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X-ray Characterization and Structure-Based Optimization of Striatal-Enriched Protein Tyrosine Phosphatase Inhibitors

Michael R. Witten,[†] Lisa Wissler,[‡] Melanie Snow,[§,○] Stefan Geschwindner,[‡] Jon A. Read,[∥] Nicholas J. Brandon,[⊥] Angus C. Nairn,[#] Paul J. Lombroso,[#,▽] Helena Käck,[*,‡] and Jonathan A. Ellman[*,†]

[†]Department of Chemistry, Yale University, New Haven, Connecticut 06520, United States

[‡]Discovery Sciences, Innovative Medicines and Early Development Biotech Unit, AstraZeneca, Gothenburg, Sweden

[§]Discovery Sciences, Innovative Medicines and Early Development Biotech Unit, AstraZeneca, Macclesfield SK10 4TG, United Kingdom

[∥]Discovery Sciences, Innovative Medicines and Early Development Biotech Unit, AstraZeneca, Cambridge CB4 0WG, United Kingdom

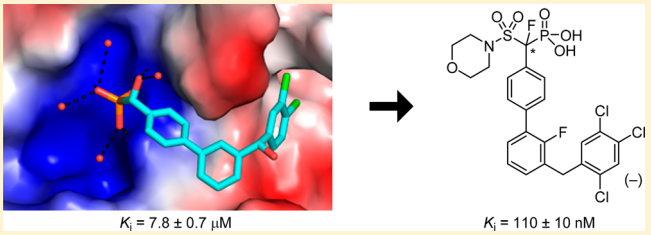
[⊥]Neuroscience, Innovative Medicines and Early Development Biotech Unit, AstraZeneca, Cambridge, Massachusetts 02139, United States

[#]Department of Psychiatry, Yale University, New Haven, Connecticut 06520, United States

[▽]Child Study Center, Yale University, New Haven, Connecticut 06520, United States

Supporting Information

ABSTRACT: Excessive activity of striatal-enriched protein tyrosine phosphatase (STEP) in the brain has been detected in numerous neuropsychiatric disorders including Alzheimer's disease. Notably, knockdown of STEP in an Alzheimer mouse model effected an increase in the phosphorylation levels of downstream STEP substrates and a significant reversal in the observed cognitive and memory deficits. These data point to the promising potential of STEP as a target for drug discovery in Alzheimer's treatment. We previously reported a substrate-based approach to the development of low molecular weight STEP inhibitors with K_i values as low as 7.8 μM. Herein, we disclose the first X-ray crystal structures of inhibitors bound to STEP and the surprising finding that they occupy noncoincident binding sites. Moreover, we utilize this structural information to optimize the inhibitor structure to achieve a K_i of 110 nM, with 15−60-fold selectivity across a series of phosphatases.



INTRODUCTION

Proper cognitive function requires robust synaptic connections possessing the ability to strengthen or weaken based upon tightly regulated neuronal signaling.[1,2] Aberrations in systems within the central nervous system (CNS) that control synaptic plasticity have been implicated in various cognitive and neurological disorders such as Alzheimer's disease (AD),[3,4] schizophrenia,[5−7] and fragile X syndrome.[8−10] Striatal-enriched protein tyrosine phosphatase (STEP, PTPN5) belongs to a family of tyrosine-specific protein phosphatases (PTPs) enriched in the CNS, particularly the striatum, hippocampus, and cortex.[11−18] Recent studies into STEP's function have led to the conclusion that it opposes synaptic strengthening through its actions on substrate proteins.

STEP-mediated dephosphorylation of extracellular signal-related kinases 1 and 2 (ERK1/2),[19] mitogen-activated protein kinase p38,[20] proline-rich tyrosine kinase 2 (Pyk2),[21] and the Src family tyrosine kinase Fyn leads to their inactivation.[22] STEP also dephosphorylates the GluN2B subunit of the *N*-methyl-D-aspartate receptor (NMDAR)[23−25] and the GluA2 subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR),[26] which induces their internalization via endocytosis. Long-term potentiation (LTP),[27,28] an increase in synaptic strength and plasticity that relies on ERK1/2[29] and Pyk2,[30] as well as transmembrane NMDAR[31] and AMPAR function,[32] is one of the fundamental neuronal mechanisms underlying learning and memory. Dephosphorylation of these kinases and transmembrane ion channels consequently results in an overall reduction in synaptic control of LTP.

The potential of STEP as a therapeutic target in AD was suggested through genetic reduction of STEP activity in a triple transgenic AD mouse model.[33] Knockout of STEP expression in these mice improved cognitive function up to the level of normal wild-type mice as determined by several memory and

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cognitive tests. Furthermore, mice null for STEP exhibited restored levels of phospho-GluN2B in hippocampal synaptosomal membranes as well as enhanced levels of phospho-ERK1/2 and phospho-Fyn. Taken together, these findings suggest that STEP represents a promising therapeutic target for AD.

However, a significant caveat toward the development of STEP inhibitors is the widespread recognition that PTPs are extremely challenging targets for the development of small molecule inhibitors due to the highly positively charged nature and the significant structural homology of PTP active sites.[34] Indeed, no PTP inhibitors have yet been approved for clinical use despite the clear physiological importance of these enzymes and their complementary activity to the well-established kinase drug targets.[35]

We have previously reported a series of low molecular weight STEP inhibitors, developed using the substrate activity screening (SAS) approach (Figure 1).[36] We have also described

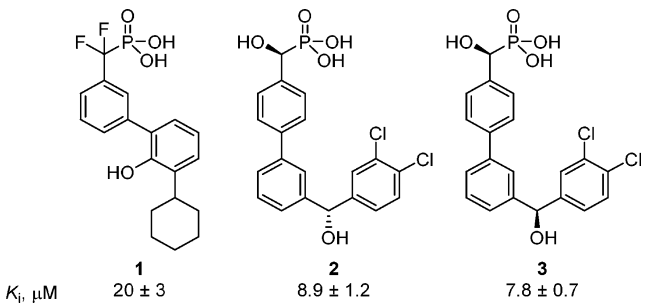

Figure 1. Previously reported inhibitors shown to bind STEP with low micromolar affinity.

benzopentathiepin inhibitors of STEP.[37,38] Since then, there has only been one report of STEP inhibitors designed by in silico virtual screening, with similar potencies to our own.[39] There has also been a cheminformatic study on drug repurposing, but this report does not provide binding data.[40]

Herein, we disclose thermodynamic characterization and X-ray crystal structures of inhibitors **1**, **2**, and **3** bound to STEP, the first structures of STEP inhibitor complexes. Unexpectedly, the inhibitors do not all reside in the same binding pocket on the enzyme, and none of them fully occupy the active site. Furthermore, we have utilized the structural information obtained from these X-ray structures to develop our lead inhibitor with a K_i of 110 nM, representing an improvement in inhibition by nearly 2 orders of magnitude.

RESULTS AND DISCUSSION

Thermodynamic Characterization of Inhibitors Bound to STEP. Isothermal titration calorimetry (ITC) was used to confirm direct binding of phosphonates **1**, **2**, and **3** to the STEP phosphatase domain. Titration experiments of the STEP phosphatase domain with the compounds indicate clear target engagement with affinities in the two-digit micromolar range (Table 1). While the related compounds **2** and **3** representing two epimers of the same scaffold show an undistinguishable and enthalpy-driven thermodynamic signature speaking toward a conserved and equivalent binding mode, compound **1** indicates a significantly weaker binding affinity. This change can be mainly attributed to the largely reduced enthalpic contribution when comparing it with **2** and **3**, which is only partially compensated by an entropic contribution to the overall binding

Table 1. Thermodynamic Parameters for Compound Interaction with STEP Phosphatase Domain Determined by ITC at 30 °C[a]

inhibitor	K_D (μM)	ΔH (kcal/mol)	$-T\Delta S$ (kcal/mol)
1	70.4 ± 4.7	−2.26 ± 0.07	−2.12
2	27.2 ± 0.6	−7.71 ± 0.06	2.77
3	31.4 ± 0.8	−7.63 ± 0.07	2.77

[a]The parameters were extracted from the complete protein titration by the best fit according to a single site binding model with fixed stoichiometry (n = 1), yielding the binding enthalpy (ΔH), entropy ($-T\Delta S$) and the association constant (K_a), from which the dissociation constant ($K_D = 1/K_a$) was calculated. The errors represent the errors from the data fitting.

energy. Combining this with information about the different chemical structures, one can postulate a major difference in the binding mode of **1** in comparison with **2** and **3** although such differences in thermodynamic profiles are not necessarily a hallmark for alterations in the ligand interaction or binding mode.[41] The multifactorial character of the enthalpy signal together with solvation changes and conformational effects always call for an additional analysis using structural data, as we discuss in the next section.

X-ray Characterization of Inhibitors Bound to STEP. To enable structure-based design with the phosphonate inhibitors **1**, **2**, and **3** as starting points and to better understand the origin of the thermodynamic differences, crystal structures were generated of these compounds in complex with STEP (Figure 2). Data was collected from cryocooled crystals

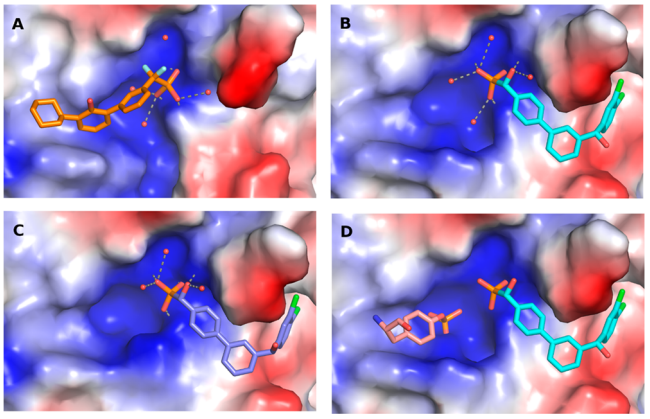

Figure 2. X-ray crystal structure of (A) inhibitor **1** bound to STEP in orange, (B) inhibitor **2** bound to STEP in cyan, and (C) inhibitor **3** bound to STEP in skyblue. (D) A superposition of a substrate bound STEP structure (PDB 1CJZ) and inhibitor **2** bound to STEP shows that the phosphonic acid in **2** binds to a distinctly different site from that of the substrate.[42] Putative hydrogen bonds are marked as dashed lines. All panels are shown in the same orientation. The enzyme is depicted as a surface model colored by electrostatics as calculated by Pymol.[43]

soaked overnight in 4−5 mM solution of compound dissolved in DMSO. The structures were subsequently solved by molecular replacement using the previously reported STEP apo structure (PDB 2BV5) as a search model.[17] Data processing and refinement statistics can be found in Supporting Information, Table S1, and the resulting electron density for the inhibitors in Supporting Information, Figure S1. The overall structure of the phosphatase domain is very similar to the apo

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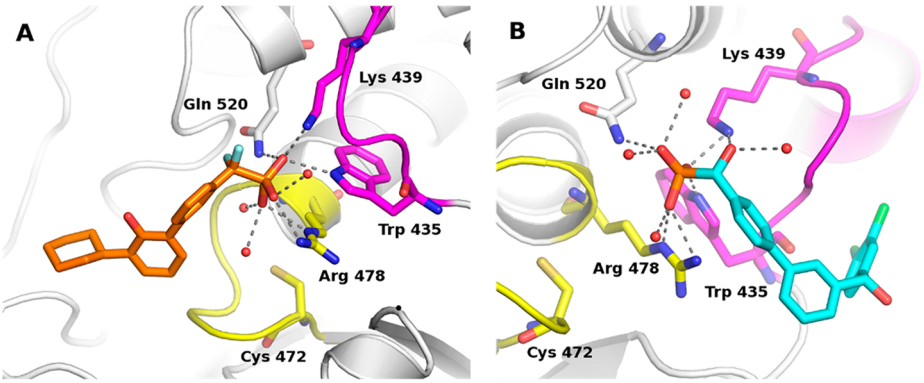

Figure 3. (A) Details of interactions made by inhibitor **1**. (B) Details of interactions made by inhibitor **2**. The WPD loop in STEP is colored purple and the active site loop yellow.

structures, and no major conformational differences are noted in the loops surrounding the catalytic site.

Inhibitor **1** binds in STEP's active site groove, but surprisingly, its negatively charged phosphonate headgroup is nearly 8 Å distant from catalytic Cys472 (Figure 3A, Supporting Information, Figure S2A). This result was unexpected insofar as the α-hydroxyphosphonic acid pharmacophore is a nonhydrolyzable phosphate mimetic that might be expected to bind at the same site as the corresponding phosphate substrate.[36] Instead, phosphonate **1** rests in a separate but nearby positively charged pocket, which in the apo structure is occupied by a sulfate ion.[17] In a previously described structure of a STEP (C472S) mutant and the substrate phosphotyrosine, the side chain of Arg478 interacts with the phosphate group of the substrate.[42] Here, Arg478 adopts a different conformation in order to coordinate one of the phosphonic acid oxygens in compound **1** (Supporting Information, Figure S3). Even though the two sites do not overlap, this shift may interfere with the integrity of the active site and thereby reduce substrate affinity. Furthermore the backbone rings of phosphonate **1** curl into a hydrophobic cleft,[44] while the phenolic −OH of the central ring does not make specific contact with the enzyme, rather it is solvent exposed.

STEP co-crystal structures were also obtained for inhibitors **2** and **3** (Figure 2B,C). The α-hydroxyphosphonic acid makes several specific, direct hydrogen-bonding contacts to the same positively charged cavity bound by inhibitor **1** and is distinct from substrate binding. The nonoverlapping occupancy of substrate phosphotyrosine and inhibitor **2** in STEP's active site is depicted in Figure 2D. The phosphonate oxygens in inhibitors **2** and **3** bind to Gln520, Lys439, Trp435, and Arg478, along with water molecules supported by Thr517, Lys439, Gln520, and Gln516 (Figure 3B, Supporting Information, Figure S2B). The α-hydroxy substituent of **2** and **3** is also directly involved in this hydrogen-bonding network, which is consistent with the fact that the (*S*)-configuration of the alcohol stereocenter is necessary for strong inhibition.[36]

Surprisingly, except for the binding site of the α-hydroxyphosphonic acid pharmacophore, inhibitors **2** and **3** interact with hydrophobic regions of the enzyme that are completely distinct from that observed for inhibitor **1**. The unexpected difference in binding mode is in line with the large difference in the thermodynamic profile shown by ITC, although the observed enthalpy gain appears at first sight counterintuitive. Hydrophobic interactions are typically not associated with enthalpy gains due to the hydrophobic effect,[41] which in this case speaks toward a more complex protein solvation behavior both within these hydrophobic regions as well as the close vicinity of the α-hydroxyphosphonic acid pharmacophore. The co-crystal structures of **2** and **3** also explain their near-identical inhibitory potency despite the opposite stereochemistry of their benzhydryl alcohols. STEP makes the same interactions with inhibitors **2** and **3** and does not make specific contacts to the benzhydryl alcohols, which are solvent exposed.

An overlay of the crystal structures of inhibitors **1** and **2** bound to STEP illustrates their unanticipated, noncoincident binding (Figure 4). Although the two compounds reside in

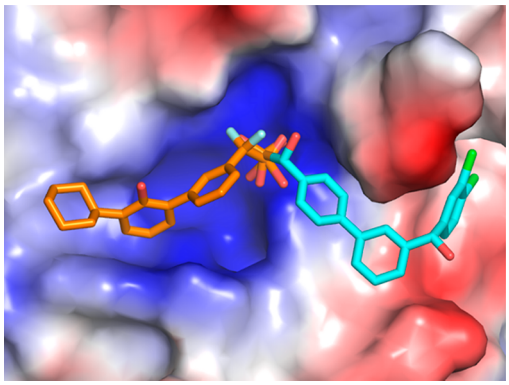

Figure 4. Overlay of X-ray crystal structures of inhibitors **1** (orange) and **2** (cyan) bound to STEP. The enzyme is depicted as a surface model colored by electrostatics as calculated by Pymol.[43]

separate shallow, hydrophobic clefts, the phosphonate head groups both align into the same noncatalytic positively charged pocket. This crystallographic understanding provided essential inspiration for expansion of the inhibitor scaffold into more potent structures (vide infra).

Structure-Based Optimization of STEP Inhibitors. We set out to improve the binding affinity of these phosphonate inhibitors. To avoid stereochemical complications and for ease of synthesis, we elected to begin optimization around the difluorophosphonic acid[45] scaffold of inhibitor (±)-**4** (Chart 1) rather than the more complex structure of chiral hydroxyphosphonic acids **2** and **3**. This highly homologous, previously reported difluorophosphonate has only slightly lower potency than alcohols **2** and **3**.[36] The use of racemates streamlined

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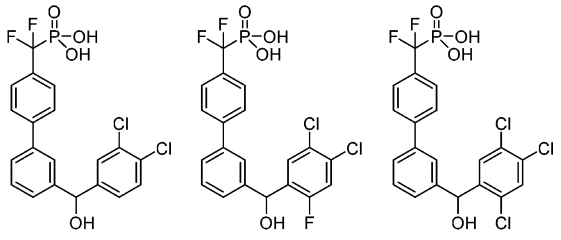
Chart 1. Optimization of Distal Aromatic Ring[a]



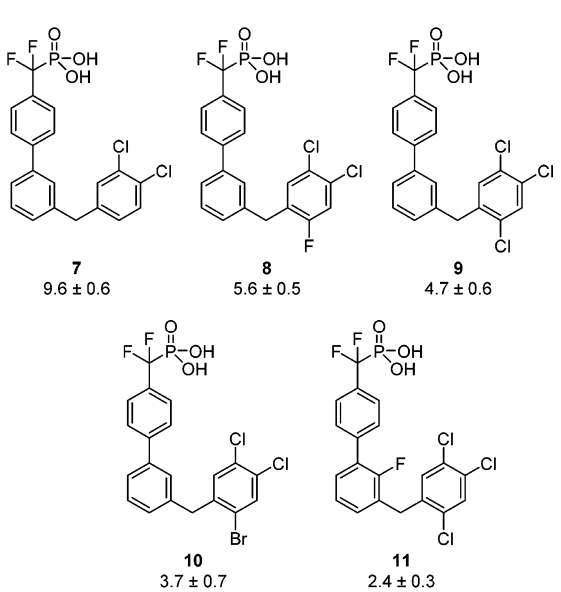
[a] K_i values were measured in duplicate or quadruplicate ((±)-**13**) using a continuous in vitro inhibition assay by employing *p*-nitrophenylphosphate (*p*NPP) as a chromogenic substrate.[46] Commercial detergent, 0.01% v/v, was included in the assay buffer to preclude incidental inhibition by nonproductive formation of micelles.[47−49]

synthetic considerations and is justified in that the benzhydryl alcohol does not make specific contacts with the enzyme target or affect activity (see **2** and **3**, vide supra).

We first explored alterations to the distal aromatic ring. In the crystal structure, we observed a small, hydrophobic cavity at the *ortho*-position. Attempting to fill this pocket with a relatively small fluorine-substituent ((±)-**5**) resulted in a negligible change in potency. However, the larger chlorine substituent ((±)-**6**) provided a small but measurable improvement.

This substitution pattern was also tested in achiral phosphonic acids lacking the benzhydryl hydroxyl group (Chart 2). The trend observed in Chart 1 of decreasing K_i with the presence of larger halogen substitution holds for this series of inhibitors (**7**−**9**) as well, and all three are more potent than the parent alcohols. Upon moving to a larger bromine atom (**10**), we observed a trivial increase in binding affinity, which was not pronounced enough to justify proceeding with the heavier halogen.

Chart 2. Removal of Benzhydryl Alcohol from Inhibitor Scaffold[a]

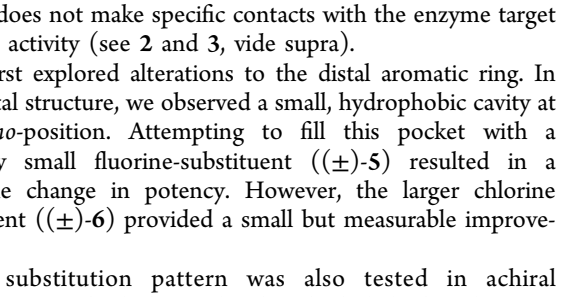


[a] K_i values were measured in duplicate or quadruplicate ((±)-**13**) using a continuous in vitro inhibition assay by employing *p*-nitrophenylphosphate (*p*NPP) as a chromogenic substrate.[46] Commercial detergent, 0.01% v/v, was included in the assay buffer to preclude incidental inhibition by nonproductive formation of micelles.[47−49]

Next, we turned to the central aromatic ring. While the hydrogen atoms at the 4-, 5-, and 6-positions all project into solvent, it appeared that we could take advantage of a small hydrophobic surface adjacent to the 2-position. Molecular modeling suggested that fluorine would be an ideal fit for this volume. Indeed, difluorophosphonic acid **11** demonstrated 2-fold better potency than inhibitor **9**.

At this point, we sought to benchmark our improved inhibitor **11** against α-hydroxyphosphonic acids that more closely resembled the compounds observed in the co-crystal structure (i.e., **2** and **3**, vide supra). Restoration of the hydroxyl group adjacent to the phosphorus atom resulted in a pair of enantiomeric inhibitors ((*R*)-**12** and (*S*)-**12**, Chart 3).

Chart 3. Enantiopure Hydroxyphosphonate and Racemic Fluorophosphonate Analogues Based on Inhibitor 11[a]



[a] K_i values were measured in duplicate or quadruplicate ((±)-**13**). K_i values were measured in triplicate using a continuous in vitro inhibition assay by employing *p*-nitrophenylphosphate (*p*NPP) as a chromogenic substrate.[46] Commercial detergent, 0.01% v/v, was included in the assay buffer to preclude incidental inhibition by the nonproductive formation of micelles.[47−49]

Consistent with the findings in our previous publication[36] and with the X-ray crystal structure of inhibitors **2** and **3**, these phosphonic acids exhibit chiral discrimination, with the (*S*)-enantiomer possessing nearly 6-fold higher activity than the (*R*)-enantiomer. Importantly, hydroxyphosphonic acid (*S*)-**12** was not more potent than the simpler achiral inhibitor **11**. However, racemic monofluorophosphonic acid (±)-**13** was measurably more active than compound **11**.

We then returned to the overlay of the co-crystal structures of inhibitors **1** and **2** bound to STEP (Figure 4B) for further guidance. Speculating that top hits **11** and (±)-**13** reside in the same binding pocket as inhibitor **2**, we hypothesized that we could build into the space occupied by phosphonic acid **1** if we grafted its first aromatic ring onto our optimized scaffold. Similar linking strategies have been reported by groups at SmithKline Beecham in the context of cathepsin K inhibitors.[50,51] Molecular modeling indicated that this could be successfully accomplished with a phenyl ketone, as in phosphonic acid (±)-**14** (Table 2). Indeed, this modification provided a 4-fold enhancement in potency over compound **11** and a 3-fold enhancement over monofluorophosphonic acid (±)-**13**.

Saturation of the newly added ring resulted in a 2-fold drop in activity ((±)-**15**), and moving to the piperidine amide ((±)-**16**) resulted in a further 3-fold diminution in binding affinity. Nonetheless, given the ability of the ketone inhibitors to potentially undergo a reverse phosphono-Claisen condensa-

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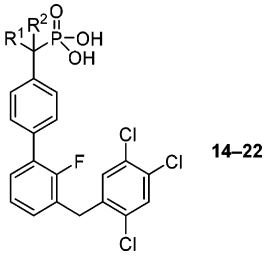
Table 2. Ligands Based on Expanding Inhibitor (±)-13 into Space Occupied by Inhibitor 1[a]



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inhibitor	R^1	R^2	K_i, μM
(±)-**14**		F	0.54 ± 0.02
(±)-**15**		F	1.0 ± 0.1
(±)-**16**		F	3.0 ± 0.2
(±)-**17**		H	2.7 ± 0.5
(±)-**18**		H	1.7 ± 0.1
(±)-**19**		H	2.4 ± 0.4
(±)-**20**		H	6.8 ± 0.8
(±)-**21**		H	0.43 ± 0.02
(+)-**22**		F	3.9 ± 0.2
(−)-**22**		F	0.11 ± 0.01

[a]K_i values were measured in duplicate, triplicate ((−)-**22**), or quadruplicate (**20**) using a continuous in vitro inhibition assay by employing *p*-nitrophenylphosphate (*p*NPP) as a chromogenic substrate.[46] Commercial detergent, 0.01% v/v, was included in the assay buffer to preclude incidental inhibition by nonproductive formation of micelles.[47−49]

tion, we were motivated to proceed with more stable amide-based inhibitors. We found that we could greatly streamline our syntheses by removal of the α-fluorine substituent ((±)-**17**) with no appreciable difference in potency (see Chemical Synthesis section for synthetic sequences). Switching from the piperidine amide to the morpholine amide ((±)-**18**) likely improved solubility and moderately enhanced efficacy. The acyclic dimethyl amide ((±)-**19**) was comparable in potency to piperidine amide (±)-**17**, but secondary amide (±)-**20** was considerably weaker.

A nearly 4-fold jump in activity accompanied the switch from amide (±)-**18** to sulfonamide (±)-**21**, a change that also engendered improved solubility. Given the submicromolar inhibition of STEP demonstrated by racemic inhibitor (±)-**21**, we wished to assay the individual enantiomers of this compound to test for chiral discrimination. We were unable to resolve the enantiomers of (±)-**21**, and the protected precursors of this inhibitor were not configurationally stable. However, we were able to access both enantiomers of α-fluorinated analogue **22** (vide infra). The (+)-enantiomer was over 35-fold less potent than the (−)-enantiomer, demonstrating substantial chiral discrimination and supporting the hypothesis that (−)-**22** makes direct and specific contacts with the binding pocket.

Given the high structural homology among PTP active sites, we tested (−)-**22** against a series of PTPs and the dual-specificity phosphatase MKP5 (Table 3). Notably, this

Table 3. Selectivity of (−)-22 against Several Phosphatases[a]

phosphatase	K_i (μM)	selectivity
STEP	0.11 ± 0.01	
PTP1B	5.9 ± 0.5	54
LMW-Ptp	6.2 ± 0.2	56
TC-Ptp	4.8 ± 0.4	44
MKP5	6.9 ± 0.1	63
LAR	1.6 ± 0.2	15

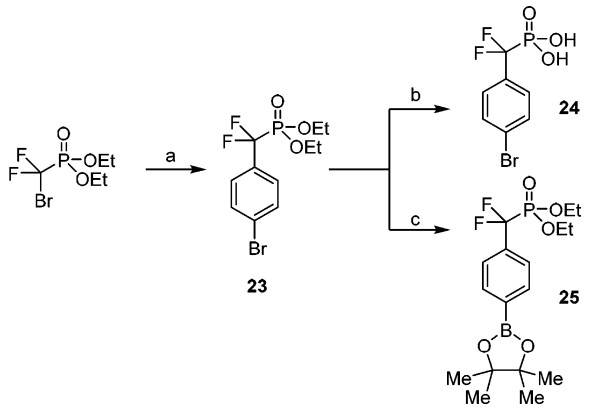
[a]K_i values were measured in duplicate using a continuous in vitro inhibition assay by employing *p*-nitrophenylphosphate (*p*NPP) as a chromogenic substrate.[46] Commercial detergent, 0.01% v/v, was included in the assay buffer to preclude incidental inhibition by nonproductive formation of micelles.[47−49]

sulfonamide exhibited greater than 40-fold selectivity against all but one (LAR) other phosphatases assayed. Furthermore, in preliminary studies for future in vivo evaluation, (−)-**22** was determined to have respectable aqueous solubility (11 ± 2 μM, in PBS at pH 7.4) and complete stability to rat plasma over 1 h as well as excellent stability to rat liver microsomes (88% and 92% remaining after 1 h with and without NADPH).[52]

CHEMICAL SYNTHESIS

The preparation of difluorophosphonate inhibitors (±)-**5**−**11** all employed either input **24** or **25** (Scheme 1). Zinc- and

Scheme 1. Synthesis of Inputs for Difluorophosphonate Inhibitors[a]



[a]Reagents: (a) (i) Zn, DMA; (ii) CuBr, (iii) 1-bromo-4-iodobenzene, DMA; (b) TMSI, CH_2Cl_2; (c) B_2pin_2, KOAc, $Pd(dppf)Cl_2$, dioxane.

CuBr-promoted coupling of diethyl (bromodifluoromethyl) phosphonate with 1-bromo-4-iodobenzene provided phosphonic acid diethyl ester **23**.[53] This material was then deprotected with iodotrimethylsilane or borylated under Miyaura conditions to provide intermediates **24** and **25**, respectively.

Inhibitors (±)-**5** and (±)-**6** were accessed through a three-step process beginning with formation of the Grignard reagent from 3-bromoiodobenzene by transmetalation with isopropylmagnesium iodide followed by addition to the appropriate

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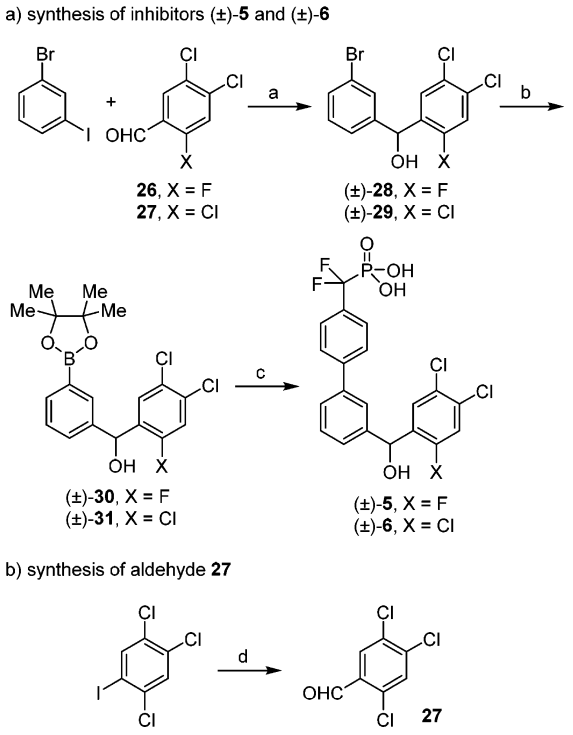
benzaldehyde (**26** or **27**) to form alcohols (±)-**28** and (±)-**29** (Scheme 2a). While the synthesis of 4,5-dichloro-2-fluoroben-

Scheme 2. Synthesis of Inhibitors (±)-5 and (±)-6[a]



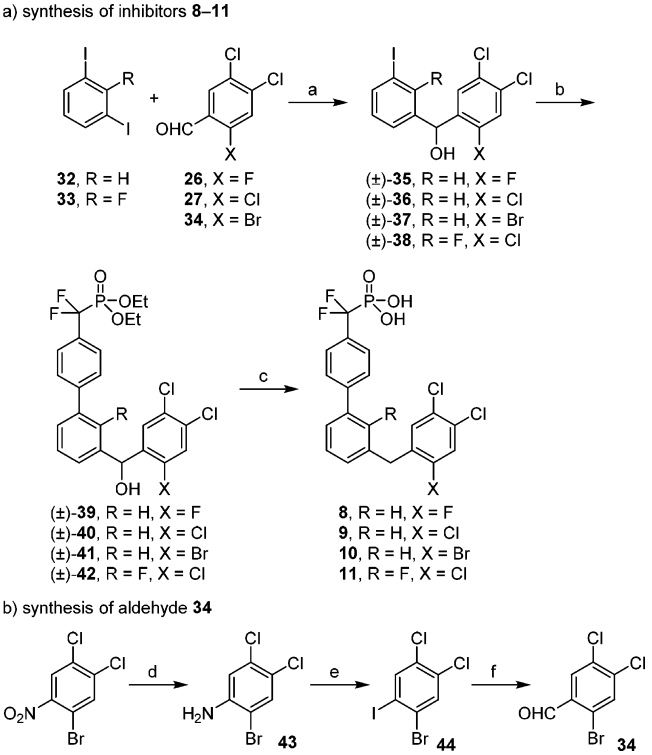
[a]Reagents: (a) (i) *i*PrMgCl, THF, (ii) aldehyde, THF; (b) B_2pin_2, KOAc, Pd(dppf)Cl_2, dioxane; (c) **24**, $Pd(PPh_3)_4$, Na_2CO_3, DME/EtOH/H_2O; (d) (i) *i*PrMgCl, THF, (ii) DMF.

zaldehyde **26** has been previously reported,[54] we approached 2,4,5-trichlorobenzaldehyde **27** by transmetalation of the corresponding 1,2,4-trichloro-5-iodobenzene with isopropylmagnesium iodide followed by addition to DMF (Scheme 2b). Miyaura borylation of aryl bromides (±)-**28** and (±)-**29** gave the corresponding pinacol boronates (±)-**30** and (±)-**31**. Subsequent Suzuki cross-coupling with phosphonic acid **24** afforded ligands (±)-**5** and (±)-**6**.

The synthesis of inhibitors **8**−**11** was accomplished through a similar sequence (Scheme 3a). Transmetalation of aryl iodide **32** or **33**[55] followed by Grignard addition to the appropriate benzaldehyde (**26**, **27**, or **34**) provided benzhydryl alcohols (±)-**35**−(±)-**38**. Benzaldehyde **34** was prepared through a three-step process beginning with the iron-mediated reduction of 1-bromo-4,5-dichloro-2-nitrobenzene to the corresponding aniline (**43**, Scheme 3b). Sandmeyer reaction of aniline **43** provided iodide **44**, which was converted to benzaldehyde **34** through the same process as used above for aldehyde **27**. Suzuki cross-coupling of aryl iodides (±)-**35**−(±)-**38** with boronic ester **25** gave phosphonate esters (±)-**39**−(±)-**42**, which were then treated with iodotrimethylsilane to concomitantly remove the ethyl ester protecting groups and the benzhydryl hydroxyl group, to provide the desired phosphonic acids **8**−**11**.

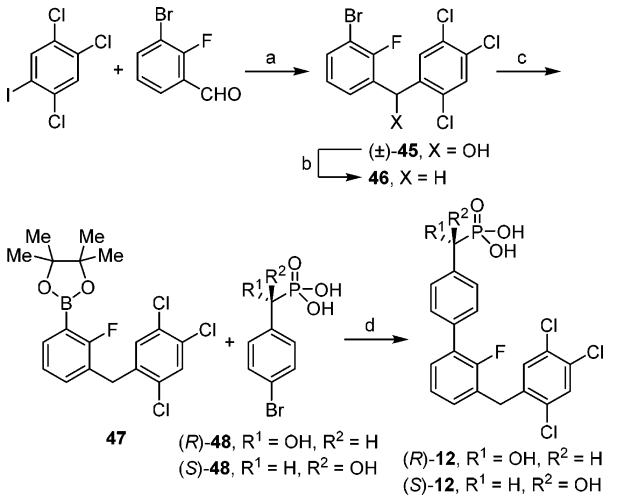
Enantiomerically pure inhibitors (*R*)-**12** and (*S*)-**12** were synthesized by using a related set of reactions (Scheme 4). First, transmetalation of 1,2,4-trichloro-5-iodobenzene and addition to 3-bromo-2-fluorobenzaldehyde generated alcohol (±)-**45**, which was reduced to aryl bromide **46** by triethylsilane

Scheme 3. Synthesis of Inhibitors 8−11[a]



[a]Reagents: (a) (i) *i*PrMgCl, THF, (ii) aldehyde, THF; (b) **25**, $Pd(PPh_3)_4$, K_2CO_3, toluene/EtOH/H_2O; (c) TMSI, CH_2Cl_2; (d) Fe, EtOH, AcOH; (e) (i) HCl, $NaNO_2$, H_2O, (ii) KI, H_2O, CH_2Cl_2; (f) (i) *i*PrMgCl, THF, (ii) DMF.

Scheme 4. Synthesis of Inhibitors (*R*)-12 and (*S*)-12[a]



[a]Reagents: (a) (i) *i*PrMgCl, THF, (ii) aldehyde, THF; (b) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2; (c) B_2pin_2, KOAc, Pd(dppf)Cl_2, dioxane; (d) $Pd(PPh_3)_4$, Na_2CO_3, DME/EtOH/H_2O.

in the presence of boron trifluoride. Miyaura borylation to afford boronic ester **47** was followed by Suzuki cross coupling with enantiomercially pure α-hydroxyphosphonic acids (*R*)-**48** and (*S*)-**48** to provide both enantiomers of inhibitor **12**.

Monofluorophosphonic acid (±)-**13** was prepared in four steps, starting with the α-fluorination of diethyl (4-bromobenzyl)phosphonate using NFSI (Scheme 5).[56] The resultant aryl bromide ((±)-**49**) was treated with bis-

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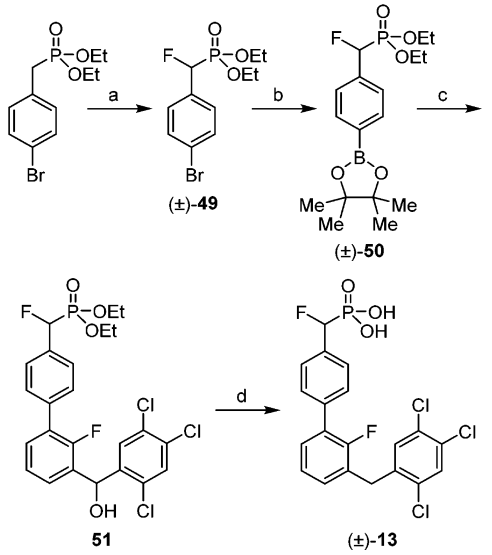
Scheme 5. Synthesis of Inhibitor (±)-13[a]

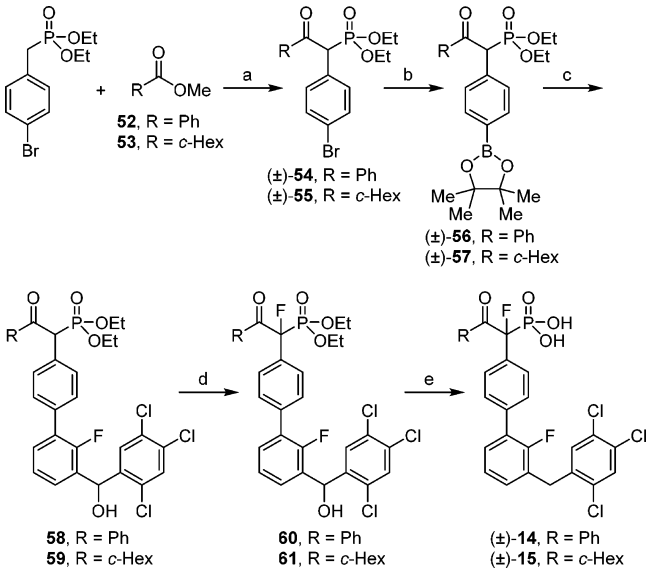


[a]Reagents: (a) (i) LiHMDS, THF, (ii) TMSCl, THF, (iii) NFSI, THF; (b) B_2pin_2, KOAc, $Pd(dppf)Cl_2$, dioxane; (c) (±)-**38**, $Pd(PPh_3)_4$, K_2CO_3, toluene/EtOH/H_2O; (d) TMSI, CH_2Cl_2.

(pinacoloto)diboron under Miyaura conditions to provide boronate (±)-**50**. Cross-coupling with the previously described aryl iodide (±)-**38** then generated a diastereomeric mixture of benzhydryl alcohols **51**. Treatment with iodotrimethylsilane resulted in cleavage of the ethyl esters and loss of the benzhydryl hydroxyl group to afford inhibitor (±)-**13**.

We accessed *β*-ketophosphonates (±)-**14** and (±)-**15** by first performing an LDA-mediated phosphono-Claisen condensation between diethyl (4-bromobenzyl)phosphonate and the appropriate commercially available ester (**52** or **53**, Scheme 6).[57] This was followed by Miyaura borylation of aryl bromides (±)-**54** and (±)-**55** to afford pinacol esters (±)-**56** and (±)-**57**,

Scheme 6. Synthesis of Inhibitors (±)-14 and (±)-15[a]

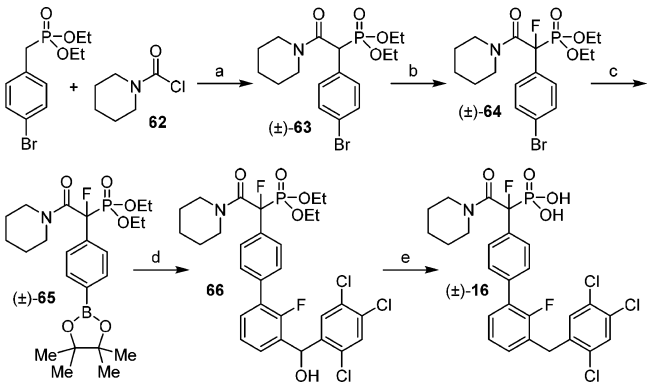


[a]Reagents: (a) LDA, THF; (b) B_2pin_2, KOAc, $Pd(dppf)Cl_2$, dioxane; (c) (±)-**38**, $Pd(PPh_3)_4$, K_2CO_3, toluene/EtOH/H_2O; (d) NFSI, selectfluor, CH_2Cl_2; (e) TMSI, CH_2Cl_2.

which were subsequently cross-coupled with aryl iodide (±)-**38**. *α*-Fluorination of ketones **58** and **59** was accomplished by treatment with a combination of NFSI and selectfluor. Subsequent deprotection and hydrodehydroxylation of **60** and **61** provided inhibitors (±)-**14** and (±)-**15**.

Amide inhibitor (±)-**16** was synthesized in five steps, starting with an LDA-promoted amide formation between diethyl (4-bromobenzyl)phosphonate and piperidine-1-carbonyl chloride (**62**) to generate phosphonate (±)-**63** (Scheme 7). Fluorination with LDA and NFSI to provide amide (±)-**64** was followed by borylation under standard conditions. Suzuki cross-coupling of boronate (±)-**65** with aryl iodide (±)-**38** afforded a diastereomeric mixture of amides **66**, which was concomitantly deprotected and hydrodehydroxylated with iodotrimethylsilane to provide phosphonate (±)-**16**.

Scheme 7. Synthesis of Inhibitor (±)-16[a]



[a]Reagents: (a) LDA, THF; (b) LDA, NFSI, THF; (c) B_2pin_2, KOAc, $Pd(dppf)Cl_2$, dioxane; (d) (±)-**38**, $Pd(PPh_3)_4$, K_2CO_3, toluene/EtOH/H_2O; (e) TMSI, CH_2Cl_2.

The synthesis of tertiary amide inhibitors (±)-**17**–(±)-**19** was carried out by first reducing benzhydryl alcohol (±)-**38** to the diarylmethane **67** with triethylsilane and borylating diethyl (4-bromobenzyl)phosphonate to boronate ester **68** (Scheme 8). These two components were subsequently cross-coupled to afford phosphonate **69**, which was treated with LDA and the appropriate carbamic chloride (**62**, **70**, or **71**). The resultant amides (±)-**72**–(±)-**74** were treated without purification with iodotrimethylsilane to give inhibitors (±)-**17**–(±)-**19**.

We approached secondary amide inhibitor (±)-**20** in six steps from commercially available methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (Scheme 9). After Suzuki coupling with aryl iodide **67** in ethanol solvent, we observed partial transesterification of the methyl ester to the ethyl ester, resulting in a trivial mixture of intermediates **75a** and **75b**, which were hydrolyzed to the corresponding acid (**76**). *α*-Bromination under Hell–Volhard–Zelinsky conditions resulted in additional bromination at the benzhydryl position, providing a diastereomeric mixture of acids **77**, which was treated with methylamine and CDI to afford amide **78**. Arbuzov reaction in neat triethyl phosphite provided phosphonate **79**. Exposure to iodotrimethylsilane resulted in removal of the ethyl ester protecting groups and reduction of the benzhydryl bromide to give inhibitor (±)-**20**.

Inhibitor (±)-**21** was produced starting with sulfonamide formation between (4-bromophenyl)methanesulfonyl chloride and morpholine to generate intermediate **80** (Scheme 10). This material was borylated to give **81**, which was then cross-coupled

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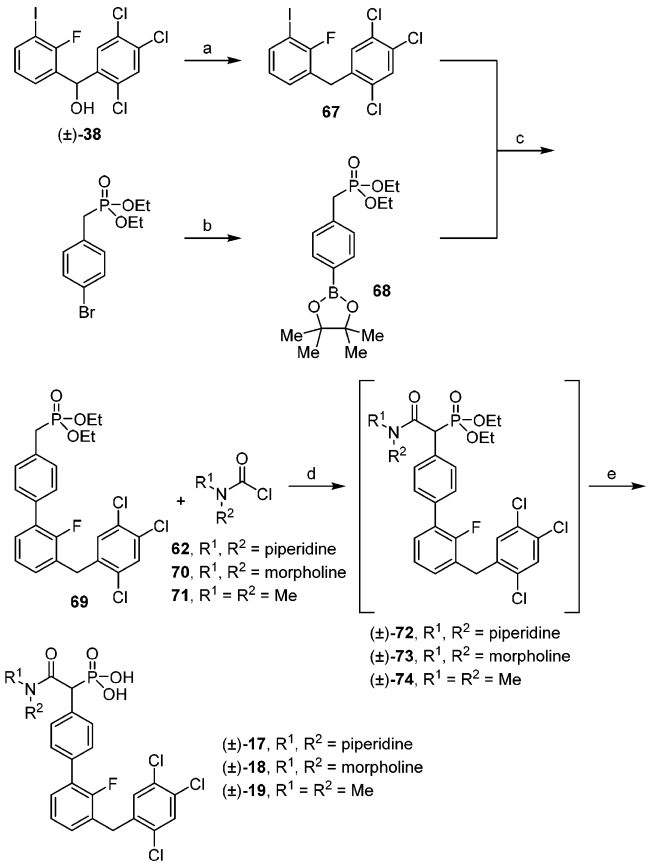
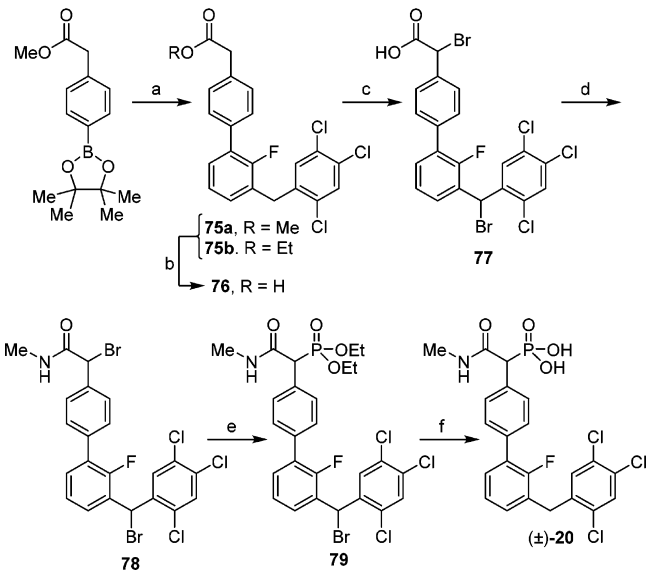
Scheme 8. Synthesis of Inhibitors (±)-17−(±)-19[a]



[a]Reagents: (a) Et_3SiH, TFA, CH_2Cl_2; (b) B_2pin_2, KOAc, $Pd(dppf)Cl_2$, dioxane; (c) $Pd(PPh_3)_4$, K_2CO_3, toluene/EtOH/H_2O; (d) LDA, THF; (e) TMSI, CH_2Cl_2.

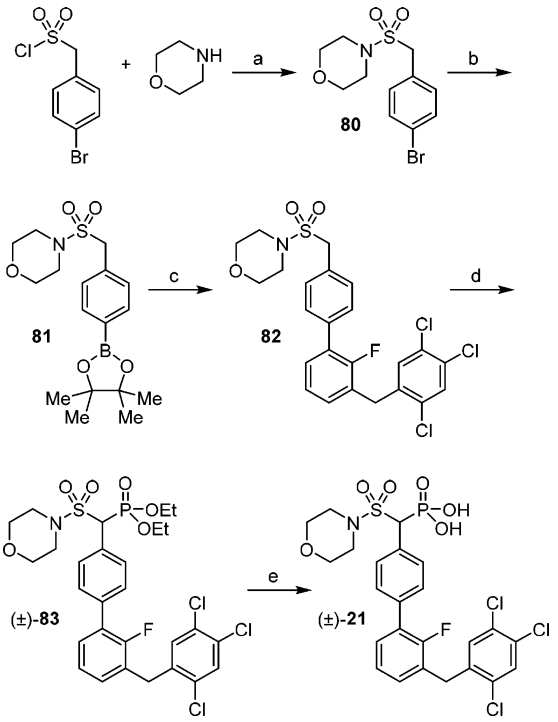
Scheme 9. Synthesis of Inhibitor (±)-20[a]



[a]Reagents: (a) **67**, $Pd(PPh_3)_4$, K_2CO_3, toluene/EtOH/H_2O; (b) NaOH, MeOH, EtOH; (c) Br_2, PCl_3, PhCl; (d) $MeNH_2$, CDI, CH_2Cl_2; (e) $P(OEt)_3$; (f) TMSI, CH_2Cl_2.

with aryl iodide **67** to provide sulfonamide **82**. From here, deprotonation with LDA followed by addition of diethyl

Scheme 10. Synthesis of Inhibitor (±)-21[a]



[a]Reagents: (a) Na_2CO_3, MeCN; (b) B_2pin_2, KOAc, $Pd(dppf)Cl_2$, dioxane; (c) **67**, $Pd(PPh_3)_4$, K_2CO_3, toluene/EtOH/H_2O; (d) (i) LDA, THF, (ii) diethyl chlorophosphate; (e) TMSI, CH_2Cl_2.

chlorophosphate[58] gave phosphonate (±)-**83**, which was deprotected with iodotrimethylsilane to afford inhibitor (±)-**21**. The enantiomers of inhibitor (±)-**21** did not separate by preparative chiral chromatography and precursor (±)-**83** racemized under separation conditions due to the highly acidic nature of the α-hydrogen. To access enantiomerically pure inhibitors, we prepared the α-fluorinated sulfonamides (+)-**22** and (−)-**22**.

Accordingly, sulfonamide **82** was fluorinated with NFSI, to give (±)-**84**, which was converted to the racemic mixture of α-fluorophosphonates (±)-**85** by deprotonation and addition of diethyl chlorophosphate (Scheme 11).[58] This racemic mixture was resolved by chiral supercritical fluid chromatography to provide isolated enantiomers **85a** and **85b**.[59] Finally, treatment of the separated isomers with iodotrimethylsilane afforded enantiomeric inhibitors (+)-**22** and (−)-**22**.

CONCLUSIONS

Despite the causative link between STEP overactivity and the hallmark symptoms of AD, only limited progress has been reported on the development of potent and selective inhibitors of this PTP. In this article, we have presented co-crystal structures of our previously reported inhibitors with STEP, displaying a surprising example of noncoincident binding of related compound structures. Furthermore, neither inhibitor scaffold fully resides in the anticipated active site of the enzyme.

We were able to successfully use structural data from the crystal structures in order to iteratively improve our inhibitor design and expand the architecture of one compound to occupy space filled by the other. Ultimately, we identified phosphonate (−)-**22** with a K_i of 110 nM. Importantly, this inhibitor exhibited promising selectivity over other tyrosine and dual-

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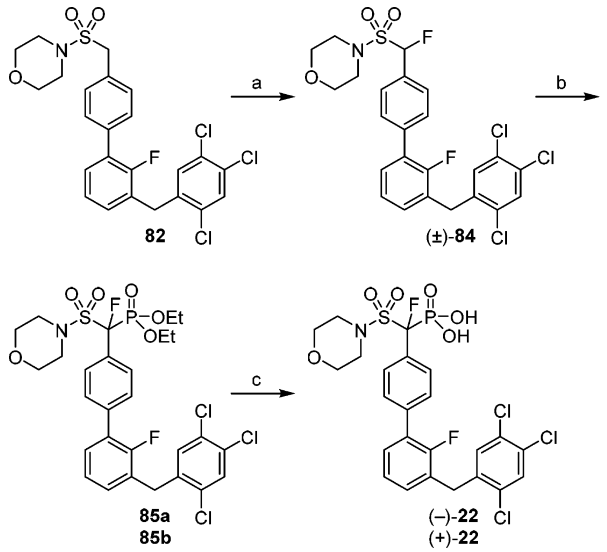
Scheme 11. Synthesis of Inhibitors (+)-22 and (−)-22[a]



[a]Reagents: (a) (i) NaHMDS, THF, (ii) NFSI, THF; (b) (i) LDA, THF, (ii) diethyl chlorophosphate, (iii) preparative chiral SFC; (c) TMSI, CH_2Cl_2.

specificity phosphatases. The determination of the co-crystal structure of sulfonamide (−)-**22** with STEP is a priority for future efforts to further enhance potency and selectivity and, most importantly, to identify suitable replacements for the polar and acidic phosphonic acid functionality as would likely be necessary for target engagement within the CNS.

EXPERIMENTAL SECTION

General Methods. Flasks were fitted with rubber septa. Reactions were conducted under air unless noted. Stainless steel syringes were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed using silica gel 60 (230−400 mesh). Commercial reagents were used as received with the following exceptions: dichloromethane, 1,4-dioxane, and tetrahydrofuran were dried by passing through columns of activated alumina. Diisopropylamine was distilled from NaOH at 760 Torr. *n*-Butyllithium was titrated using *N*-benzylbenzamide as an indicator. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$ = δ 7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$ = δ 77.2). Data are represented as follows: chemical shift (multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet), coupling constants in Hertz (Hz), integration). The mass spectral data were obtained on an Agilent 6550A quadrupole time-of-flight LC/MS spectrometer (ESI-TOF). Enzymatic assays were performed on a PerkinElmer Envision 2100 plate reader. Synthesis, characterization, and enzymatic assays of inhibitors **1**, **2**, **3**, (±)-**4**, and **7** have been previously reported.[36] The purity of all new inhibitors (≥95%) has been determined by HPLC analysis.

Protein Production for Isothermal Titration Calorimetry and Crystallography. The STEP phosphatase domain (6His-TEV-STEP258-539) DNA was synthesized and cloned by GeneArt Life Technologies and expressed in *Escherichia coli* (BL21-Gold; DE3) at 18 °C with overnight expression. Frozen *E. coli* cell paste was resuspended in lysis buffer (50 mM Tris HCl, pH 7.5, 500 mM NaCl, 0.5 mM TCEP, complete protease inhibitor tablets-EDTA free (Roche), 2.5 units/mL Benzonase) using a polytron homogenizer. Cells were lysed using one pass through a Basic Z (Constant Systems) at 25K psi. The cell lysate was then clarified by centrifugation at 25000*g*. The supernatant was loaded onto pre-equilibrated 10 mL Ni NTA Superflow (Qiagen) packed in an XK26 column (GE Healthcare) using an ÄKTA explorer (GE Healthcare). The column was then washed to A280 baseline with load buffer (50 mM Tris, pH 7.5, 500 mM NaCl, 10 mM imidazole, 0.5 mM TCEP, 5% glycerol, washed with 50 mM imidazole) and eluted with load buffer containing 250 mM imidazole. Samples of the fractions were analyzed by SDS-PAGE and those containing the protein were pooled. Protein concentration was determined by absorbance at 280 nm throughout. The pool was concentrated (10 kDa MWCO centrifugal concentrators, Millipore) and loaded onto a pre-equilibrated (50 mM HEPES, pH 7.5, 100 mM NaCl, 0.5 mM TCEP, 5% glycerol) High Load Superdex 75 16/600 (GE Healthcare). SDS-PAGE was used to pool fractions containing the phosphatase domain. The S75 pool was diluted 4× into anion exchange buffer (50 mM HEPES, pH 7.5, 1 mM TCEP, 5% glycerol) and loaded onto a pre-equilibrated 6 mL Resource Q column (GE Healthcare). The column was washed to A280 baseline and eluted with a 5 CV 10% elution buffer (anion exchange buffer +1 M NaCl) step, followed by a 20 CV gradient of 20−50% elution buffer. Fractions were pooled based on SDS-PAGE. The Q Pool was concentrated as before to 8 mL and loaded onto a Hi Load Superdex 200 26/600 (GE Healthcare) pre-equilibrated with storage buffer (20 mM HEPES, pH 7.4, 150 mM NaCl, 0.5 mM TCEP). Fractions were pooled based on SDS-PAGE, aliquoted, and snap-frozen in liquid nitrogen before storing at −80 °C.

Isothermal Titration Calorimetry (ITC). The ITC titration experiments were carried out on a MicroCal ITC-200 system (Malvern Instrument Ltd.) using protein that had been passed through a PD-10 column (GE-Healthcare) equilibrated with 20 mM Tris-HCl (pH 7.6), 150 mM NaCl, 1 mM TCEP, 0.05% (v/v) Tween 20, and 2% DMSO. Because of the expectation of low affinity and low heat signals, titrations of 52 μM STEP phosphatase domain were conducted at 30 °C by injecting 30 × 1.2 μL aliquots at a concentration of 1.6 mM of the respective compound with 90 s waiting time between subsequent injections. The thermodynamic parameters of the binding were extracted by analysis of the binding isotherms by applying a single site binding model (setting the stoichiometry value n to 1 due to low c-value titration) using the Microcal Origin version 7.0 software package, yielding binding enthalpy (ΔH), entropy (ΔS), and association constant (K_a), from which the dissociation constant K_D was calculated ($K_D = 1/K_a$)

Crystallization and Structure Determination. Prior to crystallization setup, 6His-TEV-STEP258−539 was washed with fresh buffer (20 mM HEPES, pH 7.4, 0.1 M NaCl, 1 mM TCEP) and reconcentrated to 4.9 mg/mL. Crystals were grown at 4 °C in hanging drops using 2 μL of protein and 1 μL of well solution (26−28% PEG3350, 0.1 M Bis-Tris, pH 5.5, 0.2 M lithium sulfate). Rodlike crystals typically appeared after 1−2 days but continued to grow for approximately 2 weeks. Structure complexes with compounds **1**, **2**, and **3** were obtained by soaking apo crystals in 28% PEG3350, 0.1 M Bis-tris, pH 5.5, 1 mM TCEP and 4−5 mM of compound for 18−26 h. Crystals were cryoprotected using 20% glycerol and frozen under liquid nitrogen prior to data collection. X-ray diffraction data was collected on a Rigaku A200 CDD detector mounted on a rotating anode (FRE+, Rigaku). Data were integrated and processed using autoPROC.[60] The crystals belong to space group $P2_12_12_1$ with one molecule in the asymmetric unit. The structures were solved with molecular replacement by using the Protein Data Bank (PDB) entry 2BV5 as search model.[17] Structural refinement was carried out by using autoBUSTER[61] and manual rebuilding was done using Coot.[62] Statistics from the integration, scaling, and refinement are presented in Supporting Information, Table S1. All structure illustrations were prepared using the program Pymol.[43] Crystallographic coordinates have been deposited into the Protein Data Bank (accession codes: **1**, 5OW1; **2**, 5OVR; **3**, 5OVX).

General Procedure for Determination of Inhibitor K_i. Reaction volumes of 100 μL were used in 96-well plates. An amount of 65 μL of water was added to each well, followed by 5 μL of 20× buffer (1.0 M imidazole, 1.0 M NaCl, 0.2% Triton-X 100, pH 7.0), 10 μL of 10× DTT (50 mM, 5 mM in assay), 5 μL of STEP phosphatase (1 μM, 50 nM in assay), and 5 μL of the appropriate inhibitor dilution

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in DMSO (with 2-fold serial dilutions). The assay plate was incubated for 5 min at 27 °C, at which point the reaction was started by addition of 10 μL of a 10× *p*NPP substrate (5 mM, 500 μM in assay). The plate was then immediately placed into a spectrophotometric plate reader, and 20 min of kinetic data was obtained (405 nm, 27 °C). The initial rate data collected were used for determination of K_i values. For K_i determination, the kinetic values were obtained directly from nonlinear regression of substrate−velocity curves in the presence of various concentrations of inhibitor. Assays were run in at least duplicate. Nonlinear regression analysis was accomplished in Prism (GraphPad) using single site competitive inhibition. Dose−response curves for each inhibitor as well as additional information are provided in the Supporting Information.

Synthesis and Characterization of Inhibitors and Intermediates. *(±)-((3′-((4,5-Dichloro-2-fluorophenyl)(hydroxy)methyl)-[1,1′-biphenyl]-4-yl)difluoromethyl)phosphonic Acid ((±)-**5**).* Phosphonic acid **24** (254 mg, 0.885 mmol, 1.0 equiv), boronic ester (±)-**30** (514 mg, 1.29 mmol, 1.5 equiv), and $Na_2CO_3·H_2O$ (642 mg, 5.18 mmol, 5.9 equiv) were dissolved in DME (3.9 mL), EtOH (0.97 mL), and H_2O (0.97 mL). With stirring, N_2 was bubbled through the biphasic mixture for 1 h. $Pd(PPh_3)_4$ (102 mg, 0.0879 mmol, 0.10 equiv) was then added, and N_2 was bubbled through the stirred solution for an additional 20 min. The flask was next equipped with a reflux condenser, and the reaction mixture was stirred at 80 °C under an atmosphere of N_2 for 18 h. The solution was cooled to 23 °C and concentrated. The residue was dissolved in minimal MeOH and purified by reversed-phase gradient chromatography (5−100% MeCN in H_2O with 0.1% TFA). Volatile components were removed, and the resulting aqueous solution was lyophilized to afford (±)-**5** as a white powder (99 mg, 23%). IR (film) ν_{max} 3308 (br), 1607, 1468, 1259, 1118, 1054, 921, 836, 794 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 7.55 (d, J = 7.0 Hz, 1H), 7.50−7.45 (m, 5H), 7.34 (dt, J = 7.6, 1.5 Hz, 1H), 7.22 (t, J = 7.7 Hz, 1H), 7.17−7.13 (m, 1H), 7.09 (d, J = 9.6 Hz, 1H), 5.86 (s, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ −110.9 (d, J = 113.8 Hz), −119.2. ^{31}P NMR (162 MHz, CD_3OD) δ 4.90 (t, J = 113.6 Hz). MS (ESI-TOF) calcd for $C_{20}H_{14}Cl_2F_3O_4P$ $[M - H]^-$ 474.9886, found 474.9888.

*(±)-(Difluoro(3′-(hydroxy(2,4,5-trichlorophenyl)methyl)-[1,1′-biphenyl]-4-yl)methyl)phosphonic Acid ((±)-**6**).* Reaction of phosphonic acid **24** (297 mg, 1.03 mmol, 1.0 equiv), boronic ester (±)-**31** (623 mg, 1.51 mmol, 1.5 equiv), $Na_2CO_3·H_2O$ (757 mg, 6.10 mmol, 5.9 equiv), and $Pd(PPh_3)_4$ (117 mg, 0.101 mmol, 0.10 equiv) in DME (4.4 mL), EtOH (1.1 mL), and H_2O (1.1 mL) according to the procedure for the preparation of (±)-**5** above afforded (±)-**6** as a white solid (131 mg, 26%). IR (film) ν_{max} 3296 (br), 1452, 1400, 1352, 1257, 1171, 1130, 1030, 915, 835, 699 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 7.63 (s, 1H), 7.45−7.43 (m, 4H), 7.42 (t, J = 1.7 Hz, 1H), 7.30 (d, J = 4.8 Hz, 2H), 7.17 (t, J = 7.7 Hz, 1H), 7.09 (d, J = 7.7 Hz, 1H), 5.88 (s, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ −110.9 (d, J = 113.5 Hz). ^{31}P NMR (162 MHz, CD_3OD) δ 4.85 (t, J = 112.4 Hz). MS (ESI-TOF) calcd for $C_{20}H_{14}Cl_3F_2O_4P$ $[M - H]^-$ 1:1 490.9591 and 492.9561, found 1:1 490.9592 and 492.9564.

*((3′-(4,5-Dichloro-2-fluorobenzyl)-[1,1′-biphenyl]-4-yl)difluoromethyl)phosphonic Acid (**8**).* Phosphonate (±)-**39** (218 mg, 0.410 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (1.3 mL, 0.248 M). To this mixture was added iodotrimethylsilane (0.35 mL, 492 mg, 2.46 mmol, 6.0 equiv), then the flask was sealed under a polyethylene stopper. The reaction mixture was stirred for 20 h at 23 °C, then concentrated. The residue was dissolved in minimal MeOH and purified by reversed-phase gradient chromatography (5−100% MeCN in H_2O with 0.1% TFA). Volatile components were removed, and the resulting aqueous solution was lyophilized to afford **8** as a white powder (180 mg, 95%). IR (film) ν_{max} 3373 (br), 1652, 1478, 1372, 1259, 1121, 1049, 926, 839, 783 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 7.51−7.44 (m, 4H), 7.31−7.28 (m, 2H), 7.19 (t, J = 7.4 Hz, 2H), 7.10 (d, J = 9.3 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 3.81 (s, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ −110.7 (d, J = 113.2 Hz), −118.6. ^{31}P NMR (162 MHz, CD_3OD) δ 4.93 (t, J = 105.7 Hz). MS (ESI-TOF) calcd for $C_{20}H_{14}Cl_2F_3O_3P$ $[M - H]^-$ 458.9937, found 458.9937.

*(Difluoro(3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)methyl)phosphonic Acid (**9**).* Reaction of phosphonate (±)-**40** (171 mg, 0.311 mmol, 1.0 equiv) and iodotrimethylsilane (0.27 mL, 380 mg, 1.90 mmol, 6.1 equiv) in CH_2Cl_2 (1.0 mL, 0.245 M) according to the procedure for the preparation of **8** above afforded **9** as a white solid (134 mg, 90%). IR (film) ν_{max} 1605, 1461, 1353, 1260, 1131, 1067, 984, 927, 835, 798 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 7.69−7.64 (m, 4H), 7.57 (s, 1H), 7.51−7.46 (m, 2H), 7.40−7.35 (m, 2H), 7.17 (d, J = 7.8 Hz, 1H), 4.10 (s, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ −110.9 (d, J = 113.6 Hz). ^{31}P NMR (162 MHz, CD_3OD) δ 5.12. MS (ESI-TOF) calcd for $C_{20}H_{14}Cl_3F_2O_3P$ $[M - H]^-$ 1:1 474.9641 and 476.9612, found 1:1 474.9637 and 476.9613.

*((3′-(2-Bromo-4,5-dichlorobenzyl)-[1,1′-biphenyl]-4-yl)difluoromethyl)phosphonic Acid (**10**).* Reaction of phosphonate (±)-**41** (122 mg, 0.205 mmol, 1.0 equiv) and iodotrimethylsilane (0.12 mL, 164 mg, 0.821 mmol, 4.0 equiv) in CH_2Cl_2 (0.65 mL, 0.268 M) according to the procedure for the preparation of **8** above afforded **10** as a white solid (62 mg, 58%). IR (film) ν_{max} 1609, 1458, 1347, 1254, 1132, 1053, 927, 836, 795 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 7.68 (s, 1H), 7.63−7.58 (m, 4H), 7.46−7.41 (m, 2H), 7.34−7.30 (m, 2H), 7.11 (d, J = 7.6 Hz, 1H), 4.06 (s, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ −110.7 (d, J = 113.3 Hz). ^{31}P NMR (162 MHz, CD_3OD) δ 4.81 (t, J = 113.2 Hz). MS (ESI-TOF) calcd for $C_{20}H_{14}BrCl_2F_2O_3P$ $[M - H]^-$ 1:1 518.9136 and 520.9116, found 1:1 518.9135 and 520.9115.

*(Difluoro(2′-fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)methyl)phosphonic Acid (**11**).* Reaction of phosphonate (±)-**42** (142 mg, 0.249 mmol, 1.0 equiv) and iodotrimethylsilane (0.21 mL, 299 mg, 1.50 mmol, 6.0 equiv) in CH_2Cl_2 (0.86 mL, 0.232 M) according to the procedure for the preparation of **8** above afforded **11** as a white solid (90 mg, 73%). IR (film) ν_{max} 1459, 1259, 1205, 1132, 1068, 985, 928, 839, 798 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 7.42 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 7.20 (s, 1H), 7.10 (td, J = 7.5, 2.0 Hz, 1H), 7.05 (s, 1H), 6.90 (t, J = 7.5 Hz, 1H), 6.86 (td, J = 7.7, 7.3, 2.0 Hz, 1H), 3.82 (s, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ −110.9 (d, J = 112.9 Hz), −123.7. ^{31}P NMR (162 MHz, CD_3OD) δ 4.84 (t, J = 105.4 Hz). MS (ESI-TOF) calcd for $C_{20}H_{13}Cl_3F_3O_3P$ $[M - H]^-$ 1:1 492.9547 and 494.9518, found 1:1 492.9548 and 494.9522.

*(R)-((2′-Fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)(hydroxy)methyl)phosphonic Acid ((R)-**12**).* (*R*)-((4-Bromophenyl)(hydroxy)methyl)phosphonic acid (*R*)-**48** was synthesized according to ref 36 with the following clarification. Please note that the use of L-(−)-menthol provides tris-[(1*R*,2*S*,5*R*)-menth-2-yl]phosphite. After reaction with 4-bromobenzaldehyde, the phosphonate with the (*S*)-alcohol crystallizes first at 23 °C, then the diastereomer with the (*R*)-configured alcohol crystallizes at 0 °C.[36] Reaction of (*R*)-((4-bromophenyl)(hydroxy)methyl)phosphonic acid (*R*)-**48** (96 mg, 0.360 mmol, 1.0 equiv), boronic ester **47** (167 mg, 0.401 mmol, 1.1 equiv), $Na_2CO_3·H_2O$ (279 mg, 2.25 mmol, 6.2 equiv), and $Pd(PPh_3)_4$ (43.5 mg, 0.0376 mmol, 0.10 equiv) in DME (1.74 mL), EtOH (0.42 mL), and H_2O (0.42 mL) according to the procedure for the preparation of (±)-**5** above afforded (*R*)-**12** as a white solid (5.3 mg, 3%). IR (film) ν_{max} 3365 (br), 1674, 1457, 1135, 1070, 932 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 7.64 (s, 1H), 7.60 (d, J = 7.9 Hz, 2H), 7.48−7.45 (m, 2H), 7.39−7.34 (m, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.11 (td, J = 7.7, 1.7 Hz, 1H), 4.86−4.82 (m, 1H), 4.15 (s, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ −124.0. ^{31}P NMR (162 MHz, CD_3OD) δ 17.0 (br). MS (ESI-TOF) calcd for $C_{20}H_{15}Cl_3FO_4P$ $[M - H]^-$ 1:1 472.9685 and 474.9655, found 1:1 472.9683 and 474.9654.

*(S)-((2′-Fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)(hydroxy)methyl)phosphonic Acid ((S)-**12**).* Reaction of (*S*)-((4-bromophenyl)(hydroxy)methyl)phosphonic acid (*S*)-**48** (83 mg, 0.314 mmol, 1.0 equiv), boronic ester **47** (189 mg, 0.454 mmol, 1.4 equiv), $Na_2CO_3·H_2O$ (258 mg, 2.08 mmol, 6.6 equiv), and $Pd(PPh_3)_4$ (38.6 mg, 0.0334 mmol, 0.11 equiv) in DME (1.60 mL), EtOH (0.40 mL), and H_2O (0.40 mL) according to the procedure for the preparation of (±)-**5** above afforded (*S*)-**12** as a white solid (8.6 mg, 6%). Spectroscopic results agree with data reported for the enantiomeric phosphonic acid (*R*)-**12**.

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*(Fluoro(2′-fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)-methyl)phosphonic Acid ((±)-**13**).* Reaction of phosphonate **51** (145 mg, 0.263 mmol, 1.0 equiv) and iodotrimethylsilane (0.22 mL, 309 mg, 1.54 mmol, 5.9 equiv) in CH_2Cl_2 (1.0 mL, 0.216 M) according to the procedure for the preparation of **8** above afforded (±)-**13** as a white solid (85 mg, 68%). IR (film) ν_{max} 1457, 1408, 1354, 1205, 1167, 1134, 1070, 1014, 843, 799, 757 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ 7.55 (s, 1H), 7.52−7.47 (m, 4H), 7.34−7.28 (m, 2H), 7.13 (t, J = 7.6 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 5.65 (dd, J = 44.7, 8.3 Hz, 1H), 4.07 (s, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ −123.9, −201.1 (d, J = 83.2 Hz). ^{31}P NMR (162 MHz, CD_3OD) δ 12.7 (d, J = 85.3). MS (ESI-TOF) calcd for $C_{20}H_{14}Cl_3F_2O_3P$ $[M - H]^-$ 1:1 474.9641 and 476.9612, found 1:1 474.9641 and 476.9627.

*(±)-(1-Fluoro-1-(2′-fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)-2-oxo-2-phenylethyl)phosphonic Acid ((±)-**14**).* Reaction of phosphonate **60** (186 mg, 0.285 mmol, 1.0 equiv) and iodotrimethylsilane (0.24 mL, 337 mg, 1.69 mmol, 5.9 equiv) in CH_2Cl_2 (1.2 mL, 0.198 M) according to the procedure for the preparation of **8** above afforded (±)-**14** as a white solid (46 mg, 28%). IR (film) ν_{max} 2361, 2339, 1684, 1653, 1457, 1259, 1205, 1069, 668 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ 7.82 (d, J = 8.5 Hz 2H), 7.74 (dd, J = 8.5, 2.1 Hz, 2H), 7.60−7.56 (m, 3H), 7.51 (td, J = 7.5, 1.2 Hz, 1H), 7.39−7.33 (m, 4H), 7.16 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 6.4 Hz, 1H), 4.11 (s, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ −123.9, −170.4 (d, J = 85.2 Hz). ^{31}P NMR (162 MHz, CD_3OD) δ 9.2 (d, J = 85.3). MS (ESI-TOF) calcd for $C_{27}H_{18}Cl_3F_2O_4P$ $[M - H]^-$ 1:1 578.9904 and 580.9874, found 1:1 578.9903 and 580.9880.

*(±)-(2-Cyclohexyl-1-fluoro-1-(2′-fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)-2-oxoethyl)phosphonic Acid ((±)-**15**).* Reaction of phosphonate **61** (36 mg, 0.0544 mmol, 1.0 equiv) and iodotrimethylsilane (0.05 mL, 70.3 mg, 0.351 mmol, 6.5 equiv) in CH_2Cl_2 (0.31 mL, 0.151 M) according to the procedure for the preparation of **8** above afforded (±)-**15** as a white solid (22 mg, 68%). IR (film) ν_{max} 2931, 2854, 2361, 2337, 1708, 1457, 1205, 1151, 1070, 1020 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ 7.75 (dd, J = 8.5, 2.1 Hz, 2H), 7.61 (s, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.38−7.33 (m, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.14−7.08 (m, 1H), 4.12 (s, 2H), 3.09 (tq, J = 11.2, 3.5 Hz, 1H), 1.83 (d, J = 13.1 Hz, 1H), 1.76 (dt, J = 12.9, 3.7 Hz, 1H), 1.68−1.61 (m, 3H), 1.43−1.34 (m, 1H), 1.34−1.22 (m, 2H), 1.16 (qt, J = 12.4, 3.6 Hz, 1H), 1.08 (qd, J = 13.9, 13.0, 3.8 Hz, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ −124.0, −177.8 (d, J = 81.6 Hz). ^{31}P NMR (162 MHz, CD_3OD) δ 8.5 (d, J = 82.1). MS (ESI-TOF) calcd for $C_{27}H_{24}Cl_3F_2O_4P$ $[M - H]^-$ 1:1 585.0373 and 587.0344, found 1:1 585.0374 and 587.0351.

*(±)-(1-Fluoro-1-(2′-fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)-2-oxo-2-(piperidin-1-yl)ethyl)phosphonic Acid ((±)-**16**).* Reaction of phosphonate **66** (maximum of 56.2 mg, 0.0850 mmol, 1.0 equiv) and iodotrimethylsilane (0.07 mL, 98.4 mg, 0.492 mmol, 5.8 equiv) in CH_2Cl_2 (0.35 mL, 0.203 M) according to the procedure for the preparation of **8** above afforded (±)-**16** as a white solid (17.6 mg, 35%). IR (film) ν_{max} 2940, 2858, 1629, 1456, 1404, 1354, 1256, 1205, 1163, 1069, 1022, 954, 915, 821, 794, 579 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ 7.62 (s, 1H), 7.60−7.58 (m, 4H), 7.38 (td, J = 7.6, 1.8 Hz, 1H), 7.36 (s, 1H), 7.19 (t, J = 7.6 Hz, 1H), 7.16−7.13 (m, 1H), 4.13 (s, 2H), 3.65−3.60 (m, 1H), 3.53−3.47 (m, 1H), 3.42−3.36 (m, 1H), 3.29−3.23 (m, 1H), 1.61−1.50 (m, 4H), 1.39−1.31 (m, 1H), 1.07−0.99 (m, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ −123.9, −168.9 (d, J = 91.9 Hz). ^{31}P NMR (162 MHz, CD_3OD) δ 10.4 (d, J = 91.8). MS (ESI-TOF) calcd for $C_{26}H_{23}Cl_3F_2NO_4P$ $[M - H]^-$ 1:1 586.0326 and 588.0296, found 1:1 586.0324 and 588.0298.

*(±)-(1-(2′-Fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)-2-oxo-2-(piperidin-1-yl)ethyl)phosphonic Acid ((±)-**17**).* Reaction of phosphonate (±)-**72** (131 mg assuming 100% yield in previous step, 0.209 mmol, 1.0 equiv) and iodotrimethylsilane (0.18 mL, 253 mg, 1.27 mmol, 6.0 equiv) in CH_2Cl_2 (0.89 mL, 0.196 M) according to the procedure for the preparation of **8** above afforded (±)-**17** as a white solid (52 mg, 44% over 2 steps). IR (film) ν_{max} 2938, 2858, 1606, 1515, 1457, 1409, 1354, 1205, 1134, 1069, 1016, 938 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ 7.54 (s, 1H), 7.51 (dd, J = 8.4, 2.3 Hz, 2H), 7.45 (d, J = 6.9 Hz, 2H), 7.32−7.27 (m, 2H), 7.11 (t, J = 7.6 Hz, 1H), 7.06 (td, J = 7.2, 1.7 Hz, 1H), 4.61 (d, J = 23.0 Hz, 1H), 4.06 (s, 2H), 3.68−3.61 (m, 1H), 3.42−3.33 (m, 3H), 1.53−1.47 (m, 3H), 1.45−1.34 (m, 2H), 1.07−0.99 (m, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ −123.9. ^{31}P NMR (162 MHz, CD_3OD) δ 18.7. MS (ESI-TOF) calcd for $C_{26}H_{24}Cl_3FNO_4P$ $[M - H]^-$ 1:1 568.0420 and 570.0390, found 1:1 568.0419 and 570.0396.

*(±)-(1-(2′-Fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)-2-morpholino-2-oxoethyl)phosphonic Acid ((±)-**18**).* Reaction of phosphonate (±)-**73** (56 mg crude, theoretical 0.0892 mmol, 1.0 equiv) and iodotrimethylsilane (0.07 mL, 98 mg, 0.492 mmol, ∼5.5 equiv) in CH_2Cl_2 (0.38 mL, 0.198 M) according to the procedure for the preparation of **8** above afforded (±)-**18** as a white solid (14 mg, 28% over 2 steps). IR (film) ν_{max} 2925, 2859, 1630, 1459, 1356, 1206, 1115, 1070, 1036, 939, 860, 820, 590 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ 7.63 (s, 1H), 7.59 (d, J = 6.5 Hz, 2H), 7.51 (d, J = 6.7 Hz, 2H), 7.39−7.35 (m, 2H), 7.19 (t, J = 7.6 Hz, 1H), 7.16−7.10 (m, 1H), 4.64 (d, J = 22.8 Hz, 1H), 4.14 (s, 2H), 3.68−3.59 (m, 5H), 3.58−3.53 (m, 1H), 3.46−3.41 (m, 1H), 3.34−3.30 (m, 1H). ^{19}F NMR (376 MHz, CD_3OD) δ −124.0. ^{31}P NMR (162 MHz, CD_3OD) δ 17.2. MS (ESI-TOF) calcd for $C_{25}H_{22}Cl_3FNO_5P$ $[M - H]^-$ 1:1 570.0212 and 572.0183, found 1:1 570.0213 and 572.0189.

*(±)-(2-(Dimethylamino)-1-(2′-fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)-2-oxoethyl)phosphonic Acid ((±)-**19**).* Reaction of phosphonate (±)-**74** (124 mg crude, theoretical 0.212 mmol, 1.0 equiv) and iodotrimethylsilane (0.18 mL, 253 mg, 1.27 mmol, ∼6.0 equiv) in CH_2Cl_2 (0.90 mL, 0.196 M) according to the procedure for the preparation of **8** above afforded (±)-**19** as a white solid (40 mg, 36% over 2 steps). IR (film) ν_{max} 1626, 1458, 1408, 1354, 1204, 1134, 1070, 1003, 938, 800 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ 7.61 (s, 1H), 7.58 (d, J = 6.2 Hz, 2H), 7.48 (d, J = 6.7 Hz, 2H), 7.37−7.33 (m, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.11 (td, J = 7.3, 1.8 Hz, 1H), 4.63 (d, J = 22.8 Hz, 1H), 4.12 (s, 2H), 3.04 (s, 3H), 2.95 (s, 3H). ^{19}F NMR (376 MHz, CD_3OD) δ −124.0. ^{31}P NMR (162 MHz, CD_3OD) δ 18.0. MS (ESI-TOF) calcd for $C_{23}H_{20}Cl_3FNO_4P$ $[M - H]^-$ 1:1 528.0107 and 530.0077, found 1:1 528.0106 and 530.0081.

*(±)-(1-(2′-Fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)-2-(methylamino)-2-oxoethyl)phosphonic Acid ((±)-**20**).* Reaction of phosphonate **79** (31 mg crude, maximum 0.0533 mmol, 1.0 equiv) and iodotrimethylsilane (0.05 mL, 70.3 mg, 0.351 mmol, 6.6 equiv) in CH_2Cl_2 (0.24 mL, 0.184 M) according to the procedure for the preparation of **8** above afforded (±)-**20** as a white solid (5.6 mg, 20%). IR (film) ν_{max} 1644, 1459, 1410, 1354, 1204, 1135, 1070 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ 7.63 (s, 1H), 7.60−7.57 (m, 2H), 7.44 (d, J = 6.8 Hz, 2H), 7.37−7.33 (m, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.10 (ddd, J = 8.5, 6.9, 1.7 Hz, 1H), 4.13 (s, 2H), 3.99 (d, J = 21.6 Hz, 1H), 2.78 (s, 3H). ^{19}F NMR (376 MHz, CD_3OD) δ −124.0. ^{31}P NMR (162 MHz, CD_3OD) δ 14.2. MS (ESI-TOF) calcd for $C_{22}H_{18}Cl_3FNO_4P$ $[M - H]^-$ 1:1 513.9950 and 515.9921, found 1:1 513.9945 and 515.9915.

*(±)-((2′-Fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)-(morpholinosulfonyl)methyl)phosphonic Acid ((±)-**21**).* Reaction of phosphonate (±)-**83** (249 mg crude, maximum 0.374 mmol, 1.0 equiv) and iodotrimethylsilane (0.32 mL, 450 mg, 2.25 mmol, 6.0 equiv) in CH_2Cl_2 (1.7 mL, 0.185 M) according to the procedure for the preparation of **8** above afforded (±)-**21** as a white solid (60 mg, 18% over 2 steps). IR (film) ν_{max} 2362, 2336, 1457, 1344, 1262, 1154, 1114, 1070, 1018, 941, 870, 807, 736 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ 7.77 (d, J = 7.8 Hz, 2H), 7.64 (s, 1H), 7.59 (d, J = 7.1 Hz, 2H), 7.41 (td, J = 7.5, 1.8 Hz, 1H), 7.38 (s, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.16 (ddd, J = 8.4, 7.1, 1.8 Hz, 1H), 5.00 (d, J = 21.1 Hz, 1H), 4.16 (s, 2H), 3.54 (ddd, J = 11.5, 6.4, 3.0 Hz, 2H), 3.46 (ddd, J = 11.4, 6.3, 3.0 Hz, 2H), 3.21−3.16 (m, 2H), 3.00−2.92 (m, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ −123.9. ^{31}P NMR (162 MHz, CD_3OD) δ 10.0. MS (ESI-TOF) calcd for $C_{24}H_{22}Cl_3FNO_6PS$ $[M - H]^-$ 1:1 605.9882 and 607.9853, found 1:1 605.9892 and 907.9859.

*(+)-(Fluoro(2′-fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)(morpholinosulfonyl)methyl)phosphonic Acid ((+)-**22**).* Reaction of phosphonate **85b** (30 mg, 0.0439 mmol, 1.0 equiv) and iodotrimethylsilane (0.04 mL, 56.3 mg, 0.281 mmol, 6.4 equiv) in CH_2Cl_2 (0.20 mL, 0.183 M) according to the procedure for the preparation of **8** above afforded (+)-**22** as a white solid (25 mg, 90%).

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IR (film) ν_{max} 1645, 1458, 1349, 1204, 1161, 1134, 1114, 1071, 963, 541 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 7.93 (d, J = 8.2 Hz, 2H), 7.64−7.58 (m, 3H), 7.41 (td, J = 7.5, 1.9 Hz, 1H), 7.36 (s, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.17−7.12 (m, 1H), 4.14 (s, 2H), 3.59−3.49 (m, 2H), 3.48−3.41 (m, 2H), 3.29−3.23 (m, 2H), 3.16−2.86 (m, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ −124.8, −167.5 (d, J = 70.5 Hz). ^{31}P NMR (162 MHz, CD_3OD) δ 3.6 (d, J = 69.6 Hz). MS (ESI-TOF) calcd for $C_{24}H_{21}Cl_3F_2NO_6PS$ $[M - H]^-$ 1:1 623.9788 and 625.9759, found 1:1 623.9790 and 625.9767. $[\alpha]_D^{20}$ = +2.7 (c = 0.1, DMSO).

*(−)-(Fluoro(2′-fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)(morpholinosulfonyl)methyl)phosphonic Acid ((−)-**22**).* Reaction of phosphonate **85a** (34 mg, 0.0498 mmol, 1.0 equiv) and iodotrimethylsilane (0.05 mL, 70.3 mg, 0.351 mmol, 7.1 equiv) in CH_2Cl_2 (0.23 mL, 0.178 M) according to **8** above afforded (−)-**22** as a white solid (21 mg, 66%). Spectroscopic results agree with data reported for phosphonic acid (+)-**22**. $[\alpha]_D^{20}$ = −2.5 (c = 0.1, DMSO).

*Diethyl ((4-Bromophenyl)difluoromethyl)phosphonate (**23**).* Following a reported procedure,[53] a flame-dried round-bottom flask was charged with preactivated Zn dust (3.47 g, 53.0 mmol, 5.0 equiv) and anhydrous DMA (11.2 mL), then heated to 55 °C under an atmosphere of N_2. Dropwise over 30 min, with stirring under N_2, diethyl (bromodifluoromethyl)phosphonate (9.4 mL, 14.1 g, 52.9 mmol, 5.0 equiv) was added to the Zn suspension. The reaction mixture was then stirred at 55 °C under N_2 for an additional 30 min, after which the reaction flask was removed from heating and sonicated for 3 h. Solid copper(I) bromide (7.56 g, 52.7 mmol, 4.9 equiv) was added in one portion, and the reaction mixture was stirred at 23 °C under N_2 for 30 min. Next, 1-bromo-4-iodobenzene (3.02 g, 10.7 mmol, 1.0 equiv) in anhydrous DMA (6.0 mL) was added dropwise by syringe under N_2. The reaction mixture was stirred under N_2 at 23 °C for 20 h, and then H_2O (15 mL) and Et_2O (15 mL) were added. The suspension was filtered through a pad of Celite, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The pooled organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 19:1 to 4:1 hexanes/EtOAc) to afford **23** as a yellow oil (3.53 g, 97%). R_f = 0.41 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 1596, 1487, 1397, 1271, 1128, 1099, 1009, 975, 937, 878, 821, 750, 569 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.6 Hz, 2H), 7.41 (d, J = 7.9 Hz, 2H), 4.22−4.04 (m, 4H), 1.24 (td, J = 6.5, 0.8 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.9 (d, J = 115.3 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 5.67 (t, J = 114.8 Hz). MS (ESI-TOF) calcd for $C_{11}H_{14}BrF_2O_3P$ $[M + H^+]$ 1:1 343.0 and 345.0, found 1:1 342.9 and 345.0.

*((4-Bromophenyl)difluoromethyl)phosphonic Acid (**24**).* Phosphonate **23** (643 mg, 1.87 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (5.8 mL, 0.293 M). To this mixture was added iodotrimethylsilane (0.59 mL, 828 mg, 4.14 mmol, 2.2 equiv), then the flask was sealed under a polyethylene stopper. The reaction mixture was stirred for 20 h at 23 °C, then concentrated. The residue was dissolved in minimal MeOH and purified by reversed-phase gradient chromatography (5−100% MeCN in H_2O with 0.1% TFA). Volatile components were removed, and the resulting aqueous solution was lyophilized to afford **24** as a white powder (358 mg, 67%). IR (film) ν_{max} 1595, 1487, 1398, 1254, 1126, 1051, 1014, 981, 920, 819, 560 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 7.42 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H). ^{19}F NMR (376 MHz, CD_3OD) δ −111.3 (d, J = 111.8 Hz). ^{31}P NMR (162 MHz, CD_3OD) δ 4.21 (t, J = 111.8 Hz). MS (ESI-TOF) calcd for $C_7H_6BrF_2O_3P$ $[M - H]^-$ 1:1 284.9133 and 286.9113, found 1:1 284.9135 and 286.9115.

*Diethyl(difluoro(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl)methyl)phosphonate (**25**).* Phosphonate **23** (624 mg, 1.82 mmol, 1.0 equiv), bis(pinacoloto)diboron (572 mg, 2.25 mmol, 1.2 equiv), and KOAc (541 mg, 5.51 mmol, 3.0 equiv) were dissolved in anhydrous 1,4-dioxane (8.2 mL, 0.222 M). With stirring, N_2 was bubbled through the reaction mixture for 20 min. Then, $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (148 mg, 0.182 mmol, 0.10 equiv) was added, and the flask was outfitted with a reflux condenser. The reaction mixture was stirred under N_2 at 65 °C for 18 h, then cooled to 23 °C and concentrated. The crude product was purified by flash chromatography (silica gel, 19:1 to 1:1 hexanes/EtOAc) to afford **25** as a yellow oil (480 mg, 68%). R_f = 0.30 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 1399, 1361, 1328, 1272, 1144, 1125, 1091, 1045, 1018, 963, 857, 657, 574 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.7 Hz, 2H), 7.61 (d, J = 7.4 Hz, 2H), 4.23−4.07 (m, 4H), 1.35 (s, 12H), 1.30 (t, J = 7.1 H, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −109.5 (d, J = 115.7 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 6.24 (t, J = 115.6 Hz). MS (ESI-TOF) calcd for $C_{17}H_{26}BF_2O_5P$ $[M + H^+]$ 391.1652, found 391.1659.

*2,4,5-Trichlorobenzaldehyde (**27**).* 1,2,4-Trichloro-5-iodobenzene (4.00 g, 13.0 mmol, 1.0 equiv) was dissolved in anhydrous THF (40 mL, 0.269 M), and the resultant solution was cooled to −78 °C in a dry ice/acetone bath. Dropwise by syringe, under an atmosphere of N_2, *i*PrMgCl (7.0 mL of a 2.0 M solution in THF, 14.0 mmol, 1.1 equiv) was added to the stirred reaction mixture. The mixture was then stirred for 20 min at −78 °C. At this point, anhydrous DMF (1.5 mL, 1.42 g, 19.5 mmol, 1.5 equiv) was rapidly added to the solution and the flask was allowed to warm to 23 °C. The reaction mixture was stirred under N_2 for 1 h, then the reaction was quenched with satd aq NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (2 × 40 mL), then the pooled organic phases were dried over Na_2SO_4, filtered, and concentrated to afford **27** as a white powder, which required no further purification (2.59 g, 95%). R_f = 0.70 (silica gel, 4:1 hexanes/EtOAc). IR (film) ν_{max} 1682, 1572, 1442, 1349, 1189, 1074, 931, 899 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 7.98 (s, 1H), 7.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 139.5, 136.0, 132.8, 132.2, 131.8, 130.6. MS (ESI-TOF) calcd for $C_7H_3Cl_3O$ $[M + H_3O^+]$ 226.9428, found 226.9429.

*(±)-(3-Bromophenyl)(4,5-dichloro-2-fluorophenyl)methanol ((±)-**28**).* Following our previously reported procedure,[36] 1-bromo-3-iodobenzene (0.25 mL, 559 mg, 1.97 mmol, 1.0 equiv) was dissolved in anhydrous THF (6.0 mL), and the resultant mixture was cooled to 0 °C in an ice bath. With stirring, under an atmosphere of N_2, *i*PrMgCl (0.99 mL of a 2.0 M solution in THF, 1.97 mmol, 1.0 equiv) was added to the solution dropwise by syringe. The reaction mixture was stirred under N_2 at 0 °C for 20 min. Then 4,5-dichloro-2-fluorobenzaldehyde (**26**)[54] (381 mg, 1.97 mmol, 1.0 equiv) in minimal anhydrous THF (2.0 mL) was added dropwise by syringe. The reaction mixture was allowed to slowly warm to 23 °C, and after 2 h, the reaction was quenched with satd aq NH_4Cl (5 mL) and Et_2O (5 mL). The aqueous layer was extracted with Et_2O (2 × 15 mL), and the pooled organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 19:1 to 3:1 hexanes/EtOAc) to afford (±)-**28** as a colorless oil (543 mg, 79%). R_f = 0.48 (silica gel, 4:1 hexanes/EtOAc). IR (film) ν_{max} 3326 (br), 1604, 1572, 1467, 1374, 1187, 1118, 1036, 682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.0 Hz, 1H), 7.53 (t, J = 1.9 Hz, 1H), 7.43 (ddd, J = 7.8, 2.0, 1.2 Hz, 1H), 7.29 (dq, J = 7.7, 1.0 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 7.17 (d, J = 9.4 Hz, 1H), 6.01 (d, J = 2.9 Hz, 1H), 2.43 (d, J = 3.6 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −118.3. MS (ESI-TOF) calcd for $C_{13}H_8BrCl_2FO$ $[M - OH]^+$ 1:1 330.9087 and 332.9066, found 1:1 330.9084 and 332.9064.

*(±)-(3-Bromophenyl)(2,4,5-trichlorophenyl)methanol ((±)-**29**).* Reaction of 1-bromo-3-iodobenzene (0.24 mL, 542 mg, 1.91 mmol, 1.0 equiv), *i*PrMgCl (0.95 mL of a 2.0 M solution in THF, 1.90 mmol, 1.0 equiv), and aldehyde **27** (401 mg, 1.91 mmol, 1.0 equiv) in anhydrous THF (7.2 mL, 0.228 M) according to the procedure for the preparation of (±)-**28** above afforded (±)-**29** as a colorless oil (625 mg, 89%). R_f = 0.56 (silica gel, 4:1 hexanes/EtOAc). IR (film) ν_{max} 3306 (br), 1571, 1455, 1353, 1182, 1072, 1034, 885, 794, 682 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.72−7.70 (m, 1H), 7.52−7.49 (m, 1H), 7.45−7.41 (m, 2H), 7.28−7.24 (m, 1H), 7.21 (t, J = 7.8 Hz, 1H), 6.03 (d, J = 3.0 Hz, 1H), 2.66 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 140.5, 132.6, 132.0, 131.5, 131.0, 130.9, 130.4, 130.0, 129.4, 125.6, 122.9, 71.6. MS (ESI-TOF) calcd for $C_{13}H_8BrCl_3O$ $[M - OH]^+$ 1:1 346.8791 and 348.8771, found 1:1 346.8792 and 348.8764.

*(±)-(4,5-Dichloro-2-fluorophenyl)(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol ((±)-**30**).* Benzyhydryl alcohol (±)-**28** (217 mg, 0.619 mmol, 1.0 equiv), bis(pinacoloto)diboron (185 mg, 0.727 mmol, 1.2 equiv), and KOAc (180 mg, 1.83 mmol, 3.0 equiv) were dissolved in anhydrous 1,4-dioxane (3.3 mL, 0.187 M). With stirring, N_2 was bubbled through the reaction mixture for 20 min.

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Then, $Pd(dppf)Cl_2·CH_2Cl_2$ (51 mg, 0.062 mmol, 0.10 equiv) was added and the flask was outfitted with a reflux condenser. The reaction mixture was stirred under N_2 at 65 °C for 18 h, then cooled to 23 °C and concentrated. The crude product was purified by flash chromatography (silica gel, 19:1 to 3:1 hexanes/EtOAc) to afford (±)-**30** as a colorless oil (237 mg, 97%). R_f = 0.65 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 3431 (br), 2979, 1467, 1431, 1359, 1143, 854, 707 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (t, J = 1.4 Hz, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.68 (d, J = 7.0 Hz, 1H), 7.43 (dt, J = 7.9, 1.6 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.14 (d, J = 9.4 Hz, 1H), 6.06 (d, J = 3.0 Hz, 1H), 2.35 (d, J = 3.5 Hz, 1H), 1.34 (s, 12H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −117.9. MS (ESI-TOF) calcd for $C_{19}H_{20}BCl_2FO_3$ $[M - OH]^+$ 379.0834, found 379.0834.

*(±)-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-(2,4,5-trichlorophenyl)methanol ((±)-**31**).* Reaction of benzhydryl alcohol (±)-**29** (625 mg, 1.70 mmol, 1.0 equiv), bis(pinacoloto)-diboron (523 mg, 2.06 mmol, 1.2 equiv), KOAc (496 mg, 5.06 mmol, 3.0 equiv), and $Pd(dppf)Cl_2·CH_2Cl_2$ (141 mg, 0.172 mmol, 0.10 equiv) in 1,4-dioxane (9.0 mL, 0.189 M) according to the procedure for the preparation of (±)-**30** above afforded (±)-**31** as a white solid (623 mg, 88%). R_f = 0.55 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 3433 (br), 1454, 1357, 1277, 1142, 850, 732, 707 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.78 (s, 1H), 7.75 (dt, J = 6.8, 1.5 Hz, 1H), 7.43 (s, 1H), 7.39−7.32 (m, 2H), 6.10 (s, 1H), 2.32 (br s, 1H), 1.34 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 140.6, 135.0, 133.4, 132.2, 131.7, 131.1, 130.9, 129.9, 129.6, 128.3, 84.1, 72.5, 25.0. MS (ESI-TOF) calcd for $C_{19}H_{20}BCl_3O_3$ $[M + H^+]$ 413.0644, found 413.0643.

*2-Bromo-4,5-dichlorobenzaldehyde (**34**).* Reaction of aryl iodide **44** (579 mg, 1.65 mmol, 1.0 equiv), *i*PrMgCl (0.83 mL of a 2.0 M solution in THF, 1.66 mmol, 1.0 equiv), and DMF (0.19 mL, 180 mg, 2.46 mmol, 1.5 equiv) in THF (4.6 mL, 0.293 M) according to the procedure for the preparation of **27** above afforded **34** as a white solid (338 mg, 81%). Spectroscopic results agree with previously reported data.[64]

*(±)-(4,5-Dichloro-2-fluorophenyl)(3-iodophenyl)methanol ((±)-**35**).* 1,3-Diiodobenzene **32** (966 mg, 2.93 mmol, 1.5 equiv) was dissolved in anhydrous THF (7.0 mL), and the resultant mixture was cooled to −20 °C. With stirring, under an atmosphere of N_2, *i*PrMgCl (1.46 mL of a 2.0 M solution in THF, 2.93 mmol, 1.5 equiv) was added to the solution dropwise by syringe. The reaction solution was stirred under N_2 at −20 °C for 20 min. Then 4,5-dichloro-2-fluorobenzaldehyde **26**[54] (377 mg, 1.95 mmol, 1.0 equiv) in minimal anhydrous THF (2.5 mL) was added dropwise by syringe. The reaction mixture was allowed to slowly warm to 23 °C, and after 2 h, the reaction was quenched with satd aq NH_4Cl (10 mL) and Et_2O (10 mL). The aqueous layer was extracted with Et_2O (2 × 25 mL), and the pooled organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 19:1 to 3:1 hexanes/EtOAc) to afford (±)-**35** as a colorless oil (495 mg, 64%). R_f = 0.52 (silica gel, 4:1 hexanes/EtOAc). IR (film) ν_{max} 3324 (br), 1568, 1466, 1374, 1118, 1035 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, J = 1.8 Hz, 1H), 7.64 (s, 1H), 7.62 (s, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.16 (d, J = 9.4 Hz, 1H), 7.08 (t, J = 7.8 Hz, 1H), 5.98 (d, J = 3.6 Hz, 1H), 2.42 (d, J = 3.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6 (d, J = 249.9 Hz), 144.1, 137.5, 135.4, 135.3, 130.6, 128.8, 128.7, 125.7, 118.1, 117.8, 94.8, 68.8 (d, J = 2.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −118.1. MS (ESI-TOF) calcd for $C_{13}H_8Cl_2FIO$ $[M - OH]^+$ 378.8948, found 378.8951.

*(±)-(3-Iodophenyl)(2,4,5-trichlorophenyl)methanol ((±)-**36**).* Reaction of 1,3-diiodobenzene **32** (945 mg, 2.86 mmol, 1.5 equiv), *i*PrMgCl (1.43 mL of a 2.0 M solution in THF, 2.86 mmol, 1.5 equiv), and aldehyde **27** (398 mg, 1.90 mmol, 1.0 equiv) in anhydrous THF (7.0 mL, 0.225 M) according to the procedure for the preparation of (±)-**35** above afforded (±)-**36** as a white solid (612 mg, 78%). R_f = 0.60 (silica gel, 4:1 hexanes/EtOAc). IR (film) ν_{max} 3294 (br), 1706, 1566, 1453, 1421, 1352, 1179, 1131, 1070, 1029, 904, 793, 731, 570 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.68 (m, 2H), 7.62 (dt, J = 7.9, 1.4 Hz, 1H), 7.42 (s, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.05 (t, J = 7.8 Hz, 1H), 5.96 (s, 1H), 3.0 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 140.4, 137.4, 135.9, 132.5, 131.9, 131.0, 130.8, 130.5, 129.3, 126.2, 94.7, 71.4. MS (ESI-TOF) calcd for $C_{13}H_8Cl_3IO$ $[M - OH]^+$ 1:1 394.8653 and 396.8623, found 1:1 394.8650 and 396.8624.

*(±)-(2-Bromo-4,5-dichlorophenyl)(3-iodophenyl)methanol ((±)-**37**).* Reaction of 1,3-diiodobenzene **32** (508 mg, 1.54 mmol, 1.5 equiv), *i*PrMgCl (0.77 mL of a 2.0 M solution in THF, 1.53 mmol, 1.5 equiv), and aldehyde **34** (260 mg, 1.02 mmol, 1.0 equiv) in anhydrous THF (3.8 mL, 0.224 M) according to the procedure for the preparation of (±)-**35** above afforded (±)-**37** as a colorless oil which foamed under vacuum (423 mg, 90%). R_f = 0.48 (silica gel, 4:1 hexanes/EtOAc). IR (film) ν_{max} 3301 (br), 1566, 1450, 1422, 1346, 1178, 1133, 1031, 904, 788, 733, 681 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (t, J = 1.8 Hz, 1H), 7.67−7.61 (m, 3H), 7.28 (d, J = 7.7 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 5.95 (s, 1H), 2.91 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 142.0, 137.4, 136.0, 134.0, 132.8, 132.6, 130.5, 129.7, 126.3, 120.3, 94.7, 73.5. MS (ESI-TOF) calcd for $C_{13}H_8BrCl_2IO$ $[M - OH]^+$ 1:1 438.8147 and 440.8127, found 1:1 438.8154 and 440.8132.

*(±)-(2-Fluoro-3-iodophenyl)(2,4,5-trichlorophenyl)methanol ((±)-**38**).* Reaction of 2-fluoro-1,3-diiodobenzene **33**[55] (2.00 g, 5.74 mmol, 1.2 equiv), *i*PrMgCl (2.9 mL of a 2.0 M solution in THF, 5.80 mmol, 1.2 equiv), and aldehyde **27** (1.01 g, 4.80 mmol, 1.0 equiv) in anhydrous THF (15.0 mL, 0.268 M) according to the procedure for the preparation of (±)-**35** above afforded (±)-**38** as a white solid (1.97 g, 95%). R_f = 0.56 (silica gel, 4:1 hexanes/EtOAc). IR (film) ν_{max} 3288 (br), 1446, 1353, 1225, 1130, 1074, 1034, 906, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.74−7.68 (m, 2H), 7.46 (s, 1H), 7.20 (td, J = 7.3, 6.8, 1.6 Hz, 1H), 6.90 (t, J = 7.8 Hz, 1H), 6.34 (s, 1H), 2.56 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −97.4. MS (ESI-TOF) calcd for $C_{13}H_7Cl_3FIO$ $[M - OH]^+$ 1:1 412.8558 and 414.8529, found 1:1 412.8559 and 414.8539.

*(±)-Diethyl ((3′-((4,5-Dichloro-2-fluorophenyl)(hydroxy)methyl)-[1,1′-biphenyl]-4-yl)difluoromethyl)phosphonate ((±)-**39**).* Benzhydryl alcohol (±)-**35** (302 mg, 0.760 mmol, 1.0 equiv), boronic ester **25** (366 mg, 0.938 mmol, 1.2 equiv), and K_2CO_3 (1.06 g, 7.63 mmol, 10 equiv) were dissolved in toluene (24.2 mL), EtOH (8.3 mL), and H_2O (4.9 mL). With stirring, N_2 was bubbled through the biphasic mixture for 1 h. $Pd(PPh_3)_4$ (37.3 mg, 0.0323 mmol, 0.04 equiv) was then added, and N_2 was bubbled through the stirred solution for an additional 20 min. The flask was next equipped with a reflux condenser, and the reaction mixture was stirred at 80 °C under an atmosphere of N_2 for 16 h. The solution was cooled to 23 °C and concentrated. The crude residue was purified by flash chromatography (silica gel, 19:1 to 1:1 hexanes/EtOAc) to afford (±)-**39** as an orange solid (218 mg, 54%). R_f = 0.17 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 3380 (br), 1607, 1466, 1371, 1258, 1117, 1019, 947, 838, 794, 571 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.1 Hz, 1H), 7.68−7.60 (m, 5H), 7.52 (dt, J = 7.6, 1.6 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.38 (dt, J = 7.6, 1.4 Hz, 1H), 7.15 (d, J = 9.4 Hz, 1H), 6.11 (d, J = 3.2 Hz, 1H), 4.28−4.11 (m, 4H), 2.96 (d, J = 3.7 Hz, 1H), 1.32 (td, J = 7.1, 0.7 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.3 (d, J = 117.2 Hz), −118.1. ^{31}P NMR (162 MHz, $CDCl_3$) δ 6.21 (t, J = 116.9 Hz). MS (ESI-TOF) calcd for $C_{24}H_{22}Cl_2F_3O_4P$ $[M + H^+]$ 533.0658, found 533.0660.

*(±)-Diethyl (Difluoro(3′-(hydroxy(2,4,5-trichlorophenyl)methyl)-[1,1′-biphenyl]-4-yl)methyl)phosphonate ((±)-**40**).* Reaction of benzhydryl alcohol (±)-**36** (199 mg, 0.481 mmol, 1.0 equiv), boronic ester **25** (225 mg, 0.577 mmol, 1.2 equiv), K_2CO_3 (668 mg, 4.83 mmol, 10.0 equiv), and $Pd(PPh_3)_4$ (19.5 mg, 0.0169 mmol, 0.04 equiv) in toluene (15.3 mL), EtOH (5.1 mL), and H_2O (3.1 mL) according to the procedure for the preparation of (±)-**39** above afforded (±)-**40** as a yellow oil (190 mg, 72%). R_f = 0.22 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 3382 (br), 1452, 1259, 1129, 1020, 803, 576 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.68−7.60 (m, 5H), 7.52 (dt, J = 7.7, 1.6 Hz, 1H), 7.45−7.40 (m, 2H), 7.36 (dt, J = 7.7, 1.5 Hz, 1H), 6.16 (s, 1H), 4.27−4.10 (m, 4H), 1.32 (t, J = 7.1 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.3 (d, J = 116.8 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 6.19 (t, J = 117.0 Hz). MS (ESI-TOF) calcd for $C_{24}H_{22}Cl_3F_2O_4P$ $[M + H^+]$ 1:1 549.0362 and 551.0333, found 1:1 549.0362 and 551.0329.

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*(±)-Diethyl ((3′-((2-Bromo-4,5-dichlorophenyl)(hydroxy)methyl)-[1,1′-biphenyl]-4-yl)difluoromethyl)phosphonate ((±)-**41**).* Reaction of benzhydryl alcohol (±)-**37** (129 mg, 0.281 mmol, 1.0 equiv), boronic ester **25** (112 mg, 0.287 mmol, 1.0 equiv), K_2CO_3 (389 mg, 2.82 mmol, 10.0 equiv), and $Pd(PPh_3)_4$ (10.3 mg, 0.0089 mmol, 0.03 equiv) in toluene (8.9 mL), EtOH (3.0 mL), and H_2O (1.8 mL) according to the procedure for the preparation of (±)-**39** above afforded (±)-**41** as a colorless oil (70 mg, 42%). R_f = 0.16 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 3374 (br), 1449, 1259, 1125, 1043, 800 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.70−7.62 (m, 6H), 7.54 (dt, J = 7.6, 1.6 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.38 (dt, J = 7.8, 1.5 Hz, 1H), 6.15 (d, J = 3.0 Hz, 1H), 4.29−4.11 (m, 4H), 2.63 (d, J = 3.6 Hz, 1H), 1.34 (t, J = 7.0 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.3 (d, J = 116.6 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 6.25 (t, J = 116.5 Hz). MS (ESI-TOF) calcd for $C_{24}H_{22}BrCl_2F_2O_4P$ $[M + H^+]$ 1:1 592.9857 and 594.9836, found 1:1 592.9850 and 594.9826.

*(±)-Diethyl (Difluoro(2′-fluoro-3′-(hydroxy(2,4,5-trichlorophenyl)methyl)-[1,1′-biphenyl]-4-yl)methyl)phosphonate ((±)-**42**).* Reaction of benzhydryl alcohol (±)-**38** (144 mg, 0.334 mmol, 1.0 equiv), boronic ester **25** (146 mg, 0.374 mmol, 1.0 equiv), K_2CO_3 (464 mg, 3.36 mmol, 10.1 equiv), and $Pd(PPh_3)_4$ (26.7 mg, 0.0231 mmol, 0.07 equiv) in toluene (9.4 mL), EtOH (3.2 mL), and H_2O (1.9 mL) according to the procedure for the preparation of (±)-**39** above afforded (±)-**42** as an orange oil (142 mg, 75%). R_f = 0.19 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 3374 (br), 1455, 1259, 1128, 1045, 1021 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.69−7.66 (m, 2H), 7.63−7.59 (m, 2H), 7.46 (s, 1H), 7.40 (td, J = 7.4, 2.1 Hz, 1H), 7.28−7.24 (m, 1H), 7.21 (t, J = 7.6 Hz, 1H), 6.43 (d, J = 3.1 Hz, 1H), 4.27−4.12 (m, 4H), 3.09 (d, J = 3.8 Hz, 1H), 1.33 (t, J = 7.1 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −108.4 (d, J = 116.3 Hz), −123.0. ^{31}P NMR (162 MHz, $CDCl_3$) δ 6.13 (t, J = 116.3 Hz). MS (ESI-TOF) calcd for $C_{24}H_{21}Cl_3F_3O_4P$ $[M + H^+]$ 1:1 567.0268 and 569.0238, found 1:1 567.0265 and 569.0236.

*2-Bromo-4,5-dichloroaniline (**43**).* 1-Bromo-4,5-dichloro-2-nitrobenzene (618 mg, 2.28 mmol, 1.0 equiv) was dissolved in a 1:1 mixture of EtOH and glacial AcOH (12.6 mL, 0.181 M) in a flame-dried round-bottom flask equipped with a reflux condenser. Iron powder (533 mg, 9.54 mmol, 4.2 equiv) was added to the solution, and the reaction mixture was heated to 105 °C with stirring under an atmosphere of N_2 for 90 min. At this point, the mixture was cooled to 23 °C, diluted with H_2O (30 mL), and neutralized with solid Na_2CO_3. The aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL), and then the pooled organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 19:1 to 3:1 hexanes/EtOAc) to afford **43** as a white solid (485 mg, 88%). R_f = 0.50 (silica gel, 4:1 hexanes/EtOAc). IR (film) ν_{max} 3439, 3348, 1610, 1472, 1376, 1271, 1243, 1138, 1047, 875, 850 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 6.82 (s, 1H), 4.13 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 133.2, 132.1, 121.3, 116.2, 107.3. MS (ESI-TOF) calcd for $C_6H_4BrCl_2N$ $[M + H^+]$ 1:1 239.8977 and 241.8956, found 1:1 239.8974 and 241.8952.

*1-Bromo-4,5-dichloro-2-iodobenzene (**44**).* Aniline **43** (485 mg, 2.01 mmol, 1.0 equiv) was dissolved in conc HCl (37% aq, 1.0 mL) and H_2O (2.6 mL), and the resultant mixture was cooled to 0 °C in an ice bath. Slowly, a solution of sodium nitrite (151 mg, 2.19 mmol, 1.1 equiv) in H_2O (2.2 mL) was poured into the aniline solution. This reaction mixture was stirred under an atmosphere of N_2 at 0 °C for 1 h. Slowly, a solution of potassium iodide (3.38 g, 20.4 mmol, 10.1 equiv) in ice-cold H_2O (4.4 mL) was added to the reaction mixture, immediately followed by CH_2Cl_2 (3.8 mL). The resultant biphasic mixture was vigorously stirred under N_2 at 23 °C for 18 h. The reaction was then quenched by the addition of solid Na_2SO_3 (82.4 mg, 0.654 mmol, 0.32 equiv), and resulting mixture was stirred for 15 min. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and then the pooled organic layers were washed with brine (10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified through a plug of silica gel, eluting with hexanes, to afford **44** as a white solid (569 mg, 80%). Spectroscopic results agree with previously reported data.[63]

*(±)-(3-Bromo-2-fluorophenyl)(2,4,5-trichlorophenyl)methanol ((±)-**45**).* 1,2,4-Trichloro-5-iodobenzene (458 mg, 1.49 mmol, 1.2 equiv) was dissolved in anhydrous THF (3.6 mL), and the resultant mixture was cooled to −20 °C. With stirring, under an atmosphere of N_2, *i*PrMgCl (0.73 mL of a 2.0 M solution in THF, 1.46 mmol, 1.2 equiv) was added to the solution dropwise by syringe. The reaction was stirred under N_2 at 0 °C for 20 min. Then 3-bromo-2-fluorobenzaldehyde (257 mg, 1.27 mmol, 1.0 equiv) in minimal anhydrous THF (1.5 mL) was added dropwise by syringe. The reaction mixture was allowed to slowly warm to 0 °C, and after 2 h, the reaction was quenched with satd aq NH_4Cl (15 mL) and Et_2O (15 mL). The aqueous layer was extracted with Et_2O (2 × 25 mL), and the pooled organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 19:1 to 3:1 hexanes/EtOAc) to afford (±)-**45** as a white solid (479 mg, 98%). R_f = 0.53 (silica gel, 4:1 hexanes/EtOAc). IR (film) ν_{max} 3289 (br), 1453, 1354, 1229, 1130, 1035 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.50 (ddd, J = 8.1, 6.6, 1.7 Hz, 1H), 7.44 (s, 1H), 7.08−7.14 (m, 1H), 7.00 (td, J = 7.9, 1.0 Hz, 1H), 6.31 (d, J = 3.1 Hz, 1H), 3.02 (d, J = 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7 (d, J = 249.0 Hz), 139.4, 133.7, 132.8, 131.8, 131.1, 131.0, 130.0 (d, J = 14.4 Hz), 129.7 (d, J = 1.1 Hz), 127.6 (d, J = 3.2 Hz), 125.4 (d, J = 4.5 Hz), 109.6 (d, J = 21.2 Hz), 66.5 (d, J = 3.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −111.2. MS (ESI-TOF) calcd for $C_{13}H_7BrCl_3FO$ $[M - OH]^+$ 1:1 364.8697 and 366.8677, found 1:1 364.8696 and 366.8667.

*1-(3-Bromo-2-fluorobenzyl)-2,4,5-trichlorobenzene (**46**).* Benzhydryl alcohol (±)-**45** (789 mg, 2.05 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (76 mL, 0.025 M) in a two-necked round-bottom flask equipped with a reflux condenser, and the resultant mixture was cooled to 0 °C in an ice bath. By syringe, under an atmosphere of N_2, triethylsilane (3.3 mL, 2.40 g, 20.7 mmol, 10.1 equiv) was added to the reaction mixture, followed by boron trifluoride diethyl etherate (2.5 mL, 2.88 g, 20.2 mmol, 9.9 equiv). The flask was placed in an oil bath, and the solution was refluxed at 40 °C for 18 h. The reaction mixture was then cooled to 23 °C, and the reaction was quenched by the addition of satd aq $NaHCO_3$ (25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 19:1 to 4:1 hexanes/EtOAc) to afford **46** as a colorless oil (620 mg, 82%). R_f = 0.73 (silica gel, 4:1 hexanes/EtOAc). IR (film) ν_{max} 1452, 1355, 1225, 1070, 786 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.46 (ddd, J = 8.1, 6.5, 1.8 Hz, 1H), 7.24 (s, 1H), 7.08−7.03 (m, 1H), 6.96 (t, J = 7.8 Hz, 1H), 4.07 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4 (d, J = 247.2 Hz), 136.9 (d, J = 1.0 Hz), 133.0, 132.4, 132.0 (d, J = 1.6 Hz), 131.7, 131.4, 131.0, 130.0 (d, J = 3.7 Hz), 127.0 (d, J = 16.5 Hz), 125.3 (d, J = 4.5 Hz), 109.6 (d, J = 21.4 Hz), 32.3 (d, J = 3.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ − 110.3.

*2-(2-Fluoro-3-(2,4,5-trichlorobenzyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**47**).* Reaction of aryl bromide **46** (400 mg, 1.09 mmol, 1.0 equiv), bis(pinacoloto)diboron (331 mg, 1.30 mmol, 1.2 equiv), KOAc (322 mg, 3.28 mmol, 3.0 equiv), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (89.6 mg, 0.110 mmol, 0.10 equiv) in 1,4-dioxane (6.3 mL, 0.172 M) according to the procedure for the preparation of (±)-**30** above afforded **47** as a colorless oil (387 mg, 86%). R_f = 0.63 (silica gel, 4:1 hexanes/EtOAc). IR (film) ν_{max} 1450, 1363, 1280, 1125, 1071, 850 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (ddd, J = 7.4, 5.6, 1.9 Hz, 1H), 7.47 (s, 1H), 7.24−7.18 (m, 2H), 7.09 (t, J = 7.4 Hz, 1H), 4.04 (s, 2H), 1.36 (s, 12H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.9.

*(±)-Diethyl ((4-Bromophenyl)fluoromethyl)phosphonate ((±)-**49**).* Following a reported procedure,[56] *n*BuLi (2.4 mL of a 1.92 M solution in hexanes, 4.61 mmol, 3.0 equiv) was diluted in anhydrous THF (13 mL), and the resultant solution was placed under an atmosphere of N_2 and cooled to −78 °C in a dry ice/acetone bath. Dropwise by syringe, a solution of diethyl (4-bromobenzyl)-phosphonate (0.35 mL, 480 mg, 1.56 mmol, 1.0 equiv) and bis(trimethylsilyl)amine (1.1 mL, 851 mg, 5.28 mmol, 3.4 equiv) in anhydrous THF (13 mL) was added to the reaction mixture. The mixture was stirred under N_2 at −78 °C for 10 min, then allowed to warm to 23 °C for 1 h. Rapidly, chlorotrimethylsilane (0.22 mL, 188

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mg, 1.73 mmol, 1.1 equiv) in anhydrous THF (6.5 mL) was added to the reaction mixture by syringe, and it was stirred under N_2 at 23 °C for 15 min, at which point the mixture was cooled to −90 °C in a liquid nitrogen/hexanes bath. Once the reaction mixture had cooled, NFSI (640 mg, 2.03 mmol, 1.3 equiv) in anhydrous THF (13 mL) was added slowly by syringe under N_2. The reaction mixture was stirred at −90 °C for 15 min then allowed to warm to 0 °C over the course of 1 h. The reaction was quenched at 0 °C by addition of 1 M aq LiOH, and the resulting mixture was stirred for an additional 15 min. The organic layer was washed with more 1 M aq LiOH (2 × 10 mL) then poured into a mixture of 3 M aq HCl (15 mL), CH_2Cl_2 (15 mL), and ice (10 g). The resultant aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), then the pooled organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 19:1 to 1:1 hexanes/EtOAc) to afford (±)-**49** as a colorless oil (465 mg, 92%). R_f = 0.18 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 1487, 1397, 1257, 1164, 1017, 971, 833 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.5 Hz, 2H), 7.34 (dd, J = 8.6, 1.9 Hz, 2H), 5.63 (dd, J = 44.7, 8.0 Hz, 1H), 4.20−4.00 (m, 4H), 1.30−1.23 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.1 (dd, J = 19.0, 1.6 Hz), 131.8 (d, J = 2.3 Hz), 128.4 (dd, J = 6.8, 5.6 Hz), 127.3 (dd, J = 10.7, 4.1 Hz), 88.9 (dd, J = 10.7, 4.1 Hz), 64.0 (d, J = 6.9 Hz), 63.6 (d, J = 6.9 Hz), 16.5 (d, J = 2.2 Hz), 16.4 (d, J = 2.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −201.5 (d, J = 83.7 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.2 (d, J = 83.7 Hz). MS (ESI-TOF) calcd for $C_{11}H_{15}BrFO_3P$ [M + H^+] 1:1 324.9999 and 326.9979, found 1:1 324.9999 and 326.9978.

*(±)-Diethyl (Fluoro(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methyl)phosphonate ((±)-**50**).* Reaction of phosphonate (±)-**49** (368 mg, 1.13 mmol, 1.0 equiv), bis(pinacoloto)diboron (345 mg, 1.36 mmol, 1.2 equiv), KOAc (331 mg, 3.37 mmol, 3.0 equiv), and Pd(dppf)Cl_2·CH_2Cl_2 (96.2 mg, 0.118 mmol, 0.10 equiv) in 1,4-dioxane (5.0 mL, 0.226 M) according to the procedure for the preparation of (±)-**30** above afforded (±)-**50** as a colorless oil (400 mg, 95%). R_f = 0.15 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 1613, 1448, 1359, 1261, 1144, 1022, 963, 855 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 6.3 Hz, 2H), 5.69 (dd, J = 44.9, 8.2 Hz, 1H), 4.21−3.96 (m, 4H), 1.33 (s, 12H), 1.27 (t, J = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9 (dd, J = 18.3, 1.7 Hz), 134.9 (d, J = 2.3 Hz), 125.9 (dd, J = 6.9, 5.4 Hz), 124.8 (dd, J = 10.5, 4.0 Hz), 89.5 (dd, J = 184.5, 168.6 Hz), 84.1, 63.9 (d, J = 7.0 Hz), 63.5 (d, J = 6.8 Hz), 25.0, 16.52, 16.46. ^{19}F NMR (376 MHz, $CDCl_3$) δ −202.5 (d, J = 83.4 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.7 (d, J = 83.2 Hz). MS (ESI-TOF) calcd for $C_{17}H_{27}BFO_5P$ [M + H^+] 373.1746, found 373.1746.

*Diethyl (Fluoro(2′-fluoro-3′-(hydroxy(2,4,5-trichlorophenyl)-methyl)-[1,1′-biphenyl]-4-yl)methyl)phosphonate (**51**).* Reaction of benzhydryl alcohol (±)-**38** (134 mg, 0.311 mmol, 1.0 equiv), boronic ester (±)-**50** (137 mg, 0.369 mmol, 1.2 equiv), K_2CO_3 (427 mg, 3.09 mmol, 9.9 equiv), and $Pd(PPh_3)_4$ (22.2 mg, 0.0192 mmol, 0.06 equiv) in toluene (8.7 mL), EtOH (3.0 mL), and H_2O (1.8 mL) according to the procedure for the preparation of (±)-**39** above afforded **51** as a yellow foam under vacuum (145 mg, 85%). R_f = 0.12 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 3337 (br), 1454, 1239, 1026, 803 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.58−7.52 (m, 4H), 7.46 (s, 1H), 7.39 (td, J = 7.3, 2.3 Hz, 1H), 7.24−7.17 (m, 2H), 6.43 (d, J = 3.0 Hz, 1H), 5.72 (dd, J = 44.7, 7.9 Hz, 1H), 4.22−4.03 (m, 4H), 3.09 (br s, 1H), 1.32−1.27 (m, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −123.1, −201.1 (d, J = 84.5 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.8 (d, J = 84.5 Hz). MS (ESI-TOF) calcd for $C_{24}H_{22}Cl_3F_2O_4P$ [M + H^+] 1:1 549.0362 and 551.0333, found 1:1 549.0362 and 551.0335.

*(±)-Diethyl (1-(4-Bromophenyl)-2-oxo-2-phenylethyl)-phosphonate ((±)-**54**).* Following a reported procedure,[57] iPr_2NH (0.35 mL, 253 mg, 2.50 mmol, 2.0 equiv) was diluted in anhydrous THF (1.0 mL), and the resultant solution was cooled to −78 °C in dry ice/acetone. Dropwise by syringe, with stirring under an atmosphere of N_2, nBuLi (1.4 mL of a 1.80 M solution in hexanes, 2.52 mmol, 2.0 equiv) was added to the iPr_2NH solution in order to generate LDA. Separately, diethyl (4-bromobenzyl)phosphonate (0.28 mL, 264 mg, 1.25 mmol, 1.0 equiv) and methyl benzoate **52** (0.16 mL, 174 mg, 1.28 mmol, 1.0 equiv) were dissolved in anhydrous THF (4.0 mL), and the resultant solution was cooled to 0 °C in an ice bath. Dropwise by syringe, under an atmosphere of N_2, the LDA solution was added to the stirred reaction mixture, and stirring was continued for 15 min at 0 °C. The reaction was quenched with 5 M aq HCl to a pH of 4, then diluted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), then the pooled organic layers were washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 19:1 to 1:1 hexanes/EtOAc) to afford (±)-**54** as a colorless oil (455 mg, 89%). R_f = 0.08 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 1681, 1595, 1486, 1247, 1019, 963, 773 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94−7.91 (m, 2H), 7.55−7.50 (m, 1H), 7.47−7.38 (m, 6H), 5.30 (d, J = 22.5 Hz, 1H), 4.15−3.98 (m, 4H), 1.22−1.16 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2 (d, J = 5.2 Hz), 136.4 (d, J = 5.0 Hz), 133.6, 131.9 (d, J = 2.7 Hz), 131.4 (d, J = 6.3 Hz), 130.7 (d, J = 9.1 Hz), 128.9, 128.7, 122.2 (d, J = 4.1 Hz), 63.3 (d, J = 6.8 Hz), 63.0 (d, J = 7.0 Hz), 53.6 (d, J = 137.1 Hz), 16.3 (d, J = 4.7 Hz), 16.2 (d, J = 4.7 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.7. MS (ESI-TOF) calcd for $C_{18}H_{20}BrO_4P$ [M + H^+] 1:1 411.0355 and 413.0335, found 1:1 411.0355 and 413.0337.

*(±)-Diethyl (1-(4-Bromophenyl)-2-cyclohexyl-2-oxoethyl)-phosphonate ((±)-**55**).* Reaction of iPr_2NH (0.35 mL, 253 mg, 2.50 mmol, 2.0 equiv), nBuLi (1.3 mL of a 1.88 M solution in hexanes, 2.44 mmol, 2.0 equiv), diethyl (4-bromobenzyl)phosphonate (0.28 mL, 264 mg, 1.25 mmol, 1.0 equiv), and methyl cyclohexanecarboxylate **53** (0.18 mL, 179 mg, 1.26 mmol, 1.0 equiv) according to the procedure for the preparation of (±)-**54** above afforded (±)-**55** as a colorless oil (184 mg, 35%). R_f = 0.15 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 2981, 2930, 2854, 1710, 1487, 1448, 1250, 1163, 1049, 1022, 962, 860, 760, 547 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.3 Hz, 2H), 7.33 (dd, J = 8.6, 2.4 Hz, 2H), 4.58 (d, J = 23.1 Hz, 1H), 4.12−3.97 (m, 4H), 2.58 (tt, J = 11.1, 3.4 Hz, 1H), 1.85 (d, J = 12.9 Hz, 1H), 1.80−1.69 (m, 3H), 1.64 (d, J = 10.9 Hz, 1H), 1.43−1.32 (m, 1H), 1.28−1.14 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.9 (d, J = 5.1 Hz), 131.9 (d, J = 2.6 Hz), 131.4 (d, J = 6.6 Hz), 130.4 (d, J = 9.0 Hz), 122.2 (d, J = 3.9 Hz), 63.4 (d, J = 6.8 Hz), 63.1 (d, J = 7.1 Hz), 56.5 (d, J = 132.9 Hz), 52.1 (d, J = 5.4 Hz), 28.7, 28.2, 25.8, 25.7, 25.4, 16.5 (d, J = 3.0 Hz), 16.4 (d, J = 3.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.4. MS (ESI-TOF) calcd for $C_{18}H_{26}BrO_4P$ [M + H^+] 1:1 417.0825 and 419.0804, found 1:1 417.0824 and 419.0802.

*(±)-Diethyl (2-Oxo-2-phenyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)phosphonate ((±)-**56**).* Reaction of phosphonate (±)-**54** (426 mg, 1.04 mmol, 1.0 equiv), bis(pinacoloto)-diboron (319 mg, 1.26 mmol, 1.2 equiv), KOAc (306 mg, 3.12 mmol, 3.0 equiv), and Pd(dppf)Cl_2·CH_2Cl_2 (90.2 mg, 0.111 mmol, 0.11 equiv) in 1,4-dioxane (5.9 mL, 0.178 M) according to the procedure for the preparation of (±)-**30** above afforded (±)-**56** as a white solid (421 mg, 88%). R_f = 0.08 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 1683, 1608, 1360, 1250, 1144, 1024, 963, 857, 774 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93−7.90 (m, 2H), 7.77 (d, J = 7.7 Hz, 2H), 7.53−7.49 (m, 3H), 7.41−7.36 (m, 2H), 5.33 (d, J = 22.1 Hz, 1H), 4.18−3.99 (m, 4H), 1.31 (s, 12H), 1.26−1.19 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6 (d, J = 5.3 Hz), 136.6 (d, J = 5.8 Hz), 135.3 (d, J = 2.8 Hz), 134.7 (d, J = 9.2 Hz), 133.5, 129.2, 129.11, 129.05, 128.7, 84.0, 63.4 (d, J = 6.6 Hz), 63.1 (d, J = 7.1 Hz), 55.0 (d, J = 138.2 Hz), 25.0, 16.5 (d, J = 4.1 Hz), 16.4 (d, J = 4.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.3. MS (ESI-TOF) calcd for $C_{24}H_{32}BO_6P$ [M + H^+] 459.2102, found 459.2100.

*(±)-Diethyl (2-Cyclohexyl-2-oxo-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)phosphonate ((±)-**57**).* Reaction of phosphonate (±)-**55** (184 mg, 0.440 mmol, 1.0 equiv), bis-(pinacoloto)diboron (136 mg, 0.537 mmol, 1.2 equiv), KOAc (130 mg, 1.33 mmol, 3.0 equiv), and Pd(dppf)Cl_2·CH_2Cl_2 (41.2 mg, 0.0505 mmol, 0.11 equiv) in 1,4-dioxane (2.5 mL, 0.176 M) according to the procedure for the preparation of (±)-**30** above afforded (±)-**57** as a colorless oil (119 mg, 58%). R_f = 0.14 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 2980, 2930, 2855, 1711, 1609, 1448, 1396, 1361, 1328, 1253, 1144, 1091, 1024, 964 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ

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7.77 (d, J = 7.4 Hz, 2H), 7.46−7.42 (m, 2H), 4.62 (d, J = 22.5 Hz, 1H), 4.11−3.95 (m, 4H), 2.63−2.51 (m, 1H), 1.89−1.82 (m, 1H), 1.81−1.56 (m, 4H), 1.36−1.32 (m, 13H), 1.26−1.18 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2 (d, J = 5.4 Hz), 135.1 (d, J = 2.5 Hz), 134.3 (d, J = 8.7 Hz), 131.4 (d, J = 6.6 Hz), 129.1 (d, J = 6.4 Hz), 84.0, 63.3 (d, J = 6.7 Hz), 62.9 (d, J = 7.0 Hz), 57.5 (d, J = 133.5 Hz), 51.9 (d, J = 3.9 Hz), 28.6, 28.4, 25.8, 25.7, 25.5, 25.0, 16.5 (d, J = 2.2 Hz), 16.4 (d, J = 2.3 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 18.9. MS (ESI-TOF) calcd for $C_{24}H_{38}BO_6P$ [M + H$^+$] 465.2572, found 465.2571.

*Diethyl (1-(2′-Fluoro-3′-(hydroxy(2,4,5-trichlorophenyl)methyl)-[1,1′-biphenyl]-4-yl)-2-oxo-2-phenylethyl)phosphonate (**58**).* Reaction of benzhydryl alcohol (±)-**38** (333 mg, 0.773 mmol, 1.0 equiv), boronic ester (±)-**56** (421 mg, 0.918 mmol, 1.2 equiv), K_2CO_3 (1.06 g, 7.65 mmol, 9.9 equiv), and $Pd(PPh_3)_4$ (89.7 mg, 0.0776 mmol, 0.10 equiv) in toluene (50 mL), EtOH (16 mL), and H_2O (10 mL) according to the procedure for the preparation of (±)-**39** above afforded **58** as a pale-yellow foam (341 mg, 69%). R_f = 0.08 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 3299 (br), 1682, 1452, 1239, 1048, 968, 728 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 8.4, 1.3 Hz, 2H), 7.77 (s, 1H), 7.67−7.64 (m, 1H), 7.62−7.58 (m, 1H), 7.54−7.49 (m, 3H), 7.46−7.40 (m, 3H), 7.37 (td, J = 7.5, 2.1 Hz, 1H), 7.22 (ddd, J = 8.3, 6.5, 2.0 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 6.41 (s, 1H), 5.38 (d, J = 22.2 Hz, 1H), 4.20−4.01 (m, 4H), 3.12 (br s, 1H), 1.24−1.19 (m, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −123.0. ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.4. MS (ESI-TOF) calcd for $C_{31}H_{27}Cl_3FO_5P$ [M + H$^+$] 1:1 635.0718 and 637.0689, found 1:1 635.0726 and 637.0681.

*Diethyl (2-Cyclohexyl-1-(2′-fluoro-3′-(hydroxy(2,4,5-trichlorophenyl)methyl)-[1,1′-biphenyl]-4-yl)-2-oxoethyl)-phosphonate (**59**).* Reaction of benzhydryl alcohol (±)-**38** (111 mg, 0.258 mmol, 1.0 equiv), boronic ester (±)-**57** (119 mg, 0.256 mmol, 1.0 equiv), K_2CO_3 (308 mg, 2.23 mmol, 8.6 equiv), and $Pd(PPh_3)_4$ (30.0 mg, 0.0260 mmol, 0.10 equiv) in toluene (11.1 mL), EtOH (3.6 mL), and H_2O (2.2 mL) according to the procedure for the preparation of (±)-**39** above afforded **59** as a colorless oil (112 mg, 68%). R_f = 0.08 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 2981, 2931, 2855, 1710, 1451, 1241, 1020, 965, 908, 729, 542 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 3H), 7.46−7.42 (m, 2H), 7.37 (t, J = 7.4, 1.9 Hz, 1H), 7.31 (dd, J = 8.6, 2.4 Hz, 1H), 7.23 (td, J = 7.2, 6.6, 1.9 Hz, 1H), 7.17 (t, J = 7.6 Hz, 1H), 6.41 (d, J = 3.3 Hz, 1H), 4.65 (d, J = 22.8 Hz, 1H), 4.14−3.96 (m, 4H), 3.62 (s, 1H), 2.63−2.53 (m, 1H), 1.92−1.59 (m, 5H), 1.44−1.31 (m, 1H), 1.27−1.16 (m, 10H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −123.1. ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.1. MS (ESI-TOF) calcd for $C_{31}H_{33}Cl_3FO_5P$ [M + H$^+$] 1:1 641.1188 and 643.1158, found 1:1 641.1189 and 643.1166.

*Diethyl (1-Fluoro-1-(2′-fluoro-3′-(hydroxy(2,4,5-trichlorophenyl)-methyl)-[1,1′-biphenyl]-4-yl)-2-oxo-2-phenylethyl)phosphonate (**60**).* Phosphonate **58** (341 mg, 0.537 mmol, 1.0 equiv), NFSI (513 mg, 1.63 mmol, 3.0 equiv), and selectfluor (47.7 mg, 0.135 mmol, 0.25 equiv) were dissolved in anhydrous CH_2Cl_2 (7.5 mL, 0.072 M) in the presence of 4 Å molecular sieves. The reaction mixture was stirred under an atmosphere of N_2 at 23 °C for 1 week, then concentrated. The resultant residue was purified by flash chromatography (silica gel, 1:1 CH_2Cl_2/Et_2O then 19:1 to 1:1 hexanes/EtOAc) to afford **60** as a foamy white solid (186 mg, 53%). R_f = 0.34 (silica gel, 1:1 hexanes/EtOAc). IR (film) ν_{max} 3344 (br), 2982, 1684, 1450, 1258, 1070, 1020 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dt, J = 8.6, 1.7 Hz, 2H), 7.77 (s, 1H), 7.72 (dd, J = 8.6, 2.4 Hz, 2H), 7.67−7.57 (m, 2H), 7.52 (ddt, J = 7.1, 5.6, 1.5 Hz, 1H), 7.45 (s, 1H), 7.38 (t, J = 7.7 Hz, 3H), 7.24 (dd, J = 6.6, 1.8 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 6.42 (s, 1H), 4.29−4.13 (m, 4H), 3.11 (br s, 1H), 1.33−1.23 (m, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −123.0, −169.8 (d, J = 85.8 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 11.3 (d, J = 85.9 Hz). MS (ESI-TOF) calcd for $C_{31}H_{26}Cl_3F_2O_5P$ [M + H$^+$] 1:1 653.0624 and 655.0595, found 1:1 653.0623 and 655.0601.

*Diethyl (2-Cyclohexyl-1-fluoro-1-(2′-fluoro-3′-(hydroxy(2,4,5-trichlorophenyl)methyl)-[1,1′-biphenyl]-4-yl)-2-oxoethyl)-phosphonate (**61**).* Reaction of phosphonate **59** (112 mg, 0.175 mmol, 1.0 equiv), NFSI (165 mg, 0.524 mmol, 3.0 equiv), and selectfluor (18.6 mg, 0.0524 mmol, 0.30 equiv) in CH_2Cl_2 (2.5 mL, 0.070 M) in the presence of 4 Å molecular sieves according to the procedure for the preparation of **60** above afforded **61** as a colorless oil (36 mg, 31%). R_f = 0.46 (silica gel, 1:1 hexanes/EtOAc). IR (film) ν_{max} 3367 (br), 2981, 2932, 2855, 1717, 1452, 1246, 1071, 1044, 1020 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.70 (dd, J = 8.6, 2.4 Hz, 2H), 7.58−7.50 (m, 2H), 7.46 (s, 1H), 7.40 (td, J = 7.4, 2.0 Hz, 1H), 7.25−7.17 (m, 2H), 6.43 (d, J = 3.8 Hz, 1H), 4.20−4.06 (m, 4H), 3.00 (ddt, J = 11.4, 7.7, 3.7 Hz, 1H), 2.92 (d, J = 4.2 Hz, 1H), 1.91 (d, J = 13.4 Hz, 1H), 1.79 (d, J = 12.9 Hz, 1H), 1.70−1.55 (m, 3H), 1.41 (dt, J = 15.4, 10.8 Hz, 1H), 1.32−1.23 (m, 10H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −123.0, −177.9 (d, J = 86.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 11.1 (d, J = 84.0 Hz). MS (ESI-TOF) calcd for $C_{31}H_{32}Cl_3F_2O_5P$ [M + H$^+$] 1:1 659.1094 and 661.1064, found 1:1 659.1094 and 661.1076.

*(±)-Diethyl (1-(4-Bromophenyl)-2-oxo-2-(piperidin-1-yl)ethyl)-phosphonate ((±)-**63**).* iPr$_2$NH (0.35 mL, 253 mg, 2.50 mmol, 2.0 equiv) was diluted in anhydrous THF (1.0 mL), and the resultant solution was cooled to −78 °C in dry ice/acetone. Dropwise by syringe, with stirring under an atmosphere of N_2, nBuLi (1.3 mL of a 1.92 M solution in hexanes, 2.50 mmol, 2.0 equiv) was added to the iPr$_2$NH solution in order to generate LDA. Separately, diethyl (4-bromobenzyl)phosphonate (0.28 mL, 264 mg, 1.25 mmol, 1.0 equiv) and piperidine-1-carbonyl chloride **62** (0.16 mL, 189 mg, 1.28 mmol, 1.0 equiv) were dissolved in anhydrous THF (4.0 mL), and the resultant solution was cooled to 0 °C in an ice bath. Dropwise by syringe, under an atmosphere of N_2, the LDA solution was added to the stirred reaction mixture, and stirring was continued for 15 min at 0 °C. The reaction was quenched with 5 M aq HCl to a pH of 4, and then the resulting mixture was diluted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), then the pooled organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 99:1 to 4:1 CH_2Cl_2/MeOH) to afford (±)-**63** as a colorless oil (512 mg, 98%). R_f = 0.08 (silica gel, 1:1 hexanes/EtOAc). IR (film) ν_{max} 1635, 1486, 1438, 1249, 1216, 1053, 1011, 957, 852, 780, 730, 554 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.5 Hz, 2H), 7.28 (dd, J = 8.6, 2.4 Hz, 2H), 4.42 (d, J = 22.8 Hz, 1H), 4.28−4.16 (m, 2H), 4.05−3.91 (m, 2H), 3.68 (ddd, J = 13.4, 6.3, 3.4 Hz, 1H), 3.40−3.31 (m, 1H), 3.29−3.23 (m, 2H), 1.55−1.36 (m, 5H), 1.23 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H) 1.08−0.98 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4 (d, J = 2.9 Hz), 131.8 (d, J = 2.8 Hz), 131.7 (d, J = 9.5 Hz), 131.0 (d, J = 5.9 Hz), 121.8 (d, J = 4.0 Hz), 63.6 (d, J = 6.5 Hz), 62.4 (d, J = 7.0 Hz), 49.9 (d, J = 145.0 Hz), 47.8. 43.3, 26.1, 25.4, 24.3, 16.5 (d, J = 6.1 Hz), 16.3 (d, J = 6.3 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 19.5. MS (ESI-TOF) calcd for $C_{17}H_{25}BrNO_4P$ [M + H$^+$] 1:1 418.0777 and 420.0757, found 1:1 418.0780 and 420.0763.

*(±)-Diethyl (1-(4-Bromophenyl)-1-fluoro-2-oxo-2-(piperidin-1-yl)-ethyl)phosphonate ((±)-**64**).* iPr$_2$NH (0.23 mL, 166 mg, 1.64 mmol, 1.5 equiv) was diluted in anhydrous THF (1.0 mL), and the resultant solution was cooled to −78 °C in dry ice/acetone. Dropwise by syringe, with stirring under an atmosphere of N_2, nBuLi (0.86 mL of a 1.88 M solution in hexanes, 1.62 mmol, 1.5 equiv) was added to the iPr$_2$NH solution in order to generate LDA. Separately, phosphonate (±)-**63** (452 mg, 1.08 mmol, 1.0 equiv) and NFSI (1.02 mg, 3.24 mmol, 3.0 equiv) were dissolved in anhydrous THF (6.0 mL), and the resultant solution was cooled to 0 °C in an ice bath. Dropwise by syringe, under an atmosphere of N_2, the LDA solution was added to the stirred reaction mixture, which was then allowed to warm to 23 °C. After 24 h, the reaction was quenched with satd aq NH_4Cl (10 mL), and the resulting mixture was diluted with EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL), and the pooled organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 99:1 to 4:1 CH_2Cl_2/MeOH) to afford (±)-**64** as a pale-yellow oil (154 mg, 33%). R_f = 0.12 (silica gel, 1:1 hexanes/EtOAc). IR (film) ν_{max} 2935, 1624, 1484, 1444, 1396, 1261, 1163, 1063, 1022, 972, 790, 747, 648, 579, 552 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 2H), 7.38 (dd, J = 8.8, 2.3 Hz, 2H), 4.29−4.16 (m, 4H), 3.65−3.56 (m, 1H), 3.54−3.45 (m, 1H), 3.35−3.25 (m, 1H), 3.18−3.10 (m, 1H),

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1.61−1.47 (m, 4H), 1.42−1.33 (m, 1H), 1.26 (dt, J = 11.2, 7.1 Hz, 6H), 1.05−0.95 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5 (dd, J = 17.3, 4.5 Hz), 132.8 (dd, J = 19.4, 2.9 Hz), 131.7 (dd, J = 2.3, 1.3 Hz), 126.8 (dd, J = 7.7, 4.0 Hz), 123.6 (dd, J = 4.0, 1.5 Hz), 64.4 (d, J = 6.8 Hz), 64.2 (d, J = 6.8 Hz), 46.5 (d, J = 11.3 Hz), 44.4, 25.8, 25.7, 24.4, 16.6 (d, J = 3.9 Hz), 16.5 (d, J = 4.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −167.7 (d, J = 90.8 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 11.2 (d, J = 90.7 Hz). MS (ESI-TOF) calcd for $C_{17}H_{24}BrFNO_4P$ [M + H$^+$] 1:1 436.0683 and 438.0663, found 1:1 436.0683 and 438.0668.

*(±)-Diethyl (1-Fluoro-2-oxo-2-(piperidin-1-yl)-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethyl)phosphonate ((±)-**65**).* Reaction of phosphonate (±)-**64** (54 mg, 0.123 mmol, 1.0 equiv), bis(pinacoloto)diboron (39.1 mg, 0.154 mmol, 1.3 equiv), KOAc (37.4 mg, 0.381 mmol, 3.1 equiv), and Pd(dppf)Cl_2·CH_2Cl_2 (13.6 mg, 0.0167 mmol, 0.14 equiv) in 1,4-dioxane (0.63 mL, 0.195 M) according to the procedure for the preparation of (±)-**30** above afforded (±)-**65** as a pale-yellow oil (46 mg, 76%). R_f = 0.04 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 2979, 2936, 1645, 1445, 1398, 1362, 1264, 1145, 1065, 1024, 972, 580 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 7.7 Hz, 2H), 7.49 (dd, J = 8.3, 2.2 Hz, 2H), 4.30−4.14 (m, 4H), 3.70−3.57 (m, 1H), 3.54−3.40 (m, 1H), 3.35−3.22 (m, 1H), 3.19−3.09 (m, 1H), 1.65−1.46 (m, 6H), 1.35 (s, 12H), 1.28−1.21 (m, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −168.4 (d, J = 91.9 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 11.5 (d, J = 91.9 Hz).

*Diethyl (1-Fluoro-1-(2′-fluoro-3′-(hydroxy(2,4,5-trichlorophenyl)-methyl)-[1,1′-biphenyl]-4-yl)-2-oxo-2-(piperidin-1-yl)ethyl)-phosphonate (**66**).* Reaction of benzhydryl alcohol (±)-**38** (39.7 mg, 0.0920 mmol, 1.0 equiv), boronic ester (±)-**65** (45.4 mg, 0.0939 mmol, 1.0 equiv), K_2CO_3 (109 mg, 0.788 mmol, 8.6 equiv), and Pd(PPh_3)$_4$ (10.1 mg, 0.00874 mmol, 0.09 equiv) in toluene (5.3 mL), EtOH (1.7 mL), and H_2O (1.0 mL) according to the procedure for the preparation of (±)-**39** above afforded **66** as a yellow oil (55.7 mg, 92%). Even after chromatography, **66** provided a complex ^{1}H NMR spectrum, precluding rigorous characterization. The material was identified by LCMS and brought forward in impure form to the subsequent step. MS (ESI-TOF) calcd for $C_{30}H_{31}Cl_3F_2NO_5P$ [M + H$^+$] 1:1 660.1046 and 662.1017, found 1:1 660.1047 and 662.1026.

*1,2,4-Trichloro-5-(2-fluoro-3-iodobenzyl)benzene (**67**).* Benzhydryl alcohol (±)-**38** (1.97 g, 4.56 mmol, 1.0 equiv) was dissolved in 1:1 CH_2Cl_2/TFA (8.4 mL, 0.215 M) in a flame-dried round-bottom flask equipped with a reflux condenser. To this reaction mixture, with stirring under N_2, was added triethylsilane (2.2 mL, 1.60 mg, 13.8 mmol, 3.0 equiv) by syringe. The reaction mixture was then heated to 40 °C and stirred under N_2 for 16 h. At this point, the solution was concentrated and the crude product was purified by flash chromatography (silica gel, 19:1 to 4:1 hexanes/EtOAc) to afford **67** as a colorless oil (1.14 g, 60%). R_f = 0.76 (silica gel, 4:1 hexanes/EtOAc). IR (film) ν_{max} 1445, 1354, 1222, 1134, 1068, 928, 887, 867, 840, 805, 784, 753, 710, 677 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (ddd, J = 7.8, 5.9, 1.7 Hz, 1H), 7.49 (s, 1H), 7.23 (s, 1H), 7.07 (td, J = 7.2, 1.6 Hz, 1H), 6.84 (t, J = 7.7 Hz, 1H), 4.06 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9 (d, J = 245.3 Hz), 138.3 (d, J = 1.6 Hz), 136.9, 133.0, 132.0 (d, J = 1.5 Hz), 131.6, 131.4, 131.1 (d, J = 3.8 Hz), 130.9, 126.2 (d, J = 17.9 Hz), 126.0 (d, J = 4.2 Hz), 81.8 (d, J = 26.1 Hz), 32.5 (d, J = 2.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −96.3.

*Diethyl (4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-phosphonate (**68**).* Reaction of diethyl (4-bromobenzyl)phosphonate (0.70 mL, 959 mg, 3.12 mmol, 1.0 equiv), bis(pinacoloto)diboron (957 mg, 3.77 mmol, 1.2 equiv), KOAc (921 mg, 9.39 mmol, 3.0 equiv), and Pd(dppf)Cl_2·CH_2Cl_2 (252 mg, 0.309 mmol, 0.10 equiv) in 1,4-dioxane (17.7 mL, 0.170 M) according to the procedure for the preparation of (±)-**30** above afforded **68** as a yellow oil (1.05 g, 95%). R_f = 0.18 (silica gel, 1:1 hexanes/EtOAc). IR (film) ν_{max} 2979, 1612, 1396, 1359, 1324, 1250, 1144, 1089, 1053, 1024, 960, 857, 659, 547 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 7.0 Hz, 2H), 7.28 (dd, J = 8.0, 2.5 Hz, 2H), 4.03−3.93 (m, 4H), 3.15 (d, J = 21.9 Hz, 2H), 1.32 (s, 12H), 1.25−1.19 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.1, 135.0, 129.3, 129.2, 83.9, 62.3 (d, J = 6.8 Hz), 34.2 (d, J = 137.4 Hz), 25.0, 16.5 (d, J = 6.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.9.

*Diethyl ((2′-Fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)methyl)phosphonate (**69**).* Reaction of aryl iodide **67** (816 mg, 1.97 mmol, 1.0 equiv), boronic ester **68** (835 mg, 2.36 mmol, 1.2 equiv), K_2CO_3 (2.72 g, 19.7 mmol, 10.0 equiv), and Pd(PPh_3)$_4$ (227 mg, 0.197 mmol, 0.10 equiv) in toluene (119 mL), EtOH (38 mL), and H_2O (23 mL) according to the procedure for the preparation of (±)-**39** above afforded **69** as a yellow oil (897 mg, 88%). R_f = 0.04 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 1458, 1247, 1204, 1134, 1053, 1024, 961, 856, 801, 760, 592, 543 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.47 (m, 3H), 7.38 (dd, J = 8.3, 2.5 Hz, 2H), 7.33 (dd, J = 7.5, 1.9 Hz, 1H), 7.26 (s, 1H), 7.14 (t, J = 4.6 Hz, 1H), 7.08 (td, J = 7.2, 1.9 Hz, 1H), 4.10 (s, 2H), 4.05 (dqd, 4H), 3.20 (d, J = 21.7 Hz, 2H), 1.27 (t, J = 7.1 Hz, 6H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.1. ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.1. MS (ESI-TOF) calcd for $C_{24}H_{23}Cl_3FO_3P$ [M + H$^+$] 1:1 515.0507 and 517.0478, found 1:1 515.0507 and 517.0482.

*(±)-Diethyl (1-(2′-Fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)-2-oxo-2-(piperidin-1-yl)ethyl)phosphonate ((±)-**72**).* iPr$_2$NH (0.12 mL, 86.6 mg, 0.856 mmol, 4.1 equiv) was diluted in anhydrous THF (0.4 mL), and the resultant solution was cooled to −78 °C in dry ice/acetone. Dropwise by syringe, with stirring under an atmosphere of N_2, nBuLi (0.44 mL of a 1.88 M solution in hexanes, 0.827 mmol, 4.0 equiv) was added to the iPr$_2$NH solution in order to generate LDA. Separately, phosphonate **69** (108 mg, 0.209 mmol, 1.0 equiv) and piperidine-1-carbonyl chloride **62** (0.04 mL, 47 mg, 0.320 mmol, 1.5 equiv) were dissolved in anhydrous THF (0.6 mL), and the resultant solution was cooled to 0 °C in an ice bath. Dropwise by syringe, under an atmosphere of N_2, half of the LDA solution (0.48 mL, 0.414 mmol, 2.0 equiv) was added to the stirred reaction mixture, and stirring was continued for 15 min at 0 °C. The reaction was quenched with 5 M aq HCl to a pH of 4, and the resulting mixture was then diluted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), then the pooled organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude (±)-**72** product (147 mg) was used in the next step without further purification.

*(±)-Diethyl (1-(2′-Fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)-2-morpholino-2-oxoethyl)phosphonate ((±)-**73**).* Mixture of iPr$_2$NH (0.12 mL, 86.6 mg, 0.856 mmol, 4.0 equiv) and nBuLi (0.44 mL of a 1.92 M solution in hexanes, 0.845 mmol, 4.0 equiv) in THF (0.4 mL) according to the procedure for the preparation of (±)-**72** above generated LDA. Half of this LDA solution (0.48 mL, 0.423 mmol, 2.0 equiv) was then reacted with phosphonate **69** (109 mg, 0.212 mmol, 1.0 equiv) and morpholine-4-carbonyl chloride **70** (0.03 mL, 38 mg, 0.257 mmol, 1.2 equiv) according to the procedure for the preparation of (±)-**72** above to afford crude (±)-**73** (56 mg), which was used in the next step without further purification.

*(±)-Diethyl (2-(Dimethylamino)-1-(2′-fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)-2-oxoethyl)phosphonate ((±)-**74**).* Mixture of iPr$_2$NH (0.16 mL, 116 mg, 1.14 mmol, 4.2 equiv) and nBuLi (0.56 mL of a 1.92 M solution in hexanes, 1.08 mmol, 4.0 equiv) in THF (0.4 mL) according to the procedure for the preparation of (±)-**72** above generated LDA. Half of this LDA solution (0.56 mL, 0.540 mmol, 2.0 equiv) was then reacted with phosphonate **69** (139 mg, 0.269 mmol, 1.0 equiv) and dimethylcarbamic chloride **71** (0.03 mL, 35 mg, 0.326 mmol, 1.2 equiv) according to the procedure for the preparation of (±)-**72** above to afford crude (±)-**74** (124 mg), which was used in the next step without further purification.

*Methyl 2-(2′-Fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)acetate (**75a**) and Ethyl 2-(2′-Fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)acetate (**75b**).* Aryl iodide **67** (636 mg, 1.53 mmol, 1.0 equiv), methyl 2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (509 mg, 1.84 mmol, 1.2 equiv), and K_2CO_3 (2.11 g, 15.3 mmol, 10 equiv) were dissolved in toluene (92 mL), EtOH (29 mL), and H_2O (18 mL). With stirring, N_2 was bubbled through the biphasic mixture for 1 h. Pd(PPh_3)$_4$ (178 mg, 0.154 mmol, 0.10 equiv) was then added, and N_2 was bubbled through the stirred solution for an additional 20 min. The flask was next equipped with a reflux condenser, and the reaction mixture was stirred at 80 °C under an atmosphere of N_2 for 20 h. The solution was cooled to 23 °C and concentrated. The crude residue was purified by flash chromatography

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(silica gel, 19:1 to 1:1 hexanes/EtOAc) to afford an inconsequential, separable mixture of **75a** (115 mg, 17%) and **75b** (177 mg, 26%) as yellow oils. **75a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52−7.49 (m, 3H), 7.38−7.31 (m, 3H), 7.26 (s, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.09 (ddd, J = 8.5, 7.0, 1.8 Hz, 1H), 4.11 (s, 2H), 3.72 (s, 3H), 3.68 (s, 2H). **75b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53−7.49 (m, 3H), 7.39−7.32 (m, 3H), 7.27 (s, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.13−7.06 (m, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.11 (s, 2H), 3.66 (s, 2H), 1.28 (t, J = 7.1 Hz, 3H).

*2-(2′-Fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)acetic Acid (**76**).* Esters **75a** (115 mg, 0.262 mmol) and **75b** (177 mg, 0.391 mmol) were dissolved in 3:1 MeOH/EtOH (8.8 mL, 0.071 M) in a flame-dried round-bottom flask outfitted with a reflux condenser. To this mixture, with stirring under an atmosphere of N_2, was added 5 M aq NaOH (0.39 mL, 1.95 mmol, 3.0 equiv). The reaction mixture was heated at reflux (70 °C) for 3 h, then cooled to room temperature. The solution was concentrated, and the residue was redissolved in H_2O (10 mL) and EtOAc (10 mL). The aqueous layer was washed with EtOAc (5 mL) then acidified to pH 2 by addition of 2 M aq HCl. The acidifed aqueous solution was extracted with ethyl acetate (3 × 10 mL), and these last three organic extractions were combined, dried over Na_2SO_4, filtered, and concentrated to afford spectroscopically pure **76** (276 mg, > 99%) as a pale-yellow oil, which was used in the subsequent step without further purification. R_f = 0.11 (silica gel, 4:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.49 (m, 3H), 7.40−7.31 (m, 3H), 7.27 (s, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.14−7.05 (m, 1H), 4.11 (s, 2H), 3.71 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −122.1.

*2-Bromo-2-(3′-(bromo(2,4,5-trichlorophenyl)methyl)-2′-fluoro-[1,1′-biphenyl]-4-yl)acetic Acid (**77**).* Carboxylic acid **76** (276 mg, 0.653 mmol, 1.0 equiv) was dissolved in chlorobenzene (1.55 mL, 0.400 M) in a two-neck flame-dried round-bottom flask equipped with a reflux condenser. This solution was sealed with septa under an atmosphere of N_2. To the reaction mixture was added phosphorus trichloride (0.02 mL, 32 mg, 0.229 mmol, 0.35 equiv) by syringe, then it was heated to 105 °C. Once this temperature had been achieved, bromine (0.06 mL, 187 mg, 1.17 mmol, 1.8 equiv) was added with stirring, under N_2, by syringe. After 2 h at 105 °C, additional phosphorus trichloride (0.02 mL, 32 mg, 0.229 mmol, 0.35 equiv) and bromine (0.06 mL, 187 mg, 1.17 mmol, 1.8 equiv) were consecutively added by syringe. The reaction mixture was stirred under N_2 at 105 °C for an additional 2 h before it was cooled to 23 °C. H_2O (0.5 mL) and satd aq $NaHSO_3$ (0.5 mL) were added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The pooled organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 19:1 to 1:1 hexanes/EtOAc) to afford **77** as a yellow oil (309 mg, 94%). R_f = 0.12 (silica gel, 4:1 hexanes/EtOAc). IR (film) ν_{max} 1720, 1452, 1071 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.64 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 6.0 Hz, 2H), 7.42 (td, J = 7.6, 1.8 Hz, 1H), 7.29−7.24 (m, 1H), 6.80 (s, 1H), 5.41 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −120.3.

*2-Bromo-2-(3′-(bromo(2,4,5-trichlorophenyl)methyl)-2′-fluoro-[1,1′-biphenyl]-4-yl)-N-methylacetamide (**78**).* Carboxylic acid **77** (309 mg, 0.614 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (5.8 mL, 0.100 M). To the reaction mixture was added carbonyl diimidazole (112 mg, 0.688 mmol, 1.1 equiv), and the resultant solution was stirred after sealing the flask with a polyethylene stopper for 30 min. Then, methylamine (0.34 mL of a 2.0 M solution in THF, 0.680 mmol, 1.1 equiv) was added by syringe, and the polyethylene stopper was placed back on the flask. The reaction mixture was stirred at 23 °C for 24 h, then concentrated. The crude product was purified by flash chromatography (silica gel, 19:1 to 1:1 hexanes/EtOAc) to afford **78** as a white foam (104 mg, 33%). R_f = 0.23 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 1657, 1563, 1453, 1409, 1353, 1071, 908, 733 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.53−7.49 (m, 5H), 7.41 (td, J = 7.5, 1.8 Hz, 1H), 7.28−7.22 (m, 1H), 6.79 (s, 1H), 6.74−6.69 (m, 1H), 5.48 (s, 1H), 2.93 (d, J = 4.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −120.3. MS (ESI-TOF) calcd for $C_{22}H_{15}Br_2Cl_3FNO$ [M + H$^+$] 593.8622, found 593.8620.

*Diethyl (1-(3′-(Bromo(2,4,5-trichlorophenyl)methyl)-2′-fluoro-[1,1′-biphenyl]-4-yl)-2-(methylamino)-2-oxoethyl)phosphonate (**79**).* Amide **78** (32 mg, 0.0625 mmol, 1.0 equiv) was dissolved in triethyl phosphite (0.04 mL, 38.8 mg, 0.233 mmol, 3.7 equiv) in a sealed tube. The resultant solution was heated to 120 °C for 2 h then cooled to 23 °C. The crude product was loaded directly onto a flash chromatography column (silica gel, 99:1 to 9:1 CH_2Cl_2/MeOH) to elute **79** as a yellow oil (31 mg, 85%). Even after chromatography, **79** provided a complex ^{1}H NMR spectrum, precluding rigorous characterization. The material was brought forward in impure form to the subsequent step.

*4-((4-Bromobenzyl)sulfonyl)morpholine (**80**).* Na_2CO_3 (395 mg, 3.73 mmol, 2.0 equiv) was suspended in MeCN (8.4 mL, 0.213 M), then morpholine (0.32 mL, 319 mg, 3.66 mmol, 2.0 equiv) was added to the reaction mixture. With stirring, solid (4-bromophenyl)-methanesulfonyl chloride (501 mg, 1.86 mmol, 1.0 equiv) was added, and the flask was sealed with a septum under an atmosphere of N_2. After stirring for 2 h, the reaction mixture was diluted with H_2O (15 mL), and the aqueous solution was extracted with EtOAc (2 × 20 mL). The pooled organic phases were dried over Na_2SO_4, filtered, and concentrated to afford **80** as a white solid, which required no further purification (585 mg, 98%). R_f = 0.10 (silica gel, 4:1 hexanes/EtOAc). IR (film) ν_{max} 2660, 1488, 1454, 1342, 1330, 1260, 1155, 1112, 1071, 1014, 951, 843, 762, 729 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 4.16 (s, 2H), 3.67−3.62 (m, 4H), 3.18−3.10 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.4, 132.2, 127.7, 123.4, 66.8, 55.9, 46.3.

*4-((4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-sulfonyl)morpholine (**81**).* Reaction of sulfonamide **80** (579 mg, 1.81 mmol, 1.0 equiv), bis(pinacoloto)diboron (557 mg, 2.19 mmol, 1.2 equiv), KOAc (534 mg, 5.44 mmol, 3.0 equiv), and Pd(dppf)Cl_2·CH_2Cl_2 (148 mg, 0.181 mmol, 0.10 equiv) in 1,4-dioxane (12.4 mL, 0.146 M) according to the procedure for the preparation of (±)-**30** above afforded **81** as a white solid (586 mg, 88%). R_f = 0.23 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 2978, 2916, 2859, 1612, 1453, 1402, 1362, 1342, 1323, 1296, 1259, 1150, 1111, 1092, 1072, 951, 861, 765, 659 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 4.24 (s, 2H), 3.61−3.56 (m, 4H), 3.10−3.05 (m, 4H), 1.35 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 132.4, 131.5, 130.1, 84.2, 66.8, 57.1, 46.3, 25.0. MS (ESI-TOF) calcd for $C_{17}H_{26}BNO_5S$ [M + Na$^+$] 390.1517, found 390.1518.

*4-(((2′-Fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)-methyl)sulfonyl)morpholine (**82**).* Reaction of aryl iodide **67** (465 mg, 1.12 mmol, 1.0 equiv), boronic ester **81** (488 mg, 1.33 mmol, 1.2 equiv), K_2CO_3 (1.55 g, 11.2 mmol, 10.0 equiv), and Pd(PPh$_3$)$_4$ (131 mg, 0.114 mmol, 0.10 equiv) in toluene (50 mL), EtOH (17 mL), and H_2O (9 mL) according to the procedure for the preparation of (±)-**39** above afforded **82** as a white solid (474 mg, 80%). R_f = 0.20 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 2858, 1456, 1410, 1343, 1317, 1258, 1153, 1112, 1070, 950, 735 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.3, 1.7 Hz, 2H), 7.52−7.47 (m, 3H), 7.35 (td, J = 7.4, 2.0 Hz, 1H), 7.27 (s, 1H), 7.17 (t, J = 7.6 Hz, 1H), 7.12 (td, J = 7.7, 7.2, 1.9 Hz, 1H), 4.27 (s, 2H), 4.11 (s, 2H), 3.69−3.62 (m, 4H), 3.20−3.14 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −121.9.

*(±)-Diethyl ((2′-Fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)(morpholinosulfonyl)methyl)phosphonate ((±)-**83**).* Following a reported procedure,[58] iPr$_2$NH (0.09 mL, 65.0 mg, 0.642 mmol, 1.1 equiv) was diluted in anhydrous THF (1.1 mL), and the resultant solution was cooled to 0 °C in an ice bath. Dropwise by syringe, with stirring under an atmosphere of N_2, nBuLi (0.36 mL of a 1.88 M solution in hexanes, 0.677 mmol, 1.2 equiv) was added to the iPr$_2$NH solution in order to generate LDA. The LDA solution was then cooled to −78 °C in dry ice/acetone and stirred under N_2 for 15 min. Dropwise by syringe, with stirring, under N_2, a solution of sulfonamide **82** (298 mg, 0.564 mmol, 1.0 equiv) in anhydrous THF (9.7 mL) was added to the chilled LDA solution. After addition, the reaction mixture was stirred under N_2 at −78 °C for 10 min. Then, diethyl chlorophosphate (0.13 mL, 155 mg, 0.900 mmol, 1.6 equiv) was added by syringe, and the reaction mixture was stirred at −78 °C under N_2 for 1 h. The reaction mixture was warmed to 0 °C in an ice

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bath and stirred for an additional hour before the reaction was quenched with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) then EtOAc (10 mL). The combined organic layers were washed with H_2O (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was flash chromatographed (silica gel, 99:1 to 9:1 CH_2Cl_2/MeOH) to afford recovered **82** (120 mg, 40%) and (±)-**83** as a yellow oil (249 mg), which provided a complex ^{1}H NMR spectrum, precluding rigorous characterization. The material was brought forward in impure form to the subsequent step.

*(±)-4-((Fluoro(2′-fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)methyl)sulfonyl)morpholine ((±)-**84**).* Sulfonamide **82** (474 mg, 0.896 mmol, 1.0 equiv) was dissolved in anhydrous THF (12 mL), and the resultant solution was cooled to −78 °C in a dry ice/acetone bath. Under an atmosphere of N_2, with stirring, sodium bis(trimethylsilyl)-amide (0.49 mL of a 2.0 M solution in THF, 0.980 mmol, 1.1 equiv) was added to the reaction mixture dropwise by syringe. The mixture was stirred for 30 min at −78 °C. Then, a solution of NFSI (311 mg, 0.988 mmol, 1.1 equiv) in anhydrous THF (2.5 mL) was added to the stirred solution, dropwise by syringe under N_2. The flask was warmed to 23 °C, and stirring under N_2 was continued for 4 h, at which point the reaction was quenched by the addition of satd aq NH_4Cl (15 mL). The aqueous layer was extracted with EtOAc (3 × 20 mL), then the pooled organic extracts were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, 19:1 to 2:1 hexanes/EtOAc) to afford (±)-**84** as a white foam (221 mg, 45%). R_f = 0.36 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 1459, 1407, 1353, 1300, 1261, 1204, 1162, 1114, 1070, 957, 910, 847, 736, 572 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.62 (m, 4H), 7.51 (s, 1H), 7.35 (td, J = 7.4, 2.0 Hz, 1H), 7.27 (s, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.13 (td, J = 7.2, 2.0 Hz, 1H), 6.16 (d, J = 46.0 Hz, 1H), 4.12 (s, 2H), 3.74−3.69 (m, 4H), 3.41−3.36 (m, 4H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −121.8, −176.4. MS (ESI-TOF) calcd for $C_{24}H_{20}Cl_3F_2NO_3S$ [M + Na$^+$] 1:1 568.0090 and 570.0060, found 1:1 568.0091 and 570.0070.

*(±)-Diethyl (Fluoro(2′-fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)(morpholinosulfonyl)methyl)phosphonate ((±)-**85**).* Following a reported procedure,[58] iPr$_2$NH (0.07 mL, 51.0 mg, 0.500 mmol, 1.2 equiv) was diluted in anhydrous THF (1.0 mL), and the resultant solution was cooled to 0 °C in an ice bath. Dropwise by syringe, with stirring under an atmosphere of N_2, nBuLi (0.26 mL of a 1.90 M solution in hexanes, 0.494 mmol, 1.2 equiv) was added to the iPr$_2$NH solution in order to generate LDA. The LDA solution was then cooled to −78 °C in dry ice/acetone and stirred under N_2 for 15 min. Dropwise by syringe, with stirring, under N_2, a solution of sulfonamide (±)-**84** (221 mg, 0.405 mmol, 1.0 equiv) in anhydrous THF (4.0 mL) was added to the chilled LDA solution. After addition, the reaction mixture was stirred under N_2 at −78 °C for 10 min. Then, diethyl chlorophosphate (0.09 mL, 108 mg, 0.623 mmol, 1.5 equiv) was added by syringe, and the reaction mixture was stirred at −78 °C under N_2 for 1 h. The reaction mixture was warmed to 0 °C in an ice bath and stirred for an additional 90 min before the reaction was quenched with brine (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) then EtOAc (10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was flash chromatographed (silica gel, 1:1 CH_2Cl_2/EtOAc) to afford (±)-**85** as a colorless oil (157 mg, 57%). R_f = 0.10 (silica gel, 2:1 hexanes/EtOAc). IR (film) ν_{max} 1458, 1359, 1262, 1165, 1134, 1115, 1060, 1022, 964 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.7, 1.9 Hz, 2H), 7.65 (d, J = 7.6 Hz, 2H), 7.51 (s, 1H), 7.37 (td, J = 7.4, 1.9 Hz, 1H), 7.26 (s, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.13 (td, J = 7.6, 7.2, 1.9 Hz, 1H), 4.44−4.31 (m, 2H), 4.22−3.97 (m, 6H), 3.63−3.52 (m, 2H), 3.52−3.44 (m, 2H), 3.31−3.22 (m, 2H), 1.39 (td, J = 7.1, 0.8 Hz, 3H), 1.20 (td, J = 7.1, 0.8 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ −121.7, −167.5 (d, J = 71.4 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 6.3 (d, J = 71.4 Hz). MS (ESI-TOF) calcd for $C_{28}H_{29}Cl_3F_2NO_6PS$ [M + Na$^+$] 1:1 704.0379 and 706.0350, found 1:1 704.0379 and 706.0346.

*(+)-Diethyl (Fluoro(2′-fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)(morpholinosulfonyl)methyl)phosphonate and (−)-Diethyl (Fluoro(2′-fluoro-3′-(2,4,5-trichlorobenzyl)-[1,1′-biphenyl]-4-yl)(morpholinosulfonyl)methyl)phosphonate (**85a** and **85b**).* Phosphonate (±)-**85** was separated into enantiomerically pure isomers **85a** (first peak) and **85b** (second peak) with >99% chemical purity and >99% ee using chiral preparatory supercritical fluid chromatography.[59] The racemic compound was loaded as a 5 mg/mL solution in EtOH, with an injection volume of 1.0 mL, onto a ChiralPak AD-H column (2 cm × 25 cm), and eluted with 40% MeOH/CO_2 at 100 bar, with a flow rate of 50 mL/min. Peaks were visualized using UV at 220 nm. Analytical chromatograms were obtained by injecting compound solutions onto a ChiralPak AD-H column (25 cm × 0.46 cm), followed by elution with 40% MeOH/CO_2 at a flow rate of 3 mL/min. Peaks were visualized using UV at 254 nm. See Supporting Information for SFC traces.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.7b01292.

Experimental procedures, SFC traces for **85a** and **85b**, NMR spectra for all inhibitors, dose−response curves for all inhibitors, and X-ray crystallographic details (PDF)
Molecular formula strings (CSV)

Accession Codes

The X-ray crystal structures have been deposited in the Protein Data Bank (**1**, 5OW1; **2**, 5OVR; **3**, 5OVX). Authors will release the atomic coordinates and experimental data upon article publication.

■ AUTHOR INFORMATION

Corresponding Authors

*For J.A.E.: phone, 203-432-3647; E-mail, jonathan.ellman@yale.edu.
*For H.K.: phone, +46 31 7064060; E-mail, helena.kack@astrazeneca.com.

ORCID

Stefan Geschwindner: 0000-0002-2154-8345
Helena Käck: 0000-0002-5456-3269
Jonathan A. Ellman: 0000-0001-9320-5512

Present Address

○For M.S.: Regulatory Project Management, Global Medicines Development, AstraZeneca, Macclesfield, Cheshire SK10 2NA, United Kingdom.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

AcOH, acetic acid; AD, Alzheimer's disease; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; aq, aqueous; CH_2Cl_2, dichloromethane; CNS, central nervous system; CO_2, carbon dioxide; conc, concentrated; CV, column volumes; DME, 1,2-dimethoxyethane; DMF, *N*,*N*-dimethylfor-

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mamide; DMSO, dimethyl sulfoxide; DTT, dithiothreitol; EDTA, ethylenediaminetetraacetic acid; ERK, extracellular signal related kinases; Et_2O, diethyl ether; EtOAc, ethyl acetate; EtOH, ethanol; H_2O, water; HCl, hydrochloric acid; iPr_2NH, diisopropylamine; *i*PrMgCl, isopropylmagnesium chloride; ITC, isothermal titration calorimetry; K_2CO_3, potassium carbonate; KOAc, potassium acetate; LAR, leukocyte common antigen-related protein; LCMS, liquid chromatography/mass spectrometry; LDA, lithium diisopropylamide; LiOH, lithium hydroxide; LMW-Ptp, low molecular weight protein tyrosine phosphatase; LTP, long-term potentiation; MeCN, acetonitrile; MeOH, methanol; MKP5, mitogen-activated protein (MAP) kinase phosphatase 5; MWCO, molecular weight cutoff; N_2, nitrogen; Na_2CO_3, sodium carbonate; $Na_2CO_3 \cdot H_2O$, sodium carbonate monohydrate; Na_2SO_3, sodium sulfite; Na_2SO_4, sodium sulfate; NaCl, sodium chloride; $NaHCO_3$, sodium bicarbonate; $NaHSO_3$, sodium bisulfite; NaOH, sodium hydroxide; *n*-BuLi, *n*-butyllithium; NFSI, *N*-fluorobenzenesulfonimide; NH_4Cl, ammonium chloride; NMDAR, *N*-methyl-D-aspartate receptor; PBS, phosphate-buffered saline; Pd(dppf)-$Cl_2 \cdot CH_2Cl_2$, [1,1′-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) complex with dichloromethane; Pd-$(PPh_3)_4$, tetrakis(triphenylphosphine)palladium(0); *p*NPP, *para*-nitrophenylphosphate; PTP, protein tyrosine phosphatase; PTP1B, protein tyrosine phosphatase 1B; Pyk2, proline-rich tyrosine kinase 2; SAS, substrate activity screening; satd, saturated; STEP, striatal-enriched protein tyrosine phosphatase; TCEP, tris(2-carboxyethyl)phosphine; TC-Ptp, T-cell protein tyrosine phosphatase; TFA, trifluoroacetic acid; THF, tetrahydrofuran

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