A modular approach for the installation of functionalized phosphonates to heterocycles

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Dedicated to Prof. Peter A. Jacobi on the occasion of his retirement from Dartmouth College

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Abstract

Phosphonic acids and esters are pervasive throughout the discovery sciences, from medicine and agriculture, to materials and asymmetric synthesis. The ability to install and construct molecular architecture containing phosphonic functionality has led to the development of new medicines and catalyst systems in the field of organo- and organometallic catalysis. To continue the advancement in the field, improved synthetic access to phosphorous-containing motifs is required. In particular, heterocyclic phosphonates and their acid derivatives are so far underdeveloped. The method described herein provides a robust and operationally simple procedure for the installation of various phosphonates to a wide range of electrophilic heterocycles.

![Chemical reaction diagram]

- Operationally simple
- >20 examples - up to 91% yield
- Modular disconnection
- Pharmaceutically-relevant heterocyclic scaffolds
- Biologically active analogs

Keywords: Phosphonates, heterocycles, S_NAr, transition metal-free, ANRORC

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Introduction

Phosphorus-containing compounds are ubiquitous in nature and have a myriad of uses in medicinal and agricultural chemistry, material sciences, organocatalytic and organometallic chemistry. While phosphonic acids have been regarded as formidable organocatalysts for a variety of Lewis acid-mediated transformations, phosphonates have been shown as useful ligands for organometallic transformations. Phosphonates also serve as practical synthetic reagents for the Horner-Emmons olefination utilized in countless chemical syntheses. Perhaps one of the most well-known and clinically important phosphonates is tenofovir, which is currently prescribed as a treatment for hepatitis B and HIV/AIDS. Other phosphonates, such as in Figure 1, are known to play a role in biological systems by interacting with calcium channels and phosphatases, with fostedil having been developed as a vasodilator for angina and antihypertensive indications.

Utilization of arylmethyl phosphonates transcends clinical applications into material and agricultural sciences, such as spirocyclic bisphosphonate and heterocyclic-containing phosphonates (6 and 7) respectively. The recent report of the anti-tumor activity of 2,6-diaminopyridylmethyl phosphate and the method for its preparation further exemplifies the need for new general methods for the synthesis of heterocyclic analogs. Examples of \( \alpha \)-arylated phosphonates are rather common while heterocyclic \( \alpha \)-arylated phosphonates are scarcely reported or evaluated. The lack of heterocyclic \( \alpha \)-arylated phosphonates can be attributed to an absence of synthetic access to these promising scaffolds.

![Figure 1. Biologically and industrially relevant phosphonate and phosphonic acids.](image)

Classical approaches to phosphonates (alkyl or aryl) rely on the Michaelis-Arbuzov or Michaelis-Becker reactions using trialkyl- or disubstituted phosphites with alkyl halides and extreme thermal conditions or basic conditions, respectively (Figure 2A). More modern methods utilize transition metal catalysis to forge a new C-C bond (red) at the \( \alpha \)-position with aryl halides (Figure 2B). The use of stochiometric metals and excess phosphonate are usually required with one known palladium-catalyzed report using exotic catalytic systems. Despite the advancements in organometallic catalysis for the \( \alpha \)-arylations of phosphonates, the heterocycle scope is still severely limited, hindering access to the heterocyclic \( \alpha \)-arylated phosphonates.
One of the most useful and simple tactics for the installation of heterocyclic motifs is via nucleophilic aromatic substitution (SₐAr). Phosphonates bearing α-hydrogens are capable of undergoing deprotonation with a suitable base to provide anions with the ability to partake in traditional addition and substitution chemistry as well as the HWE olefination. These “enolate-like” phosphonate anions have been used as viable nucleophilic surrogates for SₐAr chemistry (Figure 2C) with a very limited phosphate and electrophile scope, rendering the method useful only for niche applications. In order to broaden the phosphonate heterocyclic chemical space, a robust and operationally simple SₐAr procedure was developed from readily available phosphonates and electrophilic heterocycles.

Results and Discussion

To apply a modular approach toward the synthesis of phosphonate-containing heterocycles, similar to the structures found in Figure 1, a general and, ideally, operationally simple synthetic procedure was required. Screening was conducted on stabilized and non-stabilized phosphonates since both 1) are readily available (most commercially), 2) have a drastic difference in the pKa of the α-protons (>29 to 18) and 3) exhibit utility of the products. A variety of bases and reaction conditions were screened with commercially available phosphonates (Table 1) and 4,6-dichloropyrimidine 24. For methyl phosphonates (lacking anion stabilizing substituents), the base, temperature and reaction time were critical to achieve high consumption of the heterocyclic electrophile (entries 1-6). Interestingly, the order of addition had very little impact on the overall reaction outcomes. For example, the addition of pyrimidine 24 to a preformed phosphate anion at -78 °C...
provided nearly identical product distributions as compared to the addition of base to a mixture of phosphonate and pyrimidine 24 – thus providing an operationally simple procedure.

For non-stabilized phosphonates, NaHMDS proved to be superior (entry 3) to the other bases including LiHMDS (entry 4), KHMS (entry 5) and n-BuLi (entry 6). Although the reaction can occur at -78 °C, low to moderate conversion was observed after 8 hours and the reactions were warmed to room temperature to achieve high conversions and good isolated yield (see experimental section for more information). The optimized equivalents of base and reaction temperatures are depicted in Table 1 for three different phosphonate types used. In each case, 2.2 equivalents of base provided high to full conversion of pyrimidine 24. Phosphonates containing electron stabilizing groups (CO₂Et, benzylic) can undergo the SNAr reaction using NaH at room temperature or 60 °C. For triethyl acetophosphonate (entry 8) NaH as the base was determined to be optimal (75% isolated yield) compared to NaHMDS (entry 7), while diethyl (4-chlorobenzyl)phosphonate gave full consumption with NaHMDS and 91% isolated yield (entry 9) instead of NaH (entry 10).

**Table 1. Optimization of phosphonate SNAr reaction with various phosphonate nucleophiles**

| Entry | R = | R' = | Base    | equivalents | temperature  | conversion | % yield |
|-------|-----|------|---------|-------------|-------------|-----------|---------|
| 1     | Me  | H    | NaHMDS  | 1.1 eq.     | -78 °C to rt | <50%      | -       |
| 2     | Me  | H    | NaHMDS  | 2.2 eq.     | -78 °C      | <50%      | -       |
| 3     | Me  | H    | NaHMDS  | 2.2 eq.     | -78 °C to rt | >90%      | 78%     |
| 4     | Me  | H    | LiHMDS  | 2.2 eq.     | -78 °C to rt | >25%      | -       |
| 5     | Me  | H    | KHMDS   | 2.2 eq.     | -78 °C to rt | ≤75%      | 52%     |
| 6     | Me  | H    | n-BuLi  | 1 eq.       | -78 °C to rt | <50%      | -       |
| 7     | Et  | CO₂Et| NaHMDS  | 2.2 eq.     | 0 to 60 °C  | >25%      | -       |
| 8     | Et  | CO₂Et| NaH     | 2.2 eq.     | 0 to 60 °C  | >75%      | 75%     |
| 9     | Et  | Bn   | NaHMDS  | 2.2 eq.     | -78 °C to rt | >99%      | 91%     |
| 10    | Et  | Bn   | NaH     | 2.2 eq.     | -78 °C to rt | >25%      | -       |

All reactions were performed on 0.25 mmol scale. Reactions were monitored during the given temperature range to determine optimal temperature. Conversion estimated by LC/MS. Isolated yield.

With the optimal conditions in hand, a variety of phosphonate nucleophiles were screened using 4,6-dichloropyrimidine 24 as the heterocyclic electrophile (Figure 2). Three different non-stabilized phosphonate esters (OMe, OEt, OBn) performed well under the optimized reaction conditions and could be subsequently functionalized at the α-position based on the desired application. The commonly used and commercially available triethyl acetophosphonate was employed (as mentioned above) to give the SNAr product 28 in 75%
yield, where the ester functionality provides an additional diversifiable handle for further manipulations (decarboxylation, nucleophilic additions, etc.). Diethyl (cyanomethyl) phosphonate served as a viable nucleophile to afford 30 in an isolated yield of 88%. The increased acidity of the remaining α-proton and stabilization from hydrogen bonding interactions between the N–H and P=O resulted in isolation of a tautomeric form of the S_N_Ar product 25, which was unambiguously determined by single crystal X-ray crystallography. Phosphonates bearing benzylic substituents all performed exceptionally well (31-35) and provide intermediates capable of downstream modifications (e.g. reduction of NO_2 or cross-couplings with sp^2-halides). The use of diethyl (4-fluorobenzyl)phosphonate as a nucleophile is a noteworthy example due its biological implications in calcium channel antagonists such as 2 (Figure 1).

The electrophile scope was expanded to include heterocycles commonly used in drug discovery and material sciences. Triazines, pyrimidines and pyridines make up much of the heterocyclic scaffolds employed within the discovery sciences due to their commercial availability and their use in a wide variety of S_N_Ar and cross-coupling reactions. Therefore, an emphasis was placed on pyrimidine and pyridine scaffolds and their regioselective functionalization as seen in Figure 3. A morpholine-containing triazine, a popular scaffold in medicinal chemistry, underwent the phosphonate S_N_Ar smoothly with a non-stabilized phosphonate to provide 36 in 90% yield. Versatile pyrimidine building block 24 provided 26 in good yield with trimethyl phosphonate. Electron rich 2-chloro-4,6-dimethoxypyrimidine and a 2-naphthyl 4,6-dichloropyrimidine can also undergo the S_N_Ar with trimethyl phosphonate to give 37 and 38 respectively – producing products capable of later functionalization Site-selective reactivity was demonstrated by using 4,6-dichloro-2-(methylsulfonyl)pyrimidine (LG = SO_2Me) (39 and 40) with exclusive substitution at C-2. This regioselective S_N_Ar provides a late-stage intermediate to analogs of known fungicide 6 via pyrimidine 39. Benzyl protected 6-
chloropurine underwent the SₐNAr with triethyl acetophosphonate smoothly to access 41 in moderate yield. A methylene variant of 41 (without CO₂Et) has been previously prepared in 4 steps from commercially available reagents, a stark contrast to the use of phosphonate α-anion SₐNAr. The methylene variant can theoretically be made accessible using an SₐNAr-decarboxylation sequence (2 steps).

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**Figure 4.** Phosphonate electrophile scope for SₐNAr reactions with electrophilic heterocycles. All reactions were performed on 0.25 mmol scale with 2.2 eq. of NaHMDS or NaH. All yields are reported as isolated yields.

Diethyl (4-fluorobenzyl)phosphonate, previously shown to be an exceptional phosphonate nucleophile with pyrimidine 24 (Figure 3, 35), underwent the SₐNAr with 2-chloropyrimidine to give 42 in moderate yield and directly serves as a heterocyclic analog of calcium channel antagonist 2. Electron-deficient pyridines were also excellent substrates for stabilized phosphonate anionic nucleophiles. 2-Chloro-5-trifluoromethyl-, 2,4-dichloro-, and 2,4,6-trichloro-pyridines furnished respectively the phosphonates 43, 44, and 45, which can be further functionalized to extend the breadth of heterocyclic analogs of 2. Regioselectivity in the pyridine series of electrophiles was exploited using fluoride and SO₂Me as leaving groups in the presence of the less suitable chloride leaving groups. Commercially available 4-fluoro-2-chloropyridine gave C-4 selective substitution of...
the fluoride in high yield (44, 80%) with trace amounts of chloride substitution (~5%). Conversely, the SO₂Me was selectively substituted in the presence of two other chloride leaving groups to provide 45 in good yield. Lastly, 2-chlorobenzothiazole proved to be a well-suited electrophile resulting in the direct synthesis of 46, a hybrid analog of fosteril 4 and calcium channel antagonist 2.

A noteworthy example is that of 2-chloro-5-nitropyridine 48, in which an unexpected result occurred when treated with triethyl acetophosphonate 47 and NaH in THF at room temperature (heating to 60 °C accelerated the reaction without diminishment of overall yield, Figure 5). Instead of the expected S_NAr product, the main isolated compound was ring-opened 50 (confirmed by single crystal X-ray structure). The phosphonate anion is thought to undergo an anionic ring-opening ring-closing (ANRORC)-type mechanism, known to occur with 48 in the presence of OH or NH₃. It is proposed that the addition of anionic 47 to C-5 of pyridine 48 leads to stabilized anionic intermediate 52/53 that undergoes a second deprotonation with NaH. The newly formed anion results in C-N bond cleavage and elimination of Cl⁻ to provide a second stabilized anionic intermediate 55/56 that subsequently isomerizes to the more thermodynamically stable phosphonate 50. Further ring-closure that is typical of an ANRORC mechanism did not occur and a sodium salt of phosphonate 50 was isolated in 67% yield.

![Figure 5. The reaction between anionic triethyl acetophosphonate 47 and 2-chloro-5-nitropyridine 48 via a postulated ANRORC-type mechanism.](image)

**Conclusions**

Overall, a robust and modular method for the installation of phosphonates to pharmaceutically-relevant heterocycles via S_NAr has been developed, quickly producing analogs of biologically active substrates. The operationally simple procedure allows for rapid screening and analog development. A range of commercially available phosphonates and electrophilic heterocycles were shown to be compatible as nucleophiles and...
electrophiles, further outlining the usefulness of this method. The results described herein suggest other heterocycles could also serve as viable electrophiles, expanding the overall phosphonate chemical space that can be readily accessed. This method provides a quick and simple route to heterocyclic phosphonates and should prove useful to drug discovery and agricultural chemistry in the future.

Experimental Section

General. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Anhydrous tetrahydrofuran (THF), acetonitrile (MeCN), and dimethylformamide (DMF) were obtained by passing the previously degassed solvent through an activated alumina column (PPT Glass Contour Solvent Purification System). Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous material, unless otherwise stated. Room temperature (rt) refers to ambient temperature in the laboratory (ca. 22–24 °C). Reactions were monitored by LC/MS or thin layer chromatography (TLC) carried out on 250 μm SiliCycle SiliaPlates (TLC Glass-Backed Extra Hard Layer, 60 Å), using shortwave UV light as the visualizing agent and iodine or KMnO4 and heat as developing agents when needed. Flash column chromatography was performed with a Biotage Isolera One (ZIP or SNAP Ultra cartridges) or with traditional glass flash columns using SiliCycle SiliaFlash® P60 (particle size 40–63 μm). NMR spectra were recorded on a Bruker Ascend™ 500 MHz spectrometer or Bruker Neo600 spectrometer and were calibrated using residual undeuterated solvent as an internal reference (CDCl3: 7.26 ppm 1H NMR, 77.16 ppm 13C NMR; DMSO-d6: 2.50 ppm 1H NMR, 39.5 ppm 13C NMR; MeOD: 3.31 ppm 1H NMR, 49.0 ppm 13C NMR). The following abbreviations were used to explain NMR peak multiplicities: s = singlet, d = doublet, t = triplet, p = pentet, dd = doublet of doublets, tt = triplet of triplets, dt = doublet of triplets, td = triplet of doublets, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on an Agilent 6230 LC-MS TOF mass spectrometer using electrospray ionization time-of-flight (ESI-TOF) reflection experiments. Melting points were recorded on a Chemglass DMP 100 melting point apparatus.

Synthesis of phosphonate nucleophiles and heterocyclic electrophiles:
Dibenzyl methylphosphonate (58)

In a septum capped 20 mL reaction vial equipped with a stir bar and argon balloon was added 57 (1.50 g, 5.72 mol, 1 eq.) and MeCN (11.5 mL). The mixture was cooled to 0 °C and MeI (0.391 mL, 6.29 mmol, 1.1 eq.) was added followed by dropwise addition of DBU (0.939 mL, 6.29 mmol, 1.1 eq.). The reaction mixture stirred at 0 °C for 2 hours then warmed to room temperature where it stirred for 10 hours. The reaction mixture was diluted with MeCN (10 mL) and washed with hexanes (25 mL x 2). The MeCN layer was collected and the solvent removed under reduced pressure to give a crude oil that was further purified by silica gel column chromatography using hexanes/EtOAc (0% to 50% EtOAc gradient) to provide 58 (1.12 g, 4.05 mmol, 71% yield) as a clear colorless oil. TLC: Rf = 0.28 (60% EtOAc in hexanes, UV). 1H NMR: (600 MHz, CDCl3) δ 7.43 – 7.29 (m, 10H), 5.06 (dd, J 11.9, 8.8 Hz, 2H), 4.97 (dd, J 11.9, 8.4 Hz, 2H), 1.48 (d, J 17.7 Hz, 3H) ppm. 13C NMR:
(126 MHz, CDCl$_3$) $\delta$ 136.37 (d, $J$ 6.0 Hz), 128.63, 128.43, 127.93, 67.11 (d, $J$ 6.2 Hz), 11.73 (d, $J$ 144.3 Hz). $^{31}$P NMR: (243 MHz, CDCl$_3$) $\delta$ 31.70 ppm.

*Spectroscopic data are in accordance with the literature.\textsuperscript{26}

\textbf{$N$-($4,6$-Dichloro-$1,3,5$-triazin-$2$-yl)morpholine (61)}

\[
\begin{align*}
\text{Cl} & \quad \text{N} & \quad \text{N} & \quad \text{Cl} \\
\text{Cl} & \quad \text{N} & \quad \text{O} & \quad \text{H} \\
\text{59} & & \text{60} & \xrightarrow{\text{Et$_3$N \ DCM, \ -78 \ ^\circ \mathrm{C}}} \text{61} \\
& & & \text{(99\%)}
\end{align*}
\]

In a septum capped 200 mL round-bottomed flask equipped with a stir bar and argon balloon was added 59 (2.00 g, 10.9 mmol, 1 eq.) and DCM (45 mL) then cooled to -78 $^\circ$C. A solution of 60 (0.945 g, 10.9 mmol, 1 eq.) and Et$_3$N (1.51 mL, 10.9 mmol, 1 eq.) in DCM (5 mL) was added dropwise over 5 minutes. The reaction mixture stirred at -78 $^\circ$C for 1 hour then warmed to -30 $^\circ$C over 30 minutes then quenched with saturated aqueous ammonium chloride (70 mL). The aqueous layer was extracted with DCM (4 x 75 mL), combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated to give 61 (2.54 g, 10.8 mmol, 99% yield) as a white solid that was suitably pure by HPLC and NMR to be used in the next step (contaminated with Et$_3$N). TLC: $R_f$ = 0.50 (hexanes/EtOAc, 20% EtOAc, UV). $^1$H NMR: (500 MHz, CDCl$_3$) $\delta$ 3.87 (dd, $J$ 5.7, 4.1 Hz, 2H), 3.74 (dd, $J$ 5.7, 4.1 Hz, 2H) ppm. $^{13}$C NMR: (126 MHz, CDCl$_3$) $\delta$ 170.41, 164.08, 66.38, 44.47 ppm.

*Spectroscopic data are in accordance with the literature.\textsuperscript{45}

\textbf{4,6-Dichloro-$2$-(methylsulfonyl)pyrimidine (62)}

\[
\begin{align*}
\text{Cl} & \quad \text{N} & \quad \text{N} & \quad \text{Cl} \\
\text{Cl} & \quad \text{N} & \quad \text{SMe} & \xrightarrow{\text{mCPBA \ DCM, \ 0 \ ^\circ \mathrm{C}}} \text{62} \\
& & & \text{(quant.)}
\end{align*}
\]

In a 200 mL round-bottomed flask equipped with a stir bar was added 24 (1.95 g, 10 mmol, 1 eq.) and DCM (100 mL) then cooled to 0 $^\circ$C. Once cool, mCPBA (4.6 g, 20 mmol, 2 eq.) was added portionwise, continued to stir at 0 $^\circ$C for 15 minutes then warmed to room temperature where it stirred for 15 hours. The reaction was quenched with saturated aqueous Na$_2$S$_2$O$_3$ (30 mL). The organic layer was washed with saturated aqueous NaHCO$_3$ (3x 30 mL), dried over Na$_2$SO$_4$, filtered and concentrated to provide 62 (2.27 g, 10 mmol, quantitative yield) as a white solid. TLC: $R_f$ = 0.63 (50% EtOAc in hexanes, UV). $^1$H NMR: (500 MHz, CDCl$_3$) $\delta$ 7.62 (s, 1H), 3.38 (s, 3H) ppm. $^{13}$C NMR: (126 MHz, CDCl$_3$) $\delta$ 170.41, 164.08, 66.38, 44.47 ppm.

*Spectroscopic data are in accordance with the literature.\textsuperscript{46}

\textbf{4,6-Dichloro-$2$-(1-naphthyl)pyrimidine (65)}

\[
\begin{align*}
\text{Cl} & \quad \text{N} & \quad \text{Cl} \\
\text{Cl} & \quad \text{N} & \quad \text{B} & \xrightarrow{\text{Pd(PPh$_3$)$_2$Cl$_2$, \ K$_2$CO$_3$, \ toluene, \ 90 \ ^\circ \mathrm{C}}} \text{65} \\
& & & \text{(90\%)}
\end{align*}
\]
In a septum-capped 50 mL round-bottomed flask equipped with a stir bar and argon balloon was added 63 (0.521 g, 1.89 mmol, 1 eq.), 64 (0.326 g, 1.89 mmol, 1 eq.), K₂CO₃ (0.524 g, 3.79 mmol, 2 eq.) and Pd(PPh₃)₂Cl₂ (0.067 g, 0.095 mmol, 0.05 eq.). Toluene (19 mL) was added and the reaction mixture degassed using a flow of argon for 5 minutes. The reaction was heated 90 °C for 3 hours then cooled to room temperature. Water (20 mL) was added and the aqueous layer extracted with EtOAc (3 x 25 mL), combined organic layers were dried over Na₂SO₄, filtered and concentrated. Further purification using silica gel column chromatography using hexanes/EtOAc (0% to 10% EtOAc gradient) provided 65 (0.469 g, 1.70 mmol, 90% yield) as a beige solid. TLC: Rf = 0.74 (10% EtOAc in hexanes, UV). ¹H NMR: (500 MHz, CDCl₃) δ 8.79 (d, J = 8.6 Hz, 1H), 8.23 (dd, J = 7.2, 1.3 Hz, 1H), 8.02 (d, J = 6.7 Hz, 1H), 7.64 – 7.52 (m, 3H), 7.40 (s, 1H) ppm. ¹³C NMR: (126 MHz, CDCl₃) δ 167.74, 161.77, 134.09, 132.62, 132.29, 130.79, 130.74, 128.73, 127.61, 126.23, 125.28, 125.06, 118.70 ppm. HRMS: Calc’d for C₁₄H₉Cl₂N₂ [M+H⁺] 275.0137; found 275.0141.

2,6-Dichloro-4-methylsulfonylpyridine (68)

In a septum capped 30 mL vial equipped with a stir bar and argon balloon was added 66 (1.0 g, 5.5 mmol, 1 eq.) and MeOH (9.2 mL). An aqueous solution of NaSMe (2.93 mL, 8.77 mmol, 21% wt) was added and the argon balloon was removed. The resulting reaction mixture stirred at room temperature for 10 hours. Water (4 mL) was added and the reaction stirred for 5 minutes at which time a white precipitate was formed and collected by filtration. The collected solid was dried to give 67 (0.930 g, 4.79 mmol, 87% yield) as a white solid that was used in the next step without further purification or characterization.

In a 30 mL septum capped vial equipped with a stir bar was added 67 (0.810 g, 4.17 mmol, 1 eq.) and DCM (14 mL) then cooled to 0 °C. mCPBA (1.92 g, 8.35 mmol, 75% wt) was added portionwise and the resulting reaction mixture stirred at 0 °C for 15 minutes before warming to room temperature where it stirred for 8 hours. The reaction mixture was filtered through a sintered glass funnel, dried over MgSO₄, filtered and concentrated. Further purification by silica gel column chromatography using hexanes/EtOAc (0% to 15% EtOAc gradient) provided 68 (0.910 g, 4.03 mmol, 96% yield) as a white solid. TLC: Rf = 0.29 (20% EtOAc in hexanes, UV). ¹H NMR: (500 MHz, CDCl₃) δ 7.76 (s, 2H), 3.13 (s, 3H) ppm. ¹³C NMR: (126 MHz, CDCl₃) δ 152.99, 152.47, 120.23, 43.90 ppm. HRMS: Calc’d for C₆H₆Cl₂NO₂S [M+H⁺] 225.9491; found 225.9501.

9-Benzyl-6-chloropurine (70)

In a septum capped 50 mL round-bottomed flask equipped with a stir bar and argon balloon was added 69 (1.0 g, 6.5 mmol, 1 eq.) followed by K₂CO₃ (1.78 g, 12.9 mmol, 2 eq.) and MeCN (26 mL). Benzyl bromide (BnBr) (1.32 g, 0.922 mL, 7.36 mmol, 1.2 eq.) was added dropwise to the stirring reaction mixture at room temperature. The reaction continued to stir at room temperature for 42 hours at which time the solvent was removed under reduced pressure and the crude oil was taken up in DCM (60 mL). A solution of saturated
aqueous NH₄Cl (50 mL) was added and the aqueous layer extracted with DCM (4 x 50 mL). The organic layer was washed with a brine solution (35 mL), dried over Na₂SO₄, filtered and concentrated. Further purification by silica gel column chromatography using hexanes/EtOAc (0% to 40% EtOAc gradient) provided 70 (1.1 g, 4.5 mmol, 70% yield) as a light-yellow solid. TLC: Rf = 0.39 (50% EtOAc in hexanes, UV). ¹H NMR: (500 MHz, CDCl₃) δ 8.79 (s, 1H), 8.09 (s, 1H), 7.38 – 7.30 (m, 5H), 5.46 (s, 2H). NMR sample contained residual solvent.

*Spectroscopic data is in accordance with the literature.*

**Phosphonate nucleophile scope**

**General phosphonate SₐAr procedures**

**General Procedure 1 (GP-1) with NaHMDS.** In a 2-dram septum capped reaction vial equipped with a stir bar and argon balloon was added phosphonates of a general structure 24 (0.275 mmol, 1.1 eq.) and pyrimidine 24 (0.250 mmol, 1 eq.) along with THF (2.5 mL, 0.1 M). The solution was cooled to -78 °C and NaHMDS (0.275 mL, 0.550 mmol, 2.2 eq., 2 M in THF) was added. The reactions were monitored at -78 °C and warmed to room temperature when needed (see reaction times below). Once full consumption or no further consumption was observed (monitored by TLC and LC/MS), the reactions were quenched with saturated aqueous NH₄Cl (8 mL) and water (5 mL). The aqueous layer was extracted with EtOAc or DCM (15 mL x 4), dried over Na₂SO₄, filtered and concentrated. Further purification by silica gel column chromatography using hexanes/EtOAc or DCM/MeOH provided the desired products.

**General Procedure 2 (GP-2) with NaH.** In a 2-dram septum capped reaction vial equipped with a stir bar and argon balloon was added phosphonates of a general structure 24 (0.275 mmol, 1.1 eq.) and pyrimidine 24 (1 eq., 0.250 mmol) along with THF (2.5 mL, 0.1 M). The reaction mixtures were cooled to 0 °C then NaH (2.2 eq., 60% wt) was added. The reactions were stirred at 0 °C for 5 minutes before warming to room temperature then heated to 60 °C, if required (see below for reaction temperatures and times). Once full consumption or no further consumption was observed (monitored by TLC and LC/MS), the reactions were quenched with saturated aqueous NH₄Cl (8 mL) and water (5 mL). The aqueous layer was extracted with EtOAc or DCM (15 mL x 4), dried over Na₂SO₄, filtered and concentrated. Further purification by silica gel column chromatography using hexanes/EtOAc, DCM/MeOH or EtOAc/MeOH provided the desired products.

**Dimethyl [6-chloro-2-(methylthio)pyrimidin-4-yl]methylphosphonate (26)**

*GP-1 was used with commercially available dimethyl methylphosphonate. After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 1 hour. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 60% EtOAc gradient) to give 26 (55.0 mg, 0.195 mmol, 78% yield) as a light-yellow oil. TLC: Rf = 0.15 (60% EtOAc in hexanes, UV). ¹H NMR:
(500 MHz, CDCl₃) δ 7.04 (d, J 2.3 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.28 (d, J 22.4 Hz, 2H), 2.55 (s, 3H) ppm. ¹³C NMR: (151 MHz, CDCl₃) δ 173.65, 162.88 (d, J 7.8 Hz), 161.23, 116.29 (d, J 4.9 Hz), 53.20 (d, J 6.5 Hz), 35.07 (d, J 134.5 Hz), 14.32 ppm. ³¹P NMR: (243 MHz, CDCl₃) δ 24.71 ppm. HRMS: Calc’d for C₈H₁₂ClN₂O₃PSNa [M+Na⁺] 304.9887; found 304.9888.

Diethyl [6-chloro-2-(methylthio)pyrimidin-4-yl]methylphosphonate (27)

GP-1 was used with commercially available diethyl methylphosphonate. After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 2 hours. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 60% EtOAc gradient) to give 27 (54.0 mg, 0.174 mmol, 69% yield) as a yellow oil. TLC: Rf = 0.18 (60% EtOAc in hexanes, UV). ¹H NMR: (500 MHz, CDCl₃) δ 7.05 (d, J 2.3 Hz, 1H), 4.16–4.08 (m, 4H), 3.27 (d, J 22.4 Hz, 2H), 2.56 (s, 3H), 1.31 (t, J 7.3 Hz, 7H) ppm. ¹³C NMR: (126 MHz, CDCl₃) δ 173.53 (d, J 2.3 Hz), 163.25 (d, J 7.7 Hz), 161.08 (d, J 2.3 Hz), 116.33 (d, J 4.5 Hz), 62.69 (d, J 6.8 Hz), 36.04 (d, J 133.9 Hz), 16.33 (d, J 6.2 Hz) 14.26 ppm. HRMS: Calc’d for C₂₀H₂₁ClN₂O₃PS [M+H⁺] 435.0694; found 435.0695.

Dibenzyl [6-chloro-2-(methylthio)pyrimidin-4-yl]methylphosphonate (28)

GP-1 was used with previously synthesized 58. After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 2 hours. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 60% EtOAc gradient) to give 28 (77.0 mg, 0.177 mmol, 71% yield) as a clear colorless oil. TLC: Rf = 0.34 (40% EtOAc in hexanes, UV). ¹H NMR: (500 MHz, CDCl₃) δ 7.38–7.33 (m, 6H), 7.32–7.27 (m, 4H), 6.88 (d, J 2.3 Hz, 1H), 5.08 (dd, J 11.7, 9.1 Hz, 2H), 4.98 (dd, J 11.7, 8.6 Hz, 2H), 3.26 (d, J 22.6 Hz, 2H), 2.48 (s, 3H) ppm. ¹³C NMR: (126 MHz, CDCl₃) δ 173.53 (d, J 1.8 Hz), 162.74 (d, J 7.6 Hz), 161.03 (d, J 6.0 Hz), 128.68, 128.06, 116.35 (d, J 4.8 Hz), 68.12 (d, J 6.4 Hz), 36.40 (d, J 134.3 Hz), 14.22 ppm. ³¹P NMR: (243 MHz, CDCl₃) δ 23.10 ppm. HRMS: Calc’d for C₂₀H₂₁ClN₂O₃PS [M+H⁺] 435.0694; found 435.0695.

Ethyl (2-diethoxyphosphonyl-2-[6-chloro-(2-methylthio)pyrimidin-4-yl]acetate (29)
GP-2 was used with commercially available ethyl 2-(diethoxyphosphoryl)acetate. After reaching room temperature, the reaction was heated to 60 °C for 15 hours. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 50% EtOAc gradient) to give 29 (72.0 mg, 0.188 mmol, 75% yield) as a clear colorless oil. TLC: R_f = 0.22 (40% EtOAc in hexanes, UV). 1H NMR: (500 MHz, CDCl_3) δ 7.45 (d, J 2.1 Hz, 1H), 4.45 (d, J 24.0 Hz, 1H), 4.21 – 4.09 (m, 4H), 2.54 (s, 3H), 1.33 – 1.26 (m, 9H) ppm.

13C NMR: (126 MHz, CDCl_3) δ 173.19, 165.42 (d, J 5.6 Hz), 161.94 (d, J 6.8 Hz), 161.17 (d, J 2.2 Hz), 160.17 (d, J 16.8 Hz), 63.89 (d, J 6.8 Hz), 63.73 (d, J 6.7 Hz), 62.53, 54.44 (d, J 128.0 Hz), 16.27 (d, J 3.4 Hz), 16.22 (d, J 3.3 Hz), 14.26, 14.02 ppm.

31P NMR: (243 MHz, CDCl_3) δ 15.30 ppm.

HRMS: Calc’d for C_{13}H_{21}ClN_2O_5PS [M+H+] 383.0591; found 383.0591.

2-(Diethoxyphosphonyl)-2-[6-chloro-2-(methylthio)pyrimidin-4-ylidene]acetonitrile (30)

GP-2 was used with commercially available diethyl (cyanomethyl)phosphonate. After reaching room temperature, the reaction was heated to 60 °C for 11 hours. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 40% EtOAc gradient) to give 30 (74.0 mg, 0.220 mmol, 88% yield) as a yellow crystalline solid. TLC: R_f = 0.48 (5% MeOH in DCM, UV). M.P. = 164 °C.

1H NMR: (500 MHz, CDCl_3) δ 13.31 (s, 1H), 6.78 (t, J 0.9 Hz, 1H), 4.19 – 4.09 (m, 4H), 2.61 (s, 3H), 1.38 (td, J 7.1, 0.8 Hz, 6H) ppm.

13C NMR: (126 MHz, CDCl_3) δ 162.78, 159.69 (d, J 8.2 Hz), 156.53 (d, J 3.1 Hz), 117.08 (d, J 7.5 Hz), 107.87 (d, J 14.3 Hz), 63.44 (d, J 5.8 Hz), 53.94 (d, J 206.8 Hz), 16.14 (d, J 6.9 Hz), 13.75 ppm.

31P NMR: (243 MHz, CDCl_3) δ 20.25 ppm.

HRMS: Calc’d for C_{11}H_{15}ClN_3O_3PSNa [M+Na+] 358.0152; found 358.0143.

Diethyl 2-(4-nitrophenyl)-2-[6-chloro-2-(methylthio)pyrimidin-4-yl]methylphosphonate (31)

GP-2 was used with commercially available diethyl (4-nitrobenzyl)phosphonate. After reaching room temperature, the reaction continued stirring for 6 hours. Purified by silica gel column chromatography using hexanes/EtOAc (10% to 35% EtOAc gradient) to give 31 (86.0 mg, 0.199 mmol, 80% yield) as a clear colorless oil. TLC: R_f = 0.26 (40% EtOAc in hexanes, UV). 1H NMR: (500 MHz, CDCl_3) δ 8.21 (d, J 8.2 Hz, 2H), 7.76 (dd, J 8.9, 2.0 Hz, 2H), 7.22 (d, J 1.5 Hz, 1H), 4.60 (d, J 24.2 Hz, 1H), 4.15 – 3.91 (m, 4H), 2.55 (s, 3H), 1.24 (t, J 7.1 Hz, 3H), 1.18 (t, J 7.0 Hz, 3H) ppm. 13C NMR: (126 MHz, CDCl_3) δ 173.93, 165.14 (d, J 4.9 Hz), 161.57, 147.61 (d, J 14.7 Hz), 140.78 (d, J 6.8 Hz), 130.89 (d, J 6.9 Hz), 123.75 (d, J 2.2 Hz), 116.00 (d, J 5.3 Hz), 63.74 (d, J 6.9 Hz), 63.34 (d, J 7.2 Hz), 53.05 (d, J 136.3 Hz), 16.30 (d, J 5.7 Hz) ppm.

31P NMR: (243 MHz, CDCl_3) δ 19.59 ppm.

HRMS: Calc’d for C_{16}H_{20}ClN_3O_5PS [M+H+] 432.0544; found 432.0542.
Diethyl 2-(4-iodophenyl)-2-[6-chloro-2-(methylthio)pyrimidin-4-yl]methylphosphonate (32)

GP-1 was used with commercially available diethyl (4-iodobenzyl)phosphonate. After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour. The dry-ice bath was removed and the reaction quenched after 10 minutes. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 20% EtOAc gradient) to give 32 (0.105 g, 0.205 mmol, 82% yield) as a clear colorless oil. TLC: Rf = 0.40 (40% EtOAc in hexanes, UV). 1H NMR: (500 MHz, CDCl 3 ) δ 7.68 (dd, J 8.7, 0.8 Hz, 2H), 7.31 (dd, J 8.5, 2.0 Hz, 2H), 7.20 (d, J 1.5 Hz, 1H), 4.43 (d, J 24.1 Hz, 1H), 4.13 – 3.88 (m, 4H), 2.55 (s, 3H), 1.23 (t, J 6.8 Hz, 3H), 1.16 (t, J 6.8 Hz, 3H) ppm. 13C NMR: (126 MHz, CDCl 3 ) δ 173.57, 166.17 (d, J 3.8 Hz), 161.36, 137.89 (d, J 2.3 Hz), 133.18 (d, J 6.8 Hz), 131.71 (d, J 7.3 Hz), 115.85 (d, J 5.1 Hz), 93.97 (d, J 3.2 Hz), 63.59 (d, J 6.8 Hz), 63.04 (d, J 7.1 Hz), 52.81 (d, J 137.1 Hz), 16.32 (d, J 1.7 Hz), 16.28 (d, J 1.6 Hz), 14.36 ppm. 31P NMR: (243 MHz, CDCl 3 ) δ 20.51 ppm. HRMS: Calc’d for C 16 H 20 ClIN 2 O 3 PS [M+H + ] 512.9660; found 512.9657.

Diethyl 2-(3-bromophenyl)-2-[6-chloro-2-(methylthio)pyrimidin-4-yl]methylphosphonate (33)

GP-1 was used with commercially available diethyl (3-bromobenzyl)phosphonate. After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 1 hour. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 20% EtOAc gradient) to give 33 (99.0 mg, 0.212 mmol, 85% yield) as a clear colorless oil. TLC: Rf = 0.45 (40% EtOAc in hexanes, UV). 1H NMR: (500 MHz, CDCl 3 ) δ 7.73 (dd, J 1.9 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.47 – 7.41 (m, 1H), 7.23 (d, J 7.9 Hz, 1H), 7.20 (d, J 1.7 Hz, 1H), 4.45 (d, J 24.2 Hz, 1H), 4.09 – 3.91 (m, 4H), 2.56 (s, 3H), 1.23 (t, J 7.1 Hz, 3H), 1.16 (t, J 7.1 Hz, 3H) ppm. 13C NMR: (126 MHz, CDCl 3 ) δ 173.61, 165.94 (d, J 4.1 Hz), 161.34, 135.53 (d, J 6.8 Hz), 132.94 (d, J 7.3 Hz), 131.19 (d, J 2.7 Hz), 130.20 (d, J 2.3 Hz), 122.60 (d, J 1.8 Hz), 115.95 (d, J 5.0 Hz), 63.62 (d, J 7.3 Hz), 63.09 (d, J 6.8 Hz), 52.84 (d, J 137.1 Hz), 16.38 – 16.17 (m) 14.38 ppm. 31P NMR: (243 MHz, CDCl 3 ) δ 20.42 ppm. HRMS: Calc’d for C 16 H 20 BrClN 2 O 3 PS [M+H + ] 464.9799; found 464.9798.
Diethyl 2-(4-chlorophenyl)-2-[6-chloro-2-(methylthio)pyrimidin-4-yl]methylphosphonate (34)

GP-1 was used with commercially available diethyl (4-chlorobenzyl)phosphonate. After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 2 hours. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 40% EtOAc gradient) to give 34 (96.0 mg, 0.227 mmol, 91% yield) as a clear colorless oil. TLC: Rf = 0.26 (40% EtOAc in hexanes, UV). 1H NMR: (500 MHz, CDCl3) δ 7.50 (dd, J 8.6, 2.0 Hz, 2H), 7.32 (d, J 8.5 Hz, 2H), 7.20 (d, J 1.5 Hz, 1H), 4.47 (d, J 24.1 Hz, 1H), 4.14 – 3.85 (m, 4H), 2.54 (s, 3H), 1.22 (t, J 7.1 Hz, 3H), 1.15 (t, J 7.1 Hz, 3H) ppm.

13C NMR: (126 MHz, CDCl3) δ 173.56, 166.27 (d, J 3.7 Hz), 161.34, 134.17 (d, J 2.9 Hz), 131.95 (d, J 6.7 Hz), 131.17 (d, J 7.4 Hz), 128.94 (d, J 1.8 Hz), 115.85 (d, J 5.2 Hz), 63.57 (d, J 6.9 Hz), 63.02 (d, J 7.2 Hz), 52.60 (d, J 137.1 Hz), 16.31 (d, J 2.4 Hz), 16.26 (d, J 2.2 Hz), 14.34 ppm. 31P NMR: (243 MHz, CDCl3) δ 20.68 ppm. HRMS: Calc’d for C16H20Cl2N2O3PS [M+Na+] 421.0304; found 421.0296.

Diethyl 2-(4-fluorophenyl)-2-[6-chloro-2-(methylthio)pyrimidin-4-yl]methylphosphonate (35)

GP-1 was used with commercially available diethyl (4-fluorobenzyl)phosphonate. After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 1 hour. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 40% EtOAc gradient) to give 35 (84.0 mg, 0.207 mmol, 83% yield) as a clear colorless oil. TLC: Rf = 0.32 (40% EtOAc in hexanes, UV). 1H NMR: (500 MHz, CDCl3) δ 7.57 – 7.51 (m, 2H), 7.21 (d, J 1.6 Hz, 1H), 7.07 – 7.01 (m, 2H), 4.49 (d, J 24.2 Hz, 1H), 4.11 – 3.85 (m, 4H), 2.55 (s, 3H), 1.23 (t, J 7.3 Hz, 3H), 1.14 (t, J 7.4 Hz, 3H) ppm. 13C NMR: (126 MHz, CDCl3) δ 173.52, 166.27 (d, J 3.7 Hz), 161.34, 134.17 (d, J 2.9 Hz), 131.95 (d, J 6.7 Hz), 131.17 (d, J 7.4 Hz), 128.94 (d, J 1.8 Hz), 115.85 (d, J 5.2 Hz), 63.57 (d, J 6.9 Hz), 63.02 (d, J 7.2 Hz), 52.60 (d, J 137.1 Hz), 16.31 (d, J 2.4 Hz), 16.26 (d, J 2.2 Hz), 14.34 ppm. 19F NMR: (471 MHz, CDCl3) δ -113.88 (d, J 3.5 Hz) ppm. 31P NMR: (243 MHz, CDCl3) δ 20.68 ppm. HRMS: Calc’d for C16H20ClF2N2O3PS [M+H+] 405.0598; found 405.0598.
**Phosphonate SNAr Electrophile Scope**

*GP-1 and GP-2 were used. The phosphonates and heterocyclic electrophiles used are described below.

**Dimethyl (4-chloro-6-morpholino-1,3,5-triazinyl-2-yl)methylphosphonate (36)**

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\text{GP-1 was used with previously synthesized 61 and commercially available dimethyl methylphosphonate. After the addition of NaHMDS, the reaction stirred at } -78 \, ^\circ\text{C for 1 hour then warmed to room temperature where it stirred for an additional 1 hour. Purified by silica gel column chromatography using DCM/MeOH (0% to 5% MeOH gradient) to give 36 (73.0 mg, 0.226 mmol, 90% yield) as a light-yellow oil. TLC: } R_f = 0.44 \, (5\% \text{ MeOH in DCM}, \text{UV}). \text{ }^1H \text{ NMR: (500 MHz, CDCl}_3 \gamma 3.92 - 3.88 \, (m, \, 2H), 3.86 - 3.83 \, (m, \, 2H), 3.82 \, (s, \, 3H), 3.79 \, (s, \, 3H), 3.74 - 3.72 \, (m, \, 4H), 3.31 \, (s, \, 1H), 3.26 \, (s, \, 1H) \, ppm.} \text{ }^{13}C \text{ NMR: (126 MHz, CDCl}_3 \gamma 172.26 \, (d, \, J 7.1 \, Hz), 170.49, 164.27, 66.45, 53.18 \, (d, \, J 6.4 \, Hz), 44.14, 43.92, 36.80 \, (d, \, J 133.9 \, Hz) \, ppm.} \text{ }^{31}P \text{ NMR: (243 MHz, CDCl}_3 \gamma 24.65 \, ppm.} \text{ HRMS: Calc’d for C}_{10}H_{16}ClN_4O_4PNa [M+Na^+] 345.0490; found 345.0489.}
\]

**Dimethyl (4,6-dimethoxypyrimidin-2-yl)methylphosphonate (37)**

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\text{GP-1 was used with commercially available diethyl (4-chlorobenzyl)phosphonate and 2-chloro-4,6-dimethoxypyrimidine. After the addition of NaHMDS, the reaction stirred at } -78 \, ^\circ\text{C for 1 hour then warmed to room temperature where it stirred for an additional 15 hours. Purified by silica gel column chromatography using DCM/MeOH (0% to 10% MeOH gradient) to give 37 (37.0 mg, 0.141 mmol, 56% yield) as a light-yellow oil. TLC: } R_f = 0.28 \, (5\% \text{ MeOH in DCM}, \text{UV}). \text{ }^1H \text{ NMR: (500 MHz, CDCl}_3 \gamma 5.91 \, (d, \, J 1.8 \, Hz, \, 1H), 3.93 \, (s, \, 6H), 3.81 \, (s, \, 3H), 3.79 \, (s, \, 3H), 3.43 \, (d, \, J 22.2 \, Hz, \, 2H) \, ppm.} \text{ }^{13}C \text{ NMR: (126 MHz, CDCl}_3 \gamma 171.46 \, (d, \, J 1.8 \, Hz), 161.86 \, (d, \, J 8.4 \, Hz), 87.87 \, (d, \, J 2.8 \, Hz), 54.15, 52.89 \, (d, \, J 6.2 \, Hz), 36.75 \, (d, \, J 133.8 \, Hz) \, ppm.} \text{ }^{31}P \text{ NMR: (243 MHz, CDCl}_3 \gamma 26.66 \, ppm.} \text{ HRMS: Calc’d for C}_{15}H_{16}ClN_2O_5P [M+H^+] 263.0791; found 263.0789.}
\]
Dimethyl [6-chloro-2-(1-naphthyl)pyrimidin-4-yl]methylphosphonate (38)

GP-1 was used with commercially available dimethyl methylphosphonate and previously synthesized 65 (4,6-dichloro-2-(naphthalen-1-yl)pyrimidine). After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 1 hour. Purified by silica gel column chromatography using DCM/MeOH (0% to 2% MeOH gradient) to give 38 (44.0 mg, 0.135 mmol, 48% yield) as a golden oil. TLC: Rf = 0.25 (80% EtOAc in hexanes, UV). 1H NMR: (500 MHz, CDCl3) δ 8.72 (dd, J 8.7, 1.2 Hz, 1H), 8.13 (dd, J 7.2, 1.4 Hz, 1H), 8.01 – 7.97 (m, 1H), 7.93 – 7.90 (m, 1H), 7.60 – 7.51 (m, 3H), 7.40 (d, J 2.3 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.49 (d, J 22.4 Hz, 2H) ppm. 13C NMR: (126 MHz, CDCl3) δ 167.48 (d, J 2.7 Hz), 163.00 (d, J 8.2 Hz), 161.65 (d, J 2.7 Hz), 134.07 (d, J 6.8 Hz), 131.42, 130.87, 130.08, 128.58, 127.11, 126.06, 125.62, 125.12, 121.00 (d, J 4.5 Hz), 119.04 (d, J 5.0 Hz), 53.22 (d, J 6.4 Hz), 35.35 (d, J 134.4 Hz) ppm. 31P NMR: (243 MHz, CDCl3) δ 24.98 ppm. HRMS: Calc’d for C17H17ClN2O3P [M+H+] 363.0660; found 363.0661.

Diethyl [4-chlorophenyl]-2-(4,6-dichloropyrimidin-2-yl)methylphosphonate (39)

GP-1 was used with commercially available diethyl (4-chlorobenzyl)phosphonate and previously synthesized 62 (4,6-dichloro-2-(methylsulfonyl)pyrimidine). After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 20 minutes. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 40% EtOAc gradient) to give 39 (72.0 mg, 0.175 mmol, 70% yield) as a clear colorless oil. TLC: Rf = 0.22 (40% EtOAc in hexanes, UV). 1H NMR: (500 MHz, CDCl3) δ 7.57 (dd, J 8.7, 2.2 Hz, 2H), 7.33 – 7.30 (m, 2H), 7.30 (d, J 1.3 Hz, 1H), 7.30 (d, J 1.3 Hz, 1H), 4.81 (d, J 23.6 Hz, 1H), 4.20 – 4.02 (m, 4H), 1.29 – 1.21 (m, 6H) ppm. 13C NMR: (126 MHz, CDCl3) δ 167.01 (d, J 5.0 Hz), 162.05, 134.05 (d, J 3.4 Hz), 131.68 (d, J 8.2 Hz), 131.31 (d, J 6.5 Hz), 128.70 (d, J 2.2 Hz), 119.80, 63.98 (d, J 6.7 Hz), 62.95 (d, J 7.1 Hz), 54.58 (d, J 136.8 Hz), 16.37 (d, J 5.9 Hz), 16.27 (d, J 6.0 Hz) ppm. 31P NMR: (243 MHz, CDCl3) δ 19.52 ppm. HRMS: Calc’d for C15H17Cl3N2O3P [M+H+] 409.0037; found 409.0035.
Ethyl [2-diethoxyphosphonyl-2-(4,6-dichloropyrimidin-4-yl)acetate (40)

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{Cl} & \quad \text{Cl} \\
\text{CO}_2\text{Et} & \quad \text{N} \quad \text{N} \\
\end{align*}
\]

\text{GP-2} \text{ was used with commercially available ethyl 2-(diethoxyphosphoryl)acetate and previously synthesized 62 (4,6-dichloro-2-(methylsulfonyl)pyrimidine). After reaching room temperature, the reaction heated to 60 °C for 12 hours. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 40% EtOAc gradient) to give 40 (69.0 mg, 0.186 mmol, 74% yield) as a clear colorless oil that solidified upon standing. TLC: Rf = 0.42 (60% EtOAc in hexanes, UV).}^{1} \text{H NMR: (600 MHz, CDCl}_3) \delta 7.33 (d, J 1.2 Hz, 1H), 4.72 (d, J 23.1 Hz, 1H), 4.43 – 4.21 (m, 6H), 1.38 – 1.31 (m, 6H), 1.27 (t, J 7.1 Hz, 3H) ppm.}^{13} \text{C NMR: (151 MHz, CDCl}_3) \delta 165.18 (d, J 5.5 Hz), 163.63 (d, J 6.3 Hz), 162.03, 120.13, 64.32 (d, J 6.4 Hz), 63.58 (d, J 6.5 Hz), 62.40, 56.10 (d, J 133.3 Hz), 16.34 (t, J 7.4 Hz), 14.01 ppm.}^{31} \text{P NMR: (243 MHz, CDCl}_3) \delta 15.02 ppm.} \text{HRMS: Calc'd for C}_{12}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_5\text{P [M+H}^+\text{]} 371.0325; found 371.0322.

Ethyl (2-diethoxyphosphonyl)-2-(9-benzylpyrimidin-6-yl)acetate (41)

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{CO}_2\text{Et} & \quad \text{N} \\
\text{Bn} & \quad \text{F} \\
\end{align*}
\]

\text{GP-2 was used with commercially available ethyl 2-(diethoxyphosphoryl)acetate and previously synthesized 70 (9-benzyl-6-chloro-9H-purine). After reaching room temperature, the reaction heated to 60 °C for 18 hours. Purified by silica gel column chromatography using DCM/MeOH (0% to 5% MeOH gradient) to give 41 (71.0 mg, 0.164 mmol, 66% yield) as a clear colorless oil. TLC: Rf = 0.2 (5% MeOH in DCM, UV) \text{.}^{1} \text{H NMR: (500 MHz, CDCl}_3) \delta 9.03 (s, 1H), 8.03 (s, 1H), 7.38 – 7.30 (m, 5H), 5.43 (s, 2H), 5.38 (d, J 23.3 Hz, 1H), 4.38 – 4.28 (m, 2H), 4.27 – 4.19 (m, 4H), 1.30 – 1.23 (m, 9H) ppm.}^{13} \text{C NMR: (126 MHz, CDCl}_3) \delta 165.72 (d, J 4.6 Hz), 152.53 (d, J 2.1 Hz), 152.15 (d, J 8.1 Hz), 151.59, 144.53, 134.86, 132.90 (d, J 6.4 Hz), 129.22, 128.74, 128.02, 63.71 (d, J 6.3 Hz), 63.41 (d, J 6.4 Hz), 62.19, 49.57 (d, J 134.9 Hz), 47.48, 16.44 – 16.20 (m), 14.02 ppm.}^{31} \text{P NMR: (243 MHz, CDCl}_3) \delta 16.24.} \text{HRMS: Calc'd for C}_{20}\text{H}_{24}\text{N}_4\text{O}_5\text{P [M+H}^+\text{]} 433.1635; found 433.1634.

Diethyl (4-fluorophenyl)(2-pyrimidinyl)methylphosphonate (42)

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{F} & \quad \text{N} \\
\text{CO}_2\text{Et} & \quad \text{N} \\
\end{align*}
\]

\text{GP-1 was used with commercially available diethyl (4-fluorobenzyl)phosphonate and 2-chloropyrimidine. After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it}
stirred for an additional 15 hours. Purified by silica gel column chromatography using DCM/MeOH (0% to 5% MeOH gradient) to give 42 (44.0 mg, 0.135 mmol, 54% yield) as a yellow oil. TLC: Rf = 0.35 (5% MeOH in DCM, UV). 1H NMR: (600 MHz, CDCl3) δ 8.77 (d, J 4.9 Hz, 2H), 7.66 (ddq, J 10.6, 5.3, 3.2 Hz, 2H), 7.23 (td, J 4.9, 1.2 Hz, 1H), 7.02 (t, J 8.6 Hz, 2H), 4.95 (d, J 23.6 Hz, 1H), 4.14 – 3.96 (m, 4H), 1.18 (t, J 7.1 Hz, 6H) ppm.

13C NMR: (151 MHz, CDCl3) δ 166.13, 161.59, 157.45, 131.73 (d, J 7.6 Hz), 129.86 (d, J 4.6 Hz), 119.46, 115.37 (d, J 21.8 Hz), 63.26 (d, J 7.1 Hz), 62.80 (d, J 7.6 Hz), 54.40 (d, J 138.4 Hz), 16.34, 16.30 ppm.

19F NMR: (564 MHz, CDCl3) δ -114.82 (d, J 5.0 Hz) ppm.

31P NMR: (243 MHz, CDCl3) δ 21.85 ppm.

HRMS: Calc’d for C15H18FN3O3PNa [M+Na]+ 347.0931; found 347.0931.

Diethyl (4-fluorophenyl)(5-trifluoropyrimidin-2-yl)methylphosphonate (43)

GP-1 was used with commercially available diethyl (4-fluorobenzyl)phosphonate and 2-chloro-5-(trifluoromethyl)pyridine. After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 30 minutes. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 40% EtOAc gradient) to give 43 (79.0 mg, 0.201 mmol, 81% yield) as a clear colorless oil. TLC: Rf = 0.29 (40% EtOAc in hexanes, UV). 1H NMR: (500 MHz, CDCl3) δ 8.82 (dt, J 1.7, 0.8 Hz, 1H), 7.88 (dd, J 8.3, 2.4 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.59 – 7.53 (m, 2H), 7.06 – 6.98 (m, 2H), 4.76 (d, J 24.3 Hz, 1H), 4.12 – 3.89 (m, 4H), 1.19 – 1.13 (m, 6H) ppm. 13C NMR: (151 MHz, CDCl3) δ 163.16, 161.52, 160.66, 146.27 (d, J 4.6 Hz), 134.04, 131.34 (t, J 7.8 Hz), 130.55, 126.29 – 122.39 (m), 123.69 (d, J 5.1 Hz), 115.70 (d, J 21.5 Hz), 63.33 (d, J 7.0 Hz), 62.75 (d, J 7.1 Hz), 53.08 (d, J 138.2 Hz), 16.29, 16.25 ppm. 19F NMR: (471 MHz, CDCl3) δ -62.43, -114.51 (d, J 3.6 Hz) ppm. 31P NMR: (243 MHz, CDCl3) δ 22.43 ppm. HRMS: Calc’d for C17H19F4NO3P [M+H]+ 392.1033; found 392.1037.

Diethyl (4-fluorophenyl)-(2-chloropyridin-4-yl)methylphosphonate (44)

GP-1 was used with commercially available diethyl (4-fluorobenzyl)phosphonate and 2-chloro-4-fluoropyridine. After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 1 hour. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 40% EtOAc gradient) to give 44 (72.0 mg, 0.201 mmol, 80% yield) as a clear colorless oil. *A small amount of the other SnAr regioisomer was detected and was inseparable from the major product.
TLC: $R_f = 0.27$ (30% EtOAc in hexanes, UV). $^1$H NMR: (500 MHz, CDCl$_3$) δ 8.32 (d, J 5.2 Hz, 1H), 7.45 (dd, J 8.9, 5.2, 1.9 Hz, 2H), 7.42 (t, J 1.8 Hz, 1H), 7.38 (dt, J 5.2, 1.7 Hz, 1H), 7.05 (t, J 8.2 Hz, 2H), 4.35 (d, J 25.0 Hz, 1H), 4.07 – 3.94 (m, 3H), 3.89 – 3.79 (m, 1H), 1.19 (t, J 7.1 Hz, 3H), 1.12 (t, J 7.2 Hz, 3H) ppm. $^{13}$C NMR: (126 MHz, CDCl$_3$) δ 163.38 (d, J 2.3 Hz), 161.41 (d, J 2.7 Hz), 151.90, 149.82, 149.11 (d, J 4.5 Hz), 131.17 (t, J 7.9 Hz), 130.32 (dd, J 5.9, 3.6 Hz), 124.79 (d, J 8.2 Hz), 123.03 (d, J 6.8 Hz), 115.99 (d, J 21.3 Hz), 63.42 (d, J 6.8 Hz), 62.92 (d, J 7.3 Hz), 49.59 (d, J 139.4 Hz), 16.27 (d, J 3.2 Hz), 16.23 (d, J 2.7 Hz) ppm. $^{19}$F NMR: (471 MHz, CDCl$_3$) δ -113.82 (d, J 3.5 Hz) ppm. $^{31}$P NMR: (243 MHz, CDCl$_3$) δ 22.28 ppm. HRMS: Calc’d for C$_{16}$H$_{19}$ClFNO$_3$P [M+H$^+$] 358.0770; found 358.0776.

Diethyl (2,6-dichloropyridin-4-yl)(4-fluorophenyl)methylphosphonate (45)

GP-1 was used with commercially available diethyl (4-fluorobenzyl)phosphonate and previously synthesized 68 (2,6-dichloro-4-(methylsulfonyl)pyridine). After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 2 hours. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 40% EtOAc gradient) to give 45 (69.0 mg, 0.171 mmol, 68% yield) as a white solid. TLC: $R_f = 0.59$ (60% EtOAc in hexanes, UV). $^1$H NMR: (500 MHz, CDCl$_3$) δ 7.44 (ddt, J 7.0, 5.2, 1.9 Hz, 2H), 7.38 (dd, J 1.8, 0.6 Hz, 2H), 7.11 – 7.04 (m, 2H), 4.33 (d, J 25.0 Hz, 1H), 4.11 – 3.96 (m, 3H), 3.87 – 3.77 (m, 1H), 1.23 (td, J 7.0, 0.4 Hz, 3H), 1.12 (td, J 7.0, 0.7 Hz, 3H) ppm. $^{13}$C NMR: (126 MHz, CDCl$_3$) δ 163.51 (d, J 2.7 Hz), 161.53 (d, J 2.7 Hz), 151.65 (d, J 4.5 Hz), 150.80, 131.20 (t, J 7.9 Hz), 129.70 (dd, J 5.9, 3.2 Hz), 123.37 (d, J 7.3 Hz), 122.27, 116.18 (d, J 21.3 Hz), 63.65 (d, J 6.8 Hz), 63.00 (d, J 6.8 Hz), 49.38 (d, J 139.9 Hz), 16.26 (t, J 5.7 Hz) ppm. $^{19}$F NMR: (471 MHz, CDCl$_3$) δ -113.29 (d, J 2.6 Hz) ppm. $^{31}$P NMR: (243 MHz, CDCl$_3$) δ 21.60 HRMS: Calc’d for C$_{16}$H$_{18}$ClFNO$_3$P [M+H$^+$] 392.0380; found 392.0380.

Diethyl (benzotriazol-2-yl)(4-fluorophenyl)methylphosphonate (46)

GP-1 was used with commercially available diethyl (4-fluorobenzyl)phosphonate and 2-chlorobenzothiazole. After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 1 hour. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 60% EtOAc gradient) to give 46 (77.0 mg, 0.203 mmol, 81% yield) as a clear colorless oil. TLC: $R_f = 0.20$ (40% EtOAc in hexanes, UV). $^1$H NMR: (600 MHz, CDCl$_3$) δ 8.02 (d, J 8.2 Hz, 1H), 7.82 (dd, J 8.0, 1.2 Hz, 1H), 7.65
Ethyl 6-cyano-2-(diethoxyphosphoryl)-4-(sodionitrilyl)hexa-2,5-dienoate (50)

GP-2 was used with commercially available ethyl 2-(diethoxyphosphoryl)acetate and 2-chloro-5-nitropyridine. After reaching room temperature, the reaction stirred for 15 hours (heating the reaction to 60 °C for 12 hours did not appear to change the reaction profile. Purified by silica gel column chromatography using EtOAc/MeOH (0% to 10% MeOH gradient) to give 50 (58.0 mg, 0.168 mmol, 67% yield) as an orange oil that solidified upon standing. Recrystallization using THF afforded a yellow crystalline solid. TLC: Rf = 0.2 (10% MeOH in EtOAc, UV). M.P. = > 300 °C. 1H NMR: (600 MHz, MeOD) δ 7.93 (d, J 23.6 Hz, 1H), 7.22 (d, J 16.0 Hz, 1H), 5.84 (d, J 16.0 Hz, 1H), 4.23 (q, J 7.1 Hz, 2H), 4.12 (apparent p, J 7.1 Hz, 4H), 1.37 – 1.31 (m, 9H) ppm. 13C NMR: (151 MHz, MeOD) δ 166.86 (d, J 15.2 Hz, 1H), 143.61 (d, J 10.9 Hz), 141.61, 121.06, 120.45 (d, J 21.4 Hz), 106.44 (d, J 19.8 Hz), 84.78, 62.42 (d, J 5.3 Hz), 60.67, 15.19 (d, J 6.4 Hz), 13.24 ppm. 31P NMR: (243 MHz, MeOD) δ 20.12 ppm. HRMS: Calc’d for C13H20N2O7P [M+H+] 347.1003; found 347.1010.

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Supplementary Material

Copies of 1H, 13C, 19F, and 31P NMR are available in the supplementary material. X-Ray crystallographic data for compound 30 (CCDC 2060587) and 50 (CCDC 2061157) are included.

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