=4.8, 2.1 Hz), 62.2 (d, *J*=6.3 Hz), 62.1 (d, *J*=6.7 Hz), 55.4, 36.1 (d, *J*=136.0 Hz), 16.5 (dt, *J*=10.2, 5.6 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C) δ=30.2. IR (neat): ν(cm^{-1})=3292, 2982, 1594, 1206, 1018. HRMS (ESI) Calcd for $C_{13}H_{22}O_5P^+$ [M+H$^+$]: 289.1205, found: 289.1202.

*4.2.6. Diethyl (R)-(2-hydroxy-2-(naphthalen-2-yl)ethyl)-phosphonate ((R)-**2g**).*[9b] Colourless oil (24.7 mg, 32% yield, >95% *ee*); $[\alpha]_D^{20}$ −31.7 (*c* 1.4, $CDCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ=7.87–7.38 (m, 4H, Ar*H*), 7.50–7.46 (m, 3H, Ar*H*), 5.31–5.26 (m, 1H, C*H*OH), 4.20–4.07 (m, 4H, 2OCH_2CH$_3$), 2.32–2.26 (m, 2H, CH_2), 1.36 (t, *J*=7.0 Hz, 3H, OCH$_2$CH_3), 1.29 (t, *J*=7.0 Hz, 3H, OCH$_2$CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 25 °C) δ=141.0 (d, *J*=16.1 Hz), 133.4, 133.1, 128.5, 128.2, 127.8, 126.3, 126.1, 124.4, 123.7, 69.1 (d, *J*=3.1 Hz), 62.3 (d, *J*=6.5 Hz), 62.2 (d, *J*=7.6 Hz), 36.1 (d, *J*=136.0 Hz), 16.6 (d, *J*=5.4 Hz), 16.5 (d, *J*=5.6 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C) δ=30. 4. IR (neat): ν(cm^{-1})=3321, 2987, 1209, 1070, 1020, 961. HRMS (ESI) Calcd for $C_{16}H_{22}O_4P^+$ [M+H$^+$]: 309.1256, found: 309.1253.

*4.2.7. Diethyl (R)-(2-(2,4-dichlorophenyl)-2-hydroxyethyl)-phosphonate ((R)-**2h**).*[4b,9b] Yellowish oil (23.7 mg, 29% yield, >95% *ee*); $[\alpha]_D^{20}$ −42.6 (*c* 2.0, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ=7.64 (d, *J*=8.4 Hz, 1H, Ar*H*), 7.34 (d, *J*=2.1 Hz, 1H, Ar*H*), 7.30 (dd, *J*=8.4, 2.1 Hz, 1H, Ar*H*), 5.41–5.33 (m, 1H, C*H*OH), 4.24–4.06 (m, 4H,

2OCH_2CH$_3$), 2.34–2.27 (m, 1H, CH_2), 2.03–1.98 (m, 1H, CH_2), 1.39 (t, J=7.1 Hz, 3H, OCH$_2$CH_3), 1.30 (t, J=7.1 Hz, 3H, OCH$_2$CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 25 °C) δ=139.7 (d, J=17.1 Hz), 134.0, 131.8, 129.3, 128.2, 127.8, 65.6 (d, J=4.5 Hz), 62.6 (d, J=6.3 Hz), 62.4 (d, J=6.5 Hz), 34.0 (d, J=135.6 Hz), 16.7 (d, J=5.9 Hz), 16.6 (d, J=6.0 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C) δ=29.8. IR (neat): ν(cm^{-1})=3304, 2991, 1563, 1383, 1210, 1028, 950. HRMS (ESI) Calcd for $C_{12}H_{18}Cl_2O_4P^+$ [M+H$^+$]: 327.0320, found: 327.0325.

*4.2.8. Diethyl (R)-(2-hydroxy-2-(p-tolyl)ethyl)phosphonate ((R)-**2i**).*[4b,25] Yellowish oil (33.4 mg, 49% yield, 94% *ee*); $[\alpha]_D^{20}$ −33.4 (*c* 2.3, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ=7.29 (d, J=8.1 Hz, 2H, ArH), 7.16 (d, J=8.1 Hz, 2H, ArH), 5.13–5.05 (m, 1H, CHOH), 4.13–4.06 (m, 4H, 2OCH_2CH$_3$), 2.34 (s, 3H, ArCH_3), 2.26–2.15 (m, 2H, CH_2), 1.35 (t, J=7.1 Hz, 3H, OCH$_2$CH_3), 1.31 (t, J=7.0 Hz, 3H, OCH$_2$CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 25 °C) δ=140.7 (d, J=16.3 Hz), 137.5, 129.3, 125.6, 68.8 (dd, J=4.7, 1.3 Hz), 62.2 (d, J=6.6 Hz), 62.0 (d, J=6.8 Hz), 36.0 (d, J=135.7 Hz), 21.2, 16.5 (d, J=5.8 Hz), 16.5 (d, J=5.8 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C) δ=30.3.

*4.2.9. Diethyl (R)-(2-(4-fluorophenyl)-2-hydroxyethyl)-phosphonate ((R)-**2j**).*[9b] Yellowish oil (30.7 g, 44% yield, >95% *ee*); $[\alpha]_D^{20}$ −32.7 (*c* 2.3, $CDCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ=7.38–7.33 (m, 2H, ArH), 7.06–7.00 (m, 2H, ArH), 5.13–5.05 (m, 1H, CHOH), 4.18–4.03 (m, 4H, 2OCH_2CH$_3$), 2.21–2.12 (m, 2H, CH_2), 1.35 (t, J=6.9 Hz, 3H, OCH$_2$CH_3), 1.30 (t, J=6.9 Hz, 3H, OCH$_2$CH_3). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 25 °C) δ=162.3 (d, J=245.6 Hz), 139.5 (d, J=16.8 Hz), 127.4 (d, J=8.1 Hz), 115.4 (d, J=21.4 Hz), 68.3 (d, J=3.9 Hz), 62.3 (d, J=6.2 Hz), 62.1 (d, J=6.7 Hz), 36.1 (d, J=136.2 Hz), 16.7 (d, J=5.6 Hz), 16.6 (d, J=5.7 Hz). ^{31}P NMR (121 MHz, $CDCl_3$, 25 °C) δ=29.9. IR (neat): ν(cm^{-1})=3333, 2984, 1604, 1509, 1217, 1020, 957, 836. HRMS (ESI) Calcd for $C_{12}H_{19}FO_4P^+$ [M+H$^+$]: 277.1005, found: 277.1008.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.102.

References and notes

1. For review on asymmetric synthesis, see for example: (a) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008–2022; (b) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734–2793.
2. For selected examples of applications of *sec*-alcohols in different areas see: applications in medicine: (a) Yamauchi, S.; Kinoshita, Y. *Biosci. Biotechnol. Biochem.* **2001**, *65*, 1559–1567; (b) Xiao, H.-Y.; Wu, D.-R.; Malley, M. F.; Gougoutas, J. Z.; Habte, S. F.; Cunningham, M. D.; Somerville, J. E.; Dodd, J. H.; Barrish, J. C.; Nadler, S. G.; Dhar, T. G. M. *J. Med. Chem.* **2010**, *53*, 1270–1280; (c) Sontakke, J. B.; Yadav, G. D. *Ind. Eng. Chem. Res.* **2011**, *50*, 12975–12983; (d) Wei, S.; Messerer, R.; Tsogoeva, S. B. *Chem.—Eur. J.* **2011**, *17*, 14380–14384 Applications in agriculture and food: (e) Deger, W.; Gessner, M.; Guenther, C.; Singer, G.; Mosandl. *J. Agric. Food Chem.* **1988**, *36*, 1260–1264; (f) Hirohara, H.; Nishizawa, M. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 1–9; (g) Mori, K.; Ohtaki, T.; Ohrui, H.; Berkebile, D. R.; Carlson, D. A. *Eur. J. Org. Chem.* **2004**, 1089–1096; (h) Fujii, T.; Yamakawa, R.; Terashima, Y.; Imura, S.; Ishigaki, K.; Kinjo, M.; Ando. *J. Chem. Ecol.* **2013**, *39*, 28–36 Application in liquid crystal field: (i) Parra, M.; Vergara, J.; Hidalgo, P.; Barberá, J.; Sierra, T. *Liq. Cryst.* **2006**, *33*, 739–745.
3. Kitamura, M.; Tokunaga, M.; Noyori. *J. Am. Chem. Soc.* **1995**, *117*, 2931–2932.
4. (a) Maier, L.; Diel, P. J. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *107*, 245–255; (b) Xu, C.; Yuan, C. *Eur. J. Org. Chem.* **2004**, 4410–4415.
5. (a) Hara, N.; Natsume, Y.; Hara, Y.; Goto, Y. *Eur. J. Pharmacol.* **1990**, *179*, 17–23; (b) Ong, J.; Kerr, D. I. B.; Abbenante, J.; Prager, R. H. *Eur. J. Pharmacol.* **1991**, *205*, 319–322; (c) Abbenante, G.; Hughes, R.; Prager, R. H. *Aust. J. Chem.* **1997**, *50*, 523–527; (d) Ong, J.; Marino, V.; Parker, D. A. S.; Kerr, D. I. B. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1998**, *357*, 408–412.
6. Woschek, A.; Lindner, W.; Hammerschmidt, F. *Adv. Synth. Catal.* **2003**, *345*, 1287–1298.
7. For review on asymmetric synthesis of hydroxyphosphonates: Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **2005**, *16*, 3295–3340.
8. Selected examples of asymmetric reduction of β-ketophosphonates: using chiral metal complexes: (a) Madec, J.; Pfister, X.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genet, J. P. *Tetrahedron* **2001**, *57*, 2563–2568; (b) Chávez, M. A.; Vargas, S.; Suárez, A.; Álvarez, E.; Pizzano, A. *Adv. Synth. Catal.* **2011**, *353*, 2775–2794; (c) Tao, X.; Li, W.; Ma, X.; Li, X.; Fan, W.; Zhu, L.; Xie, X.; Zhang, Z. *J. Org. Chem.* **2012**, *77*, 8401–8409 Chirally modified metal hydrides: (d) Meier, C.; Laux, W. H. G. *Tetrahedron: Asymmetry* **1995**, *6*, 1089–1092 Chiral reagents: (e) Nesterov, V. V.; Kolodiazhnyi, O. I. *Tetrahedron* **2007**, *63*, 6720–6731 Biotransformation: (f) Zymanczyk-Duda, E.; Brzezinska-Rodak, M.; Klimek-Ochab, M.; Latajka, R.; Kafarski, P.; Lejczak, B. *J. Mol. Catal. B: Enzym.* **2008**, *52–53*, 74–77; (g) Zymanczyk-Duda, E.; Lejczak, B.; Kafarski, P.; Grimaud, J.; Fischer, P. *Tetrahedron* **1995**, *51*, 11809–11814.
9. Kinetic resolution of 2-hydroxy-2-arylethylphosphonates. Hydrolytic kinetic resolution, selected examples: (a) Zhang, Y.; Yuan, C.; Li, Z. *Tetrahedron* **2002**, *58*, 2973–2978; (b) Zhang, Y.; Li, Z.; Yuan, C. *Tetrahedron Lett.* **2002**, *43*, 3247–3249; (c) Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2003**, *68*, 4815–4818 Acylative kinetic resolution: (d) Moriyama, A.; Matsumura, S.; Kuriyama, M.; Onomura, O. *Tetrahedron: Asymmetry* **2010**, *21*, 810–824 Diastereomeric methods: (e) Rojas-Cabrera, H.; Fernández-Zertuche, M.; García-Barradas, O.; Muñoz-Muñiz, O.; Ordóñez, M. *Tetrahedron: Asymmetry* **2007**, *18*, 142–148.
10. For review on kinetic resolution, see: (a) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5–26 For review on non-enzymatic kinetic resolution, see: (b) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407–1446; (c) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 1613–1666 For a recent review on non-enzymatic acylative kinetic resolution, see: (d) Müller, C. E.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 6012–6042.
11. For a recent review on chiral DMAP derivatives, see: Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570–5595.
12. (a) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809–1810; (b) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584–2585.
13. Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230–7231.
14. (a) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492–1493; (b) Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794–2795.
15. Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu. *J. Am. Chem. Soc.* **1999**, *121*, 5091–5092.
16. Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *Chem. Commun.* **2000**, 1009–1010.
17. (a) Lee, S. Y.; Murphy, J. M.; Ukai, A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 15149–15153; (b) Díaz-Álvarez, A. E.; Mesas-Sánchez, L.; Dinér, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 502–504.
18. Mesas-Sánchez, L.; Díaz-Álvarez, A. E.; Dinér, P. *Tetrahedron* **2013**, *69*, 753–757.
19. For a recent review on assignment of absolute configuration using chiral reagents and NMR spectroscopy, see: (a) Wenzel, T. J.; Chisholm, C. D. *Chirality* **2011**, *23*, 190–214 For a selected example where quinine is used as a chiral solvating agent, see: (b) Maly, A.; Lejczak, B.; Kafarski, P. *Tetrahedron: Asymmetry* **2003**, *14*, 1019–1024.
20. Kolodyazhnyi, O. I.; Kolodyazhnaya, A. O.; Kukhar, V. P. *Russ. J. Gen. Chem.* **2006**, *76*, 1342–1343.
21. All the ^{31}P NMR spectra of the racemic substrates **2a**–**j** both in the absence and in presence of quinine are included in the Supplementary data.
22. (a) Li, X.; Liu, P.; Houk, K. N.; Birman, V. B. *J. Am. Chem. Soc.* **2008**, *130*, 13836–13837; (b) Wei, Y.; Held, I.; Zipse, H. *Org. Biomol. Chem.* **2006**, *4*, 4223–4230; (c) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169–3170.
23. (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249–330; (b) Goodman, J. M.; Kohler, A.-K.; Alderton, S. C. M. *Tetrahedron Lett.* **1999**, *40*, 8715–8718; (c) http://www.jmg.ch.cam.ac.uk/tools/magnus/KinRes.html.
24. Coutrot, P.; Youssefi-Tabrizi, M.; Grison, C. *J. Organomet. Chem.* **1986**, *316*, 13–18.
25. Truel, I.; Mohamed-Hachi, A.; About-Jaudet, E.; Collignon, N. *Synth. Commun.* **1997**, *27*, 297–302.