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Cu-Catalyzed [3 + 3] Annulation for the Synthesis of Pyrimidines via β-C(sp^3)−H Functionalization of Saturated Ketones

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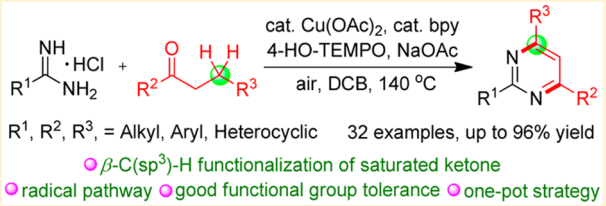
Supporting Information

ABSTRACT: A novel, efficient, and facile approach for the synthesis of structurally important pyrimidines has been successfully developed by Cu-catalyzed and 4-HO-TEMPO-mediated [3 + 3] annulation of commercially available amidines with saturated ketones. This method provides a new protocol for the synthesis of pyrimidines by a cascade reaction of oxidative dehydrogenation/annulation/oxidative aromatization via direct β-C(sp^3)−H functionalization of saturated ketones followed by annulation with amidines.



Pyrimidine derivatives are one of the most important parts of heterocyclic compounds. They have been found to have broad applications in organic synthesis,[1] natural products,[2] medicinal chemistry,[3] and materials chemistry.[4] Especially, due to their special biological and pharmacological activities, pyrimidine scaffolds are widely present in numerous drug molecules such as vitamin B1,[5a] estrogen antagonists,[5b] and antimalarial,[5c] anticoagulant,[5d] and antineuropathic pain drugs (Figure 1).[5e] In view of their remarkable significance, the synthesis of pyrimidine derivatives has drawn much attention from chemists and pharmacologists. To date, several efficient methods for the synthesis of pyrimidines have been developed by the reaction of amidines with various partners, including the condensation with 1,3-dicarbonyl derivatives,[6] α,β-unsaturated ketones,[7] or alkynones,[8] iridium-catalyzed multicomponent reaction,[9] and the inverse electron demanding Diels−Alder reactions with 1,2,3-triazines,[10] etc. (Scheme 1).[11] However, the majority of these methods suffered from harsh reaction conditions (microwave irradiation, strong basic conditions),[7a,8] starting materials that require multistep synthesis,[6−8,10] expensive catalysts,[9] and less atom efficiency.[10] Therefore, a simple and effective method for the synthesis of pyrimidine from simple and readily available starting materials still remains highly desirable.

With our continuing interest in the construction of important heterocyclic skeletons via radical cyclization and circularization,[12] herein, we intend to establish a facile and efficient [3 + 3] annulation for the synthesis of pyrimidines via a Cu-catalyzed and 4-HO-TEMPO-mediated cascade β-C(sp^3)−H dehydrogenation of saturated ketones followed by annulation with amidines and an oxidative aromatization reaction through a radical process (Scheme 1). Saturated carbonyl compounds, as cheap and commercially available raw chemicals and essential synthetic elements, are widely applied in organic synthesis. Direct unactivated β-C(sp^3)−H functionalization of saturated ketones undoubtedly is always a challenging target for chemists to pursue.[13] In this context, this strategy not only provides a novel radical method for β-Csp^3−H functionalization of saturated ketones but also realizes a direct oxidative [3 + 3] annulation toward potential bioactive pyrimidines.

To achieve this strategy, the reaction of benzamidine hydrochloride (**1a**, 0.4 mmol) and propiophenone (**2a**, 1.2 mmol) in toluene was chosen as a model reaction for the optimization investigation. Initially, the model reaction was stirred under the conditions of $Cu(OAc)_2$ (0.04 mmol, 0.1 equiv), 4-HO-TEMPO (0.4 mmol, 1 equiv), Cs_2CO_3 (0.8 mmol, 2 equiv), and 2,2′-bipyridine (bpy, 10 mol %) at 120 °C under air (Table 1, entry 1). To our delight, the desired product 2,4-diphenylpyrimidine **3a** was obtained in 20% yield (Table 1, entry 1). Next, various bases, such as Li_2CO_3, NaOAc, NEt_3, 1,4-diazabicyclooctane triethylenediamine (DABCO), and pyridine were investigated (Table 1, entries 2−6), and we found that NaOAc was the most efficient base to give **3a** in 68% yield. Other Cu catalysts, such as CuI, CuCl, $CuBr_2$, and $Cu(OTf)_2$, have also been examined (Table 1, entries 7−10), but no better results were obtained. Screening other solvents, such as DMF, DMSO, and 1,2-dichlorobenzene (DCB) (Table 1, entries 11−13), revealed that DCB was the best solvent and the yield of **3a** was improved to 80%. With the raising of the reaction temperature to 140 °C, the yield of **3a** was further increased to 85%; in contrast, lowering the reaction temperature led to a decrease of the yield of **3a** to 68% (Table 1, entries 14 and 15). Furthermore, the usage amount of base was also investigated and we found that 1.5 equiv of NaOAc gave a better result (Table 1, entries 16 and 17). With reducing the usage amount of 4-HO-TEMPO from 1 equiv to 0.5 equiv, the yield of **3a** was decreased to 65% (Table 1, entry 18). We also used the catalytic system 4-HO-TEMPO/$Cu(OAc)_2$/O_2 to

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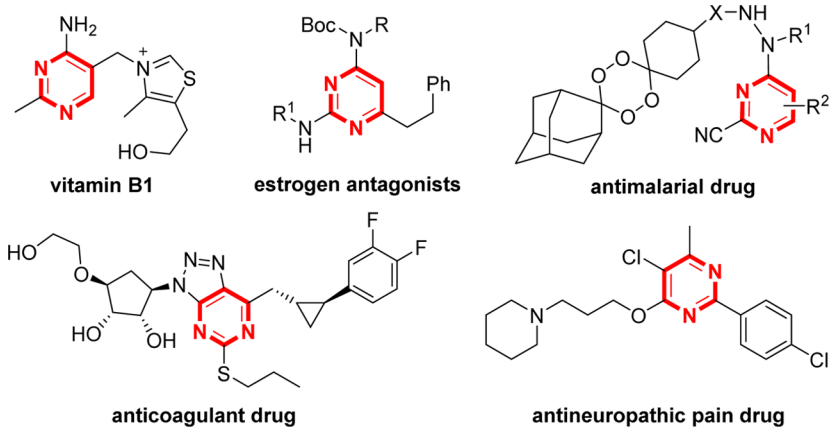
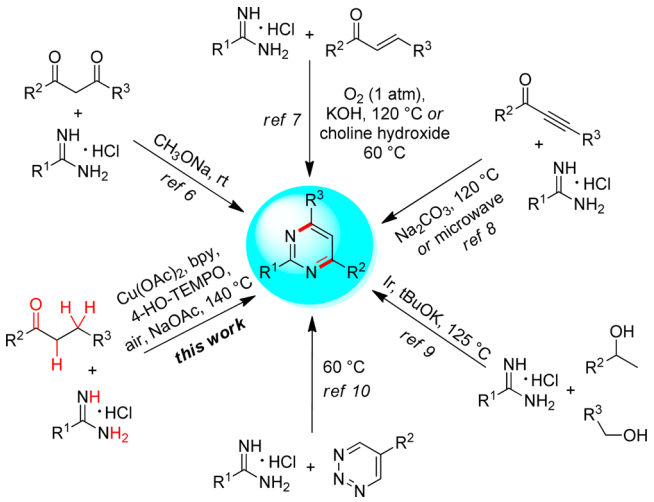


Figure 1. Bioactive pyrimidine derivatives.

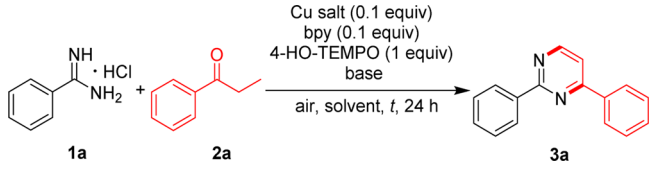
Scheme 1. Strategies for the Synthesis of Pyrimidines from Amidines



catalyze the reaction; unfortunately, the product **3a** was only obtained in a trace amount (Table 1, entry 19). These results demonstrated clearly that the stoichiometric amount of 4-HO-TEMPO is necessary for an efficient process.

With the optimized conditions in hand (Table 1, entry 16), the scope of the reaction with various ketones was investigated as shown in Scheme 2. First, the electronic effect, steric effect, and functional groups tolerance on the aromatic ring of the propiophenones were explored. Propiophenones with a wide range of electronic properties at the *para*-position of the phenyl moiety all proceeded well in the reaction, affording 2,6-disubstituted pyrimidines **3a**–**f** in good to excellent yields. In addition, *meta*-/*ortho*-methyl substituted propiophenones also participated well in the reaction, giving rise to pyrimidines **3g** and **3h** in excellent yields. Moreover, 3,4-disubstituted phenylpropanone also reacted swimmingly and gave the corresponding product **3i** in moderate yield. Aryl ketones, such as 1-(naphthalen-2-yl) and 1-(pyren-1-yl)propan-1-ones, reacted well with benzimidamide, delivering **3j** and **3k** in 96% and 91% yields, respectively. 1-(Thiophen-2-yl), 1-(pyridin-2-yl), and 1-(9-ethyl-9*H*-carbazol- 3-yl) substituted propan-1-ones were also good candidates in the protocol, as demonstrated in the cases **3l**–**n**. Notably, cyclohexylpropan-1-one reacted with **2a** very well and gave the corresponding pyrimidine **3o** in 81% yield. Besides substituted propan-1-ones,

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	Cu salt	base	solvent	t (°C)	yield (%)[b]
1	$Cu(OAc)_2$	Cs_2CO_3	toluene	120	20
2	$Cu(OAc)_2$	Li_2CO_3	toluene	120	59
3	$Cu(OAc)_2$	NaOAc	toluene	120	68
4	$Cu(OAc)_2$	NEt_3	toluene	120	55
5	$Cu(OAc)_2$	DABCO	toluene	120	55
6	$Cu(OAc)_2$	pyridine	toluene	120	50
7	CuI	NaOAc	toluene	120	36
8	CuCl	NaOAc	toluene	120	41
9	$CuBr_2$	NaOAc	toluene	120	40
10	$Cu(OTf)_2$	NaOAc	toluene	120	59
11	$Cu(OAc)_2$	NaOAc	DMF	120	52
12	$Cu(OAc)_2$	NaOAc	DMSO	120	38
13	$Cu(OAc)_2$	NaOAc	DCB	120	80
14	$Cu(OAc)_2$	NaOAc	DCB	100	68
15	$Cu(OAc)_2$	NaOAc	DCB	140	85
16[c]	**$Cu(OAc)_2$**	**NaOAc**	**DCB**	**140**	**87**
17[d]	$Cu(OAc)_2$	NaOAc	DCB	140	74
18[e]	$Cu(OAc)_2$	NaOAc	DCB	140	65
19[f]	$Cu(OAc)_2$	NaOAc	DCB	140	<5

[a]All reactions were carried out by using **1a** (0.4 mmol), **2a** (3.0 equiv), Cu (10 mol %), bpy (10 mol %), 4-HO-TEMPO (1 equiv), base (2 equiv), and solvent (2 mL) and stirred for 24 h under an air atmosphere except as noted. [b]Isolated yield. [c]NaOAc (1.5 equiv) was used. [d]NaOAc (1 equiv) was used. [e]4-HO-TEMPO (0.5 equiv) was used. [f]4-HO-TEMPO (0.2 equiv) and O_2 (1 atm) were used.

other ketones such as 1-phenylbutan-1-one, 4-phenylbutan-2-one, heptan-2-one, 1-cyclohexyldecan-1-one, 1-phenyl-3-(pyridin-2- yl)propan-1-one, and 1,4-diphenylbutane-1,4-dione were all well-tolerated in the protocol; thus, 2,4,6-trisubstituted pyrimidines **3p**–**t** were successively obtained in moderate to excellent yields.

Having successfully achieved the tandem reaction with various ketones, we then shifted our attention to explore the scope of amidines. The reactions of a variety of amidines **1** with **2a** were tested, and the results are illustrated in Scheme 3. No obvious electronic effect was observed for the substituted

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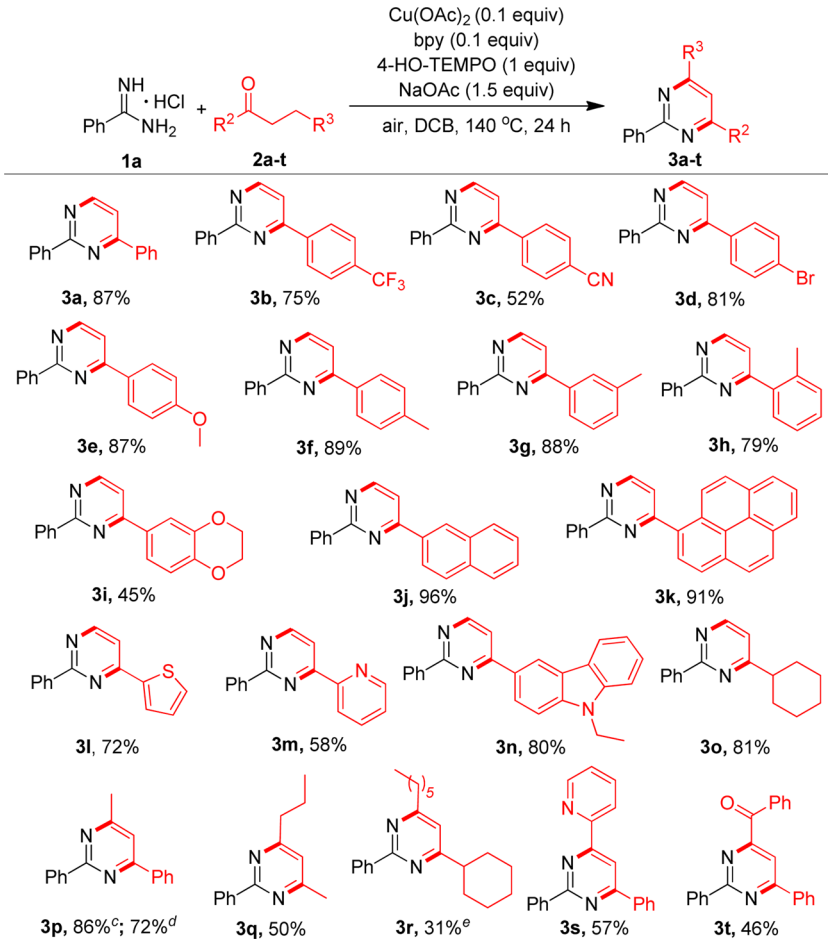
Scheme 2. Scope of Ketones[a,b]



[a]All reactions run in 0.2 M DCB using **1a** (0.4 mmol), **2** (1.2 mmol), $Cu(OAc)_2$ (0.04 mol), bpy (0.04 mol), 4-HO-TEMPO (0.4 mmol), and NaOAc (0.6 mmol) at 140 °C for 24 h under air except as noted. [b]Isolated yields are shown. [c]Substrate was 4-phenyl-2-butanone. [d]Substrate was 1-phenyl-butanone. [e]Reaction run in **2r** (0.2 mmol), **1a** (0.6 mmol), $Cu(OAc)_2$ (0.02 mmol), bpy (0.02 mmol), 4-HO-TEMPO (0.2 mmol), and NaOAc (0.6 mmol) at 140 °C for 24 h.

groups on the phenyl moiety of amidines in this reaction. *p*-Me, *p*-NH_2, *p*-NO_2, and *p*-Br substituted benzamidines participated swimmingly in the reaction, delivering the expected product **4b−e** in excellent yields. Remarkably, aliphatic amidines were also suitable for the transformation, as demonstrated in the cases **4f−h**. In addition, when heterocyclic substituted amidines such as 4-Py and 3-Py substituted ones were allowed to react with **2a**, the desired products **4i** and **4j** were obtained in 94% and 76% yields, respectively. Unfortunately, 2-pyridinyl and 1-triazole substituted ones hardly gave the corresponding products **4k** and **4l**, probably due to the strong chelate effect of substrates **1k** and **1l** with $Cu(OAc)_2$ that result in the deactivation of the catalyst $Cu(OAc)_2$.[14] Significantly, the reaction could be carried out in gram-scale without any difficulty, as demonstrated by the product **4f** which was obtained in 60% yield (1.02 g) when acetamidine hydrochloride (**1f**, 10 mmol) was used, exhibiting the practicability of this methodology in organic synthesis.

To investigate the mechanism of this reaction, several control experiments were conducted. Neither the condensation product **5** nor **6** was obtained when **1a** was allowed to react with **2a** in the presence of NaOAc (Scheme 4, eq 1). This result attested clearly that **5** or **6** was not the intermediate in this reaction. When substrate **2a** was treated under the standard reaction conditions without **1a**, α,β-unsaturated ketone **7** was obtained in 41% yield (Scheme 4, eq 2). Expressively, when compound **7** was reacted with **1a** under the standard reaction conditions, the desired product **3a** was generated in 87% yield (Scheme 4, eq 3). Obviously, these consequences revealed that enone was the key intermediate in this reaction.

Based on the experimental results and aforementioned control experiments, a proposed mechanism for this transformation is illustrated in Figure 2. Initially, $Cu(OAc)_2$ as a Lewis acid coordinates with ligand bpy and ketone **2** to form the Ln-Cu(II)-enolate complex **A**,[15] which subsequently undergoes inner sphere single electron transfer to produce Cu(I) species and C-centered radical **B** under heating conditions. The latter is immediately trapped by 4-HO-TEMPO to yield the intermediate **C** which undergoes a Cope-like elimination by losing 4-HO-TEMPOH via a five centered cyclic transition state to give the enone **D**.[12h,13e,16,17h] 4-HO-TEMPO can be regenerated through the auto-oxidation of 4-HO-TEMPOH by air.[17] The intermolecular Michael addition of amidine with enone **D** forms intermediate **E** which follows a subsequently intramolecular condensation to give the intermediate **F** along with the release of H_2O. Finally, oxidative aromatization of **F** produces the desired product **3** or **4**.

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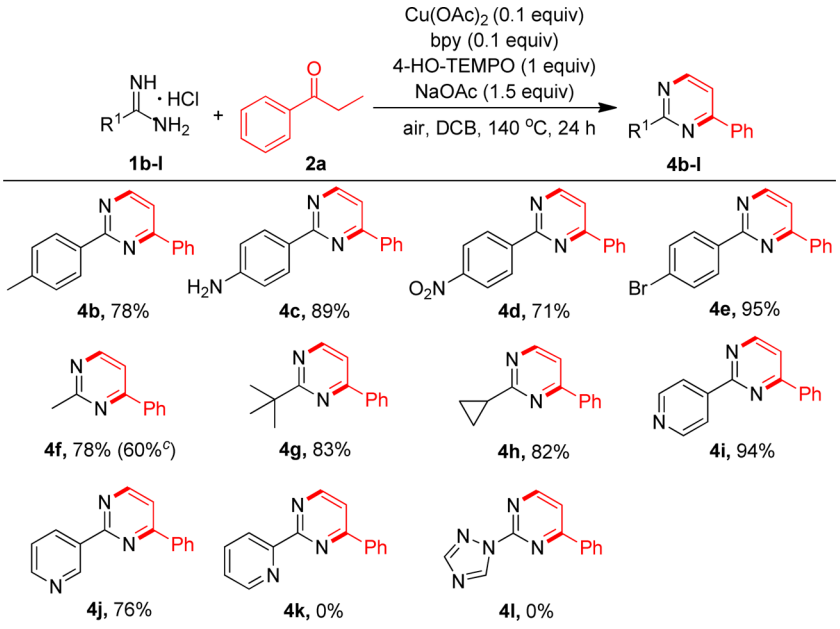
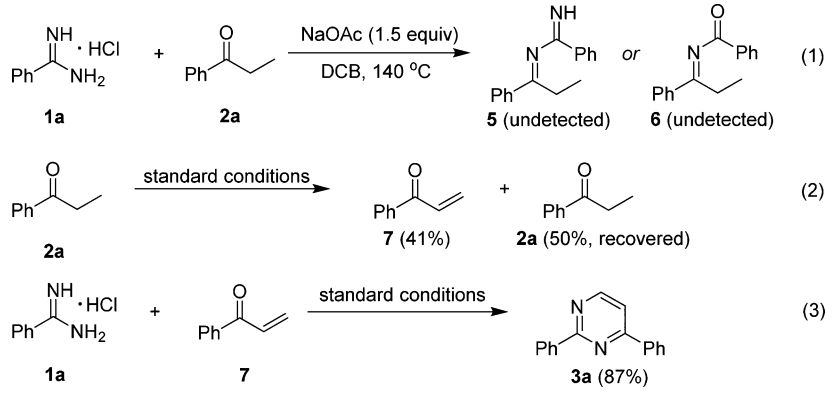
Scheme 3. Scope of Amidines[a,b]



[a]All reactions run in 0.2 M in DCB using **1** (0.4 mmol), **2a** (1.2 mmol), $Cu(OAc)_2$ (0.04 mmol), 2,2′-bipyridine (0.04 mol), 4-HO-TEMPO (0.4 mmol), and NaOAc (0.6 mmol) at 140 °C for 24 h under air. [b]Isolated yields. [c]Acetamidine hydrochloride **1f** (10 mmol) was used, and the corresponding product **4f** was obtained in 1.02 g.

Scheme 4. Control Experiments



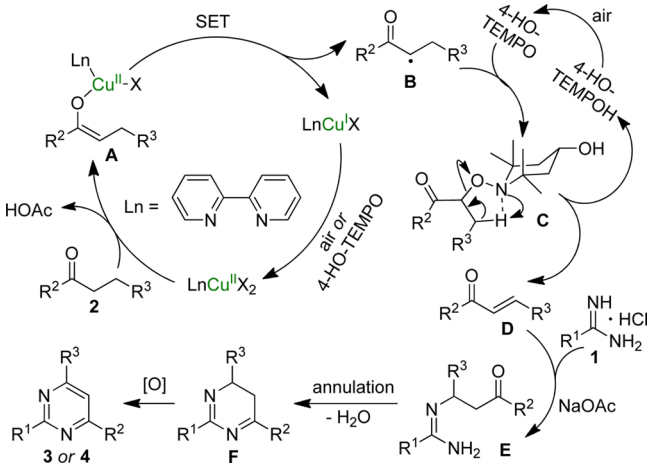


Figure 2. Proposed mechanism.

In conclusion, we have developed a novel and efficient radical protocol for the synthesis of structurally important pyrimidine derivatives via Cu-catalyzed and 4-HO-TEMPO-mediated cascade oxidative dehydrogenation/annulation/aromatization processes from commercially available amidines and saturated ketones. To the best of our knowledge, this protocol presents the first example for the construction of pyrimidine scaffolds through unactivated β-C(sp^3)–H functionalization of saturated ketones.

EXPERIMENTAL SECTION

General Methods. All reagents were purchased from commercial suppliers and used without further purification. Flash chromatography was carried out with silica gel (200–300 mesh). Analytical TLC was performed with silica gel GF254 plates, and the products were visualized by UV detection. Melting points were determined without correction on a digital melting-point apparatus. ^{1}H NMR (400 MHz), ^{13}C NMR (100.6 MHz) spectra were recorded in $CDCl_3$ and DMSO-d_6. Chemical shifts (δ) are reported in ppm using TMS as the internal standard, and spin–spin coupling constants (J) are given in Hz. The high resolution mass spectra (HRMS) were measured on an electrospray ionization (ESI) apparatus using a time-of-flight (TOF) mass spectrometry. Data collections for crystal structure were

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performed at room temperature (293 K) using Mo Kα radiation on a diffractometer. The copies of ^{1}H and ^{13}C NMR spectra of all compounds are provided in the Supporting Information. THF was distilled immediately before use from Na/benzophenone. Other commercially available reagents and solvents were used without further purification.

General Experimental Procedure. A 25 mL oven-dried reaction tube was charged with amidine (0.4 mmol), $Cu(OAc)_2$ (7.3 mg, 0.04 mmol, 10 mol %), 2,2′-bipyridine (6.3 mg, 0.04 mmol, 10 mol %), 4-HO-TEMPO (68.8 mg, 0.4 mmol), and NaOAc (49.2 mg, 0.6 mmol). Then 1,2-dichlorobenzene (2.0 mL) and ketone (1.2 mmol) were added to the tube. The tube was then sealed, and the mixture was stirred at 140 °C for 24 h. Upon cooling to room temperature, the reaction mixture was diluted with 10 mL of ethyl acetate, followed by filtration through a pad of silica gel. The filtrate was concentrated under reduced pressure and then purified by flash chromatography on silica gel (gradient eluent of hexane/ethyl acetate: 100/1 to 3/1) to provide the corresponding product in yields listed in Schemes 2 and 3. The identity and purity of products were confirmed by ^{1}H, ^{13}C HRMS, and X-ray single crystal diffractometer spectroscopic analysis.

*2,4-Diphenylpyrimidine (**3a**).*[18] White solid (79 mg, 85%); mp: 66−68 °C; R_f = 0.36 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (d, J = 5.2 Hz, 1H), 8.60−8.57 (m, 2H), 8.20−8.18 (m, 2H), 7.53−7.48 (m, 7H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.5, 163.7, 157.8, 137.8, 136.8, 130.9, 130.6, 128.8, 128.5, 128.2, 127.1, 114.4; ESI-HRMS: m/z: calcd for $C_{16}H_{12}N_2$ + H^+: 233.1073; found: 233.1069.

*2-Phenyl-4-(4-(trifluoromethyl)phenyl)pyrimidine (**3b**).*[14a] White solid (90 mg, 75%); mp: 108−110 °C; R_f = 0.23 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (d, J = 5.2 Hz, 1H), 8.56 (d, J = 3.6 Hz, 2H), 8.27 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.54−7.51 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.7, 162.3, 158.2, 140.2, 137.4, 132.5 (q, $^{C,F}J_2$ = 32 Hz), 130.9, 128.6, 128.3, 127.5, 125.8 (q, $^{C,F}J_3$ = 4 Hz), 123.9 (q, $^{C,F}J_1$ = 271 Hz), 114.7; ESI-HRMS: m/z calcd for $C_{17}H_{11}F_3N_2$ + H^+: 301.0947; found: 301.0944.

*4-(2-Phenylpyrimidin-4-yl)benzonitrile (**3c**).* White solid (54 mg, 52%); mp: 123−124 °C; R_f = 0.26 (hexane/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (d, J = 5.2 Hz, 1H), 8.57−8.53 (m, 2H), 8.28 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 5.2 Hz, 1H), 7.52 (t, J = 3.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.8, 161.6, 158.4, 140.9, 137.2, 132.6, 131.0, 128.6, 128.2, 127.6, 118.3, 114.7, 114.2; ESI-HRMS: m/z calcd for $C_{17}H_{11}N_3$ + H^+: 258.1026; found: 258.1023.

*4-(4-Bromophenyl)-2-phenylpyrimidine (**3d**).*[19] Pale yellow solid (101 mg, 81%); mp: 100−102 °C; R_f = 0.30 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, J = 5.2 Hz, 1H), 8.55−8.53 (m, 2H), 8.04 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.50−7.46 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.6, 162.6, 158.0, 137.6, 135.7, 132.1, 130.8, 128.6, 128.5, 128.2, 125.6, 114.1; MS (ESI, m/z): calcd for $C_{16}H_{11}BrN_2$ + H^+: 311.0178; found: 311.0174.

*4-(4-Methoxyphenyl)-2-phenylpyrimidine (**3e**).*[14a] White solid (92 mg, 87%); mp: 95−97 °C; R_f = 0.21 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 5.2 Hz, 1H), 8.58−8.56 (m, 2H), 8.15 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 2H), 7.53−7.47 (m, 3H), 7.43 (d, J = 5.6 Hz, 1H), 6.98 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.3, 163.2, 161.9, 157.4, 138.0, 130.5, 129.2, 128.6, 128.4, 128.2, 114.2, 113.5, 55.3; ESI-HRMS: m/z calcd for $C_{17}H_{14}N_2O$ + H^+: 263.1179; found: 263.1175.

*2-Phenyl-4-(p-tolyl)pyrimidine (**3f**).*[19] White solid (88 mg, 89%); mp: 103−104 °C; R_f = 0.34 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, J = 5.2 Hz, 1H), 8.59−8.57 (m, 2H), 8.10 (d, J = 8.4 Hz, 2H), 7.53−7.48 (m, 4H), 7.30 (d, J = 8.4 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.4, 163.7, 157.6, 141.3, 137.9, 134.1, 130.6, 129.6, 128.4, 128.2, 127.0, 114.1, 21.4; ESI-HRMS: m/z calcd for $C_{17}H_{14}N_2$ + H^+: 247.1230; found: 247.1226.

*2-Phenyl-4-(m-tolyl)pyrimidine (**3g**).* Yellow oil (88 mg, 89%); R_f = 0.42 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, J = 5.2 Hz, 1H), 8.59−8.57 (m, 2H), 8.03 (s, 1H), 7.99 (d, J = 7.6 Hz, 1H), 7.56−7.49 (m, 4H), 7.41 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 2.47 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.6, 164.0, 157.7, 138.6, 137.9, 136.9, 131.7, 130.6, 128.8, 128.5, 128.3, 127.8, 124.4, 114.6, 21.5; ESI-HRMS: m/z calcd for $C_{17}H_{14}N_2$ + H^+: 247.1230; found: 247.1226.

*2-Phenyl-4-(o-tolyl)pyrimidine (**3h**).* Pale yellow oil (78 mg, 79%); R_f = 0.37 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, J = 5.2 Hz, 1H), 8.54−8.52 (m, 2H), 7.52−7.45 (m, 4H), 7.37−7.26 (m, 4H), 2.52 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 167.2, 164.0, 157.2, 137.9, 137.8, 136.4, 131.2, 130.6, 129.6, 129.4, 128.4, 128.2, 126.1, 118.6, 20.6; ESI-HRMS: m/z calcd for $C_{17}H_{14}N_2$ + H^+: 247.1230; found: 247.1227.

*4-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)-2-phenylpyrimidine (**3i**).* Yellow oil (52 mg, 45%); R_f = 0.31 (hexane/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 5.2 Hz, 1H), 8.57−8.55 (m, 2H), 7.80 (d, J = 2.0 Hz, 1H), 7.69 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.52−7.47 (m, 3H), 7.43 (d, J = 5.2 Hz, 1H), 6.96 (d, J = 8.4 Hz, 1H), 4.27 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.2, 162.9, 157.5, 146.2, 143.8, 137.9, 130.5, 130.2, 128.4, 128.2, 120.5, 123.8, 117.6, 116.2, 113.7, 64.5, 64.2; ESI-HRMS: m/z calcd for $C_{18}H_{14}N_2O_2$ + H^+: 291.1128; found: 291.1125.

*4-(Naphthalen-2-yl)-2-phenylpyrimidine (**3j**).* Pale yellow solid (109 mg, 96%); mp: 100−102 °C; R_f = 0.30 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (d, J = 5.6 Hz, 1H), 8.68 (s, 1H), 8.62 (dd, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 2H), 8.30 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.99−7.95 (m, 2H), 7.89−7.87 (m, 1H), 7.67 (d, J = 5.6 Hz, 1H), 7.55−7.52 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.6, 163.7, 157.8, 137.9, 134.7, 134.2, 133.2, 130.7, 129.0, 128.7, 128.5, 128.3, 127.8, 127.42, 127.38, 126.6, 124.0, 114.7; ESI-HRMS: m/z calcd for $C_{20}H_{14}N_2$ + H^+: 283.1230; found: 283.1228.

*2-Phenyl-4-(pyren-1-yl)pyrimidine (**3k**).* Brown solid (130 mg, 91%); mp: 191−193 °C; R_f = 0.27 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (d, J = 5.2 Hz, 1H), 8.64−8.59 (m, 3H), 8.22−8.16 (m, 4H), 8.11−8.04 (m, 3H), 8.00 (t, J = 7.6 Hz, 1H), 7.56−7.50 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 166.9, 164.5, 157.4, 137.8, 133.0, 132.3, 131.3, 130.8, 130.7, 128.8, 128.60, 128.55, 128.5, 128.4, 127.5, 127.2, 126.2, 125.7, 125.4, 125.1 124.8, 124.6, 124.4, 120.2; ESI-HRMS: m/z calcd for $C_{26}H_{16}N_2$ + H^+: 357.1386; found: 357.1383.

*2-Phenyl-4-(thiophen-2-yl)pyrimidine (**3l**).*[14a] Pale yellow oil (69 mg, 72%); R_f = 0.27 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, J = 5.2 Hz, 1H), 8.54−8.52 (m, 2H), 7.74 (d, J = 3.2 Hz, 1H), 7.48 (d, J = 1.6 Hz, 4H), 7.33 (d, J = 5.2 Hz, 1H), 7.10 (t, J = 4.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.4, 158.8, 157.4, 142.7, 137.4, 130.7, 130.0, 128.4, 128.24, 128.16, 127.3, 112.6; ESI-HRMS: m/z calcd for $C_{14}H_{10}N_2S$ + H^+: 239.0637; found: 239.0633.

*2-Phenyl-4-(pyridin-2-yl)pyrimidine (**3m**).* White solid (54 mg, 58%); mp: 70−72 °C; R_f = 0.24 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (d, J = 4.8 Hz, 1H), 8.71−8.66 (m, 2H), 8.58 (d, J = 5.6 Hz, 2H), 8.23 (d, J = 4.8 Hz, 1H), 7.86 (t, J = 7.2 Hz, 1H), 7.52−7.51 (m, 3H), 7.38 (t, J = 6.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.2, 162.8, 158.3, 154.2, 149.4, 137.7, 137.0, 130.7, 128.5, 128.2, 125.3, 121.7, 115.0; ESI-HRMS: m/z calcd for $C_{15}H_{11}N_3$ + H^+: 234.1026; found: 234.1022.

*9-Ethyl-3-(2-phenylpyrimidin-4-yl)-9H-carbazole (**3n**).* Yellow oil (112 mg, 80%); R_f = 0.31 (hexane/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (d, J = 1.2 Hz, 1H), 8.68 (d, J = 5.2 Hz, 1H), 8.64−8.62 (m, 2H), 8.25 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 8.16 (d, J = 7.6 Hz, 1H), 7.55−7.43 (m, 5H), 7.33 (d, J = 8.4 Hz, 2H), 7.25 (t, J = 7.6 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.3, 164.2, 157.2, 141.6, 140.4, 138.2, 130.4, 128.4, 128.2, 127.4, 126.1, 124.8, 123.3, 123.0, 120.6, 119.6, 119.4, 113.8, 108.7, 108.5, 37.5, 13.7; MS (ESI, m/z): calcd for $C_{24}H_{19}N_3$ + H^+: 350.1652; found: 350.1649.

*4-Cyclohexyl-2-phenylpyrimidine (**3o**).* Colorless oil (77 mg, 81%); R_f = 0.46 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, J = 4.8 Hz, 1H), 8.48−8.46 (m, 2H), 7.48−7.46 (m, 3H), 7.00 (d, J = 5.2 Hz, 1H), 2.71 (tt, J_1 = 11.6 Hz, J_2 = 3.2 Hz, 1H), 2.02−1.99 (m, 2H), 1.89−1.86 (m, 2H), 1.79−1.76 (m, 1H), 1.64−1.54 (m, 2H), 1.48−1.38 (m, 2H), 1.35−1.25 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.7, 164.0, 156.9, 138.1, 130.3, 128.4,

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128.1, 116.3, 46.0, 32.0, 26.2, 25.9; ESI-HRMS: m/z calcd for $C_{16}H_{18}N_2 + H^+$: 239.1543; found: 239.1540.

*4-Methyl-2,6-diphenylpyrimidine (**3p**).*[14a] White solid (85 mg, 86%, 72%); mp: 86−88 °C; R_f = 0.48 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60−8.58 (m, 2H), 8.18−8.16 (m, 2H), 7.50−7.44 (m, 6H), 7.39 (s, 1H), 2.59 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 167.7, 164.2, 163.6, 138.1, 137.2, 130.6, 130.4, 128.8, 128.4, 128.3, 127.1, 113.9, 24.5; ESI-HRMS: m/z calcd for $C_{17}H_{14}N_2$ + H^+: 247.1230; found: 247.1225.

*4-Methyl-2-phenyl-6-propylpyrimidine (**3q**).* Pale yellow oil (43 mg, 50%); R_f = 0.59 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46−8.44 (m, 2H), 7.48−7.43 (m, 3H), 6.87 (s, 1H), 2.73 (t, J = 7.6 Hz, 2H), 2.52 (s, 3H), 1.86−1.77 (m, 2H), 1.00 (t, J = 7.6 Hz 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.3, 166.6, 164.0, 138.3, 130.1, 128.3, 128.2, 117.3, 39.7, 24.2, 22.0, 13.8; ESI-HRMS: m/z calcd for $C_{14}H_{16}N_2$ + H^+: 213.1386; found: 213.1383.

*4-Cyclohexyl-6-hexyl-2-phenylpyrimidine (**3r**).* Colorless oil (40 mg, 31%); R_f = 0.44 (hexane/ethyl acetate 100:1); ^{1}H NMR (400 MHz, $CDCl_3$): 8.48−8.46 (m, 2H), 8.48−8.41 (m, 3H), 6.86 (s, 1H), 2.79−2.74 (m, 2H), 2.72−2.64 (m, 1H), 2.02−1.98 (m, 2H), 1.89−1.86 (m, 2H), 1.82−1.75 (m, 3H), 1.64−1.54 (m, 2H), 1.48−1.25 (m, 9H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 174.3, 170.7, 163.8, 138.6, 130.0, 128.32, 128.27, 115.0, 46.0, 38.0, 32.2, 31.7, 29.1, 28.8, 26.3, 26.0, 22.6, 14.1; ESI-HRMS: m/z calcd for $C_{22}H_{30}N_2$ + H^+: 323.2482; found: 323.2479.

*2,4-Diphenyl-6-(pyridin-2-yl)pyrimidine (**3s**).* White solid (71 mg, 57%); mp: 211−213 °C; R_f = 0.50 (hexane/ethyl acetate 5:1); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.72−8.71 (m, 5H), 8.36 (d, J = 6.0 Hz 2H), 7.86 (t, J = 7.2 Hz, 1H), 7.54−7.52 (m, 6H), 7.38 (t, J = 5.6 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.0, 164.2, 163.5, 154.6, 149.3, 138.0, 137.3, 137.0, 130.8, 130.6, 128.8, 128.43, 128.37, 127.4, 125.2, 121.8, 110.5; ESI-HRMS: m/z calcd for $C_{21}H_{15}N_3$ + H^+: 310.1339; found: 310.1336.

*(2,6-Diphenylpyrimidin-4-yl)(phenyl)methanone (**3t**).* Yellow solid (62 mg, 46%); mp: 124−126 °C; R_f = 0.52 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61−8.58 (m, 2H), 8.32−8.28 (m, 2H), 8.26−8.24 (m, 2H), 8.17 (s, 1H), 7.67−7.63 (m, 1H), 7.56−7.49 (m, 8H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 192.8, 165.9, 163.8, 162.4, 137.3, 136.5, 135.3, 133.6, 131.4, 131.2, 131.1, 129.0, 128.6, 128.5, 128.3, 127.4, 113.3; ESI-HRMS: m/z calcd for $C_{23}H_{16}N_2O$ + H^+: 337.1335; found: 337.1333.

*4-Phenyl-2-(p-tolyl)pyrimidine (**4b**).*[14a] Colorless solid (77 mg, 78%); mp: 84−86 °C; R_f = 0.50 (hexane/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, J = 5.2 Hz, 1H), 8.47 (d, J = 8.0 Hz, 2H), 8.19−8.17 (m, 2H), 7.50−7.48 (m, 4H), 7.30 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.6, 163.7, 157.7, 140.8, 137.0, 135.2, 130.8, 129.2, 128.8, 128.2, 127.1, 114.1, 21.4; MS (ESI, m/z): calcd for $C_{17}H_{14}N_2$ + H^+: 247.1230; found: 247.1226.

*4-(4-Phenylpyrimidin-2-yl)aniline (**4c**).*[20] Yellow solid (88 mg, 89%); mp: 145−146 °C; R_f = 0.47 (hexane/ethyl acetate 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 5.2 Hz, 1H), 8.40 (dd, J_1 = 6.8 Hz, J_2 = 1.6 Hz, 2H), 8.19−8.17 (m, 2H), 7.52−7.48 (m, 3H), 7.44 (d, J = 5.2 Hz, 1H), 6.75 (dd, J_1 = 6.8 Hz, J_2 = 1.6 Hz, 2H), 3.95 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.6, 163.5, 157.6, 149.0, 137.2, 130.6, 129.8, 128.8, 128.1, 127.1, 114.6, 113.3; ESI-HRMS: m/z calcd for $C_{16}H_{13}N_3$ + H^+: 248.1182; found: 248.1177.

*2-(4-Nitrophenyl)-4-phenylpyrimidine (**4d**).*[14a] White solid (79 mg, 71%); mp: 196−197 °C; R_f = 0.35 (hexane/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (d, J = 5.2 Hz, 1H), 8.76 (d, J = 8.4 Hz, 2H), 8.35 (d, J = 8.8 Hz, 2H), 8.24−8.21 (m, 2H), 7.70 (d, J = 5.2 Hz, 1H), 7.57 (t, J = 3.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.3, 162.5, 158.0, 149.3, 143.6, 136.4, 131.4, 129.14, 129.08, 127.2, 123.7, 115.6; ESI-HRMS: m/z calcd for $C_{16}H_{11}N_3O_2$ + H^+: 278.0924; found: 278.0922.

*2-(4-Bromophenyl)-4-phenylpyrimidine (**4e**).*[14a] Pale yellow solid (118 mg, 95%); mp: 95−96 °C; R_f = 0.33 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (d, J = 5.6 Hz, 1H), 8.43 (d, J = 8.8 Hz, 2H), 8.18−8.16 (m, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 5.2 Hz, 1H), 7.51 (t, J = 3.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.9, 163.6, 157.8, 136.8, 136.7, 131.6, 131.0, 129.8, 128.9, 127.1, 125.4, 114.6; ESI-HRMS: m/z calcd for $C_{16}H_{11}BrN_2$ + H^+: 311.0178; found: 311.0175.

*2-Methyl-4-phenylpyrimidine (**4f**).*[14a] Pale yellow solid (53 mg, 78%); mp: 47−49 °C; R_f = 0.21 (hexane/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, J = 5.6 Hz, 1H), 8.08−8.06 (m, 2H), 7.50−7.48 (m, 4H), 2.80 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 168.3, 164.0, 157.4, 136.8, 130.7, 128.8, 127.1, 113.8, 26.2; ESI-HRMS: m/z calcd for $C_{11}H_{10}N_2$ + H^+: 171.0917; found: 171.0914.

*2-(tert-Butyl)-4-phenylpyrimidine (**4g**).* Colorless oil (71 mg, 83%); R_f = 0.44 (hexane/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 5.2 Hz, 1H), 8.15−8.13 (m, 2H), 7.49−7.46 (m, 4H), 1.49 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 177.3, 162.9, 157.1, 137.2, 130.6, 128.8, 127.1, 113.2, 39.6, 29.6; ESI-HRMS: m/z calcd for $C_{14}H_{16}N_2$ + H^+: 213.1386; found: 213.1382.

*2-Cyclopropyl-4-phenylpyrimidine (**4h**).*[14a] Colorless oil (65 mg, 82%); R_f = 0.39 (hexane/ethyl acetate 5:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (d, J = 5.6 Hz, 1H), 8.05 (t, J = 3.2 Hz, 2H), 7.46 (t, J = 3.2 Hz, 3H), 7.40 (d, J = 5.6 Hz, 1H), 2.35−2.29 (m, 1H), 1.25−1.22 (m, 2H), 1.10−1.06 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 172.0, 163.4, 157.1, 136.9, 130.6, 128.7, 127.0, 113.3, 18.3, 10.6; ESI-HRMS: m/z calcd for $C_{13}H_{12}N_2$ + H^+: 197.1073; found: 197.1070.

*4-Phenyl-2-(pyridin-4-yl)pyrimidine (**4i**).*[14a] Pale yellow solid (88 mg, 94%); mp: 80−81 °C; R_f = 0.34 (hexane/ethyl acetate 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82−8.78 (m, 3H), 8.38 (d, J = 5.6 Hz, 2H), 8.19−8.17 (m, 2H), 7.63 (d, J = 5.2 Hz, 1H), 7.53−7.52 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 164.0, 162.4, 157.9, 150.3, 144.9, 136.2, 131.2, 128.9, 127.0, 121.9, 115.7; ESI-HRMS: m/z calcd for $C_{15}H_{11}N_3$ + H^+: 234.1026; found: 234.1022.

*4-Phenyl-2-(pyridin-3-yl)pyrimidine (**4j**).*[14a] Yellow solid (71 mg, 76%); mp: 83−85 °C; R_f = 0.36 (hexane/ethyl acetate 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (d, J = 1.2 Hz, 1H), 8.79−8.77 (m, 2H), 8.73−8.71 (m, 1H), 8.18−8.16 (m, 2H), 7.58 (d, J = 5.6 Hz, 1H), 7.51−7.50 (m, 3H), 7.41−7.38 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 163.8, 162.6, 157.8, 151.2, 149.8, 136.3, 135.3, 133.2, 131.0, 128.8, 127.0, 123.2, 114.9; ESI-HRMS: m/z calcd for $C_{15}H_{11}N_3$ + H^+: 234.1026; found: 234.1022.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02181.

^{1}H NMR and ^{13}C NMR spectra for all products (PDF)

Crystallographic data for the compound **4d** (CIF)

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Notes

The authors declare no competing financial interest.

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