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Oxidative Dehydrosulfurative Carbon−Oxygen Cross-Coupling of 3,4-Dihydropyrimidine-2-thiones with Aryl Alcohols

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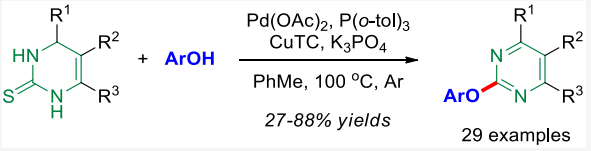
ABSTRACT: A Pd-catalyzed/Cu-mediated oxidative dehydrosulfurative carbon−oxygen cross-coupling reaction of 3,4-dihydropyrimidin-1*H*-2-thiones (DHPMs) with aryl alcohols is described. Due to the ready availability of diverse DHPMs and aryl alcohols, the reaction method offers facile access to biologically and pharmacologically valuable 2-aryloxypyrimidine derivatives with rapid diversification.



As well as being an integral part of DNA and RNA, the pyrimidine motif has been of interest to organic and medicinal chemists due to its diverse biological and pharmacological properties.[1] Comprehensive research on this privileged scaffold has generated several commercial drugs, such as the hypocholesterolemic agent rosuvastatin,[2] the potent anticancer drug imatinib,[3] the tyrosine kinase inhibitors ruxolitinib, tofacitinib,[4] baricitinib,[5] and ribociclib,[6] and the antifungal agent voriconazole.[7] In addition to these 2-amino- and 2-(*H*)pyrimidine drugs, 2-aryloxypyrimidine compounds, such as bispyribac-sodium[8] and pyriminobac-methyl[9] as herbicides and purmorphamine[10] as an osteogenesis inducer, have exhibited potent biological activity (Figure 1). Recently, 2-aryloxypyrimidine compounds were shown to selectively inhibit PDGFRα, which induces apoptosis and autophagy in carcinoma cells.[11]

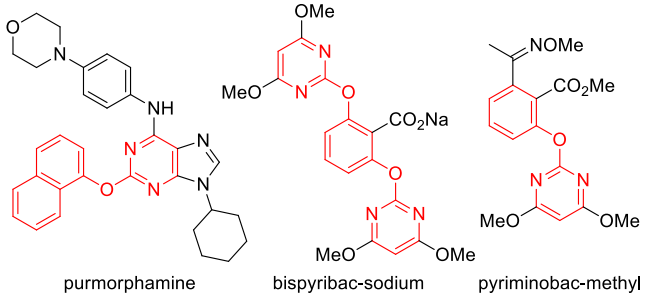
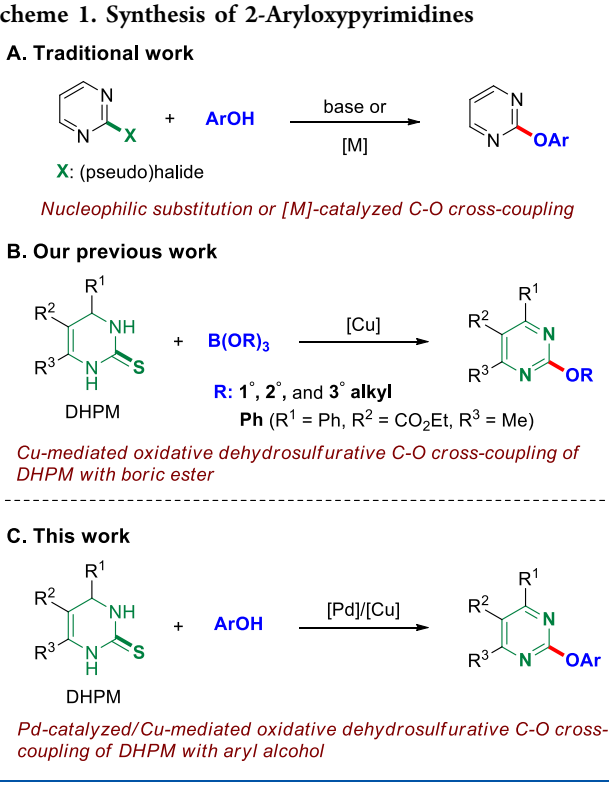


Figure 1. Structures of purmorphamine, bispyribac-sodium, and pyriminobac-methyl.

Traditionally, 2-aryloxypyrimidines have been prepared by nucleophilic aromatic substitution[12] or Ullmann-type C−O cross-coupling of pyrimidine possessing (pseudo)halide at the C2 position with aryl alcohol (Scheme 1A).[13] Due to the requirement for multistep synthesis of most of the pyrimidine partners, especially for densely substituted ones, these reaction protocols are limited with respect to rapid diversification. To overcome this limitation, we have used 3,4-dihydropyrimidin-1*H*-2-thione (DHPM), which is readily available via the

Scheme 1. Synthesis of 2-Aryloxypyrimidines



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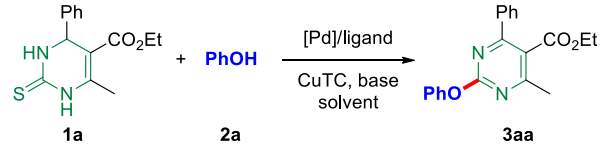
Biginelli three-component reaction,[14] as a surrogate for the C2-(pseudo)halopyrimidine.

DHPMs with diverse substituents at the C4−C6 positions were demonstrated to be suitable substrates for Pd-catalyzed/Cu-mediated dehydrosulfurative C−C or C−N cross-coupling with concomitant oxidative dehydrogenation (aromatization) to yield C2-arylated (azolated),[15] -alkynylated,[16] and -aminated pyrimidines[17] in a single step.[18,19] Recently, we reported a Cu-mediated oxidative dehydrosulfurative C−O cross-coupling of DHPMs with primary, secondary, and tertiary trialkylborates (boric esters) to yield the corresponding 2-alkoxypyrimidines, in moderate-to-good yields (Scheme 1B).[20] In the course of these studies, we found that triphenylborate was also compatible with this method for producing the 2-phenoxypyrimidine derivative (R^1 = Ph, R^2 = CO_2Et, and R^3 = Me). However, this reaction protocol is not practical for preparing various 2-aryloxypyrimidine derivatives due to nontrivial triarylborate synthesis. This hurdle led us to use readily available aryl alcohols instead of triarylborates. We report herein a Pd-catalyzed/Cu-mediated oxidative dehydrosulfurative C−O cross-coupling of DHPMs with aryl alcohols to yield 2-aryloxypyrmidines in a single step (Scheme 1C). Due to the ready availability of both coupling partners, the reaction method offers a shortcut to 2-aryloxypyrimidine derivatives with rapid diversification. To our knowledge, no other reports describing transition-metal-catalyzed direct C−O cross-coupling of the substrate bearing the thiono (latent free-thiol) leaving group with alcohol have been published.

Previously, we found that the oxidative dehydrogenation (aromatization) occurred under an argon atmosphere in both the Pd-catalyzed/Cu-mediated and Cu-mediated reactions of DHPMs, in which Cu species presumably served as oxidants.[15−17,20] Thus, our initial studies were accomplished under an argon atmosphere with the reaction of DHPM **1a** and phenol. The reaction in the presence of palladium(II) acetate ($Pd(OAc)_2$) (20 mol %), Cu(I)-thiophene-2-carboxylate (CuTC, 3.0 equiv), and K_2CO_3 (3.0 equiv) in toluene at 100 °C for 18 h provided the desired 2-phenoxypyrimidine **3aa**[21] in 47% yield. This result motivated us to perform subsequent optimization studies under various reaction conditions (Table 1). With respect to the base, we observed that K_3PO_4, which provided the desired product in 63% yield, was better than the other bases examined in the studies, such as K_2CO_3, potassium *t*-butoxide (*t*-BuOK), lithium hexamethyldisilazide (LiHMDS), and Cs_2CO_3 (entries 1−5). Solvents such as *N*,*N*-dimethylformamide (DMF), 1,4-dioxane, acetonitrile (MeCN), *o*-xylene, and *N*-methyl-2-pyrrolidone (NMP) were less effective than toluene (entries 6−10). When phosphine ligands, such as 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), 1,1′-bis(diphenylphosphino)ferrocene (dppf), tris(*o*-tolyl)phosphine ($P(o\text{-tolyl})_3$), 1,3-bis-(diphenylphosphino)propane (dppp), 1,10-phenanthroline (1,10-phen), 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl (Tol-BINAP), and triphenylphosphine (PPh_3), were investigated for further optimization (entries 11−17), we found that $P(o\text{-tolyl})_3$ improved the reaction yield up to 80%. With respect to Pd sources, tris(dibenzylideneacetone)-dipalladium(0) ($Pd_2(dba)_3$), $PdCl_2$, and $PdCl_2(PPh_3)_2$ were less effective than $Pd(OAc)_2$ (entries 18−20). The CuTC was best among the Cu sources examined in the studies, and three equivalents of it were optimal for generating the desired product,[22,23] as shown in our previous studies on the synthesis of 2-aryl- and 2-aminopyrimidines.[15,17] In the absence of a Cu or Pd source, the reaction afforded the desired product in 10% or 38% yield, respectively (entries 21 and 22). When both Cu and Pd sources were not present in the reaction, the desired product was not produced (entry 23).[24]

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

entry	Pd/ligand	base	solvent	yield (%)
1	$Pd(OAc)_2$	K_2CO_3	PhMe	47
2	$Pd(OAc)_2$	^{t}BuOK	PhMe	37
3	$Pd(OAc)_2$	LiHMDS	PhMe	28
4	$Pd(OAc)_2$	Cs_2CO_3	PhMe	20
5	$Pd(OAc)_2$	K_3PO_4	PhMe	63
6	$Pd(OAc)_2$	K_3PO_4	DMF	trace
7	$Pd(OAc)_2$	K_3PO_4	dioxane	trace
8	$Pd(OAc)_2$	K_3PO_4	MeCN	trace
9	$Pd(OAc)_2$	K_3PO_4	*o*-xylene	55
10	$Pd(OAc)_2$	K_3PO_4	NMP	trace
11	$Pd(OAc)_2$/BINAP	K_3PO_4	PhMe	51
12	$Pd(OAc)_2$/dppf	K_3PO_4	PhMe	30
13	$Pd(OAc)_2$/$P(o\text{-tolyl})_3$	K_3PO_4	PhMe	80
14	$Pd(OAc)_2$/dppp	K_3PO_4	PhMe	65
15	$Pd(OAc)_2$/1,10-phen	K_3PO_4	PhMe	58
16	$Pd(OAc)_2$/Tol-BINAP	K_3PO_4	PhMe	48
17	$Pd(OAc)_2$/PPh_3	K_3PO_4	PhMe	35
18	$Pd_2(dba)_3$/$P(o\text{-tolyl})_3$	K_3PO_4	PhMe	45
19	$PdCl_2$/$P(o\text{-tolyl})_3$	K_3PO_4	PhMe	78
20	$PdCl_2(PPh_3)_2$/$P(o\text{-tolyl})_3$	K_3PO_4	PhMe	53
21[b]	$PdCl_2(PPh_3)_2$/$P(o\text{-tolyl})_3$	K_3PO_4	PhMe	10
22	$P(o\text{-tolyl})_3$	K_3PO_4	PhMe	38
23[b]	$P(o\text{-tolyl})_3$	K_3PO_4	PhMe	0

[a]Reaction conditions: DHPM **1a** (0.18 mmol), PhOH **2a** (0.18 mmol), Pd catalyst (20 mol %), phosphine ligand (30 mol %), CuTC (0.54 mmol), base (0.54 mmol), and solvent (1.0 mL) at 100 °C for 18 h under Ar. [b]The reaction in the absence of a Cu source.

Under the optimal reaction conditions, we examined the scope of the reaction with diverse DHPM and aryl alcohol coupling partners. With respect to aryl alcohols, we found no clear preference for either electron-withdrawing or -donating substituents at the *para* position of aryl alcohols. When DHPM **1a** was reacted with *p*-cresol or 4-methoxyphenol, the desired pyrimidine products **3ab**[21] and **3ac** were produced in 63% and 78% yields, respectively (Scheme 2). Halides Cl, Br, and I at the *para* position of the aryl alcohol provided the corresponding products **3ad**,[21] **3ae**,[25] and **3af** in 70−73% yields. Other electron-withdrawing groups, such as cyano and nitro groups yielding **3ag** (52%) and **3ah**[12e] (70%), respectively, were also compatible with the reaction, albeit with a low yield in the case of the formyl group providing **3ai**.

We next examined the reaction scope with respect to DHPM substrates by varying the substituents at the C4−C6 positions. For R^1 at the C5 position, methyl, *i*-propyl, and *t*-butyl groups afforded the desired products **3aj**,[12a] **3ak**, and **3al**, respectively, in good yields. With respect to the substituents at C6 (R^2), we found that both alkyl and aryl groups, which gave the corresponding products **3am**−**ao** in 65−79% yields, were suitable for the reaction method. A functionalized aryl group, such as 4-fluorophenyl at C6, also yielded the desired product

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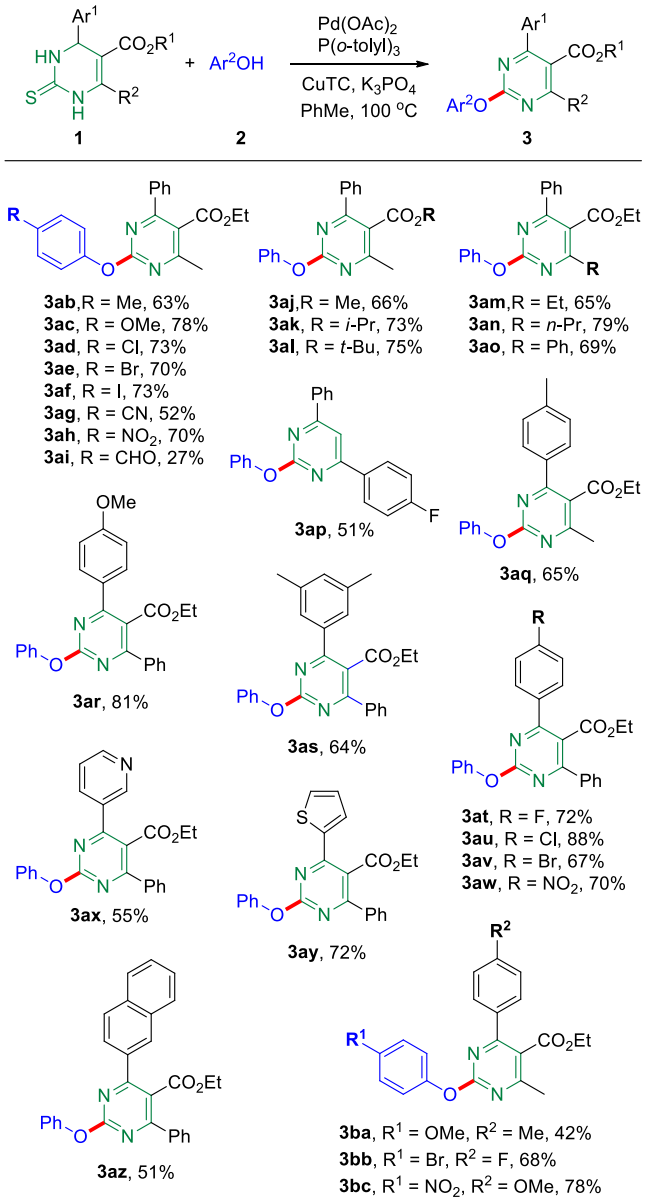
Scheme 2. Scope of the Reaction[a]

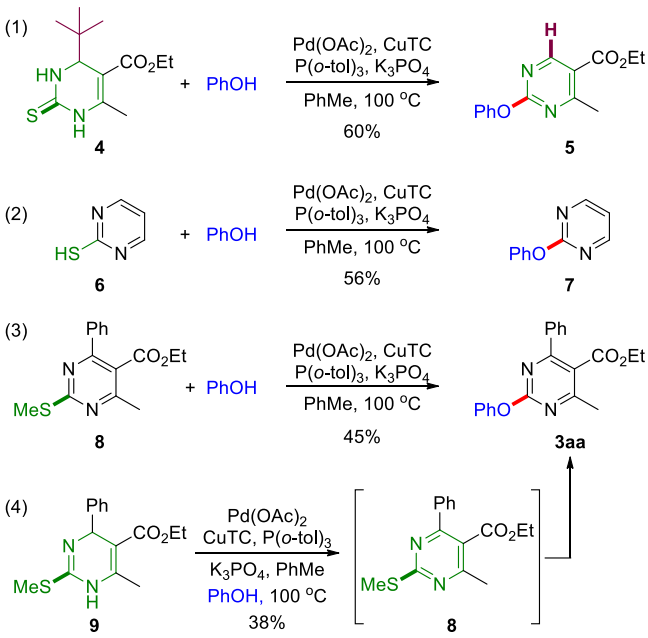


[a]Reaction conditions: DHPM **1** (0.18 mmol), aryl alcohol **2** (0.18 mmol), $Pd(OAc)_2$ (0.036 mmol), P(*o*-tolyl)$_3$ (0.054 mmol), CuTC (0.54 mmol), K_3PO_4 (0.54 mmol), and PhMe (1.0 mL) at 100 °C under Ar.

3ap (51%). Regarding the aryl group at the C4 position (Ar^1), the reaction of DHPM, bearing a 4-methyl, 4-methoxy group, or 3,5-dimethyl group at the C4 aryl position, provided the desired products **3aq**,[21] **3ar**, and **3as** in 64−81% yields. Halides F, Cl, and Br at the C4 aryl *para* position provided **3at**−**3av** without formation of the potentially competitive biaryl ether between the C4 aryl and phenol. The nitro group at the C4 aryl position, giving **3aw** in 70% yield, was also suitable for the reaction method. The DHPMs possessing a heterocyclic pyridinyl and thiophenyl group, or bicyclic naphthyl group, at the C4 position were efficiently transformed into the corresponding products **3ax**−**az**. When some of the above DHPMs were reacted with other aryl alcohols, such as *p*-cresol, 4-bromophenol, and 4-nitrophenol, the corresponding products **3ba**, **3bb**,[21] and **3bc**[12d] were produced in 42−78% yields.

Our previous oxidative dehydrosulfurative C−C, C−N, or C−O cross-coupling of DHPM possessing the *t*-butyl group at the C4 position provided the debutylated pyrimidine as the major product.[15−17,20] Similarly, the reaction of the DHPM **4** bearing the C4 *t*-butyl group with phenol also resulted in the debutylated product **5**[26] as the major product (eq 1, Scheme 3). The results support that the aromatization of the

Scheme 3. Related Reaction Studies



dihydropyrimidine proceeds via the generation of a radical intermediate presumably due to the Cu species present in the reaction, as described in the oxidative dehydrogenation of 2-alkylthiodihydropyrimidines.[27] When 2-mercaptopyrimidine **6** was reacted with phenol, the corresponding ether **7** was obtained in 56% yield (eq 2), which is in line with the proposition that tautomerization of the DHPM yielding the corresponding thiol is involved in the reaction. We found that pyrimidinyl thioether **8**[28] was also compatible with the reaction method (eq 3), and the reaction of dihydropyrimidinyl thioether **9**[29] proceeded via oxidative dehydrogenation to yield **8** as an intermediate, prior to the C−O coupling (eq 4). On the basis of these results, it is likely that the reaction proceeds via tautomerization and oxidative dehydrogenation, followed by C−O coupling.

In conclusion, we have developed a Pd-catalyzed/Cu-mediated oxidative dehydrosulfurative C−O cross-coupling of DHPMs with aryl alcohols to yield 2-aryloxypyrimidine derivatives in a single step.[30] The method is compatible with diverse DHPM and aryl alcohol coupling partners. Together with the ready availability of DHPM substrates prepared by the Biginelli three-component reaction, the reaction method allows facile access to biologically and pharmacologically valuable 2-aryloxypyrimidine derivatives with rapid diversification.

EXPERIMENTAL SECTION

General. Common solvents were purified before use. Toluene (PhMe) was purified by distillation from sodium-benzophenone ketyl. All reagents were reagent grade and purified where necessary. CuTC

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was prepared following the synthetic procedure described in the literature.[31] Reactions were monitored by thin-layer chromatography (TLC) using Whatman precoated silica gel plates. Flash column chromatography was performed over ultrapure silica gel (230−400 mesh) from Merck. Melting points (mp) were determined in opened capillary tubes and are uncorrected. ^{1}H NMR and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker AVANCE 300 (300 MHz) or 600 (600 MHz) spectrometer using residual solvent peaks as an internal standard ($CHCl_3$ δ 7.26 ppm for proton and δ 77.0 ppm for carbon and CH_2Cl_2 δ 5.32 ppm for proton and δ 54.0 ppm for carbon). Multiplicities for ^{1}H NMR are designated as s = singlet, d = doublet, t = triplet, q = quartet, sext = sextet, sept = septet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets, m = multiplet, and br = broad. Infrared spectra (IR) were recorded on a JASCO FT/IR-4100 spectrometer and are reported in reciprocal centimeters (cm^{-1}). High-resolution mass spectra (HRMS) were obtained on a BrukermicroTOF-Q.

Synthesis of DHPMs. Following the literature procedure,[32] ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1a**),[32] methyl 4-methyl-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1b**),[32] isopropyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1c**),[33] *tert*-butyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1d**),[34] ethyl 6-ethyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1e**),[35] ethyl 4-phenyl-6-propyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1f**),[16] ethyl 4,6-diphenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1g**),[36] 6-(4-fluorophenyl)-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-thione (**1h**),[37] ethyl 6-methyl-2-thioxo-4-(*p*-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1i**),[32] ethyl 4-(4-methoxyphenyl)-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1j**),[36] ethyl 4-(3,5-dimethylphenyl)-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1k**),[16] ethyl 4-(4-fluorophenyl)-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1l**),[35] ethyl 4-(4-chlorophenyl)-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1m**),[36] ethyl 4-(4-bromophenyl)-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1n**),[38] ethyl 4-(4-nitrophenyl)-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1o**),[36] ethyl 6-phenyl-4-(pyridin-3-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1p**),[17] ethyl 6-phenyl-4-(thiophen-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1q**),[15b] ethyl 4-(naphthalen-2-yl)-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1r**),[17] ethyl 6-methyl-2-thioxo-4-(*p*-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1s**),[32] ethyl 4-(4-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1t**),[32] and ethyl 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**1u**)[39] were prepared.

General Procedure for the Synthesis of 2-Aryloxypyrimidine. To an oven-dried test tube with a magnetic stirring bar were added DHPM or pyrimidine-2-thiol (0.18 mmol, 1.0 equiv), aryl alcohol (0.18 mmol, 1.0 equiv), CuTC (103 mg, 0.54 mmol, 3.0 equiv), $Pd(OAc)_2$ (8.0 mg, 0.036 mmol, 0.20 equiv), P(*o*-tolyl)$_3$ (13 mg, 0.043 mmol, 0.24 equiv), and K_3PO_4 (114 mg, 0.54 mmol, 3.0 equiv) in PhMe (1 mL). The reaction mixture was degassed with Ar and then stirred at 100 °C in an oil bath under Ar until the DHPM completely disappeared. The mixture was filtered through a silica gel pad and washed with EtOAc (25 mL). The filtrate was washed with saturated aqueous K_2CO_3 solution (5 mL) and brine (5 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel; eluent: *n*-hexane/EtOAc, 10:1 to 4:1) to give the corresponding 2-aryloxypyrimidine **3**, **5**, or **7**.

*Ethyl 4-Methyl-2-phenoxy-6-phenylpyrimidine-5-carboxylate (**3aa**).*[21] Yield: 48.1 mg, 80%; pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 (m, 2H), 7.46−7.38 (m, 5H), 7.24 (m, 3H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.58 (s, 3H), 1.06 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 169.1, 168.0, 166.5, 163.9, 152.7, 137.2, 130.2, 129.3, 128.33, 128.27, 125.1, 121.5, 121.0, 61.7, 22.7, 13.5. For the scale-up synthesis, to an oven-dried round-bottom flask with a magnetic stirring bar were added DHPM **1a** (1.00 g, 3.60 mmol), PhOH (339 mg, 3.60 mmol), $Pd(OAc)_2$ (161 mg, 0.717 mmol), P(*o*-tolyl)$_3$ (262 mg, 0.861 mmol), CuTC (2.06 g, 10.8 mmol), and K_3PO_4 (2.29 g, 10.8 mmol). The reaction vessel was sealed by a septum and degassed with argon three times. To the reaction mixture was added PhMe (20 mL), and the resulting mixture was allowed to stir at 100 °C in an oil bath for 18 h. The mixture was filtered through a Celite pad and rinsed with EtOAc (100 mL). The filtrate was washed with saturated aqueous K_2CO_3 solution (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (*n*-hexane/EtOAc, 10:1) to give **3aa** (939 mg, 78%).

*Ethyl 4-Methyl-6-phenyl-2-(p-tolyloxy)pyrimidine-5-carboxylate (**3ab**).*[21] Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 39.4 mg, 63%; pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 (m, 2H), 7.45−7.38 (m, 3H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.56 (s, 3H), 2.37 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 169.1, 168.1, 166.6, 164.0, 150.5, 137.4, 134.7, 130.2, 129.8, 128.39, 128.35, 121.2, 120.9, 61.8, 22.7, 20.9, 13.6.

*Ethyl 2-(4-Methoxyphenoxy)-4-methyl-6-phenylpyrimidine-5-carboxylate (**3ac**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 51.1 mg, 78%; yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (m, 2H), 7.41 (m, 3H), 7.16 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 2.56 (s, 3H), 1.05 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.1, 168.1, 166.6, 164.2, 156.8, 146.3, 137.3, 130.2, 128.4, 128.3, 122.4, 120.8, 114.3, 61.8, 55.6, 22.7, 13.6. IR (film) cm^{-1}: 3053, 2971, 1703, 1603, 1565, 1412, 1263, 729. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_4$, 365.1501; found, 365.1514.

*Ethyl 2-(4-Chlorophenoxy)-4-methyl-6-phenylpyrimidine-5-carboxylate (**3ad**).*[21] Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 48.4 mg, 73%; pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (d, *J* = 1.4 Hz, 1H), 7.57 (d, *J* = 1.8 Hz, 1H), 7.46−7.34 (m, 5H), 7.19 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.57 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 169.3, 167.9, 166.7, 163.6, 151.3, 137.1, 130.5, 130.4, 129.4, 128.5, 128.3, 123.0, 121.3, 61.9, 22.7, 13.6.

*Ethyl 2-(4-Bromophenoxy)-4-methyl-6-phenylpyrimidine-5-carboxylate (**3ae**).*[25] Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 52.0 mg, 70%; white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 (m, 2H), 7.51 (m, 2H), 7.44 (m, 3H), 7.14 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.57 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 169.3, 167.9, 166.7, 163.5, 151.8, 137.1, 132.4, 130.4, 128.5, 128.3, 123.4, 121.4, 118.2, 61.9, 22.7, 13.6.

*Ethyl 2-(4-Iodophenoxy)-4-methyl-6-phenylpyrimidine-5-carboxylate (**3af**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 60.4 mg, 73%; yellow solid, mp 58−59 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 (m, 2H), 7.59 (m, 2H), 7.44 (m, 3H), 7.03 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.57 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 169.3, 167.9, 166.7, 163.5, 152.7, 138.4, 137.1, 130.4, 128.5, 128.3, 123.8, 121.4, 89.0, 61.9, 22.7, 13.6. IR (film) cm^{-1}: 3012, 2932, 1722, 1544, 1476, 1365, 1236, 1081,999, 766, 695. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{18}IN_2O_3$, 461.0362; found, 461.0351.

*Ethyl 2-(4-Cyanophenoxy)-4-methyl-6-phenylpyrimidine-5-carboxylate (**3ag**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 33.6 mg, 52%; yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.7 Hz, 2H), 7.57 (m, 2H), 7.47 (m, 1H), 7.42 (m, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.58 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 169.5, 167.6, 166.8, 162.9, 156.1, 136.8, 133.7, 130.6, 128.5, 128.3, 122.5, 121.9, 118.4, 108.9, 62.0, 22.7, 13.6. IR (film) cm^{-1}: 2917, 2849, 2123, 1719, 1540, 1243, 1082, 725. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{18}N_3O_3$, 360.1348; found, 360.1355.

*Ethyl 4-Methyl-2-(4-nitrophenoxy)-6-phenylpyrimidine-5-carboxylate (**3ah**).*[12e] Eluent in chromatography: *n*-hexane/EtOAc 5:1. Yield: 47.8 mg, 70%; white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (m, 2H), 7.58 (m, 2H), 7.50−7.39 (m, 5H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.59 (s, 3H), 1.07 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz,

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$CDCl_3$): δ 169.5, 167.6, 166.8, 162.9, 157.6, 144.8, 136.8, 130.6, 128.6, 128.4, 128.3, 125.3, 122.1, 62.0, 22.7, 13.6.

*Ethyl 2-(4-Formylphenoxy)-4-methyl-6-phenylpyrimidine-5-carboxylate (**3ai**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 17.6 mg, 27%; yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.01 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 2H), 7.59 (m, 2H), 7.46 (m, 1H), 7.41 (m, 4H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.59 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 191.0, 169.4, 167.8, 166.8, 163.2, 157.6, 136.9, 133.5, 131.3, 130.5, 128.5, 128.3, 122.1, 121.8, 62.0, 22.7, 13.6. IR (film) cm^{-1}: 2953, 2843, 1713, 1553, 1263, 1054, 863, 731. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{21}H_{19}N_2O_4$, 363.1345; found, 363.1358.

*Methyl 4-Methyl-2-phenoxy-6-phenylpyrimidine-5-carboxylate (**3aj**).*[12d] Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 38.1 mg, 66%; pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 (d, *J* = 6.9 Hz, 2H), 7.45−7.39 (m, 5H), 7.25 (m, 3H), 3.70 (s, 3H), 2.56 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 169.2, 168.6, 166.4, 164.0, 152.7, 137.1, 130.4, 129.3, 128.5, 128.3, 125.2, 121.6, 120.7, 52.6, 22.8.

*Isopropyl 4-Methyl-2-phenoxy-6-phenylpyrimidine-5-carboxylate (**3ak**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 45.8 mg, 73%; yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 (m, 2H), 7.45−7.37 (m, 5H), 7.24 (m, 3H), 5.08 (sept, *J* = 6.3 Hz, 1H), 2.56 (s, 3H), 1.09 (d, *J* = 6.3 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 168.8, 167.5, 166.4, 163.8, 152.8, 137.3, 130.2, 129.3, 128.41, 128.37, 125.1, 121.53, 121.52, 69.7, 22.6, 21.3. IR (film) cm^{-1}: 2954, 2836, 1722, 1535, 1479, 1245, 1223, 1009, 765, 670. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_3$, 349.1552; found, 349.1560.

*tert-Butyl 4-Methyl-2-phenoxy-6-phenylpyrimidine-5-carboxylate (**3al**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 48.9 mg, 75%; yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (m, 2H), 7.45−7.38 (m, 5H), 7.24 (m, 3H), 2.59 (s, 3H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 168.5, 166.8, 166.1, 163.4, 152.8, 137.3, 130.0, 129.2, 128.5, 128.2, 125.0, 122.5, 121.4, 82.8, 27.5, 22.5. IR (film) cm^{-1}: 2925, 2842, 1710, 1542, 1486, 1387, 1266, 1197, 1142, 1088, 836, 771, 691. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{23}N_2O_3$, 363.1709; found, 363.1700.

*Ethyl 4-Ethyl-2-phenoxy-6-phenylpyrimidine-5-carboxylate (**3am**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 40.7 mg, 65%; yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (m, 2H), 7.43−7.36 (m, 5H), 7.26−7.20 (m, 3H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.84 (q, *J* = 7.5 Hz, 2H), 1.28 (t, *J* = 7.5 Hz, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 173.5, 168.1, 166.6, 164.2, 152.8, 137.4, 130.2, 129.3, 128.4, 128.3, 125.1, 121.6, 120.7, 61.8, 28.9, 13.6, 12.6. IR (film) cm^{-1}: 2926, 2836, 1716, 1540, 1485, 1379, 1250, 1239, 1079, 1025, 763, 689. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{21}H_{21}N_2O_3$, 349.1552; found, 349.1539.

*Ethyl 2-Phenoxy-4-phenyl-6-propylpyrimidine-5-carboxylate (**3an**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 51.5 mg, 79%; yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (m, 2H), 7.47−7.36 (m, 5H), 7.24 (m, 3H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.80 (t, *J* = 7.6 Hz, 2H), 1.77 (sext, *J* = 7.5 Hz, 2H), 1.07 (t, *J* = 7.1 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 172.4, 168.1, 166.6, 164.1, 152.8, 137.4, 130.2, 129.3, 128.4, 128.3, 125.1, 121.5, 121.0, 61.7, 37.4, 21.9, 13.9, 13.6. IR (film) cm^{-1}: 2927, 2840, 1719, 1540, 1486, 1376, 1238, 1078, 1004, 765, 691. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{23}N_2O_3$, 363.1709; found, 363.1701.

*Ethyl 2-Phenoxy-4,6-diphenylpyrimidine-5-carboxylate (**3ao**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 49.2 mg, 69%; white solid, mp 58−59 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.0 Hz, 4H), 7.48−7.40 (m, 8H), 7.29 (d, *J* = 7.7 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 4.07 (q, *J* = 7.1 Hz, 2H), 0.96 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 168.1, 167.5, 164.1, 152.8, 137.1, 130.3, 129.4, 128.4, 128.3, 125.2, 121.5, 120.9, 61.9, 13.4. IR (film) cm^{-1}: 2929, 2844, 1714, 1533, 1486, 1385, 1252, 1059, 767, 693, 523. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{25}H_{21}N_2O_3$, 397.1552; found, 397.1538.

*4-(4-Fluorophenyl)-2-phenoxy-6-phenylpyrimidine (**3ap**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 31.4 mg, 51%; yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09 (m, 4H), 7.83 (s, 1H), 7.52−7.43 (m, 5H), 7.33 (d, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 7.4 Hz, 1H), 7.17 (t, *J* = 8.6 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 167.6, 166.3, 165.8, 165.6 (C−F, $^1J_{C-F}$ = 252.2 Hz), 163.9 (C−F, $^1J_{C-F}$ = 252.2 Hz), 153.2, 136.4, 132.7, 131.2, 129.42 (C−F, $^3J_{C-F}$ = 8.8 Hz), 129.37 (C−F, $^3J_{C-F}$ = 8.8 Hz), 129.3, 128.9, 127.3, 125.0, 121.8, 116.0 (C−F, $^2J_{C-F}$ = 21.7 Hz), 115.9 (C−F, $^2J_{C-F}$ = 21.7 Hz), 107.0. IR (film) cm^{-1}: 2920, 2833, 1727, 1524, 1339, 1216, 948, 833, 762, 686, 563. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{22}H_{16}FN_2O$, 343.1247; found, 343.1261.

*Ethyl 4-Methyl-2-phenoxy-6-(p-tolyl)pyrimidine-5-carboxylate (**3aq**).*[21] Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 40.4 mg, 65%; pale yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 (m, 2H), 7.45−7.38 (m, 3H), 7.20 (d, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.57 (s, 3H), 2.37 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 169.0, 168.1, 166.6, 164.0, 150.5, 137.3, 134.7, 130.2, 129.8, 128.4, 128.3, 121.2, 120.9, 61.8, 22.7, 20.9, 13.6.

*Ethyl 4-(4-Methoxyphenyl)-2-phenoxy-6-phenylpyrimidine-5-carboxylate (**3ar**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 62.1 mg, 81%; brown oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.65 (m, 4H), 7.47−7.40 (m, 5H), 7.29 (m, 2H), 7.23 (m, 1H), 6.93 (m, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 3H), 1.00 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 168.5, 167.5, 166.6, 164.0, 161.5, 152.9, 137.3, 130.2, 130.1, 129.3, 128.36, 128.35, 125.1, 121.6, 120.3, 113.9, 61.9, 55.3, 13.5. IR (film) cm^{-1}: 2922, 2835, 1725, 1532, 1364, 1246, 1125, 1059, 1015, 843, 767, 694, 534. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{26}H_{23}N_2O_4$, 427.1658; found, 427.1655.

*Ethyl 4-(3,5-Dimethylphenyl)-2-phenoxy-6-phenylpyrimidine-5-carboxylate (**3as**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 48.9 mg, 64%; yellow oil. ^{1}H NMR (600 MHz, CD_2Cl_2): δ 7.60 (d, *J* = 7.0 Hz, 2H), 7.50−7.43 (m, 5H), 7.28−7.23 (m, 5H), 7.14 (s, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 2.35 (s, 6H), 1.00 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, CD_2Cl_2): δ 168.6, 168.4, 167.7, 164.7, 153.6, 138.8, 137.9, 137.7, 132.4, 130.8, 130.0, 129.0, 128.8, 126.5, 125.9, 122.2, 121.7, 62.4, 21.6, 13.9. IR (film) cm^{-1}: 3017, 2934, 1720, 1538, 1472, 1344, 1236, 1152, 1021, 965, 721. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{27}H_{25}N_2O_3$, 425.1865; found, 425.1890.

*Ethyl 4-(4-Fluorophenyl)-2-phenoxy-6-phenylpyrimidine-5-carboxylate (**3at**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 53.7 mg, 72%; yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 (m, 4H), 7.44 (m, 5H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.12 (t, *J* = 8.6 Hz, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 0.99 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 168.1, 167.7, 166.2, 164.9 (C−F, $^1J_{C-F}$ = 251.3 Hz), 164.0, 163.2 (C−F, $^1J_{C-F}$ = 251.3 Hz), 152.8, 137.0, 133.1, 130.7 (C−F, $^3J_{C-F}$ = 8.8 Hz), 130.6 (C−F, $^3J_{C-F}$ = 8.8 Hz), 130.3, 129.4, 128.42, 128.36, 125.3, 121.5, 120.7, 115.6 (C−F, $^2J_{C-F}$ = 21.9 Hz), 115.5 (C−F, $^2J_{C-F}$ = 21.9 Hz), 62.0, 13.5. IR (film) cm^{-1}: 2925, 2832, 1706, 1533, 1378, 847, 693, 569, 523. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{25}H_{20}FN_2O_3$, 415.1458; found, 415.1471.

*Ethyl 4-(4-Chlorophenyl)-2-phenoxy-6-phenylpyrimidine-5-carboxylate (**3au**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 68.2 mg, 88%; yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (m, 4H), 7.50−7.40 (m, 6H), 7.37 (m, 2H), 7.24 (m, 2H), 4.07 (q, *J* = 7.1 Hz, 2H), 0.96 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 168.0, 167.7, 166.1, 164.1, 152.7, 136.9, 136.7, 135.4, 130.4, 129.8, 129.4, 128.7, 128.4, 128.3, 125.3, 121.5, 120.7, 62.1, 13.5. IR (film) cm^{-1}: 2918, 2844, 1721, 1530, 1483, 1385, 1250, 1131, 1060, 1005, 951, 768, 693, 524. HRMS (ESI) *m*/*z*: [M + H]$^+$ calcd for $C_{25}H_{20}ClN_2O_3$, 431.1162; found, 431.1160.

*Ethyl 4-(4-Bromophenyl)-2-phenoxy-6-phenylpyrimidine-5-carboxylate (**3av**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 57.3 mg, 67%; yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.1 Hz, 2H), 7.58 (m, 4H), 7.49 (m, 1H), 7.45 (m, 4H), 7.28 (m, 3H), 4.10 (q, *J* = 7.1 Hz, 2H), 1.02 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$): δ 168.0, 167.8, 166.2, 164.1, 152.8, 136.9,

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135.9, 131.7, 130.4, 130.1, 129.4, 128.5, 128.4, 125.3, 125.1, 121.5, 120.7, 62.1, 13.5. IR (film) cm^{-1}: 2923, 2835, 1722, 1530, 1484, 1385, 1249, 1130, 1059, 1004, 951, 768, 693, 523. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{20}BrN_2O_3$, 475.0657; found, 475.0673.

*Ethyl 4-(4-Nitrophenyl)-2-phenoxy-6-phenylpyrimidine-5-carboxylate (**3aw**).* Eluent in chromatography: *n*-hexane/EtOAc 5:1. Yield: 55.6 mg, 70%; yellow solid, mp 58−59 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, J = 8.6 Hz, 2H), 7.84 (d, J = 8.6 Hz, 2H), 7.68 (m, 2H), 7.47 (m, 5H), 7.28 (m, 3H), 4.10 (q, J = 7.1 Hz, 2H), 1.00 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.2, 167.5, 165.1, 164.2, 152.6, 148.8, 143.0, 136.6, 130.7, 129.6, 129.5, 128.5, 128.4, 125.5, 123.6, 121.5, 121.0, 62.3, 13.4. IR (film) cm^{-1}: 2922, 2832, 1725, 1532, 1347, 1249, 1134, 1056, 1009, 852, 768, 690, 525. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{20}N_3O_5$, 442.1403; found, 442.1390.

*Ethyl 2-Phenoxy-4-phenyl-6-(pyridin-3-yl)pyrimidine-5-carboxylate (**3ax**).* Eluent in chromatography: *n*-hexane/EtOAc 4:1. Yield: 39.4 mg, 55%; yellow oil. ^1H NMR (600 MHz, $CDCl_3$): δ 8.54 (t, J = 1.9 Hz, 1H), 8.33 (ddd, J = 8.3, 2.3, 1.1 Hz, 1H), 8.02 (ddd, J = 7.7, 1.7, 1.1 Hz, 1H), 7.64 (m, 3H), 7.50 (m, 1H), 7.44 (m, 4H), 7.30−7.25 (m, 3H), 4.11 (q, J = 7.1 Hz, 2H), 1.02 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 168.2, 167.7, 164.7, 164.2, 152.6, 148.1, 138.5, 136.7, 134.5, 130.6, 129.5, 128.5, 128.4, 125.5, 124.9, 123.6, 121.5, 120.9, 62.4. 13.5. IR (film) cm^{-1}: 2949, 2846, 1711, 1548, 1335, 1262, 1167, 1032, 865, 731. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{20}N_3O_3$, 398.1505; found, 398.1486.

*Ethyl 2-Phenoxy-4-phenyl-6-(thiophen-2-yl)pyrimidine-5-carboxylate (**3ay**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 52.1 mg, 72%; yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (m, 2H), 7.61 (d, J = 3.9 Hz, 1H), 7.49 (d, J = 5.0 Hz, 1H) 7.42 (m, 5H), 7.25 (m, 3H), 7.06 (t, J = 4.8 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 1.04 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.3, 167.9, 163.7, 158.5, 152.7, 140.6, 137.2, 131.5, 130.2, 129.8, 129.3, 129.1, 128.4, 128.3, 125.2, 121.7, 117.8, 62.3, 13.5. IR (film) cm^{-1}: 2922, 2833, 1713, 1526, 1381, 1253, 1029, 856, 764, 688, 629. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{19}N_2O_3S$, 403.1116; found, 403.1129.

*Ethyl 4-(Naphthalen-2-yl)-2-phenoxy-6-phenylpyrimidine-5-carboxylate (**3az**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 41.1 mg, 51%; colorless oil. ^1H NMR (600 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.87 (dd, J = 7.7, 2.9 Hz, 2H), 7.76 (d, J = 8.5 Hz, 1H) 7.69 (d, J = 7.3 Hz, 2H), 7.54 (m, 2H), 7.45 (m, 5H), 7.33 (d, J = 8.2 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 0.95 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 168.3, 167.5, 167.3, 164.1, 152.9, 137.1, 134.4, 134.0, 132.8, 130.3, 129.4, 128.80, 128.77, 128.42, 128.39, 128.3, 127.7, 127.4, 126.6, 125.3, 125.2, 121.6, 121.1, 62.0, 13.5. IR (film) cm^{-1}: 2925, 2843, 1713, 1555, 1374, 1263, 1063, 823, 731. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{23}N_2O_3$, 447.1709; found, 447.1721.

*Ethyl 2-(4-Methoxyphenoxy)-4-phenyl-6-(p-tolyl)pyrimidine-5-carboxylate (**3ba**).* Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 33.3 mg, 42%; yellow solid, mp 116−118 °C. ^1H NMR (600 MHz, $CDCl_3$): δ 7.64 (m, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.44 (m, 3H), 7.22 (d, J = 8.0 Hz, 2H), 7.20 (m, 2H), 6.92 (m, 2H), 4.07 (d, J = 7.1 Hz, 2H), 3.82 (s, 3H), 2.39 (s, 3H), 0.98 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.4, 167.4, 167.3, 164.3, 156.7, 146.4, 140.6, 137.2, 134.2, 130.2, 129.2, 128.41, 128.36, 122.4, 120.5, 120.0, 114.3, 61.9, 55.6, 21.4, 13.5. IR (film) cm^{-1}: 2948, 2838, 1716, 1567, 1537, 1422, 1349, 1263, 863, 730. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{25}N_2O_4$, 441.1814; found, 441.1818.

*Ethyl 2-(4-Bromophenoxy)-4-(4-fluorophenyl)-6-methylpyrimidine-5-carboxylate (**3bb**).*[21] Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 52.6 mg, 68%; white solid. ^1H NMR (600 MHz, $CDCl_3$): δ 7.60 (m, 2H), 7.53 (m, 2H), 7.12 (m, 4H), 4.21 (q, J = 7.1 Hz, 2H), 2.56 (m, 3H), 1.13 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 169.4, 167.8, 165.3, 165.0 (C−F, $^1J_{C-F}$ = 251.6 Hz), 163.5, 163.3 (C−F, $^1J_{C-F}$ = 251.6 Hz), 151.8, 133.2, 132.4, 130.52 (C−F, $^3J_{C-F}$ = 8.8 Hz), 130.46 (C−F, $^3J_{C-F}$ = 8.8 Hz), 123.4, 121.1, 118.2, 115.7 (C−F, $^2J_{C-F}$ = 21.9 Hz), 115.6 (C−F, $^2J_{C-F}$ = 21.9 Hz), 61.9, 22.7, 13.7.

*Ethyl 4-(4-Methoxyphenyl)-6-methyl-2-(4-nitrophenoxy)-pyrimidine-5-carboxylate (**3bc**).*[12d] Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 57.4 mg, 78%; white solid. ^1H NMR (600 MHz, $CDCl_3$): δ 8.31 (d, J = 9.1 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 9.1 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 2.56 (s, 3H), 1.17 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 169.2, 168.1, 165.8, 162.8, 161.9, 157.8, 144.8, 130.1, 129.0, 125.3, 122.1, 121.4, 114.1, 62.0, 55.4, 22.7, 13.8.

*Ethyl 4-Methyl-2-phenoxypyrimidine-5-carboxylate (**5**).*[26] Eluent in chromatography: *n*-hexane/EtOAc 10:1. Yield: 27.8 mg, 60%; pale yellow oil. ^1H NMR (600 MHz, $CDCl_3$): δ 9.00 (s, 1H), 7.43 (t, J = 7.9 Hz, 2H), 7.28 (d, J = 7.4 Hz, 1H), 7.20 (d, J = 7.9 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 2.79 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$): δ 173.1, 165.6, 164.4, 162.2, 152.5, 129.6, 125.7, 121.6, 118.9, 61.3, 24.7, 14.2.

*2-Phenoxypyrimidine (**7**).*[13d] Eluent in chromatography: *n*-hexane/EtOAc 4:1. Yield: 17.3 mg, 56%; white solid. ^1H NMR (300 MHz, CD_2Cl_2): δ 8.55 (d, J = 2.7 Hz, 2H), 7.44 (m, 2H), 7.27 (t, J = 7.4 Hz, 2H), 7.20 (m, 2H), 7.04 (t, J = 4.7 Hz, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, CD_2Cl_2): δ 165.9, 160.1, 153.6, 130.1, 125.8, 122.3, 116.8.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00273.

^1H and $^{13}C\{^1H\}$ NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **3aa**−**3az**, **3ba**−**3bc**, **5**, and **7** (ZIP)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Lagoja, M. Pyrimidine as Constituent of Natural Biologically Active Compounds. *Chem. Biodiversity* **2005**, *2*, 1−50. (b) *Pharmaceutical Substances: Synthesis, Patents, Applications*; Kleemann, A., Engel, J., Eds.; Thieme: Stuttgart, Germany, 2001.

(2) Watanabe, M.; Koike, H.; Ishiba, T.; Okada, T.; Seo, S.; Hirai, K. Synthesis and Biological Activity of Methanesulfonamide Pyrimidine- and N-Methanesulfonyl Pyrrole-Substituted 3,5-Dihydroxy-6-hepte-

noates, a Novel Series of HMG-CoA Reductase Inhibitors. *Bioorg. Med. Chem.* **1997**, *5*, 437−444.
(3) Capdeville, R.; Buchdunger, E.; Zimmermann, J.; Matter, A. Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. *Nat. Rev. Drug Discovery* **2002**, *1*, 493−502.
(4) Singh, P. K.; Singh, H.; Silakari, O. Kinases inhibitors in lung cancer: from benchside to bedside. *Biochim. Biophys. Acta, Rev. Cancer* **2016**, *1866*, 128−140.
(5) Burmester, G. R.; Bijlsma, J. W.; Cutolo, M.; McInnes, I. B. Managing rheumatic and musculoskeletal diseases- past, present and future. *Nat. Rev. Rheumatol.* **2017**, *13*, 443−448.
(6) Sammons, S. L.; Topping, D. L.; Blackwell, K. L. HR+, HER2- advanced breast cancer and CDK4/6 inhibitors: mode of action, clinical activity, and safety profiles. *Curr. Cancer Drug Targets* **2017**, *17*, 637−649.
(7) Scott, L. J.; Simpson, D. Voriconazole: a review of its use in the management of invasive fungal infections. *Drugs* **2007**, *67*, 269−298.
(8) Fischer, A. J.; Bayer, D. E.; Carriere, M. D.; Ateh, C. M.; Yim, K. − O. Mechanisms of Resistance to Bispyribac-Sodium in an Echinochloa phyllopogon Accession. *Pestic. Biochem. Physiol.* **2000**, *68*, 156−165.
(9) Hirai, K.; Uchida, A.; Ohno, R. Major synthetic routes for modern herbicide classes and agrochemical characteristics. In *Herbicide Classes in Development: Mode of action, Targets, Genetic Engineering, Chemistry*; Böger, P., Wakabayashi, K., Hirai, K., Eds.; Springer-Verlag: Berlin, Germany, 2002.
(10) Wu, X.; Walker, J.; Zhang, J.; Ding, S.; Schultz, P. G. Purmorphamine induces osteogenesis by activation of the hedgehog signaling pathway. *Chem. Biol.* **2004**, *11*, 1229−1238.
(11) Wang, J.; Sun, P.; Chen, Y.; Yao, H.; Wang, S. Novel 2-phenyloxypyrimidine derivative induces apoptosis and autophagy via inhibiting PI3K pathway and activating MAPK/ ERK signaling in hepatocellular carcinoma cells. *Sci. Rep.* **2018**, *8*, 10923.
(12) For selected recent examples of the nucleophilic aromatic substitutions, see: (a) Kang, F. A.; Kodah, J.; Guan, Q.; Li, X.; Murray, W. V. Efficient Conversion of Biginelli 3,4-Dihydropyrimidin-2(1*H*)-one to Pyrimidines via PyBroP-Mediated Coupling. *J. Org. Chem.* **2005**, *70*, 1957−1960. (b) Wang, Y. − F.; Liu, W. − M.; Zhu, Y. − Q.; Zou, X. − M.; Hu, F. − Z.; Yang, H. − Z. Design, synthesis and biological evaluation of novel 6,7,8,9-tetrahydro-2-(2-aryloxypyrimidin-4-yl)-2*H*-[1,2,4]triazolo[4,3-*a*]azepin-3(5*H*)-ones. *J. Heterocycl. Chem.* **2006**, *43*, 1275−1280. (c) Venu, T. D.; Khanum, S. A.; Firdouse, A.; Manuprasad, B. K.; Shashikanth, S.; Mohamed, R.; Vishwanth, B. S. Synthesis and anti-inflammatory activity of 2-(2-aroylaroxy)-4,6-dimethoxypyrimidines. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4409−4412. (d) Wang, X. C.; Yang, G. J.; Jia, X. D.; Zhang, Z.; Da, Y. X.; Quan, Z. J. Synthesis of C2-functionalized pyrimidines from 3,4-dihydropyrimidin-2(1*H*)-ones by the Mitsunobu coupling reaction. *Tetrahedron* **2011**, *67*, 3267−3272. (e) Quan, Z.; Jing, F.; Zhang, Z.; Da, Y.; Wang, X. Cross-Coupling Reactions of Pyrimidin-2-yl Sulfonates with Phenols and Anilines: An Efficient Approach to C2-Functionalized Pyrimidines. *Chin. J. Chem.* **2013**, *31*, 1495−1502. (f) Walsh, K.; Sneddon, H. F.; Moody, C. J. An efficient method for the synthesis of heteroaryl C-O bonds in the absence of added transition metal catalysts. *RSC Adv.* **2014**, *4*, 28072−28077. (g) Meng, J. − P.; Wang, W. − W.; Chen, Y. − L.; Bera, S.; Wu, J. Switchable solvent-controlled divergent synthesis: an efficient and regioselective approach to pyrimidine and dibenzo[b,f][1,4]oxazepine derivatives. *Org. Chem. Front.* **2020**, *7*, 267−272.
(13) For selected recent examples of Ullmann-type C-O cross-couplings, see: (a) D'Angelo, N. D.; Peterson, J. J.; Booker, S. K.; Fellows, I.; Dominguez, C.; Hungate, R.; Reider, P. J.; Kim, T. − S. Effect of microwave heating on Ullmann-type heterocycle-aryl ether synthesis using chloro-heterocycles. *Tetrahedron Lett.* **2006**, *47*, 5045−5048. (b) Bardhan, S.; Wacharasindhu, S.; Wan, Z. − K.; Mansour, T. S. Heteroaryl Ethers by Oxidative Palladium Catalysis of Pyridotriazol-1-yloxy Pyrimidines with Arylboronic Acids. *Org. Lett.* **2009**, *11*, 2511−2514. (c) Gu, S.; Chen, C.; Chen, W. Ortho-Functionalization of 2-Phenoxypyrimidines via Palladium-Catalyzed C-H Bond Activation. *J. Org. Chem.* **2009**, *74*, 7203−7206. (d) Platon, M.; Cui, L.; Mom, S.; Richard, P.; Saeys, M.; Hierso, J. − C. Etherification of Functionalized Phenols with Chloroheteroarenes at Low Palladium Loading: Theoretical Assessment of the Role of Triphosphane Ligands in C-O Reductive Elimination. *Adv. Synth. Catal.* **2011**, *353*, 3403−3414.
(14) For recent representative reviews, see: (a) Singh, K.; Singh, K. Biginelli Condensation: Synthesis and Structure Diversification of 3,4-Dihydropyrimidin-2(1H)-one Derivatives. *Adv. Heterocycl. Chem.* **2012**, *105*, 223−308. (b) Suresh; Sandhu, J. S. Past, present and future of the Biginelli reaction: a critical perspective. *ARKIVOC* **2012**, 66−133. (c) Patil, R. V.; Chavan, J. U.; Dalal, D. S.; Shinde, V. S.; Beldar, A. G. Biginelli Reaction: Polymer Supported Catalytic Approaches. *ACS Comb. Sci.* **2019**, *21* (3), 105−148.
(15) (a) Kim, H.; Phan, N. H. T.; Shin, H.; Lee, H. S.; Sohn, J.-H. Dehydrosulfurative arylation with concomitant oxidative dehydrogenation for rapid access to pyrimidine derivatives. *Tetrahedron* **2017**, *73*, 6604−6613. (b) Yang, H.; Pham, N. S. L.; Shin, H.; Sohn, J. − H. Oxidative Dehydrosulfurative Azolation of 3,4-Dihydropyrimidin-1*H*-2-thiones. *Bull. Korean Chem. Soc.* **2020**, *41*, 881−883.
(16) Pham, N. S. L.; Shin, H.; Kang, J. Y.; Sohn, J. − H. Oxidative Dehydrosulfurative Cross-Coupling of 3,4- Dihydropyrimidine-2-thiones with Alkynes for Access to 2-Alkynylpyrimidines. *J. Org. Chem.* **2020**, *85*, 5087−5096.
(17) Phan, N. H. T.; Kim, H.; Shin, H.; Lee, H.-S.; Sohn, J.-H. Dehydrosulfurative C−N Cross-Coupling and Concomitant Oxidative Dehydrogenation for One-Step Synthesis of 2-Aryl(alkyl)-aminopyrimidines from 3,4-Dihydropyrimidin-1*H*-2-thiones. *Org. Lett.* **2016**, *18*, 5154−5157.
(18) Since Kappe's seminal work, thioamides, thiourethanes, and thioureas bearing latent free-thiol have been utilized as promising electrophilic partners in Pd-catalyzed/Cu-mediated dehydrosulfurative C−C cross-couplings, as a notable extension of the Liebeskind−Srogl reaction. (a) Lengar, A.; Kappe, C. O. Tunable Carbon−Carbon and Carbon−Sulfur Cross-Coupling of Boronic Acids with 3,4-Dihydropyrimidine-2-thiones. *Org. Lett.* **2004**, *6*, 771−774. (b) Prokopcova, H.; Kappe, C. O. Palladium(0)-Catalyzed, Copper(I)-Mediated Coupling of Boronic Acids with Cyclic Thioamides. Selective Carbon−Carbon Bond Formation for the Functionalization of Heterocycles. *J. Org. Chem.* **2007**, *72*, 4440−4448. (c) Arshad, N.; Hashim, J.; Kappe, C. O. Palladium(0)-Catalyzed, Copper(I)-Mediated Coupling of Cyclic Thioamides with Alkenylboronic Acids, Organostannanes, and Siloxanes. *J. Org. Chem.* **2009**, *74*, 5118−5121.
(19) For the dehydrosulfurative C−C cross-couplings of five- or six-membered heterocycles possessing thioamide, thiourea, or thiourethane fragments with boronic acids, stannanes, siloxanes, or terminal alkynes, see: (a) Silva, S.; Sylla, B.; Suzenet, F.; Tatibouët, A.; Rauter, A. P.; Rollin, P. Oxazolinethiones and Oxazolidinethiones for the First Copper-Catalyzed Desulfurative Cross-Coupling Reaction and First Sonogashira Applications. *Org. Lett.* **2008**, *10*, 853−856. (b) Silva, S.; Tardy, S.; Routier, S.; Suzenet, F.; Tatibouët, A.; Rauter, A. P.; Rollin, P. 1,3-Oxazoline- and 1,3-oxazolidine-2-thiones as substrates in direct modified Stille and Suzuki cross-coupling. *Tetrahedron Lett.* **2008**, *49*, 5583−5586. (c) Guinchard, X.; Roulland, E. Total Synthesis of the Antiproliferative Macrolide (+)-Neopeltolide. *Org. Lett.* **2009**, *11*, 4700−4703. (d) Sun, Q.; Suzenet, F.; Guillaumet, G. Desulfitative Cross-Coupling of Protecting Group-Free 2-Thiouracil Derivatives with Organostannanes. *J. Org. Chem.* **2010**, *75*, 3473−3476. (e) Sun, Q.; Suzenet, F.; Guillaumet, G. Optimized Liebeskind−Srogl coupling reaction between dihydropyrimidines and tributyltin compounds. *Tetrahedron Lett.* **2012**, *53*, 2694−2698. (f) Quan, Z.-J.; Hu, W. H.; Jia, X. D.; Zhang, Z.; Da, Y.-X.; Wang, X.-C. A Domino Desulfitative Coupling/Acylation/Hydration Process Cocatalyzed by Copper(I) and Palladium(II): Synthesis of Highly Substituted and Functionalized Pyrimidines. *Adv. Synth. Catal.* **2012**, *354*, 2939−2948. (g) Yan, Z. F.; Quan, Z.-J.; Da, Y.-X.; Zhang, Z.; Wang, X.-C. A domino desulfurative coupling−acylation−hydration−Michael addition process for the synthesis of polysubstituted tetrahydro-4*H*-pyrido[1,2-

https://doi.org/10.1021/acs.joc.1c00273
J. Org. Chem. 2021, 86, 5423−5430

a]pyrimidines. *Chem. Commun.* **2014**, *50*, 13555−13558. (h) Wu, Y.; Xing, Y.; Wang, J.; Sun, Q.; Kong, W.; Suzenet, F. Palladium-catalyzed desulfurative Sonogashira cross-coupling reaction of 3-cyano assisted thioamide-type quinolone derivatives with alkynes. *RSC Adv.* **2015**, *5*, 48558−48562. (i) Zou, W.; Huang, Z.; Jiang, K.; Wu, Y.; Xue, Y.; Suzenet, F.; Sun, Q.; Guillaumet, G. Chelation-assisted C-S activation/cascade heteroannulation of pyridine-2-thione derivatives in Pd-catalyzed cross-coupling reaction with alkynes. *Tetrahedron* **2017**, *73*, 5485−5492. For the dehydrosulfurative C−C cross-couplings of mercaptopyrimidines with terminal alkynes, see: (j) Maltsev, O. V.; Pöthig, A.; Hintermann, L. Synthesis of Soai Aldehydes for Asymmetric Autocatalysis by Desulfurative Cross-Coupling. *Org. Lett.* **2014**, *16*, 1282−1285.

(20) Kim, H.; Lee, J.; Shin, H.; Sohn, J.-H. Boric Ester and Thiourea as Coupling Partners in a Copper-Mediated Oxidative Dehydrosulfurative Carbon−Oxygen Cross-Coupling Reaction. *Org. Lett.* **2018**, *20*, 1961−1965.

(21) Thorat, P. B.; Waghmode, N. A.; Karade, N. N. Direct metal-free O-arylation of Biginelli 4-aryl-6-methylpyrimidine-2(1H)-one derivatives using diaryliodonium salts. *Tetrahedron Lett.* **2014**, *55*, 5718−5721.

(22) Further efforts to stoichiometrically optimize the $Pd(OAc)_2$, CuTC, and K_3PO_4 amounts did not improve the product yield.

(23) According to the proposition by the Kappe group, 2−3 equivalents of CuTC are needed to facilitate desulfuration via Cu coordination to S for facile ligand exchange in desulfurative C−C cross-coupling of thioamide fragments; see reference 18c.

(24) A possible component for the reduction of Pd(II) to Pd(0) in entries 1−5 and 9 could be (dihydro)pyrimidinylcopper species, which is supported by the production of the desired product **3aa** in the absence of a Pd source.

(25) Zhang, P.; Guo, Y.; Quan, Z. J. C-O and C-S coupling reaction of 1,2-di(pyrimidin-2-yl) disulfides with phenols/thiophenols promoted by copper(I) chloride. *Heteroat. Chem.* **2017**, *28*, e21397.

(26) Abe, T.; Tamai, R.; Ito, M.; Tamaru, M.; Yano, H.; Takahashi, S.; Muramatsu, N. Preparation of difluoroalkene derivatives as pest control agents containing the same, and intermediate therefor. WO Patent No. WO2003029211, 2003.

(27) (a) Yamamoto, K.; Chen, Y. G.; Buono, F. G. Oxidative Dehydrogenation of Dihydropyrimidinones and Dihydropyrimidines. *Org. Lett.* **2005**, *7*, 4673−4676. (b) Han, B.; Han, R. F.; Ren, Y. W.; Duan, X. Y.; Xu, Y. C.; Zhang, W. Efficient aerobic oxidative dehydrogenation of dihydropyrimidinones and dihydropyrimidines. *Tetrahedron* **2011**, *67*, 5615−5620.

(28) Karade, N. N.; Gampawar, S. V.; Tale, N. P.; Kedar, S. B. Mild and efficient oxidative aromatization of 4-substituted-1,4-dihydropyrimidines using (diacetoxyiodo)benzene. *J. Heterocycl. Chem.* **2010**, *47*, 740−744.

(29) Matloobi, M.; Kappe, C. O. Microwave-Assisted Solution- and Solid-Phase Synthesis of 2-Amino-4-arylpyrimidine Derivatives. *J. Comb. Chem.* **2007**, *9*, 275−284.

(30) The reaction of DHPM **1a** with several heteroaromatic alcohols, such as quinolin-7-ol, pyridin-3-ol, pyrimidin-4-ol, pyridin-2-ol, pyridin-4-ol, or benzo[*d*]thiazol-2-ol, under the optimal conditions did not give a noticeable amount of the desired product.

(31) Gallagher, W. P.; Maleczka, R. E., Jr. PMHS Mediated Couplings of Alkynes or Benzothiazoles with Various Electrophiles: Application to the Synthesis of (−)-Akolactone A. *J. Org. Chem.* **2003**, *68*, 6775−6779.

(32) Khatri, C. K.; Potadar, S. M.; Chaturbhuj, G. U. A reactant promoted solvent free synthesis of 3,4-dihydropyrimidin-2(1H)-thione analogues using ammonium thiocyanate. *Tetrahedron Lett.* **2017**, *58*, 1778−1780.

(33) Chitra, S.; Pandiarajan, K. Calcium fluoride: an efficient and reusable catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and their corresponding 2(1H)thione: an improved high yielding protocol for the Biginelli reaction. *Tetrahedron Lett.* **2009**, *50*, 2222−2224.

(34) Afradi, M.; Foroughifar, N.; Pasdar, H.; Moghanian, H. L-proline N-sulfonic acid-functionalized magnetic nanoparticles: a novel and magnetically reusable catalyst for one-pot synthesis of 3,4-dihydropyrimidine-2-(1H)-thiones under solvent-free conditions. *RSC Adv.* **2016**, *6*, 59343−5935.

(35) Sari, O.; Roy, V.; Metifiot, M.; Marchand, C.; Pommier, Y.; Bourg, S.; Bonnet, P.; Schinazi, R. F.; Agrofoglio, L. A. Synthesis of dihydropyrimidine α,γ-diketobutanoic acid derivatives targeting HIV integrase. *Eur. J. Med. Chem.* **2015**, *104*, 127−138.

(36) Hayashi, M.; Okunaga, K. − I.; Nishida, S.; Kawamura, K.; Eda, K. Oxidative transformation of thiols to disulfides promoted by activated carbon-air system. *Tetrahedron Lett.* **2010**, *51*, 6734−6736.

(37) Lokwani, D.; Azad, R.; Sarkate, A.; Reddanna, P.; Shinde, D. Structure Based Library Design (SBLD) for new 1,4-dihydropyrimidine scaffold as simultaneous COX-1/COX-2 and 5-LOX inhibitors. *Bioorg. Med. Chem.* **2015**, *23*, 4533−4543.

(38) Nemr, M. T. M.; AboulMagd, A. M. New fused pyrimidine derivatives with anticancer activity: Synthesis, topoisomerase II inhibition, apoptotic inducing activity and molecular modeling study. *Bioorg. Chem.* **2020**, *103*, 104134.

(39) Fu, N. − Y.; Yuan, Y. − F.; Cao, Z.; Wang, S. − W.; Wang, Ji. − T.; Peppe, C. Indium(III) bromide-catalyzed preparation of dihydropyrimidinones: improved protocol conditions for the Biginelli reaction. *Tetrahedron* **2002**, *58*, 4801−4807.

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