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# *N*-Directed Pd-Catalyzed Photoredox-Mediated C–H Arylation for Accessing Phenyl-Extended Analogues of Biginelli/Suzuki-Derived Ethyl 4-Methyl-2,6-diphenylpyrimidine-5-carboxylates

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**Abstract:** The availability and application of direct, functional group-compatible C–H activation methods for late-stage modification of small-molecule bioactives and other valuable materials remains an ongoing challenge in organic synthesis. In the current study, we demonstrate that a LED-activated, photoredox-mediated, $Pd(OAc)_2$-catalyzed C–H arylation, employing a phenyldiazonium aryl source and either tris(2,2′-bipyridine)ruthenium(II) or (2,2′-bipyridine)bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-kN][phenyl-kC]iridium(III) as photoredox initiator, may successfully produce unprecedented mono- and bis-phenyl derivatives of functionality-rich 2,6-diphenylpyrimidine substrates at room temperature. The series of 19 substrates employed herein, which share the biologically-relevant 4-methyl-2,6-diphenylpyrimidine-5-carboxylate scaffold, were generated via a synthetic route involving (3-component) Biginelli condensation, oxidative dehydrogenation of the obtained 3,4-dihydropyrimidin-2(1*H*)-one to 2-hydroxypyrimidine, *O*-sulfonylation, and Suzuki-Miyaura C–C cross-coupling. Submission of these substrates to pyrimidine-N-atom-directed C–H arylation conditions led to regioselective phenylation at the *ortho* site(s) of the pyrimidine-C2-connected phenyl ring, revealing substituent-dependent electronic and steric effects. A focused library of 18 mono- and 10 bis-phenyl derivatives was generated. Its members exhibit interesting 3D and peripheral substitution features that render them promising for evaluation in drug discovery efforts.

**Keywords:** C–H arylation; photoredox catalysis; LED; Suzuki-Miyaura C–C cross-coupling; Biginelli reaction; pyrimidine-based compound library



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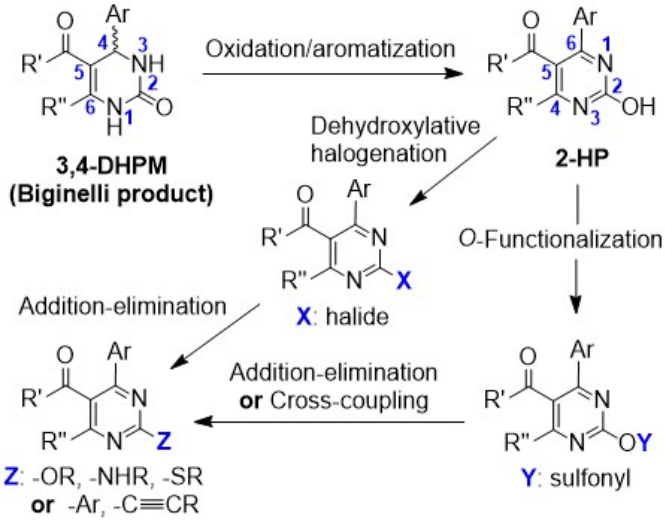
## 1. Introduction

The Biginelli 3-component condensation belongs to a set of multi-component, atom-economic chemical transformations, frequently employed by medicinal chemists for single-stage generation of *N*-based heterocyclic scaffolds from readily available building blocks [1,2]. The classic Biginelli, which generates substituted 3,4-dihydropyrimidin-2(1*H*)-ones (3,4-DHPMs, Scheme 1) from urea, an aldehyde, and a beta-ketoester or surrogate, as well as several Biginelli variants, have been exploited in the context of combinatorial chemistry to deliver new molecular libraries for biological screening [3–7]. Previous efforts have led to the discovery of Biginelli products exhibiting a diverse range of biological activities, including anti-inflammatory, anti-viral, anti-cancer, anti-mitotic, anti-microbial, anti-tubercular, anti-fungal, anti-diabetic, anti-oxidant, anti-hypertensive, adrenoreceptor antagonistic, and calcium channel blocking [8,9]. Moreover, another biologically significant *N*-based scaffold, the 2-hydroxypyrimidine (2-HP, Scheme 1), can be readily obtained by oxidative dehydrogenation of 3,4-DHPMs and ensuing aromatization [10–14]. Notably, 2-hydroxypyrimidines may serve as synthetic precursors to nucleobases, vitamins, synthetic/unnatural amino-acids, natural products, and pharmaceuticals [15–19].




**Scheme 1.** Known transformations via which Biginelli reaction-generated 3,4-DHPMs can be converted to C2-functionalized derivatives. [Ar = aryl; R = alkyl or aryl; R′ = alkyl, aryl, alkoxy, aryloxy, alkylamino, or arylamino; R″ = alkyl].

Synthetic methodologies so far described for derivatization of Biginelli products are largely dictated by the intrinsic reactivity of the 3,4-DHPM scaffold, addressing concerns of compatibility with the existing functionalities, namely, the multiple heteroatoms, an α,β-unsaturated carbonyl moiety and a reaction-prone alkyl substituent on C6. Specifically, analogues have been reported, resulting from the following processes: N1 or N3 alkylation or acylation [20–25]; C6 alkyl substituent elaboration to a functionalized derivative [26,27]; and various intramolecular cyclizations (e.g., N1–C6, C2–N3, C4–C5, C4–C6, C5–C6) [24,26,28–30] depending on the nature of substituents on each position.

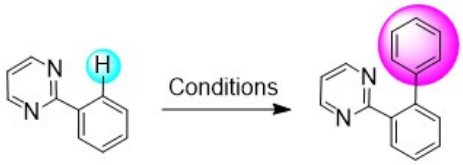
Access to multi-substituted pyrimidines, by means of C2 modification of 3,4-DHPMs, to eventually form a C–heteroatom or C–C bond, requires prior aromatization of Biginelli products [10–14] and conversion of the resulting C2–OH to a good leaving group, such as halide or sulfonate (Scheme 1) [31–33]. This is eventually replaced by nucleophiles [34–36] or submitted to cross-coupling reactions [37–40]. Interestingly, in cases of C–C cross-couplings, further catalytic functionalization of the C2-installed aryl systems, by taking advantage of the proximal pyrimidine moiety's directing capacity, has not been exploited to date for this biologically significant compound class.

Recognizing an untapped potential of C2-arylated Biginelli derivatives to undergo late-stage diversification and provide access to unprecedented oligo-aryl compound structures with "drug-like" features and novel 3D properties, we decided to apply a C–H activation approach. The recent emergence of numerous C–H activation, specifically C–H arylation, methodologies allows for alternative functionalization of biologically-relevant scaffolds [41–46] compatible with sensitive functionalities, which may afford access to derivatives previously unattainable by conventional methods. In this case, we envisaged that direct (single-step) $sp^2$ C–H arylation of 2-aryl-pyrimidines would enable installation of additional aryl–aryl bonds in a programmable manner. This aryl-extension on Biginelli–Suzuki generated precursors would afford precious derivatives of enhanced hydrophobicity and steric bulk relative to the mother compound.

Analogous $sp^2$ C–H arylations benefit from exploiting Lewis-basic functional groups already present in the substrate, most notably, pyridines [47–51], amides [52–55], or oximes [56,57], to direct catalysts regioselectively to the *ortho* position of a neighbouring phenyl ring. While pyrimidines are less frequently encountered as directing groups, a limited number of protocols for direct C–H arylation of simple 2-aryl-pyrimidines have been described. Among these, pyrimidine-directed $sp^2$ C–H arylation has been shown to occur under iron catalysis in combination with Ph-Grignard reagents [58], rhodium catalysis employing $ArSi(OMe)_3$ [59], or $Ar_3In$ [60] as the aryl source, as well as cobalt-manganese

co-catalysis in combination with arylboronic acids [61] (Table 1, entries 1–4). Some of the forementioned methods may pose practical limitations for compound library generation via parallel synthesis due to their requirement for high-temperature conditions or need for aryl sources that are too reactive, incompatible with sensitive functionalities, or not readily available. In contrast, a promising report by Sanford and co-workers, employing a CFL-photoactivated Pd(II)/Ru(II) system and readily-obtained diazonium salts as aryl source, at room temperature (Table 1, entry 5), was demonstrated on pyridines, amides, and other substrate classes, including a single pyrimidine example [62]. However, pyrimidines, and in particular substituted ones, were not further investigated in this transformation. Variations of this protocol were demonstrated on purine-directed [63] and lactam- and pyridine-directed [64] cases, with the latter replacing the diazonium phenyl source and Ru(II) photoinitiator with diphenyliodonium salt and Ir(III) photoinitiator, respectively.

**Table 1.** Synthetic methods previously reported for the *N*-directed C–H arylation of simple, unsubstituted 2-phenylpyrimidines.




| Entry | Ph Source | Conditions | Ref. |
|---|---|---|---|
| 1 | PhMgBr | $Fe(acac)_3$, Phenanthroline, $ZnCl_2$.TMEDA, THF, $ClC(Me)_2CH_2Cl$, $N_2$, 0 °C, 16 h | [58] |
| 2 | $PhSi(OMe)_3$ | $[Cp^*RhCl_2]_2$, $Cu(OAc)_2$, AgF, THF-$H_2O$, $N_2$, 80 °C, 24 h | [59] |
| 3 | $Ph_3In$ | $Rh(PPh_3)_3Cl$, PhCl-THF, Ar, 120 °C, 48 h | [60] |
| 4 | $PhB(OH)_2$ | $Co(acac)_2$, $Mn(OAc)_2.4H_2O$, HFIP, air, 80 °C, 12 h | [61] |
| 5 | $PhN_2.BF_4$ | $Pd(OAc)_2$, $Ru(bpy)_3Cl_2.6H_2O$, MeOH, $N_2$, CFL, r.t., 8 h | [62] |

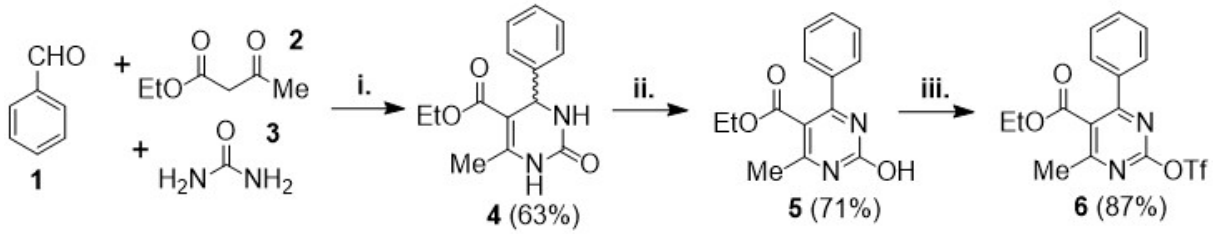
These reports prompted us to develop a variation of the Sanford catalytic method, that introduces a LED light source in place of the CFL, rendering it amenable to small-scale, parallel solution synthesis for production of compound libraries. Our aim focused on delivering unprecedented aryl-extended derivatives via $sp^2$ C–H arylation on a set of ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylate substrates, obtained via a Biginelli–oxidation–*O*-sulfonylation–Suzuki route. To the best of our knowledge, this is the first time 2,6-diphenylpyrimidine substrates, especially functionality-rich ones, have been successfully examined in a transformation of this type with the purpose of creating structural/peripheral diversity. The obtained compounds are anticipated to be of great interest for systematic biological screening, owing to their biologically-privileged central scaffold, expected to favourably bias any focused libraries that incorporate it in terms of retaining similar activities, as well as their tunable hydrophobicity and steric bulk relative to their precursors and their unusual oligo-aryl connectivity and "drug-like" features.

## 2. Results and Discussion

An efficient synthetic strategy had to be developed in order to deliver a series of ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylate-based compounds. These were to serve in the role of precursors toward an unprecedented library of tetraaryl and/or pentaaryl end-products in an intended final photoactivated C–H arylation step that would expand the aryl–aryl-connected carbon skeleton of the molecules.

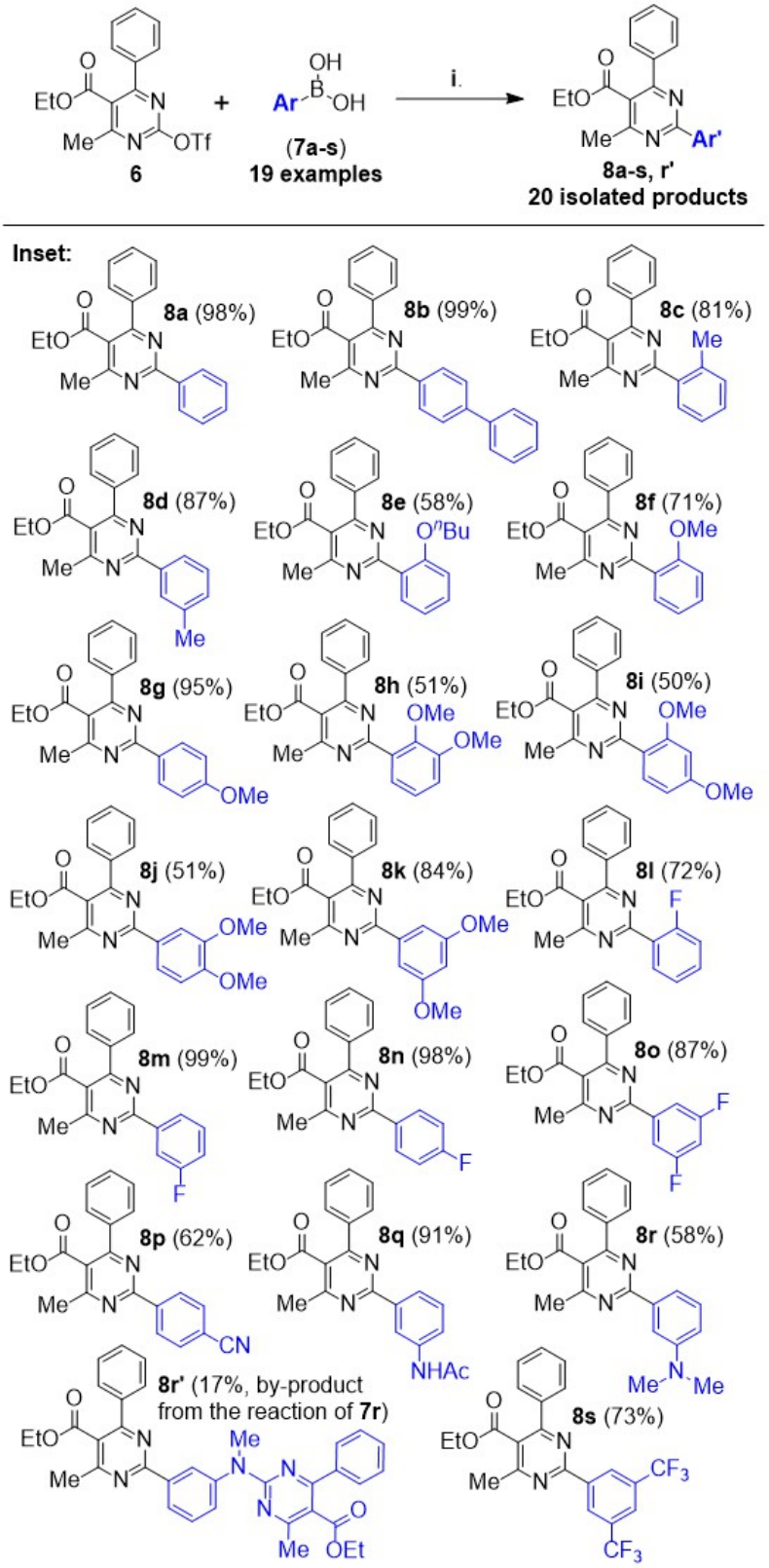
First, a Biginelli 3-component condensation was employed to generate an initial 3,4-DHPM precursor (Scheme 2). In the current study, we selected a Biginelli protocol

involving $SnCl_2$ as Lewis acid catalyst [65], which, after modification, was carried out in methoxyethanol solvent under reflux. The combination of benzaldehyde (**1**), ethyl acetoacetate (**2**) and urea (**3**) afforded multi-substituted dihydropyrimidinone **4** in 63% yield, sufficiently pure to be used in the next step of the synthesis without need for chromatography. Intermediate **4** was subsequently converted to its oxidized counterpart, ethyl 2-hydroxy-4-methyl-6-phenyl-pyrimidine-5-carboxylate (**5**) in 71% yield, via copper-mediated oxidation, with TBHP as the oxidant and $K_2CO_3$ as the base, in a biphasic DCM-$H_2O$ system under mild heating conditions [38]. In turn, compound **5,** which, based on $^1H$ NMR data, in $CDCl_3$ is encountered in the 2-hydroxypyrimidine form rather than a tautomeric form, was readily converted to trifluoromethanesulfonyl ester **6** in 87% yield, using $Tf_2O$ in DCM in the presence of $Et_3N$.



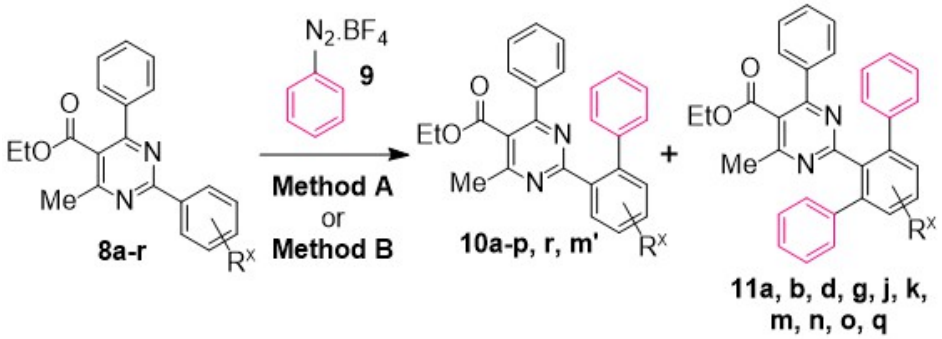

**Scheme 2.** Three-step process used in this study, involving Biginelli 3-component condensation, oxidative dehydrogenation, and trifluoromethanesulfonyl (Tf) ester formation, to afford key intermediate **6** from simple building blocks. Key: i. Methoxyethanol, $SnCl_2.\frac{1}{2}H_2O$, 125 °C, 48 h; ii. DCM, $CuCl_2$, $K_2CO_3$, TBHP, 35–40 °C, 24 h; iii. DCM, $Et_3N$, $Tf_2O$, 0 °C, 1 h, then r.t., 12 h.

Compound **6** was subsequently submitted to a series of Suzuki–Miyaura C–C cross-coupling reactions [38] with a set of 19 phenylboronic acids (**7a–s**) to deliver a small library of ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylates (**8a–s**, Ar = Ar′, Scheme 3) that exhibit peripheral (substituent) diversity. The selection of phenylboronic acids for this diversity-introducing step covered a range of electron-withdrawing and electron-donating substituents, substituent steric sizes, as well as aromatic mono- and di-substitution patterns. The expected Suzuki–Miyaura C–C cross-coupling products were obtained in all cases (Scheme 3, inset) in good to excellent yields (50–99%). In the case of boronic acid **7r** (substituted with 3-$NMe_2$ group), the formation of a minor side-product (**8r′**, 17%) was observed in addition to the (major) Suzuki–Miyaura product, **8r**. This side-product is the result of a C–N cross-coupling with an additional unit of **6** on the amine nitrogen atom of the substituent following a single N-demethylation.



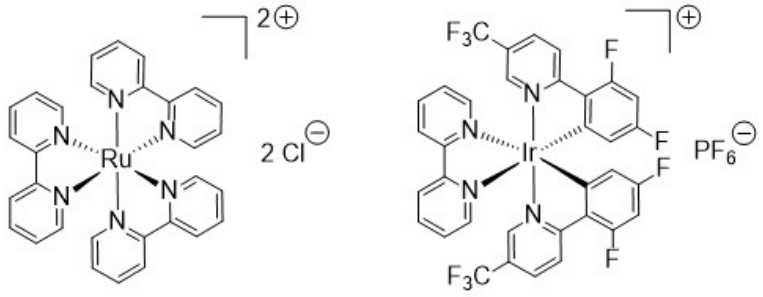

**Scheme 3.** Diversity-introducing step (parallel Suzuki–Miyaura C–C cross-coupling reactions) employed for generating a library of ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylates (**8a–s, r′**) from intermediate **6**. Aryl (Ar) groups contributed by the phenylboronic acid building blocks (**7a–s**) are highlighted in blue. For all products except **8r′** (an unexpected C–C and C–N bis-adduct produced alongside **8r**), Ar = Ar′. Key: i. 1,4-Dioxane, $Pd(OAc)_2$, $PPh_3$, $K_3PO_4$, 110 °C, 16 h.

In the final stage of our synthetic process, we intended to explore the application of a pyrimidine-N-atom-directed C–H arylation on the obtained ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylates (**8a–s**) using phenyldiazonium tetrafluoroborate (**9**) as phenyl donor (Scheme 4). This phenyl source was chosen for the ease of preparation [66], low cost, and the fact that it produces no organic by-product. Prior to submitting the entire set of available precursors (**8a–s**) to this transformation, it was necessary to screen a number of conditions on the simplest model system, **8a** ($R^X$ = H, Scheme 4), in order to determine operational reaction parameters. The choice of 0.1 equivalents of catalyst $Pd(OAc)_2$ to 0.05 equivalents of photoredox initiator, as well as 0.1 M substrate concentration, were adopted from the published process by Sanford and co-workers [62] and remained fixed during parameter optimization. All reactions took place under $N_2$ atmosphere. Due to the existence of more than one possible reactive sites in the substrate, we initially chose to employ an excess of $PhN_2.BF_4$ (4 equivalents) and reaction time of 8 h (Table 2, entry 1). Lower amounts of phenyl source were found to hamper conversion (Table 2, entries 2,3). Shorter reaction times proved insufficient, while longer reaction times did not have any beneficial effect on reaction conversion (Table 2, entries 4,5). The original Sanford protocol was simplified herein by introducing a commercially available, household 12.5 W (1521 lumen) white LED lamp as a viable light source, which rendered the process simple and applicable to parallel solution synthesis. Our initial control experiments indicated that both catalyst and photoredox initiator are essential components in order for the reaction to proceed under the LED lamp. Notably, no product formation was observed when the reaction mixture was stirred in the dark. The white LED was preferred over a 36 W blue LED (460 nm, matching the absorption wavelength of the Ru(II)-photoinitiator), which afforded lower conversion (Table 2, entries 6,7), appearing to enhance formation of a degradation product of the phenyldiazonium precursor.




**Scheme 4.** LED light-induced direct C–H arylation of ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylates (**8a–r**) leads to mono-phenyl (type **10**) and/or di-phenyl (type **11**) derivatives. Newly added Ph rings are highlighted in magenta. $R^X$ = pre-existing substituent(s). Key: Method A. MeOH, $Pd(OAc)_2$, Ru(II) photoinitiator, AgOAc, white LED, r.t., 8 h. Method B. MeOH, $Pd(OAc)_2$, Ir(III) photoinitiator, white LED, r.t., 8 h.

**Table 2.** Various conditions screened for application in the photoactivated C–H arylation step, based on the reaction of model compound **8a** with $PhN_2.BF_4$ (**9**), under LED light, $Pd(OAc)_2$ catalysis and Ru(II) or Ir(III) photoinitiation (for reaction, see Scheme 4).[a]




| Entry | LED Type | Equiv of $PhN_2.BF_4$ [b] | Solvent | Photo-Initiator | Additive | Reaction Time (h) | % Conversion [c] |
|---|---|---|---|---|---|---|---|
| 1 | white | 4 | MeOH | Ru(II) | - | 8 | 41 |
| 2 | white | 1 | MeOH | Ru(II) | - | 8 | 12 |
| 3 | white | 2 | MeOH | Ru(II) | - | 8 | 22 |
| 4 | white | 4 | MeOH | Ru(II) | - | 4 | 31 |
| 5 | white | 4 | MeOH | Ru(II) | - | 16 | 38 |
| 6 | blue | 4 | MeOH | Ru(II) | - | 8 | 16 |
| 7 | blue | 4 | 1,4-Dioxane | Ru(II) | $Cs_2CO_3$ | 8 | 9 |
| 8 | white | 4 | $MeO(CH_2)_2OH$ | Ru(II) | - | 8 | <5 |
| 9 | white | 4 | EG | Ru(II) | - | 8 | 28 |
| 10 | white | 4 | HFIP | Ru(II) | - | 8 | <5 |
| 11 | white | 4 | $CH_3CN$ | Ru(II) | - | 8 | 0 |
| 12 | white | 4 | NMP | Ru(II) | - | 8 | 0 |
| 13 | white | 4 | DMSO | Ru(II) | - | 8 | N/A [d] |
| 14 | white | 4 | 1,4-Dioxane | Ru(II) | - | 8 | 15 |
| 15 | white | 4 | Toluene | Ru(II) | - | 8 | 0 |
| 16 | white | 4 | MeOH | Ru(II) | $Cs_2CO_3$ | 8 | 10 |
| **17** | **white** | **4** | **MeOH** | **Ru(II)** | **AgOAc** | **8** | **59** |
| 18 | white | 4 | MeOH | Ru(II) | NaOAc | 8 | 25 |
| 19 | white | 4 | MeOH | Ru(II) | $NH_4OAc$ | 8 | 30 |
| 20 | white | 4 | MeOH | Ru(II) | $KO^tBu$ | 8 | 35 |
| **21** | **white** | **4** | **MeOH** | **Ir(III)** | **-** | **8** | **56** |
| 22 | white | 4 | EG | Ir(III) | - | 8 | 35 |
| 23 | white | 4 | 1,4-Dioxane | Ir(III) | - | 8 | 10 |
| 24 | white | 4 | MeOH | Ir(III) | AgOAc | 8 | 52 |
| 25 | white | 4 | EG | Ir(III) | AgOAc | 8 | 35 |
| 26 | white | 4 | 1,4-Dioxane | Ir(III) | AgOAc | 8 | 17 |

[a] In all cases, $PhN_2.BF_4$ served as the phenyl source, 0.1 equiv $Pd(OAc)_2$ and 0.05 equiv of photoredox initiator were used, and reactions took place at 0.1 M substrate (**8a**) concentration; [b] White LED was a Phillips, 12.5 W, 1521 lumen bulb; blue LED was a Highgrow, 36 W (18 × 2 W), 460 nm bulb; [c] Based on $^1$H NMR analysis of the crude mixture of the reaction of substrate **8a**, after aqueous workup; [d] In this case the reaction took a different path, producing different products, and was not processed further.

Keeping the fore-mentioned parameters fixed, we carried out investigations of the effect of the solvent, additive, and photoredox initiator on reaction conversion (Table 2, entries 8–26). Some bases were included in this screening in hope of facilitating the C–H activation step by sequestering AcOH. AgOAc was expected to serve as re-oxidant for the Pd-catalyst, as previously suggested by others [67,68], in case catalyst reductive degradation turned out to compromise reaction conversion. Notably, all conditions found to convert substrate **8a**, with the sole exception of DMSO solvent conditions (Table 2, entry 13), showed similar behaviour with regard to product distribution. Based on TLC monitoring, the same two products were always obtained, later shown to be the result of either mono- or bis-phenylation on the two equivalent ortho-positions of the phenyl ring attached to the C2-position of the pyrimidine. Structure elucidation took place after successful chromatographic isolation and $^1$H NMR characterization of the two products,

showing integration factor reduction by 1 or complete disappearance of the most downfield proton signal, which corresponds to the 2 equivalent ortho-protons of substrate **8a**. This change was accompanied by increase of proton count by either 5 or 10 for the mono- and bis-phenylated derivative, respectively, indicating successful phenyl incorporation. This assessment was independently confirmed by obtaining a single crystal X-ray structure of the mono-phenylated product **10a** (Figure 1), documenting that C–H arylation had indeed occurred on the ortho position of the C2-attached phenyl ring.

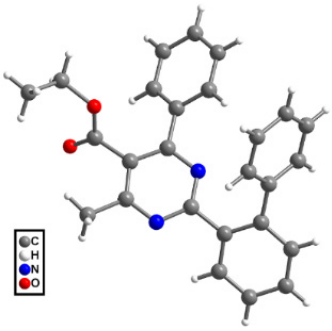



**Figure 1.** Single crystal X-ray structure of mono-phenylated product **10a** (CCDC identification number: 1935971) in ball-and-stick representation.

As shown in Table 2, the most promising of the solvents tried in combination with the homoleptic Ru(II) photoredox initiator, tris(2,2′-bipyridine)ruthenium(II) chloride hexahydrate, in the absence of any additives (entries 1, 8–15), were MeOH, ethylene glycol, and 1,4-dioxane (in this order). The best of these, MeOH, a "green" solvent, was also tested in the presence of various additives (entries 16–20), with AgOAc being the only one to noticeably improve yield (entry 17). Finally, the best three solvents were tested in combination with the heteroleptic Ir(III) photoredox initiator, (2,2′-bipyridine)bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl-kN][phenyl-kC]iridium(III) hexafluorophosphate, in the absence or presence of AgOAc (entries 21-26). Absence of the additive afforded somewhat better results with this catalyst (entry 21). The two optimal sets of conditions (highlighted in bold in Table 2) were termed Method A and Method B and were selected for application on the full set of substrates, i.e., **8a–s**. Table 3 indicates which of the two methods was used on each substrate.

**Table 3.** Isolated products from LED-activated, Pd-catalyzed C–H arylation reaction.

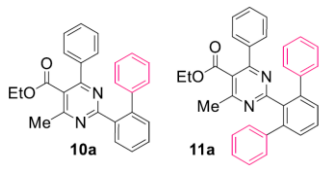
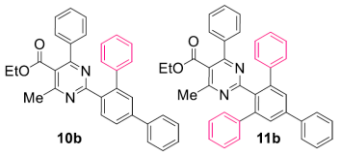
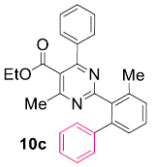
| Entry | Substrate | Method/Conversion/Product Ratio | Isolated Products |
|---|---|---|---|
| 1 | **8a** | A (59%); **10a**/**11a** = 1.24:1 |  |
| 2 | **8b** | A (58%); **10b**/**11b** = 1.27:1 |  |
| 3 | **8c** | B (52%); **10c** only |  |

**Table 3.** *Cont.*

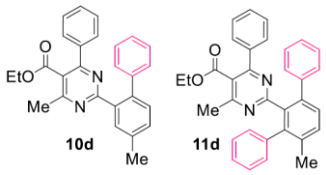
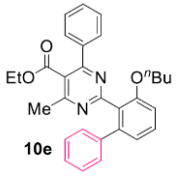
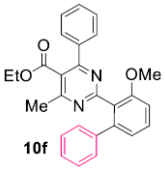
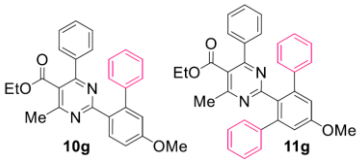
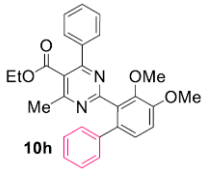
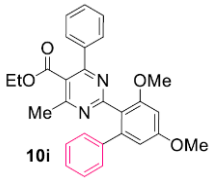
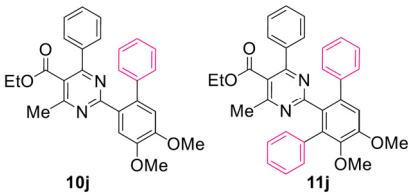
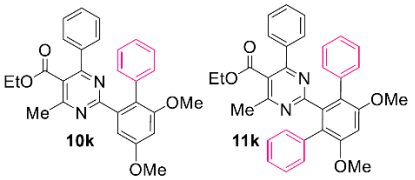
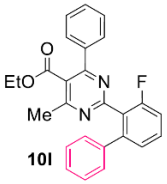
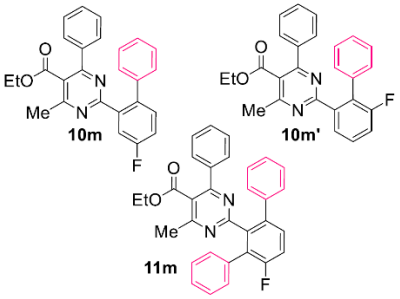
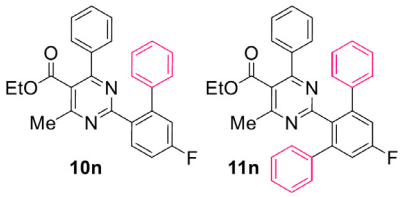
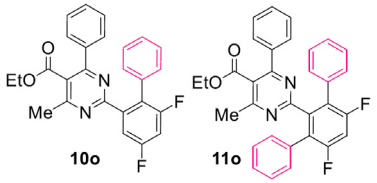
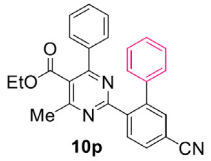
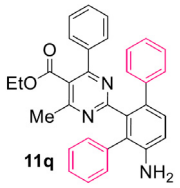
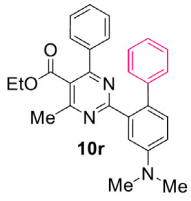
| Entry | Substrate | Method/Conversion/Product Ratio | Isolated Products |
|---|---|---|---|
| 4 | **8d** | A (42%); **10d**/**11d** = 3.67:1 |  |
| 5 | **8e** | A (30%); **10**e only |  |
| 6 | **8f** | B (31%); **10f** only |  |
| 7 | **8g** | A (33%); **10g**/**11g** = 1.22:1 |  |
| 8 | **8h** | B (42%); **10h** only |  |
| 9 | **8i** | B (30%); **10i** only |  |
| 10 | **8j** | A (47%); **10j**/**11j** = 1.85:1 |  |
| 11 | **8k** | A (44%); **10k**/**11k** = 1.20:1 |  |
| 12 | **8l** | A (20%); **10l** only |  |

**Table 3.** *Cont.*

| Entry | Substrate | Method/Conversion/Product Ratio | Isolated Products |
|---|---|---|---|
| 13 | **8m** | A (28%); **10m**/**10m'**/**11m** = 3.33:1:1 |  |
| 14 | **8n** | A (24%); **10n**/**11n** = 4.05:1 |  |
| 15 | **8o** | A (26%); **10o**/**11o** = 1.60:1 |  |
| 16 | **8p** | A (58%); **10p** only |  |
| 17 | **8q** | A (33%); **11q** only |  |
| 18 | **8r** | A (64%); **10r** only |  |

Ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylate substrates **8a–s** were submitted in parallel to the C–H arylation reaction (Scheme 4). To the best of our knowledge, this is the first time that functionality-rich 2,6-diphenylpyrimidines (comprising ester, alkoxide, amide, tertiary amine, fluoride, and cyanide substituents) have been examined in a C–H arylation. This class of substrates imposes a considerable synthetic challenge, since the pyrimidine moiety intended to serve as catalyst directing group is electron-deficient, further so due to the presence of an electron-withdrawing C5-ethyl ester substituent. This challenge is reflected in the moderate conversions (Table 3), determined after product isolation by (flash) liquid chromatography, with the recovered starting material in all cases accounting for >95% of the non-converted percentage. The mono- and bis-derivatives were successfully

separated. Despite its limitations, this method's utility resides in providing direct access to novel biologically-relevant compounds, some of which are not attainable by alternative methods. The multi-milligram quantities of products obtained in this study are deemed sufficient for small-scale, high-throughput screening applications.

Systematic and meticulous $^{1}$H and $^{13}$C NMR analysis was used for structural elucidation of the chromatographically isolated products in each case (original spectra can be found in Supplementary Materials). This revealed that all substrates (except **8s**) behaved very similarly to substrate **8a** in terms of regioselectivity, with the only observed products being those from pyrimidine-C2-attached phenyl ring ortho C–H arylation. Interestingly, no products were detected from C–H arylation on the pyrimidine-C6-attached phenyl ring. This observed regioselectivity could be attributed to: (a) different steric hindrance imposed at the two alternative N-atom sites of the pyrimidine, controlling placement of the catalyst; (b) different electron density distributions at the two N-atoms; (c) a difficulty of the C6-phenyl ring to reach co-planar orientation relative to the directing pyrimidine due to the C5-carboxylate; d) a statistical advantage of the C2-phenyl ring reaction site due to its proximity to two pyrimidine N-atoms rather than one. Computational studies, planned in a future stage, are expected to shed light into the origins of this observed regioselectivity.

Seven substrates (**8a**, **8b**, **8g**, **8k**, **8n**, **8o,** and **8p**) feature a symmetric substitution pattern on the C2-attached phenyl ring undergoing C–H arylation. In all these cases, except for **8p**, two products, the mono- and bis-phenyl derivative, were obtained. The mono-product was the major one, despite the presence of excess diazonium salt in the reaction mix. This suggests that the first phenylation imposes a restriction to the second phenylation, presumably by altering the pyrimidine-phenyl ring N–C2–C1′–C2′ dihedral angle, thus, compromising catalyst placement by the directing N-atom prior to the C–H activation. The ratio of (isolated) mono- to bis-phenyl derivative was somewhat higher in examples involving electron-withdrawing substituents, with substrate **8p** ($R^X$ = 4-CN) affording exclusively the mono-phenylated product, **10p** (58% yield). While the bis-products, obtained in low yields, generally limit the synthetic utility of the reaction with regard to mono-product formation, for the purposes of this particular project, they were considered as one additional contribution to the generated molecular library's peripheral and 3D diversity. Substrate **8s** did not afford any products in repeated attempts employing either Method A or Method B conditions (hence, not included in Table 3) and was recovered quantitatively, indicating that the 3,5-di($CF_3$) substitution pattern leads to deactivation, likely due to a combination of steric hindrance and the significant electron-withdrawing impact of the two $CF_3$ substituents.

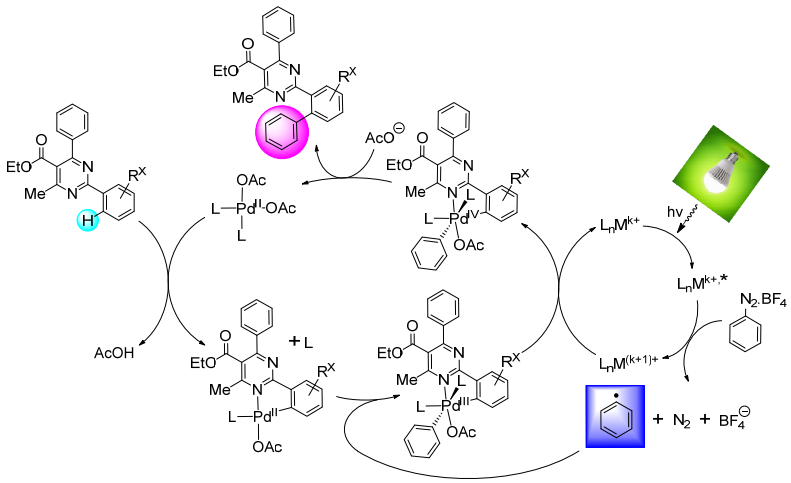
In the cases of ortho-substituted substrates **8c**, **8e**, **8f**, **8h**, **8i,** and **8l**, the expected mono-phenyl derivatives were obtained from reaction on the single unoccupied ortho site. Several of these substrates proved challenging when treated under the conditions of either Method A or B, with poor conversions observed, probably due to a detrimental effect of the pre-existing ortho substituent on the pyrimidine-phenyl ring N–C2–C1′–C2′ dihedral angle. Presence of alkoxy ortho-substituent (Table 3, entries 5, 6, and 9) correlated with reduced yields (**10e**—30%; **10f**—31%; **10i**—30% respectively), but the presence of a second alkoxy substituent, para to the incoming phenyl group (Table 3, entry 8) seemed to counterbalance this effect (**10h**—42%). Moreover, a 2-F substituent (Table 3, entry 12) appeared to deactivate the system (**10l**—20%), while this was not the case for a 2-Me substituent (Table 3, entry 3) which afforded the highest yield in this sub-group (**10c**—52%).

The remaining substrates (**8d**, **8j**, **8m**, **8q,** and **8r**) were unsymmetrically substituted, with two non-equivalent ortho sites for reaction on the C2-phenyl ring. The respective mono-phenyl derivatives, with the incoming phenyl ring being added para to a pre-existing electron donating substituent, were dominant in the cases of **8d**, **8j,** and **8r**. This is indicative of a combined result of electronic and steric effects, as the preferred reaction site is both electron-rich and sterically less hindered compared to the alternative site (adjacent to a pre-existing substituent). In these three examples, the alternative mono-phenyl derivative at the most hindered site did not form or formed only in trace (as suggested by TLC) however, it

was non-isolable chromatographically. In the cases of **8d** and **8j**, a bis-phenyl derivative also formed as a minor product. Substrate **8m** was the only one to afford both possible mono-phenyl derivatives (**10m** and **10m'**), with the first occurring in higher yield, presumably due to electronic control from a pre-existing F. A bis-phenyl derivative (**11m**) was also isolated. These unusual fluorinated products, as well as other fluorinated derivatives in this study, represent new and potentially valuable entries due to fluoride widely being used as a hydrogen isosteric replacement in medicinal chemistry. In the case of **8r**, where the electron-donating effect of the 3-$NMe_2$ substituent is more pronounced and the steric hindrance on the ortho site adjacent to this substituent is enhanced, the mono-phenyl derivative from reaction on the less hindered position, para to the amino-substituent, was the sole isolated product (**10r**), obtained in high yield (64%). The structure assignment was confirmed by a 2D NMR $^1$H-$^1$H NOESY experiment, which revealed a relay between the N-Me and two of the aromatic protons, including the "isolated" one (see Supplementary Materials). Finally, the reaction of **8q** led to isolation of only bis-arylated product (**11q**—33%), despite the unsymmetric substitution pattern. The observed degradation of the acetamide moiety to an aniline may be responsible for this, since $-NH_2$ could potentially enhance reactivity of both the ortho and para positions relative to it without placing considerable steric hindrance on the most adjacent one (the ortho), unlike $-NMe_2$.

Overall, the effect of electron-withdrawing substituents appeared to reduce conversion to aryl-extended products in contrast to electron-donating substituents, which increased conversion if positioned para to a possible reaction site.

In alignment with previous reports employing Pd(II) as catalyst and photoredox initiators of the types used herein [62–64], a mechanistic hypothesis can be formulated for the C–H arylation (Scheme 5). A Pd(II) catalytic species is responsible for the C–H activation of the ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylate substrate, directed by coordination of the catalyst to a pyrimidine N-atom. Presence of electron-donating groups, particularly positioned para to the carbopalladation site, as in the case of substrate **8r**, is likely to facilitate this early C–H activation step. Photoactivation of the $M^{k+}$ ($Ru^{2+}$ or $Ir^{3+}$) species by LED lamp produces an excited $M^{k+,*}$ species which, via SET to phenyl-diazonium tetrafluoroborate, leads to generation of phenyl radicals and $M^{(k+1)+}$ ($Ru^{3+}$ or $Ir^{4+}$) species. The phenyl radical may add to the palladium center, generating a transient Pd(III) species, which is subsequently oxidized to Pd(IV), with the oxidation being coupled to $M^{k+}$ regeneration. The Pd(IV) species undergoes reductive elimination to release the C–C coupled product and regenerate the Pd(II) catalyst.




**Scheme 5.** Proposed mechanism for the photoredox-initiated, Pd-catalyzed C–H phenylation of ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylates employed in this study. The photoredox initiator is tris(2,2′-bipyridine)ruthenium(II) chloride hexahydrate (Method A, $M^{k+}$ = $Ru^{2+}$) or (2,2′-bipyridine)bis[3,5-difluoro-2-[5-(trifluoro-methyl)-2-pyridinyl-kN][phenyl-kC]iridium(III) hexa-fluorophosphate (Method B, $M^{k+}$ = $Ir^{3+}$).

## 3. Materials and Methods

### *3.1. General Methods*

Organic chemicals and Pd-catalysts were purchased from TCI Europe N.V. (Zwijndrecht, Belgium); photoredox initiators from Strem Chemicals (Newburyport, MA, USA); other inorganic chemicals from Sigma-Aldrich (Saint Lewis, MO, USA); anhydrous organic solvents from Carlo Erba Reagents (Val de Reuil, France); silica gel 60, TLC plates and NMR deuterated solvents from Merck (Kenilworth, NJ, USA).

All reactions were performed under nitrogen atmosphere and in anhydrous solvents, unless otherwise stated. Silica gel 60 (0.06–0.2 mm) was employed in (flash) liquid chromatography purifications. Reactions were monitored by TLC, using silica-coated F254 aluminum TLC plates.

NMR spectra were obtained on a Bruker Avance III Ultrashield Plus spectrometer (Billerica, MA, USA), at 500 MHz for $^{1}$H NMR and 125 MHz for $^{13}$C NMR (25 °C, chemical shifts relative to tetramethylsilane). MS data (ES-API) were collected on an Agilent InfinityLab LC/MSD–1260 Infinity II system (Santa Clara, CA, USA). Melting points were obtained on a Bibby Sterilin Stuart SMP11 melting point apparatus (Staffordshire, UK).

### *3.2. Synthetic Methods and Characterization Data*

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4**): Urea (**3**) (2.70 g, 45 mmol, 1.5 equiv) and $SnCl_2.\frac{1}{2}H_2O$ (0.30 g, 1.5 mmol, 0.05 equiv) were transferred to a round-bottom flask, which was fitted with a vertical condenser and set under nitrogen atmosphere. Methoxyethanol (30 mL) was added, followed by benzaldehyde (**1**) (3.0 mL, 30 mmol, 1 equiv) and ethyl acetoacetate (**2**) (3.8 mL, 30 mmol, 1 equiv), and the mixture was refluxed at 125 °C for 48 h. It was then cooled down and the solvent was removed under vacuum. The resulting crude solid was suspended in $CH_3CN$ and collected by filtration, washed with cold $CH_3CN$, and dried under house vacuum overnight. Overall, 4.90 g (18.8 mmol, 63%) of compound **4** were isolated as white powder. It was shown to be pure by $^{1}$H and $^{13}$C NMR and was progressed to the next step without further purification. $^{1}$H NMR (DMSO-$d_6$), δ (ppm): 1.09 (3H, t, J = 7.1 Hz), 2.24 (3H, s), 3.98 (2H, q, J = 7.1 Hz), 5.14 (1H, d, J = 3.3 Hz), 7.21–7.27 (3H, m, signals overlapping), 7.32 (2H, app. t, J = 7.6 Hz), 7.72 (1H, bs), 9.17 (1H, s). $^{13}$C NMR (DMSO-$d_6$), δ (ppm): 14.07, 17.77, 53.95, 59.17, 99.24, 126.23, 127.25, 128.38, 144.86, 148.36, 152.11, 165.33. MS (ES-API), m/z: calcd for $C_{14}H_{16}N_2O_3$: 260.12; found 261.10 [M + $H^+$]. m.p. 178 °C.

Ethyl 2-hydroxy-4-methyl-6-phenylpyrimidine-5-carboxylate (**5**): Compound **4** (2.60 g, 10 mmol, 1 equiv), $CuCl_2$ (0.134 g, 1 mmol, 0.1 equiv), and $K_2CO_3$ (0.691 g, 5 mmol, 0.5 equiv) were transferred to a round-bottom flask, and the flask was fitted with a vertical condenser and set under nitrogen atmosphere. DCM (30 mL) was added, and the mixture was heated at 35–40 °C. This was followed by slow dropwise addition of TBHP 70% wt solution (6.9 mL solution, 50 mmol, 5 equiv) under vigorous stirring, and the reaction continued for 24 h, maintaining the same temperature. The mixture was then cooled down to r.t. Aqueous sodium thiosulfate 0.5 M solution and aqueous $NH_4Cl$ 25% wt solution were added, and the mixture was stirred at r.t. for 1 h. The pH was checked to be around 7–8 at the end of the stirring time. The mixture was then transferred to a separatory funnel and extracted. The organic layer was collected and dried over $Na_2SO_4$. After filtering out the drying agent, the solvent was concentrated under vacuum. The crude sample was applied to a silica column for flash chromatography and eluted with hexane-ethyl acetate step gradient (from 1:2 to 1:10) to afford 1.83 g (7.1 mmol, 71%) of compound **5** as a pale yellow powder. $^{1}$H NMR ($CDCl_3$), δ (ppm): 0.93 (3H, t, J = 7.1 Hz), 2.62 (3H, s), 4.05 (2H, q, J = 7.1 Hz), 7.43 (2H, app. t, J = 7.5 Hz), 7.48 (1H, tt, $J_1$ = 7.2 Hz, $J_2$ = 1.3 Hz), 7.60 (2H, d, J = 7.8 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.44, 19.32, 61.62, 111.50, 128.01, 128.38, 130.83, 158.23, 166.08 (three signals overlapping with other peaks). MS (ES-API), m/z: calcd for $C_{14}H_{14}N_2O_3$: 258.10; found 259.00 [M + $H^+$]. m.p. 174 °C.

Ethyl 4-methyl-6-phenyl-2-(((trifluoromethyl)sulfonyl)oxy)pyrimidine-5-carboxylate (**6**): Compound **5** (0.493 g, 1.9 mmol, 1 equiv) was transferred to a round-bottom flask, and

the flask was sealed and set under nitrogen atmosphere. Anhydrous DCM (5 mL) was added, followed by $Et_3N$ (0.66 mL, 4.75 mmol, 2.5 equiv), and the mixture was stirred and cooled at 0 °C. A solution of triflic anhydride ($Tf_2O$) (0.48 mL, 2.85 mmol, 1.5 equiv) in DCM (2 mL) was added dropwise and the mixture was vigorously stirred at the same temperature for 1 h. The reaction mixture was then brought up to r.t., and the stirring continued for 12 h. The mixture was subsequently diluted with DCM and washed with aqueous NaCl saturated solution and water. The organic layer was collected and dried over $Na_2SO_4$. After filtering out the drying agent, the solvent was concentrated under vacuum. The crude sample was applied to a silica column for flash chromatography and eluted with hexane-ethyl acetate step gradient (from 10:1 to 6:1), to afford 0.644 g (1.65 mmol, 87%) of compound **6** as a colorless viscous oil. $^1$H NMR ($CDCl_3$), δ (ppm): 1.12 (3H, t, J = 7.1 Hz), 2.67 (3H, s), 4.26 (2H, q, J = 7.1 Hz), 7.48 (2H, app. t, J = 7.5 Hz), 7.54 (1H, t, J = 7.3 Hz), 7.69 (2H, d, J = 7.7 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.61, 22.62, 62.51, 118.55 ($CF_3$, q, J = 321.1 Hz), 125.51, 128.58, 128.80, 131.34, 135.55, 157.27, 166.66, 167.44, 170.69. MS (ES-API), m/z: calcd for $C_{15}H_{13}F_3N_2O_5S$: 390.05; found 391.00 [M + $H^+$].

General method for the synthesis of ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylates via Suzuki–Miyaura C–C cross-coupling: Boronic acid **7** (0.75 mmol, 1.5 equiv), $Pd(OAc)_2$ (0.006 g, 0.025 mmol, 0.05 equiv), $PPh_3$ (0.026 g, 0.1 mmol, 0.2 equiv), and $K_3PO_4$ (0.265 g, 1.25 mmol, 2.5 equiv) were transferred to a round-bottom flask, and the flask was fitted with a vertical condenser and set under nitrogen atmosphere. A solution of compound **6** (0.195 g, 0.5 mmol, 1 equiv) in anhydrous 1,4-dioxane (3.5 mL) was syringed in, and the resulting mixture was refluxed at 110 °C for 16 h. It was then cooled down to r.t., quenched with aqueous $NH_4Cl$ 25% wt solution, and extracted three times with diethyl ether. The combined organic phase was washed with aqueous $Na_2CO_3$ and NaCl solution and dried over $Na_2SO_4$. After filtering out the drying agent, the solvent was removed under vacuum. The crude sample was re-dissolved in DCM, applied to a silica column for flash chromatography, and eluted first with hexane and then with hexane-ethyl acetate step gradient (the end-ratio of solvents was different in each case, depending on product polarity).

• Ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylate (**8a**): Yield: 98%; white solid. $^1$H NMR ($CDCl_3$), δ (ppm): 1.09 (3H, t, J = 7.1 Hz), 2.70 (3H, s), 4.22 (2H, q, J = 7.1 Hz), 7.45–7.53 (6H, m, signals overlapping), 7.76 (2H, m), 8.56 (2H, m). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.66, 22.87, 61.76, 123.35, 128.45, 128.47, 128.50, 128.63, 129.96, 131.03, 137.16, 138.23, 163.57, 163.70, 165.39, 168.46. MS (ES-API), m/z: calcd for $C_{20}H_{18}N_2O_2$: 318.14; found 319.10 [M + $H^+$]. m.p. 64 °C.

• Ethyl 2-([1,1′-biphenyl]-4-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8b**): Yield: 99%; white solid. $^1$H NMR ($CDCl_3$), δ (ppm): 1.10 (3H, t, J = 7.1 Hz), 2.73 (3H, s), 4.23 (2H, q, J = 7.1 Hz), 7.39 (1H, t, J = 7.5 Hz), 7.47–7.51 (5H, m, signals overlapping), 7.69 (2H, d, J = 7.5 Hz), 7.74 (2H, d, J = 8.5 Hz), 7.79 (2H, dd, $J_1$ = 7.2 Hz, $J_2$ = 2.0 Hz), 8.65 (2H, d, J = 8.5 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.66, 22.89, 61.75, 123.27, 127.17, 127.19, 127.70, 128.44, 128.47, 128.80, 129.10, 129.95, 136.09, 138.25, 140.52, 143.67, 163.44, 163.59, 165.40, 168.45. MS (ES-API), m/z: calcd for $C_{26}H_{22}N_2O_2$: 394.17; found 395.10 [M + $H^+$]. m.p. 69 °C.

• Ethyl 4-methyl-6-phenyl-2-(*o*-tolyl)pyrimidine-5-carboxylate (**8c**): Yield: 81%; white solid. $^1$H NMR ($CDCl_3$), δ (ppm): 1.11 (3H, t, J = 7.1 Hz), 2.63 (3H, s), 2.70 (3H, s), 4.24 (2H, q, J = 7.1 Hz), 7.31 (2H, app. t, J = 7.5 Hz), 7.35 (1H, app. dt, $J_1$ = 7.3 Hz, $J_2$ = 1.5 Hz), 7.44–7.50 (3H, m, signals overlapping), 7.73 (2H, m), 7.90 (1H, d, J = 7.3 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.67, 21.34, 22.78, 61.87, 122.83, 125.95, 128.44, 128.50, 129.68, 129.98, 130.61, 131.35, 137.53, 137.69, 138.02, 163.16, 165.02, 166.80, 168.40. MS (ES-API), m/z: calcd for $C_{21}H_{20}N_2O_2$: 332.15; found 333.10 [M + $H^+$]. m.p. 70 °C.

• Ethyl 4-methyl-6-phenyl-2-(*m*-tolyl)pyrimidine-5-carboxylate (**8d**): Yield: 87%; colorless viscous oil. $^1$H NMR ($CDCl_3$), δ (ppm): 1.09 (3H, t, J = 7.1 Hz), 2.46 (3H, s), 2.70 (3H, s), 4.22 (2H, q, J = 7.1 Hz), 7.32 (1H, d, J = 7.6 Hz), 7.39 (1H, app. t, J = 7.8 Hz), 7.47–7.51 (3H, m, signals overlapping), 7.75 (2H, m), 8.35 (1H, d, J = 8.0 Hz), 8.36 (1H, s). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.65, 21.48, 22.86, 61.74, 123.28, 125.85, 128.43, 128.44, 128.46, 129.12,

129.94, 131.86, 137.09, 138.16, 138.28, 163.56, 163.87, 165.33, 168.47. MS (ES-API), m/z: calcd for $C_{21}H_{20}N_2O_2$: 332.15; found 333.10 [M + $H^+$].

• Ethyl 2-(2-butoxyphenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8e**): Yield: 58%; colorless viscous oil. $^1$H NMR ($CDCl_3$), δ (ppm): 0.90 (3H, t, J = 7.3 Hz), 1.10 (3H, t, J = 7.1 Hz), 1.45 (2H, app. hex, J = 7.5 Hz), 1.75 (2H, app. quint, J = 7.1 Hz), 2.69 (3H, s), 4.05 (2H, t, 6.5 Hz), 4.22 (2H, q, J = 7.1 Hz), 7.03 (2H, m, signals overlapping), 7.39 (1H, dt, $J_1$ = 7.9 Hz, $J_2$ = 1.8 Hz), 7.43–7.47 (3H, m, signals overlapping), 7.71 (2H, m), 7.78 (1H, dd, $J_1$ = 7.6 Hz, $J_2$ = 1.8 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.66, 13.84, 19.26, 22.69, 31.40, 61.77, 68.46, 113.17, 120.48, 122.95, 128.22, 128.38, 128.40, 129.78, 131.12, 131.66, 138.16, 157.50, 163.33, 164.74, 165.27, 168.41. MS (ES-API), m/z: calcd for $C_{24}H_{26}N_2O_3$: 390.19; found 391.10 [M + $H^+$].

• Ethyl 2-(2-methoxyphenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8f**): Yield: 71%; colorless viscous oil. $^1$H NMR ($CDCl_3$), δ (ppm): 1.09 (3H, t, J = 7.1 Hz), 2.70 (3H, s), 3.89 (3H, s), 4.22 (2H, q, J = 7.1 Hz), 7.03 (1H, d, J = 8.4 Hz), 7.06 (1H, app. dt, $J_1$ = 7.5 Hz, $J_2$ = 0.7 Hz), 7.42 (1H, m), 7.43–7.47 (3H, m, signals overlapping), 7.73 (3H, m, signals overlapping). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.64, 22.75, 56.01, 61.78, 112.18, 120.68, 123.15, 128.33, 128.45, 128.46, 129.86, 131.09, 131.52, 138.06, 157.74, 163.34, 164.89, 165.27, 168.30. MS (ES-API), m/z: calcd for $C_{21}H_{20}N_2O_3$: 348.15; found 349.10 [M + $H^+$].

• Ethyl 2-(4-methoxyphenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8g**): Yield: 95%; white wax. $^1$H NMR ($CDCl_3$), δ (ppm): 1.08 (3H, t, J = 7.1 Hz), 2.68 (3H, s), 3.89 (3H, s), 4.20 (2H, q, J = 7.1 Hz), 7.00 (2H, d, J = 9.1 Hz), 7.45–7.51 (3H, m, signals overlapping), 7.74 (2H, m), 8.52 (2H, d, J = 9.1 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.67, 22.88, 55.37, 61.69, 113.83, 122.60, 128.41, 128.42, 128.43, 129.86, 130.36, 138.43, 162.15, 163.44, 163.57, 165.28, 168.60. MS (ES-API), m/z: calcd for $C_{21}H_{20}N_2O_3$: 348.15; found 349.10 [M + $H^+$].

• Ethyl 2-(2,3-dimethoxyphenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8h**): Yield: 51%; white wax. $^1$H NMR ($CDCl_3$), δ (ppm): 1.09 (3H, t, J = 7.2 Hz), 2.69 (3H, s), 3.91 (3H, s), 3.96 (3H, s), 4.22 (2H, q, J = 7.2 Hz), 7.03 (1H, dd, $J_1$ = 8.2 Hz, $J_2$ = 1.3 Hz), 7.15 (1H, app. t, J = 8.0 Hz), 7.37 (1H, dd, $J_1$ = 7.8 Hz, $J_2$ = 1.3 Hz), 7.42–7.48 (3H, m, signals overlapping), 7.72 (2H, m). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.66, 22.78, 56.05, 61.69, 61.82, 113.97, 122.91, 123.36, 123.99, 128.44, 128.49, 129.88, 133.77, 138.10, 147.99, 153.51, 163.38, 164.91, 165.01, 168.35. MS (ES-API), m/z: calcd for $C_{22}H_{22}N_2O_4$: 378.16; found 379.10 [M + $H^+$].

• Ethyl 2-(2,4-dimethoxyphenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8i**): Yield: 50%; colorless viscous oil. $^1$H NMR ($CDCl_3$), δ (ppm): 1.08 (3H, t, J = 7.2 Hz), 2.68 (3H, s), 3.86 (3H, s), 3.89 (3H, s), 4.20 (2H, q, J = 7.2 Hz), 6.57 (1H, d, J = 2.3 Hz), 6.60 (1H, dd, $J_1$ = 8.5 Hz, $J_2$ = 2.3 Hz), 7.42–7.48 (3H, m, signals overlapping), 7.71 (2H, m), 7.82 (1H, d, J = 8.5 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.65, 22.78, 55.46, 56.08, 61.70, 99.56, 105.04, 121.16, 122.52, 128.43, 128.48, 129.79, 133.08, 138.29, 159.47, 162.46, 163.31, 164.81, 164.86, 168.44. MS (ES-API), m/z: calcd for $C_{22}H_{22}N_2O_4$: 378.16; found 379.10 [M + $H^+$].

• Ethyl 2-(3,4-dimethoxyphenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8j**): Yield: 51%; colorless viscous oil. $^1$H NMR ($CDCl_3$), δ (ppm): 1.07 (3H, t, J = 7.1 Hz), 2.68 (3H, s), 3.95 (3H, s), 4.01 (3H, s), 4.19 (2H, q, J = 7.1 Hz), 6.96 (1H, d, J = 8.5 Hz), 7.45–7.51 (3H, m, signals overlapping), 7.74 (2H, m), 8.11 (1H, d, J = 2.0 Hz), 8.20 (1H, dd, $J_1$ = 8.5 Hz, $J_2$ = 2.0 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.63, 22.86, 55.91, 55.96, 61.64, 110.65, 111.12, 122.23, 122.66, 128.38, 128.41, 129.83, 129.99, 138.37, 148.85, 151.66, 163.31, 163.53, 165.24, 168.51. MS (ES-API), m/z: calcd for $C_{22}H_{22}N_2O_4$: 378.16; found 379.10 [M + $H^+$].

• Ethyl 2-(3,5-dimethoxyphenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8k**): Yield: 84%; white wax. $^1$H NMR ($CDCl_3$), δ (ppm): 1.09 (3H, t, J = 7.2 Hz), 2.69 (3H, s), 3.89 (6H, s), 4.21 (2H, q, J = 7.2 Hz), 6.62 (1H, t, J = 2.2 Hz), 7.45–7.51 (3H, m, signals overlapping), 7.72–7.78 (4H, m, signals overlapping). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.65, 22.83, 55.56, 61.79, 103.76, 106.44, 123.53, 128.45, 128.49, 129.98, 138.15, 139.26, 160.94, 163.31, 163.47, 165.33, 168.43. MS (ES-API), m/z: calcd for $C_{22}H_{22}N_2O_4$: 378.16; found 379.10 [M + $H^+$].

• Ethyl 2-(2-fluorophenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8l**): Yield: 72%; colorless viscous oil. $^1$H NMR ($CDCl_3$), δ (ppm): 1.10 (3H, t, J = 7.2 Hz), 2.71 (3H, s), 4.23 (2H, q, J = 7.2 Hz), 7.19 (1H, app. t, J = 9.5 Hz), 7.26 (1H, app. t, J = 7.5 Hz), 7.42–7.50

(4H, m, signals overlapping), 7.75 (2H, m), 8.11 (1H, app. t, J = 7.6 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.62, 22.77, 61.87, 116.84 (d, J = 22.2 Hz), 123.44, 124.06 (d, J = 3.5 Hz), 126.31 (d, J = 10.1 Hz), 128.46, 128.52, 130.07, 131.91, 131.92 (d, J = 8.6 Hz), 137.77, 161.27 (d, J = 256.0 Hz), 162.65 (d, J = 4.5 Hz), 163.48, 165.36, 168.11. MS (ES-API), m/z: calcd for $C_{20}H_{17}FN_2O_2$: 336.13; found 337.10 [M + $H^+$].

• Ethyl 2-(3-fluorophenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8m**): Yield: 99%; white solid. $^1$H NMR ($CDCl_3$), δ (ppm): 1.09 (3H, t, J = 7.2 Hz), 2.70 (3H, s), 4.22 (2H, q, J = 7.2 Hz), 7.19 (1H, ddt, $J_1$ = 8.2 Hz, $J_2$ = 2.7 Hz, $J_3$ = 1.1 Hz), 7.46 (1H, m, $J_1$ = 7.8 Hz, $J_2$ = 5.7 Hz), 7.47–7.51 (3H, m, signals overlapping), 7.75 (2H, dd, $J_1$ = 7.8 Hz, $J_2$ = 2.0 Hz), 8.26 (1H, ddd, $J_1$ = 10.3 Hz, $J_2$ = 2.7 Hz, $J_3$ = 1.5 Hz), 8.35 (1H, app. td, $J_1$ = 7.8 Hz, $J_2$ = 1.1 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.65, 22.83, 61.86, 115.42 (d, J = 23.9 Hz), 117.90 (d, J = 20.9 Hz), 123.78, 124.24 (d, J = 2.8 Hz), 128.44, 128.52, 129.97 (d, J = 7.8 Hz), 130.11, 137.97, 139.54 (d, J = 7.7 Hz), 162.51 (d, J = 3.3 Hz), 163.13 (d, J = 244.8 Hz), 163.62, 165.56, 168.27. MS (ES-API), m/z: calcd for $C_{20}H_{17}FN_2O_2$: 336.13; found 337.10 [M + $H^+$]. m.p. 101 °C.

• Ethyl 2-(4-fluorophenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8n**): Yield: 98%; white wax. $^1$H NMR ($CDCl_3$), δ (ppm): 1.08 (3H, t, J = 7.2 Hz), 2.69 (3H, s), 4.21 (2H, q, J = 7.2 Hz), 7.16 (2H, app. t, J = 8.7 Hz), 7.45–7.53 (3H, m, signals overlapping), 7.74 (2H, dd, $J_1$ = 7.6 Hz, $J_2$ = 2.2 Hz), 8.57 (2H, dd, $J_1$ = 8.9 Hz, $J_2$ = 5.6 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.64, 22.86, 61.79, 115.46 (d, J = 21.7 Hz), 123.26, 128.41, 128.49, 130.02, 130.80 (d, J = 8.7 Hz), 133.33 (d, J = 3.3 Hz), 138.14, 162.73, 163.63, 164.91 (d, J = 250.7 Hz), 165.48, 168.38. MS (ES-API), m/z: calcd for $C_{20}H_{17}FN_2O_2$: 336.13; found 337.10 [M + $H^+$].

• Ethyl 2-(3,5-difluorophenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8o**): Yield: 87%; white solid. $^1$H NMR ($CDCl_3$), δ (ppm): 1.10 (3H, t, J = 7.2 Hz), 2.69 (3H, s), 4.23 (2H, q, J = 7.2 Hz), 6.94 (1H, tt, $J_1$ = 8.6 Hz, $J_2$ = 2.4 Hz), 7.47–7.53 (3H, m, signals overlapping), 7.74 (2H, dd, $J_1$ = 7.8 Hz, $J_2$ = 2.0 Hz), 8.10 (2H, m). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.67, 22.79, 61.94, 106.19 (t, J = 25.9 Hz), 111.39 (dd, $J_1$ = 19.9 Hz, $J_2$ = 6.4 Hz), 124.22, 128.43, 128.57, 130.24, 137.75, 140.69 (t, J = 9.6 Hz), 161.39 (t, J = 3.7 Hz), 163.19 (dd, $J_1$ = 248.7 Hz, $J_2$ = 12.6 Hz), 163.68, 165.72, 168.07. MS (ES-API), m/z: calcd for $C_{20}H_{16}F_2N_2O_2$: 354.12; found 355.10 [M + $H^+$]. m.p. 124 °C.

• Ethyl 2-(4-cyanophenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8p**): Yield: 62%; white solid. $^1$H NMR ($CDCl_3$), δ (ppm): 1.10 (3H, t, J = 7.2 Hz), 2.71 (3H, s), 4.23 (2H, q, J = 7.2 Hz), 7.46–7.54 (3H, m, signals overlapping), 7.75 (2H, m), 7.79 (2H, d, J = 8.6Hz), 8.68 (2H, d, J = 8.6 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.65, 22.81, 61.99, 114.25, 118.77, 124.29, 128.42, 128.60, 129.06, 130.29, 132.30, 137.70, 141.16, 161.77, 163.78, 165.79, 168.01. MS (ES-API), m/z: calcd for $C_{21}H_{17}N_3O_2$: 343.13; found 344.10 [M + $H^+$]. m.p. 101 °C.

• Ethyl 2-(3-acetamidophenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8q**): Yield: 91%; beige solid. $^1$H NMR ($CDCl_3$), δ (ppm): 1.08 (3H, t, J = 7.2 Hz), 2.20 (3H, s), 2.69 (3H, s), 4.21 (2H, q, J = 7.2 Hz), 7.36 (1H, bs), 7.44–7.52 (4H, m, signals overlapping), 7.74 (2H, m), 7.99 (1H, dd, $J_1$ = 7.7 Hz, $J_2$ = 1.4 Hz), 8.30 (1H, d, J = 7.9 Hz), 8.37 (1H, app. t, J = 1.7 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.61, 22.75, 24.41, 61.82, 119.79, 122.78, 123.45, 124.40, 128.34, 128.40, 129.16, 129.94, 137.66, 138.01, 138.31, 163.03, 163.50, 165.31, 168.36, 168.86. MS (ES-API), m/z: calcd for $C_{22}H_{21}N_3O_3$: 375.16; found 376.10 [M + $H^+$], 398.10 [M + $Na^+$]. m.p. 153 °C.

• Ethyl 2-(3-(dimethylamino)phenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8r**): The general method was modified in this case to include 3.5 equiv (instead of 2.5 equiv) of $K_3PO_4$ due to the fact that the boronic acid **7r** was in the form of HCl salt. Yield: 58%; pale yellow solid. $^1$H NMR ($CDCl_3$), δ (ppm): 1.08 (3H, t, J = 7.1 Hz), 2.69 (3H, s), 3.05 (6H, s), 4.21 (2H, q, J = 7.1 Hz), 6.91 (1H, d, J = 7.0 Hz), 7.36 (1H, app. t, J = 8.0 Hz), 7.46–7.50 (3H, m, signals overlapping), 7.75 (2H, m), 7.92 (1H, d, J = 7.5 Hz), 7.96 (1H, bs). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.69, 22.95, 40.83, 61.75, 112.68, 115.47, 117.36, 123.20, 128.42, 128.48, 129.20, 129.84, 137.89, 138.40, 150.85, 163.40, 164.29, 165.21, 168.60. MS (ES-API), m/z: calcd for $C_{22}H_{23}N_3O_2$: 361.18; found 362.10 [M + $H^+$]. m.p. 78 °C.

• Ethyl 2-(3-((5-(ethoxycarbonyl)-4-methyl-6-phenylpyrimidin-2-yl)(methyl)amino) phenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8r′**): This compound occurred as a

by-product alongside the main product, **8r**, in the reaction of compound **6** with boronic acid **7r**. Yield: 17%; colorless viscous oil. $^{1}$H NMR ($CDCl_3$), δ (ppm): 0.99 (3H, t, J = 7.1 Hz), 1.09 (3H, t, J = 7.1 Hz), 2.49 (3H, s), 2.70 (3H, s), 3.69 (3H, s), 4.09 (2H, q, J =7.1 Hz), 4.22 (2H, q, J = 7.1 Hz), 7.32 (2H, t, J = 7.5 Hz), 7.37 (1H, t, J = 7.1 Hz), 7.45–7.49 (3H, m, signals overlapping), 7.51 (2H, m), 7.59 (2H, d, J = 7.8 Hz), 7.75 (2H, m), 8.42 (1H, dt, $J_1$ = 4.0 Hz, $J_2$ = 1.8 Hz), 8.62 (1H, bs). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.60, 13.67, 22.85, 23.11, 38.50, 61.07, 61.79, 115.45, 123.43, 125.76, 126.54, 128.09, 128.33, 128.47, 128.48, 128.83, 128.93, 129.45, 129.97, 137.89, 138.18, 139.06, 145.33, 160.48, 163.37, 163.58, 165.13, 165.41, 166.80, 168.48, 169.25. MS (ES-API), m/z: calcd for $C_{35}H_{33}N_5O_4$: 587.25; found 588.20 [M + $H^+$].

• Ethyl 2-(3,5-bis(trifluoromethyl)phenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**8s**): Yield: 73%; white solid. $^{1}$H NMR ($CDCl_3$), δ (ppm): 1.11 (3H, t, J = 7.1 Hz), 2.73 (3H, s), 4.24 (2H, q, J = 7.1 Hz), 7.52 (3H, m, signals overlapping), 7.76 (2H, m), 8.00 (1H, s), 9.04 (2H, s). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.65, 22.79, 62.05, 123.35 (q, J = 272.8 Hz), 124.30 (hep, J = 3.7 Hz), 124.68, 128.46, 128.63 (q, J = 3.3 Hz), 128.67, 130.40, 131.95 (q, J = 33.4 Hz), 137.52, 139.22, 160.73, 163.97, 166.03, 167.90. MS (ES-API), m/z: calcd for $C_{22}H_{16}F_6N_2O_2$: 454.11; found 455.10 [M + $H^+$]. m.p. 92 °C.

Phenyldiazonium tetrafluoroborate (**9**): In a round-bottom flask open to air, 9.13 mL (0.1 mol, 1 equiv) of aniline were dissolved in a mixture of water (40 mL) and 50% aqueous tetrafluoroboric acid solution (35.12 mL solution, 17.56 g $HBF_4$, 0.2 mol, 2 equiv). The resulting solution was cooled at 0 °C, followed by dropwise addition of a solution of sodium nitrite (7.59 g, 0.11 mol, 1.1 equiv) in water (15 mL), while the temperature was maintained at 0–5 °C. Stirring was continued at the same temperature for 2 more hours. The crude solid product was collected by filtration and washed with cold water. It was then dissolved in acetone and precipitated again by addition of diethyl ether. The solid was collected by filtration and dried under house vacuum. In total, 14 g (0.073 mol, 73%) of product **9** were isolated. It was stored in small portions in a fridge until use.

General Method A for Pd(II)-catalyzed, Ru(II)-photoinitiated (mono- and bis-) C–H phenylation of ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylates: Phenyldiazonium tetrafluoroborate (**9**) (0.115 g, 0.6 mmol, 4 equiv), $Pd(OAc)_2$ (0.003 g, 0.015 mmol, 0.1 equiv), $Ru(bpy)_3Cl_2.6H_2O$ (0.006 g, 0.0075 mmol, 0.05 equiv) and AgOAc (0.050 g, 0.3 mmol, 2 equiv) were transferred to a small round-bottom flask and the flask was sealed and set under nitrogen atmosphere. Anhydrous MeOH (1 mL) was added, and the mixture was vigorously stirred for 5 min. The substrate ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylate of type **8** (0.15 mmol, 1 equiv), dissolved in MeOH (1 mL), was syringed in, and the flask was submitted to irradiation with two white household LED lamps (Phillips, 12.5 W, 1521 lumen) placed on opposite sides of the sample at 1–2 cm distance from the flask at ambient temperature for 8 h. Subsequently, the reaction mixture was diluted with diethyl ether and washed first with aqueous $NH_4Cl$ 25% wt solution. The aqueous phase was back-extracted 2 more times with diethyl ether. The combined organic phase was then washed with aqueous $Na_2CO_3$ 10% wt and aqueous NaCl saturated solution and dried over $Na_2SO_4$. The drying agent was removed by filtration and the solvent was removed under vacuum. The sample was re-dissolved in DCM and applied to a silica column prepared with hexane. Elution took place first with hexane and then with hexane-ethyl acetate step gradient (the end-ratio of solvents was different in each case depending on product polarity), leading to isolation of mono- and bis- (where applicable) CH-arylation products of types **10** and **11**, respectively.

General Method B for Pd(II)-catalyzed, Ir(III)-photoinitiated (mono- and bis-) C–H phenylation of ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylates: Phenyldiazonium tetrafluoroborate (**9**) (0.115 g, 0.6 mmol, 4 equiv), $Pd(OAc)_2$ (0.003 g, 0.015 mmol, 0.1 equiv), and (2,2′-bipyridine)bis[3,5-difluoro-2-[5-(trifluoro-methyl)-2-pyridinyl-kN][phenyl-kC]iridium(III) hexa-fluorophosphate (0.008 g, 0.0075 mmol, 0.05 equiv) were transferred to a small round-bottom flask, and the flask was sealed and set under nitrogen atmosphere. Anhydrous MeOH (1 mL) was added, and the mixture was vigorously stirred for 5 min. The substrate ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylate of type **8** (0.15 mmol, 1 equiv),

dissolved in MeOH (1 mL), was syringed in, and the flask was submitted to irradiation with two white household LED lamps (Phillips, 12.5 W, 1521 lumen) placed on opposite sides of the sample at 1–2 cm distance from the flask at ambient temperature for 8 h. Subsequently, the reaction mixture was diluted with diethyl ether and washed first with aqueous $NH_4Cl$ 25% wt solution. The aqueous phase was back-extracted 2 more times with diethyl ether. The combined organic phase was then washed with aqueous $Na_2CO_3$ 10% wt and aqueous NaCl saturated solution and dried over $Na_2SO_4$. The drying agent was removed by filtration and the solvent was removed under vacuum. The sample was re-dissolved in DCM and applied to a silica column prepared with hexane. Elution took place first with hexane and then with hexane-ethyl acetate step gradient (the end-ratio of solvents was different in each case depending on product polarity), leading to isolation of mono- and bis- (where applicable) CH-arylation products of types **10** and **11**, respectively.

Reaction of substrate **8a**: Method A; conversion 59%; ratio of **10a/11a** = 1.24:1.

• Ethyl 2-([1,1′-biphenyl]-2-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10a**): White solid. $^1$H NMR ($CDCl_3$), δ (ppm): 1.10 (3H, t, J = 7.2 Hz), 2.59 (3H, s), 4.21 (2H, q, J = 7.2 Hz), 7.08 (2H, d, J = 7.8 Hz), 7.23 (2H, d, J= 7.2 Hz), 7.28 (2H, app. t, J = 7.7 Hz), 7.31–7.39 (4H, m, signals overlapping), 7.45–7.55 (3H, m, signals overlapping), 7.98 (1H, d, J = 7.6 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.67, 22.67, 61.82, 122.52, 126.40, 127.52, 128.11, 128.18, 128.32, 129.30, 129.71, 129.79, 130.79, 130.94, 137.39, 137.53, 142.04, 142.29, 162.70, 165.12, 166.59, 168.22. MS (ES-API), m/z: calcd for $C_{26}H_{22}N_2O_2$: 394.17; found 395.10 [M + $H^+$]. m.p. 116 °C.

• Ethyl 2-([1,1′:3′,1″-terphenyl]-2′-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**11a**): White wax. $^1$H NMR ($CDCl_3$), δ (ppm): 1.06 (3H, t, J = 7.1 Hz), 2.31 (3H, s), 4.16 (2H, q, J = 7.1 Hz), 7.00 (2H, d, J = 8.0 Hz), 7.20 (4H, dd, $J_1$ = 7.7 Hz, $J_2$ = 2.0 Hz), 7.26–7.30 (8H, m, signals overlapping), 7.37 (1H, tt, $J_1$ = 7.3 Hz, $J_2$ = 1.3 Hz), 7.51 (2H, d, J = 7.7 Hz), 7.57 (1H, t, J = 6.6 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.63, 22.09, 61.77, 122.26, 126.52, 127.85, 128.12, 128.15, 128.94, 129.31, 129.54, 129.62, 136.98, 137.58, 141.59, 141.95, 162.60, 164.04, 166.96, 167.95. MS (ES-API), m/z: calcd for $C_{32}H_{26}N_2O_2$: 470.20; found 471.20 [M + $H^+$].

Reaction of substrate **8b**: Method A; conversion 58%; ratio of **10b**/**11b** = 1.27:1.

• Ethyl 2-([1,1′:3′,1″-terphenyl]-4′-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10b**): Colorless viscous oil. $^1$H NMR ($CDCl_3$), δ (ppm): 1.11 (3H, t, J = 7.1 Hz), 2.60 (3H, s), 4.22 (2H, q, J = 7.1 Hz), 7.11 (2H, d, J = 8.0 Hz), 7.27–7.31 (4H, m, signals overlapping), 7.34–7.40 (5H, m, signals overlapping), 7.47 (2H, app. t, J = 7.6 Hz), 7.68 (2H, d, J = 8.0 Hz), 7.72 (2H, m, signals overlapping), 8.09 (1H, d, J = 8.8 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.67, 22.67, 61.86, 122.49, 126.16, 126.53, 127.28, 127.73, 128.16, 128.19, 128.37, 128.83, 129.31, 129.82, 129.84, 131.43, 136.21, 137.55, 140.41, 142.38, 142.52, 142.59, 162.72, 165.13, 166.28, 168.25. MS (ES-API), m/z: calcd for $C_{32}H_{26}N_2O_2$: 470.20; found 471.10 [M + $H^+$].

• Ethyl 4-methyl-6-phenyl-2-(5′-phenyl-[1,1′:3′,1″-terphenyl]-2′-yl)pyrimidine-5-carboxylate (**11b**): Colorless viscous oil. $^1$H NMR ($CDCl_3$), δ (ppm): 1.05 (3H, t, J = 7.1 Hz), 2.30 (3H, s), 4.15 (2H, q, J = 7.1 Hz), 7.00 (2H, d, J = 8.0 Hz), 7.21–7.31 (12H, m, signals overlapping), 7.36 (1H, t, J = 7.6 Hz), 7.38 (1H, t, J = 7.6 Hz), 7.46 (2H, app. t, J = 7.6 Hz), 7.69 (2H, d, J = 8.0 Hz), 7.73 (2H, s). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.62, 22.14, 61.77, 122.27, 126.67, 127.33, 127.72, 127.94, 128.15, 128.17, 128.35, 128.85, 129.35, 129.69, 135.90, 137.58, 140.45, 141.60, 141.80, 142.56, 162.63, 164.12, 166.82, 167.98. MS (ES-API), m/z: calcd for $C_{38}H_{30}N_2O_2$: 546.23; found 547.20 [M + $H^+$].

Reaction of substrate **8c**: Method B; conversion 52%; only **10c**.

• Ethyl 4-methyl-2-(3-methyl-[1,1′-biphenyl]-2-yl)-6-phenylpyrimidine-5-carboxylate (**10c**): Colorless viscous oil. $^1$H NMR ($CDCl_3$), δ (ppm): 1.01 (3H, t, J = 7.2 Hz), 2.27 (3H, s), 2.49 (3H, s), 4.12 (2H, q, J = 7.2 Hz), 7.06 (2H, m), 7.12 (1H, m), 7.15 (2H, d, J = 7.4 Hz), 7.19 (2H, d, J = 7.3 Hz), 7.22 (1H, d, J = 7.4 Hz), 7.24 (1H, d, J = 6.4 Hz), 7.26 (2H, app. t, J = 7.4 Hz), 7.30 (1H, d, J = 7.4 Hz), 7.31 (1H, t, J = 7.2 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.63, 20.38, 22.50, 61.84, 122.74, 126.39, 127.79, 127.81, 128.23, 128.28, 128.80, 129.19, 129.65, 129.78, 136.31, 137.61, 137.69, 141.54, 141.84, 162.99, 164.44, 167.26, 168.07. MS (ES-API), m/z: calcd for $C_{27}H_{24}N_2O_2$: 408.18; found 409.10 [M + $H^+$].

Reaction of substrate **8d**: Method A; conversion 42%; ratio of **10d/11d** = 3.67:1.

• Ethyl 4-methyl-2-(4-methyl-[1,1′-biphenyl]-2-yl)-6-phenylpyrimidine-5-carboxylate (**10d**): White solid. $^{1}$H NMR ($CDCl_3$), δ (ppm): 1.10 (3H, t, J = 7.2 Hz), 2.46 (3H, s), 2.59 (3H, s), 4.21 (2H, q, J = 7.2 Hz), 7.08 (2H, d, J = 8.0 Hz), 7.21 (2H, d, J = 7.5 Hz), 7.28 (2H, app. t, J = 7.3 Hz), 7.30–7.38 (6H, m, signals overlapping), 7.78 (1H, bs). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.65, 21.09, 22.63, 61.78, 122.50, 126.18, 128.03, 128.16, 128.35, 129.34, 129.75, 130.48, 130.89, 131.27, 137.19, 137.23, 137.61, 139.32, 142.30, 162.70, 165.04, 166.76, 168.25. MS (ES-API), m/z: calcd for $C_{27}H_{24}N_2O_2$: 408.18; found 409.10 [M + $H^+$]. m.p. 133 °C.

• Ethyl 4-methyl-2-(4′-methyl-[1,1′:3′,1″-terphenyl]-2′-yl)-6-phenylpyrimidine-5-carboxylate (**11d**): Colorless viscous oil. $^{1}$H NMR ($CDCl_3$), δ (ppm): 1.00 (3H, t, J =7.1 Hz), 2.21 (3H, s), 2.26 (3H, s), 4.10 (2H, q, J = 7.1 Hz), 7.03 (2H, d, J = 8.2 Hz), 7.15 (2H, app. t, J = 7.7 Hz), 7.16–7.24 (8H, m, signals overlapping), 7.28 (2H, app. t, J =7.6 Hz), 7.35 (1H, t, J = 7.4 Hz), 7.39 (1H, d, J= 8.0 Hz), 7.41 (1H, d, J = 8.0 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.56, 20.69, 21.99, 61.63, 121.88, 126.33, 126.40, 127.50, 127.79, 128.09, 128.12, 129.13, 129.35, 129.49, 129.96, 130.58, 135.69, 137.76, 137.85, 139.02, 140.04, 141.11, 141.63, 162.38, 163.67, 167.17, 167.96. MS (ES-API), m/z: calcd for $C_{33}H_{28}N_2O_2$: 484.22; found 485.20 [M + $H^+$].

Reaction of substrate **8e**: Method A; conversion 30%; only **10e**.

• Ethyl 2-(3-butoxy-[1,1′-biphenyl]-2-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10e**): Colorless viscous oil. $^{1}$H NMR ($CDCl_3$), δ (ppm): 0.83 (3H, t, J = 7.5 Hz), 1.06 (3H, t, J = 7.2 Hz), 1.32 (2H, hex, J = 7.5 Hz), 1.62 (2H, quint, J = 7.0 Hz), 2.58 (3H, s), 4.00 (2H, t, J = 6.5 Hz), 4.18 (2H, q, J = 7.2 Hz), 6.99 (1H, d, J = 8.4 Hz), 7.06 (1H, d, J = 7.8 Hz), 7.16–7.26 (7H, m, signals overlapping), 7.32 (2H, app. t, J = 7.7 Hz), 7.36 (1H, t, J = 7.2 Hz), 7.40 (1H, app. t, J = 8.1 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.62, 13.72, 19.14, 22.43, 31.19, 61.73, 68.43, 111.52, 122.29, 122.78, 126.57, 127.80, 127.95, 128.20, 128.22, 129.22, 129.57, 129.90, 137.85, 141.16, 142.70, 156.99, 163.01, 164.11, 165.39, 168.17. MS (ES-API), m/z: calcd for $C_{30}H_{30}N_2O_3$: 466.23; found 467.20 [M + $H^+$].

Reaction of substrate **8f**: Method B; conversion 31%; only **10f**.

• Ethyl 2-(3-methoxy-[1,1′-biphenyl]-2-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10f**): Colorless viscous oil. $^{1}$H NMR ($CDCl_3$), δ (ppm): 1.07 (3H, t, J = 7.1 Hz), 2.59 (3H, s), 3.82 (3H, s), 4.18 (2H, q, J = 7.1 Hz), 7.01 (1H, d, J = 8.2 Hz), 7.07 (1H, dd, $J_1$ = 7.8 Hz, $J_2$ = 0.8 Hz), 7.17 (2H, m), 7.20 (1H, m), 7. 22 (2H, m), 7.25 (2H, m), 7.32 (2H, app. t, J = 7.5 Hz), 7.37 (1H, tt, $J_1$ = 7.3 Hz, $J_2$ = 1.5 Hz), 7.43 (1H, app. t, J = 8.0 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.65, 22.57, 56.00, 61.76, 110.50, 122.47, 123.02, 126.63, 127.80, 128.25, 128.26, 128.51, 129.20, 129.62, 129.92, 137.79, 141.02, 142.81, 157.32, 163.05, 164.32, 165.34, 168.13. MS (ES-API), m/z: calcd for $C_{27}H_{24}N_2O_3$: 424.18; found 425.10 [M + $H^+$].

Reaction of substrate **8g**: Method A; conversion 33%; ratio of **10g/11g** = 1.22:1.

• Ethyl 2-(5-methoxy-[1,1′-biphenyl]-2-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10g**): Colorless viscous oil. $^{1}$H NMR ($CDCl_3$), δ (ppm): 1.09 (3H, t, J = 7.2 Hz), 2.55 (3H, s), 3.88 (3H, s), 4.19 (2H, q, J = 7.2 Hz), 6.97 (1H, d, J = 2.6 Hz), 7.00 (1H, dd, $J_1$ = 8.6 Hz, $J_2$ = 2.6 Hz), 7.06 (2H, d, J = 8.2 Hz), 7.25 (2H, dd, $J_1$ = 7.8 Hz, $J_2$ =1.6 Hz), 7.27 (2H, d, J = 8.0 Hz), 7.32–7.38 (4H, m, signals overlapping), 7.99 (1H, d, J = 8.6 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.66, 22.67, 55.47, 61.74, 113.06, 116.37, 121.97, 126.48, 128.11, 128.12, 128.33, 129.15, 129.70, 130.11, 132.63, 137.67, 142.56, 143.97, 160.61, 162.56, 164.99, 166.12, 168.39. MS (ES-API), m/z: calcd for $C_{27}H_{24}N_2O_3$: 424.18; found 425.10 [M + $H^+$].

• Ethyl 2-(5′-methoxy-[1,1′:3′,1″-terphenyl]-2′-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**11g**): Colorless viscous oil. $^{1}$H NMR ($CDCl_3$), δ (ppm): 1.03 (3H, t, J = 7.2 Hz), 2.26 (3H, s), 3.90 (3H, s), 4.13 (2H, q, J = 7.2 Hz), 6.93 (2H, d, J = 8.0 Hz), 7.02 (2H, s), 7.18 (4H, dd, $J_1$ = 7.6 Hz, $J_2$ = 2.1 Hz), 7.22–7.28 (7H, m, signals overlapping), 7.34 (2H, t, J = 7.6 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.60, 22.08, 55.54, 61.70, 115.05, 122.62, 127.86, 128.10, 128.14, 129.15, 129.23, 129.55, 132.64, 137.67, 141.73, 143.75, 159.49, 162.49, 163.96, 166.80, 168.06. MS (ES-API), m/z: calcd for $C_{33}H_{28}N_2O_3$: 500.21; found 501.10 [M + $H^+$].

Reaction of substrate **8h**: Method B; conversion 42%; only **10h**.

• Ethyl 2-(3,4-dimethoxy-[1,1′-biphenyl]-2-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10h**): White wax. $^{1}$H NMR ($CDCl_3$), δ (ppm): 1.08 (3H, t, J = 7.1 Hz), 2.58 (3H, s), 3.88 (3H, s), 3.94 (3H, s), 4.20 (2H, q, J = 7.1 Hz), 7.06 (1H, d, J = 8.5 Hz), 7.12 (2H, m), 7.18–7.22 (4H, m, signals overlapping), 7.29 (2H, d, J = 8.3 Hz), 7.33 (2H, app. t, J = 7.6 Hz), 7.39 (1H, t, $J_1$ = 7.3 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.65, 22.45, 56.09, 61.57, 61.83, 113.22, 125.68, 126.32, 127.02, 127.84, 128.28, 128.29, 129.25, 129.76, 133.35, 134.61, 137.69, 140.69, 147.28, 152.37, 163.00, 164.32, 164.93, 168.04. MS (ES-API), m/z: calcd for $C_{28}H_{26}N_2O_4$: 454.19; found 455.10 [M + $H^+$].

Reaction of substrate **8i**: Method B; conversion 30%; only **10i**.

• Ethyl 2-(3,5-dimethoxy-[1,1′-biphenyl]-2-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10i**): White wax. $^{1}$H NMR ($CDCl_3$), δ (ppm): 1.07 (3H, t, J = 7.1 Hz), 2.58 (3H, s), 3.80 (3H, s), 3.86 (3H, s), 4.18 (2H, q, J = 7.1 Hz), 6.57 (1H, d, J = 2.2 Hz), 6.60 (1H, d, J = 2.2 Hz), 7.17 (2H, m), 7.19–7.25 (5H, m, signals overlapping), 7.31 (2H, app. t, J = 7.4 Hz), 7.36 (1H, t, J = 7.3 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.64, 22.55, 55.52, 55.96, 61.72, 98.15, 106.68, 121.13, 122.69, 126.74, 127.83, 128.19, 128.23, 129.10, 129.56, 137.81, 141.32, 143.90, 158.63, 160.91, 162.94, 164.21, 165.20, 168.19. MS (ES-API), m/z: calcd for $C_{28}H_{26}N_2O_4$: 454.19; found 455.10 [M + $H^+$].

Reaction of substrate **8j**: Method A; conversion 47%; ratio of **10j/11j** = 1.85:1.

• Ethyl 2-(4,5-dimethoxy-[1,1′-biphenyl]-2-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10j**): Colorless wax. $^{1}$H NMR ($CDCl_3$), δ (ppm): 1.09 (3H, t, J = 7.2 Hz), 2.58 (3H, s), 3.95 (3H, s), 4.01 (3H, s), 4.20 (2H, q, J = 7.2 Hz), 6.95 (1H, s), 7.05 (2H, d, J = 7.8 Hz), 7.24 (2H, d, J = 7.6 Hz), 7.27 (2H, app. t, J = 7.8 Hz), 7.31–7.39 (4H, m, signals overlapping), 7.58 (1H, s). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.67, 22.68, 56.08, 56.15, 61.77, 113.64, 113.98, 122.13, 126.23, 128.12, 128.13, 128.34, 129.37, 129.60, 129.74, 135.85, 137.62, 142.55, 148.23, 150.03, 162.63, 165.04, 166.05, 168.31. MS (ES-API), m/z: calcd for $C_{28}H_{26}N_2O_4$: 454.19; found 455.10 [M + $H^+$].

• Ethyl 2-(4′,5′-dimethoxy-[1,1′:3′,1″-terphenyl]-2′-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**11j**): Colorless wax. $^{1}$H NMR ($CDCl_3$), δ (ppm): 1.01 (3H, t, J = 7.2 Hz), 2.24 (3H, s), 3.57 (3H, s), 3.96 (3H, s), 4.11 (2H, q, J = 7.2 Hz), 6.97 (2H, d, J = 7.7 Hz), 7.05 (1H, s), 7.17–7.29 (12H, m, signals overlapping), 7.34 (1H, t, J = 7.4 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.59, 21.99, 56.10, 60.69, 61.68, 113.71, 121.85, 126.57, 127.36, 127.89, 128.08, 128.09, 128.13, 129.33, 129.55, 130.33, 131.17, 136.49, 136.76, 137.67, 138.01, 141.61, 146.16, 153.16, 162.49, 163.82, 166.38, 167.96. MS (ES-API), m/z: calcd for $C_{34}H_{30}N_2O_4$: 530.22; found 531.20 [M + $H^+$].

Reaction of substrate **8k**: Method A; conversion 44%; ratio of **10k/11k** = 1.20:1.

• Ethyl 2-(4,6-dimethoxy-[1,1′-biphenyl]-2-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10k**): White wax. $^{1}$H NMR ($CDCl_3$), δ (ppm): 1.07 (3H, t, J = 7.2 Hz), 2.55 (3H, s), 3.76 (3H, s), 3.90 (3H, s), 4.18 (2H, q, J = 7.2 Hz), 6.66 (1H, d, J =2.5 Hz), 7.05 (1H, d, J = 2.5 Hz), 7.11 (2H, m), 7.19 (2H, m), 7.24 (1H, tt, $J_1$ = 7.3 Hz, $J_2$ = 1.8 Hz), 7.27–7.31 (4H, m, signals overlapping), 7.37 (1H, tt, $J_1$ = 7.4 Hz, $J_2$ = 1.6 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.64, 22.57, 55.55, 56.03, 61.77, 100.51, 106.32, 122.56, 123.87, 126.12, 127.54, 128.12, 128.40, 129.75, 131.09, 137.20, 137.58, 139.98, 158.24, 159.82, 162.75, 164.88, 166.66, 168.16. MS (ES-API), m/z: calcd for $C_{28}H_{26}N_2O_4$: 454.19; found 455.20 [M + $H^+$].

• Ethyl 2-(4′,6′-dimethoxy-[1,1′:3′,1″-terphenyl]-2′-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**11k**): White wax. $^{1}$H NMR ($CDCl_3$), δ (ppm): 0.99 (3H, t, J = 7.2 Hz), 2.23 (3H, s), 3.83 (6H, s), 4.08 (2H, q, J = 7.2 Hz), 6.75 (1H, s), 7.02 (2H, m), 7.12–7.20 (10H, m, signals overlapping), 7.28 (2H, app. t, J = 7.5 Hz), 7.35 (1H, tt, $J_1$ = 7.5 Hz, $J_2$ = 1.3 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.53, 21.91, 56.25, 61.60, 96.89, 121.88, 123.14, 126.23, 127.29, 128.06, 128.11, 129.46, 130.95, 136.65, 137.73, 140.63, 157.23, 162.37, 163.57, 166.42, 167.86. MS (ES-API), m/z: calcd for $C_{34}H_{30}N_2O_4$: 530.22; found 531.20 [M + $H^+$]. m.p. 145 °C.

Reaction of substrate **8l**: Method A; conversion 20%; only **10l**.

• Ethyl 2-(3-fluoro-[1,1′-biphenyl]-2-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10l**): Colorless viscous oil. $^{1}$H NMR ($CDCl_3$), δ (ppm): 1.10 (3H, t, J = 7.2 Hz), 2.59 (3H, s), 4.21 (2H, q, J = 7.2 Hz), 7.18 (2H, m, signals overlapping), 7.22 (2H, d, J = 7.2 Hz), 7.26–7.30 (5H, m, signals overlapping), 7.33 (2H, app. t, J = 8.0 Hz), 7.39 (1H, tt, $J_1$ = 7.3 Hz, $J_2$ = 1.5 Hz), 7.46 (1H, app. dt, $J_1$ = 8.0 Hz, $J_2$ = 5.7 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.66, 22.60, 61,91, 114.99 (d, J = 22.2 Hz), 123.40, 125.91 (d, J = 3.1 Hz), 126.43 (d, J = 14.5 Hz), 127.06, 128.09, 128.25, 128.35, 129.20, 129.90, 130.45 (d, J = 9.2 Hz), 137.38, 140.15

(d, J = 2.1 Hz), 143.69 (d, J = 2.7 Hz), 160.56 (d, J = 248.8 Hz), 162.93, 163.17, 164.86, 167.83. MS (ES-API), m/z: calcd for $C_{26}H_{21}FN_2O_2$: 412.16; found 413.10 [M + $H^+$].

Reaction of substrate **8m**: Method A; conversion 28%; ratio of **10m/10m'/11m** = 3.33:1:1.

• Ethyl 2-(4-fluoro-[1,1'-biphenyl]-2-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10m**): Colorless viscous oil. $^1$H NMR ($CDCl_3$), δ (ppm): 1.10 (3H, t, J = 7.1 Hz), 2.58 (3H, s), 4.21 (2H, q, J = 7.1 Hz), 7.09 (2H, d, J = 7.5 Hz), 7.21 (3H, m, signals overlapping), 7.29 (2H, app. t, J = 7.5 Hz), 7.31–7.35 (3H, m, signals overlapping), 7.38 (1H, t, J = 7.1 Hz), 7.43 (1H, dd, $J_1$ = 9.4 Hz, $J_2$ = 5.6 Hz), 7.72 (1H, dd, $J_1$ = 9.4 Hz, $J_2$ = 3.0 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.66, 22.61, 61.91, 116.57 (d, J = 21.4 Hz), 117.58 (d, J = 22.9 Hz), 122.91, 126.52, 128.14, 128.23, 128.33, 129.31, 129.92, 132.64 (d, J = 8.1 Hz), 137.37, 138.23 (d, J = 3.7 Hz), 139.07 (d, J = 7.4 Hz), 141.44, 162.07 (d, J = 247.2 Hz), 162.85, 165.31, 165.35, 168.05. MS (ES-API), m/z: calcd for $C_{26}H_{21}FN_2O_2$: 412.16; found 413.10 [M + $H^+$].

• Ethyl 2-(6-fluoro-[1,1'-biphenyl]-2-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10m'**): Colorless viscous oil. $^1$H NMR ($CDCl_3$), δ (ppm): 1.08 (3H, t, J = 7.1 Hz), 2.56 (3H, s), 4.20 (2H, q, J = 7.1 Hz), 7.08 (2H, m), 7.25 (2H, m), 7.27 (1H, m), 7.30 (2H, app. t, J = 7.5 Hz), 7.34–7.40 (4H, m, signals overlapping), 7.45 (1H, app. dt, $J_1$ = 7.9 Hz, $J_2$ = 5.3 Hz), 7.79 (1H, d, J = 7.5 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.65, 22.57, 61.89, 117.08 (d, J = 23.6 Hz), 122.79, 126.45 (d, J = 3.2 Hz), 127.07, 127.98, 127.99, 128.22, 128.34, 128.86 (d, J = 8.9 Hz), 129.93, 130.35, 134.82, 137.35, 139.82, 160.07 (d, J = 245.8 Hz), 162.85, 165.13, 165.37, 168.02. MS (ES-API), m/z: calcd for $C_{26}H_{21}FN_2O_2$: 412.16; found 413.10 [M + $H^+$].

• Ethyl 2-(4'-fluoro-[1,1':3',1''-terphenyl]-2'-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**11m**): Colorless viscous oil. $^1$H NMR ($CDCl_3$), δ (ppm): 1.02 (3H, t, J = 7.1 Hz), 2.27 (3H, s), 4.12 (2H, q, J = 7.1 Hz), 6.98 (2H, d, J = 8.0 Hz), 7.15 (2H, dd, $J_1$ = 7.5 Hz, $J_2$ = 2.2 Hz), 7.20–7.24 (6H, m, signals overlapping), 7.26–7.30 (4H, m, signals overlapping), 7.32 (1H, app. t, J = 8.8 Hz), 7.36 (1H, t, J = 7.4 Hz), 7.46 (1H, dd, $J_1$ = 8.6 Hz, $J_2$ = 5.2 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.58, 22.04, 61.79, 116.23 (d, J = 22.6 Hz), 122.47, 126.67, 127.23, 127.73, 127.94, 128.11, 128.19, 129.32, 129.72, 130.30, 130.32, 130.89 (d, J = 8.7 Hz), 134.26, 137.46, 137.92, 139.29, 140.77, 159.26 (d, J = 246.8 Hz), 162.68, 164.13, 165.69, 167.75. MS (ES-API), m/z: calcd for $C_{32}H_{25}FN_2O_2$: 488.19; found 489.20 [M + $H^+$].

Reaction of substrate **8n**: Method A; conversion 24%; ratio of **10n/11n** = 4.05:1.

• Ethyl 2-(5-fluoro-[1,1'-biphenyl]-2-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10n**): White solid. $^1$H NMR ($CDCl_3$), δ (ppm): 1.10 (3H, t, J = 7.2 Hz), 2.57 (3H, s), 4.21 (2H, q, J = 7.2 Hz), 7.07 (2H, d, J = 7.9 Hz), 7.18 (2H, m, signals overlapping), 7.22 (2H, dd,] $J_1$ = 7.3 Hz, $J_2$ = 2.5 Hz), 7.28 (2H, app. t, J = 7.8 Hz), 7.36 (4H, m, signals overlapping), 8.00 (1H, m). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.66, 22.64, 61.86, 114.39 (d, J = 21.8 Hz), 117.76 (d, J = 21.8 Hz), 122.56, 126.91, 128.22, 128.26, 128.28, 129.07, 129.88, 133.01 (d, J = 8.8 Hz), 133.59 (d, J = 2.9 Hz), 137.42, 141.28 (d, J = 2.0 Hz), 144.58 (d, J = 8.4 Hz), 162.76, 163.31 (d, J = 249.3 Hz), 165.21, 165.65, 168.13. MS (ES-API), m/z: calcd for $C_{26}H_{21}FN_2O_2$: 412.16; found 413.10 [M + $H^+$]. m.p. 118 °C.

• Ethyl 2-(5'-fluoro-[1,1':3',1''-terphenyl]-2'-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**11n**): Colorless viscous oil. $^1$H NMR ($CDCl_3$), δ (ppm): 1.03 (3H, t, J = 7.1 Hz), 2.28 (3H, s), 4.14 (2H, q, J = 7.1 Hz), 6.96 (2H, d, J = 7.5 Hz), 7.16 (4H, m), 7.20 (2H, d, J = 9.1 Hz), 7.23–7.29 (8H, m, signals overlapping), 7.35 (1H, t, J = 7.2 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.66, 22.10, 61.87, 116.21 (d, J = 21.7 Hz), 122.38, 127.03, 128.01, 128.10, 128.20, 129.11, 129.72, 133.41, 137.46, 140.60 (d, J = 2.0 Hz), 144.47 (d, J = 9.1 Hz), 162.28 (d, J = 246.2 Hz), 162.70, 165.00, 166.19, 167.86. MS (ES-API), m/z: calcd for $C_{32}H_{25}FN_2O_2$: 488.19; found 489.10 [M + $H^+$].

Reaction of substrate **8o**: Method A; conversion 26%; ratio of **10o/11o** = 1.60:1.

• Ethyl 2-(4,6-difluoro-[1,1'-biphenyl]-2-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10o**): Colorless wax. $^1$H NMR ($CDCl_3$), δ (ppm): 1.09 (3H, t, J = 7.1 Hz), 2.55 (3H, s), 4.20 (2H, q, J = 7.1), 7.02 (1H, app. dt, $J_1$ = 9.0 Hz, $J_2$ = 2.8 Hz), 7.09 (2H, d, J = 8.0 Hz), 7.22 (2H, d, J = 7.0 Hz), 7.30 (2H, app. t, J = 7.7 Hz), 7.33–7.37 (3H, m, signals overlapping), 7.39 (1H, t, J = 7.4 Hz), 7.57 (1H, ddd, $J_1$ = 9.0 Hz, $J_2$ = 2.8 Hz, $J_3$ = 1.3 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.66, 22.57, 61.94, 105.25 (dd, $J_1$ = 27.8 Hz, $J_2$ = 25.5 Hz), 113.64 (dd, $J_1$ = 23.0 Hz, $J_2$ = 3.6 Hz), 123.15, 125.88, 127.19, 128.06, 128.26, 128.33, 130.03, 130.39, 134.15, 137.17,

140.76 (dd, $J_1$ = 9.0 Hz, $J_2$ = 4.5 Hz), 160.31 (dd, $J_1$ = 246.5 Hz, $J_2$ = 12.0 Hz), 161.78 (dd, $J_1$ = 250.2 Hz, $J_2$ = 13.0 Hz), 162.96, 164.34, 165.33, 167.88. MS (ES-API), m/z: calcd for $C_{26}H_{20}F_2N_2O_2$: 430.15; found 431.10 [M + $H^+$].

• Ethyl 2-(4′,6′-difluoro-[1,1′:3′,1″-terphenyl]-2′-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**11o**): Colorless viscous oil. $^1$H NMR ($CDCl_3$), δ (ppm): 1.01 (3H, t, J = 7.1 Hz), 2.26 (3H, s), 4.11 (2H, q, J = 7.1 Hz), 7.00 (2H, d, J = 7.9 Hz), 7.12 (1H, t, J = 9.2 Hz), 7.19 (4H, dd, $J_1$ = 7.3 Hz, $J_2$ = 2.0 Hz), 7.23–7.27 (6H, m, peaks overlapping), 7.29 (2H, t, J = 7.9 Hz), 7.37 (1H, t, J = 7.5 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.63, 22.00, 61.82, 104.74 (t, J = 26.6 Hz), 122.58, 127.38, 127.70, 127.86, 128.06, 128.22, 129.83, 130.40, 133.50, 137.29, 141.20 (dd, $J_1$ = 25.3 Hz, $J_2$ = 11.0 Hz), 159.12 (dd, $J_1$ = 248.6 Hz, $J_2$ = 12.7 Hz), 162.74, 164.18, 164.51, 167.59. MS (ES-API), m/z: calcd for $C_{32}H_{24}F_2N_2O_2$: 506.18; found 507.10 [M + $H^+$].

Reaction of substrate **8p**: Method A; conversion 58%; only **10p**.

• Ethyl 2-(5-cyano-[1,1′-biphenyl]-2-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10p**): White wax. $^1$H NMR ($CDCl_3$), δ (ppm): 1.10 (3H, t, J = 7.1 Hz), 2.58 (3H, s), 4.22 (2H, q, J = 7.1 Hz), 7.09 (2H, m), 7.20 (2H, m), 7.30 (2H, app. t, J = 7.6 Hz), 7.34–7.42 (4H, m, signals overlapping), 7.76 (1H, dd, $J_1$ = 7.7 Hz, $J_2$ = 1.6 Hz), 7.77 (1H, s), 8.10 (1H, d, $J_1$ = 7.7 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.67, 22.61, 62.04, 113.34, 118.48, 123.31, 127.39, 128.27, 128.33, 128.46, 129.05, 130.12, 130.84, 131.62, 134.49, 137.10, 140.11, 141.46, 143.20, 162.96, 164.85, 165.54, 167.84. MS (ES-API), m/z: calcd for $C_{27}H_{21}N_3O_2$: 419.16; found 420.10 [M + $H^+$].

Reaction of substrate **8q**: Method A; conversion 33%; only **11q**.

• Ethyl 2-(4′-amino-[1,1′:3′,1″-terphenyl]-2′-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**11q**): Brown wax. $^1$H NMR ($CDCl_3$), δ (ppm): 1.01 (3H, t, J =7.1 Hz), 2.26 (3H, s), 4.10 (2H, q, J = 7.1 Hz), 6.93 (1H, d, J = 8.2 Hz), 7.01 (2H, d, J = 8.0 Hz), 7.12 (2H, d, J = 7.6 Hz), 7.16 (1H, t, J = 7.0 Hz), 7.19 (2H, d, J = 7.3 Hz), 7.21 (1H, t, J = 7.0 Hz), 7.22–7.30 (6H, m, signals overlapping), 7.31 (1H, d, J =8.2 Hz), 7.34 (1H, t, J = 7.3 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.57, 22.01, 61.64, 116.08, 121.94, 125.81, 127.00, 127.75, 128.08, 128.12, 128.33, 129.33, 129.49, 130.37, 130.40, 130.41, 132.08, 137.37, 137.72, 138.23, 141.79, 143.36, 162.38, 163.73, 167.02, 167.98. MS (ES-API), m/z: calcd for $C_{32}H_{27}N_3O_2$: 485.21; found 486.20 [M + $H^+$].

Reaction of substrate **8r**: Method A; conversion 64%; only **10r**.

• Ethyl 2-(4-(dimethylamino)-[1,1′-biphenyl]-2-yl)-4-methyl-6-phenylpyrimidine-5-carboxylate (**10r**): Orange film. $^1$H NMR ($CDCl_3$), δ (ppm): 1.11 (3H, t, J = 7.1 Hz), 2.71 (3H, s), 3.12 (6H, s), 4.24 (2H, q, J = 7.1 Hz), 6.85 (1H, dd, $J_1$ = 9.1 Hz, $J_2$ = 2.9 Hz), 7.13 (1H, d, J = 2.9 Hz), 7.33 (1H, t, J = 7.1 Hz), 7.37 (4H, m, signals overlapping), 7.42 (1H, t, J = 7.3 Hz), 7.67 (4H, m, signals overlapping), 7.88 (1H, d, J = 9.1 Hz). $^{13}$C NMR ($CDCl_3$), δ (ppm): 13.71, 22.77, 40.39, 61.86, 112.75, 113.16, 118.66, 122.55, 123.18, 128.39, 128.51, 128.72, 129.31, 129.80, 137.99, 139.68, 141.66, 151.94, 153.31, 162.90, 164.50, 166.56, 168.41. MS (ES-API), m/z: calcd for $C_{28}H_{27}N_3O_2$: 437.21; found 467.2 [M + $Li^+$ + $Na^+$], 543.2 [M + $Pd^{2+}$].

## 4. Conclusions

Direct C–H arylation has proven to be a valuable tool for the late-stage installation of aryl–aryl bonds in medicinally-relevant scaffolds, creating products that may correspond to unchartered areas of 3D chemical space. In this context, we have demonstrated a productive combination of a multicomponent reaction (Biginelli) with a LED-activated photoredox-mediated C–H arylation approach. The Biginelli generated a 3,4-DHPM scaffold that, via efficient oxidation/dehydrogenation, trifluorosulfonylation, and Suzuki–Miyaura reactions, was converted to a series of ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylates, a compound class of potential biological interest, owing to the bioactivity bias introduced by the central scaffold. These substituted substrates were submitted to C–H arylation conditions involving Pd(II) catalysis merged with Ru(II) or Ir(III) photoredox initiation to provide a focused library of unusual tetra-aryl and penta-aryl "drug-like" end-products. Importantly, mono- and bis-phenyl products are separable.

The described synthetic route exploits the ability of the pyrimidine ring present in the substrates to participate in C–H arylation by directing the arylation event to the 2-position of the adjacent C2-connected phenyl ring. On one hand, the reaction proceeds (albeit in moderate yields) on a series of challenging substrates loaded with functional groups. On the other hand, it exhibits remarkable regioselectivity, as indicated by absence of any products from arylation on the C6-connected phenyl ring. While there remains a window for improvement, which future efforts will attempt to address by conducting the C–H arylation in a continuous flow fashion, this method has been successful in delivering a focused library of potentially interesting compounds from a biological perspective. At the same time, the current study exemplifies how light-induced C–H activation processes can be rendered compatible with small-scale, parallel synthesis in solution for the purpose of generating novel compound collections.

In the C–H phenylation reaction, the diverse set of substrates employed, featuring a range of substituents with different electronic and steric contributions, has revealed a dependence of reaction outcome on these factors. A more systematic investigation involving a larger set of substrates, and supported by computational modeling, is deemed necessary in order to expand the scope of this transformation, fully understand the driving factors for the preferred product distribution, and be able to make predictions for substrates not yet synthesized. This will form the body of future work in our laboratory.

**Supplementary Materials:** The following are available online at https://www.mdpi.com/article/10.3390/catal11091071/s1: $^{1}$H NMR and $^{13}$C NMR Spectra of Isolated Products; $^{1}$H-$^{1}$H COSY and NOESY NMR Spectra of Compound **10r**; Single Crystal X-ray Crystallography Procedures; Crystallographic Data of Compound **10a** (Table S1: Crystal data and structure refinement for compound **10a** at 108.15(10) K; Table S2: Bond lengths [Å] for compound **10a** at 108.15(10) K with estimated standard deviations in parentheses; Table S3: Bond angles [°] for compound **10a** at 108.15(10) K with estimated standard deviations in parentheses).

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