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Diastereoselective Synthesis of Phosphinyl Peptides via Rh-Catalyzed 1,4-Addition in Coparticipation of a *P*-Chiral Moiety and Difluorphos

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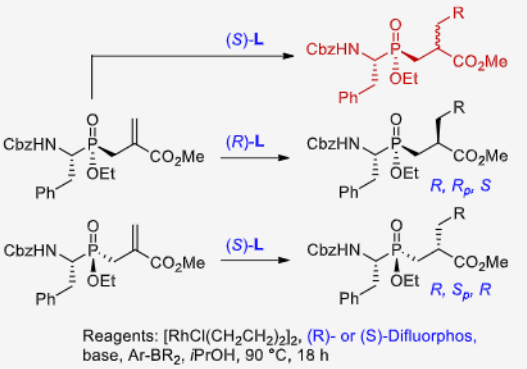
ABSTRACT: The asymmetric Rh-catalyzed 1,4-addition of aryl/heteroaryl moieties to α,β-unsaturated esters was achieved in high diastereoselectivity via the coparticipation of a *P*-chiral phosphinyl moiety at Cβ to the prochiral center and (*R*)- or (*S*)-Difluorphos. This methodology expands the synthetic toolbox available for the preparation of structurally diverse chiral phosphinyl peptides.



INTRODUCTION

The phosphinic acid moiety is a stable transition state mimic of enzymatic proteolysis and has found useful applications in the design of inhibitors targeting zinc metalloproteases (Figure 1).[1] Such inhibitors include those designed to inhibit the angiotensin-1-converting enzyme (ACE1),[2] the M14 metallocarboxypeptidase (MCP),[3] and the endoplasmic reticulum aminopeptidase 2 (ERAP2).[1b,4] Additionally, due to mechanistic similarities,[5] phosphinyl peptides have also been explored as inhibitors of aspartyl proteases, such as the HIV1 protease (HIV1 PR)[6] and the β-site amyloid precursor protein cleaving enzyme 1 (BACE1).[7]

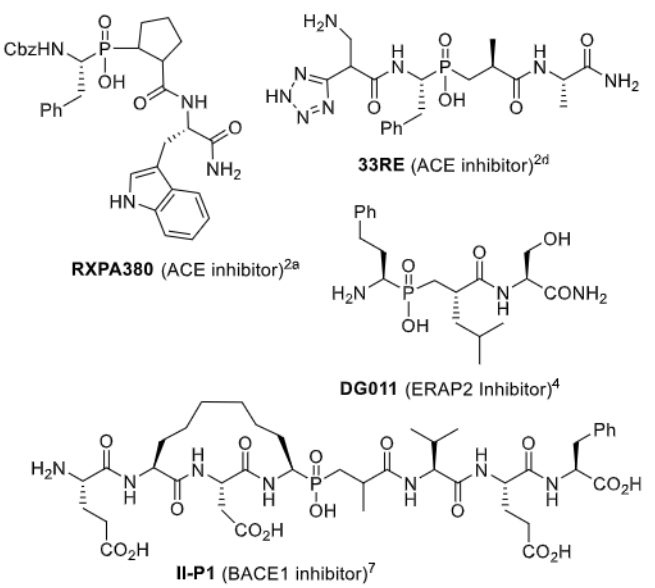


Figure 1. Examples of biologically active phosphinyl peptides.

The synthesis of diastereomerically enriched phosphinyl peptides has been under investigation for several decades. Initially, a variety of key synthetic building blocks were prepared as diastereomeric mixtures and subsequently separated by chromatography, chiral HPLC or crystallization.[8] Building blocks, such as the phosphinic acid dipeptide **2** (Scheme 1), are presumed to mimic the P_1-P_1' residues of the natural substrates of zinc metalloproteases. The enantioselective synthesis of building blocks leading to analogs with general structure **2** has been reported, using Evan's oxazolidinone chiral auxiliary[9] and Rh-catalyzed asymmetric hydrogenation.[10] However, these methodologies did not employ a complete asymmetric synthesis for the preparation of diastereomerically enriched phosphinyl dipeptides.

Methods that are amendable to high throughput library synthesis are highly valuable in drug discovery for the efficient identification of potent inhibitors of a therapeutic targets. For

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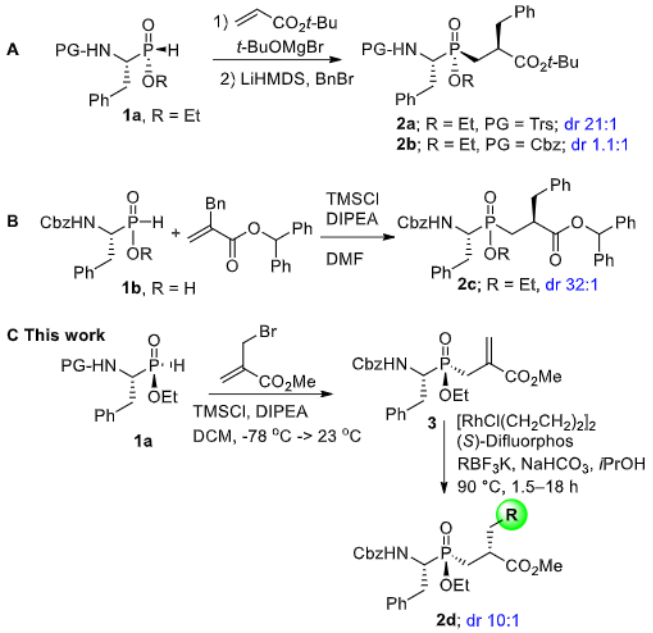
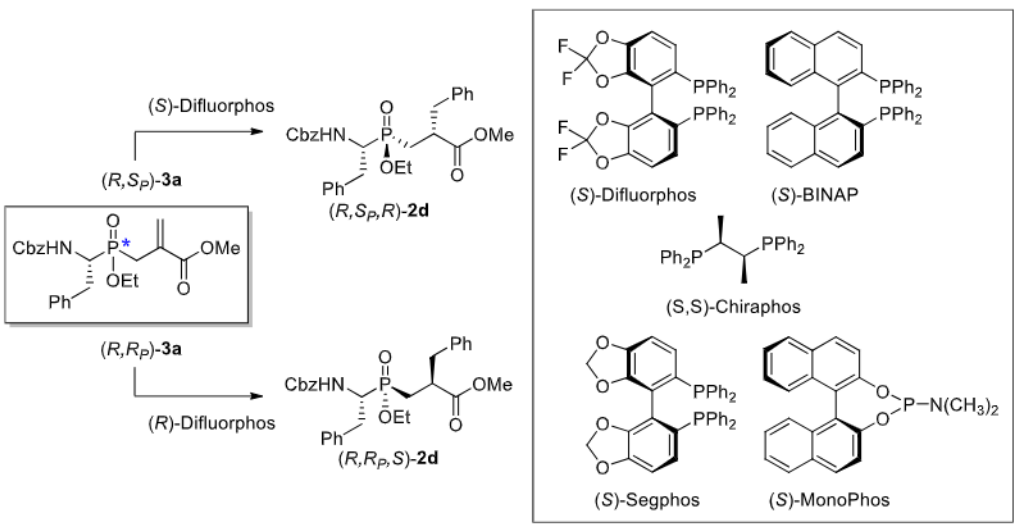
Scheme 1. Diastereoselective Synthesis Phosphinyl Dipeptides 2



example, the synthesis of a 96-member library of peptidomimetics (prepared using automation) was reported in the discovery of inhibitors targeting the HCV NS3/4A protease.[31] However, such efforts have not been reported for the synthesis of diastereomerically enriched phosphinyl peptide libraries, most likely due to the challenges associated with the preparation of such compounds. The parallel synthesis of large libraries of compounds requires methodologies that are robust and reliable for a variety of building blocks, have reasonably short reaction times, and do not require extensive purification steps nor unusual protecting group manipulations.

Yokomatsu was the first to report the synthesis of diastereomerically enriched dipeptides of general structure **2** from the *P*-chiral *α*-amino-*H*-phosphinate **1a**. This methodology involves the stereospecific Michael addition of **1a** to an acrylate, followed by the asymmetric alkylation of a lithium-mediate cyclic enolate (Scheme 1A).[11] Although the chirality of the phosphorus atom is of paramount importance, the chirality of the C*α* in the *α*-amino-*H*-phosphinates, in addition to two bulky *N*- and *C*-capping groups, also play a key role in the diastereoselectivity achieved during the asymmetric alkylation step. In spite of the excellent diastereomeric control provided by this methodology, the removal of the *N*-terminal 2,4,6-triisopropylbenzenesulfonyl (Trs) group could be some-

Table 1. Optimization of the Rh-Catalyzed 1,4-Addition Reaction[a]



entry	3a	ligand	boronate	% yield[b]	dr[c]
1	R,S_p	(*S*)-Difluorphos	$PhB(OH)_2$	89	4:1
2	R,S_p	(*S*)-Difluorphos	$PhBF_3K$	83	6:1
3	R,S_p	(*S*)-BINAP	$PhB(OH)_2$	71	3:1
4	R,S_p	(*R*)-BINAP	$PhB(OH)_2$	60	1:1
5	R,S_p	(*S,S*)-Chiraphos	$PhBF_3K$	0	-
6	R,S_p	(*S*)-Segphos	$PhBF_3K$	trace	-
7	R,S_p	(*S*)-MonoPhos	$PhB(OH)_2$	80	1:1
8	R,S_p	(*R*)-MonoPhos	$PhB(OH)_2$	63	1:1
9	R,S_p	none	$PhB(OH)_2$	76	1:1
10	R,S_p	(*R*)-Difluorphos	$PhB(OH)_2$	80	1:1
11	R,R_p	(*R*)-Difluorphos	$PhBF_3K$	90	6:1
12	R,R_p	(*R*)-Difluorphos	$PhBF_3K$	68	11:1[d,e]
13[f]	R,S_p	(*S*)-Difluorphos	$PhB(OH)_2$	0	-

[a]Reaction conditions: $[RhCl(CH_2CH_2)_2]_2$ (1.5 mol %), ligand (3.3 mol %); boronate (2 equiv), $NaHCO_3$ (1 equiv), *i*-PrOH, 90 °C, 18 h. [b]Isolated yield. [c]Indicated values were estimated by ^{31}P NMR of the crude reaction mixture. [d]Diastereomer was isolated in >99:1 dr after a single crystallization. [e]Reaction time of 1.5 h. [f]No base added.

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what problematic in high throughput library synthesis of analogs. More recently Georgiadis reported another excellent example of a diastereoselective synthesis of analogs **2** via a domino chirality transfer during a stereocontrolled *P*-Michael reaction (Scheme 1B).[12] The chirality at the Cα of the precursor α-amino-*H*-phosphinate **1b** and the C-terminal bulky capping group of the acrylate reagent control the asymmetric addition, whereas the presence of a *P*-chiral precursor (**1b**) is not required. The structural diversity of the final compounds is determined by the substitution of the acrylate moiety and only one stereochemical configuration at the Cβ to the phosphinyl moiety was described. Additionally, the transformation of **1b** to **2c** is very slow (3 days), which may be a challenge for high throughput library synthesis in medicinal chemistry. In the present study, we developed an efficient methodology that is amenable to late-stage structural diversification in parallel library synthesis of analogs **2** using common protecting groups at both the *C*- and *N*-terminus, in order to support our medicinal chemistry efforts. We describe here, an asymmetric Rh-catalyzed 1,4-addition of various aryl moieties to the α,β-unsaturated methyl ester **3** (Table 1) via the coparticipation of the *P*-chiral phosphinyl moiety at Cβ to the pro-chiral center. This methodology allows high throughput preparation of various phosphinyl dipeptides with general structure **2**, with either the (*R*)- or (*S*)-stereochemistry at Cβ to the *P*-chiral center.

RESULTS AND DISCUSSION

We began our investigation with the pseudophosphinyl dipeptide **3**, synthesized via Michael addition of the *P*-chiral α-amino-*H*-phosphinate ethyl ester **1a**[13] to the methyl 2-(bromomethyl)acrylate;[14] details for the synthesis of **3** are described in Supporting Information. Intermediate **3** can itself serve as a Michael acceptor and similar analogs were previously reported by Yiotakis in the nucleophilic addition of thiols to give nonchiral analogs.[15] We envisioned that Rh-catalyzed asymmetric 1,4-addition of aryl or heteroaryl moieties could be achieved using a related methodology to that previously reported by Darses[16] and Miller and Key[17] for the preparation of chiral α-aminophosphonates and α-amino acids, respectively, from their corresponding dehydroalanine-like bioisosteres.

Initially, we screened the Rh-catalyzed 1,4-addition to intermediate (R,S_P)-**3** with phenylboronic acid, phenyl pinacolboranes and phenyltrifluoroborate in the presence of several bidentate chiral ligands that have been previously explored in such methodologies (Table 1),[16,17] including (*S*)-Difluorphos (entries 1 and 2), (*S*)-BINAP (entry 3), (*S,S*)-Chiraphos (entry 5), (*S*)-Segphos (entry 6) and the monodentate ligand (*S*)-MonoPhos (entry 7). The best outcome, in both conversion and diastereoselectivity, was achieved with (*S*)-Difluorphos (entries 1 and 2), leading to the formation of the phosphinyl dipeptide (R,S_P,R)-**2d** in 89% yield and 4:1 dr with the boronic acid, or 83% yield and 6:1 dr with the trifluoroborate after an 18 h reaction time at 90 °C (entry 1 vs 2). Surprisingly, both (*S,S*)-Chiraphos and (*S*)-Segphos blocked the formation of product almost entirely (entries 5 and 6, respectively); these ligands were not investigated any further. Although the exact reason for this outcome is unclear, we presume that these relatively more electron rich phosphine ligands (as compared to Difluorphos) would be stronger σ-donors to the metal and poorer π-acceptors from the metal to ligands and consequently, induce a weaker coordination between the rhodium metal and substrate **3**.

In contrast, the monodentate ligand (*S*)-MonoPhos led to good isolated yield, without any asymmetric induction (entry 7). Interestingly, similar results were also observed in the absence of any chiral ligand (entry 9), as well as when the (*S*)-Difluorphos was replaced by the (*R*)-enantiomer of this ligand (entry 10). These observations indicated a competing background reaction, which is likely responsible for the relatively low diastereoselectivity observed with (*S*)-Difluorphos (entries 1 and 2), and in spite of the presence of a *P*-chiral center at the Cβ position to the prochiral carbon. Additionally, a stereochemical mismatch between (*R*)-Difluorphos and the Rh-(R,S_P)-**3a** complex could be preventing the formation of a stable coordination, thus allowing only the background reaction to proceed. To test this hypothesis, we conducted the same reaction using the (R,R_P)-**3a** with the (*R*)-Difluorphos ligand and we were pleased to isolate the (R,R_P,S)-**2d** in high isolated yield (90%) and identical diastereomeric excess (6:1 dr) as that observed for the formation of the (R,S_P,R)-**2d** (entries 11 and 2, respectively). Finally, we confirmed that in the absence of a base, the reaction did not proceed (entry 13).

After the above initial optimization of the reaction conditions, we evaluated the substrate scope using several substituted phenyltrifluoroborates and heteroaryltrifluoroborates with both the (R,S_P)-**3a** and (R,R_P)-**3a** starting materials (Figure 2). All reactions were initially carried out in a parallel library mode, without any individual optimization. We were able to obtain both epimers at the Cβ to *P*-chiral center by simply changing the chirality of the phosphorus atom and the chirality of the Difluorphos ligand, yet keeping the same chirality at the Cα of the aminophosphinyl moiety. Acceptable yields and diastereoselectivity were observed with most of the phenyltrifluoroborates [e.g., (R,S_P,R)-**2d**−**j**, as well as (R,R_P,S)-**2d**−**g**, (R,R_P,S)-**2l**, (R,R_P,S)-**2m**, and (R,R_P,S)-**2o**]. However, steric hindrance (e.g., (R,S_P,R)-**2k**) and heteroatoms (especially pyridine) were detrimental to the outcome, under these conditions. For example, under the conditions of entry 11 (Table 1), a negligible amount of product **2p** was formed, whereas the yields of products **2q** and **2s** were only 59% and 53%, respectively. It is also noteworthy that in addition to steric hindrance, (2,4,6-trimethyl)boronic acid (i.e., **2k**) is known to be chemically unstable in photocatalytic and metal-mediated cross-coupling reactions, leading to protodeboronation and the formation of mesitylene as a side product.[28] In contrast, although steric hindrance also plays a role in the conversion of the (2,6-dimethoxyphenyl)trifluoroboroanate (**2g**), the combination of an electron rich aryl group and the potential for additional coordination of the oxygen atoms with the rhodium metal may provide additional stabilization to the transmetalation step of the reaction.

A systematic evaluation of various heteroarylboronates in the Rh-catalyzed 1,4-addition to enones was previously reported by Boysen[18] In that study, heteroarylboronates, such as 3-pyridyl, were found to give higher yields when a pinacole borane (Bpin) was used. However, in our methodology, neither the 3-pyrboronic acid nor the 3-pyrBpin reagents provided satisfactory results. We expected that some coordination of the rhodium metal to the pyridine nitrogen could decrease the amount of free catalyst available to catalyze the reaction and consequently, we increased the catalyst loading to 7.5 mol % and used the 3-pyrBF$_3$K reagent.

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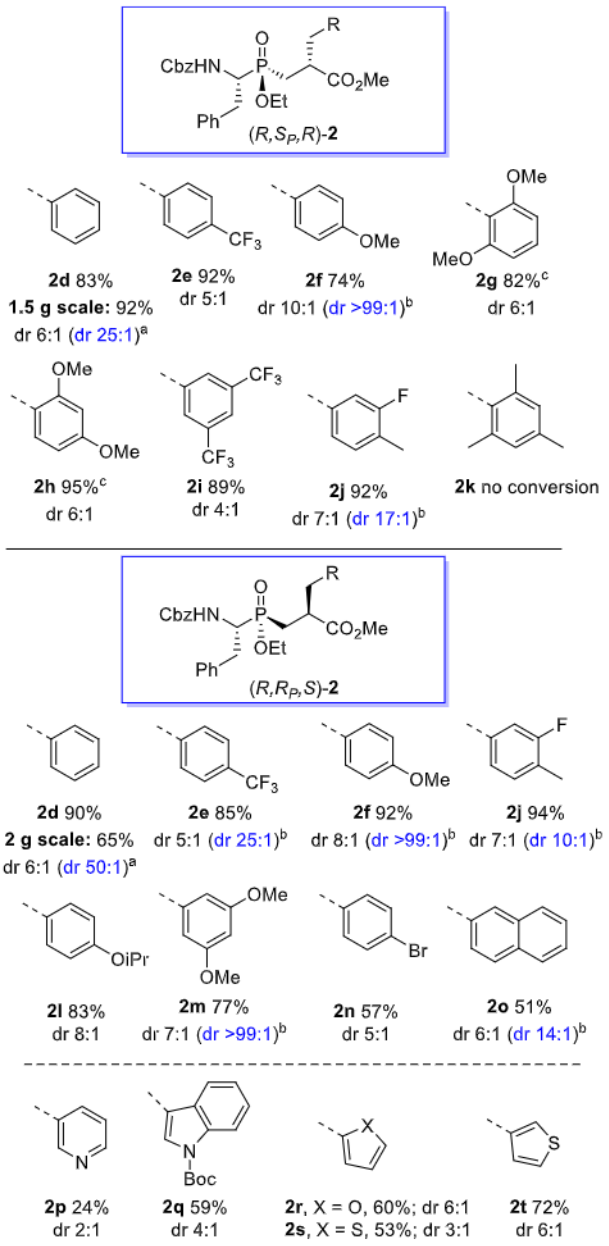

Figure 2. Library of phosphinyl dipeptides (R,S_P,R)- and (R,R_P,S)-**2**. Reaction conditions for analogs **2d**−**o**: $[RhCl(CH_2Cl_2)_2]_2$ (1.5 mol %),(*R*)- or (*S*)-Difluorphos (3.3 mol %), $ArylBF_3K$ (2 equiv); $NaHCO_3$ (1 equiv), *i*-PrOH, 90°C, 18 h. The dr values were estimated by ^{31}P NMR of the crude reaction mixture. Reaction conditions for analogs **2p**−**t**: $[RhCl(CH_2Cl_2)_2]_2$ (7.5 mol %),(*R*)-Difluorphos (16.5 mol %), $NaHCO_3$ (1 equiv), premixed to form the active catalyst, $ArylBF_3K$ (1 equiv), *i*-PrOH, 90°C, 18 h. [a]After one recrystallization from the initial crystals. [b]After crystallization directly from the diastereomeric mixture. [c]Indicated yield is based on the recovery of starting material; the conversion observed over the 18 h reaction time for **2g** and **2h** was 56% and 63%, respectively.

Additionally, we observed that preforming the active catalyst-ligand complex was required,[19] in order to obtain even a very modest yield of the desired product (R,R_P,S)-**2p**. However, we also observed a significant amount of the hydrogenated starting material, presumably via a competing transfer hydrogenation reaction; the transfer hydrogenation, where isopropanol was the hydride source was previously observed in similar reactions.[30] Co-elution of this hydrogenated byproduct with analog **2p** on column chromatography further decreased the isolated yield of the desired compound. Fortunately, the transfer hydrogenation side reaction was only observed in very few other cases and in those cases, <10% of this byproduct was observed. Under these modified conditions, products (R,R_P,S)-**2q**−**t** were isolated in reasonable yields and diastereoselectivities. Full details on the reaction optimization are provided in Table S2.

In a parallel library synthesis of many structurally related compounds, individual optimization of the reaction conditions for each set of reagents is impractical, particularly when the focus is on advancing a medicinal chemistry project. However, for the scale-up of a specific analog, identifying the conditions that could suppress the background reaction (i.e., in the reaction that proceeds in the absence of any chiral phosphine ligand; e.g., Table 1, entry 7) is of importance. We presumed that in the presence of a relatively electronically deficient phosphine ligand, such as Difluorphos, the rate of the reaction may be accelerated,[16b,20] as compared to the reaction without this ligand. As a test case, the progress of the Rh-catalyzed 1,4-addition of $PhBF_3K$ to (R,S_P)-**3a** in the presence and absence of (*S*)-Difluorphos was followed by HPLC and the diastereoselectivity was estimated by ^{31}P NMR at select time points (Figure 3). As expected, in the presence of (*S*)-Difluorphos the reaction rate was significantly faster, resulting in 85% conversion to product within 1 h. After 1.5 h the conversion of starting material to product was nearly quantitative, leading to the formation of (R,S_P,R)-**2d** in diastereomeric ratio of 10:1. In contrast, in the absence of the chiral phosphine ligand, after 1 h the conversion was only 10%. We also explored the effects of lowering the temperature, however, the reaction did not proceed at 70 °C at a rate acceptable for high throughput library synthesis (Figure 3).

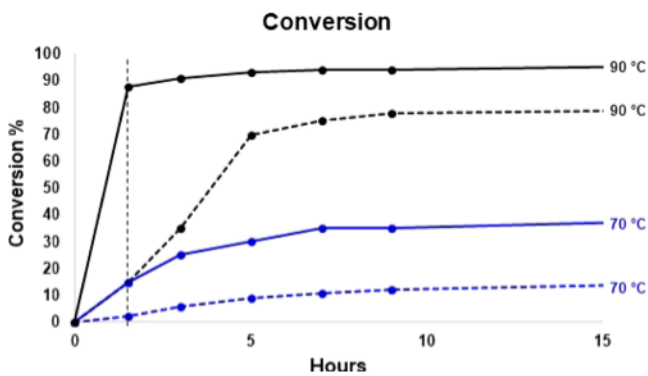

Figure 3. Progress of reaction: Rh-catalyzed 1,4-addition of $PhBF_3K$ to (R,S_P)-**3** in the presence (solid line) and absence (dash line) of (*S*)-Difluorphos.

Finally, the methodology was also tested on larger scale reactions. For example on a 2 g scale of (R,R_P)-**3a**, using the initial reaction conditions (e.g., Table 1, entry 11, 18 h reaction time) the (R,R_P,S)-**2d** product was formed in 6:1 dr in the reaction mixture and was isolated after column chromatography in 65% yield, and 50:1 dr after recrystallization. It is noteworthy that normal flash column chromatography on silica gel does not separate the diastereomers. However, when the reaction was carried out (on the same 2 g scale) using the optimized reaction conditions (i.e., only 1.5 h), (R,R_P,S)-**2d** product was formed in 68% isolated yield and 11:1 dr in the crude reaction mixture, leading to the isolation of a single

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diastereomer after only a crystallization (39% recovery on the first crop of crystallization). The absolute stereochemistry of both diastereomers of **2d** was confirmed by single-crystal X-ray structures (Figure 4; ORTEP diagrams are provided in Figure S10). It should be noted that exposing a diastereomerically pure product to the same reaction conditions for 7 h, did not lead to any erosion of its diastereomeric excess (Page S42).

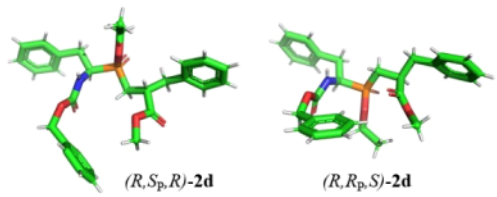
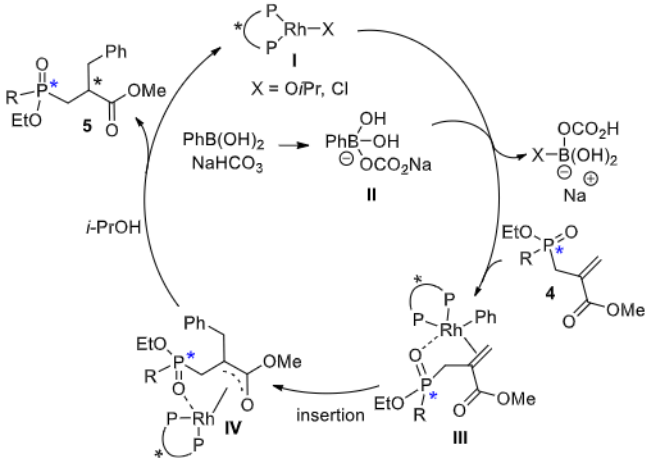


Figure 4. Single-crystal X-ray structures of (R,S_p,R)-**2d** and (R,R_p,S)-**2d**.

It is reasonable to assume that the mechanism of our reaction would follow the general mechanism previously reported for other such Rh-catalyzed 1,4-addition reactions (Scheme 2).[21] Coordination of the bidentate phosphine ligand,

Scheme 2. Proposed Mechanism of the Reaction



(R)- or (S)-Difluorphos, to the rhodium metal would form the active catalyst **I**, which upon transmetalation of the aryl moiety from the boron reagent **II** to the rhodium, and simultaneous coordination of the metal to both the olefin moiety and the chiral phosphinyl moiety of **3** would give complex **III**. The formation of intermediate **III** is consistent with our observations of the stereochemical outcome observed at the Cα to the methyl ester, which is greatly controlled by the chirality of the phosphorus atom.

Many examples of itaconate-type moieties are known to form a 5- or 6-membered ring coordination with rhodium.[22] Similar examples of bidentate coordination, involving an *N*-heterocyclic carbene (NHC) substituted with a phosphine oxide, have been observed with Pd,[23] Ni,[24] and Cu,[25] as well as a tridentate coordination of a diphosphine-phosphine oxide with rhodium.[26] Therefore, there is substantial literature precedent for the proposed intermediate **III**, which can subsequently lead to the insertion of the aryl group at Cβ to the ester, leading to the formation of the pro-chiral enolate **IV**. We presume that the chirality at the Cα to the ester is set at the protonation step of intermediate **IV**, however, the enantioselectivity is likely predetermined by the overall chirality of the Rh complex **III**. A similar hypothesis based on steric factors was previously proposed by Kobayashi in the asymmetric 1,4-addition of aryl boronic acids to nitroalkenes.[27]

■ CONCLUSIONS

In summary, we have developed a Rh-catalyzed asymmetric 1,4-addition reaction that allows the synthesis of diastereomerically enriched phosphinyl dipeptides with general structure **2**, having either the *R*- or *S*-chirality at Cα to the methyl ester and Cβ to the *P*-chiral moiety. Compounds of general structures **2** (Scheme 1C) represent a key building block in the preparation of zinc metalloprotease inhibitors. Our methodology may be particularly relevant for medicinal chemistry efforts in allowing the efficient late-stage structural diversification of large compound libraries.

■ EXPERIMENTAL SECTION

General Information. All reactions were carried out in oven- or flamed-dried glassware and under an inert atmosphere unless otherwise specified. Catalysts and reagents (including boronic acids), were purchased from commercial sources and were used without further purification, unless otherwise indicated. Solvents were obtained from a solvent purification system (PureSolv MD7, Innovative Technologies or MB SPS 800, Mbraun). Isopropanol was either distilled over CaH_2 under argon or an anhydrous commercial bottle was used after degassing. All the reactions that required heating were carried out in an oil bath. Flash column chromatography was performed on silica gel (MiliporeSigma, 60 Å, 230–400 mesh, 40–63 μm). Reactions were monitored by thin-layer chromatography (TLC) on glass plates precoated with silica gel (MiliporeSigma, 60G F_{254}). TLC spots were visualized by UV and/or by staining with a solution of cerium sulfate, polymolybdic acid, and sulfuric acid, or in an iodine chamber, or with a solution of curcumin in ethanol for boronic acids. All final compounds were fully characterized by ^{1}H, ^{13}C, ^{31}P NMR and HRMS. Potassium trifluoroborate reagent were prepared as previously reported,[29] and characterized by ^{1}H, ^{13}C, ^{19}F, and ^{11}B. Chemical shifts (δ) are reported in ppm relative to the internal deuterated solvent, except ^{31}P NMR for which H_3PO_2 was used as the external reference. The high resolution MS spectra of final products were recorded using electrospray ionization (ESI$^{\pm}$) and Fourier transform ion cyclotron resonance mass analyzer (FTMS). The chiral HPLC spectra were obtained using the Agilent 1100 series instrument with Chiralpak AD and Chiralcel OD columns, with an isopropanol/hexane eluent system. LC–MS data were obtained using the Waters e2695 and 3100 mass detector system with Atlantis T3 column, with acetonitrile/water with formic acid (0.1%) eluent system.

General Procedure for Asymmetric 1,4-Addition with Arylboronic Acids or Aryltrifluoroborates. In a microwave vial, (R,S_p,R)-**3a** or (R,R_p,S)-**3a** (1 equiv), aryl boronic acid or potassium (aryl)trifluoroborate (2 equiv), $NaHCO_3$ (1 equiv), (*S*)- or (*R*)-Difluorphos (3.3 mol %), and chlorobis(ethylene) rhodium dimer (1.5 mol %) were added. The vial was purged with argon and dry/degassed isopropanol was added to a final concentration of 0.24 M. The solution was stirred for 18 h at 90 °C. Then the mixture was cooled to room temperature, concentrated, and purified using flash column chromatography

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on silica gel using an ethyl acetate/hexane gradient from 50−100%.

General Procedure for Asymmetric 1,4-Addition with Heteroaryltrifluoroborates. In a microwave vial, (R,R_p,S)-**3a** (1.0 equiv), $NaHCO_3$ (1 equiv), (S)- or (R)-Difluorphos (16.5 mol %), and chlorobis(ethylene)rhodium dimer (7.5 mol %) were added. The vial was purged with argon and dry/degassed isopropanol was added to a final concentration of 0.24 M. The solution was stirred for 10 min at room temperature, and then potassium trifluoro(heteroaryl)borate (1 equiv) was added. The solution was stirred for 18 h at 90 °C. Then the mixture was cooled to room temperature, concentrated, and purified using flash column chromatography on silica gel using an isopropanol/hexane gradient from 2.5 to 10% and ethyl acetate/hexane gradient from 50−100%.

General Procedure for Crystallization/Recrystallization. Column chromatography was first used to remove any unreacted stating material and minor side products. However, in the majority of cases, the diastereomeric ratio of the desired phosphinyl dipeptide was identical before and after chromatography, with the exception of products **2p**, **2r**, **2s** and **2t**, where some improvement was observed in the dr values (pages S28−S32). The diastereomeric mixture was first dissolved in minimum amount of DCM and then diluted with Et_2O. Finally, hexane was added while mixing rapidly to a final ratio of DCM:Et2O: hexane of 0.1:1:1 at a final concentration of approximately 3o mM. The solution was then kept undisturbed at room temperature for 2−18 h, before the crystalline sold was isolated by filtration.

*Methyl (R)-2-Benzyl-3-((S)-((R)-1-(((benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)propanoate ((R,Sp,R)-**2d**).* Intermediate (R,S_p)-**3a** (3.1 mmol, 1.4 g) was used for the synthesis of compound (R,S_p,R)-**2d**, which was isolated as a white solid (1.5 g, 92%), and was further crystallized and recrystallized one time to increase the dr of (R,S_p,R)-**2d** from 6:1 to 25:1 (recovery of 0.91 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.09 (m, 15H), 4.97 (dd, J = 24.6, 8.0 Hz, 3H), 4.31 (t, J = 10.2 Hz, 1H), 4.09−3.92 (m, 2H), 3.66 (s, 3H), 3.27 (q, J = 8.1 Hz, 1H), 3.16 (s, 1H), 3.01 (dd, J = 13.5, 7.5 Hz, 1H), 2.80 (ddd, J = 33.7, 11.9, 7.6 Hz, 2H), 2.25 (td, J = 14.4, 10.0 Hz, 1H), 1.86 (ddd, J = 15.4, 11.6, 3.8 Hz, 1H), 1.22 (t, J = 7.1 Hz, 3H). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 49.9. ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 174.8, 155.8 (d, J = 5.3 Hz), 137.8, 136.6 (d, J = 11.4 Hz), 136.3, 129.4, 129.2, 128.7, 128.7, 128.6, 128.6, 128.3, 128.1, 127.0, 67.2, 61.6 (d, J = 6.8 Hz), 52.1, 51.3 (d, J = 101.2 Hz), 41.3, 40.2 (d, J = 12.7 Hz), 34.7, 28.0 (d, J = 87.7 Hz), 16.7 (d, J = 5.4 Hz). HRMS (ESI+) calcd for $C_{29}H_{34}NO_6Pna$ m/z: 546.2016; found 546.2004 $[M + Na]^+$.

*Methyl (R)-3-((S)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(4-(trifluoromethyl)-benzyl)propanoate ((R,Sp,R)-**2e**).* Intermediate (R,S_p)-**3a** (0.042 mmol, 19 mg) was used for the synthesis of compound (R,S_p,R)-**2e**, which was isolated as a colorless oil (23 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59−7.50 (m, 2H), 7.39−7.16 (m, 12H), 5.06−4.94 (m, 2H), 4.32 (d, J = 10.4 Hz, 1H), 4.18−3.95 (m, 2H), 3.65 (s, 3H), 3.30 (q, J = 8.3 Hz, 1H), 3.26−3.11 (m, 1H), 3.11−2.88 (m, 2H), 2.80 (dt, J = 14.3, 9.5 Hz, 1H), 2.24 (td, J = 14.8, 9.3 Hz, 1H), 1.84 (ddd, J = 15.4, 10.9, 4.5 Hz, 1H), 1.24 (t, J = 9.6 Hz, 3H). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 49.8. ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.3, 155.8, 142.0, 136.5 (d, J = 11.2 Hz), 136.3, 129.5, 129.4, 129.4, 128.7, 128.3, 128.1, 128.0, 127.0, 125.6, 123.2, 67.2, 61.7 (d, J = 7.1 Hz), 52.2, 51.3 (d, J = 102.0 Hz), 41.0, 39.7 (d, J = 11.7 Hz), 34.6, 28.1 (d, J = 87.7 Hz), 16.7. HRMS (ESI+) calcd for $C_{30}H_{34}NF_3O_6P$ m/z: 592.2070; found 592.2064 $[M + H]^+$

*Methyl (R)-3-((S)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(4-methoxybenzyl)-propanoate ((R,Sp,R)-**2f**).* Intermediate (R,S_p)-**3a** (0.080 mmol, 36 mg) was used for the synthesis of compound (R,S_p,R)-**2f**, which was isolated as a colorless oil (33 mg, 74%), and was further crystallized to increase the dr of (R,S_p,R)-**2f** from 10:1 to >99:1 (recovery of 12 mg, 26%). ^{1}H NMR (800 MHz, $CDCl_3$) δ 7.34−7.28 (m, 3H), 7.26−7.17 (m, 7H), 7.04 (d, J = 8.1 Hz, 2H), 6.81 (d, J = 8.4 Hz, 2H), 5.05−4.88 (m, 2H), 4.84 (d, J = 10.4 Hz, 1H), 4.26 (tdd, J = 10.2, 7.9, 4.2 Hz, 1H), 4.07−3.91 (m, 2H), 3.76 (s, 3H), 3.63 (s, 3H), 3.23 (ddd, J = 14.4, 7.8, 4.3 Hz, 1H), 3.07 (ddq, J = 10.5, 7.0, 3.5 Hz, 1H), 2.92 (ddd, J = 13.7, 7.5, 1.5 Hz, 1H), 2.78−2.69 (m, 2H), 2.25−2.14 (m, 1H), 1.82 (ddd, J = 15.4, 11.5, 3.8 Hz, 1H), 1.19 (t, J = 7.1 Hz, 3H). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 50.1. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 174.8, 158.6, 155.7, 136.6 (d, J = 11.5 Hz), 136.3, 130.2, 129.8, 129.4, 128.7, 128.6, 128.3, 128.1, 127.0, 114.1, 67.2, 61.6 (d, J = 6.7 Hz), 55.3, 52.1, 51.3 (d, J = 101.6 Hz), 41.5, 39.4 (d, J = 12.4 Hz), 34.7, 27.9 (d, J = 88.0 Hz), 16.7 (d, J = 5.3 Hz). HRMS (ESI+) calcd for $C_{30}H_{36}NO_7PNa$ m/z: 576.2122; found 576.2125 $[M + Na]^+$.

*Methyl (R)-3-((S)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(2,6-dimethoxybenzyl)-propanoate ((R,Sp,R)-**2g**).* Intermediate compound (R,S_p)-**3a** (0.056 mmol, 25 mg) was used for the synthesis of compound (R,S_p,R)-**2g**, which was isolated as a colorless oil (27 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.28 (m, 3H), 7.26−7.14 (m, 7H), 6.93 (d, J = 8.2 Hz, 1H), 6.44−6.33 (m, 2H), 5.02−4.82 (m, 3H), 4.23 (d, J = 9.3 Hz, 1H), 3.97 (dt, J = 13.8, 7.1 Hz, 2H), 3.76 (s, 3H), 3.63 (s, 3H), 3.19 (d, J = 10.3 Hz, 2H), 2.89 (dd, J = 13.6, 7.2 Hz, 1H), 2.78 (dd, J = 14.2, 8.4 Hz, 2H), 2.24 (q, J = 13.0 Hz, 1H), 1.91−1.78 (m, 1H), 1.17 (t, J = 7.0 Hz, 3H). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 50.3. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 175.3, 160.1, 155.7, 136.7 (d, J = 11.8 Hz), 136.4, 131.3, 129.5, 128.6, 128.6, 128.1, 126.9, 118.5, 104.0, 98.6, 67.1, 61.5 (d, J = 6.8 Hz), 55.4 (d, J = 7.5 Hz), 52.0, 51.3 (d, J = 100.8 Hz), 39.6, 34.8, 34.7 (d, J = 13.5 Hz), 28.1 (d, J = 88.0 Hz), 16.6 (d, J = 5.3 Hz). HRMS (ESI+) calcd for $C_{31}H_{38}NO_8PNa$ m/z: 606.2227; found 606.2226 $[M + Na]^+$.

*Methyl (R)-3-((S)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(2,4-dimethoxybenzyl)-propanoate ((R,Sp,R)-**2h**).* Intermediate (R,S_p)-**3a** (0.063 mmol, 28 mg) was used for the synthesis of compound (R,S_p,R)-**2h**, which was isolated as a colorless oil (35 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 6.8 Hz, 3H), 7.24−7.15 (m, 7H), 6.93 (d, J = 8.2 Hz, 1H), 6.44−6.35 (m, 2H), 4.98−4.88 (m, 2H), 4.22 (d, J = 9.6 Hz, 1H), 3.97 (dt, J = 13.6, 7.2 Hz, 2H), 3.76 (s, 6H), 3.63 (s, 3H), 3.29−3.13 (m, 2H), 2.89 (dd, J = 13.3, 7.1 Hz, 1H), 2.78 (dd, J = 14.7, 9.1 Hz, 2H), 2.24 (d, J = 13.0 Hz, 1H), 1.94−1.73 (m, 1H), 1.17 (t, J = 7.0 Hz, 3H). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 50.0. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 175.3, 160.1, 158.7, 155.7 (d, J = 5.7 Hz), 136.7 (d, J = 11.3 Hz), 136.4, 131.3, 129.5, 128.6, 128.6, 128.3, 128.1, 126.9, 118.5, 104.0, 98.6, 67.1, 61.6 (d, J = 6.9 Hz), 55.4, 55.4, 52.0, 51.3 (d, J = 101.1 Hz), 39.6 (d, J = 3.3 Hz), 34.8, 34.7 (d, J = 13.4 Hz), 28.1 (d, J = 88.1 Hz), 16.6 (d, J = 5.1 Hz). HRMS (ESI+)

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calcd for $C_{31}H_{38}NO_8PNa$ *m/z*: 606.2227; found 606.2218 [M + Na]$^+$.

*Methyl (R)-3-((S)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(3,5-bis(trifluoromethyl)-benzyl)propanoate ((R,S$_P$,R)-**2i**).* Intermediate (*R*,*S*$_P$)-**3a** (0.077 mmol, 34 mg) was used for the synthesis of compound (*R*,*S*$_P$,*R*)-**2i**, which was isolated as a pale yellow oil (45 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.63 (s, 2H), 7.37−7.28 (m, 5H), 7.24−7.21 (m, 3H), 5.16−4.91 (m, 3H), 4.45−4.25 (m, 1H), 4.07 (ddt, *J* = 31.4, 16.7, 8.0 Hz, 2H), 3.61 (s, 3H), 3.30 (ddd, *J* = 13.4, 8.0, 4.5 Hz, 1H), 3.03 (d, *J* = 7.1 Hz, 2H), 2.82 (q, *J* = 10.9 Hz, 1H), 2.23 (td, *J* = 14.5, 8.2 Hz, 1H), 1.84 (ddd, *J* = 15.6, 10.4, 5.1 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{31}P {^{1}H} NMR (202 MHz, $CDCl_3$) δ 49.5. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 173.9, 155.9, 140.7, 136.3, 131.8 (q, *J* = 33.3 Hz), 129.4, 129.3, 128.7 (d, *J* = 2.0 Hz), 128.7, 128.4, 128.1, 127.1, 124.1, 122.7, 122.0−120.7 (m), 67.3, 61.9, 52.2, 51.5 (d, *J* = 101.3 Hz), 41.1, 39.4, 34.5, 28.5 (d, *J* = 87.0 Hz), 16.7. HRMS (ESI+) calcd for $C_{31}H_{32}NF_6O_6PNa$ *m/z*: 682.1764; found 682.1771[M + Na]$^+$.

*Methyl (R)-3-((S)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(3-fluoro-4-methylbenzyl)propanoate ((R,S$_P$,R)-**2j**).* Intermediate (*R*,*S*$_P$)-**3a** (0.20 mmol, 89 mg) was used for the synthesis of compound (*R*,*S*$_P$,*R*)-**2j**, which was isolated as a colorless oil (0.10 g, 92%), and was further crystallized to increase the dr of (*R*,*S*$_P$,*R*)-**2j** from 7:1 to 17:1 (recovery of 45 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.17 (m, 11H), 7.07 (t, *J* = 7.9 Hz, 1H), 6.82−6.77 (m, 1H), 5.10−4.90 (m, 2H), 4.83 (d, *J* = 10.4 Hz, 1H), 4.37−4.19 (m, 1H), 4.10−3.89 (m, 2H), 3.64 (s, 3H), 3.32−3.19 (m, 1H), 3.09 (s, 1H), 2.92 (dd, *J* = 13.5, 7.5 Hz, 1H), 2.81−2.69 (m, 2H), 2.29−2.09 (m, 4H), 1.80 (ddd, *J* = 15.4, 11.4, 4.1 Hz, 1H), 1.20 (t, *J* = 7.0 Hz, 3H). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$ + 1% MeOH) δ 51.4. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 174.6, 162.0, 160.7, 155.8, 137.4, 136.5, 136.3, 131.6, 129.4, 128.7, 128.4, 128.1, 127.0, 124.6, 123.4, 115.7 (d, *J* = 22.0 Hz), 67.3, 61.7, 52.2, 51.3 (d, *J* = 101.6 Hz), 41.1, 39.5 (d, *J* = 12.0 Hz), 34.7, 28.0 (d, *J* = 87.9 Hz), 16.7, 14.4. HRMS (ESI+) calcd for $C_{30}H_{35}NFO_6PNa$ *m/z*: 578.2078; found 578.2079 [M + Na]$^+$.

*Methyl (S)-2-Benzyl-3-((R)-((R)-1-(((benzyloxy)carbonyl)-amino)-2-phenylethyl)(ethoxy)phosphoryl)propanoate ((R,R$_P$,S)-**2d**).* Intermediate (*R*,*R*$_P$)-**3a** (5.9 mmol, 2.6 g) was used for the synthesis of compound (*R*,*R*$_P$,*S*)-**2d**, which was isolated as a white solid (2.0 g, 65%), and was further crystallized then recrystallized to increase the dr of (*R*,*R*$_P$,*S*)-**2d** from 6:1 to 50:1 (recovery of 0.93 g, 30%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.20 (m, 13H), 7.15−7.11 (m, 2H), 5.04−4.96 (m, 2H), 4.35−4.21 (m, 1H), 4.20−4.04 (m, 2H), 3.64 (s, 3H), 3.28−3.17 (m, 1H), 3.17−3.08 (m, 1H), 3.07−2.94 (m, 1H), 2.90−2.79 (m, 2H), 2.24 (dt, *J* = 15.6, 11.0 Hz, 1H), 1.89 (t, *J* = 14.0 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 50.0. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 175.0 (d, *J* = 4.5 Hz), 156.0, 137.8, 136.5 (d, *J* = 11.0 Hz), 136.4, 129.3, 129.1, 128.7, 128.7, 128.6, 128.2, 127.9, 127.0, 127.0, 67.1, 61.7 (d, *J* = 7.2 Hz), 52.1, 51.4 (d, *J* = 105.6 Hz), 41.5 (d, *J* = 4.4 Hz), 40.1 (d, *J* = 11.8 Hz), 34.6, 28.1 (d, *J* = 88.2 Hz), 16.6 (d, *J* = 5.9 Hz). HRMS (ESI+) calcd for $C_{29}H_{34}NO_6PNa$ *m/z*: 546.2016; found 546.2020 [M + Na]$^+$.

*Methyl (S)-3-((R)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(4-(trifluoromethyl)-benzyl)propanoate ((R,R$_P$,S)-**2e**).* Intermediate (*R*,*R*$_P$)-**3a** (0.31 mmol, 0.14 g) was used for the synthesis of compound (*R*,*R*$_P$,*S*)-**2e**, which was isolated as a colorless oil (0.16 mg, 85%), and was further crystallized to increase the dr of (*R*,*R*$_P$,*S*)-**2e** from 5:1 to 25:1 (recovery of 43 mg, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 2H), 7.30−7.14 (m, 10H), 5.22 (d, *J* = 10.3 Hz, 1H), 5.08−4.90 (m, 2H), 4.36−4.19 (m, 1H), 4.19−4.00 (m, 2H), 3.59 (s, 3H), 3.24−3.05 (m, 2H), 2.99−2.76 (m, 3H), 2.30−2.12 (m, 1H), 1.95−1.79 (m, 1H), 1.30−1.25 (m, 3H). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 49.9. ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.3, 155.9, 141.9, 136.3, 136.2, 129.4, 129.1, 128.6, 128.5, 128.1, 127.7, 126.9, 125.4, 123.1, 67.0, 61.8 (d, *J* = 6.8 Hz), 52.0, 51.4 (d, *J* = 106.1 Hz), 41.0 (d, *J* = 4.0 Hz), 39.4 (d, *J* = 10.7 Hz), 34.3, 29.7, 28.2 (d, *J* = 88.2 Hz), 16.5 (d, *J* = 5.7 Hz). HRMS (ESI+) calcd for *m/z*: $C_{30}H_{33}NF_3O_6PNa$ 614.1890; found 614.1897 [M + Na]$^+$.

*Methyl (S)-3-((R)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(4-methoxybenzyl)-propanoate ((R,R$_P$,S)-**2f**).* Intermediate (*R*,*R*$_P$)-**3a** (0.24 mmol, 0.11 g) was used for the synthesis of compound (*R*,*R*$_P$,*S*)-**2f**, which was isolated as a colorless oil (0.12 g, 92%), and was further crystallized to increase the dr of (*R*,*R*$_P$,*S*)-**2f** from 8:1 to >99:1 (recovery of 31 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.15 (m, 10H), 7.05 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 2H), 5.17 (d, *J* = 10.2 Hz, 1H), 4.99 (q, 2H), 4.30 (d, *J* = 9.7 Hz, 1H), 4.18−4.10 (m, 2H), 3.80 (s, 3H), 3.66 (s, 3H), 3.22 (d, *J* = 14.7 Hz, 1H), 3.09 (s, 1H), 2.96−2.86 (m, 1H), 2.86−2.76 (m, 1H), 2.24 (q, *J* = 12.3 Hz, 1H), 1.90 (t, *J* = 13.8 Hz, 1H), 1.31 (s, 3H). ^{31}P {^{1}H} NMR (202 MHz, $CDCl_3$) δ 49.8. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 175.1 (d, *J* = 4.7 Hz), 158.5, 156.0, 136.5 (d, *J* = 22.0 Hz), 130.1, 129.8, 129.3, 128.7, 128.6, 128.6, 128.2, 127.8, 127.0, 114.0, 67.0, 61.8 (d, *J* = 6.8 Hz), 55.3, 52.1, 51.4 (d, *J* = 105.5 Hz), 41.7 (d, *J* = 3.9 Hz), 39.3 (d, *J* = 11.5 Hz), 34.5, 27.9 (d, *J* = 88.6 Hz), 16.6 (d, *J* = 5.7 Hz). HRMS (ESI+) calcd for $C_{30}H_{36}NO_7PNa$ *m/z*: 576.2122; found 576.2107 [M + Na]$^+$.

*Methyl (S)-3-((R)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(3-fluoro-4-methylbenzyl)propanoate ((R,R$_P$,S)-**2j**).* Intermediate (*R*,*R*$_P$)-**3a** (0.16 mmol, 72 mg) was used for the synthesis of compound (*R*,*R*$_P$,*S*)-**2j**, which was isolated as a colorless oil (84 mg, 94%), and was further crystallized to increase the dr of (*R*,*R*$_P$,*S*)-**2j** from 7:1 to 10:1 (recovery of 41 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.13 (m, 10H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.85−6.68 (m, 2H), 5.24−5.04 (m, 1H), 5.03−4.88 (m, 2H), 4.25 (td, *J* = 10.9, 4.0 Hz, 1H), 4.18−3.98 (m, 2H), 3.61 (s, 3H), 3.24−3.14 (m, 1H), 3.05 (dq, *J* = 16.2, 6.5 Hz, 1H), 2.88 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.81−2.74 (m, 1H), 2.28−2.10 (m, 4H), 1.84 (ddd, *J* = 15.7, 11.3, 4.3 Hz, 1H), 1.27 (t, *J* = 7.0 Hz, 3H). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 50.0. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 174.8 (d, *J* = 5.7 Hz), 162.3, 160.3, 156.0, 137.4 (d, *J* = 7.6 Hz), 136.5 (d, *J* = 20.8 Hz), 131.6 (d, *J* = 5.8 Hz), 129.3, 128.7, 128.6, 128.2, 127.8, 127.0, 124.5 (d, *J* = 3.0 Hz), 123.3 (d, *J* = 17.0 Hz), 115.6 (d, *J* = 22.1 Hz), 67.1, 61.8 (d, *J* = 6.8 Hz), 52.1, 51.5 (d, *J* = 105.6 Hz), 41.3 (d, *J* = 4.2 Hz), 39.3 (d, *J* = 11.3 Hz), 34.5, 28.1 (d, *J* = 88.3 Hz), 16.6 (d, *J* = 5.8 Hz), 14.3 (d, *J* = 3.4 Hz). HRMS (ESI+) calcd for $C_{30}H_{35}NFO_6PNa$ *m/z*: 578.2078; found 578.2059 [M + Na]$^+$.

*Methyl (S)-3-((R)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(4-isopropoxybenzyl)-propanoate ((R,R$_P$,S)-**2l**).* Intermediate (*R*,*R*$_P$)-**3a** (0.26 mmol, 0.11 g) was used for the synthesis of compound (*R*,*R*$_P$,*S*)-**2l**,

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which was isolated as a pale yellow oil (0.12 g, 83%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.16 (m, 10H), 6.98 (d, J = 8.6 Hz, 2H), 6.77 (d, J = 8.2 Hz, 2H), 5.20 (d, J = 10.3 Hz, 1H), 4.95 (q, J = 12.5 Hz, 2H), 4.48 (p, J = 6.1 Hz, 1H), 4.27 (s, 1H), 4.07 (t, J = 6.6 Hz, 2H), 3.60 (s, 3H), 3.27−3.11 (m, 1H), 3.04 (s, 1H), 2.94−2.67 (m, 3H), 2.31−2.11 (m, 1H), 1.88 (s, 1H), 1.30 (d, J = 6.0 Hz, 6H), 1.28−1.23 (m, 5H). ^{31}P {^{1}H} NMR (202 MHz, $CDCl_3$) δ 50.1. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 175.1, 156.9, 156.0, 136.5, 136.4, 130.1, 129.6, 129.3, 128.7, 128.6, 128.2, 127.8, 127.0, 116.0, 69.9, 67.0, 61.7, 52.1, 51.4 (d, J = 105.4 Hz), 41.7, 39.3 (d, J = 11.3 Hz), 34.5, 28.0 (d, J = 88.2 Hz), 22.2 (d, J = 1.7 Hz), 16.6 (d, J = 5.4 Hz). HRMS (ESI+) calcd for $C_{32}H_{40}NO_7PNa$ m/z: 604.2435; found 604.2444 [M + Na]$^+$.

*Methyl (S)-3-((R)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(3,5-dimethoxybenzyl)-propanoate ((R,R$_P$,S)-**2m**).* Intermediate (R,R_P)-**3a** (0.26 mmol, 0.12 g) was used for the synthesis of compound (R,R_P,S)-**2m**, which was isolated as a colorless oil (0.12 g, 77%), and was further crystallized to increase the dr of (R,R_P,S)-**2m** from 7:1 to >99:1 (recovery of 14 mg, 26%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.27 (m, 3H), 7.26−7.13 (m, 7H), 6.38−6.26 (m, 3H), 5.15 (d, J = 10.2 Hz, 1H), 5.09−4.81 (m, 2H), 4.26 (s, 1H), 4.20−4.04 (m, 2H), 3.73 (s, 6H), 3.64 (s, 3H), 3.27−3.01 (m, 2H), 2.95−2.65 (m, 3H), 2.20 (dt, J = 15.4, 11.4 Hz, 1H), 1.89 (t, J = 12.6 Hz, 1H), 1.27−1.25 (m, 3H). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 50.2. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 175.0, 161.0, 156.0, 140.1, 136.53, 136.46, 129.3, 128.7, 128.6, 128.1, 127.8, 127.0, 107.1, 99.0, 67.0, 61.8, 55.4, 52.2, 51.4 (d, J = 106.2 Hz), 41.3, 40.3, 34.5, 28.0 (d, J = 88.8 Hz), 16.6. HRMS (ESI+) calcd for $C_{31}H_{38}NO_8PNa$ m/z: 606.2227; found 606.2221 [M + Na]$^+$.

*Methyl (S)-3-((R)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(4-bromobenzyl)-propanoate ((R,R$_P$,S)-**2n**).* Intermediate (R,R_P)-**3a** (0.18 mmol, 78 mg) was used for the synthesis of compound (R,R_P,S)-**2n**, which was isolated as a white solid (60 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 6.5 Hz, 3H), 7.23 (dd, J = 11.8, 7.0 Hz, 3H), 7.18 (tt, J = 7.7, 4.0 Hz, 4H), 6.96 (d, J = 5.7 Hz, 2H), 5.33−5.23 (m, 1H), 5.04−4.85 (m, 2H), 4.26 (qd, J = 10.6, 4.2 Hz, 1H), 4.17−4.04 (m, 2H), 3.58 (s, 3H), 3.22−3.13 (m, 1H), 3.10−3.01 (m, 1H), 2.90−2.74 (m, 3H), 2.25−2.14 (m, 1H), 1.85 (ddd, J = 15.9, 11.5, 4.4 Hz, 1H), 1.27 (t, J = 6.9 Hz, 3H). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 49.9. ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.6, 156.0, 137.8, 136.6 (d, J = 61.1 Hz), 131.7, 130.9, 129.3, 128.6, 128.6, 128.2, 127.8, 127.0, 126.9, 120.8, 67.1, 61.8, 52.1, 51.1, 41.2, 39.2, 34.4, 28.1 (d, J = 88.0 Hz), 16.6. HRMS (ESI+) calcd for $C_{29}H_{33}NNaBrO_6P$ m/z: 624.1121; found 624.1124[M + Na]$^+$.

*Methyl (S)-3-((R)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(naphthalen-2-ylmethyl)propanoate ((R,R$_P$,S)-**2o**).* Intermediate (R,R_P)-**3a** (0.039 mmol, 17 mg) was used for the synthesis of compound (R,R_P,S)-**2o**, which was isolated as a colorless oil (12 mg, 51%), and was further crystallized to increase the dr of (R,R_P,S)-**2o** from 6:1 to 14:1 (recovery of 7.2 mg, 32%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81−7.72 (m, 3H), 7.56 (s, 1H), 7.48−7.40 (m, 2H), 7.32−7.08 (m, 11H), 4.98 (d, J = 10.2 Hz, 1H), 4.87 (d, J = 12.5 Hz, 1H), 4.76 (d, J = 12.5 Hz, 1H), 4.26 (d, J = 9.7 Hz, 1H), 4.09 (ddp, J = 10.6, 7.1, 3.2 Hz, 2H), 3.60 (s, 3H), 3.25−3.06 (m, 3H), 2.96 (dd, J = 13.5, 7.1 Hz, 1H), 2.81 (q, J = 10.5 Hz, 1H), 2.32−2.17 (m, 1H), 1.91 (t, J = 14.1 Hz, 1H), 1.26 (t, J = 7.0 Hz, 3H). ^{31}P {^{1}H} NMR (202 MHz, $CDCl_3$) δ 50.1. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 175.0 (d, J = 4.6 Hz), 155.9 (d, J = 5.7 Hz), 136.5 (d, J = 11.4 Hz), 136.4, 135.4, 133.6, 132.5, 129.3, 128.7, 128.6, 128.6, 128.4, 128.1, 127.8, 127.8, 127.8, 127.3, 127.0, 126.3, 125.8, 67.0, 61.8 (d, J = 6.6 Hz), 52.2, 51.4 (d, J = 105.6 Hz), 41.5 (d, J = 3.9 Hz), 40.3 (d, J = 11.8 Hz), 34.5, 28.1 (d, J = 88.4 Hz), 16.6 (d, J = 5.7 Hz). HRMS (ESI+) calcd for $C_{33}H_{36}NO_6PNa$ m/z: 596.2172; found 596.2188[M + Na]$^+$.

*Methyl (S)-3-((R)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(pyridin-3-ylmethyl)-propanoate ((R,R$_P$,S)-**2p**).* Intermediate (R,R_P)-**3a** (0.099 mmol, 44 mg) was used for the synthesis of compound (R,R_P,S)-**2p**, which was isolated as a pale yellow oil (12 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.41 (m, 1H), 7.34−7.14 (m, 13H), 5.11−5.00 (m, 1H), 4.98 (s, 2H), 4.40−4.22 (m, 1H), 4.07 (ddd, J = 31.0, 14.2, 7.1 Hz, 2H), 3.59 (s, 3H), 3.23−3.02 (m, 2H), 2.88 (d, J = 7.5 Hz, 2H), 2.32−2.10 (m, 1H), 1.86 (ddd, J = 16.1, 10.6, 4.0 Hz, 1H), 1.31−1.24 (m, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 49.6. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 174.4 (d, J = 6.0 Hz), 156.0 (d, J = 6.3 Hz), 150.4, 148.4, 136.5, 136.4 (d, J = 14.5 Hz), 129.3, 128.7, 128.6, 128.3, 127.9, 127.1, 123.6, 67.2 (d, J = 5.9 Hz), 61.9 (d, J = 6.8 Hz), 52.2, 51.5 (d, J = 106.4 Hz), 41.1 (d, J = 4.3 Hz), 37.0 (d, J = 11.0 Hz), 34.5, 28.3 (d, J = 88.4 Hz), 16.7 (d, J = 5.7 Hz). HRMS (ESI+) calcd for $C_{28}H_{34}N_2O_6PNa$ m/z: 525.2149; found 525.2164 [M + H]$^+$.

*tert-Butyl 3-((S)-2-(((R)-((R)-1-(((Benzyloxy)carbonyl)-amino)-2-phenylethyl)(ethoxy)phosphoryl)methyl)-3-methoxy-3-oxopropyl)-1H-indole-1-carboxylate ((R,R$_P$,S)-**2q**).* Intermediate (R,R$_P$)-**3a** (0.071 mmol, 32 mg) was used for the synthesis of compound (R,R_P,S)-**2q**, which was isolated as a pale yellow solid (28 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.39 (s, 1H), 7.32−7.26 (m, 4H), 7.26−7.11 (m, 8H), 5.01−4.78 (m, 2H), 4.41−4.23 (m, 1H), 4.12−3.96 (m, 2H), 3.62 (s, 3H), 3.24−3.02 (m, 3H), 2.98−2.75 (m, 2H), 2.40−2.15 (m, 1H), 2.03−1.88 (m, 1H), 1.66 (s, 9H), 1.26−1.22 (m, 3H). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 50.0. ^{13}C {^{1}H} NMR (201 MHz, $CDCl_3$) δ 175.1, 156.0, 149.8, 136.5, 136.4, 130.3, 129.3, 128.7, 128.6, 128.2, 127.9, 127.0, 124.7, 124.1, 122.7, 119.0, 116.84, 116.78, 115.4, 83.8, 67.1, 61.8, 52.3, 51.3 (d, J = 104.5 Hz), 40.0, 29.6 (d, J = 86.1 Hz), 28.4, 16.6 (d, J = 5.6 Hz). HRMS (ESI+) calcd for $C_{36}H_{43}N_2O_8PNa$ m/z: 685.2649; found 685.2639 [M + Na]$^+$.

*Methyl (S)-3-((R)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(furan-2-ylmethyl)-propanoate ((R,R$_P$,S)-**2r**).* Intermediate (R,R$_P$)-**3a** (0.20 mmol, 87 mg) was used for the synthesis of compound (R,R_P,S)-**2r**, which was isolated as a colorless oil (60 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.17 (m, 11H), 6.24 (t, J = 2.4 Hz, 1H), 6.02 (d, J = 3.2 Hz, 1H), 5.46 (d, J = 10.4 Hz, 1H), 5.04−4.91 (m, 2H), 4.42−4.24 (m, 1H), 4.09 (dt, J = 17.3, 8.4 Hz, 2H), 3.66 (d, J = 4.2 Hz, 3H), 3.18 (q, J = 6.4 Hz, 2H), 2.94 (d, J = 7.1 Hz, 1H), 2.90−2.83 (m, 1H), 2.41−2.16 (m, 1H), 2.05−1.80 (m, 1H), 1.27 (t, J = 6.9 Hz, 3H). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 49.8. ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.5 (d, J = 6.1 Hz), 156.1, 151.7, 141.9, 136.5 (d, J = 29.6 Hz), 129.2, 128.6, 128.5, 128.1, 127.8, 126.9, 110.3 (d, J = 4.5 Hz), 107.4, 66.9, 61.7 (d, J = 6.9 Hz), 52.3 (d, J = 4.3 Hz), 51.4 (d, J = 106.3 Hz), 39.0, 34.4, 31.9 (d, J = 10.9 Hz), 27.6 (d, J = 88.7 Hz), 16.6 (d, J = 5.5 Hz). HRMS (ESI+)

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calcd for $C_{27}H_{32}NNaO_7P$ *m/z*: 536.1809; found 536.1808 [M + Na]$^+$.

*Methyl (S)-3-((R)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(thiophen-2-ylmethyl)-propanoate ((R,R$_P$,S)-**2s**).* Intermediate (R,R$_P$)-**3a** (0.15 mmol, 66 mg) was used for the synthesis of compound (*R*,*R*$_P$,*S*)-**2s**, which was isolated as a colorless oil (42 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.12 (m, 11H), 6.92 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.81 (d, *J* = 3.4 Hz, 1H), 5.15−4.91 (m, 3H), 4.42−4.23 (m, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.70 (s, 3H), 3.27−3.09 (m, 4H), 2.86 (q, *J* = 11.1 Hz, 1H), 2.24 (td, *J* = 13.8, 7.9 Hz, 1H), 2.06−1.87 (m, 1H), 1.31 (t, *J* = 7.0 Hz, 3H). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 50.0. ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.5, 156.0, 139.8, 136.5, 136.4, 129.3, 128.7, 128.6, 128.2, 127.9, 127.1, 127.0, 126.5, 124.6, 67.1, 61.8, 52.3, 51.4 (d, *J* = 106.2 Hz), 41.7, 34.5, 33.6 (d, *J* = 11.2 Hz), 27.6 (d, *J* = 88.6 Hz), 16.7. HRMS (ESI+) calcd for $C_{27}H_{32}NO_6PSNa$ *m/z*: 552.1580; found 552.1575 [M + Na]$^+$.

*Methyl (S)-3-((R)-((R)-1-(((Benzyloxy)carbonyl)amino)-2-phenylethyl)(ethoxy)phosphoryl)-2-(thiophen-3-ylmethyl)-propanoate ((R,R$_P$,S)-**2t**).* Intermediate (R,R$_P$)-**3a** (0.15 mmol, 65 mg) was used for the synthesis of compound (*R*,*R*$_P$,*S*)-**2t**, which was isolated as a colorless oil (56 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.23 (m, 11H), 7.04 (s, 1H), 6.94 (d, *J* = 4.9 Hz, 1H), 5.18 (d, *J* = 10.3 Hz, 1H), 5.12−4.96 (m, 2H), 4.36 (d, *J* = 12.1 Hz, 1H), 4.26−4.09 (m, 2H), 3.73 (s, 3H), 3.34−3.13 (m, 2H), 3.07 (dd, *J* = 14.2, 7.0 Hz, 1H), 3.02−2.82 (m, 2H), 2.29 (q, *J* = 12.6 Hz, 1H), 2.02−1.91 (m, 1H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{31}P {^{1}H} NMR (162 MHz, $CDCl_3$) δ 50.1. ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.9, 156.0, 138.0, 136.5, 136.4, 129.3, 128.7, 128.6, 128.3, 128.2, 127.9, 127.0, 126.0, 122.4, 67.1, 61.8 (d, *J* = 6.7 Hz), 52.2, 51.4 (d, *J* = 106.5 Hz), 40.7 (d, *J* = 4.3 Hz), 34.5, 34.2 (d, *J* = 11.1 Hz), 27.9 (d, *J* = 88.6 Hz), 16.7 (d, *J* = 5.7 Hz). HRMS (ESI+) calcd for $C_{27}H_{32}NO_6PSNa$ *m/z*: 552.1580; found 552.1575 [M + Na]$^+$.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c01556.

Preparation of starting materials; starting materials diastereomer analysis; phosphinyl dipeptide diastereomer analysis; optimization table for phenyl substrate; optimization table for pyridyl substrate; determination of diastereomeric ratio by ^{31}P NMR of crude mixtures; identification of byproduct by LCMS of crude mixtures; reaction monitoring and background reaction comparison; diastereomeric ratio of 2 gram scale synthesis of (*R*,*R*$_P$,*S*)-**2d**; epimerization study on (*R*,*R*$_P$,*S*)-**2d** under the reaction condition; single crystal X-ray data; experimental data; spectral data (PDF)

Accession Codes

CCDC 2321915232191623219172321918 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif., or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

T.K. developed the methodology and synthesized all of the compounds. F.J. (undergraduate research participant) prepared some of the arylBF$_3$K reagents. H.T. conducted all of the crystallographic studies. Y.S.T. conceived the project and wrote the manuscript with the assistance of T.K. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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