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Synthesis of Tetrasubstituted Thiophenes via Direct Metalation

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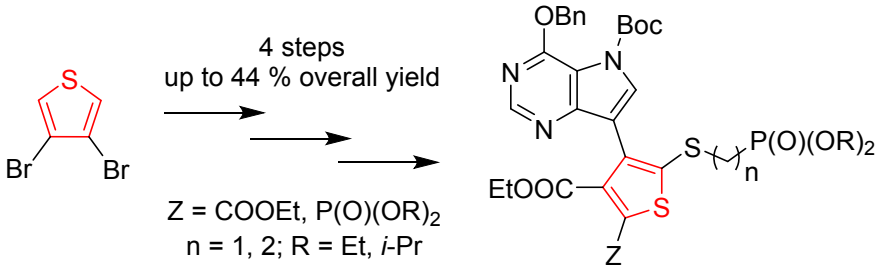
Abstract



Thiophene moiety can be derivatized by various synthetic procedures. The most convenient method seems to be derivatization via direct metalation but synthesis of polysubstituted thiophenes bearing reactive groups is difficult due to high reactivity of organometallic reagents. This work reports the preparation of complex heterocyclic compounds using direct metalation of thiophenes with various reagents (Knochel-Hauser bases, LDA) as an efficient synthetic tool.

INTRODUCTION

In our research group, we focus on a study of modified nucleotide analogues for medical use in order to treat various viral[1] or parasitic[2–8] infections, among others. Recently, we were interested in structures, which would mimic geometry and charge distribution of transition states involved in the enzymatic transformation of 6-oxopurines and phosphoribosyl pyrophosphate, as natural substrates, by phosphoribosyl transferases (Figure 1). Hypoxanthine-guanine-(xanthine) phosphoribosyltransferase (HG(X)PRT), for example, represents a recognized target for development of potential anti-malarial chemotherapeutics.

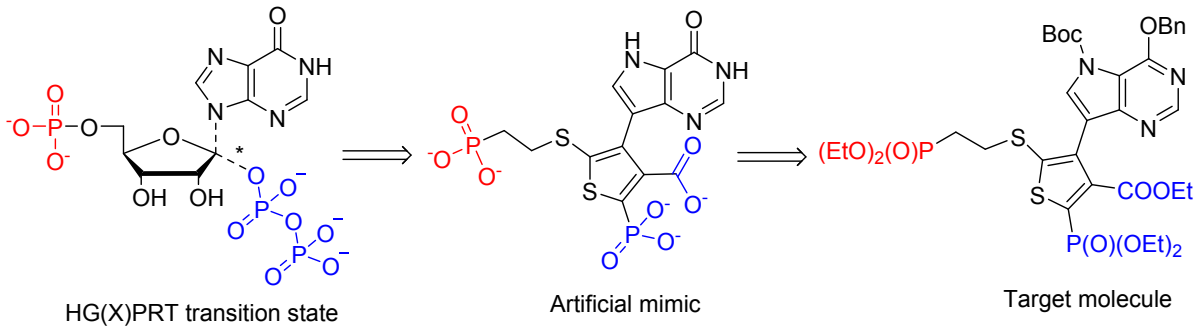


Figure 1. Comparison of geometry and charge distribution between the HG(X)PRT transition state and our target molecule

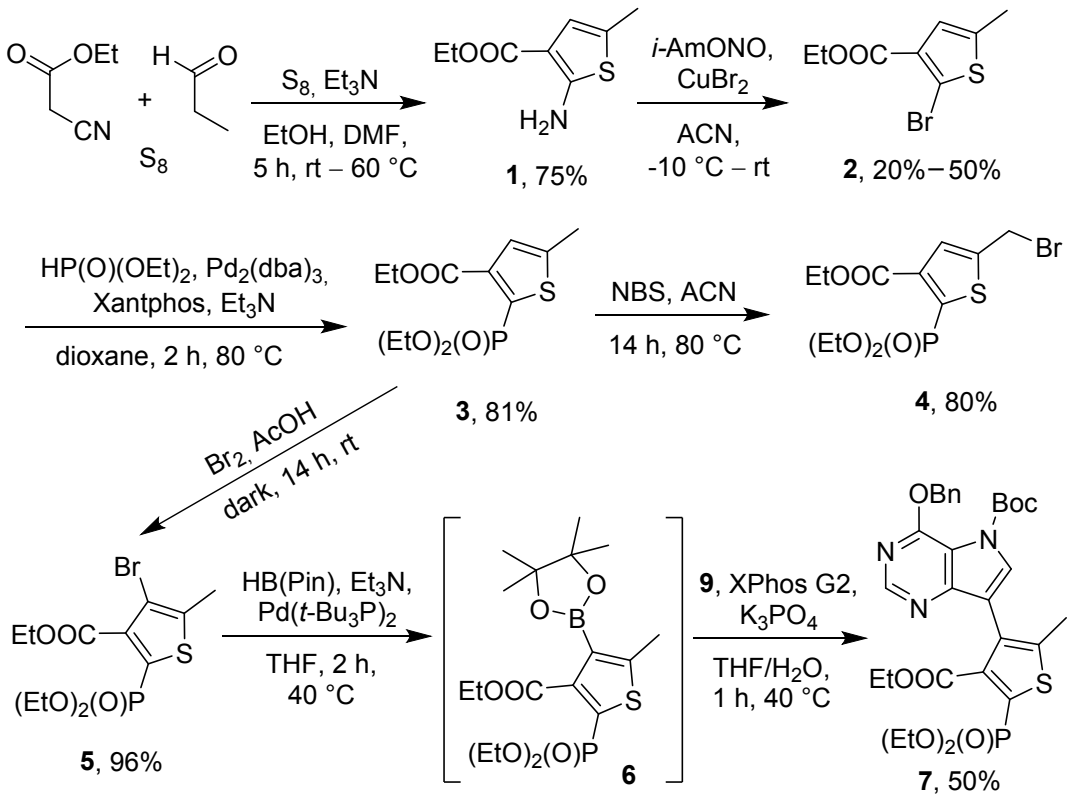
We have attempted to design artificial nucleotide mimics based on a thiophene moiety (Figure 1), which could be exploited as a tool to search for novel medicinal targets and new therapeutic opportunities. The Reaxys database contains approx. 900k compounds derived from the thiophene moiety, but only approx. 21k molecules contain the tetrasubstituted thiophene core and, moreover, mostly in a symmetrical fashion. To our surprise, no structures similar to our target molecule (Figure 1) were present in available databases, although thiophene moiety is commonly part of agrochemicals, pharmaceuticals and electronics based on organic molecules.[9–12] Therefore, we have developed a new synthetic strategy for a fully regioselectivelly controlled synthesis of asymmetrically substituted thiophenes.

Thiophene derivatives are usually synthesized by aromatic electrophilic substitution[13] or by heterocyclization methods,[14] but these approaches require additional transformations, which increase number of steps in the synthesis. In addition, standard transformations often require energetic conditions not compatible with sensitive and/or reactive functional groups. Thus, we employed a straightforward introduction of functional groups by direct metalation combined

with subsequent reactions of intermediates with corresponding electrophiles.[15] As the key reagents, Knochel-Hauser bases, like tetramethylpiperidinylmagnesium chloride lithium chloride complex (TMPMgCl·LiCl),[16] were used. Such mixed amide base exhibits remarkable functional group tolerance and allows straightforward synthesis of tetrasubstituted heterocycles.[17,18] However, the complexity of final molecules was quite limited. In this work, we explored applications of amide bases for selective, late-stage deprotonation of complex molecules.

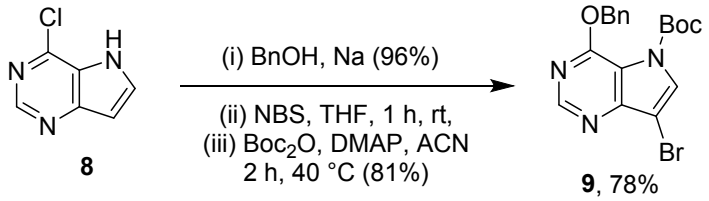
RESULTS AND DISCUSSION

Since no similarly polysubstituted structures (Figure 1) have been reported, the questions regarding to stability of the target molecules arose. We needed a proof-of-concept synthesis. First, amino thiophene (**1**, Scheme 1) was prepared in a 75% yield by the Gewald condensation.[19] Compound **1** was then converted into 2-bromothiophene (**2**)[20] by diazotation and subsequent reaction with copper (II) bromide. The diazotation step proceeded in variable yields (20% – 50%) and turned-out to be difficult to optimize. The bromine substituent was transformed catalytically to diethyl phosphonate derivative **3** (75%).[21] Bromination of substrate **3** under various reaction conditions led to completely different products. Halogenation of **3** with NBS in acetonitrile at 80 °C without radical initiator led exclusively to the formation of bromomethyl derivative **4**. When catalytic amount of acetic or trifluoroacetic acid was used, the reaction afforded a mixture of products (we assume that the diethyl phosphonate moiety was converted into free phosphonic acid, which acted as a leaving group and got substituted by bromine). On the other hand, bromination in an amber flask using bromine in acetic acid at room temperature led to a formation of the desired 4-bromothiophene **5** in a quantitative yield. In order to prepare boronic ester **6**, derivative **5** was subjected to Pd-catalyzed borylation with $Pd(P\textit{t}\text{-}Bu_3)_2$ and pinacolborane in the presence of triethylamine. Nevertheless, boronate **6** could not be isolated since (hetero)aromatic boronic acids/esters bearing electron withdrawing groups are usually prone to protodeboronation.[22,23] Thus, boronate **6** was used in the next reaction without isolation.



Scheme 1. Synthesis of target tetrasubstituted thiophene **7**.

Bromo derivative **9** (Scheme 2) was chosen as a reaction partner for compound **6** (Scheme 1) in the subsequent Suzuki coupling. Compound **9** was synthesized from 6-chloro-9-deazapurine (**8**) by nucleophilic substitution with benzyl alcoholate, followed by electrophilic bromination with NBS and introduction of Boc group to 7-NH position. The pyrrole ring in 9-deazapurines is relatively electron rich, which is generally problematic for Pd-catalyzed couplings. Thus, the Boc group was used here to deplete part of electron density since the carbamate group is more electron-withdrawing group compared to amide- or sulfonamide-containing protecting groups.[24]



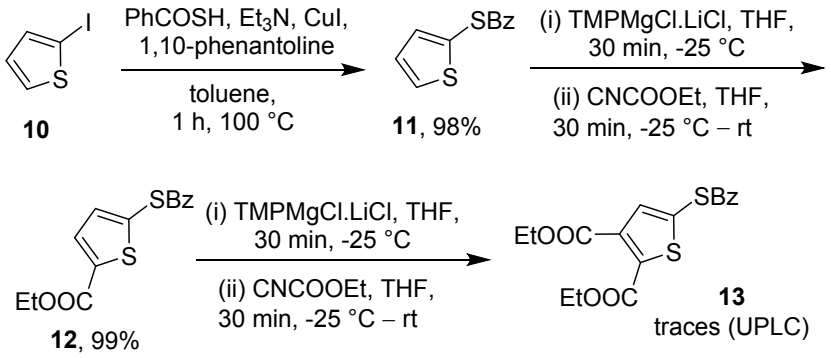
Scheme 2. Synthesis of suitably protected 9-bromo-9-deazapurine **9**.

The optimized procedure for catalytic borylation of bromothiophene **5**, followed by filtration of the reaction mixture through celite and evaporation afforded crude **6**. Compound **6** was used

directly in Suzuki coupling with 9-deazapurine **9** to offer target product **7** (Scheme 1) in a 50% yield (from **5**).

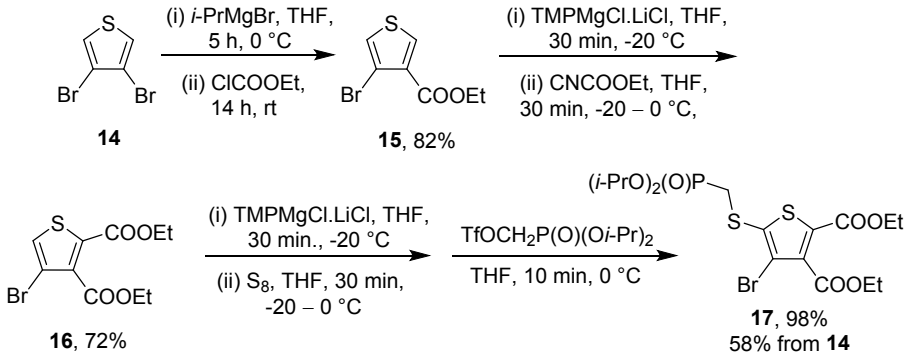
The direct metalation was chosen for the synthesis of desired tetrasubstituted thiophenes. Because of presence of reactive or sensitive functional groups, the selected metalating reagent should react under mild reaction conditions. Such requirements were completely implemented by use of TMPMgCl·LiCl. This base was used previously for the synthesis of polysubstituted aromatic compounds.[25–28]

First, we selected metalation of 2-benzoylthiothiophene **11** (Scheme 3) which was prepared quantitatively using the Ullmann coupling of 2-iodothiophene (**10**) and thiobenzoic acid.[29] Then, ethyl carboxylate moiety was introduced in a high yield by the reaction of the metalated intermediate and ethyl cyanoformate, to give compound **12**. Nevertheless, the second metalation on **12** only led to a cleavage of the benzoyl group, resulting in a complex product mixture (including traces of **13**). These results suggested that a successful synthetic strategy would require using 3-bromo substituted thiophenes as the starting material.



Scheme 3. An attempt to prepare compound **13** using direct metalation.

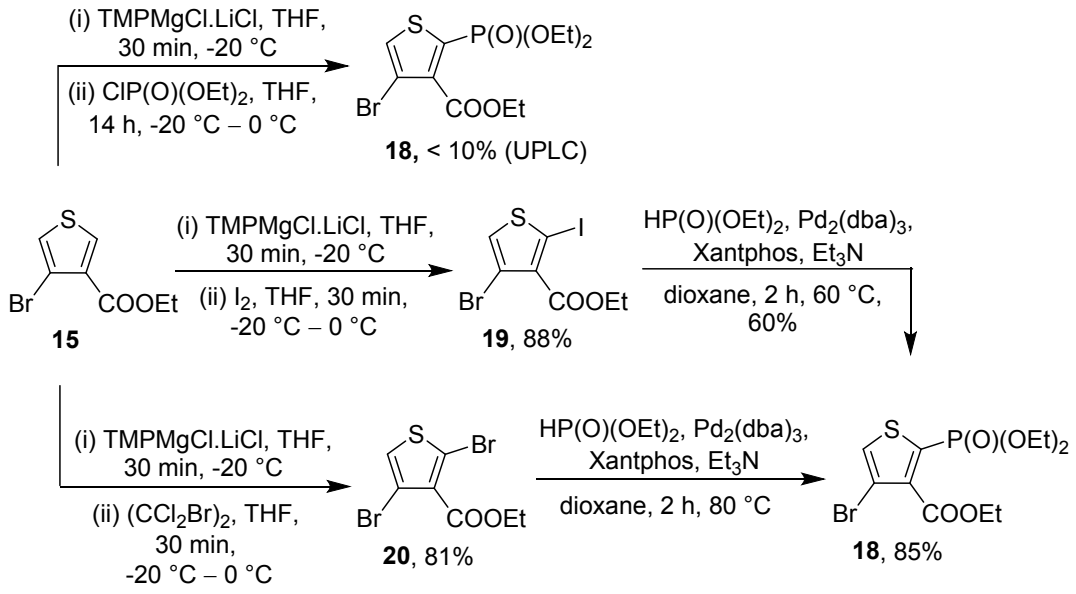
Commercially available 3,4-dibromothiophene (**14**, Scheme 4) was used for the halogen-metal exchange preparation of the Grignard reagent and its subsequent reaction with ethyl chloroformate to obtain ethyl 4-bromothiophene-3-carboxylate (**15**) in a 82% yield. This substitution activated C2 position of thiophene **15** towards Knochel-Hauser base. Deprotonation of **15** followed by the reaction with ethyl cyanoformate gave trisubstituted thiophene **16** in an excellent yield. The last substituent was introduced by deprotonation of **16** and by subsequent reaction of organometallic C5-intermediate with sulfur. In-situ alkylation of formed thiolate with diisopropyl triflyloxymethylphosphonate afforded the desired tetrasubstituted thiophene **17** in a 58% overall yield (4 reaction steps).



Scheme 4. Synthesis of tetrasubstituted thiophene **17** using direct metalation.

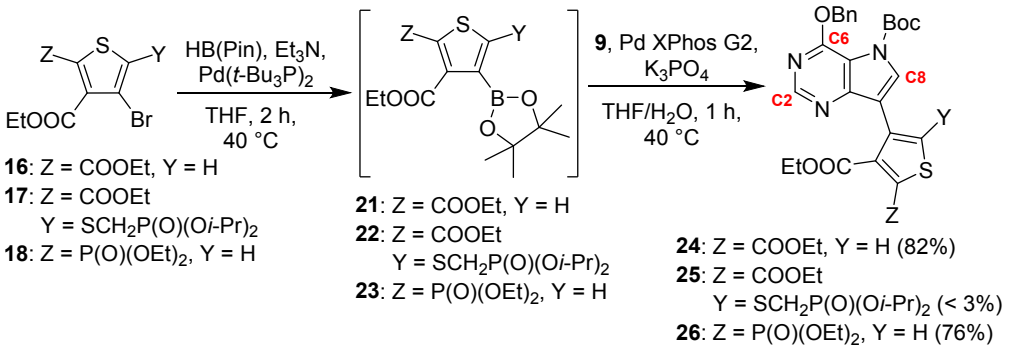
In contrast, the reaction of metalated intermediate of compound **15** with diethyl chlorophosphate afforded the desired diethyl thiophene-2-phosphonate **18** (Scheme 5) in a low yield (< 10% by UPLC). Therefore, halogenation of the C2 position followed by the Pd-catalyzed introduction of diethyl phosphonate group was studied and optimized.

2-Iodothiophene **19** and 2-bromothiophene **20** (Scheme 5) was prepared in high yields by the reaction of metalated **15** with iodine or 1,2-dibromo-1,1,2,2-tetrachloroethane, respectively. Subsequent coupling of 2-halothiophenes with diethyl phosphite was much more robust in the case of 2-bromo derivative **20** (85% of **18**) than in the case of 2-iodo derivative **19** (14–60% of **18**). The coupling with 2-iodo derivative **19** was extremely sensitive towards oxygen and/or water residues and it suffered from major dehalogenation of iodine in starting material as well as from cleavage of ethyl ester groups from the diethyl phosphonate moiety in product **18**. The yields were variable and such a method was not applicable for multigram scale-up. In contrast, the procedure using 2-bromo derivative **20** afforded desired compound **18** smoothly in high yields even in multigram scale-ups.



Scheme 5. Synthetic approached to trisubstituted thiophene **18**.

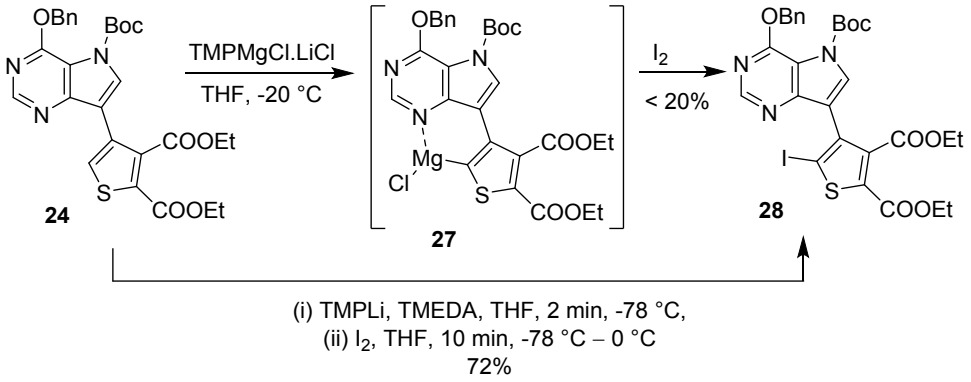
Compound **17**, containing a single bromine substituent, was then used for the catalytic borylation and subsequent Suzuki coupling. Although the borylation step worked with reasonable conversion (UPLC), subsequent Suzuki coupling did not proceed and the reaction resulted in deborylation. This may be caused by the steric hindrance of the borylated C3 position and all attempts for the improvement failed. The same procedure worked perfectly with compounds **16** and **18** (Scheme 6), lacking the heteroarylphosphonate moiety, and the reaction provided desired products **24** and **26**, respectively, in high yields.



Scheme 6. Synthesis of tetrasubstituted thiophenes bearing 9-deazapurine moiety.

Due to these complications, we decided to carry out metalation reactions with relatively complex compounds **24** and **26**. The 9-deazapurine moiety of both compounds contains acidic protons at positions C2 and C8, nucleophilic sensitive positions C2 and C6, and relatively labile Boc protecting group. Moreover, the thiophene moiety contains basic and nucleophilic sensitive esters (carboxylate and phosphonate).

First, we decided to study the course of metalation with compound **24** using trapping with iodine to obtain product **28** (Scheme 7). Despite the drawbacks described in the previous paragraph, Knochel-Hauser base was able to selectively deprotonate only position C5 at the thiophene moiety without formation of any observable side products. Nevertheless, yields of iodo derivative **28** were below 20%, probably due to chelation of the magnesium ion by N3 nitrogen in the metalated intermediate **27** (Scheme 7), which may interfere with the subsequent reaction of the electrophile. The utilization of TMP_2Mg, that keeps the bulky TMP ligand bound to the magnesium ion, resulted only in a small improvement in the yields.



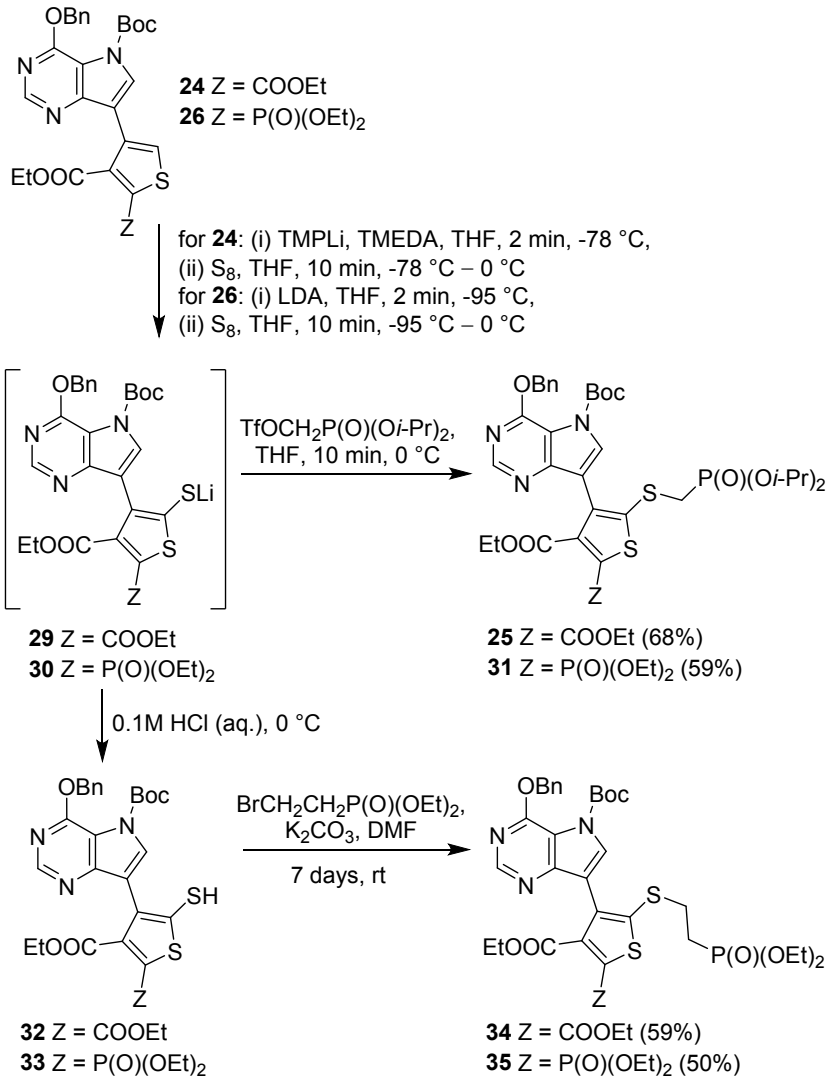
Scheme 7. A study of the metalation of compound **24** followed by trapping with iodine and optimized synthesis of compound **28**.

Logically, a replacement of the bivalent magnesium ion for the monovalent lithium ion was studied next. Use of TMPLi at -78 °C provided higher, yet very variable, yields of lithiated product (not shown). Further improvement was observed after a TMEDA addition but the yields of lithiation were still quite variable. A careful study of the reaction course using UPLC revealed that deprotonation of substrate **24** with TMPLi at -78 °C took only about 1 min and the lithiated intermediate was stable for about 5 min, followed by its complete decomposition within 40 min. Thus, addition of iodine 2 min after lithiation afforded compound **28** in a 72% yield (Scheme 7).

Similarly, addition of sulfur within 1–2 min after lithiation provided desired intermediate **29** (Scheme 8) with high and reproducible conversion (UPLC). Subsequent in-situ alkylation of **29** with diisopropyl triflyloxymethylphosphonate delivered final compound **25** in a 68% yield (4 isolated intermediates, 33% overall yield from **14**). For the introduction of the thioethylphosphonate moiety, it was necessary to treat intermediate **29** with hydrochloric acid (to get intermediate **32**) and then perform mild alkylation of the crude mixture with diethyl 2-bromoethylphosphonate in the presence of potassium carbonate in DMF. This procedure

afforded final compound **34** (Scheme 8) in a 59% yield (5 isolated intermediates, 29% overall yield from **14**).

However, the above optimized reaction conditions did not work in the case of compound **26**, bearing the phosphonate moiety instead of the carboxylate at position C2 of thiophene. Simple solution was to decrease the reaction temperature bellow -78 °C, down to -95 °C. This change led to a dramatic increase of stability of the lithiated intermediate (UPLC), which was fully stable for 30 min. In addition, it was possible to replace TMPLi/TMEDA for LDA as a metalating agent, while magnesium amides were not reactive enough to deprotonate substrates **24** and **26** at temperatures below -40 °C. Moreover, larger excess of LDA resulted in multiple-lithiated compounds (possible lithiation at positions C2, C8 of purine and at position C5 of thiophene). The excess of TMPLi in the previous reaction conditions led to decomposition of the starting material. Thus, using the optimized conditions for lithiation, followed by the reaction with sulfur and subsequent alkylation, final compounds **31** and **35** (via crude **33**, Scheme 8) were prepared in good yields.



Scheme 8. Synthesis of target tetrasubstituted thiophenes bearing the 9-deazapurine moiety and a linker with the phosphonate group.

CONCLUSIONS

In summary, we have developed and optimized a new strategy for the synthesis of asymmetrically tetrasubstituted thiophenes. Direct metalation turned out to be an extremely useful approach for regioselective halogenation of electron deficient aromatics, where electrophilic aromatic substitution fails and/or provides a mixture of regioisomers. The chemistry presented here afforded target polysubstituted thiophenes in high overall yields, with low number of reaction steps, and with excellent regioselectivity control. Moreover, the synthetic methodology may be transferable to other heterocycles in order to gain access to a plethora of compounds with potential applications in medicinal and material chemistry.

EXPERIMENTAL SECTION

General Methods. Unless otherwise stated, solvents were evaporated at 40 °C/2 kPa and prepared compounds were dried at 30 °C at 2 kPa. Starting compounds and reagents were purchased from commercial suppliers (Sigma-Aldrich, Fluorochem, Acros Organics, Carbosynth, TCI) and used without further purification or were prepared according to published procedures. Reaction flasks were heated in aluminium heating blocks. Diethyl ether, tetrahydrofuran, dioxane, and acetonitrile were dried by activated neutral alumina (drysphere®). Dimethylformamide was dried by activated molecular sieves (3Å). Other dry solvents were purchased from commercial suppliers (Sigma-Aldrich, Acros Organics). Triethylamine was dried with potassium hydroxide under argon atmosphere in dark flask sealed with septum. Large-scale reactions were carried-out in the Syrris Atlas Potassium system with 2 l, 1 l or 0.5 l jacket reactor coupled with Julabo FP50-HL Refrigerated/Heating Circulator. Analytical TLC was performed on silica gel pre-coated aluminium plates with fluorescent indicator (Merck 60 F_{254}). Flash column chromatography was carried out by Teledyne ISCO CombiFlash Rf200 with dual absorbance detector. Various types of columns were used: a) Teledyne ISCO columns RediSepRf HP Silica GOLD in sizes 12 g, 40 g, 80 g and 120 g; b) Teledyne ISCO columns RediSepRf HP C18 Aq GOLD in sizes 50 g and 100 g; c) column Chromabond Flash DL 40, DL 80, DL 120 and DL 200, filled with FLUKA silica gel 60; d) Interchim puriFlash C18 Aq in sizes F0040 and F0080. Eluents were used: methanol (A), cyclohexane (B), ethyl acetate modified with 10% (v/v) of methanol (C), chloroform (D), water (E), cyclohexane modified with 0.5% of triethylamine (F). Mass spectra, UV spectra and purity of compounds were measured on Waters UPLC-MS system consisted of Waters UPLC H-Class Core System (column Waters Acquity UPLC BEH C18 1.7 mm, 2.1 x 100 mm), Waters Acquity UPLC PDA detector and Mass spectrometer Waters SQD2. The universal LC method was used (eluent H_2O/ CH_3CN, gradient 0 – 100%, run length 7 min) and MS method (ESI+ and/or ESI-, cone voltage = 30 V, mass detector range 100 – 1000 Da). Spectra are screened as a PDA acquisition, absorption at 254 nm, and mass spectrum of the main peak at 254 nm. HRMS spectra were recorded on Q-Tof micro (Waters) with CI ionization method or LTQ Orbitrap XL spectrometer (Thermo Fisher Scientific) with ESI ionization method. NMR spectra were recorded on Bruker Avance 400 or 500 spectrometers referenced to the residual solvent signal or a specified additive. Assignments of NMR signals are stated in supplement data and are based on heteronuclear correlation experiments HSQC, HMBC, COSY and NOESY in specific cases. Melting points were measured on BÜCHI Melting Point B-545.

*Ethyl 2-amino-5-methylthiophene-3-carboxylate (**1**)*.[19] Ethyl cyanoacetate (26.6 mL, 250 mmol, 1 eq.), sulfur (8.00 g, 250 mmol, 1 eq.) and triethylamine (34.8 mL, 250 mmol, 1 eq.) were dissolved in dimethylformamide (50 mL) at room temperature. Then, a solution of propanal (20.00 mL, 275 mmol, 1.1 eq.) in ethanol (7.50 mL) was added dropwise to the mixture (exothermic reaction!). The reaction mixture was stirred at 60 °C and monitored by UPLC/MS. The reaction was quenched by addition of water and extracted with ethyl acetate. The extract was washed with water and brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (B to 10% of C) afforded 34 g (74%) of the title compound as a red oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 6.59 (q, *J* = 1.3 Hz, 1H), 5.71 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.23 (d, *J* = 1.3 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.4, 161.6, 122.6, 120.9, 106.4, 59.6, 14.9, 14.6. MS (ESI-QMS) m/z: $[M + H]^+$ Calcd for $C_8H_{12}NO_2S$ 186.1; Found 186.2.

*Ethyl 2-bromo-5-methylthiophene-3-carboxylate (**2**)*.[20] Copper (I) bromide (7.24 g, 32.4 mmol, 1.2 eq.) was suspended in dioxane (50 mL) and the mixture was cooled to 0 °C. Then, *tert*-butyl nitrite (4.82 mL, 40.5 mmol, 1.5 eq.) was added and the mixture was stirred at 0 °C for 30 minutes. Subsequently, a solution of ethyl 2-amino-5-methylthiophene-3-carboxylate (**1**) (5 g, 27.0 mmol, 1 eq.) in acetonitrile (50 mL) was added and the mixture was stirred 30 minutes at 0 °C and 2 hours at room temperature. The reaction was quenched by addition of 1M HCl (aq.) and extracted with ethyl acetate. Extract was washed with water and brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (B to 5% of C) afforded 3.36 g (50%) of the title compound as a yellowish oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 7.01 (q, *J* = 1.2 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.38 (d, *J* = 1.2 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 162.1, 134.0, 131.0, 127.0, 116.6, 60.9, 15.4, 14.4. MS (ESI-QMS) m/z: $[M + H]^+$ Calcd for $C_8H_{10}BrO_2S$ 249.0; Found 249.0.

*Ethyl 2-(diethoxyphosphoryl)-5-methylthiophene-3-carboxylate (**3**)*. $Pd_2(dba)_3$ (92 mg, 0.10 mmol, 0.05 eq.) and xantphos (116 mg, 0.20 mmol, 0.1 eq.) were dissolved in dioxane (50 mL), then triethylamine (419 µL, 3.00 mmol, 1.5 eq.) was added. The mixture was stirred 15 minutes at room temperature and a solution of ethyl 2-bromo-5-methylthiophene-3-carboxylate (**2**) (500 mg, 2.01 mmol, 1 eq.) and diethyl phosphite (57 µL, 2.21 mmol, 1.1 eq.) in dioxane (10 mL) was added. The mixture was stirred 2 hours at 80 °C, an then it was cooled to 0 °C, quenched with 1M HCl (aq.), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (B to 20% of C) afforded 500 mg (81%) of the title compound as a yellow oil. ^{1}H NMR (401 MHz,

Chloroform-*d*) δ 7.27 (dd, *J* = 4.1, 1.0 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.27 – 4.09 (m, 4H), 2.48 (d, *J* = 1.0 Hz, 3H), 1.39 – 1.34 (m, 3H), 1.35 – 1.29 (m, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 162.1 (d, *J* = 2.9 Hz), 146.8 (d, *J* = 7.3 Hz), 138.6 (d, *J* = 8.8 Hz), 131.2 (d, *J* = 209.1 Hz), 129.8 (d, *J* = 14.6 Hz), 63.1 (d, *J* = 5.8 Hz), 61.3, 16.4 (d, *J* = 7.1 Hz), 15.2, 14.3. $^{31}P\{^{1}H\}$ NMR (162 MHz, Chloroform-*d*) δ 11.47. HRMS (CI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{20}O_5PS$ 307.0769; Found 307.0770.

*Ethyl 5-(bromomethyl)-2-(diethoxyphosphoryl)thiophene-3-carboxylate (**4**)*. Ethyl 2-(diethoxyphosphoryl)-5-methylthiophene-3-carboxylate (**3**) (100 mg, 0.3266 mmol, 1 eq.) was dissolved in dry acetonitrile (1 mL). Then, *N*-bromosuccinimide (233 mg, 1.31 mmol, 4 eq.) was added and the mixture was stirred overnight at 80 °C. The mixture was cooled to room temperature, quenched with water, extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (B to 20% of C) afforded 100 mg (80%) of the title compound as a clear oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 7.50 (d, *J* = 4.4 Hz, 1H), 4.56 (s, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.20 – 3.98 (m, 4H), 1.40 – 1.05 (m, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 161.3 (d, *J* = 2.9 Hz), 146.5 (d, *J* = 7.4 Hz), 138.0 (d, *J* = 8.8 Hz), 134.9 (d, *J* = 206.7 Hz), 131.3 (d, *J* = 14.5 Hz), 63.2 (d, *J* = 5.8 Hz), 61.4, 24.3, 16.2 (d, *J* = 6.6 Hz), 14.0. $^{31}P\{^{1}H\}$ NMR (162 MHz, Chloroform-*d*) δ 10.23. HRMS (ESI-FTMS) m/z: $[M + H]^+$ Calcd for $C_{12}H_{19}BrO_5PS$ 384.9869; Found 384.9868.

*Ethyl 4-bromo-2-(diethoxyphosphoryl)-5-methylthiophene-3-carboxylate (**5**)*. Ethyl 2-(diethoxyphosphoryl)-5-methylthiophene-3-carboxylate (**3**) (100 mg, 0.3266 mmol, 1 eq.) was dissolved in acetic acid (1 mL) in amber glass vial. Then, bromine (67 µL, 1.31 mmol, 4 eq.) was added and the mixture was stirred overnight at room temperature. The mixture was cooled to 0 °C, diluted with water, neutralized with sodium bicarbonate, extracted with ethyl acetate, washed with saturated solution (aq.) of sodium thiosulfate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (B to 20% of C) afforded 120 mg (96%) of the title compound a clear oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 4.36 (q, *J* = 7.2 Hz, 2H), 4.21 – 3.96 (m, 4H), 2.41 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.29 (td, *J* = 7.1, 0.7 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 163.0 (d, *J* = 3.1 Hz), 143.3 (d, *J* = 5.8 Hz), 140.2 (d, *J* = 10.1 Hz), 126.7 (d, *J* = 206.7 Hz), 110.8 (d, *J* = 18.4 Hz), 63.2 (d, *J* = 5.2 Hz), 62.2, 16.2 (d, *J* = 7.0 Hz), 15.4 (d, *J* = 1.8 Hz), 14.0. $^{31}P\{^{1}H\}$ NMR (162 MHz, Chloroform-*d*) δ 10.12. HRMS (ESI-FTMS) m/z: $[M + H]^+$ Calcd for $C_{12}H_{19}BrO_5PS$ 384.9869; Found 384.9868.

*Tert-butyl 4-(benzyloxy)-7-(5-(diethoxyphosphoryl)-4-(ethoxycarbonyl)-2-methylthiophen-3-yl)-5H-pyrrolo[3,2-d]pyrimidine-5-carboxylate (**7**)*. Ethyl 4-bromo-2-(diethoxyphosphoryl)-5-methylthiophene-3-carboxylate (**5**) (75 mg, 0.1947 mmol, 1 eq.) was dissolved in tetrahydrofuran (1 mL) and triethylamine (81 µL, 0.5841 mmol, 3 eq.) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (57 µL, 0.3894 mmol, 2 eq.) were added. The mixture was stirred at room temperature and a solution of Pd(*t*-$Bu_3P)_2$ (5 mg, 0.0097 mmol, 0.05 eq.) in tetrahydrofuran (1 mL) was added. The resulting mixture was stirred 2 hours at 40 °C, and then filtered through syringe filter, washed with dry tetrahydrofuran and evaporated. The flask with evaporated boronic ester was charged with *tert*-butyl 4-(benzyloxy)-7-bromo-5*H*-pyrrolo[3,2-*d*]pyrimidine-5-carboxylate (**9**) (83 mg, 0.2044 mmol, 1.05 eq.), XPhos Pd G2 (8 mg, 0.0097 mmol, 0.05 eq.), potassium phosphate tribasic (83 mg, 0.3894 mmol, 2 eq.), and the flask was flushed with argon. A mixture of tetrahydrofuran (4 mL) and water (1 mL) was added and the reaction was stirred 1 hour at 40 °C. The reaction was quenched with a mixture of saturated solution of NH_4Cl (aq.) and water (1:1), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (F to 20% of C) and on reverse phase (E to A) afforded 61 mg (50 %) of the title compound as a clear oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 7.87 (s, 1H), 7.58 – 7.49 (m, 2H), 7.41 – 7.34 (m, 2H), 7.34 – 7.28 (m, 1H), 5.65 (s, 2H), 4.27 – 4.11 (m, 4H), 4.14 (q, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 1.53 (s, 9H), 1.35 (td, *J* = 7.0, 0.7 Hz, 6H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 164.0 (d, *J* = 3.0 Hz), 156.5, 153.3, 152.3, 148.0, 146.2 (d, *J* = 6.4 Hz), 141.0 (d, *J* = 9.7 Hz), 136.5, 131.4, 129.9 (d, *J* = 15.5 Hz), 128.5, 128.4 – 128.0 (m), 126.9 (d, *J* = 208.3 Hz), 114.5 – 113.9 (m), 85.4, 68.4, 63.1 (d, *J* = 5.5 Hz), 61.5, 27.9, 16.4 (d, *J* = 6.8 Hz), 14.7 (d, *J* = 2.0 Hz), 13.9. ^{31}P{^{1}H} NMR (162 MHz, Chloroform-*d*) δ 11.66. HRMS (ESI-FTMS) m/z: $[M + H]^+$ Calcd for $C_{30}H_{37}O_8N_3PS$ 630.2034; Found 630.2031.

*4-(Benzyloxy)-7-bromo-5-((tert-butoxycarbonyl))-5H-pyrrolo[3,2-d]pyrimidine (**9**)*
The jacket reactor (2 l) was flushed with nitrogen, charged with benzyl alcohol (1 l) and the system was set to retain temperature 20 °C. Sodium metal (22.5 g, 977 mmol, 1.5 eq.) was added in portions and the mixture was stirred 20 hours under a small flow of nitrogen. The mixture was heated at 80 °C for 1 hour, and then it was cooled to 20 °C. 4-Chloro-5*H*-pyrrolo[3,2-*d*]pyrimidine (**8**) (100 g, 651 mmol, 1 eq.) was charged and the mixture was stirred at 80 °C until complete conversion was achieved (ca. 4 hours). The mixture was cooled to 5 °C, diluted with water (400 mL), pH was adjusted to pH 7 with 3M HCl (aq.) (ca. 100 - 130 mL) and it was heated to 20 °C. The mixture was extracted with chloroform (3 x 400 mL) and the organic phase was washed with brine (500 mL). The mixture was concentrated and benzyl

alcohol was evaporated at high vacuum at ca. 90 °C. The solid was filtered through a short pad of silica gel (600 g) with eluent (100% of D, then D with 5% of A). Solvents were evaporated and the residue was just dissolved in a refluxed mixture of ethyl acetate/methanol (1:1) and the solution was cooled to 30 °C. An anti-solvent pentane was slowly added (same volume as the mixture), the mixture was cooled to -20 °C within 3 hours, and it was stirred overnight. Crystals were collected, washed with pentane and dried. The procedure afforded 141 g (96%) of 4-(benzyloxy)-5*H*-pyrrolo[3,2-*d*]pyrimidine as white crystals, m. p. = 157.0 – 159.0 °C. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 9.33 (s, 1H), 8.58 (s, 1H), 7.49 – 7.43 (m, 2H), 7.41 (m, 1H), 7.38 – 7.32 (m, 2H), 7.35 (s, 1H), 6.67 (dd, *J* = 3.2, 2.1 Hz, 1H), 5.59 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 155.5, 150.6, 150.1, 136.2, 128.8 – 128.3 (m), 115.1, 103.3, 67.9. MS (ESI-QMS) m/z: $[M + H]^+$ Calcd for $C_{13}H_{12}N_3O$ 226.1; Found 226.1. The jacket reactor (1 l) was flushed with nitrogen and 4-(benzyloxy)-5*H*-pyrrolo[3,2-*d*]pyrimidine (40 g, 178 mmol, 1 eq.) was dissolved in tetrahydrofuran (500 mL) and *N*-bomosuccinimide (34.7 g, 195 mmol, 1.1 eq.) was added. The mixture was stirred at room temperature for 1 hour, during which the product crystalized. The solvent was evaporated to dryness and the crude mixture was used in the next step. The jacket reactor (1 l) was flushed with nitrogen and the crude mixture was dissolved in acetonitrile (400 mL). Then, 4-(dimethylamino)pyridine (2.2 g, 18 mmol, 0.1 eq.) was added, followed by slow addition (30 minutes) of a di-*tert*-butyl dicarbonate (58.2 g, 267 mmol, 1.5 eq.) solution in dry acetonitrile (100 mL). The reaction was stirred at room temperature until gas release ceased (ca. 2 hours). Solvents were evaporated and the solid was filtered through a short pad of neutral alumina (300 g) in a mixture of cyclohexane/ethylacetate (3:1, v/v). Solvents were evaporated and the solid was lyophilized from dioxane to yield 58 g (81%) of title compound **9** as a white solid, m.p. = 75.0 – 76.0 °C. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 8.68 (s, 1H), 7.92 (s, 1H), 7.56 – 7.48 (m, 2H), 7.43 – 7.27 (m, 4H), 5.65 (s, 2H), 1.54 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 156.5, 152.9, 152.0, 147.2, 136.3, 131.3, 128.6, 128.2, 128.1, 114.3, 96.8, 85.9, 68.7, 27.9. HRMS (ESI-FTMS) m/z: $[M + H]^+$ Calcd for $C_{18}H_{19}O_3N_3Br$ 404.0604; Found 404.0603.

*S-(thiophen-2-yl) benzothioate (**11**)* A flask was charged with CuI (900 mg, 4.76 mmol, 0.1 eq.) and 1,10-phenantroline (1.7 g, 9.52 mmol, 0.2 eq.) and the flask was flushed with argon. Toluene (100 mL) was added, followed by triethylamine (9.94 mL, 71.4 mmol, 1.5 eq.). The mixture was heated to 100 °C, then, 2-iodothiophene (10 g, 47.6 mmol, 1 eq.) and thiobenzoic acid (6.72 mL, 57.1 mmol, 1.2 eq.) were added simultaneously at once (otherwise major dehalogenation of 2-iodothiophene was observed). The reaction was quenched with mixture of saturated solution of $NaHCO_3$ (aq.) and water (1:1), extracted with ethyl acetate, washed with

brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (B to 2% of C) afforded 10.3 g (98%) of the title compound, which was lyophilized from dioxane to obtain yellowish solid. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 8.04 (d, *J* = 7.7 Hz, 2H), 7.67 – 7.58 (m, 2H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.28 (dd, *J* = 3.4, 1.0 Hz, 1H), 7.18 (dd, *J* = 5.3, 3.6 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 189.8, 136.4, 136.0, 134.0, 132.2, 128.9, 128.0, 127.7, 124.2. HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{11}H_8OS_2$ 220.0017; Found 220.0019.

*Ethyl 5-(benzoylthio)thiophene-2-carboxylate (**12**)* S-(thiophen-2-yl) benzothioate (**11**) (1 g, 4.54 mmol, 1 eq.) was dissolved in tetrahydrofuran (20 mL) and cooled to -50 °C. A solution of 2,2,6,6-tetramethylpiperidinylmagnesium chloride lithium chloride complex (9.99 mL, 9.99 mmol, 2.2 eq., 1M) in tetrahydrofuran was added dropwise and the mixture was stirred 30 minutes at -50 °C. Then, ethyl cyanoformate (989 µL, 9.99 mmol, 2.2 eq.) was added and the resulting mixture was stirred 30 minutes at -25 °C. The reaction was quenched with a mixture of saturated solution of NH_4Cl (aq.) and water (1:1), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (B to 10% of C) afforded 1.31 g (99%) of the title compound as a red oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 7.97 (dd, *J* = 8.4, 1.3 Hz, 2H, 9, 13), 7.78 (d, *J* = 3.9 Hz, 1H, 3), 7.63 – 7.54 (m, 1H, 11), 7.51 – 7.42 (m, 2H, 10, 12), 7.19 (d, *J* = 3.9 Hz, 1H, 4), 4.35 (q, *J* = 7.2 Hz, 2H, 18), 1.36 (t, *J* = 7.2 Hz, 3H, 19). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 188.0, 161.3, 138.7, 135.5, 135.3, 134.2, 133.1, 132.2, 128.9, 127.6, 61.4, 14.3. HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{14}H_{12}O_3S_2$ 292.0230; Found 292.0228.

*Ethyl 4-bromothiophene-3-carboxylate (**15**)*.[30] 3,4-Dibromothiophene (**14**) (10 g, 41.3 mmol, 1 eq.) was dissolved in tetrahydrofuran (100 mL) and cooled to 0 °C. A solution of isopropylmagnesium bromide (19.1 mL, 51.7 mmol, 1.25 eq., 2.7M) was added to the mixture keeping the temperature below 5 °C and the mixture was stirred 5 hours at 0 °C. Then, ethyl chloroformate (7.9 mL, 82.7 mmol, 2 eq.) was added keeping the temperature below 5 °C. The resulting mixture was stirred 15 minutes at 0 °C and overnight at room temperature. The reaction was cooled to 0 °C, quenched with 1M HCl (aq.), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (B to 10% of C) afforded 8.0 g (82%) of the title compound as a yellow oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 8.07 (d, *J* = 3.7 Hz, 1H), 7.27 (d, *J* = 3.6 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 161.3, 134.2, 131.3, 125.3, 110.8, 61.0, 14.3. MS (ESI-QMS) m/z: $[M + H]^+$ Calcd for $C_7H_8BrO_2S$ 234.9; Found 235.0.

*Diethyl 4-bromothiophene-2,3-dicarboxylate (**16**)*. Ethyl 4-bromothiophene-3-carboxylate (**15**) (5 g, 21.3 mmol, 1 eq.) was dissolved in tetrahydrofuran (50 mL) and cooled to -20 °C. A solution of 2,2,6,6-tetramethylpiperidinylmagnesium chloride lithium chloride complex (25.5 mL, 25.5 mmol, 1.2 eq., 1M) in tetrahydrofuran was added dropwise and the mixture was stirred 30 minutes at -20 °C. Then, ethyl cyanoformate (3.6 mL, 31.9 mmol, 1.5 eq.) was added and the resulting mixture was stirred 30 minutes at 0 °C. The reaction was quenched with mixture of saturated solution of NH_4Cl (aq.) and water (1:1), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (B to 10% of C) afforded 5.79 g (72%) of the title compound as a clear oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 4.41 – 4.23 (m, 4H), 1.30 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 163.2, 159.3, 139.2, 131.6, 131.3, 108.2, 62.1, 62.0, 13.9. HRMS (CI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{12}BrO_4S$ 306.9640; Found 306.9641.

*Diethyl 4-bromo-5-(((diisopropoxyphosphoryl)methyl)thio)thiophene-2,3-dicarboxylate (**17**)*. Diethyl 4-bromothiophene-2,3-dicarboxylate (**16**) (1 g, 3.26 mmol, 1 eq.) was dissolved in tetrahydrofuran (20 mL) and cooled to -20 °C. A solution of 2,2,6,6-tetramethylpiperidinylmagnesium chloride lithium chloride complex (3.9 mL, 3.91 mmol, 1.2 eq., 1M) in tetrahydrofuran was added dropwise and the mixture was stirred 30 minutes at -20 °C. Then, a solution of sulfur (156 mg, 4.89 mmol, 1.5 eq.) in tetrahydrofuran (10 mL) was added and the resulting mixture was stirred at 0 °C. After 30 minutes, diisopropyl triflyloxymethylphosphonate (1.46 g, 4.89 mmol, 1.5 eq.) was added and the mixture was stirred additional 30 minutes at 0 °C. The reaction was quenched with mixture of saturated solution of NH_4Cl (aq.) and water (1:1), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (B to 10% of C) afforded 1.65 g (98%) of the title compound as a yellow oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 4.75 (dhept, J = 7.7, 6.2 Hz, 2H), 4.42 (q, J = 7.2 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.17 (d, J = 14.0 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H), 1.36 – 1.30 (m, 15H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 163.6, 159.5, 140.4, 138.9 (d, J = 8.0 Hz), 131.9, 114.9, 72.0 (d, J = 6.9 Hz), 62.6, 62.3, 31.2 (d, J = 147.9 Hz), 26.5 – 22.4 (m), 14.2, 14.1. HRMS (ESI-FTMS) m/z: $[M + H]^+$ Calcd for $C_{17}H_{27}O_7BrPS_2$ 517.0114; Found 517.0107.

*Ethyl 4-bromo-2-(diethoxyphosphoryl)thiophene-3-carboxylate (**18**)*. $Pd_2(dba)_3$ (729 mg, 0.80 mmol, 0.05 eq.) and xantphos (922 mg, 1.59 mmol, 0.1 eq.) were dissolved in dioxane (100 mL) and triethylamine (3.32 mL, 23.9 mmol, 1.5 eq.) was added. The mixture was stirred 15 minutes at room temperature and a solution of ethyl 2,4-dibromothiophene-3-carboxylate

(**20**) (5 g, 15.9 mmol, 1 eq.) and diethyl phosphite (2.25 mL, 17.5 mmol, 1.1 eq.) in dioxane (20 mL) was added. The mixture was stirred 2 hours at 80 °C, then it was cooled to 0 °C, quenched with 1M HCl (aq.), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (B to 20% of C) afforded 5.04 g (85%) of the title compound as a yellow oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 6.0 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 4.26 – 4.05 (m, 5H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.37 – 1.29 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 162.7 (d, *J* = 2.9 Hz), 139.8 (d, *J* = 10.3 Hz), 131.8 (d, *J* = 204.0 Hz), 131.1 (d, *J* = 5.8 Hz), 111.6 (d, *J* = 19.7 Hz), 63.6 – 63.2 (m), 62.4, 16.8 – 16.0 (m), 14.1. ^{31}P{^{1}H} NMR (162 MHz, Chloroform-*d*) δ 9.46. HRMS (CI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{17}BrO_5PS$ 370.9718; Found 370.9717.

*Ethyl 4-bromo-2-iodothiophene-3-carboxylate (**19**)*. Ethyl 4-bromothiophene-3-carboxylate (**15**) (5 g, 21.3 mmol, 1 eq.) was dissolved in tetrahydrofuran (50 mL) and cooled to -20 °C. A solution of 2,2,6,6-tetramethylpiperidinylmagnesium chloride lithium chloride complex (25.5 mL, 25.52 mmol, 1.2 eq., 1M) in tetrahydrofuran was added dropwise and the mixture was stirred 30 minutes at -20 °C. Then, a solution of iodine (8.1 g, 31.91 mmol, 1.5 eq.) in tetrahydrofuran (30 mL) was added and the resulting mixture was stirred 30 minutes at 0 °C. The reaction was quenched with mixture of saturated solution of NH_4Cl (aq.) and water (1:1), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (B to 10% of C) afforded 6.8 g (88%) of the title compound as a clear oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 7.41 (s, 1H), 4.40 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 162.1, 136.6, 130.5, 108.9, 79.6, 61.9, 14.3. HRMS (CI-TOF) m/z: $[M + H]^+$ Calcd for $C_7H_7BrIO_2S$ 360.8395; Found 360.8395.

*Ethyl 2,4-dibromothiophene-3-carboxylate (**20**)*. Ethyl 4-bromothiophene-3-carboxylate (**15**) (5 g, 21.3 mmol, 1 eq.) was dissolved in tetrahydrofuran (50 mL) and cooled to -20 °C. A solution of 2,2,6,6-tetramethylpiperidinylmagnesium chloride lithium chloride complex (25.5 mL, 25.52 mmol, 1.2 eq., 1M) in tetrahydrofuran was added dropwise and the mixture was stirred 30 minutes at -20 °C. Then, a solution of 1,2-dibromotetrachloroethane (10.4 g, 31.9 mmol, 1.5 eq.) in tetrahydrofuran (30 mL) was added and the resulting mixture was stirred 30 minutes at 0 °C. The reaction was quenched with mixture of saturated solution of NH_4Cl (aq.) and water (1:1), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (B to 10% of C) afforded 5.4 g (81%) of the title compound as a yellowish oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 7.27 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.41 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR

(101 MHz, Chloroform-*d*) δ 161.8, 132.5, 125.2, 117.3, 109.6, 62.0, 14.3. HRMS (CI-TOF) m/z: $[M + H]^+$ Calcd for $C_7H_7Br_2O_2S$ 312.8533; Found 312.8532.

*Diethyl 4-(4-(benzyloxy)-5-(tert-butoxycarbonyl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)thiophene-2,3-dicarboxylate (**24**)*. Diethyl 4-bromothiophene-2,3-dicarboxylate (**16**) (3 g, 9.77 mmol, 1 eq.) was dissolved in tetrahydrofuran (30 mL) and triethylamine (4.1 mL, 29.3 mmol, 3 eq.) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.8 mL, 19.5 mmol, 2 eq.) were added. The mixture was stirred at room temperature and a solution of $Pd(t\text{-}Bu_3P)_2$ (250 mg, 0.49 mmol, 0.05 eq.) in tetrahydrofuran (5 mL) was added. The resulting mixture was stirred 2 hours at 40 °C, and then filtered through celite, washed with dry tetrahydrofuran and evaporated. The flask with evaporated boronic ester was charged with *tert*-butyl 4-(benzyloxy)-7-bromo-5*H*-pyrrolo[3,2-*d*]pyrimidine-5-carboxylate (**9**) (4.1 g, 10.3 mmol, 1.05 eq.), XPhos Pd G2 (231 mg, 0.29 mmol, 0.03 eq.), potassium phosphate tribasic (4.1 g, 19.54 mmol, 2 eq.), and the flask was flushed with argon. A mixture of tetrahydrofuran (60 mL) and water (15 mL) was added and the reaction was stirred 1 hour at 40 °C. The reaction was quenched with a mixture of saturated solution of NH_4Cl (aq.) and water (1:1), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (F to 20% of C) and on reverse phase (E to A) afforded 3.37 g (82%) of the title compound as a yellowish solid, which was lyophilized from dioxane. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.61 (s, 1H), 7.98 (s, 1H), 7.53 (d, J = 7.3 Hz, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.32 (t, J = 7.3 Hz, 1H), 5.63 (s, 2H), 4.44 – 4.18 (m, 4H), 1.48 (s, 9H), 1.31 – 1.25 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 165.4, 160.3, 155.9, 152.3, 151.8, 147.2, 137.4, 136.3, 131.6, 131.0, 129.6, 128.6, 128.4, 128.0, 127.8, 113.6, 112.7, 85.6, 67.9, 61.9, 61.7, 27.2, 14.0, 13.8. HRMS (ESI-FTMS) m/z: $[M + H]^+$ Calcd for $C_{28}H_{30}N_3O_7S$ 552.1799; Found 552.1792.

*Diethyl 4-(4-(benzyloxy)-5-(tert-butoxycarbonyl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-5-(((diisopropoxyphosphoryl)methyl)thio)thiophene-2,3-dicarboxylate (**25**)*. A flask was charged with tetrahydrofuran (2 mL), 2,2,6,6-tetramethylpiperidine (370 µL, 2.18 mmol, 1.2 eq.), *N,N,N′,N′*-tetramethylethylenediamine (326 µL, 2.18 mmol, 1.2 eq.) and the mixture was stirred and cooled to -78 °C. Then, *n*-butyllithium (870 µL, 2.18 mmol, 1.2 eq., 2.5M) was added dropwise and the mixture was stirred for 5 minutes at -78 °C. This solution was added during 30 seconds to a solution of diethyl 4-(4-(benzyloxy)-5-(tert-butoxycarbonyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)thiophene-2,3-dicarboxylate (**24**) (1 g, 1.81 mmol, 1 eq.) in tetrahydrofuran (20 mL) at -78 °C. After 2 minutes of stirring, a room temperature solution of sulfur (116 mg, 3.62 mmol, 2 eq.) in tetrahydrofuran (15 mL) was added at once. The resulting mixture was

stirred 2 minutes at -78 °C, and then 10 minutes at 0 °C. Then, diisopropyl triflyloxymethylphosphonate (892 mg, 2.72 mmol, 1.5 eq.) was added and the mixture was stirred for 30 minutes at 0 °C. The reaction was quenched with a mixture of saturated solution of NH_4Cl (aq.) and water (1:1), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (F to 20% of C) afforded 939 mg (68%) of the title compound as a yellow oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 7.96 (s, 1H), 7.53 – 7.43 (m, 2H), 7.36 – 7.29 (m, 2H), 7.29 – 7.23 (m, 1H), 5.61 (s, 2H), 4.60 (dhept, *J* = 7.8, 6.2 Hz, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.13 (d, *J* = 14.4 Hz, 2H), 1.49 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 4H), 1.22 (d, *J* = 6.2 Hz, 6H), 1.17 (d, *J* = 6.0 Hz, 6H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 164.4, 159.9, 156.2, 152.8, 152.0, 147.5, 141.0 (d, *J* = 8.9 Hz), 139.6, 136.2, 133.5, 132.3, 131.8, 128.3, 127.9, 113.9, 112.5, 85.3, 71.5 (d, *J* = 6.6 Hz), 68.1, 61.6, 32.9 (d, *J* = 146.3 Hz), 27.6, 23.8 (d, *J* = 4.2 Hz), 23.6 (d, *J* = 4.6 Hz), 14.0, 13.7. ^{31}P{^{1}H} NMR (162 MHz, Chloroform-*d*) δ 21.48. HRMS (ESI-FTMS) m/z: $[M + H]^+$ Calcd for $C_{35}H_{45}N_3O_{10}PS_2$ 762.2279; Found 762.2276.

*Tert-butyl 4-(benzyloxy)-7-(5-(diethoxyphosphoryl)-4-(ethoxycarbonyl)thiophen-3-yl)-5H-pyrrolo[3,2-d]pyrimidine-5-carboxylate (**26**)*. Ethyl 4-bromo-2-(diethoxyphosphoryl)thiophene-3-carboxylate (**18**) (1 g, 2.69 mmol, 1 eq.) was dissolved in tetrahydrofuran (10 mL) and triethylamine (1.1 mL, 8.08 mmol, 3 eq.) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (780 µL, 5.39 mmol, 2 eq.) were added. The mixture was stirred at room temperature and a solution of $Pd(t\text{-}Bu_3P)_2$ (69 mg, 0.13 mmol, 0.05 eq.) in tetrahydrofuran (2 mL) was added. Resulting mixture was stirred 2 hours at 40 °C, and then filtered through celite, washed with dry tetrahydrofuran and evaporated. The flask with evaporated boronic ester was charged with *tert*-butyl 4-(benzyloxy)-7-bromo-5*H*-pyrrolo[3,2-*d*]pyrimidine-5-carboxylate (**9**) (1.14 g, 2.82 mmol, 1.05 eq.), XPhos Pd G2 (64 mg, 0.08 mmol, 0.03 eq.), potassium phosphate tribasic (1.1 g, 5.34 mmol, 2 eq.), and the flask was flushed with argon. A mixture of tetrahydrofuran (20 mL) and water (5 mL) was added and the reaction was stirred 1 hour at 40 °C. The reaction was quenched with mixture of saturated solution of NH_4Cl (aq.) and water (1:1), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (F to 20% of C) afforded 1.26 g (76%) of the title compound as a clear oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 8.64 (s, 1H), 8.33 (d, *J* = 6.1 Hz, 1H), 8.04 (s, 1H), 7.56 – 7.49 (m, 2H), 7.41 – 7.29 (m, 3H), 5.66 (s, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 4.29 – 4.08 (m, 4H), 1.54 (s, 9H), 1.41 – 1.27 (m, 9H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.10 (d, *J* = 2.9 Hz), 156.6, 152.9, 152.4, 147.9, 139.6 (d, *J* =

11.1 Hz), 136.5, 132.5 (d, *J* = 16.9 Hz), 132.0 (d, *J* = 6.5 Hz), 131.4, 130.2 (d, *J* = 204.7 Hz), 129.8, 128.6, 128.2, 128.1, 114.5, 114.1, 85.1, 68.4, 63.4 – 63.0 (m), 62.2, 27.9, 16.7 – 15.9 (m), 14.1. $^{31}P\{^{1}H\}$ NMR (162 MHz, Chloroform-*d*) δ 11.47. HRMS (ESI-FTMS) m/z: $[M + H]^+$ Calcd for $C_{29}H_{35}N_3O_8PS$ 616.1877; Found 616.1876.

*Diethyl 4-(4-(benzyloxy)-5-(tert-butoxycarbonyl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-5-iodothiophene-2,3-dicarboxylate (**28**)*. A flask was charged with tetrahydrofuran (2 mL), 2,2,6,6-tetramethylpiperidine (370 µL, 2.18 mmol, 1.2 eq.), *N,N,N′,N′*-tetramethylethylenediamine (326 µL, 2.18 mmol, 1.2 eq.) and the mixture was stirred and cooled to -78 °C. Then, *n*-butyllithium (870 µL, 2.18 mmol, 1.2 eq., 2.5M) was added dropwise and the mixture was stirred for 5 minutes at -78 °C. This solution was added during 30 seconds to a solution of diethyl 4-(4-(benzyloxy)-5-(tert-butoxycarbonyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-7-yl)thiophene-2,3-dicarboxylate (**24**) (1 g, 1.81 mmol, 1 eq.) in tetrahydrofuran (20 mL) at -78 °C. After 2 minutes of stirring, a room temperature solution of iodine (919 mg, 3.62 mmol, 2 eq.) in tetrahydrofuran (15 mL) was added at once. The resulting mixture was stirred 2 minutes at -78 °C and then 10 minutes at 0 °C. The reaction was quenched with a mixture of saturated solution of NH_4Cl (aq.) and water (1:1), extracted with ethyl acetate, washed with a saturated aqueous solution of $Na_2S_2O_5$, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (F to 20% of C) afforded 882 mg (72%) of the title compound as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.15 (s, 1H), 7.59 – 7.53 (m, 2H), 7.43 – 7.36 (m, 2H), 7.38 – 7.31 (m, 1H), 5.64 (s, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 1.49 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) δ 162.9, 159.4, 155.9, 152.0, 151.9, 147.3, 139.1, 136.9, 136.3, 135.5, 132.2, 128.4, 128.0, 128.0, 113.7, 113.1, 91.6, 85.8, 68.0, 61.9, 61.5, 27.1, 13.9, 13.5. HRMS (ESI-FTMS) m/z: $[M + H]^+$ Calcd for $C_{28}H_{29}IN_3O_7S$ 678.0771; Found 678.0770 $[M + H]^+$.

*Tert-butyl 4-(benzyloxy)-7-(5-(diethoxyphosphoryl)-2-(((diisopropoxyphosphoryl)methyl)thio)-4-(ethoxycarbonyl)thiophen-3-yl)-5H-pyrrolo[3,2-d]pyrimidine-5-carboxylate (**31**)*. *Tert*-butyl 4-(benzyloxy)-7-(5-(diethoxyphosphoryl)-4-(ethoxycarbonyl)thiophen-3-yl)-5*H*-pyrrolo[3,2-*d*]pyrimidine-5-carboxylate (**26**) (1 g, 1.62 mmol, 1 eq.) was dissolved in tetrahydrofuran (20 mL) and the solution was cooled to -95 °C in bath containing methanol and liquid nitrogen. Then, a solution of lithium diisopropylamide (2.43 mL, 2.43 mmol, 1.5 eq., 1M) was added dropwise and the mixture was stirred 5 minutes. Then, a room temperature solution of sulfur (104 mg, 3.24 mmol, 2 eq.) in tetrahydrofuran (10 mL) was added at once. The resulting mixture was stirred 2 minutes at -95 °C, and then 10

minutes at 0 °C. Then, diisopropyl triflyloxymethylphosphonate (797 mg, 2.72 mmol, 1.5 eq.) was added and the mixture was stirred additional 30 minutes at 0 °C. The reaction was quenched with mixture of saturated solution of NH_4Cl (aq.) and water (1:1), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (F to 20% of C) afforded 843 g (59%) of the title compound as a yellow oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 8.45 (s, 1H), 7.96 (s, 1H), 7.47 – 7.39 (m, 2H), 7.30 – 7.22 (m, 2H), 7.24 – 7.13 (m, 1H), 5.55 (s, 2H), 4.54 (hept, *J* = 7.7, 6.2 Hz, 2H), 4.19 – 4.07 (m, 4H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.04 (d, *J* = 14.3 Hz, 2H), 1.43 (s, 9H), 1.26 (td, *J* = 7.1, 0.6 Hz, 6H), 1.16 (d, *J* = 6.2 Hz, 6H), 1.11 (d, *J* = 6.2 Hz, 6H), 1.03 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 162.9 (d, *J* = 3.5 Hz), 156.1, 152.9, 151.8, 147.5, 141.3 (dd, *J* = 9.0, 6.2 Hz), 140.4 (d, *J* = 9.5 Hz), 136.1, 135.1 (d, *J* = 14.7 Hz), 132.2 (d, *J* = 205.1 Hz), 131.8, 128.2, 127.8, 113.7, 113.0, 85.1, 71.4 (d, *J* = 6.6 Hz), 68.0, 62.9 (d, *J* = 5.3 Hz), 61.3, 32.6 (d, *J* = 146.0 Hz), 27.5, 23.6 (dd, *J* = 14.9, 4.6 Hz), 16.0 (d, *J* = 6.7 Hz), 13.4. ^{31}P{^{1}H} NMR (162 MHz, Chloroform-*d*) δ 21.35, 9.92. HRMS (ESI-FTMS) m/z: $[M + H]^+$ Calcd for $C_{36}H_{50}N_3O_{11}P_2S_2$ 826.2357; Found 826.2351.

*Diethyl 4-(4-(benzyloxy)-5-(tert-butoxycarbonyl)-5H-pyrrolo[3,2-d]pyrimidin-7-yl)-5-((2-(diethoxyphosphoryl)ethyl)thio)thiophene-2,3-dicarboxylate (**34**)*. Followed the previous procedure, after the addition of the sulfur solution and 10 minutes of stirring, the reaction was quench with 0.1M HCl (aq.) and extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. The crude solid was then dissolved in *N,N*-dimethylformamide (30 mL) and potassium carbonate (749 mg, 5.43 mmol, 3 eq.) was added, followed by addition of diethyl 2-bromoethylphosphonate (1.3 mL, 7.24 mmol, 4 eq.). The mixture was stirred 7 days at room temperature. The reaction was quenched with mixture of saturated solution of NH_4Cl (aq.) and water (1:1), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (F to 20% of C) afforded 800 mg (59%) of the title compound as a yellow oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 8.55 (d, *J* = 0.8 Hz, 1H), 7.92 (d, *J* = 0.6 Hz, 1H), 7.55 – 7.44 (m, 2H), 7.38 – 7.32 (m, 2H), 7.32 – 7.27 (m, 1H), 5.61 (s, 2H), 4.30 (qt, *J* = 7.1, 1.0 Hz, 2H), 4.21 – 4.11 (m, 2H), 4.07 – 3.91 (m, 4H), 3.10 – 2.98 (m, 2H), 2.07 – 1.88 (m, 2H), 1.59 – 1.43 (m, 9H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 6H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 164.6, 160.1, 156.3, 152.9, 152.1, 147.7, 140.7, 139.9, 136.3, 133.2, 132.1, 131.8, 128.4, 128.0, 114.0, 112.7, 85.5, 68.3, 61.9 (d, *J* = 6.6 Hz), 61.8, 61.8, 30.9 (d, *J* = 3.2 Hz), 27.7, 26.4 (d, *J* = 137.0 Hz), 16.4 (d, *J* = 6.2 Hz), 14.2, 13.8.

$^{31}P\{^{1}H\}$ NMR (162 MHz, Chloroform-*d*) δ 29.94. HRMS (ESI-FTMS) m/z: $[M + H]^+$ Calcd for $C_{34}H_{43}N_3O_{10}PS_2$ 748.2122; Found 748.2120.

*Tert-butyl 4-(benzyloxy)-7-(5-(diethoxyphosphoryl)-2-((2-(diethoxyphosphoryl)ethyl)thio)-4-(ethoxycarbonyl)thiophen-3-yl)-5H-pyrrolo[3,2-d]pyrimidine-5-carboxylate (**35**)*. Followed the previous procedure, after the addition of the sulfur solution and 10 minutes of stirring, the reaction was quench with 0.1M HCl (aq.) and extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. The crude solid was then dissolved in *N,N*-dimethylformamide (30 mL) and potassium carbonate (671 mg, 4.86 mmol, 3 eq.) was added, followed by addition of diethyl 2-bromoethylphosphonate (1.2 mL, 6.48 mmol, 4 eq.). The mixture was stirred 3 days at room temperature. The reaction was quenched with mixture of saturated solution of NH_4Cl (aq.) and water (1:1), extracted with ethyl acetate, washed with brine, dried with magnesium sulfate and evaporated. Purification by flash chromatography on silica gel (F to 20% of C) afforded 658 mg (50%) of the title compound as a yellow oil. ^{1}H NMR (401 MHz, Chloroform-*d*) δ 8.54 (s, 1H), 7.96 (s, 1H), 7.58 – 7.46 (m, 2H), 7.40 – 7.33 (m, 2H), 7.33 – 7.27 (m, 1H), 5.63 (s, 2H), 4.29 – 4.15 (m, 4H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.07 – 3.94 (m, 4H), 3.11 – 2.93 (m, 2H), 2.03 – 1.89 (m, 2H), 1.52 (s, 9H), 1.35 (td, *J* = 7.1, 0.7 Hz, 6H), 1.25 (t, *J* = 7.1 Hz, 6H), 1.13 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, Chloroform-*d*) δ 163.4 (d, *J* = 3.0 Hz), 156.5, 153.2, 152.1, 147.9, 141.2 (d, *J* = 6.1 Hz), 140.8 (d, *J* = 9.4 Hz), 136.5, 135.2 (d, *J* = 14.7 Hz), 132.4 (d, *J* = 205.4 Hz), 132.1, 128.5, 128.1, 114.1, 113.4, 85.5, 68.4, 63.4 (d, *J* = 5.3 Hz), 62.0 (d, *J* = 6.6 Hz), 61.7, 30.9 (d, *J* = 3.2 Hz), 27.8, 26.5 (d, *J* = 137.1 Hz), 16.5 (d, *J* = 5.9 Hz), 16.4 (d, *J* = 7.3 Hz), 13.8. $^{31}P\{^{1}H\}$ NMR (162 MHz, Chloroform-*d*) δ 29.93, 10.14. HRMS (ESI-FTMS) m/z: $[M + H]^+$ Calcd for $C_{35}H_{48}N_3O_{11}P_2S_2$ 812.2200; Found 812.2198.

ASSOCIATED CONTENT

Supporting Information. Copies of the NMR (^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$) and UPLC/MS spectra with full signal assignment.

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Notes

The authors declare no conflict of interest.

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