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Rh(I)-catalyzed asymmetric transfer hydrogenation of α-enamidophosphonates to α-aminophosphonates

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ABSTRACT

An asymmetric Rh-catalyzed transfer hydrogenation was developed for the conversion of α-enamidophosphonates to α-aminophosphonates (α-APs) using isopropanol as the hydride donor. This methodology is amenable to a broad substrate scope. A library of structurally diverse α-APs was synthesized in moderate to good yield and enantiomeric excess, having a methylene moiety at C_β and aryl, heteroaryl or alkyl side chains.

1. Introduction

Bioisosteres of α-amino acids, such as α-aminophosphonic acids (α-APAs), are valuable building blocks in medicinal chemistry, particularly in the design of peptidomimetic drugs [1]. Examples of biologically active compounds containing α-APAs include the antimicrobial agent alafosfalin (**1**) [2], the angiotensin converting enzyme (ACE) inhibitor K-26 (**2**) [3], and the hepatitis C virus (HCV) NS3/4A protease inhibitor **3** [4] (Fig. 1). Recently, we reported a novel class of thienopyrimidine-based allosteric inhibitors of the human farnesyl pyrophosphate synthase (hFPPS) that contain an α-APA moiety as part of their key pharmacophore (**4**) [5]. In the course of our medicinal chemistry investigations, we discovered that the stereochemistry at C_α of analogs **4** directs the binding orientation of these inhibitors to the biological target, leading to two distinct and divergent SAR models for the (*R*)- and (*S*)-enantiomers [5]. Consequently, the development of efficient asymmetric methodologies for the preparation of structurally diverse α-APAs became essential to our research and of general value in medicinal chemistry.

Although numerous catalytic methods have been reported for the asymmetric synthesis of α-APAs [6], previous investigations have focused mainly on the synthesis of analogs with aryl substituents directly attached on the C_α [7], cyclic quaternary APAs [8], or APAs having a C_β that is tertiary or quaternary [9]. In contrast, only a few reports provide a limited number of examples bearing a methylene moiety at C_β (Scheme 1) [10]. Some of the challenges associated with the synthesis of such compounds include the tautomerization of aldimines to the more stable enamine [5,10a], the need for high pressure of H_2 [11a,b] (with one notable exception [10e]), and the use of sophisticated organocatalysts [10d,e,g], thus somewhat hindering the utility of these methodologies for library synthesis of structurally diverse α-APAs building blocks for medicinal chemistry.

Although metal-catalyzed asymmetric hydrogenation reactions using H_2 gas can be highly successful, in some cases, the need for very high pressures of H_2 gas can present a safety concern, require the use of costly specialized equipment and consequently, decrease the practical applications of a methodology, particularly in large-scale reactions [11c]. Regarding the preparation of chiral α-APAs, a new methodology that is amenable to the synthesis of structurally diverse analogs having a methylene at C_β, preferably without the use of high-pressure H_2 gas and using commercially available metal catalysts and ligands would be highly desirable. To this end, an asymmetric Rh-catalyzed transfer hydrogenation was developed using isopropanol as the hydride donor, to prepare a series α-APAs in good yield and enantiomeric excess.

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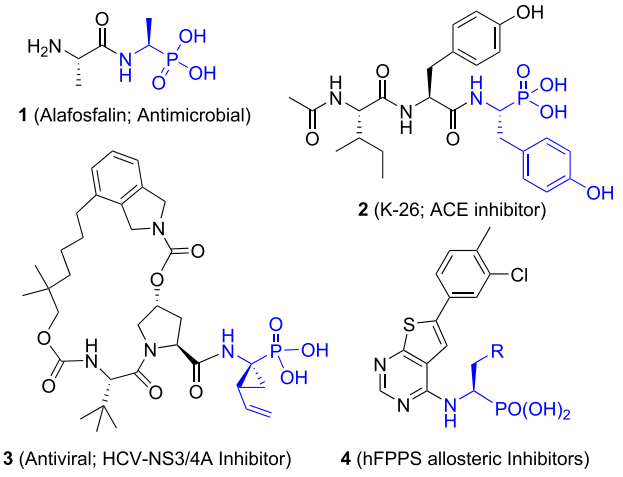
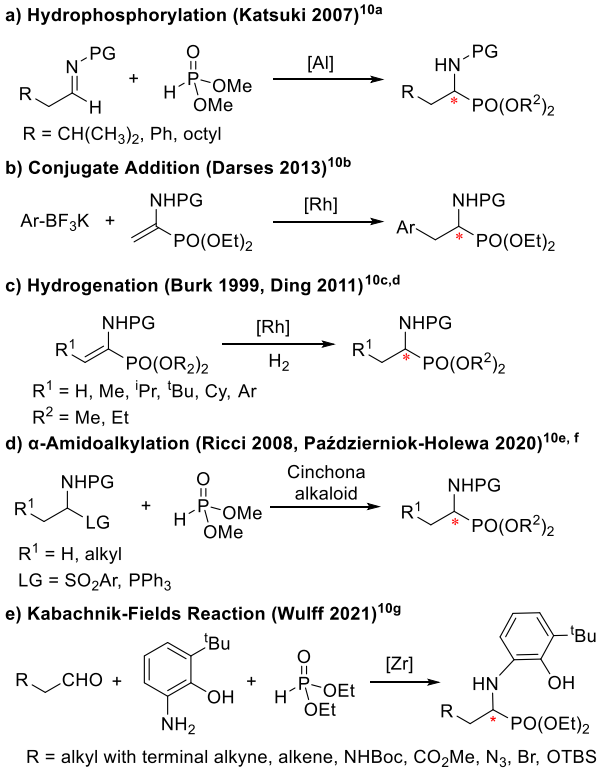


Fig. 1. Examples of biologically active compounds containing α-amino phosphonic acid (C_α-APA).



Scheme 1. Examples of Asymmetric Synthesis of C_α-APAs having a Methylene Moiety at C_β

2. Results and discussion

Initially, the transfer hydrogenation of the model substrate diethyl (1-acetamido-2-phenylvinyl) phosphonate (*E*/*Z*-**5a**) to the diethyl (1-acetamido-2-phenyl)phosphonate (**6a**) was surveyed. Using 2.5–5 mol% of $Rh(nbd)_2BF_4$ as the rhodium precursor, 25 commercially available ligands were evaluated, including phosphine-based ligands (*R,R,R,R*)-MeO-BIBOP (**L1**), (*S,S*)-Chiraphos (**L6**), (*S*)-BINAP (**L7**), (*S*)-SEGPHOS (**L8**), (R)-QuinoxP* (**L11**) and (*1R,1′R,2S,2′S*)-DuanPhos (**L13**) (Fig. 2); for a complete list of the ligands evaluated refer to Figure S1. The precursor (*E*/*Z*)-**5a** was

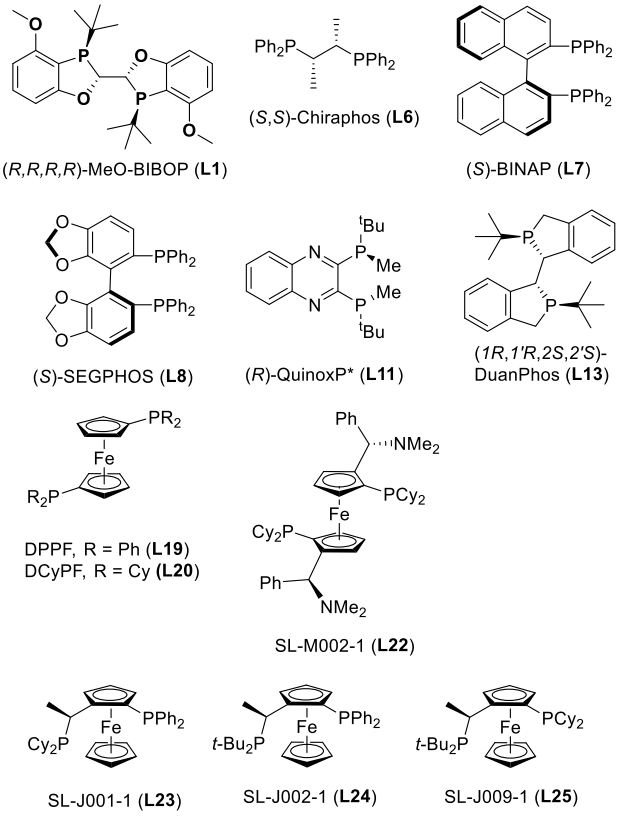
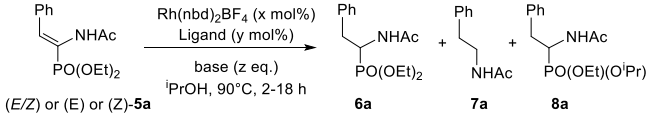


Fig. 2. Evaluation of ligands in Asymmetric transfer hydrogenation of **5a**.

prepared using Zard's previously reported protocol [12], and % conversion to the desired product **6a** was estimated by ^{31}P NMR (Table 1). We noted that some of the chiral bidentate ligands

Table 1
Examples of Ligand Evaluation for the Transfer Hydrogenation of (*E*/*Z*)-**5a** to α-Aminophosphonate **6a**..



Entry	5a	Ligand	Conv. 6a (%)[a]	Yield 6a (%)[b]	%ee (S)[c]
1[d]	E/Z	L6/8	15–20	–	–
2[d]	E/Z	L11	<5	–	–
3[d]	E/Z	L1	95	–	0
4[d]	E/Z	L19	85	–	0
5[d]	E/Z	L7	14	–	–
6[e]	E	L7	87	–	0
7[e]	Z	L7	<5	–	–
8[f]	E	L22	<40	–	–
9[f]	E	L23	0	–	–
10[f]	E	L24	>98	40	65
11[f]	E	L25	>98	78	80
12[f]	Z	L25	73	27	<10
13[f, g]	E	L25	0	–	–

[a] Estimated by ^{31}P NMR based on decrease of starting material.
[b] Isolated yields.
[c] %ee as determined by chiral HPLC.
[d] 5 mol% $Rh(nbd)_2BF_4$, Ligand, 1 eq. EtONa, 90 °C, 16 h.
[e] 2.5 mol% $Rh(nbd)_2BF_4$, 2.8 mol% **L7**, 1 eq. ^{i}PrONa, 90 °C, 18 h.
[f] 3 mol% $Rh(nbd)_2BF_4$, 3.3 mol% **L25**, 0.2 eq. ^{i}PrONa, 80 °C, 14 h.
[g] Without base.

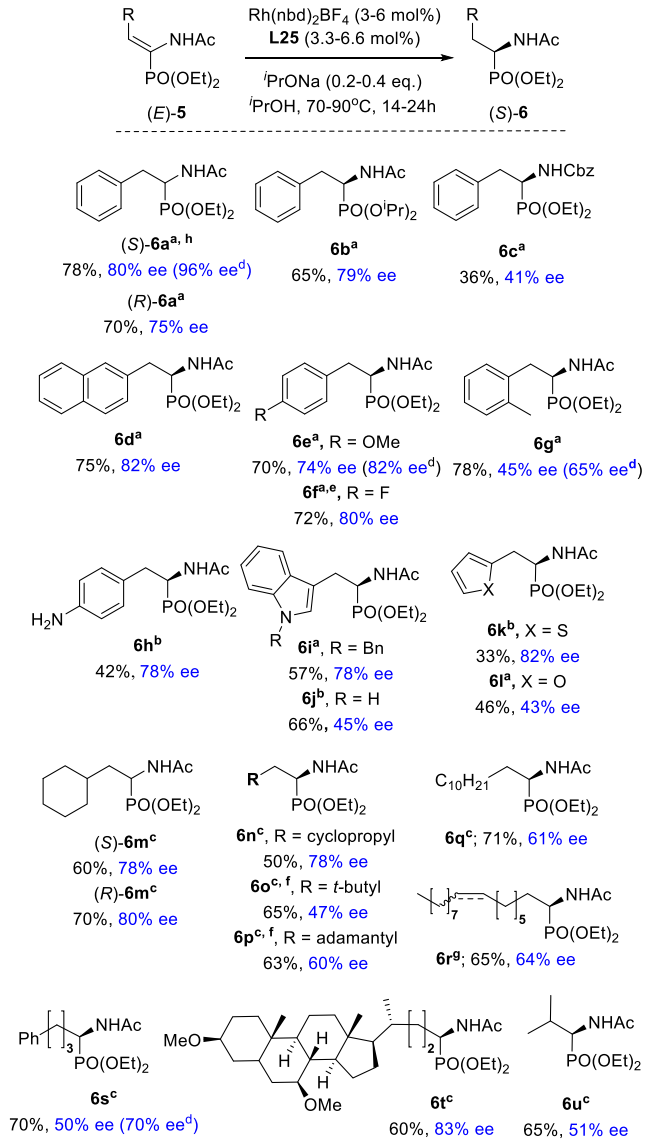
commonly used in asymmetric hydrogenation, such as **L6**, **L8** (entry 1; 15–20%) and **L11** (entry 2; <5%), lead to very low conversion to the desired product **6a.** The formation of two major by-products, the dephosphorylated compound **7a** and the transesterification product **8a**, was observed in all three cases. In contrast, very high conversion to **6a** was observed with **L1** and **L19**, although the product formed (in both cases) was racemic (entries 3 and 4). Replacement of the ferrocene ligand **L19** with the structurally related analog **L20** lead to the same conversion in only 2 h, suggesting that the use of more electron-rich ligands can accelerate the reaction rate (Table S1; entries 22 and 23).

The effects of the double bond stereochemistry on the reaction rate were probed using the standard conditions and BINAP (**L7**) as a representative ligand. However, extensive isomerization of (*Z*)-**5a** to (*E*)-**5a** was observed with only 14% conversion to **6a** after 18 h of reaction time with 5 mol% rhodium precursor and ligand (entry 5, Table 1; Figure S1). With 2.5 mol% catalyst, <5% conversion of the (*Z*)-**5a** to product was detected, whereas the conversion of (*E*)-**5a** to **6a** was estimated to 87%, *albeit* without any enantioselectivity (entries 6 and 7, Table 1). These observations suggested that the isomerization of (*Z*)- to (*E*)-**5a** was faster than the conversion of either isomer to product **6a**, leading to an overall decrease in the reaction rate.

Based on the above preliminary evaluation and the encouraging results we observed with the non-chiral ferrocene ligands (**L19**/**L20**), we continued our investigations using only the (*E*)-**5a** to screen a number of other chiral ferrocene-based ligands.

After further investigations, optimal conditions were determined to be 3 mol% % $Rh(nbd)_2BF_4$, 3.3 mol % **L25**, and 0.2 eq. of freshly prepared ^{i}PrONa at 80 °C (for full optimization refer to Table S2-3). These conditions allowed for improved yield and enantioselectivity (Table 1; entries 10 and 11). Although the conversion was poor when the ferrocene-based Mandyphos (**L22**; entry 8) was used, modulation of the steric and electronic properties of these ligands provided insight into the factors improving conversion and enantioselectivity (entries 8–13). For example, the reaction run with **L23**, having a relatively electron-poor diphenyl phosphine and a relatively less hindered dicyclohexyl phosphine than **L22**, resulted in negligible conversion after 14 h (entry 9). However, replacement of the cyclohexyl groups with more sterically demanding *t*-butyl groups lead to high overall conversion, *albeit* with low isolated yield of (*S*)-**6a** and in 65% ee; the low isolated yield was due to the formation of some by-products including **7a** and **8a** (entry 10). Subsequent replacement of the diphenyl phosphine with a more electron-rich alkylphosphine, such as in **L25** (SL-J009-1), lead to clean conversion to (*S*)-**6a** with a significant increase in both the isolated yield (78%) and the enantiomeric purity (80%ee; 96%ee after crystallization) of (*S*)-**6a** (entry 11) [13]. It is noteworthy that under the same reaction conditions (as in entry 11), (*Z*)-**5a** showed much lower conversion and <10% ee (entry 12). Our data suggests that this methodology is stereospecific with regard to the (*E/Z*)-geometry of the α-enamidophosphonate double bond, leading to an enantiodivergent outcome [14]. Additionally, in the absence of an alkoxide base (preferably ^{i}PrONa) the reaction does not proceed (entry 13), which is consistent with previous reports for metal-catalyzed transfer hydrogenation [15]. Although the reaction also proceeded in EtOH under the optimized condition, the conversion was much lower (Table S3; entry 6) possibly due to the formation of a stable Rh-carbonyl complex that arises from acetaldehyde decarbonylation after EtOH hydride transfer, which leads to catalyst deactivation [16].

We then turned our attention to exploring the substrate scope of this methodology. A library of α-enamidophosphonates bearing aryl, heteroaryl and alkyl side chains were tested (Scheme 2). It is noteworthy that although (*S*)-**6a** was obtained in 78% isolated yield



[a]Condition A: 3 mol% $Rh(nbd)_2BF_4$, 3.3 mol% **L25**, 0.2 eq. ^{i}PrONa, ^{i}PrOH, 80°C, 14 h; [b]Condition B: 6 mol% $Rh(nbd)_2BF_4$, 6.6 mol% **L25**, 0.4 eq. ^{i}PrONa, ^{i}PrOH, 90°C, 14 h; [c]Condition C: 3 mol% $Rh(nbd)_2BF_4$, 3.3 mol% **L25**, 0.2 eq. ^{i}PrONa, ^{i}PrOH, 70°C, 12 h. [d]mother liquor after crystallization of racemate. [e]24 h reaction time. [f]72°C for 90% conversion on ^{31}P NMR after 14 h. [g]Condition D: 6 mol% $Rh(nbd)_2BF_4$, 6.6 mol% **L25**, 0.4 eq. ^{i}PrONa, ^{i}PrOH, 70°C, 12 h. [h]1 mmol scale.

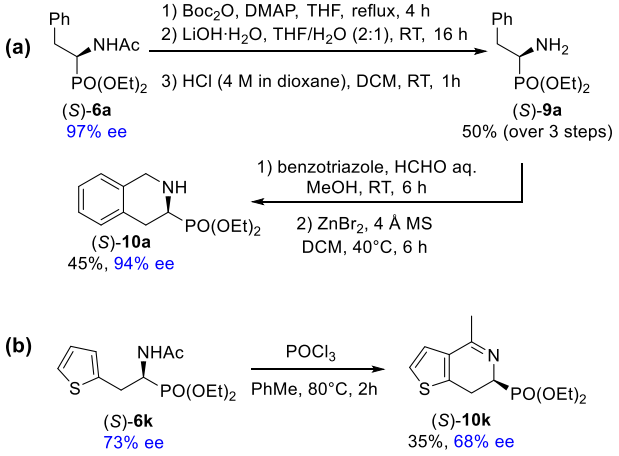
Scheme 2. Substrate Scope.

with 80% ee, crystallization of this product led to racemate crystals and isolation of the (*S*)-**6a** in 97% ee in the mother liquor. We were also able to synthesize (*R*)-**6a** in comparable yield and enantiomeric purity by simply exchanging the ligand **L25** with its enantiomer (SL-J009-2)**.** We also noted that whereas increasing the steric bulk of the phosphonate ester groups (from Et to ^{i}Pr; analog **6b**) did not significantly impact the enantioselectivity nor the yield of this reaction, replacement of the *N*-acetyl with *N*-Cbz resulted in a dramatic decrease in both yield and enantiomeric excess (**6c**), and led to the formation of some transesterification product on the carbamate (*i.e.* benzyloxy to isopropoxy). Naphthyl (**6d**) and phenyl bearing electron donating or withdrawing groups (**6e**, **6f**) were prepared in similar yields and %ee, although analogs substituted with electron-withdrawing groups proceeded with lower

efficiency. It is noteworthy that the *R*-enantiomers of compounds **6e** and **6f** were previously reported by Darses [10c]; we assigned the absolute stereochemistry of our compounds as the *S*-enantiomers by comparison using the same type of chiral HPLC column. However, the olefin of diethyl (*E*)-(1-acetamido-2-(4-nitrophenyl) vinyl) phosphonate (**5h**) was particularly resistant to this transformation at 80 °C with 3 mol% rhodium precursor. In the presence of higher amounts of rhodium precursor (6 mol%) and base (0.4 eq. ^{i}PrONa), the hydrogenated product **6h** was observed in modest yield and good enantiomeric excess (42% yield, 78% ee). α-Aminophosphonates with various heterocyclic side chains (**6i-6l**) could also be synthesized in yields ranging from 33 to 66% and enantiomeric excess of 43–82%. We suspect that the less favorable outcomes may be due to the undesirable coordination of the heteroatom to the rhodium center. For example, the *N*-benzyl 3-indolyl analog **6i** was isolated in 78% ee, whereas its corresponding unprotected analog **6j** was isolated in only 45% ee. Efficient transfer hydrogenation of several alkyl substituted substrates was also achieved in modest to good yield and enantiomeric excess at lower temperature and in shorter reaction time. For example, both the (*S*)- and (*R*)-enantiomers of the cycloalkyl analog **6m** were obtained in 60–70% yield and 78–80% ee.

Steric hindrance near the olefin moiety in analogs with either an aryl or alkyl side chains appeared to be detrimental to the enantioselectivity (*e.g.* **6a** vs. **6g** and **6n** vs. **6o**). However, substrates with additional double bonds on their side chain, such as the oleic acid derivative **5r**, could only be fully hydrogenated to give **6r** in the presence of 6 mol% catalyst and 0.4 eq. ^{i}PrONa in 12 h. The selective transfer hydrogenation at the $C_\alpha = C_\beta$ of **5r** could be achieved with 3 mol% catalyst, while isomerization of the oleyl side chain from *cis* to *trans* was also observed. More complex substrates, such as the ursodeoxycholic acid analog **5t** was converted to the corresponding product **6t** in good yield (60%) and enantioselectivity (83% ee). Finally, tetrasubstituted olefinic precursor **5u** could also be transformed to the phosphonate equivalent of valine in moderate yield and enantiomeric excess. At even lower catalyst loading (1.5 mol%) the conversion of **5u** to **6t** occurred in 12 h, without increase in the enantiomeric excess of the product, suggesting that steric hindrance on the C_β was detrimental to the asymmetric induction.

It should be noted that all of the above reactions were run in a library mode with only minor adjustments. Therefore, it is entirely possible that optimization of each substrate individually can lead to better yield and enantiomeric excess of each product. To test this hypothesis, we decided to monitor the enantiomeric purity of product formation from our model substrate (*E*)-**5a** under our optimized reaction conditions over the course of different time intervals. We previously noted that the transfer hydrogenation of (*E*)-**5a** to (*S*)-**6a** was achieved without the formation of any significant amounts of by-products (**7a** and **8a**) in 78% yield and 80% ee when the reaction was performed with $Rh(nbd)_2BF_4$ (3 mol%) in the presence of ligand **L25** (3.3 mol%) and ^{i}PrONa (0.2 eq) in ^{i}PrOH at 80 °C over 14 h. We ran the same reaction over an 18 h period and the formation of the desired product (*S*)-**6a** was monitored by its ^{31}P NMR. Additionally, at different time intervals, the product was isolated, and its enantiomeric purity was determined by chiral HPLC (Figure S3). We noticed an erosion of enantiomeric purity with time, ranging from 93% ee at 6 h (~40–50% conversion), to 80% ee at 14 h (complete conversion) and 76% ee at 18 h. The prolonged reaction period was also associated with more by-product formation. Collectively these results suggest that the mechanism of this reaction likely involves some reversible step(s) that can lead to scrambling of the stereochemistry and dephosphorylation of the desired product.



Scheme 3. Conversion of α-Aminophosphonates to Heterocycles.

In addition to the direct applications of α-aminophosphonates in medicinal chemistry, they can also serve as precursors for the synthesis of heterocycles. To showcase our methodology, the transfer hydrogenation protocol was used in the synthesis of a few enantioenriched saturated heterocycles. For example, following the *N*-deacetylation of (*S*)-**6a**, using a mild 3-step protocol [5,17], the amine (*S*)-**9a** can cyclize to generate the (*S*)-tetrahydroisoquinolinephosphonate (*S*)-**10a** via the Pictet-Spengler reaction as recently reported (Scheme 3a) [18]. Other examples includes cyclization of analog (*S*)-**6k** to diethyl (*S*)-(4-methyl-6,7-dihydrothieno[3,2-c]pyridin-6-yl)phosphonate (*S*)-**10k** using Bischler-Napieralski reaction (Scheme 3b) [19]. To the best of our knowledge, compound (*S*)-**10k** has not been previously reported and it represents an expansion of structural diversity in heterocyclic chemistry.

Finally, to probe the mechanism of the transfer hydrogenation reaction, deuterium labelling experiments were conducted (Scheme S1). When the reaction was carried out in ^{i}PrOD-d_8, ^{2}H-incorporation was observed at both the C_α and C_β to >95%, confirming that both hydrogens were donated by isopropanol. Furthermore, when the reaction was run in 1:1 ^{i}PrOH: ^{i}PrOD-d_8, a primary kinetic isotope effect (H:D = 4:1) was observed for the hydrogen incorporation at both the C_α and C_β, suggesting that the hydride transfer to the alkene is involved in the rate-limiting step (rds) (Scheme S1) [20]. Additionally, we observed two broad chemical shifts in the ^{1}H NMR spectrum of the reaction mixture (at 80 °C after 2 h) at −2.7 ppm and −2.8 ppm, suggesting the formation of a rhodium-hydride complex. Based on literature precedence [15,21] and our experimental observations, the mechanism shown in Fig. 3 was postulated.

3. Conclusion

In summary, a Rh(I)-catalyzed asymmetric transfer hydrogenation reaction was developed for a library synthesis of α-aminophosphonates (α-APs) from α-enamidophosphonates, using isopropanol as the hydrogen source. This methodology has a broad substrate scope, allowing for the synthesis of underrepresented aryl and alkyl substituted α-APs containing a methylene moiety at the C_β. These compounds and their corresponding cyclized heterocycles are valuable building blocks in medicinal chemistry and open new chemical space in heterocyclic chemistry.

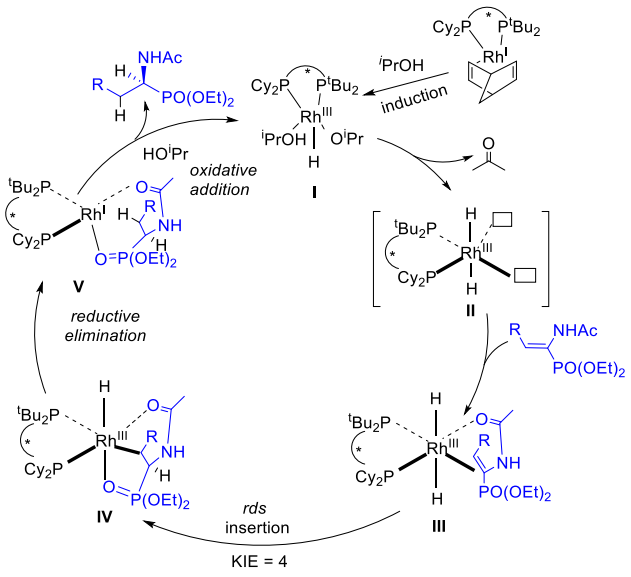


Fig. 3. Proposed reaction mechanism.

4. Experimental section

4.1. General

All reactions were carried out under argon unless otherwise specified. DCM, THF and isopropanol were dried using CaH_2 or Na/benzophenone under argon. Other anhydrous solvents were obtained directly from solvent purification system (SPS) flushed with N_2. Commercial reagents were used directly, unless otherwise indicated. Completion of all reactions was monitored by TLC, LC-MS and/or ^{31}P NMR. Normal-phase flash column chromatography was performed on silica gel (Sigma Aldrich, 60 Å, 230–400 mesh, 40–63 μm). Reversed-phase flash column chromatography was performed on prepacked C18 silica gel (Teledyne ISCO, RediSep® Rf Gold, 20 to 40 μm, 100 Å, 5.5 g/15 g/30 g) using Combiflash Rf® (Teledyne ISCO). Thin Layer Chromatography (TLC) was performed on glass plates pre-coated with silica gel (Silicycle, 60 Å, F254), and visualized by UV fluorescence when applicable (λ_{max} = 254 nm) and/or by staining with basic aqueous $KMnO_4$ solution or ninhydrin. All compounds were fully characterized by ^{1}H, $^{13}C\{^{1}H\}$, $^{19}F\{^{1}H\}$, $^{31}P\{^{1}H\}$ NMR. HRMS were reported for new compounds. ^{1}H NMR were recorded at 400 or 500 MHz and coupling constants (J) are reported to ± 0.5 Hz. $^{13}C\{^{1}H\}$ NMR were recorded at 126 MHz and $^{31}P\{^{1}H\}$ NMR were recorded at 202 or 162 MHz, unless otherwise indicated. Chemical shifts (δ) are reported in ppm relative to the internal deuterated solvent. Overnight Variable Temperature NMR (VT-NMR) experiments were conducted in Bruker Avance III HD 400 spectrometer (with BBFO + SmartProbe) under inert atmosphere in a sealed NMR tube. Enantiomeric purity of chiral compounds was determined by chiral HPLC using an Agilent 1100 series instrument and the column type and solvent system indicated. The absolute stereochemistry of the major enantiomer in each product is presumed to be the same as that of compound **6a**, which was previously assigned by X-ray crystallography [5]. Reversed-phase HPLC-LRMS was conducted on Waters e2695 Separations Module and 3100 Mass Detector using an Atlantis T3 OBD, 5 μm, 4.6 mm × 100 mm column and a linear gradient of H_2O:MeCN from 95:5 to 5:95 in 13 min then 100% MeCN for 2 min at a flow rate of 1 mL/min (all solvents contained 0.1% formic acid) with ESI ± modes. HRMS were obtained using ESI ± ionization and Fourier transform ion cyclotron resonance mass analyzer (FTMS), and the quoted masses are accurate to ±5 ppm.

4.2. General procedure of asymmetric transfer hydrogenation from α-enamidophosphonates 5 to α-aminophosphonates **6**

All operations were done under inert atmosphere with proper Schlenk line techniques. Isopropanol was freshly distilled with CaH_2 under argon before reaction setup. Reaction vessels were 10 or 25 mL Biotage® microwave tubes with crimp caps and Teflon septa. For 0.1 mmol scale reactions, $Rh(nbd)_2BF_4$ (3–6 mol%) and ligand (3.3–6.6 mol%) were mixed with freshly made ^{i}PrONa (0.1 M ^{i}PrOH solution, 0.2–0.4 eq.) in total volume of 0.5 mL ^{i}PrOH and stirred 50 °C for 10 min (forming bright orange clear solution). 0.2 M ^{i}PrOH solution of α-enamidophosphonate **5** was added dropwise into the catalyst solution and the mixture was stirred for another 15 min before heating to 70–90 °C for the corresponding reaction time (12–24 h, reddish orange to crimson solution before full conversion). The crude was concentrated and directly purified by reversed-phase column chromatography with prepacked C18 silica gel column using a gradient of 10–100% MeCN in H_2O to obtain the desired product unless specified. The racemate can be crystallized out of solution by using minimal amount of DCM in pentane at −20 or 0 °C.

Condition A: 3 mol% $Rh(nbd)_2BF_4$, 3.3 mol% **L25**, 0.2 eq. ^{i}PrONa, ^{i}PrOH, 80 °C, 14 h.
Condition B: 6 mol% $Rh(nbd)_2BF_4$, 6.6 mol% **L25**, 0.4 eq. ^{i}PrONa, ^{i}PrOH, 90 °C, 14 h.
Condition C: 3 mol% $Rh(nbd)_2BF_4$, 3.3 mol% **L25**, 0.2 eq. ^{i}PrONa, ^{i}PrOH, 70 °C, 12 h.
Condition D: 6 mol% $Rh(nbd)_2BF_4$, 6.6 mol% **L25**, 0.4 eq. ^{i}PrONa, ^{i}PrOH, 70 °C, 12 h.

4.2.1. Diethyl (S)-(1-acetamido-2-phenylethyl)phosphonate (**6a**)

Condition A was used. It should be noted that both the (*S*)-**6a** and (*R*)-**6a** were previously reported [5,10c,10e]. Enantioenriched product as colorless oil. A 1 mmol reaction was completed with (*E*)-**5a** to yield 235 mg (*S*)-**6a** as colorless mixture of oil and solid (78% yield, 80% ee). After crystallization of racemate, 175 mg colorless oil was isolated from the mother liquor as (*S*)-**6a** with 96% ee. A 0.1 mmol reaction was completed using Josiphos SL-J009-2 to yield (*R*)-**6a** as colorless oil (70% yield, 75% ee). Spectra are consistent with previous report [5]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.13 (m, 5H), 6.68 (d, J = 9.8 Hz, 1H, *NH*), 4.78 (dtd, J = 16.2, 10.4, 4.9 Hz, 1H), 4.25–4.00 (m, 4H), 3.22 (ddd, J = 14.5, 8.1, 4.7 Hz, 1H), 2.94 (dt, J = 14.5, 10.7 Hz, 1H), 1.91 (d, J = 1.2 Hz, 3H), 1.31 (t × 2, J = 7.0 Hz, 6H). $^{31}P\{^{1}H\}$ NMR (203 MHz, $CDCl_3$) δ 24.22. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 169.7 (d, J = 5.0 Hz), 136.8 (d, J = 13.3 Hz), 129.2 (s, C × 2), 128.5 (s, C × 2), 126.8, 62.7 (d × 2, J = 6.9 Hz), 46.1 (d, J = 156.6 Hz), 35.7 (d, J = 3.2 Hz), 22.9, 16.5 (d × 2, J = 6.0 Hz). Chiral HPLC condition: CHIRALCEL OD (4.6 mm × 250 mm), 95:5 Hexane:^{i}PrOH, 0.8 ml/min, 214 nm. (*R*)-**6a** t_R = 13.8 min, (*S*)-**6a** t_R = 15.2 min.

4.2.2. Diisopropyl (S)-(1-acetamido-2-phenylethyl)phosphonate (**6b**)

The (*R*)-**6b** was previously reported [10i]. Condition A was used. Enantio-enriched product (21 mg) as colorless oil (65% yield, 79% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.23 (m, 2H), 7.24–7.17 (m, 3H), 5.95 (d, J = 10.4 Hz, 1H, *NH*), 4.78–4.67 (m, 3H), 3.21 (ddd, J = 14.0, 8.9, 4.5 Hz, 1H), 2.86 (dt, J = 14.2, 10.1 Hz, 1H), 1.86 (s, 3H), 1.32 (t × 2, J = 5.7 Hz, 9H), 1.25 (d, J = 6.3 Hz, 3H). $^{31}P\{^{1}H\}$ NMR (162 MHz, $CDCl_3$) δ 22.27. $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 169.3 (d, J = 6.0 Hz), 136.9 (d, J = 13.3 Hz), 129.3 (s, C × 2), 128.5 (s, C × 2),

126.9, 71.6 (d × 2, J = 7.3 Hz), 46.8 (d, J = 158.4 Hz), 36.1 (d, J = 3.7 Hz), 24.3 (d, J = 3.7 Hz), 24.2 (d, J = 3.7 Hz), 24.1 (d, J = 5.0 Hz), 23.9 (d, J = 5.0 Hz), 23.10. HRMS: Calcd. for $C_{16}H_{27}O_4NP^+$ [M + H^+]: 328.1672; Found: 328.1670. Chiral HPLC condition: CHIRALPAK AD (4.6 mm × 250 mm), 97:3 Hexane:^{i}PrOH, 1 ml/min, 214 nm. (*R*)-**6b** t_R = 20.6 min, (*S*)-**6b** t_R = 25.0 min.

4.2.3. Benzyl (S)-(1-(diethoxyphosphoryl)-2-phenylethyl) carbamate (**6c**)

The *N*-Cbz derivative was previously reported [10e]. Condition A was used. Enantio-enriched product (14 mg) as colorless oil (36% yield, 41% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.04 (m, 10H), 5.00 (s, 2H), 4.94 (d, J = 10.0 Hz, 1H, *NH*), 4.40 (dq, J = 16.5, 5.7 Hz, 1H), 4.18–3.95 (m, 4H), 3.24 (ddd, J = 14.2, 9.5, 4.6 Hz, 1H), 2.85 (dt, J = 14.2, 9.5 Hz, 1H), 1.26 (t × 2, J = 7.1 Hz, 6H). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 23.88 (major), 23.27 (minor). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 155.8 (d, J = 5.8 Hz), 136.6 (d, J = 12.9 Hz), 136.4, 129.4 (s, C × 2), 128.6 (s × 2, C × 4), 128.2, 128.1, 126.9, 67.1, 62.8 (d × 2, J = 6.9 Hz), 48.7 (d, J = 156.9 Hz), 36.1 (d, J = 4.3 Hz), 16.5 (d, C × 2, J = 6.2 Hz). HRMS: Calcd. for $C_{20}H_{26}O_5NPNa^+$ [M + Na^+]: 414.1441; Found: 414.1434. Chiral HPLC condition: CHIRALPAK AD (4.6 mm × 250 mm), 90:10 Hexane:^{i}PrOH, 1 ml/min, 220 nm. (*R*)-**6c** t_R = 15.0 min, (*S*)-**6c** t_R = 20.1 min.

4.2.4. Diethyl (S)-(1-acetamido-2-(naphthalen-2-yl)ethyl) phosphonate (**6d**)

The (*R*)-**6d** was previously reported [10i]. Condition A was used. Enantio-enriched product (26 mg) as yellow oil (75% yield, 80% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83–7.73 (m, 3H), 7.67 (s, 1H), 7.50–7.39 (m, 2H), 7.38 (dd, J = 8.5, 1.8 Hz, 1H), 6.13 (d, J = 10.0 Hz, 1H, *NH*), 4.89 (dtd, J = 16.4, 10.1, 4.9 Hz, 1H), 4.20–4.03 (m, 4H), 3.38 (ddd, J = 14.2, 8.8, 4.9 Hz, 1H), 3.08 (dt, J = 14.5, 10.5 Hz, 1H), 1.85 (s, 3H), 1.29 (t × 2, J = 7.0 Hz, 6H). ^{31}P{^{1}H} NMR (203 MHz, $CDCl_3$) δ 24.28.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.6 (d, J = 5.1 Hz), 134.2 (d, J = 12.5 Hz), 133.5, 132.5, 128.2, 127.9, 127.8, 127.7, 127.4, 126.2, 125.7, 62.8 (d × 2, J = 7.0 Hz), 46.1 (d, J = 156.3 Hz), 36.1 (d, J = 3.4 Hz), 23.1, 16.5 (d × 2, J = 6.4 Hz). HRMS: Calcd. for $C_{18}H_{25}O_4NP^+$ [M + H^+]: 350.1516; Found: 350.1515. Chiral HPLC condition: CHIRALCEL OD (4.6 mm × 250 mm), 95:5 Hexane:^{i}PrOH, 1 ml/min, 220 nm. (*R*)-**6d** t_R = 15.5 min, (*S*)-**6d** t_R = 20.9 min.

4.2.5. Diethyl (S)-(1-acetamido-2-(4-methoxyphenyl)ethyl) phosphonate (**6e**)

The (*R*)-**6e** was previously reported [10c]. Condition A was used. Enantioenriched product (23 mg) as colorless oil (70% yield, 74% ee). Crystallization of racemate yielded 82% ee in the mother liquor. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.78 (d, J = 10.1 Hz, 1H, *NH*), 4.72 (dtd, J = 15.0, 10.1, 4.8 Hz, 1H), 4.26–3.99 (m, 4H), 3.77 (s, 3H), 3.16 (ddd, J = 14.2, 9.2, 4.9 Hz, 1H), 2.83 (dt, J = 14.6, 10.2 Hz, 1H), 1.89 (s, 3H), 1.30 (t × 2, J = 7.0 Hz, 6H). ^{31}P{^{1}H} NMR (203 MHz, $CDCl_3$) δ 24.35.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.5 (d, J = 5.1 Hz), 158.6, 130.2 (s, C × 2), 128.6 (d, J = 12.8 Hz), 114.0 (s, C × 2), 62.8 (d × 2, J = 6.9 Hz), 55.4, 46.3 (d, J = 155.6 Hz), 35.0 (d, J = 3.1 Hz), 23.2, 16.5 (d × 2, J = 5.5 Hz). HRMS: Calcd. for $C_{15}H_{25}O_5NP^+$ [M + H^+]: 330.1465; Found: 330.1455. Chiral HPLC condition: CHIRALCEL OD (4.6 mm × 250 mm), 95:5 Hexane:^{i}PrOH, 0.8 ml/min, 220 nm. (*R*)-**6e** t_R = 18.8 min, (*S*)-**6e** t_R = 23.2 min.

4.2.6. Diethyl (S)-(1-acetamido-2-(4-fluorophenyl)ethyl) phosphonate (**6f**)

The (*R*)-**6f** was previously reported [10c]. Condition A was used; reaction time was 24 h to achieve full conversion. Enantio-enriched product (24 mg) as colorless oil (72% yield, 82% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (dd, J = 8.6, 5.4 Hz, 2H), 6.97 (t, J = 8.7 Hz, 2H), 5.62 (d, J = 9.5 Hz, 1H, *NH*), 4.73 (dtd, J = 15.0, 10.1, 5.0 Hz, 1H), 4.19–4.01 (m, 4H), 3.19 (ddd, J = 14.4, 9.5, 5.0 Hz, 1H), 2.85 (dt, J = 14.8, 10.3 Hz, 1H), 1.89 (s, 3H), 1.30 (t × 2, J = 7.0 Hz, 6H). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 24.00.^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ −116.06.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.6, 162.0 (d, J = 244.9 Hz), 132.4 (d, J = 11.6 Hz), 130.8 (d, C × 2, J = 7.8 Hz), 115.4 (d, C × 2, J = 21.5 Hz), 62.8 (d × 2, J = 6.9 Hz), 46.2 (d, J = 156.1 Hz), 35.2 (d, J = 3.2 Hz), 23.1, 16.5 (d × 2, J = 5.5 Hz). HRMS: Calcd. for $C_{14}H_{22}O_4NFP^+$ [M + H^+]: 318.1265; Found: 318.1267. Chiral HPLC condition: CHIRALCEL OD (4.6 mm × 250 mm), 97:3 Hexane:^{i}PrOH, 1 ml/min, 220 nm. (*R*)-**6f** t_R = 16.6 min, (*S*)-**6f** t_R = 23.3 min.

4.2.7. Diethyl (S)-(1-acetamido-2-(o-tolyl)ethyl)phosphonate (**6g**)

The *N*-Cbz derivative was previously reported [10e]. Condition A was used. Enantio-enriched product (24 mg) as colorless oil (78% yield, 45% ee). Crystallization of racemate yielded 65% ee in the mother liquor. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18–7.07 (m, 4H), 5.95 (d, J = 11.1 Hz, 1H, *NH*), 4.76 (dtd, J = 15.4, 10.3, 4.1 Hz, 1H), 4.27–4.02 (m, 4H), 3.24 (dt, J = 14.8, 5.3 Hz, 1H), 2.85 (dt, J = 14.8, 10.9 Hz, 1H), 2.35 (s, 3H), 1.87 (s, 3H), 1.31 (t × 2, J = 7.2 Hz, 6H). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 24.48.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.5 (d, J = 4.8 Hz), 136.7, 134.9 (d, J = 12.9 Hz), 130.6, 129.7, 127.1, 125.9, 62.8 (d × 2, J = 6.9 Hz), 45.1 (d, J = 156.4 Hz), 33.4 (d, J = 3.8 Hz), 23.1, 19.6, 16.6 (d × 2, J = 6.0 Hz). HRMS: Calcd. for $C_{15}H_{25}O_4NP^+$ [M + H^+]: 314.1516; Found: 314.1517. Chiral HPLC condition: CHIRALCEL OD (4.6 mm × 250 mm), 95:5 Hexane:^{i}PrOH, 0.8 ml/min, 220 nm. (*R*)-**6g** t_R = 12.6 min, (*S*)-**6g** t_R = 15.4 min.

4.2.8. Diethyl (S)-(1-acetamido-2-(4-aminophenyl)ethyl) phosphonate (**6h**)

Condition B was used. Enantio-enriched product (13 mg) as yellow oil, turning to darker color quickly due to oxidation (42% yield, 78% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 8.2 Hz, 2H), 6.62 (d, J = 8.3 Hz, 2H), 5.75 (d, J = 10.4 Hz, 1H, *NH*), 4.71 (dtd, J = 14.9, 10.1, 4.8 Hz, 1H), 4.29–4.02 (m, 4H), 3.14 (ddd, J = 14.2, 9.3, 4.6 Hz, 1H), 2.80 (dt, J = 14.8, 10.1 Hz, 1H), 1.91 (s, 3H), 1.33 (t × 2, J = 7.1 Hz, 6H). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 24.55.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.4 (d, J = 5.2 Hz), 145.2, 130.1 (s, C × 2), 126.4 (d, J = 12.9 Hz), 115.4 (s, C × 2), 62.7 (d × 2, J = 6.7 Hz), 46.3 (d, J = 155.0 Hz), 35.0 (d, J = 3.8 Hz), 23.2, 16.6 (d × 2, J = 5.5 Hz). HRMS: Calcd. for $C_{14}H_{24}O_4N_2P^+$ [M + H^+]: 315.1468; Found: 315.1468. Chiral HPLC condition: CHIRALCEL OD (4.6 mm × 250 mm), 80:20 Hexane:^{i}PrOH, 0.8 ml/min, 220 nm. (*S*)-**6h** t_R = 17.9 min (broad), (*R*)-**6h** t_R = 24.3 min (broad).

4.2.9. Diethyl (S)-(1-acetamido-2-(1-benzyl-1H-indol-3-yl)ethyl) phosphonate (**6i**)

Condition A was used. Enantio-enriched product (24 mg) as white solid (57% yield, 78% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.8 Hz, 1H), 7.31–7.23 (m, 4H), 7.16 (t, J = 7.5 Hz, 1H), 7.14–7.06 (m, 3H), 7.04 (s, 1H), 5.76 (s, 1H, *NH*), 5.27 (s, 2H), 4.84 (dtd, J = 14.8, 9.8, 4.6 Hz, 1H), 4.21–4.00 (m, 4H), 3.34 (ddd, J = 15.9, 11.5, 4.6 Hz, 1H), 3.14 (dt, J = 15.7, 9.3 Hz, 1H), 1.82 (s, 3H), 1.27 (t × 2, J = 7.0 Hz, 6H).^{31}P{^{1}H} NMR (203 MHz, $CDCl_3$) δ 24.51.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.6 (d, J = 5.0 Hz), 137.7, 136.6, 128.8 (s, C × 2), 128.6, 127.7, 126.9 (s, C × 2), 126.7, 122.0, 119.4, 118.9, 110.1 (d, J = 13.3 Hz), 109.9, 62.7 (d × 2, J = 7.0 Hz), 50.1, 45.7 (d, J = 155.8 Hz), 25.6 (d, J = 3.5 Hz), 23.2, 16.5 (d × 2, J = 5.9 Hz). HRMS: Calcd. for $C_{23}H_{29}O_4N_2P^+$ [M + H^+]: 429.1938; Found: 429.1933. Chiral HPLC condition: CHIRALCEL OJ-H (4.6 mm × 250 mm), 95:5 Hexane:^{i}PrOH, 1 ml/min, 220 nm. (*R*)-**6i** t_R = 17.9 min, (*S*)-**6i** t_R = 24.0 min.

*4.2.10. Diethyl (S)-(1-acetamido-2-(1H-indol-3-yl)ethyl) phosphonate (**6j**)*

Condition B was used. Enantio-enriched product (22 mg) as white solid (66% yield, 45% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H), 7.14–7.09 (m, 2H), 5.80 (d, J = 10.4 Hz, 1H, *NH*), 4.87 (dtd, J = 16.1, 9.5, 4.6 Hz, 1H), 4.23–3.93 (m, 4H), 3.33 (ddd, J = 16.2, 11.8, 4.7 Hz, 1H), 3.15 (dt, J = 15.4, 9.4 Hz, 1H), 1.87 (s, 3H), 1.29 (t × 2, J = 7.1 Hz, 6H). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 24.47.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.8, 136.3, 127.9, 122.6, 122.2, 119.7, 118.6, 111.3, 110.9 (d, J = 13.3 Hz), 62.8 (d × 2, J = 7.1 Hz), 45.7 (d, J = 156.1 Hz), 25.7 (d, J = 3.0 Hz), 23.3, 16.5 (t, J = 5.8 Hz). HRMS: Calcd. for $C_{16}H_{24}O_4N_2P^+$ [M + H$^+$]: 339.1468; Found: 339.1469. Chiral HPLC condition: CHIRALCEL OJ-H (4.6 mm × 250 mm), 90:10 Hexane:^{i}PrOH, 1 ml/min, 220 nm. (*R*)-**6j** t_R = 11.0 min, (*S*)-**6j** t_R = 14.7 min.

*4.2.11. Diethyl (S)-(1-acetamido-2-(thiophen-2-yl)ethyl) phosphonate (**6k**)*

The *N*-Cbz derivative was previously reported [10e]. Condition B was used. Enantio-enriched product (10 mg) as yellow oil (33% yield, 82% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, J = 5.1 Hz, 1H), 6.94–6.90 (m, 1H), 6.88 (d, J = 3.4 Hz, 1H), 5.84 (d, J = 10.0 Hz, 1H, *NH*), 4.72 (dtd, J = 16.4, 9.9, 4.3 Hz, 1H), 4.24–4.01 (m, 4H), 3.40 (ddd, J = 15.3, 10.7, 4.4 Hz, 1H), 3.14 (dt, J = 15.5, 9.0 Hz, 1H), 1.31 (t × 2, J = 7.0 Hz, 6H). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 23.36.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.7 (d, J = 5.3 Hz), 138.6 (d, J = 14.6 Hz), 127.0, 126.5, 124.7, 62.9 (d × 2, J = 6.8 Hz), 46.5 (d, J = 156.1 Hz), 30.3 (d, J = 4.0 Hz), 23.3, 16.5 (d × 2, J = 5.8 Hz). HRMS: Calcd. for $C_{12}H_{21}O_4NPS^+$ [M + H$^+$]: 306.0923; Found: 306.0923. Chiral HPLC condition: (*S,S*)-WHELK-O1 Kromasil (4.6 mm × 250 mm), 85:15 Hexane:^{i}PrOH, 0.8 ml/min, 220 nm. (*R*)-**6k** t_R = 20.7 min, (*S*)-**6k** t_R = 22.6 min.

*4.2.12. Diethyl (S)-(1-acetamido-2-(furan-2-yl)ethyl)phosphonate (**6l**)*

Condition A was used. Enantio-enriched product (13 mg) as yellow oil (46% yield, 45% ee). Decomposition under room temperature. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J = 2.3 Hz, 1H), 6.28 (dd, J = 3.2, 1.8 Hz, 1H), 6.13 (d, J = 3.2 Hz, 1H), 5.98 (d, J = 10.8 Hz, 1H, *NH*, minor), 5.93 (d, J = 9.6 Hz, 1H, *NH*, major), 4.78 (dtd, J = 16.5, 9.8, 4.4 Hz, 1H), 4.20–4.01 (m, 4H), 3.17 (ddd, J = 15.9, 11.5, 4.4 Hz, 1H), 2.97 (dt, J = 15.6, 9.1 Hz, 1H), 1.96 (s, 3H), 1.30 (t × 2, J = 7.0 Hz, 6H). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 23.42.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.5 (d, J = 5.5 Hz), 151.0 (d, J = 14.2 Hz), 142.0, 110.5, 107.6, 62.9 (d × 2, J = 6.9 Hz), 44.5 (d, J = 157.9 Hz), 28.8 (d, J = 3.7 Hz), 23.2, 16.5 (d × 2, J = 5.8 Hz). HRMS: Calcd. for $C_{12}H_{20}O_5NPNa^+$ [M + Na$^+$]: 312.0971; Found: 312.0964. Chiral HPLC condition: CHIRALPAK AD (4.6 mm × 250 mm), 95:5 Hexane:^{i}PrOH, 1 ml/min, 220 nm. (*R*)-**6l** t_R = 16.8 min, (*S*)-**6l** t_R = 19.1 min.

*4.2.13. Diethyl (S)-(1-acetamido-2-cyclohexylethyl)phosphonate (**6 m**)*

The *N*-Cbz derivative was previously reported [10e]. Condition C was used. Enantio-enriched product (16 mg) as colorless oil (60% yield, 78% ee). (*R*)-**6m** was synthesized using Josiphos SL-J009-2 as 20 mg colorless oil (70% yield, 80% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.26 (d, J = 10.0 Hz, 1H, *NH*), 6.07 (d, J = 10.1 Hz, 1H, *NH*), 4.53 (dddd, J = 16.2, 11.3, 10.1, 3.8 Hz, 1H), 4.10 (pd, J = 7.1, 3.4 Hz, 4H), 2.01 (d, J = 1.2 Hz, 3H), 1.90–1.78 (m, 1H), 1.76–1.44 (m, 6H), 1.39–1.32 (m, 1H), 1.30 (t × 2, J = 7.1 Hz, 6H), 1.25–1.05 (m, 3H), 0.96 (qd, J = 12.3, 3.3 Hz, 1H), 0.80 (qd, J = 12.1, 3.5 Hz, 1H). ^{31}P{^{1}H} NMR (203 MHz, $CDCl_3$) δ 25.76.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.6 (d, J = 4.6 Hz), 62.6 (d × 2, J = 6.9 Hz), 42.9 (d, J = 155.8 Hz), 37.1, 34.1, 33.9 (d, J = 12.8 Hz), 32.0, 26.5, 26.4, 26.1, 23.2 (d, J = 5.4 Hz), 16.5 (d × 2, J = 5.8 Hz). HRMS: Calcd. for $C_{14}H_{29}O_4NP^+$ [M + H$^+$]: 306.1829; Found: 306.1828. Chiral HPLC condition: CHIRALCEL OD (4.6 mm × 250 mm), 98:2 Hexane:^{i}PrOH, 0.8 ml/min, 214 nm. (*R*)-**6m**, t_R = 14.4 min, (*S*)-**6m** t_R = 17.1 min.

*4.2.14. Diethyl (S)-(1-acetamido-2-cyclopropylethyl)phosphonate (**6n**)*

Condition C was used. Enantio-enriched product (13 mg) as colorless oil (50% yield, 78% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (d, J = 10.0 Hz, 1H, *NH*, minor), 6.32 (d, J = 10.5 Hz, 1H, *NH*, major), 4.63–4.45 (m, 1H), 4.18–3.99 (m, 4H), 2.02 (s, 3H), 1.59 (td, J = 7.1, 4.6 Hz, 2H), 1.29 (t × 2, J = 7.2 Hz, 6H), 0.93–0.70 (m, 1H), 0.45 (dqt, J = 13.3, 9.4, 4.5 Hz, 2H), 0.11 (dq, J = 9.4, 4.7 Hz, 2H), 0.03 (dq, J = 9.4, 4.7 Hz, 2H). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 24.87.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.7 (d, J = 6.0 Hz), 62.6 (d × 2, J = 6.9 Hz), 45.9 (d, J = 155.2 Hz), 35.1 (d, J = 2.7 Hz), 23.3, 16.6 (d × 2, J = 5.5 Hz), 8.0 (d, J = 14.6 Hz), 5.0, 4.2. HRMS: Calcd. for $C_{11}H_{23}O_4NP^+$ [M + H$^+$]: 264.1359; Found: 264.1359. Chiral HPLC condition: CHIRALCEL OJ-H (4.6 mm × 250 mm), 98:2 Hexane:^{i}PrOH, 0.4 ml/min, 214 nm. (*S*)-**6n** t_R = 18.6 min, (*R*)-**6n** t_R = 20.8 min.

*4.2.15. Diethyl (S)-(1-acetamido-3,3-dimethylbutyl)phosphonate (**6o**)*

The *N*-Cbz derivative was previously reported [10e]. Condition C was used; reaction time was set to 72 °C to achieve 90% conversion in ^{31}P NMR after 14 h. Enantio-enriched product (17 mg) as colorless oil (65% yield, 47% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (d, J = 10.1 Hz, 1H, *NH*), 4.55 (dtd, J = 17.5, 10.5, 1.7 Hz, 1H), 4.20–4.03 (m, 4H), 1.98 (d, J = 1.7 Hz, 3H), 1.80 (dddd, J = 14.3, 10.5, 3.8, 1.7 Hz, 1H), 1.51–1.41 (m, 1H), 1.31 (t × 2, J = 7.1 Hz, 6H), 0.94 (s, 9H). ^{31}P{^{1}H} NMR (203 MHz, $CDCl_3$) δ 25.52.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.1 (d, J = 3.7 Hz), 62.7 (d × 2, J = 7.1 Hz), 42.9 (d, J = 2.3 Hz), 42.8 (d, J = 155.8 Hz), 31.1 (d, J = 14.6 Hz), 29.6 (s, C × 3), 23.5, 16.6 (d × 2, J = 6.0 Hz). HRMS: Calcd. for $C_{12}H_{27}O_4NP^+$ [M + H$^+$]: 280.1672; Found: 280.1672. Chiral HPLC condition: CHIRALPAK AD (4.6 mm × 250 mm), 97:3 Hexane:^{i}PrOH, 0.8 ml/min, 214 nm. (*S*)-**6o** t_R = 19.3 min, (*R*)-**6o** t_R = 23.0 min.

*4.2.16. Diethyl (S)-(1-acetamido-2-((3r,5r,7r)-adamantan-1-yl) ethyl)phosphonate (**6p**)*

Condition C was used; reaction time was set to 72 °C to achieve 90% conversion in ^{31}P NMR after 14 h. Enantio-enriched product (22 mg) as colorless oil (63% yield, 60% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50 (d, J = 10.1 Hz, 1H, *NH*), 4.58 (dtd, J = 17.1, 10.4, 1.7 Hz, 1H), 4.23–3.99 (m, 4H), 1.98 (d, J = 1.4 Hz, 3H), 1.96–1.91 (m, 3H), 1.72–1.58 (m, 7H), 1.56–1.44 (m, 7H), 1.31 (t × 2, J = 7.0 Hz, 6H).^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 25.81.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.9 (d, J = 3.6 Hz), 62.7 (d × 2, J = 7.0 Hz), 43.8 (d, J = 2.4 Hz), 42.3 (s, C × 3), 41.1 (d, J = 156.4 Hz), 36.9 (s, C × 3), 32.9 (d, J = 14.4 Hz), 28.6 (s, C × 3), 23.4, 16.6 (d × 2, J = 5.7 Hz). HRMS: Calcd. for $C_{18}H_{33}O_4NP^+$ [M + H$^+$]: 358.2142; Found: 358.2138. Chiral HPLC condition: (*S,S*)-WHELK-O1 Kromasil (4.6 mm × 250 mm), 90:10 Hexane:^{i}PrOH, 1 ml/min, 214 nm. (*R*)-**6p** t_R = 9.7 min, (*S*)-**6p** t_R = 12.3 min.

*4.2.17. Diethyl (S)-(1-acetamidododecyl)phosphonate (**6q**)*

Condition C was used. Enantio-enriched product (25 mg) as colorless oil (71% yield, 61% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (d, J = 10.1 Hz, 1H, *NH*, minor), 5.92 (d, J = 10.2 Hz, 1H, *NH*, major), 4.41 (ddt, J = 14.6, 10.3, 5.2 Hz, 1H), 4.17–4.04 (m, 4H), 2.02 (s, 3H), 1.82 (dt, J = 9.3, 4.6 Hz, 1H), 1.54 (td, J = 9.6, 4.6 Hz, 1H), 1.46–1.35 (m, 2H), 1.31 (t × 2, J = 7.0 Hz, 6H), 1.29–1.10 (m, 16H), 0.87 (t, J = 6.9 Hz, 3H). ^{31}P{^{1}H} NMR (203 MHz, $CDCl_3$) δ 25.22.^{13}C{^{1}H} NMR (126 MHz,

$CDCl_3$) δ 169.8 (d, J = 5.1 Hz), 62.6 (d × 2, J = 6.9 Hz), 45.3 (d, J = 155.4 Hz), 32.0, 29.9 (d, J = 2.6 Hz), 29.8, 29.7 (s, C × 2), 29.5, 29.5, 29.3, 26.0 (d, J = 12.6 Hz), 23.3, 22.8, 16.6 (d × 2, J = 5.8 Hz), 14.2. HRMS: Calcd. for $C_{18}H_{39}O_4NP^+$ [M + H^+]: 364.2611; Found: 364.2610. Chiral HPLC condition: CHIRALPAK AD (4.6 mm × 250 mm), 97:3 Hexane:^{i}PrOH, 0.8 ml/min, 214 nm. (*R*)-**6q** t_R = 14.9 min, (*S*)-**6q** t_R = 16.6 min.

*4.2.18. Diethyl (S)-(1-acetamidooctadecyl)phosphonate (**6r**)*

Condition D was used. Enantio-enriched product (26 mg) as colorless solid (65% yield, 64% ee). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (d, J = 11.0 Hz, 1H, *NH*, minor), 5.64 (d, J = 10.2 Hz, 1H, *NH*, major), 4.42 (dtd, J = 16.8, 10.0, 4.2 Hz, 1H), 4.19–4.05 (m, 4H), 2.03 (s, 3H), 1.84 (dq, J = 9.5, 4.2 Hz, 1H), 1.55 (dq, J = 9.2, 4.5 Hz, 1H), 1.47–1.35 (m, 1H), 1.32 (t × 2, J = 7.2 Hz, 6H), 1.31–1.19 (m, 29H), 0.88 (t, J = 6.9 Hz, 3H). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 25.19.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.7 (d, J = 5.0 Hz), 62.6 (d × 2, J = 6.9 Hz), 45.4 (d, J = 154.7 Hz), 32.1, 30.0, 29.9, 29.8 (m, C × 7), 29.7, 29.5, 29.5, 29.4, 26.0 (d, J = 12.8 Hz), 23.4, 22.8, 16.6 (d × 2, J = 5.5 Hz), 14.3. HRMS: Calcd. for $C_{24}H_{50}O_4NPNa^+$ [M + Na^+]: 470.3370; Found: 470.3366. Chiral HPLC condition: CHIRALPAK AD (4.6 mm × 250 mm), 98:2 Hexane:^{i}PrOH, 0.8 ml/min, 214 nm. (*R*)-**6r** t_R = 17.1 min, (*S*)-**6r** t_R = 21.5 min.

*4.2.19. Diethyl (S)-(1-acetamido-4-phenylbutyl)phosphonate (**6s**)*

Condition C was used. Enantio-enriched product (23 mg) as colorless oil (70% yield, 50% ee). Crystallization of racemate yielded 70% ee in the mother liquor. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, J = 7.4 Hz, 2H), 7.19–7.11 (m, 3H), 6.17 (d, J = 10.1 Hz, 1H, *NH*, minor), 6.03 (d, J = 10.1 Hz, 1H, *NH*, major), 4.48 (dtd, J = 14.6, 10.2, 4.2 Hz, 1H), 4.16–4.03 (m, 4H), 2.68 (dt, J = 14.2, 7.4 Hz, 1H), 2.57 (dt, J = 14.2, 7.4 Hz, 1H), 2.02 (s, 3H), 1.86 (tt, J = 9.6, 4.1 Hz, 1H), 1.80–1.55 (m, 3H), 1.29 (t × 2, J = 7.1 Hz, 6H).^{31}P{^{1}H} NMR (203 MHz, $CDCl_3$) δ 24.94.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.9 (d, J = 5.7 Hz), 141.8, 128.6 (s, C × 2), 128.5 (s, C × 2), 126.0, 62.7 (d × 2, J = 6.9 Hz), 45.0 (d, J = 155.8 Hz), 35.3, 29.4, 27.7 (d, J = 12.7 Hz), 23.2, 16.5 (d × 2, J = 5.7 Hz). HRMS: Calcd. for $C_{16}H_{27}O_4NP^+$ [M + H^+]: 328.1672; Found: 328.1674. Chiral HPLC condition: CHIRALPAK AD (4.6 mm × 250 mm), 96:4 Hexane:^{i}PrOH, 0.8 ml/min, 214 nm. (*R*)-**6s** t_R = 19.6 min, (*S*)-**6s** t_R = 22.9 min.

*4.2.20. Diethyl (1S,4R)-(1-acetamido-4-((3S,7S,8R,9S,10S,13R,14S,17R)-3,7-dimethoxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentyl)phosphonate (**6t**)*

Condition C was used. Enantio-enriched product (39 mg) as very pale-yellow oil (60% yield, 83% ee at C_α). Two diastereomers show up in ^{31}P{^{1}H} NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (d, J = 10.4 Hz, 1H, *NH*), 4.38 (ddd, J = 17.0, 12.0, 8.0 Hz, 1H), 4.19–4.03 (m, 4H), 3.34 (s, 3H), 3.22 (s, 3H), 3.16–3.04 (m, 1H), 3.01–2.92 (m, 1H), 2.02 (s, 3H), 1.95 (d, J = 13.1 Hz, 1H), 1.82–1.69 (m, 6H), 1.68–1.53 (m, 3H), 1.52–1.36 (m, 8H), 1.31 (t × 2, J = 7.1 Hz, 6H), 1.26–0.85 (m, 14H), 0.63 (s, 3H). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 24.60 (major), 24.52 (minor). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.6 (d, J = 5.0 Hz), 80.4, 80.1, 62.5 (d × 2, J = 6.9 Hz), 56.2, 55.6, 55.4, 55.1, 45.3 (d, J = 155.6 Hz), 43.6, 42.2, 41.5, 40.3, 39.3, 35.0, 34.9, 34.4, 33.8, 32.1, 31.9 (d, J = 12.8 Hz), 28.6, 26.6, 26.4, 26.3 (d, J = 2.1 Hz), 23.4, 23.2, 21.3, 18.6, 16.4 (d × 2, J = 5.5 Hz), 12.2. HRMS: Calcd. for $C_{32}H_{58}O_6NPNa^+$ [M + Na^+]: 606.3894; Found: 606.3887. Chiral HPLC condition: CHIRALPAK AD (4.6 mm × 250 mm), 95:5 Hexane:^{i}PrOH, 1 ml/min, 214 nm. (*S*)-**6t** t_R = 14.8 min, (*R*)-**6t** t_R = 18.0 min.

*4.2.21. Diethyl (S)-(1-acetamido-2-methylpropyl)phosphonate (**6u**)*

The racemic compound was previously reported [10j]. Condition C was used. Enantio-enriched product (15 mg) as colorless oil (65% yield, 51% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (d, J = 10.2 Hz, 1H, *NH*), 4.39 (ddd, J = 18.5, 10.5, 4.2 Hz, 1H), 4.19–4.01 (m, 4H), 2.20 (dp, J = 11.0, 6.5 Hz, 1H), 2.06 (s, 3H), 1.32 (t × 2, J = 7.2 Hz, 6H), 1.01 (t, J = 6.5 Hz, 6H). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 24.40.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.0 (d, J = 5.5 Hz), 62.5 (d × 2, J = 7.1 Hz), 50.1 (d, J = 152.9 Hz), 29.1 (d, J = 3.7 Hz), 23.3, 20.6 (d, J = 12.8 Hz), 18.0 (d, J = 4.6 Hz), 16.5 (d × 2, J = 5.5 Hz). HRMS: Calcd. for $C_{10}H_{23}O_4NP^+$ [M + H^+]: 252.1359; Found: 252.1359. Chiral HPLC condition: CHIRALPAK AD (4.6 mm × 250 mm), 97:3 Hexane:^{i}PrOH, 0.8 ml/min, 214 nm. (*R*)-**6u** t_R = 14.8 min, (*S*)-**6u** t_R = 16.9 min.

*4.2.22. 3-Diethyl 1,2,3,4-tetrahydroisoquinoline-3-phosphonate ((S)-**10a**)*

The synthesis of (*S*)-**10a** followed previously reported procedure with minor modification [18]. Enantio-enriched product (16 mg) as colorless oil (45% yield, 94% ee). The NMR spectra were consistent with the previous report. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18–7.08 (m, 3H), 7.08–6.96 (m, 1H), 4.21 (q, J = 7.3 Hz, 4H), 4.07 (s, br, 2H), 3.31 (s, 1H), 3.16–2.83 (m, 2H), 1.36 (t × 2, J = 7.3 Hz, 6H). ^{31}P{^{1}H} NMR (203 MHz, $CDCl_3$) δ 26.05.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 135.1, 133.2, 129.3, 126.5, 126.3 (s, C × 2), 62.6 (d × 2, J = 5.7 Hz), 51.2 (d, J = 159.8 Hz), 48.5, 29.0, 16.7 (d, C × 2, J = 5.3 Hz). Chiral HPLC condition: CHIRALPAK AD (4.6 mm × 250 mm), 95:5 Hexane:^{i}PrOH, 1 ml/min, 220 nm. (*R*)-**10a** t_R = 17.4 min, (*S*)-**10a** t_R = 22.7 min.

*4.3. Synthesis of diethyl (S)-(4-methyl-6,7-dihydrothieno[3,2-c] pyridin-6-yl) phosphonate ((S)-**10k**)*

The synthesis of (*S*)-**10k** was developed based on the previously reported protocol. [22] (*S*)-**6k** (1 eq., 10 mg, batch enantiopurity = 73% ee) was dissolved in toluene (0.1 M) and mixed with 0.1 M toluene solution of $POCl_3$ (4 eq.) under argon. Reaction mixture was heated to 80 °C for 2 h. After cooling to room temperature, the mixture was quenched with distilled water. After removing impurities using EtOAc, the acidic aqueous layer contained most desired product. The crude was purified by reversed-phase chromatography in a gradient 10–100% MeCN in H_2O to isolate desired product as pale-yellow solid (3.5 mg, 35% yield, 68% ee, decomposition observed after staying in $CDCl_3$ overnight). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11–7.08 (m, 2H), 4.26–4.01 (m, 5H), 3.19–3.08 (m, 2H), 2.36 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ 25.27.^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.8, 141.1, 132.0, 124.1, 122.6, 62.6 (d × 2, J = 7.0 Hz), 56.4 (d, J = 170.7 Hz), 24.2, 22.4, 16.5 (d × 2, J = 5.7 Hz). HRMS: Calcd. for $C_{12}H_{19}O_3NPS^+$ [M + H^+]: 288.0818; Found: 288.0819. Chiral HPLC condition: CHIRALPAK AD (4.6 mm × 250 mm), 90:10 Hexane:^{i}PrOH, 1 ml/min, 214 nm. (*R*)-**10k** t_R = 8.6 min, (*S*)-**10k** t_R = 9.9 min.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2022.132908.

Appendix A. Supplementary data

Experimental procedures for the synthesis of all starting materials (compounds **5**), NMR spectra and chiral HPLC chromatograms can be found online.

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