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Transition Metal-Free Decyanative Cross-Coupling of Cyanopyrimidines with *O*-, *S*-, and *N*-Nucleophiles: A Route to Alkoxylpyrimidines, Aminopyrimidines and Alkylthiopyrimidines

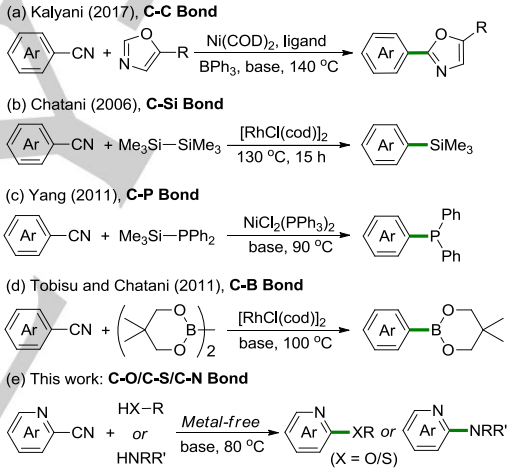
Xiangyang Wei,[a] Caiyang Zhang,[a] Yifei Wang,[a] Qi Zhan,[a] Guiying Qiu,[a] Ling Fan,[a] and Guodong Yin*[a]

Dedication ((optional))

Abstract: The transition metal-free cross-coupling reactions of cyanopyrimidines with aliphatic alcohols, thiols (or *S*-alkylisothiourea salts) and amines, giving the corresponding alkoxylpyrimidines, aminopyrimidines and alkylthiopyrimidines, are reported. Preliminary mechanistic studies reveal that it probably involves a sequential nucleophilic addition-intramolecular rearrangement process, which is promoted by an intramolecular N–H···N five-membered hydrogen bonding interaction. The presence of a nitrogen atom next to the cyano group is indispensable. The wide substrate scope with excellent yields makes cyanopyrimidines a promising alternative substrate class to the frequently used pyrimidines halides for the formation of C–O, C–S and C–N bonds *via* the decyanative cross-coupling reaction.

Introduction

Cross-coupling reactions for C–C bond and C–heteroatom bond formation have been established as an attractive research area in organic synthesis. Substrates such as aryl halides are the most commonly chosen coupling partners because of the low dissociation energy of the C–halogen bonds.[1,2] Aryl nitriles are a useful class of intermediates in organic synthesis, although the conversion of their cyano group into other valuable functional groups such as amides, amines, amidines, aldehydes, carboxylic acids and heterocycles has also been extensively explored.[3] However, because of the high dissociation energy of Ar–CN bonds (~132.7 kcal·mol^{-1}) in comparison with Ar–X (X=Cl, Br, I) bonds (<100 kcal·mol^{-1}), aryl nitriles have rarely been regarded as a suitable substrate to participate in cross-coupling reactions.[4–6] If the cyano group could be employed as the leaving group, Ar–CN would become an alternative substrate to Ar–X for the cross-coupling reaction.[7,8] Since Miller first reported the synthesis of unsymmetrical biaryls *via* the cross-coupling of aryl nitriles with Grignard reagents using a phosphine-based Ni catalyst,[9] continued attention has been paid to decyanative cross-coupling reactions.[10–16] Recently, Kalyani described a Ni-catalyzed cross-coupling of aryl nitriles with azoles by using the corresponding ligand and BPh_3 at 140 °C (Scheme 1a).[17,18] Chatani demonstrated a Rh(I)-catalyzed silylation reaction of aryl cyanides with hexamethyldisilane involving the cleavage of Ar–CN and Si–Si bonds (Scheme 1b).[19–21] Yang established a phosphination of aryl cyanides with Me_3SiPPh_2 *via* Ni-catalyzed Ar–CN bond cleavage for the synthesis of various diphenylphosphoryl compounds (Scheme 1c).[22–24] Tobisu and Chatani also disclosed the borylation of aryl cyanides with diboron in the presence of a Rh(I)/Xantphos catalyst and DABCO to afford a variety of arylboronic esters (Scheme 1d).[25–27]



Scheme 1. General types of Decyanative Cross-coupling Reactions.

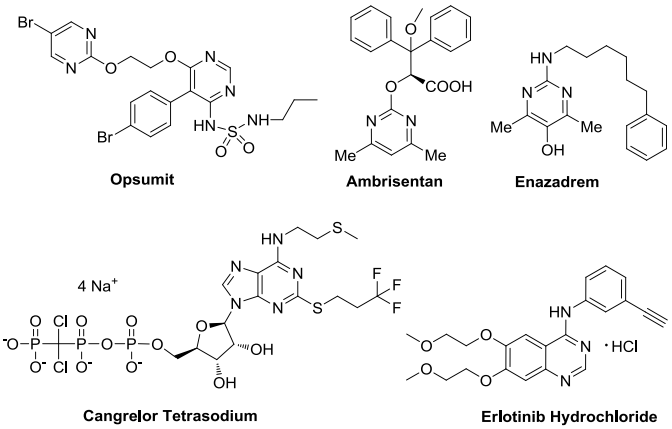


Figure. 1 Commercial Drugs Containing Alkoxylpyrimidine, Alkylthiopyrimidine and Aminopyrimidine Fragments.

Alkoxylpyrimidine is a particularly important structural motif that occurs in many natural products and pharmaceutically active molecules (Figure 1),[28,29] and is usually prepared from a pyrimidine halide and an aliphatic alcohol. To the best of our

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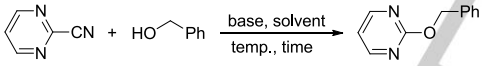
knowledge, few examples for the formation of a C–O bond by the cross-coupling reaction of a (hetero)aryl cyanide with an aliphatic alcohol have been reported.[30] Herein, we communicate a *O*-alkylation of cyanopyrimidines *via* the cleavage of an Ar–CN bond, delivering alkoxylpyrimidines without the need of a transition metal catalyst. Similarly, some alkylthiopyrimidines and aminopyrimidines are also obtained by this decyanative cross-coupling reaction (Scheme 1e).

Results and discussion

At the beginning of our study, the reaction of 2-cyanopyrimidine (**1a**) and phenylmethanol (**2a**) was carried out in DMSO at 80 °C in the presence of K_2CO_3, and 2-(benzyloxy)pyrimidine (**3a**) was obtained in 80% yield (Table 1, entry 1). Na_2CO_3, $NaHCO_3$ and Et_3N were less effective for the reaction (entries 2–4). Only a trace amount of product was observed in the absence of base (entry 5). Satisfyingly, when Cs_2CO_3 was used as the base, the yield of **3a** reached 96% (entry 6). Reducing the amount of base or **2a** led to a slightly lower yield (entries 7–10). The reaction was heavily affected by the temperature and **3a** was obtained in 65% yield at room temperature after 24 h (entries 11, 12). Several commonly used solvents (DMF, MeCN, 1,4-dioxane, THF) and a mixture of DMSO/H_2O (1:1) were screened, and DMF proved roughly as efficient as DMSO (entries 13–17).

Table 1 Screening and Optimization of Conditions for the Synthesis of **3a**[a]

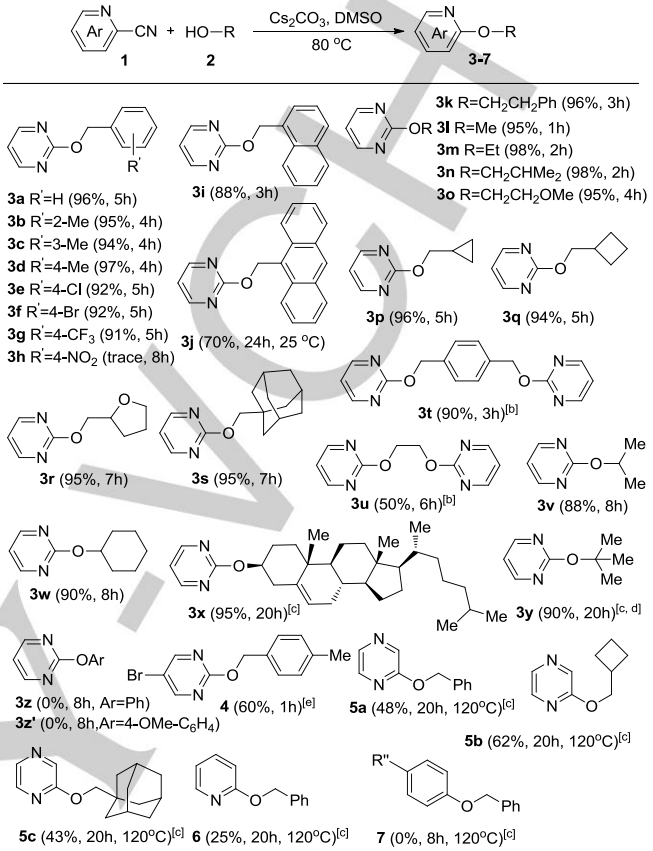


1a **2a** **3a**

Entry	Base	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	K_2CO_3	DMSO	80	7	80
2	Na_2CO_3	DMSO	80	7	45
3	$NaHCO_3$	DMSO	80	7	32
4	Et_3N	DMSO	80	7	<5
5	None	DMSO	80	7	<5
6	Cs_2CO_3	DMSO	80	5	96
7	Cs_2CO_3	DMSO	80	7	85[c]
8	Cs_2CO_3	DMSO	80	7	67[d]
9	Cs_2CO_3	DMSO	80	7	90[e]
10	Cs_2CO_3	DMSO	80	7	82[f]
11	Cs_2CO_3	DMSO	60	7	92
12	Cs_2CO_3	DMSO	25	24	65
13	Cs_2CO_3	DMF	80	7	90
14	Cs_2CO_3	MeCN	80	7	72
15	Cs_2CO_3	1,4-dioxane	80	7	28
16	Cs_2CO_3	THF	80	7	27
17	Cs_2CO_3	DMSO:H_2O (1:1)	80	7	75

[a] Unless otherwise specified, the reactions were carried out using **1a** (0.2 mmol), **2a** (0.3 mmol) in 2 mL solvent; [b] Isolated yield. [c] 0.1 mmol base was employed. [d] 0.04 mmol base was employed. [e] **2a** (0.24 mmol) was employed. [f] **2a** (0.2 mmol) was employed.

Table 2 The Decyanative Cross-coupling of Cyanopyrimidines with Aliphatic Alcohols[a]

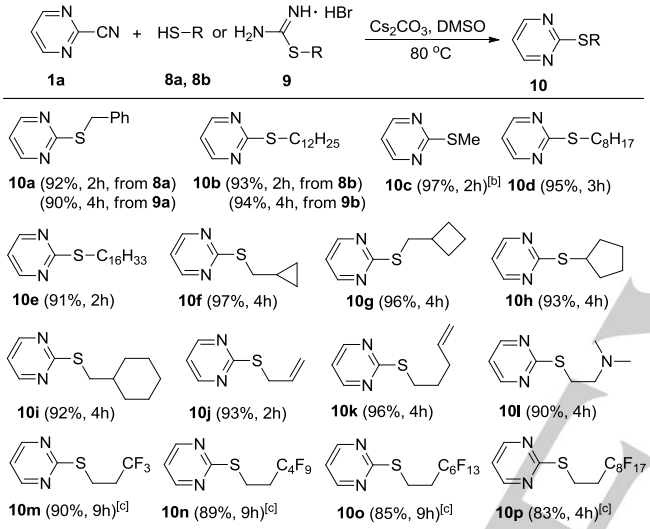


[a] Unless otherwise specified, all of the reactions were carried out using **1** (1.0 mmol), **2** (1.5 mmol) and Cs_2CO_3 (1.0 mmol) in DMSO (3 mL) at 80 °C; Isolated yields. [b] The molar ratio of **1a** (1.5 mmol) and alcohols (**2t**, **2u**) was 3:1. [c] *t*-BuOK and anhydrous DMF were employed as the base and solvent. [d] *t*-BuOK (4.0 mmol) was employed as the starting material. [e] The molar ratio of **1b** and alcohol was 1:1.

With the optimized reaction conditions in hand (Table 1, entry 6), the scope of aliphatic alcohols was examined, as shown in Table 2. It was found that 2-, 3-, and 4-methyl-substituted benzyl alcohols gave the corresponding products **3b–3d** in 94–97% yields. Substrates bearing an electron-withdrawing group (-Cl, -Br and -CF_3) on the phenyl ring afforded **3e–3g** in 91–92% yields. However, only a trace amount of 3h was observed when using (4-nitrophenyl)methanol as the substrate after several attempts, probably because the presence of strong electron-withdrawing NO_2 group could weaken its nucleophilicity of alcohol. The reactions of **1a** with other primary alcohols proceeded smoothly to give the target products **3i–3s** in 70–94% yields. 1,4-Phenylenedimethanol and ethylene glycol were also suitable for the reaction, giving the symmetrical products **3t** and **3u**. Several representative secondary alcohols including *i*-propyl alcohol, cyclohexanol and cholesterol were also effective for this transformation, although a stronger base, *t*-BuOK, was required. No reaction occurred between **1a** and *t*-butyl alcohol under the above-mentioned standard conditions,

while **3y** was obtained in 90% yield using *t*-BuOK as the starting material. The reaction was ineffective for phenol and 4-methoxyphenol, probably because of its weaker *O*-nucleophilicity compared with aliphatic alcohols. 5-Bromopyrimidine-2-carbonitrile only gave the corresponding decyanated **4** as the main product, and prolonging the reaction time was not conducive to the desired reaction. **5a–5c** and **6** were also obtained starting from pyrazine-2-carbonitrile and 2-cyanopyridine using *t*-BuOK as the base in anhydrous DMF at 120 °C for 20 h. However, the non-nitrogenous substrates benzonitrile and 4-nitrobenzonitrile were ineffective for this transformation, which indicates that the N atom on the aryl ring is crucial.

Table 3 The Decyanative Cross-coupling of Cyanopyrimidines with Thiols and *S*-Alkylisothiourea salts[a]

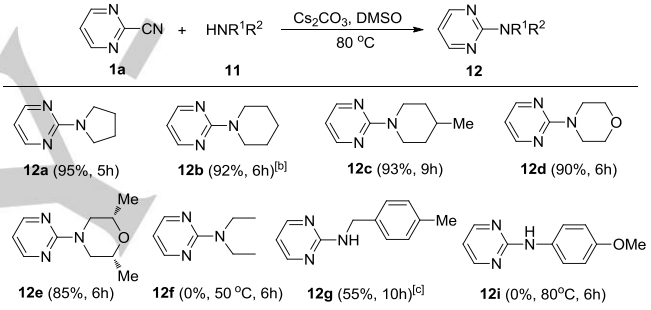


[a] Unless otherwise specified, all of the reactions were carried out using **1** (1.0 mmol), thiols (**8**, 1.5 mmol)/*S*-alkylisothiourea hydrogen bromide **9** (1.5 mmol) and Cs_2CO_3 (2.0 mmol) in DMSO (3 mL) at 80 °C; Isolated yields. [b] *S*-methylisothiourea sulfate (**9c**) was the starting material. [c] *S*-alkylisothiourea hydrogen iodides (**9m–9p**) were the starting materials, at 100 °C.

Encouraged by the results above, the decyanative cross-coupling of cyanopyrimidines with thiols for the formation of C–S bonds was examined, as shown in Table 3. It was found that the reactions of **1a** with phenylmethanethiol (**8a**) and dodecane-1-thiol (**8b**) afforded the expected products **10a** and **10b** in 92% and 93% yields, respectively. Recently, we have developed an efficient synthesis of aryl alkyl sulfides by the reactions of aryl halides with *S*-alkylisothiourea salts.[31] These odorless solids can be simply prepared from alkyl halides and thiourea, and can be used as substitutes for malodorous thiols. In the present study, products **10a–10l** were also obtained in excellent yields from **1a** and their corresponding *S*-alkylisothiourea salts. Particular attention has been paid to the introduction of polyfluorinated alkylthio groups into molecules,[32] because polyfluorinated compounds are a major class of commercial drugs, such as cangrelor tertrasodium[33] (Figure 1). Here, we found **1a** could also successfully react with several representative polyfluorinated *S*-alkylisothiourea hydrogen iodides, delivering the corresponding products **10m**–**10p** in 83–90% yields. However, trace amount of expected product was only detected by mass spectra using 4-methoxybenzenethiol and methylpropane-2-thiol as the substrates.

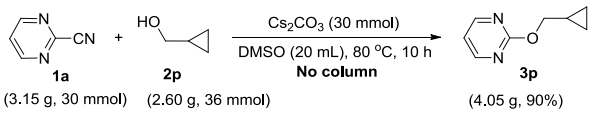
Only one class of examples of the synthesis of aminopyridines by the direct nucleophilic aromatic substitution of cyanopyridines with lithium amides has been reported.[34] To our delight, we found that the reactions of **1a** with five- and six-membered cyclic secondary amines gave the corresponding products **12a**–**12e** in 85**–**95% yields. No reaction was observed using diethylamide as the starting material probably owing to the steric hindrance. *N*-(4-methylbenzyl)pyrimidin-2-amine (**12g**) was also obtained from *p*-tolylmethanamine in 55% yield. No reaction occurred between **1a** and 4-methoxyaniline (Table 4).

Table 4 The Decyanative Cross-coupling of Cyanopyrimidines with Amines[a]

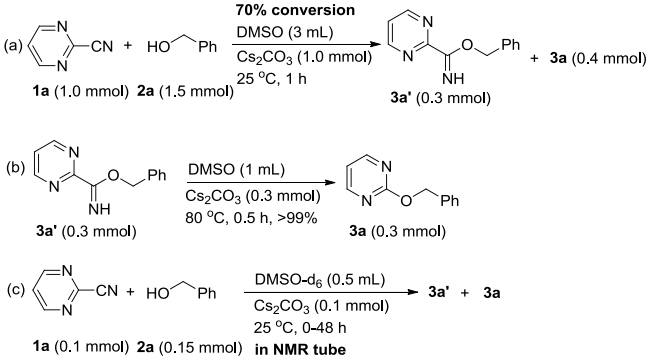


[a] Unless otherwise specified, all of the reactions were carried out using **1a** (1.0 mmol), **11** (2.0 mmol) and Cs_2CO_3 (2.0 mmol) in DMSO (3 mL) at 80 °C; Isolated yields. [b] 25% yield of **12b** was obtained in the absence of Cs_2CO_3. [c]1.0 mmol *p*-tolylmethanamine was employed.

To further investigate the synthetic utility of this transformation, the gram-scale reaction between **1a** and cyclopropylmethanol (**2p**) was explored. The expected product **3p** was easily isolated in 90% yield (Scheme 2).



Scheme 2 Gram-scale Experiment for the Synthesis of **3p**.



Scheme 3 Control Experiments.

A controlled experiment was conducted to survey the reaction mechanism (Scheme 3). When a mixture of **1a** and **2a** was reacted at 25 °C for 1 h, the conversion of **1a** was 70%, affording benzyl pyrimidine-2-carbimidate (**3a'**) and the target product **3a** in 30% and 40% yields, respectively (Scheme 3a). Next, the newly separated product **3a'** could be almost quantitatively converted into **3a** at 80 °C within 0.5 h (Scheme 3b). Then, the reaction was carried out in an NMR tube at 25 °C for 48 h using DMSO-d_6 as the solvent (Scheme 3c). The main product after 48 h was **3a**, which was generated from **3a'** during the reaction (Figure. 2).

On the basis of these experimental results, a possible reaction mechanism was proposed using the synthesis of **3a** as an example, as shown in Scheme 4. In the presence of base, **2a** is converted into alkoxy anion intermediate **I**, which is easily reacted with **1a** through nucleophilic addition to give intermediate **II**.[35] The latter then gives the intermediate benzyl pyrimidine-2-carbimidate (**3a'**) by capturing H^+. We propose that there exists an intramolecular N–H···N five-membered hydrogen bond, which undergoes a rearrangement.[36] The oxygen atom attacks the carbon atom of the pyrimidine ring, and the hydrogen atom on the imine migrates to the pyrimidine nitrogen atom to afford intermediate **III**. This process is accompanied by a C–C bond cleavage and a new C–O bond formation. Finally, intermediate **IV** is obtained from **III**, affording the product **3a** after releasing a cyanide anion.

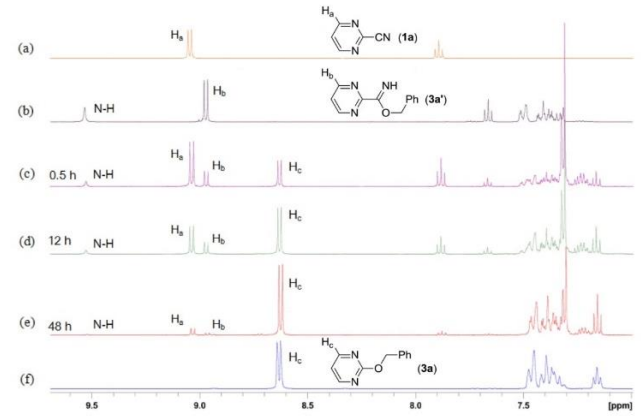
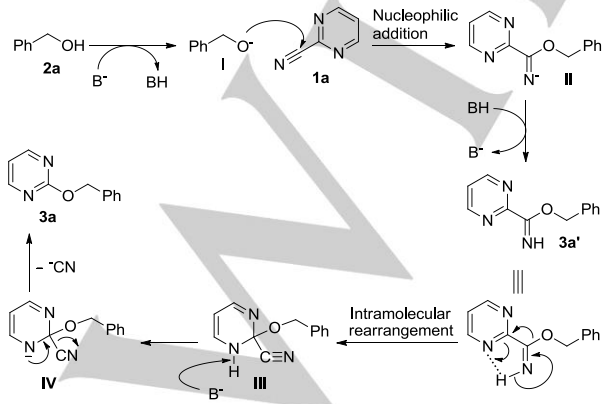


Figure 2 ^{1}H NMR Spectra for Monitoring the Intermediate.



Scheme 4 Possible Reaction Mechanism.

Conclusions

We have developed an efficient route to alkoxylpyrimidines, alkylthiopyrimidines and aminopyrimidines by the decyanative cross-coupling reactions of cyanopyrimidines with the corresponding alcohols, thiols (or *S*-alkylisothiourea salts) and amines under transition metal-free conditions. Gram-scale synthesis is feasible and the products do not require chromatographic purification. Preliminary mechanistic studies revealed that the reaction probably involves a sequential nucleophilic addition–intramolecular rearrangement process, which is promoted by an intramolecular N–H···N five-membered hydrogen bonding interaction. The presence of a nitrogen atom next to the cyano group is indispensable. The wide substrate scope with excellent yields makes cyanopyrimidines a promising alternative substrate class to the frequently used pyrimidines halides for the formation of C–O, C–S and C–N bonds *via* the decyanative cross-coupling reaction.

Experimental

General Methods. All the chemicals were commercially available and used without further purification. All solvents were dried and distilled according to standard procedures. ^{1}H and ^{13}C NMR experiments were performed on Bruker Avance II 300 MHz spectrometer at 300 and 75 MHz in $CDCl_3$ or DMSO-d_6. ^{19}F NMR experiments were performed on a Bruker Avance II 400 MHz spectrometer at 376 MHz in $CDCl_3$. Chemical shifts are reported relative to internal standard tetramethylsilane (TMS). Mass spectra were measured on LCQ Advantage MAX (ESI) or Solanx 70 FT-MS (HRMS). Infrared spectra (IR) were obtained as KBr pellet samples using a Nicolet 5700 FTIR. Flash column chromatography was performed on silica gel (200–300 mesh). Melting points were determined using an uncorrected X-4 apparatus.

General synthetic procedure for alkoxylpyrimidines 3–6 (Table 2). A mixture of cyanopyrimidines (**1**, 1.0 mmol), alcohols (**2**, 1.5 mmol) and cesium carbonate (326 mg, 1.0 mmol) in DMSO (3 mL) was heated at 80 °C for 1–24 h. After completion of the reaction, the mixture was poured into the water and extracted with dichloromethane (3×15 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtered. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel using the mixture of petroleum ether and ethyl acetate (v:v, 30:1 to 8:1) as the eluent to afford the target products **3–6**.

Gram-scale reaction for the synthesis of 3p (Scheme 2). A mixture of 2-cyanopyrimidine (**1a**, 3.15 g, 30 mmol), cyclopropylmethanol (**2p**, 2.60 g, 36 mmol), cesium carbonate (**9**, 75 g, 30 mmol) and DMSO (20 mL) was heated at 80 °C for 10 h. After completion of the reaction, the mixture was poured into the water and extracted with dichloromethane (3×40 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtered. After removal of the solvent, the residue was drying in vacuum oven to give **3p** as colorless oil (4.05 g, 90% yield), which was pure enough for structural analysis.

2-(Benzyloxy)pyrimidine (**3a**)[37]
Yield 96% (179 mg); yellow oil; IR (KBr) ν 3439, 3038, 3034, 2948, 1578, 1564, 1421, 1366, 1323, 1007, 809. 737, 698, 534 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.51 (d, *J* = 4.8 Hz, 2H), 7.49 (d, *J* = 7.1 Hz, 2H), 7.39−7.28 (m, 3H), 6.93 (t, *J* = 4.8 Hz, 1H), 5.45 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.9, 159.2, 136.4, 128.3, 127.9, 127.8, 115.0, 68.9. ESI-MS: *m/z* 187.03 $[M+H]^+$.

2-((2-Methylbenzyl)oxy)pyrimidine (**3b**)
Yield 95% (190 mg); yellow oil; IR (KBr) ν 3445, 3037, 2744, 2283, 1962, 1578, 1422, 1364, 1002, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.51 (d, *J* = 4.8 Hz, 2H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.25−7.16 (m, 3H), 6.92 (t, *J* = 4.8Hz, 1H), 5.44 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.0, 159.2, 136.7, 134.3, 130.1, 128.8, 128.1, 125.7, 115.0, 67.3, 18.9; HRMS (ESI): *m/z* calcd for $C_{12}H_{13}N_2O$: 201.1023, found: 201.1038 $[M+H]^+$.

2-((3-Methylbenzyl)oxy)pyrimidine (**3c**)
Yield 94% (188 mg); yellow solid; mp 91−93 °C; IR (KBr) ν 3434, 3093, 2922, 2189, 1565, 1232, 1103, 981, 798, 657 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.53 (d, *J* = 4.8 Hz, 2H), 7.32 (s, 1H), 7.29−7.23 (m, 2H), 7.13 (d, *J* = 6.3 Hz, 1H), 6.95 (t, *J* = 4.8 Hz, 1H), 5.42 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.1, 159.3, 138.1, 136.3, 128.6, 128.5, 128.3, 124.9, 115.1, 69.0, 21.4; HRMS (ESI): *m/z* calcd for $C_{12}H_{13}N_2O$: 201.1023, found: 201.1038 $[M+H]^+$.

2-((4-Methylbenzyl)oxy)pyrimidine (**3d**)
Yield 97% (194 mg); yellow solid; mp 41−43 °C; IR (KBr) ν 3442, 3046, 2923, 1903, 1578, 1427, 1327, 1005, 806, 537 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.50 (d, *J* = 4.8 Hz, 2H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 6.90 (t, *J* = 4.8 Hz 1H), 5.40 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.9, 159.1, 137.5, 133.3, 128.9, 127.9, 114.9, 68.8, 21.0; HRMS (ESI): *m/z* calcd for $C_{12}H_{13}N_2O$: 201.1023, found: 201.1038 $[M+H]^+$.

2-((4-Chlorobenzyl)oxy)pyrimidine (**3e**)
Yield 92% (199 mg); yellow solid; mp 76−79 °C; IR (KBr) ν 3405, 3048, 2925, 1911, 1602, 1580, 1440, 1008, 807, 531 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.53 (d, *J* = 4.8 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 6.96 (t, *J* = 4.8 Hz, 1H), 5.41 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.8, 159.3, 135.0, 133.7, 129.3, 128.6, 115.3, 68.1; HRMS (ESI): *m/z* calcd for $C_{11}H_{10}ClN_2O$: 221.0482, found: 221.0493 $[M+H]^+$.

2-((4-Bromobenzyl)oxy)pyrimidine (**3f**)
Yield 92% (244 mg); yellow solid; mp 71−73 °C; IR (KBr) ν 3383, 3041, 2940, 1905, 1576, 1428, 1323, 1024, 808, 528 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.53 (d, *J* = 4.8 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 6.96 (t, *J* = 4.8 Hz, 1H), 5.40 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.8, 159.3, 135.5, 131.5, 129.6, 121.9, 115.3, 68.1; HRMS (ESI): *m/z* calcd for $C_{11}H_{10}BrN_2O$: 264.9977, found: 264.9985 $[M+H]^+$.

2-((4-(Trifluoromethyl)benzyl)oxy)pyrimidine (**3g**)
Yield 91% (231 mg); yellow solid; mp 126−128 °C; IR (KBr) ν 3426, 2076, 1630, 1567, 1447, 1420, 1071, 824, 526, 446 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.54 (d, *J* = 4.8 Hz, 2H), 7.64−7.58 (m, 4H), 6.98 (t, *J* = 4.8 Hz 1H), 5.51 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.8, 159.4, 140.6, 130.0 (q, *J* = 32.2 Hz), 127.7, 125.4 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 270.4 Hz) 115.4, 68.0; HRMS (ESI): *m/z* calcd for $C_{12}H_{10}F_3N_2O$: 255.0740, found: 255.0751 $[M+H]^+$.

2-(Naphthalen-1-ylmethoxy)pyrimidine (**3i**)[37]
Yield 88% (208 mg); yellow oil; IR (KBr) ν 3426, 3046, 2922, 1956, 1577, 1564, 1422, 1317, 1001, 799, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.51 (d, *J* = 4.8 Hz, 2H), 8.13 (d, *J* = 8.0 Hz, 1H), 7.87−7.80 (m, 2H), 7.68 (d, *J* = 6.9 Hz, 1H), 7.56−7.41 (m, 3H), 6.90 (t, *J* = 4.8 Hz, 1H), 5.90 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.9, 159.1, 133.5, 131.7, 131.4, 128.7, 128.5, 126.6, 126.3, 125.7, 125.1, 123.6, 115.0, 67.1; ESI-MS: *m/z* 237.16 $[M+H]^+$.

2-(Anthracen-9-ylmethoxy)pyrimidine (**3j**)
Yield 70% (200 mg); white solid, mp 67−68 °C. IR (KBr) ν 3426, 2924, 2853, 1653, 1421, 1310, 979, 887, 731, 600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.58 (d, *J* = 7.7 Hz, 2H), 8.51 (s, 1H), 8.46 (d, *J* = 8.5 Hz, 2H), 8.02 (d, *J* = 7.9 Hz, 2H), 7.57−7.45 (m, 4H), 6.97 (t, *J* = 4.8 Hz 1H), 6.45 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.3, 159.4, 131.4, 131.3, 129.03, 128.96, 126.7, 126.4, 125.0, 124.4, 115.1, 61.8; HRMS (ESI): *m/z* calcd for $C_{19}H_{15}N_2O$: 287.1179, found: 287.1187 $[M+H]^+$

2-Phenethoxypyrimidine (**3k**)
Yield 96% (192 mg); yellow oil; IR (KBr) ν 3427, 2924, 2853, 1653, 1576, 1421, 1310, 979, 731, 505 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.28 (d, *J* = 4.6Hz, 2H), 7.18−7.02 (m, 5H), 6.66 (t, *J* = 4.7 Hz, 1H), 4.41 (t, *J* = 7.1 Hz, 2H), 2.96 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.6, 158.7, 137.6, 128.6, 128.0, 126.0, 114.4, 67.6, 34.8; HRMS (ESI): *m/z* calcd for $C_{12}H_{13}N_2O$: 201.1028, found: 201.1041 $[M+H]^+$.

2-Methoxypyrimidine (**3l**)[38]
Yield 95% (105 mg); colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.52 (d, *J* = 4.7 Hz, 2H), 6.94 (t, *J* = 4.7 Hz, 1H), 4.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.6, 159.2, 114.8, 54.7; ESI-MS: *m/z* 111.11 $[M+H]^+$.

2-Ethoxypyrimidine (**3m**)[39]
Yield 98% (122 mg); colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.51 (d, *J* = 4.8 Hz, 2H), 6.92 (t, *J* = 4.8 Hz, 1H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.44 (t, *J* = 7.1Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.2, 159.2, 114.7, 63.3, 14.4; ESI-MS: *m/z* 125.15 $[M+H]^+$.

2-Isobutoxypyrimidine (**3n**)
Yield 98% (149 mg); yellow oil; IR (KBr) ν 3422, 2924, 2853, 1654, 1632, 1581, 1428, 1401, 1082, 1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.51 (d, *J* = 4.7 Hz, 2H), 6.93 (t, *J* = 4.8 Hz, 1H), 4.13 (d, *J* = 6.7 Hz, 2H), 2.15 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.2, 159.0, 114.6, 73.7, 27.7, 19.1; HRMS (ESI): *m/z* calcd for $C_8H_{13}N_2O$: 153.1022, found: 153.1043 $[M+H]^+$.

2-(2-Methoxyethoxy)pyrimidine (**3o**)
Yield 95% (147 mg); yellow oil; IR (KBr) ν 3462, 3046, 2930, 2893, 2817, 1578, 1459, 1424, 1321, 1289 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.52 (d, *J* = 4.7 Hz, 2H), 6.94 (t, *J* = 4.7 Hz, 1H), 4.53 (t, *J* = 5.0 Hz, 2H), 3.78 (t, *J* = 5.1 Hz, 2H), 3.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.0, 159.2, 115.0, 70.5, 66.5, 59.0; HRMS (ESI): *m/z* calcd for $C_7H_{11}N_2O_2$: 155.0815, found: 155.0835 $[M+H]^+$.

2-(Cyclopropylmethoxy)pyrimidine (**3p**)
Yield 96% (114 mg); colorless oil; IR (KBr) ν 3439, 3083, 3006, 2949, 1580, 1563, 1457, 1430, 1392, 1351 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.51 (d, *J* = 4.8 Hz, 2H), 6.93 (t, *J* = 4.8 Hz, 1H), 4.20 (d, *J* = 7.2 Hz, 2H), 1.39−1.29 (m, 1H), 0.65−0.59 (m, 2H), 0.40−0.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.1, 159.0, 114.6, 72.1, 9.7, 3.1; HRMS (ESI): *m/z* calcd for $C_8H_{11}N_2O$: 151.0866, found: 151.0885 $[M+H]^+$.

2-(Cyclobutylmethoxy)pyrimidine (**3q**)
Yield 94% (154 mg); yellow oil; IR (KBr) ν 3446, 2942, 2862, 1578, 1426, 1377, 1314, 1015, 808, 639 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.51 (d, *J* = 4.8 Hz, 2H), 6.92 (t, *J* = 4.8 Hz, 1H), 4.33 (d, *J* = 6.8 Hz, 2H),

2.87−2.78 (m, 1H), 2.17−2.06 (m, 2H), 2.01−1.86 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.3, 159.1, 114.7, 71.4, 34.1, 24.7, 18.4; HRMS (ESI): *m/z* calcd for $C_9H_{13}N_2O$: 165.1028, found: 165.1041 $[M+H]^+$.

2-((Tetrahydrofuran-2-yl)methoxy)pyrimidine (**3r**)

Yield 95% (171 mg); yellow oil; IR (KBr) ν 3443, 3046, 2954, 2873, 1778, 1579, 1424, 1389, 1319, 1186, 1031 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.52 (d, *J* = 4.8 Hz, 2H), 6.95 (t, *J* = 4.8 Hz, 1H), 4.43−4.29 (m, 3H), 3.97−3.90 (m, 1H), 3.86−3.79 (m, 1H), 2.14−1.78 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.0, 159.1, 114.9, 76.4, 69.2, 68.3, 28.0, 25.6; HRMS (ESI): *m/z* calcd for $C_9H_{13}N_2O_2$: 181.0972, found: 181.0988 $[M+H]^+$.

2-((3r,5r,7r)-Adamantan-1-ylmethoxy)pyrimidine (**3s**)

Yield 95% (232 mg); white solid, mp 60−62 °C; IR (KBr) ν 3442, 2899, 2873, 2873, 2846, 2671, 1582, 1443, 1427, 1329, 1029 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.51 (d, *J* = 4.7 Hz, 2H), 6.91 (t, *J* = 4.7 Hz, 1H), 3.94 (s, 2H), 2.01 (s, 3H), 1.77−1.70 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.6, 159.1, 114.6, 77.4, 39.3, 37.0, 33.4, 28.1; HRMS (ESI): *m/z* calcd for $C_{15}H_{21}N_2O$: 245.1648, found: 245.1662 $[M+H]^+$.

1,4-Bis((pyrimidin-2-yloxy)methyl)benzene (**3t**)

Yield 90% (132 mg); yellow solid; mp 187−189 °C; IR (KBr) ν 3419, 3078, 2924, 1583, 1424, 1505, 1051, 1029, 841, 797 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.52 (d, *J* = 4.8 Hz, 4H), 7.49 (s, 4H), 6.94 (t, *J* = 4.8 Hz, 2H), 5.45 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 165.0, 159.3, 136.2, 127.9, 115.1, 68.6; HRMS (ESI): *m/z* calcd for $C_{16}H_{15}N_4O_2$: 295.1195, found: 295.1196 $[M+H]^+$.

1,2-Bis(pyrimidin-2-yloxy)ethane (**3u**)

Yield 50% (55 mg); white solid, mp 93−95 °C; IR (KBr) ν 3446, 3138, 3090, 2976, 2963, 1981, 1565, 1444, 1307, 1048 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.52 (d, *J* = 4.8 Hz, 4H), 6.96 (t, *J* = 4.8 Hz, 2H), 4.77 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.8, 159.1, 115.1, 65.2; HRMS (ESI): *m/z* calcd for $C_{10}H_{11}N_4O_2$: 219.0877, found: 219.0893 $[M+H]^+$.

2-Isopropoxypyrimidine (**3v**)[40]

Yield 88% (122 mg); yellow oil; IR (KBr) ν 3440, 3156, 2936, 2858, 1580, 1561, 1424, 1327, 1020, 992, 971, 808, 641 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.50 (d, *J* = 4.7 Hz, 2H), 6.89 (t, *J* = 4.8 Hz, 1H), 5.34−5.22 (m, 1H), 1.40 (d, *J* = 6.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.8, 159.1, 114.4, 70.1, 21.8. ESI-MS: *m/z* 138.84 $[M+H]^+$.

2-(Cyclohexyloxy)pyrimidine (**3w**)

Yield 90% (160 mg); yellow oil; IR (KBr) ν 3446, 3040, 2936, 2857, 1579, 1423, 1367, 1313, 1041, 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.49 (d, *J* = 4.7 Hz, 2H), 6.88 (t, *J* = 4.8 Hz, 1H), 5.06−4.97 (m, 1H), 2.11−2.01 (m, 2H), 1.86−1.80 (m, 2H), 1.67−1.55 (m, 3H), 1.49−1.25 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.8, 159.1, 114.4, 75.1, 31.5, 25.4, 23.7; HRMS (ESI): *m/z* calcd for $C_{10}H_{15}N_2O$: 179.1179, found: 179.1199 $[M+H]^+$.

2-(Cholesterol)pyrimidine (**3x**)

Yield 95% (442 mg); yellow oil; IR (KBr) ν 3415, 2930, 2851, 1631, 1562, 1437, 1419, 1382, 1124, 1029 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.48 (d, *J* = 4.8 Hz, 2H), 6.87 (t, *J* = 4.7 Hz, 1H), 5.41 (d, *J* = 5.1 Hz, 1H), 4.94−4.83 (m, 1H), 2.56−2.50 (m, 2H), 2.08−1.94 (m, 4H), 1.90−1.78 (m, 4H), 1.60−1.45 (m, 6H), 1.33−1.26 (m, 4H), 1.12−1.01 (m, 7H), 0.93−0.86 (m, 12H), 0.69−0.68 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.9, 159.2, 140.1, 122.4, 114.5, 56.8, 56.2, 50.2, 42.4, 39.8, 39.5, 38.2, 37.1, 36.8, 36.2, 35.8, 31.9, 29.7, 28.2, 28.0, 27.8, 24.3, 23.8, 22.8, 22.5, 21.1, 19.4, 18.7, 11.9; HRMS (ESI): *m/z* calcd for $C_{31}H_{49}N_2O$: 465.3845, found: 465.3840 $[M+H]^+$.

2-(*Tert*-butoxy)pyrimidine (**3y**)[40]

Yield 90% (137 mg); yellow oil; IR (KBr) ν 3421, 2925, 2854, 1632, 1579, 1559, 1417, 1355, 1172, 947 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.46 (d, *J* = 4.7 Hz, 2H), 6.85 (t, *J* = 4.7 Hz, 1H), 1.63 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 164.9, 158.6, 114.2, 80.9, 28.1; ESI-MS: *m/z* 152.85 $[M+H]^+$.

5-Bromo-2-((4-methylbenzyl)oxy)pyrimidine (**4**)

Yield 60% (168 mg) yellow oil; IR (KBr) ν 3426, 2923, 2854, 1902, 1654, 1567, 1433, 1040, 932, 799 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.52 (s, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 5.37 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 163.7, 159.6, 137.9, 133.0, 129.1, 128.1, 111.9, 69.6, 21.2; HRMS (ESI): *m/z* calcd for $C_{12}H_{12}BrN_2O$: 279.0133, found: 279.0125 $[M+H]^+$.

2-(Benzyloxy)pyrazine (**5a**)[37]

Yield 48% (89 mg); yellow oil; IR (KBr) ν 3426, 3062, 2920, 1956, 1533, 1455, 1414, 1363, 1286, 1153, 1007, 838, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.29 (d, *J* = 1.2 Hz, 1H), 8.14−8.09 (m, 2H), 7.48−7.31 (m, 5H), 5.39 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.1, 140.5, 136.7, 136.3, 136.1, 128.5, 128.2, 128.1, 67.9. ESI-MS: *m/z* 185.88 $[M+H]^+$.

2-(Cyclobutylmethoxy)pyrazine (**5b**)

Yield 62% (102 mg); yellow oil; IR (KBr) ν 3441, 3060, 2977, 2940, 2864, 1533, 1415, 1286, 1151, 1005, 837, 603 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.22 (d, *J* = 1.3 Hz, 1H), 8.09−8.05 (m, 2H), 4.29 (d, *J* = 6.8 Hz, 2H), 2.83−2.73 (m, 1H), 2.18-2.08 (m, 2H), 1.99−1.83 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.5, 140.3, 136.1, 136.0, 70.1, 34.1, 24.7, 18.4; HRMS (ESI): *m/z* calcd for $C_9H_{13}N_2O$: 165.1028, found: 165.1024 $[M+H]^+$.

2-((3r,5r,7r)-Adamantan-1-ylmethoxy)pyrazine (**5c**)

Yield 43% (105 mg); yellow oil; IR (KBr) ν 3423, 3059, 2920, 2849, 2673, 1581, 1418, 1313, 845, 445 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.23 (d, *J* = 1.2 Hz, 1H), 8.08−8.04 (m, 2H), 3.90 (s, 2H), 2.02 (s, 3H), 1.78−1.65 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.8, 140.3, 136.04, 136.02, 76.0, 39.3, 37.0, 33.4, 28.1; HRMS (ESI): *m/z* calcd for $C_{15}H_{21}N_2O$: 245.1654, found: 245.1650 $[M+H]^+$.

2-(Benzyloxy)pyridine (**6**)[37]

Yield 25% (46 mg); yellow oil; IR (KBr) ν 3440, 3064, 3032, 2928, 1596, 1570, 1474, 1432, 1285, 1272, 1143, 990, 779, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.17 (dd, J_1 = 5.0 Hz, J_2 = 1.4Hz, 1H), 7.58−7.53 (m, 1H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.39−7.23 (m, 3H), 6.88−6.84 (m, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 5.38 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 163.6, 146.8, 138.6, 137.3, 128.4, 127.9, 127.8, 116.8, 111.3, 67.5. ESI-MS: *m/z* 186.23 $[M+H]^+$.

General synthetic procedure for alkylthiopyrimidines 10 (Table 3). A mixture of cyanopyrimidines (**1**, 1.0 mmol), thiols (**8**, 1.5 mmol)/*S*-alkylisothiourea hydrogen bromide or *S*-alkylisothiourea hydrogen iodides (**9**, 1.5 mmol) and cesium carbonate (652 mg, 2.0 mmol) in DMSO (3 mL) was heated at 80 °C for 2**–**9 h. After completion of the reaction, the mixture was poured into the water and extracted with dichloromethane (3×15 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtered. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel using the mixture of petroleum ether and ethyl acetate (v:v, 30:1 to 10:1) as the eluent to afford the target products **10**. The characterization data for **10c** and **10l** were agree with our recent published paper.[31]

2-(Benzylthio)pyrimidine (**10a**)[41]

Yield 92% (186 mg); yellow solid; IR (KBr) v 3415, 2924, 2853, 2361, 1566, 1546, 1382, 1185, 773, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.52 (d, *J* = 4.8 Hz, 2H), 7.43 (d, *J* = 7.3 Hz, 2H), 7.33−7.24 (m, 3H), 6.96 (t, *J* = 4.8 Hz, 1H), 4.42 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.1, 157.2, 137.4, 129.0, 128.4, 127.2, 116.5, 35.2; ESI-MS: *m/z* 203.05 $[M+H]^+$.

2-(dodecylthio)pyrimidine (**10b**)[42]

Yield 93% (261 mg); yellow oil; IR (KBr) v 3749, 3648, 3445, 3031, 2924, 2853, 1566, 1546, 1464, 1383, 1205, 774, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.49 (d, *J* = 4.8 Hz, 2H), 6.93 (t, *J* = 4.8 Hz, 1H), 3.14 (t, *J* = 7.3 Hz, 2H), 1.78−1.68 (m, 2H), 1.47−1.40 (m, 2H), 1.26 (s, 16H), 0.90−0.85 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.7, 156.9, 116.0, 31.7, 30.7, 29.5, 29.45, 29.42, 29.3, 29.2, 29.0, 28.9, 28.7, 22.5, 13.9; ESI-MS: *m/z* 281.13 $[M+H]^+$.

2-(Dodecylthio)pyrimidine (**10d**)[43]

Yield 95% (213 mg); yellow oil; IR (KBr) v 3852, 3749, 3648, 3444, 3031, 2956, 2926, 2855, 1566, 1383, 1205, 774, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm):8.50 (d, *J* = 4.8 Hz, 2H), 6.93 (t, *J* = 4.8 Hz, 1H), 3.14 (t, *J* = 7.4 Hz, 2H), 1.78−1.68 (m, 2H), 1.48-1.43 (m, 2H), 1.29−1.28 (m, 8H), 0.90−0.86 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):172.8, 157.1, 116.2, 31.8, 30.8, 29.1, 29.0, 28.9, 22.6, 14.0; ESI-MS: *m/z* 225.10 $[M+H]^+$.

2-(Hexadecylthio)pyrimidine (**10e**)[42]

Yield 91% (306 mg); yellow solid; IR (KBr) v 3854, 3439, 2952, 2918, 2848, 2362, 1565, 1378, 1190, 801, 773, 751, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.50 (d, *J* = 4.8 Hz, 2H), 6.94 (t, *J* = 4.8 Hz, 1H), 3.14 (t, *J* = 7.4 Hz, 2H), 1.73−1.64 (m, 2H), 1.37−1.25 (m, 26H), 0.90−0.86 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.9, 157.1, 116.2, 31.9, 30.9, 29.7, 29.65, 29.59, 29.5, 29.3, 29.2, 29.1, 28.9, 22.7, 14.1; ESI-MS: *m/z* 337.12 $[M+H]^+$.

2-((Cyclopropylmethyl)thio)pyrimidine (**10f**)[42]

Yield 97% (161 mg); yellow oil; IR (KBr) v 3396, 3079, 3004, 2923, 2852, 1565, 1547, 1382, 1190, 1018, 773, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.50 (t, *J* = 4.9 Hz, 2H), 6.95 (t, *J* = 4.9 Hz, 1H), 3.10 (t, *J* = 7.1 Hz, 2H), 1.65 (s, 1H), 0.64−0.58 (m, 2H), 0.36−0.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.9, 157.1, 116.3, 36.7, 10.4, 5.7; ESI-MS: *m/z* 167.09 $[M+H]^+$.

2-((Cyclobutylmethyl)thio)pyrimidine (**10g**)[42]

Yield 96% (173 mg); yellow oil; IR (KBr) v 3438, 3030, 2972, 2864, 2131, 1957, 1565, 1382, 1189, 980, 773, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.50 (d, *J* = 4.8 Hz, 2H), 6.95 (t, *J* = 4.8 Hz, 1H), 3.24 (d, *J* = 7.5 Hz, 2H), 2.70−2.64 (m, 1H), 2.16−2.13 (m, 2H), 1.87−1.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.8, 157.1, 116.3, 37.1, 34.6, 27.7, 18.0; ESI-MS: *m/z* 181.02 $[M+H]^+$.

2-(Cyclopentylthio)pyrimidine (**10h**)[42]

Yield 93% (167 mg); yellow oil; IR (KBr) v 3438, 3111, 2959, 2867, 2131, 1957, 1565, 1382, 1189, 980, 773, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.42 (d, *J* = 4.8 Hz, 2H), 6.86 (t, *J* = 4.9 Hz, 1H), 3.98−3.89 (m, 1H), 2.14−2.12 (m, 2H), 1.77−1.58 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 173.4, 157.0, 116.1, 43.5, 33.1, 24.8; ESI-MS: *m/z* 1181.18 $[M+H]^+$.

2-((Cyclohexylmethyl)thio)pyrimidine (**10i**)[42]

Yield 92% (192 mg); yellow oil; IR (KBr) v 3437, 3029, 2929, 2246, 1957, 1730, 1564, 1382, 1207, 1070, 773, 699, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.50 (d, *J* = 4.8 Hz, 2H), 6.94 (t, *J* = 4.9 Hz, 1H), 3.07 (d, *J* = 6.8 Hz, 2H), 1.94−1.89 (m, 2H), 1.75−1.59 (m, 4H), 1.27−1.00 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 173.0, 157.0, 116.1, 37.7, 37.5, 32.6, 26.2, 26.0; ESI-MS: *m/z* 209.12 $[M+H]^+$.

2-(Allylthio)pyrimidine (**10j**)[42]

Yield 93% (142 mg); yellow oil; IR (KBr) v 3434, 3082, 3032, 2925, 1960, 1565, 1547, 1382, 1203, 1186, 920, 773, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.52 (d, *J* = 4.8 Hz, 2H), 6.97 (t, *J* = 4.9 Hz, 1H), 6.04−5.93 (m, 1H), 5.33 (dd, J_1 = 17.0 Hz, J_2 = 1.4 Hz, 1H), 5.14 (d, *J* = 10 Hz, 1H), 3.83 (d, *J* = 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.0, 157.2, 133.3, 117.8, 116.5, 33.7; ESI-MS: *m/z* 153.16 $[M+H]^+$.

2-(Pent-4-en-1-ylthio)pyrimidine (**10k**)[42]

Yield 96% (173 mg); yellow oil; IR (KBr) v 3437, 3077, 2927, 2853, 1641, 1438, 1251, 1193, 990, 849, 770, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.51 (d, *J* = 4.9 Hz, 2H), 6.96 (t, *J* = 4.9 Hz, 1H), 5.90−5.77 (m, 1H), 5.11−5.09 (m, 2H), 3.16 (t, *J* = 7.2 Hz, 2H), 2.23 (dd, J_1 = 14.8 Hz, J_2 = 7.0 Hz, 2H), 1.90−1.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.6, 157.2, 137.7, 116.3, 115.3, 32.8, 30.2, 28.2; ESI-MS: *m/z* 181.06 $[M+H]^+$.

2-((3,3,3-Trifluoropropyl)thio)pyrimidine (**10m**)

Yield 90% (187 mg); yellow oil; IR (KBr) v 3446, 3039, 2939, 1567, 1550, 1384, 1261, 1243, 1138, 1098, 956, 774, 642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.54 (d, *J* = 4.9 Hz, 2H), 7.01 (t, *J* = 4.8 Hz, 1H), 3.32−3.27 (m, 2H), 2.65−2.56 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ (ppm): 171.1, 157.4, 126.1 (q, *J* = 275.6Hz), 116.8, 34.2 (q, *J* = 28.4 Hz), 23.0 (q, *J* = 3.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm):-66.43; HRMS (ESI): *m/z* calcd for $C_7H_8F_3N_2S$: 209.0355, found: 209.0358 $[M+H]^+$.

2-((3,3,4,4,5,5,6,6,6-Nonafluorohexyl)thio)pyrimidine (**10n**)

Yield 89% (319 mg); yellow oil; IR (KBr) v 3443, 3039, 2943, 2354, 1567, 1551, 1415, 1385, 1352, 1223, 1133, 1011, 879, 749, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.55 (d, *J* = 4.9 Hz, 2H), 7.02 (t, *J* = 4.9 Hz, 1H), 3.38−3.32 (m, 2H), 2.70−2.53 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):171.1, 157.5, 116.9, 31.6 (t, *J* = 21.8Hz), 21.9 (t, *J* = 4.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -81.02−-81.09, -114.65−-114.67, -124.37−-124.41, -125.99−-126.07; HRMS (ESI): *m/z* calcd for $C_{10}H_8F_9N_2S$: 359.0259, found: 359.0255 $[M+H]^+$

2-((3,3,4,4,5,5,6,6,7,7,8,8,8-Tridecafluorooctyl)thio)pyrimidine (**10o**)

Yield 85% (390 mg); yellow oil; IR (KBr) v 3447, 3039, 3943, 1567, 1551, 1416, 1238, 1144, 983, 775, 737, 649, 564 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.55 (d, *J* = 4.9 Hz, 2H), 7.02 (t, *J* = 4.8 Hz, 1H), 3.38−3.33 (m, 2H), 2.71−2.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):171.1, 157.5, 116.9, 31.7 (t, *J* = 21.8 Hz), 21.9 (t, *J* = 4.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -80.80−-80.85, -114.35−-114.47, -121.91, -122.89, -123.44, -126.12−-126.21; HRMS (ESI): *m/z* calcd for $C_{12}H_8F_{13}N_2S$: 459.0195, found: 459.0198 $[M+H]^+$

2-((3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-Heptadecafluorodecyl)thio)-pyrimidine (**10p**)

Yield 83% (390 mg); yellow oil; IR (KBr) v 3441, 3923, 2852, 1565, 1549, 1383, 1205, 1147, 1115, 1035, 773, 652, 559 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.55 (d, *J* = 4.9 Hz, 2H), 7.02 (t, *J* = 4.9 Hz, 1H), 3.38−3.32 (m, 2H), 2.71−2.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm):171.1, 157.5, 116.9, 31.7 (t, *J* = 21.8 Hz), 21.9 (t, *J* = 4.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm): -80.75 (t, *J* = 9.8 Hz), -114.38 (t, *J* = 13.0 Hz), -121.66, -121.89, -122.69, -123.35, -126.05−-126.11; HRMS (ESI): *m/z* calcd for $C_{14}H_8F_{17}N_2S$: 559.0131, found: 559.0136 $[M+H]^+$

General synthetic procedure for aminopyrimidines 12 (Table 4). A mixture of cyanopyrimidines (**1**, 1.0 mmol), amines (**11**, 2.0 mmol) and cesium carbonate (326 mg, 1.0 mmol) in DMSO (3 mL) was heated at 80 °C for 6–10 h. After completion of the reaction, the

mixture was poured into the water and extracted with dichloromethane (3×15 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtered. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel using the mixture of petroleum ether and ethyl acetate (v:v, 10:1 to 5:1) as the eluent to afford the target products **12**.

2-(Pyrrolidin-1-yl)pyrimidine (**12a**)[44]

Yield 95% (142 mg); yellow oil; IR (KBr) ν 3851, 3712, 3688, 3445, 2918, 2848, 1660, 1465, 1379, 1190, 802, 630 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.31 (d, *J* = 4.8 Hz, 2H), 6.45 (t, *J* = 4.8 Hz, 1H), 3.57 (t, *J* = 6.8 Hz, 4H), 2.02–1.98 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.1, 157.7, 108.8, 46.5, 25.5; ESI-MS: *m/z* 150.31 $[M+H]^+$.

2-(Piperidin-1-yl)pyrimidine (**12b**)[44]

Yield 92% (150 mg); yellow oil; IR (KBr) ν 3852, 3749, 3714, 3439, 2924, 2852, 1631, 1400, 1008, 979, 832 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.28 (d, *J* = 4.7 Hz, 2H), 6.42 (t, *J* = 4.7 Hz, 1H), 3.78 (t, *J* = 5.7 Hz, 4H), 1.71−1.57 (m, 6H); ^{13}C NMR(75 MHz, $CDCl_3$) δ (ppm): 161.6, 157.6, 109.0, 44.7, 25.7, 24.8; ESI-MS: *m/z* 164.32 $[M+H]^+$.

2-(4-Methylpiperidin-1-yl)pyrimidine (**12c**)[44]

Yield 93% (165 mg); yellow oil; IR (KBr) ν 3843, 3759, 3424, 2923, 2850, 2202, 1586, 1545, 1454, 1361, 1254, 1082, 969, 831 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.28 (d, *J* = 4.7 Hz, 2H), 6.42 (t, *J* = 4.7 Hz, 1H), 4.73−4.67 (m, 2H), 2.91−2.82 (m, 2H), 1.74−1.63 (m, 3H), 1.23−1.09 (m, 2H), 0.96 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.6, 157.6, 109.1, 44.1, 34.0, 31.3, 21.9; ESI-MS: *m/z* 178.26 $[M+H]^+$.

2-(Pyrimidin-2-yl)morpholine (**12d**)[44]

Yield 90% (148 mg); yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.33 (d, *J* = 4.7 Hz, 2H), 6.53 (t, *J* = 4.8 Hz, 1H), 3.82−3.75 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.8, 157.7, 110.3, 66.8, 44.2.

(2R,6S)-2,6-Dimethyl-4-(pyrimidin-2-yl)morpholine (**12e**)

Yield 85% (164 mg); yellow oil; IR (KBr) ν 3443, 2973, 2856, 1588, 1498, 1263, 1083, 1012, 797, 523 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.32 (d, *J* = 4.8 Hz, 2H), 6.51 (t, *J* = 4.7 Hz, 1H), 4.56−4.52 (m, 2H), 3.70−3.60 (m, 2H), 2,64−2.56 (m, 2H), 1.26 (d, *J* = 6.2 Hz, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.4, 157.7, 110.2, 71.7, 49.2, 18.8; HRMS (ESI): *m/z* calcd for $C_{10}H_{16}N_3O$: 194.1293, found: 194.1309 $[M+H]^+$.

***N*-(4-Methylbenzyl)pyrimidin-2-amine** (**12g**)[45]

Yield 55% (110 mg); IR (KBr) ν 3726, 3359, 2924, 2855, 2041, 1666, 1567, 1533, 1413, 1384, 1117, 893, 795, 634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.87 (d, *J* = 4.9 Hz, 2H), 8.26 (s, 1H), 7.43 (t, *J* = 4.9 Hz, 1H), 7.28 (s, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 4.68 (d, *J* = 5.9 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 162.0, 157.4, 137.4, 134.8, 129.4, 128.0, 122.5, 43.7, 21.1.

Synthesis of intermediate 3a' at room temperature (Scheme 3a). A mixture of 2-cyanopyrimidine (**1a**, 105 mg, 1.0 mmol), phenylmethanol (**2a**, 162 mg, 1.5 mmol) and cesium carbonate (326 mg, 1.0 mmol) in DMSO (3 mL) was stirred at 25 °C for 1 h, and stopped the reaction. The mixture was poured into the water and extracted with dichloromethane (3×15 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtered. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel using the mixture of petroleum ether and ethyl acetate (v:v, 30:1) as the eluent to afford **3a** (74 mg, 0.4 mmol), **3a'** (64 mg, 0.3 mmol), and unreacted starting material **1a** (32 mg, 0.3 mmol).

Synthesis of 3a from 3a' (Scheme 3b). The mixture of benzyl pyrimidine-2-carbimidate (**3a'**, 64 mg, 0.3 mmol), and cesium carbonate (98 mg, 0.3 mmol) in DMSO (1 mL) was stirred at 80 °C for 0.5 h. After completion of the reaction, the mixture was poured into the water and extracted with dichloromethane (3×15 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtered. After removal of the solvent, the residue was drying in vacuum oven to give **3a** (56 mg, >99% yield), which was pure enough for structural analysis.

Benzyl pyrimidine-2-carbimidate (**3a'**)

Yield 50% (107 mg); yellow oil; IR (KBr) ν 3759, 3450, 3044, 2957, 1741, 1565, 1413, 1315, 1155, 963, 706, 631 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.53 (s, 1H), 8.97 (d, *J* = 4.9 Hz, 2H), 7.66 (t, *J* = 4.9 Hz, 1H), 7.52−7.49 (m, 2H), 7.44−7.31 (m,3H), 5.38 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 164.4, 158.0, 136.7, 128.3, 128.1, 127.9, 126.4, 122.6, 67.7. HRMS (ESI): *m/z* calcd for $C_{12}H_{12}N_3O$: 214.0975, found: 214.0990 $[M+H]^+$.

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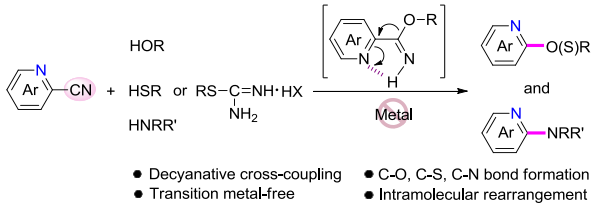

The transition metal-free cross-coupling reactions of cyanopyrimidines with aliphatic alcohols, thiols (or S-alkylisothiourea salts) and amines, giving the corresponding alkoxylpyrimidines, aminopyrimidines and alkylthiopyrimidines, are reported. The wide substrate scope with excellent yields makes cyanopyrimidines a promising alternative substrate class to the frequently used pyrimidines halides for the formation of C–O, C–S and C–N bonds.

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Transition Metal-Free Decyanative Cross-Coupling of Cyanopyrimidines with *O*-, *S*-, and *N*-Nucleophiles: A Route to Alkoxylpyrimidines, Aminopyrimidines and Alkylthiopyrimidines