

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

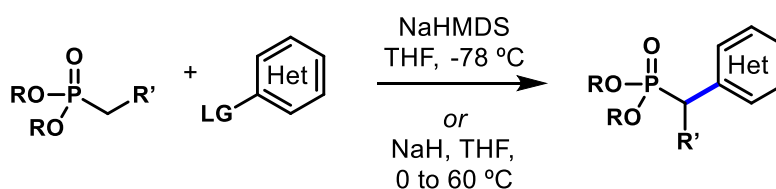
Received 02-05-2021

Accepted 03-07-2021

Published on line 03-11-2021

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.



- Operationally simple
- >20 examples - up to 91% yield
- no transition metals required
- Modular disconnection
- Pharmaceutically-relevant heterocyclic scaffolds

[Biologically active analogs]

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

Introduction

Phosphorus-containing compounds are ubiquitous in nature and have a myriad of uses in medicinal and agricultural chemistry,¹⁻³ material sciences,^{4,5} organocatalytic and organometallic chemistry.⁶⁻¹⁰ While phosphonic acids have been regarded as formidable organocatalysts for a variety of Lewis acid-mediated transformations,^{11,12} phosphonates have been shown as useful ligands for organometallic transformations.⁹ Phosphonates also serve as practical synthetic reagents for the Horner-Wadsworth-Emmons (HWE) olefination utilized in countless chemical syntheses.¹³ Perhaps one of the most well-known and clinically important phosphonates is tenofovir (**1**, Viread), which is currently prescribed as a treatment for hepatitis B and HIV/AIDS.^{14,15} Other phosphonates, such as **2-4** in Figure 1, are known to play a role in biological systems by interacting with calcium channels and phosphatases,^{16,17} with fostedil (**4**) having been developed as a vasodilator for angina and antihypertensive indications.^{18,19}

Utilization of arylmethyl phosphonates transcends clinical applications into material and agricultural sciences, such as spirocyclic bisphosphonate (**5**)⁵ and heterocyclic-containing phosphonates (**6** and **7**)^{20,21} respectively. The recent report of the anti-tumor activity of 2,6-diaminopyridylmethyl phosphonate **8**,²² and the method for its preparation,^{23,24} further exemplifies the need for new general methods for the synthesis of heterocyclic analogs. Examples of α -arylated phosphonates (**2-5** and **7**) are rather common while heterocyclic α -arylated phosphonates (**6** and **8**) are scarcely reported or evaluated. The lack of heterocyclic α -arylated phosphonates can be attributed to an absence of synthetic access to these promising scaffolds.

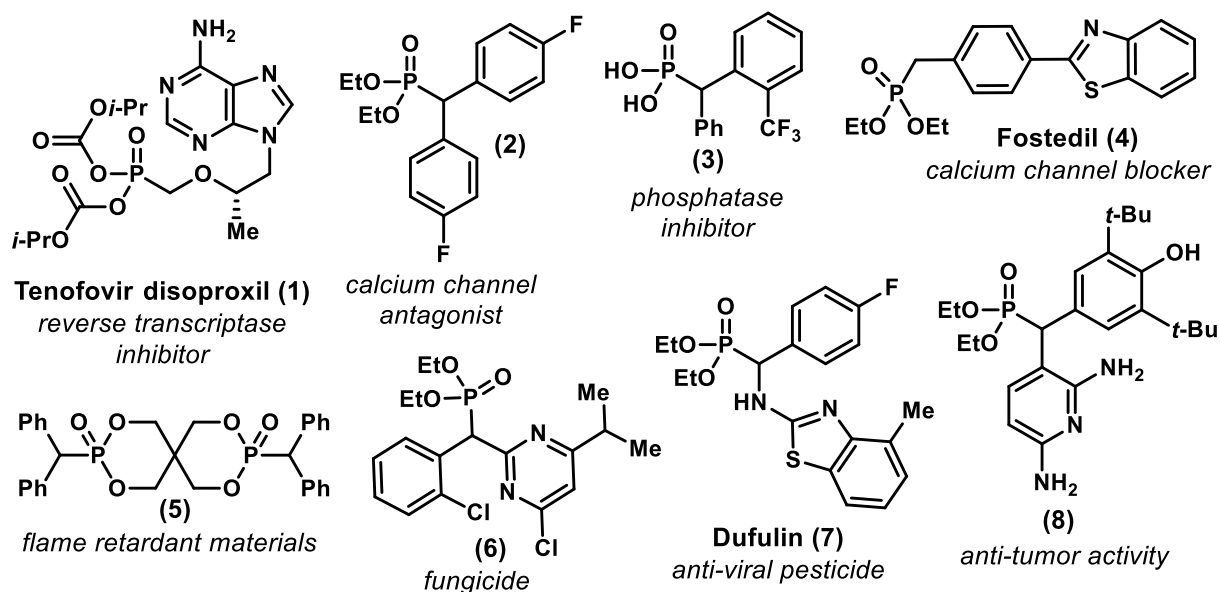


Figure 1. Biologically and industrially relevant phosphonate and phosphonic acids.

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).^{25,26} More modern methods utilize transition metal catalysis to forge a new C-C bond (red) at the α -position with aryl halides (Figure 2B).²⁷⁻³¹ The use of stoichiometric metals and excess phosphonate are usually required with one known palladium-catalyzed report using exotic catalytic systems.³¹ Despite the advancements in organometallic catalysis for the α -arylations of phosphonates, the heterocycle scope is still severely limited, hindering access to the heterocyclic α -arylated phosphonates.

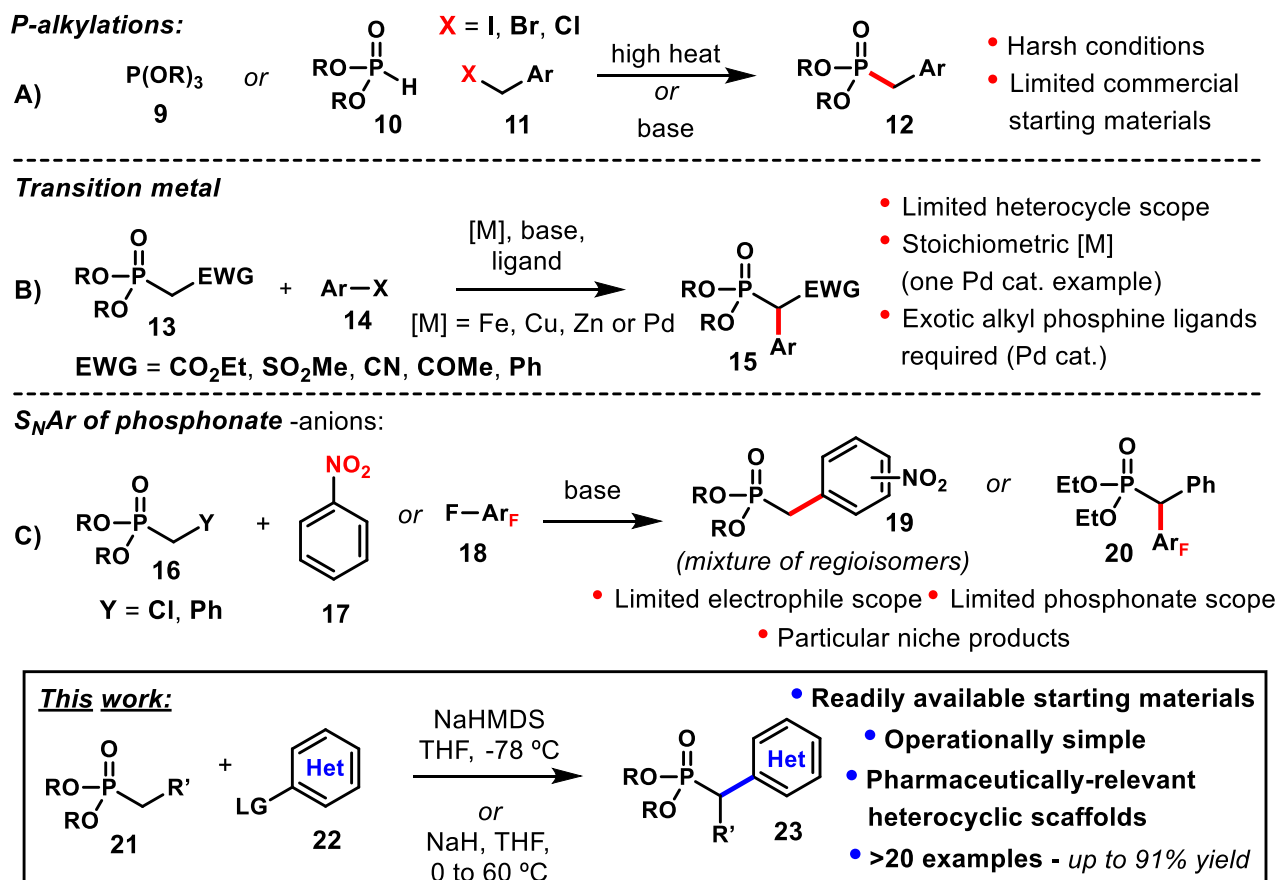


Figure 2. Classical and modern methods for preparing α -arylated phosphonates compared to this work.

One of the most useful and simple tactics for the installation of heterocyclic motifs is via nucleophilic aromatic substitution ($\text{S}_{\text{N}}\text{Ar}$). 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.³²⁻³⁴ These “enolate-like” phosphonate anions have been used as viable nucleophilic surrogates for $\text{S}_{\text{N}}\text{Ar}$ chemistry (Figure 2C) with a very limited phosphonate and electrophile scope,^{35,36} rendering the method useful only for niche applications. In order to broaden the phosphonate heterocyclic chemical space, a robust and operationally simple $\text{S}_{\text{N}}\text{Ar}$ procedure was developed from readily available phosphonates and electrophilic heterocycles.

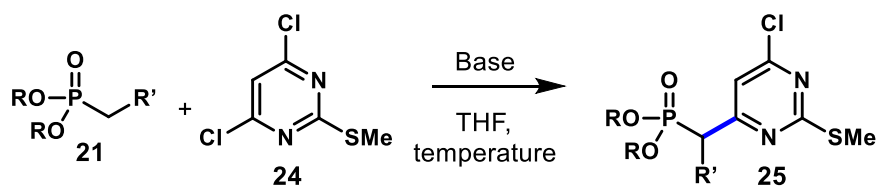
Results and Discussion

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)^{37,38} 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 phosphonate 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), KHMDS (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 S_NAr 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 S_NAr reaction with various phosphonate nucleophiles



Entry	R =	R' =	Base	equivalents	temperature ^a	conversion ^b	% yield ^c
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	<i>n</i> -BuLi	1 eq.	-78 °C to rt	<50%	-
7	Et	CO ₂ Et	NaHMDS	2.2 eq.	0 to 60 °C	>25%	-
8	Et	CO ₂ Et	NaH	2.2 eq.	0 to 60 °C	>75%	75%
9	Et	Bn (4-Cl)	NaHMDS	2.2 eq.	-78 °C to rt	99%	91%
10	Et	Bn (4-Cl)	NaH	2.2 eq.	-78 °C to rt	>25%	-

All reactions were performed on 0.25 mmol scale. ^aReactions were monitored during the given temperature range to determine optimal temperature. ^bConversion estimated by LC/MS. ^cIsolated 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 S_NAr 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_NAr product **25**, which was unambiguously determined by single crystal X-ray crystallography.³⁹ 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 to its biological implications in calcium channel antagonists such as **2** (Figure 1).

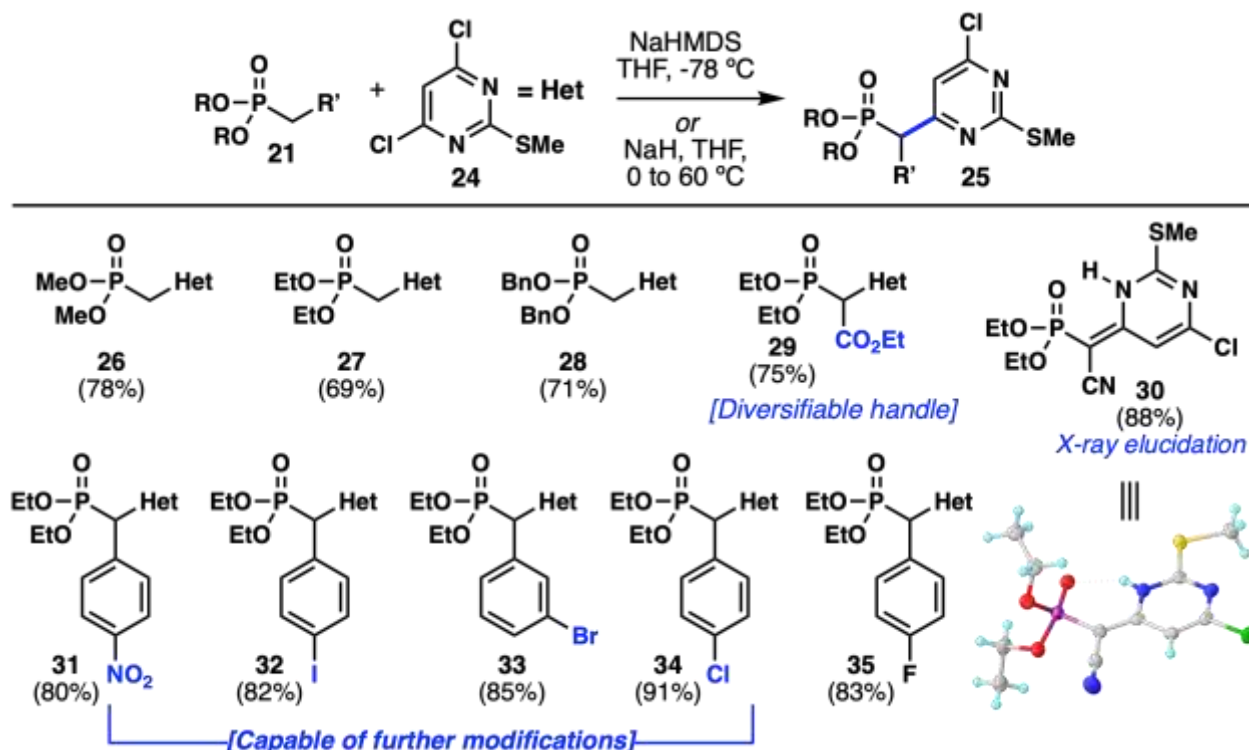


Figure 3. Phosphonate nucleophile scope for S_NAr reactions with pyrimidine **24**. All reactions were performed on 0.25 mmol scale with 2.2 eq. of NaHMDS or NaH. All yields are reported as isolated yields.

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_NAr and cross-coupling reactions.⁴⁰ 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,⁴¹ underwent the phosphonate S_NAr 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_NAr 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_NAr provides a late-stage intermediate to analogs of known fungicide **6** via pyrimidine **39**. Benzyl protected 6-

chloropurine underwent the S_NAr with triethyl acetophosphonate smoothly to access **41** in moderate yield. A methylene variant of **41** (without CO_2Et) has been previously prepared in 4 steps from commercially available reagents,⁴² a stark contrast to the use of phosphonate α -anion S_NAr . The methylene variant can theoretically be made accessible using an S_NAr -decarboxylation sequence (2 steps).

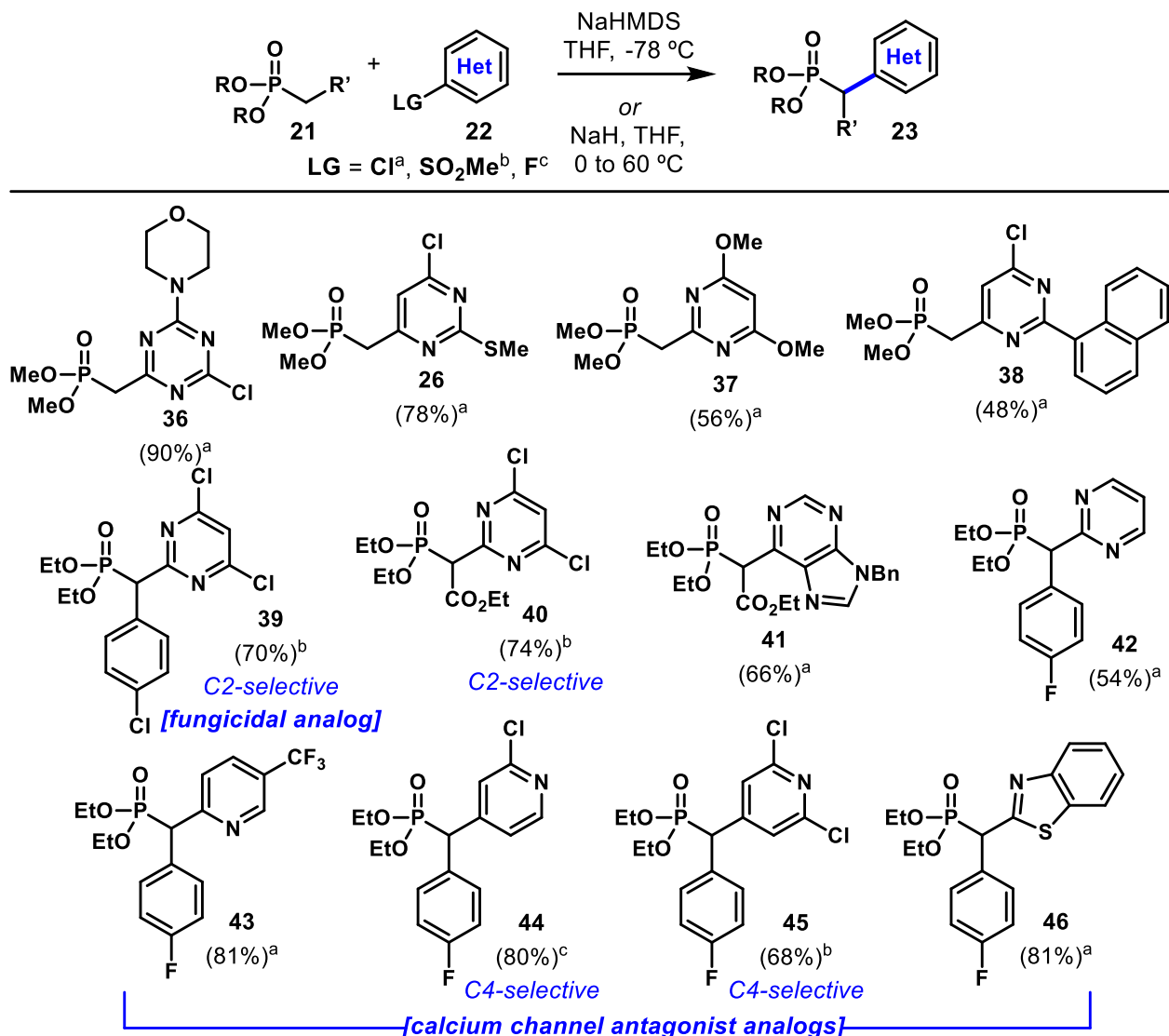


Figure 4. Phosphonate electrophile scope for S_NAr reactions with electrophilic heterocycles. All reactions were performed on 0.25 mmol scale with 2.2 eq. of NaHMDS or NaH. All yields are reported as isolated yields.

Diethyl (4-fluorobenzyl)phosphonate, previously shown to be an exceptional phosphonate nucleophile with pyrimidine **24** (Figure 3, **35**), underwent the S_NAr 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 SO_2Me 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 fostedil **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.^{43,44} 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.

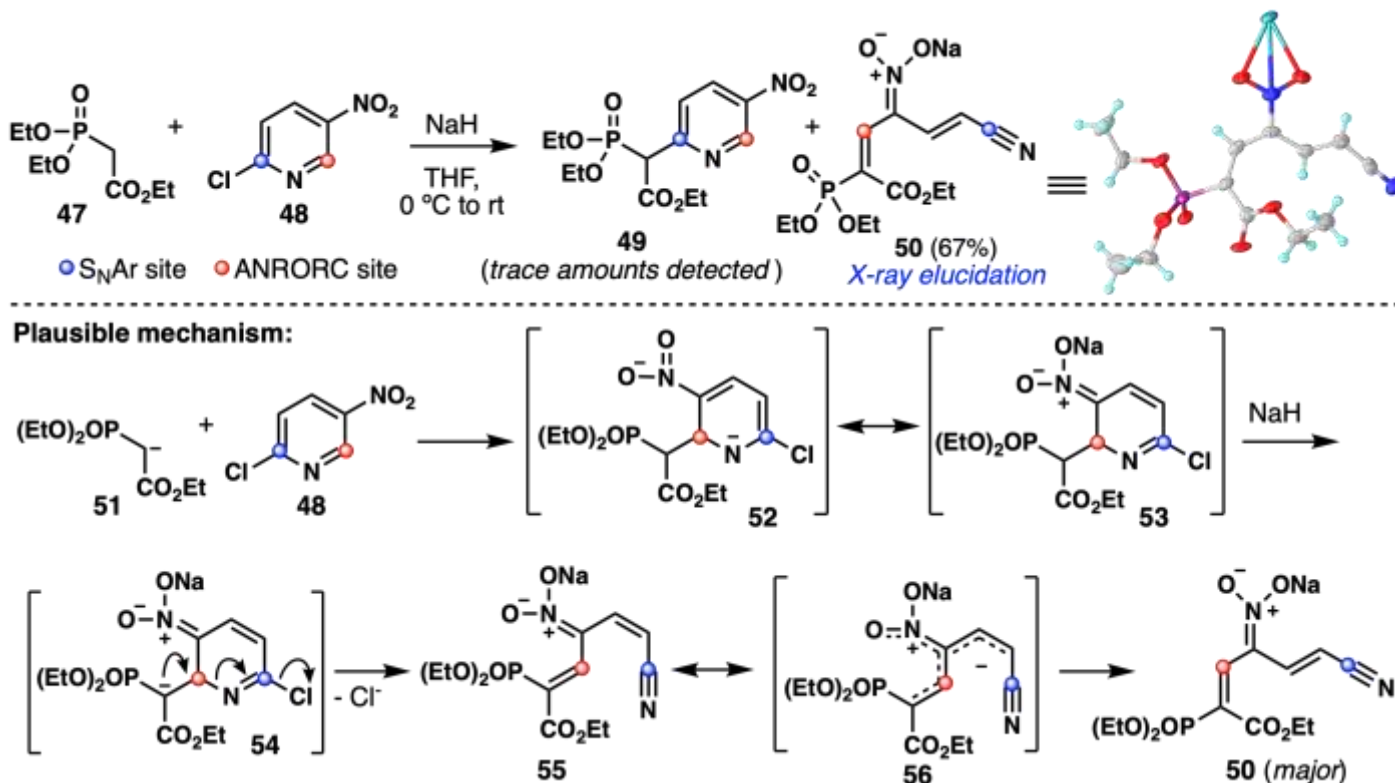


Figure 5. The reaction between anionic triethyl acetophosphonate **47** and 2-chloro-5-nitropyridine **48** via a postulated ANRORC-type mechanism.

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

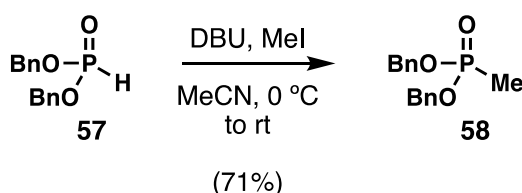
electrophiles, further outlining the usefulness of this method. The results described herein suggest other heterocycles could also serve as viable electrophiles, expanding the overall phosphonate chemical space that can be readily accessed. This method provides a quick and simple route to heterocyclic 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 KMnO_4 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 (CDCl_3 : 7.26 ppm ^1H NMR, 77.16 ppm ^{13}C NMR; $\text{DMSO}-d_6$: 2.50 ppm ^1H NMR, 39.5 ppm ^{13}C NMR; MeOD: 3.31 ppm ^1H NMR, 49.0 ppm ^{13}C 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**)

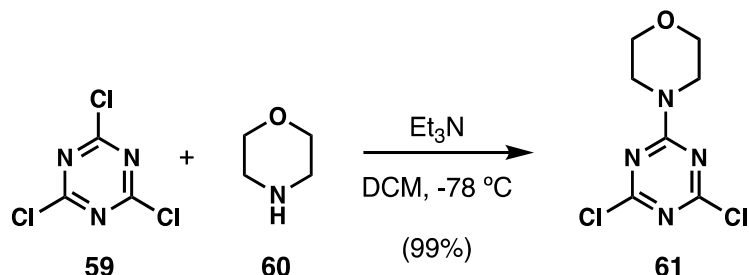


In a septum capped 20 mL reaction vial equipped with a stir bar and argon balloon was added **57** (1.50 g, 5.72 mol, 1 eq.) and MeCN (11.5 mL). The mixture was cooled to 0 °C and MeI (0.391 mL, 6.29 mmol, 1.1 eq.) was added followed by dropwise addition of DBU (0.939 mL, 6.29 mmol, 1.1 eq.). The reaction 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: R_f = 0.28 (60% EtOAc in hexanes, UV). ^1H NMR: (600 MHz, CDCl_3) 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. ^{13}C NMR:

(126 MHz, CDCl_3) δ 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) δ 31.70 ppm.

*Spectroscopic data are in accordance with the literature.²⁶

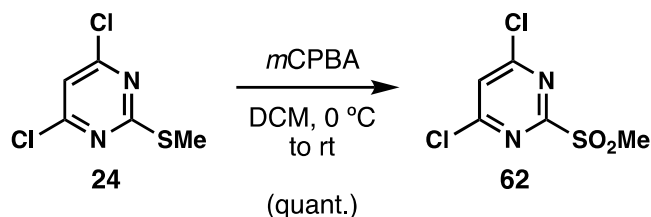
***N*-(4,6-Dichloro-1,3,5-triazin-2-yl)morpholine (61)**



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 °C. A solution of **60** (0.945 g, 10.9 mmol, 1 eq.) and Et_3N (1.51 mL, 10.9 mmol, 1 eq.) in DCM (5 mL) was added dropwise over 5 minutes. The reaction mixture stirred at -78 °C for 1 hour then warmed to -30 °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_2SO_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_3N). TLC: R_f = 0.50 (hexanes/ EtOAc , 20% EtOAc , UV). ^1H NMR: (500 MHz, CDCl_3) δ 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) δ 170.41, 164.08, 66.38, 44.47 ppm.

*Spectroscopic data are in accordance with the literature.⁴⁵

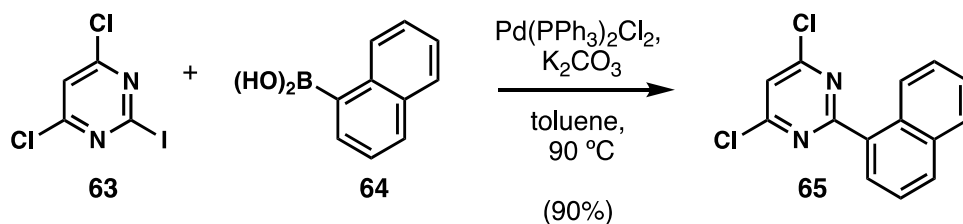
4,6-Dichloro-2-(methylsulfonyl)pyrimidine (62)



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 °C. Once cool, *m*CPBA (4.6 g, 20 mmol, 2 eq.) was added portionwise, continued to stir at 0 °C for 15 minutes then warmed to room temperature where it stirred for 15 hours. The reaction was quenched with saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (30 mL). The organic layer was washed with saturated aqueous NaHCO_3 (3x 30 mL), dried over Na_2SO_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). ^1H NMR: (500 MHz, CDCl_3) δ 7.62 (s, 1H), 3.38 (s, 3H) ppm. ^{13}C NMR: (126 MHz, CDCl_3) δ 166.01, 163.89, 124.50, 39.17 ppm.

*Spectroscopic data are in accordance with the literature.⁴⁶

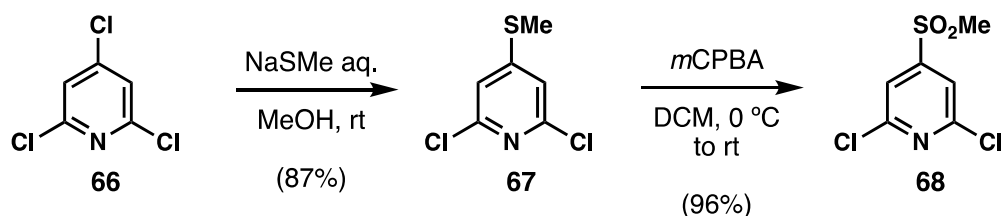
4,6-Dichloro-2-(1-naphthyl)pyrimidine (65)



In a septum-capped 50 mL round-bottomed flask equipped with a stir bar and argon balloon was added **63**⁴⁷ (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: R_f = 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* 8.3 Hz, 1H), 7.92 (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.

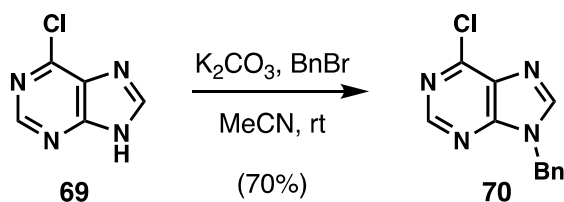
2,6-Dichloro-4-methylsulfonylpyridine (**68**)



In a septum capped 30 mL vial equipped with a stir bar and an 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. *m*CPBA (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: R_f = 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**)



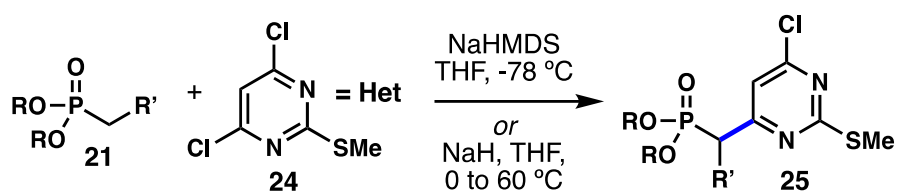
In a septum capped 50 mL round-bottomed flask equipped with a stir bar and argon balloon was added **69** (1.0 g, 6.5 mmol, 1 eq.) followed by K₂CO₃ (1.78 g, 12.9 mmol, 2 eq.) and MeCN (26 mL). Benzyl bromide (BnBr) (1.32 g, 0.922 mL, 7.36 mmol, 1.2 eq.) was added dropwise to the stirring reaction mixture 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 NH_4Cl (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 Na_2SO_4 , 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: $R_f = 0.39$ (50% EtOAc in hexanes, UV). ^1H NMR: (500 MHz, CDCl_3) 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.⁴⁸

Phosphonate nucleophile scope

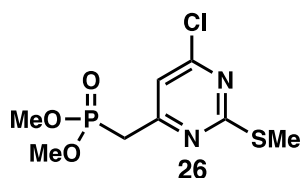
General phosphonate $\text{S}_\text{N}\text{Ar}$ procedures



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 **21** (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 $-78\text{ }^\circ\text{C}$ and NaHMDS (0.275 mL, 0.550 mmol, 2.2 eq., 2 M in THF) was added. The reactions were monitored at $-78\text{ }^\circ\text{C}$ 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 NH_4Cl (8 mL) and water (5 mL). The aqueous layer was extracted with EtOAc or DCM (15 mL x 4), dried over Na_2SO_4 , 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 to **21** (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 $0\text{ }^\circ\text{C}$ then NaH (2.2 eq., 60% wt) was added. The reactions were stirred at $0\text{ }^\circ\text{C}$ for 5 minutes before warming to room temperature then heated to $60\text{ }^\circ\text{C}$, 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 NH_4Cl (8 mL) and water (5 mL). The aqueous layer was extracted with EtOAc or DCM (15 mL x 4), dried over Na_2SO_4 , filtered and concentrated. Further purification by silica gel column chromatography using hexanes/EtOAc, DCM/MeOH or EtOAc/MeOH provided the desired products.

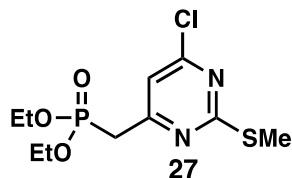
Dimethyl [6-chloro-2-(methylthio)pyrimidin-4-yl]methylphosphonate (**26**)



GP-1 was used with commercially available dimethyl methylphosphonate. After the addition of NaHMDS, the reaction stirred at $-78\text{ }^\circ\text{C}$ for 1 hour then warmed to room temperature where it stirred for an additional 1 hour. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 60% EtOAc gradient) to give **26** (55.0 mg, 0.195 mmol, 78% yield) as a light-yellow oil. TLC: $R_f = 0.15$ (60% EtOAc in hexanes, UV). ^1H NMR:

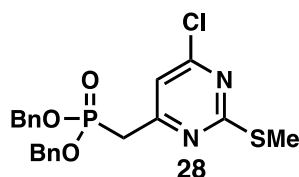
(500 MHz, CDCl₃) δ 7.04 (d, *J* 2.3 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.28 (d, *J* 22.4 Hz, 2H), 2.55 (s, 3H) ppm. ¹³C NMR: (151 MHz, CDCl₃) δ 173.65, 162.88 (d, *J* 7.8 Hz), 161.23, 116.29 (d, *J* 4.9 Hz), 53.20 (d, *J* 6.5 Hz), 35.07 (d, *J* 134.5 Hz), 14.32 ppm. ³¹P NMR: (243 MHz, CDCl₃) δ 24.71 ppm. HRMS: Calc'd for C₈H₁₂ClN₂O₃PSNa [M+Na⁺] 304.9887; found 304.9888.

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



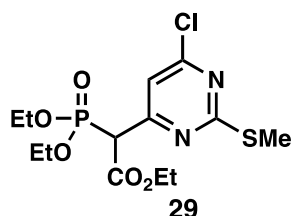
GP-1 was used with commercially available diethyl methylphosphonate. After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 2 hours. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 60% EtOAc gradient) to give **27** (54.0 mg, 0.174 mmol, 69% yield) as a yellow oil. TLC: *R*_f = 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⁺] 311.0381; found 311.0382.

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



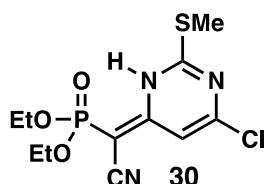
GP-1 was used with previously synthesized **58**. After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 2 hours. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 60% EtOAc gradient) to give **28** (77.0 mg, 0.177 mmol, 71% yield) as a clear colorless oil. TLC: *R*_f = 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 173.54 (d, *J* 1.8 Hz), 162.74 (d, *J* 7.6 Hz), 161.03 (d, *J* 2.3 Hz), 135.75 (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**)



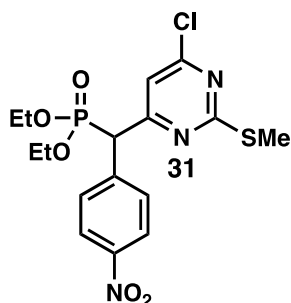
GP-2 was used with commercially available ethyl 2-(diethoxyphosphoryl)acetate. After reaching room temperature, the reaction was heated to 60 °C for 15 hours. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 50% EtOAc gradient) to give **29** (72.0 mg, 0.188 mmol, 75% yield) as 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), 4.29 – 4.21 (m, 2H), 4.21 – 4.09 (m, 4H), 2.54 (s, 3H), 1.33 – 1.26 (m, 9H) ppm. ^{13}C 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), 116.50 (d, J 3.2 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. ^{31}P NMR: (243 MHz, CDCl_3) δ 15.30 ppm. HRMS: Calc'd for $\text{C}_{13}\text{H}_{21}\text{ClN}_2\text{O}_5\text{PS}$ [$\text{M}+\text{H}^+$] 383.0592; found 383.0591.

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

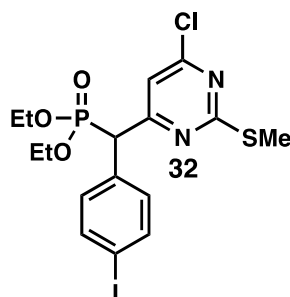


GP-2 was used with commercially available diethyl (cyanomethyl)phosphonate. After reaching room temperature, the reaction was heated to 60 °C for 11 hours. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 40% EtOAc gradient) to give **30** (74.0 mg, 0.220 mmol, 88% yield) as a 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. ^{13}C 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. ^{31}P NMR: (243 MHz, CDCl_3) δ 20.25 ppm. HRMS: Calc'd for $\text{C}_{11}\text{H}_{15}\text{ClN}_3\text{O}_3\text{PSNa}$ [$\text{M}+\text{Na}^+$] 358.0152; found 358.0143.

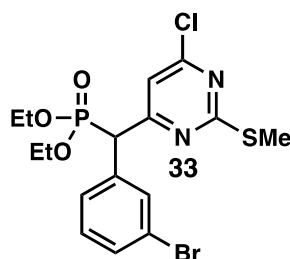
Diethyl 2-(4-nitrophenyl)-2-[6-chloro-2-(methylthio)pyrimidin-4-yl]methylphosphonate (**31**)



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. ^{13}C NMR: (126 MHz, CDCl_3) δ 173.93, 165.14 (d, J 4.9 Hz), 161.57, 147.61 (d, J 2.8 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) 14.37 ppm. ^{31}P NMR: (243 MHz, CDCl_3) δ 19.59 ppm. HRMS: Calc'd for $\text{C}_{16}\text{H}_{20}\text{ClN}_3\text{O}_5\text{PS}$ [$\text{M}+\text{H}^+$] 432.0544; found 432.0542.

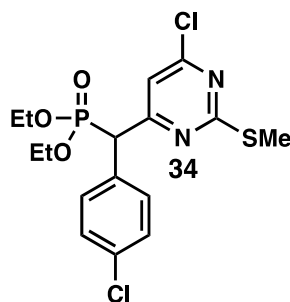
Diethyl 2-(4-iodophenyl)-2-[6-chloro-2-(methylthio)pyrimidin-4-yl]methylphosphonate (32)

GP-1 was used with commercially available diethyl (4-iodobenzyl)phosphonate. After the addition of NaHMDS, the reaction stirred at $-78\text{ }^{\circ}\text{C}$ 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: $R_f = 0.40$ (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. ^{13}C 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. ^{31}P NMR: (243 MHz, CDCl_3) δ 20.51 ppm. HRMS: Calc'd for $\text{C}_{16}\text{H}_{20}\text{ClIN}_2\text{O}_3\text{PS}$ [$\text{M}+\text{H}^+$] 512.9660; found 512.9657.

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

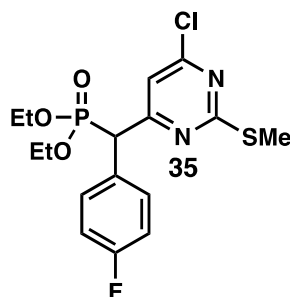
GP-1 was used with commercially available diethyl (3-bromobenzyl)phosphonate. After the addition of NaHMDS, the reaction stirred at $-78\text{ }^{\circ}\text{C}$ for 1 hour then warmed to room temperature where it stirred for an additional 1 hour. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 20% EtOAc gradient) to give **33** (99.0 mg, 0.212 mmol, 85% yield) as a clear colorless oil.

TLC: $R_f = 0.45$ (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. ^{13}C 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. ^{31}P NMR: (243 MHz, CDCl_3) δ 20.42 ppm. HRMS: Calc'd for $\text{C}_{16}\text{H}_{20}\text{BrClIN}_2\text{O}_3\text{PS}$ [$\text{M}+\text{H}^+$] 464.9799; found 464.9798.

Diethyl 2-(4-chlorophenyl)-2-[6-chloro-2-(methylthio)pyrimidin-4-yl]methylphosphonate (34)

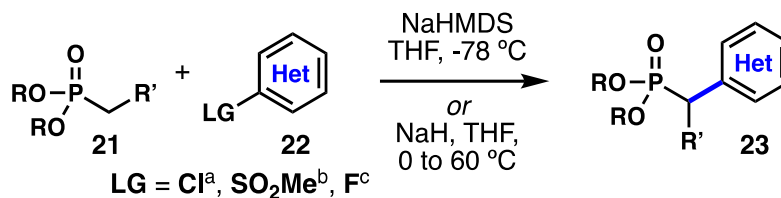
GP-1 was used with commercially available diethyl (4-chlorobenzyl)phosphonate. After the addition of NaHMDS, the reaction stirred at $-78\text{ }^{\circ}\text{C}$ for 1 hour then warmed to room temperature where it stirred for an additional 2 hours. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 40% EtOAc gradient) to give **34** (96.0 mg, 0.227 mmol, 91% yield) as a clear colorless oil. TLC: $R_f = 0.26$ (40% EtOAc in hexanes, UV). ^1H NMR: (500 MHz, CDCl_3) 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.

^{13}C NMR: (126 MHz, CDCl_3) 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. ^{31}P NMR: (243 MHz, CDCl_3) δ 20.68 ppm. HRMS: Calc'd for $\text{C}_{16}\text{H}_{20}\text{Cl}_2\text{N}_2\text{O}_3\text{PS}$ [$\text{M}+\text{Na}^+$] 421.0304; found 421.0296.

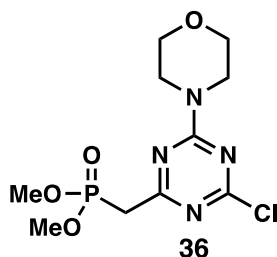
Diethyl 2-(4-fluorophenyl)-2-[6-chloro-2-(methylthio)pyrimidin-4-yl]methylphosphonate (35)

GP-1 was used with commercially available diethyl (4-fluorobenzyl)phosphonate. After the addition of NaHMDS, the reaction stirred at $-78\text{ }^{\circ}\text{C}$ for 1 hour then warmed to room temperature where it stirred for an additional 1 hour. Purified by silica gel column chromatography using hexanes/EtOAc (0% to 40% EtOAc gradient) to give **35** (84.0 mg, 0.207 mmol, 83% yield) as a clear colorless oil. TLC: $R_f = 0.32$ (40% EtOAc in hexanes, UV). ^1H NMR: (500 MHz, CDCl_3) 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. ^{13}C NMR: (126 MHz, CDCl_3) δ 173.52, 166.52 (d, J 3.6 Hz), 163.51 (d, J 2.5 Hz), 161.54 (d, J 2.7 Hz), 161.32, 131.53 (t, J 7.7 Hz), 129.19 (dd, J 6.7, 3.5 Hz), 115.84 (d, J 2.7 Hz), 115.81, 115.65, 63.52 (d, J 6.9 Hz), 62.96 (d, J 7.2 Hz), 52.44 (d, J 137.4 Hz), 16.30 (d, J 5.2 Hz), 16.26 (d, J 5.0 Hz), 14.34 ppm. ^{19}F NMR: (471 MHz, CDCl_3) δ -113.88 (d, J 3.5 Hz) ppm. ^{31}P NMR: (243 MHz, CDCl_3) δ 21.02 ppm. HRMS: Calc'd for $\text{C}_{16}\text{H}_{20}\text{ClF}\text{N}_2\text{O}_3\text{PS}$ [$\text{M}+\text{H}^+$] 405.0599; found 405.0598.

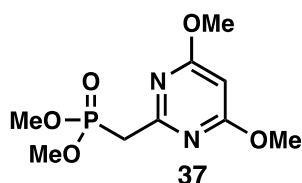
Phosphonate SNAr Electrophile Scope-



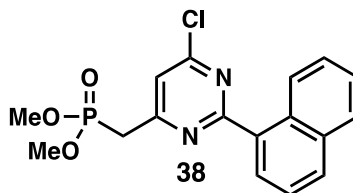
*GP-1 and GP-2 were used. The phosphonates and heterocyclic electrophiles used are described below.

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

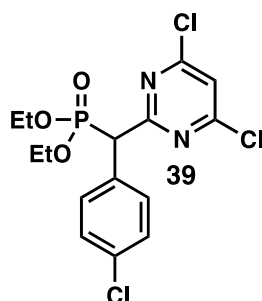
GP-1 was used with previously synthesized **61** and commercially available dimethyl methylphosphonate. After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 1 hour. Purified by silica gel column chromatography using 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% MeOH in DCM, UV). ¹H NMR: (500 MHz, CDCl₃) δ 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. ¹³C NMR: (126 MHz, CDCl₃) δ 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. ³¹P NMR: (243 MHz, CDCl₃) δ 24.65 ppm. HRMS: Calc'd for C₁₀H₁₆ClN₄O₄PNa [M+Na⁺] 345.0490; found 345.0489.

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

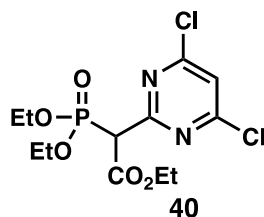
GP-1 was used with commercially available diethyl (4-chlorobenzyl)phosphonate and 2-chloro-4,6-dimethoxypyrimidine. After the addition of NaHMDS, the reaction stirred at -78 °C for 1 hour then warmed to room temperature where it stirred for an additional 15 hours. Purified by silica gel column chromatography 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% MeOH in DCM, UV). ¹H NMR: (500 MHz, CDCl₃) δ 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. ¹³C NMR: (126 MHz, CDCl₃) δ 171.46 (d, J 2.0 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. ³¹P NMR: (243 MHz, CDCl₃) δ 26.66 ppm. HRMS: Calc'd for C₉H₁₆N₂O₅P [M+H⁺] 263.0791; found 263.0789.

Dimethyl [6-chloro-2-(1-naphthyl)pyrimidin-4-yl]methylphosphonate (38)

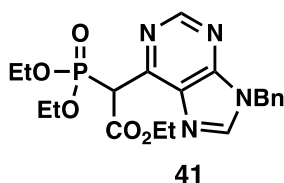
GP-1 was used with commercially available dimethyl methylphosphonate and previously synthesized **65** (4,6-dichloro-2-(naphthalen-1-yl)pyrimidine). After the addition of NaHMDS, the reaction stirred at $-78\text{ }^{\circ}\text{C}$ for 1 hour then warmed to room temperature where it stirred for an additional 1 hour. Purified by silica gel column chromatography using DCM/MeOH (0% to 2% MeOH gradient) to give **38** (44.0 mg, 0.135 mmol, 48% yield) as a golden oil. TLC: $R_f = 0.25$ (80% EtOAc in hexanes, UV). ^1H NMR: (500 MHz, CDCl_3) 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. ^{13}C NMR: (126 MHz, CDCl_3) 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. ^{31}P NMR: (243 MHz, CDCl_3) δ 24.98 ppm. HRMS: Calc'd for $\text{C}_{17}\text{H}_{17}\text{ClN}_2\text{O}_3\text{P}$ [$\text{M}+\text{H}^+$] 363.0660; found 363.0661.

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

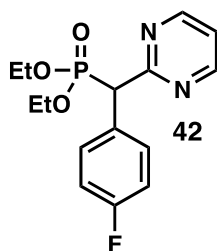
GP-1 was used with commercially available diethyl (4-chlorobenzyl)phosphonate and previously synthesized **62** (4,6-dichloro-2-(methylsulfonyl)pyrimidine). After the addition of NaHMDS, the reaction stirred at $-78\text{ }^{\circ}\text{C}$ for 1 hour then warmed to room temperature where it stirred 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: $R_f = 0.22$ (40% EtOAc in hexanes, UV). ^1H NMR: (500 MHz, CDCl_3) 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), 4.81 (d, J 23.6 Hz, 1H), 4.20 – 4.02 (m, 4H), 1.29 – 1.21 (m, 6H) ppm. ^{13}C NMR: (126 MHz, CDCl_3) 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. ^{31}P NMR: (243 MHz, CDCl_3) δ 19.52 ppm. HRMS: Calc'd for $\text{C}_{15}\text{H}_{17}\text{Cl}_3\text{N}_2\text{O}_3\text{P}$ [$\text{M}+\text{H}^+$] 409.0037; found 409.0035.

Ethyl [2-diethoxyphosphonyl-2-(4,6-dichloropyrimidin-4-yl)]acetate (40)

GP-2 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: R_f = 0.42 (60% EtOAc in hexanes, UV). ^1H NMR: (600 MHz, CDCl_3) δ 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}C NMR: (151 MHz, CDCl_3) δ 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}P NMR: (243 MHz, CDCl_3) δ 15.02 ppm. HRMS: Calc'd for $\text{C}_{12}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_5\text{P}$ [$\text{M}+\text{H}^+$] 371.0325; found 371.0322.

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

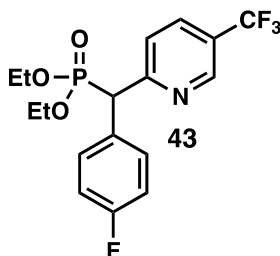
GP-2 was used with commercially available ethyl 2-(diethoxyphosphoryl)acetate and previously synthesized **70** (9-benzyl-6-chloro-9H-purine). After reaching room temperature, the reaction heated to 60 °C for 18 hours. Purified by silica gel column chromatography using DCM/MeOH (0% to 5% MeOH gradient) to give **41** (71.0 mg, 0.164 mmol, 66% yield) as a clear colorless oil. TLC: R_f = 0.2 (5% MeOH in DCM, UV) ^1H NMR: (500 MHz, CDCl_3) δ 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}C NMR: (126 MHz, CDCl_3) δ 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}P NMR: (243 MHz, CDCl_3) δ 16.24. HRMS: Calc'd for $\text{C}_{20}\text{H}_{26}\text{N}_4\text{O}_5\text{P}$ [$\text{M}+\text{H}^+$] 433.1635; found 433.1634.

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

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

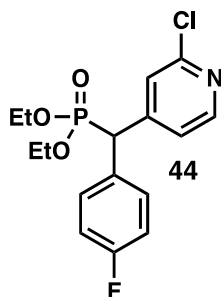
stirred for an additional 15 hours. Purified by silica gel column chromatography using DCM/MeOH (0% to 5% MeOH gradient) to give **42** (44.0 mg, 0.135 mmol, 54% yield) as a yellow oil. TLC: $R_f = 0.35$ (5% MeOH in DCM, UV). ^1H NMR: (600 MHz, CDCl_3) δ 8.77 (d, J 4.9 Hz, 2H), 7.66 (ddq, J 10.6, 5.3, 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. ^{13}C NMR: (151 MHz, CDCl_3) 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), 54.44 (d, J 138.4 Hz), 16.34, 16.30 ppm. ^{19}F NMR: (564 MHz, CDCl_3) δ -114.82 (d, J 5.0 Hz) ppm. ^{31}P NMR: (243 MHz, CDCl_3) δ 21.85 ppm. HRMS: Calc'd for $\text{C}_{15}\text{H}_{18}\text{FN}_2\text{O}_3\text{PNa}$ [$\text{M}+\text{Na}^+$] 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 $-78\text{ }^\circ\text{C}$ 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: $R_f = 0.29$ (40% EtOAc in hexanes, UV). ^1H NMR: (500 MHz, CDCl_3) 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. ^{13}C NMR: (151 MHz, CDCl_3) 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. ^{19}F NMR: (471 MHz, CDCl_3) δ -62.43, -114.51 (d, J 3.6 Hz) ppm. ^{31}P NMR: (243 MHz, CDCl_3) δ 22.43 ppm. HRMS: Calc'd for $\text{C}_{17}\text{H}_{19}\text{F}_4\text{NO}_3\text{P}$ [$\text{M}+\text{H}^+$] 392.1033; found 392.1037.

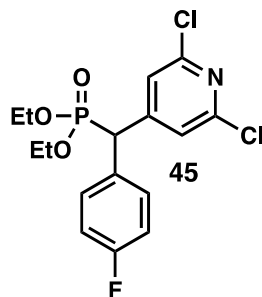
Diethyl (4-fluorophenyl)-(2-chloropyridin-4-yl)methylphosphonate (**44**)



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 $-78\text{ }^\circ\text{C}$ for 1 hour then warmed to room temperature where it stirred for an additional 1 hour. Purified by silica gel column chromatography using 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 $\text{S}_{\text{N}}\text{Ar}$ regioisomer was detected and was inseparable from the major product.

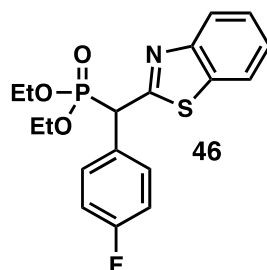
TLC: $R_f = 0.27$ (30% EtOAc in hexanes, UV). ^1H NMR: (500 MHz, CDCl_3) δ 8.32 (d, J 5.2 Hz, 1H), 7.45 (ddd, J 8.9, 5.2, 1.9 Hz, 2H), 7.42 (t, J 1.8 Hz, 1H), 7.38 (dt, J 5.2, 1.7 Hz, 1H), 7.05 (t, J 8.2 Hz, 2H), 4.35 (d, J 25.0 Hz, 1H), 4.07 – 3.94 (m, 3H), 3.89 – 3.79 (m, 1H), 1.19 (t, J 7.1 Hz, 3H), 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 $\text{C}_{16}\text{H}_{19}\text{ClFNO}_3\text{P}$ [$\text{M}+\text{H}^+$] 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 $-78\text{ }^\circ\text{C}$ 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). ^1H 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 $\text{C}_{16}\text{H}_{18}\text{Cl}_2\text{FNO}_3\text{P}$ [$\text{M}+\text{H}^+$] 392.0380; found 392.0380.

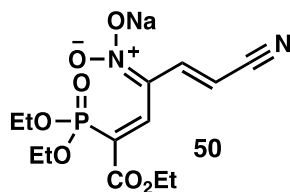
Diethyl (benzotriazol-2-yl)(4-fluorophenyl)methylphosphonate (46)



GP-1 was used with commercially available diethyl (4-fluorobenzyl)phosphonate and 2-chlorobenzothiazole. After the addition of NaHMDS, the reaction stirred at $-78\text{ }^\circ\text{C}$ for 1 hour then warmed to room temperature where it stirred for an additional 1 hour. Purified by silica gel column chromatography using 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). ^1H 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

(ddd, J 8.9, 5.1, 2.1 Hz, 2H), 7.44 (ddd, J 8.3, 7.1, 1.3 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.05 (t, J 8.6 Hz, 2H), 5.02 (d, J 24.8 Hz, 1H), 4.19 – 4.01 (m, 3H), 4.00 – 3.89 (m, 1H), 1.21 (t, J 7.1 Hz, 3H), 1.15 (t, J 7.1 Hz, 3H) ppm. ^{13}C NMR: (151 MHz, CDCl_3) δ 165.80, 163.36, 161.72, 152.80, 135.73, 131.47 (t, J 7.4 Hz), 129.88 (d, J 4.4 Hz), 126.12, 125.30, 123.26, 121.49, 115.77 (d, J 21.4 Hz), 63.56 (d, J 6.9 Hz), 63.42 (d, J 7.1 Hz), 50.13 (d, J 139.5 Hz), 16.34 (d, J 5.6 Hz), 16.28 (d, J 6.3 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 20.25 ppm. HRMS: Calc'd for $\text{C}_{16}\text{H}_{19}\text{ClFNO}_3\text{P}$ [$\text{M}+\text{H}^+$] 380.0880; found 380.0877.

Ethyl 6-cyano-2-(diethoxyphosphonyl)-4-(sodionitronyl)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: R_f = 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. ^{13}C NMR: (151 MHz, MeOD) δ 166.86 (d, J 15.2 Hz), 143.61 (d, J 10.9 Hz), 141.61, 121.06, 120.45 (d, J 21.4 Hz), 106.44 (d, J 191.8 Hz), 84.78, 62.42 (d, J 5.3 Hz), 60.67, 15.19 (d, J 6.4 Hz), 13.24 ppm. ^{31}P NMR: (243 MHz, MeOD) δ 20.12 ppm. HRMS: Calc'd for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_7\text{P}$ [$\text{M}+\text{H}^+$] 347.1003; found 347.1010.

Acknowledgements

We gratefully acknowledge the H. Lee Moffitt Cancer Center & Research Institute for financial support. This work has also been supported in part by the Chemical Biology Core Facility (NMR, LC-MS, HRMS) at the H. Lee Moffitt Cancer Center & Research Institute, an NCI designated Comprehensive Cancer Center (P30-CA076292).

Supplementary Material

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

References

- De Clercq, E.; Holý, A. *Nat. Rev. Drug Discov.* **2005**, *4*, 928–940.
<https://doi.org/10.1038/nrd1877>
- Wang, P.-C.; Fang, J.-M.; Tsai, K.-C.; Wang, S.-Y.; Huang, W.-I.; Tseng, Y.-C.; Cheng, Y.-S. E.; Cheng, T.-J. R.; Wong, C.-H. *J. Med. Chem.* **2016**, *59*, 5297–5310.
<https://doi.org/10.1021/acs.jmedchem.6b00029>

3. Warren, T. K.; Jordan, R.; Lo, M. K.; Ray, A. S.; Mackman, R. L.; Soloveva, V.; Siegel, D.; Perron, M.; Bannister, R.; Hui, H. C.; Larson, N.; Strickley, R.; Wells, J.; Stuthman, K. S.; Van Tongeren, S. A.; Garza, N. L.; Donnelly, G.; Shurtleff, A. C.; Retterer, C. J.; Gharaibeh, D.; Zamani, R.; Kenny, T.; Eaton, B. P.; Grimes, E.; Welch, L. S.; Gomba, L.; Wilhelmsen, C. L.; Nichols, D. K.; Nuss, J. E.; Nagle, E. R.; Kugelman, J. R.; Palacios, G.; Doerffler, E.; Neville, S.; Carra, E.; Clarke, M. O.; Zhang, L.; Lew, W.; Ross, B.; Wang, Q.; Chun, K.; Wolfe, L.; Babusis, D.; Park, Y.; Stray, K. M.; Trancheva, I.; Feng, J. Y.; Barauskas, O.; Xu, Y.; Wong, P.; Braun, M. R.; Flint, M.; McMullan, L. K.; Chen, S.-S.; Fearn, R.; Swaminathan, S.; Mayers, D. L.; Spiropoulou, C. F.; Lee, W. A.; Nichol, S. T.; Cihlar, T.; Bavari, S. *Nature* **2016**, *531*, 381–385.
<https://doi.org/10.1038/nature17180>
4. Gagnon, K. J.; Perry, H. P.; Clearfield, A. *Chem. Rev.* **2012**, *112*, 1034–1054.
<https://doi.org/10.1021/cr2002257>
5. Yamanaka, K.; Imazato, K.; Takahashi, N. Preparation of organophosphorus compounds as a flame retardant. PCT Intl. Patent WO20180561553, 2018; *Chem. Abstr.* **2018**, *168*, 317057.
6. Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3070.
<https://doi.org/10.1021/cr020049i>
7. Benaglia, M.; Rossi, S. *Org. Biomol. Chem.* **2010**, *8*, 3824–3830.
<https://doi.org/10.1039/C004681G>
8. Roch-Neirey, C.; Le Bris, N.; Laurent, P.; Clément, J.-C.; des Abbayes, H. *Tetrahedron Lett.* **2001**, *42*, 643–645.
[https://doi.org/10.1016/S0040-4039\(00\)02028-1](https://doi.org/10.1016/S0040-4039(00)02028-1)
9. Contrella, N. D.; Sampson, J. R.; Jordan, R. F. *Organometallics* **2014**, *33*, 3546–3555.
<https://doi.org/10.1021/om5004489>
10. Engel, R. *Chem. Rev.* **1977**, *77*, 349–367.
<https://doi.org/10.1021/cr60307a003>
11. Maji, R.; Mallojjala, S. C.; Wheeler, S. E. *Chem. Soc. Rev.* **2018**, *47*, 1142–1158.
<https://doi.org/10.1039/C6CS00475J>
12. Sevrain, C. M.; Berchel, M.; Couthon, H.; Jaffrès, P. A. *Beilstein J. Org. Chem.* **2017**, *13*, 2186–2213.
<https://doi.org/10.3762/bjoc.13.219>
13. Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87–99.
<https://doi.org/10.1021/cr60287a005>
14. Gilead Sciences. Viread (tenofovir disoproxil fumarate) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022577lbl.pdf Revised January 2012. Accessed January 22, 2021.
15. De Clercq, E. *Int. J. Antimicrob. Agents* **2009**, *33*, 307–320.
<https://doi.org/10.1016/j.ijantimicag.2008.10.010>
16. Schwender, C. F.; Beers, S. A.; Malloy, E. A.; Cinicola, J. J.; Wustrow, D. J.; Demarest, K. D.; Jordan, J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 311–314.
[https://doi.org/10.1016/0960-894X\(96\)00018-2](https://doi.org/10.1016/0960-894X(96)00018-2)
17. Younes, S.; Baziard-Mouysset, G.; de Saqui-Sannes, G.; Stigliani, J. L.; Payard, M.; Bonnafous, R.; Tisne-Versailles, J. *Eur. J. Med. Chem.* **1993**, *28*, 943–948.
[https://doi.org/10.1016/0223-5234\(93\)90049-K](https://doi.org/10.1016/0223-5234(93)90049-K)
18. Khurmi, N. S.; Bowles, M. J.; O'Hara, M. J.; Lahiri, A.; Raftery, E. B. *Int. J. Cardiol.* **1985**, *9*, 289–302.
[https://doi.org/10.1016/0167-5273\(85\)90027-0](https://doi.org/10.1016/0167-5273(85)90027-0)

19. Takada, T.; Miyawaki, N.; Kageyama, M.; Matsuno, K.; Ishida, N.; Yamauchi, H.; Iso, T. *J. Cardiovasc. Pharmacol.* **1991**, *18*.
https://journals.lww.com/cardiovascularpharm/Abstract/1991/12000/Antihypertensive_Effect_of_a_Novel_Calcium.11.aspx
20. Yamada, H.; Tanaka, K.; Adachi, H.; Yamada, S.; Shimoda, S. Preparation of 2-benzoylpyrimidine derivatives as herbicides and agrochemical fungicides. PCT Intl. Patent WO9408975, 1994; *Chem. Abstr.* **1994**, *121*, 230784
21. Chen, Z.; Zeng, M.; Song, B.; Hou, C.; Hu, D.; Li, X.; Wang, Z.; Fan, H.; Bi, L.; Liu, J.; Yu, D.; Jin, L.; Yang, S. *PLoS One* **2012**, *7*, e37944.
<https://doi.org/10.1371/journal.pone.0037944>
22. Gibadullina, E.; Nguyen, T. T.; Strelnik, A.; Sapunova, A.; Voloshina, A.; Sudakov, I.; Vyshtakalyuk, A.; Voronina, J.; Pudovik, M.; Burilov, A. *Eur. J. Med. Chem.* **2019**, *184*, 111735.
<https://doi.org/10.1016/j.ejmech.2019.111735>
23. Zhang, B.; Liu, L.; Mao, S.; Zhou, M.-D.; Wang, H.; Li, L. *Eur. J. Org. Chem.* **2019**, 3898–3907.
<https://doi.org/10.1002/ejoc.201900606>
24. Xiong, B.; Wang, G.; Zhou, C.; Liu, Y.; Xu, W.; Xu, W.-Y.; Yang, C.-A.; Tang, K.-W. *Eur. J. Org. Chem.* **2019**, 3273–3282.
<https://doi.org/10.1002/ejoc.201900419>
25. Babu, B. H.; Prasad, G. S.; Raju, C. N.; Basaveswara Rao, M. V. *Curr. Org. Synth.* **2017**, *14*, 883–903.
<https://doi.org/10.2174/1570179414666161230144455>
26. Gavara, L.; Petit, C.; Montchamp, J.-L. *Tetrahedron Lett.* **2012**, *53*, 5000–5003.
<https://doi.org/10.1016/j.tetlet.2012.07.019>
27. Minami, T.; Isonaka, T.; Okada, Y.; Ichikawa, J. *J. Org. Chem.* **1993**, *58*, 7009–7015.
<https://doi.org/10.1021/jo00077a018>
28. Rout, L.; Regati, S.; Zhao, C.-G. *Adv. Synth. & Catal.* **2011**, *353*, 3340–3346.
<https://doi.org/10.1002/adsc.201100605>
29. Pallikonda, G.; Chakravarty, M. *Eur. J. Org. Chem.* **2013**, 944–951.
<https://doi.org/10.1002/ejoc.201201352>
30. Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2007**, *26*, 4105–4108.
<https://doi.org/10.1021/om700475t>
31. Montel, S.; Raffier, L.; He, Y.; Walsh, P. J. *Org. Lett.* **2014**, *16*, 1446–1449.
<https://doi.org/10.1021/ol5002413>
32. Petrova, I.; Momchilova, S.; Vasilev, N. *Phosphorus, Sulfur Silicon Relat. Elem.* **1992**, *68*, 45–52.
<https://doi.org/10.1080/10426509208038370>
33. Wang, H.; Huang, L.; Cao, X.; Liang, D.; Peng, A.-Y. *Org. Biomol. Chem.* **2017**, *15*, 7396–7403.
<https://doi.org/10.1039/C7OB01436H>
34. He, T.-J.; Zhu, S.; Lu, X.-W.; Wu, Y.; Li, Y. *Eur. J. Org. Chem.* **2015**, 647–654.
<https://doi.org/10.1002/ejoc.201403287>
35. Mąkosza, M.; Sulikowski, D. *J. Org. Chem.* **2009**, *74*, 3827–3832.
<https://doi.org/10.1021/jo900204e>
36. Fujii, K.; Ito, S.; Mikami, K. *J. Org. Chem.* **2019**, *84*, 12281–12291.
<https://doi.org/10.1021/acs.joc.9b01402>
37. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.
<https://doi.org/10.1021/ar00156a004>

38. Blasdel, L. K.; Myers, A. G. *Org. Lett.* **2005**, *7*, 4281–4283.
<https://doi.org/10.1021/ol051785m>
39. Tulyasheva, M.; Rasulev, B.; Tojiboev, A.; Turgunov, K.; Tashkhodjaev, B.; Abdullaev, N.; Shakhidoyatov, K. *Molecules* **2005**, *10*, 1209–1217.
<https://doi.org/10.3390/10091209>
40. Chiacchio, M. A.; Iannazzo, D.; Romeo, R.; Giofrè, S. V.; Legnani, L. *Curr. Med. Chem.* **2019**, *26*, 7166–7195.
<https://doi.org/10.2174/0929867325666180904125400>
41. Al-Zaydi, K. M.; Khalil, H. H.; El-Faham, A.; Khattab, S. N. *Chem. Cent. J.* **2017**, *11*, 39.
<https://doi.org/10.1186/s13065-017-0267-3>
42. Hasník, Z.; Pohl, R.; Hocek, M. *Tetrahedron Lett.* **2010**, *51*, 2464–2466.
<https://doi.org/10.1016/j.tetlet.2010.02.167>
43. Van der Plas, H. C. *Acc. Chem. Res.* **1978**, *11*, 462–468.
<https://doi.org/10.1021/ar50132a005>
44. Haynes, L. W.; Pett, V. B. *J. Org. Chem.* **2007**, *72*, 633–635.
<https://doi.org/10.1021/jo062003l>
45. Kaur, S.; Kumari, P.; Singh, G.; Bhatti, R.; Singh, P. *ACS Omega* **2018**, *3*, 5825–5845.
<https://doi.org/10.1021/acsomega.8b00445>
46. Robke, L.; Laraia, L.; Carnero Corrales, M. A.; Konstantinidis, G.; Muroi, M.; Richters, A.; Winzker, M.; Engbring, T.; Tomassi, S.; Watanabe, N.; Osada, H.; Rauh, D.; Waldmann, H.; Wu, Y.-W.; Engel, J. *Angew. Chem. Int. Ed.* **2017**, *56*, 8153–8157.
<https://doi.org/10.1002/anie.201703738>
47. Parra, J.; Mercader, J. V.; Agulló, C.; Abad-Fuentes, A.; Abad-Somovilla, A. *Tetrahedron* **2011**, *67*, 624–635.
<https://doi.org/10.1016/j.tet.2010.11.054>
48. Boudet, N.; Dubbaka, S. R.; Knochel, P. *Org. Lett.* **2008**, *10*, 1715–1718.
<https://doi.org/10.1021/ol800353s>

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