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Ag-Assisted Fluorination of Unprotected 4,6-Disubstituted 2-Aminopyrimidines with Selectfluor

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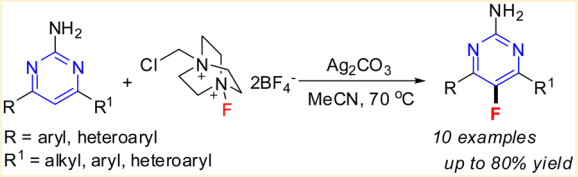
Supporting Information

ABSTRACT: A direct fluorination of 4,6-disubstituted 2-aminopyrimidines with Selectfluor in the presence of Ag(I) is presented, affording the corresponding 4,6-disubstituted 5-fluoro-2-aminopyrimidines with acceptable to high yield. Ag(I) is crucial for this chemoselective fluorination process. The transformation of 4,6-diphenyl 5-fluoro-2-aminopyrimidine into *N*-(5-fluoro-4,6-diphenylpyrimidin-2-yl)-4-methylbenzenesulfonamide is discussed, and the reaction mechanism is investigated, as well.



The incorporation of fluorine atoms into organic molecules could significantly influence their physicochemical and biological properties and is now a strategy for modulating the characteristics of chemical leads in drug discovery.[1] Approximately, up to 40% of all agrochemicals and 20% of all pharmaceuticals on the current market are fluorinated organic molecules.[2] Therefore, the development of practical methods for the formation of the carbon−fluorine (C−F) bond has a remarkable significance in pharmaceuticals,[3] agrochemicals,[4] materials,[5] and radiotracers for positron emission tomography (PET).[6] In addition, fluorinated organic compounds play an important role in the investigation of covalent chemistry of carbon nanotubes (CNTs) for F-CNT exhibiting possible large-scale applications.[7] 2-Aminopyrimidine is a ubiquitous substructure found in various bioactive pharmaceutical intermediates and materials. One of the most popular anticancer drugs is Irance (Palbociclib), which in conjunction with Letrozole provides a new treatment option for women diagnosed with metastatic breast cancer.[8] There are several drugs containing the 4,6-disubstituted 2-aminopyrimidine moiety including Minoxidil sulfate,[9] Aronixil,[10] Sulfadimidin,[11] Ibrance,[8] and Rosuvastatin[12] (Figure 1). The aminopyrimidine-containing drugs comprise the halogen atoms; halogenation of aminopyrimidines, such as chlorination,[13] bromination,[14] and iodonation,[15] has been consequently reported in recent decades. Furthermore, there are also some drugs containing fluorinated aminopyrimidine, for example, Fostamatinib disodium hydrate,[16] Abemaciclib mesylate,[17] and fluorinated Imatinib base.[18]

The synthetic methods for 5-fluorinated 2-aminopyrimidines are (i) the cyclization of trifluorinated allyl derivatives with guanidine[17] and (ii) the amination of 2-chloro-5-fluoropyrimidines with amines that requires strongly electron-deficient heteroarenes.[16] Notably, direct fluorination of 2-aminopyrimidines is rarely reported. More recently, we have developed a method for the synthesis of 4,6-disubstituted 2-aminopyrimidines.[19] In this paper, we report a direct

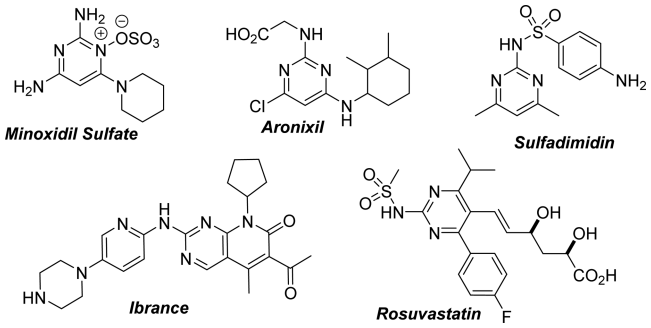


Figure 1. Several representative drugs bearing a 4,6-disubstituted 2-aminopyrimidine.

fluorination of 4,6-disubstituted 2-aminopyrimidines with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)[20] (Selectfluor) in the presence of silver carbonate, which gives 5-fluorinated 2-aminopyrimidines.

At the start, we carried out a fluorination of 4-benzyl-6-phenylpyrimidin-2-amine **1a** with Selectfluor **2a** in the presence of various transition-metal salts in acetonitrile (MeCN) at 70 °C (Table 1, entries 1−5). The formation of the fluorinated pyrimidine **3a** was observed when the silver salt was examined.[21] The molecular structure of **3a** was also supported by its X-ray analysis (see the Supporting Information).[22] Among these silver salts, Ag_2CO_3 gave a superior result (Table 1, entry 1), whereas both Ag_3PO_4 and AgF led to decreasing yields (entries 2 and 3). Either $Cu(OAc)_2$ or $Pd(OAc)_2$ was employed, and the fluorinated product was not detected (entries 4 and 5); no C−H fluorination product **3a′** was observed when $Pd(OAc)_2$ was applied.[23] The fluorination of the activated aromatic compounds with Selectfluor could give an *ortho*/*para* mixture

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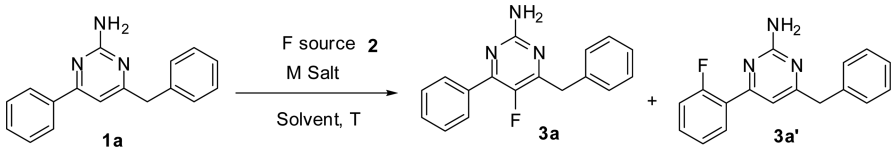
Table 1. Reaction Conditions for Fluorination of 1a[a]



entry	M salt	solvent	F source	temp (°C)	yield of **3a** (%)[b]
1	Ag_2CO_3	MeCN	Selectfluor	70	70 (50)
2	Ag_3PO_4	MeCN	Selectfluor	70	45
3	AgF	MeCN	Selectfluor	70	32
4	$Cu(OAc)_2$	MeCN	Selectfluor	70	NR
5	$Pd(OAc)_2$	MeCN	Selectfluor	70	NR
6		MeCN	Selectfluor	70	NR
7	Ag_2CO_3	DCE	Selectfluor	70	5
8	Ag_2CO_3	toluene	Selectfluor	70	10
9	Ag_2CO_3	dioxane	Selectfluor	70	trace
10	Ag_2CO_3	MeCN	Selectfluor	50	58
11	Ag_2CO_3	MeCN	Selectfluor	80	58
12	Ag_2CO_3	MeCN	Selectfluor	100	45
13	Ag_2CO_3	MeCN	Selectfluor	70	40[c]
14	K_2CO_3	MeCN	Selectfluor	70	complex
15	Ag_2CO_3	MeCN	NFSi	70	NR
16	Ag_2CO_3	MeCN	AgF_2	70	NR
17	Ag_2CO_3	MeCN	TBAF	70	NR

[a]Reaction conditions: transition-metal salt (0.2 mmol), **1a** (0.1 mmol), **2a** (0.12 mmol) in solvent (2 mL) at 50−100 °C for 3 h. [b]Determined by ^{19}F NMR of the crude product with trifluoromethylbenezene as an internal standard; isolated yield in parentheses. [c]1 h.

of the products.[20,24] However, no phenyl-fluorinated products[24] were observed in this case. It is noteworthy that the reaction in the absence of the silver salt did not occur (entry 6). These results suggest that Ag_2CO_3 is essential to this chemoselective fluorination. The examination of different solvents including MeCN, 1,2-dichloroethane (DCE), toluene, and dioxane revealed that MeCN is a suitable solvent; both toluene and DCE gave poor yields, and dioxane is not suitable for this fluorination (entries 1 and 7−9). Variation of the reaction temperature indicated that the reaction at 70 °C gave the best result, and the other temperatures of 50, 80, and 100 °C resulted in decreasing yields (entries 1 and 10−12). K_2CO_3 instead of Ag_2CO_3 was also explored in MeCN at 70 °C, and it gave small amount of complex products (entry 14). The fluorine reagents including Selectfluor **2a**, *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide (NFSI, **2b**), AgF_2 (**2c**),[25] and tetrabutylammonium fluoride (TBAF, **2d**) were also screened, and only Selectfluor **2a** was effective for this fluorination reaction (entries 1 and 14−16).

Having established the optimized reaction conditions shown in entry 1 of Table 1, we subsequently exploited the scope of 4,6-disubstituted 2-aminopyrimidines (**1a−j**) bearing diverse substituents at the C(4) and C(6) positions of the pyrimidine ring.

In the series of 4,6-disubstituted 2-aminopyrimidines (**1a−c**) prepared, those containing both an aryl at the C(4) and an aliphatic group at the C(6) position (e.g., **1a−c**) were obtained in moderate to good yield (Table 2). No phenyl-fluorinated products were observed, although they had the aliphatic group on the phenyl ring. These results disagree with those in the reported works.[20,24] 4,6-Diphenyl-2-aminopyrimidine (**1d**) and symmetrical 4,6-diaryl-substituted 2-aminopyrimidines (**1e−j**) bearing an electron-poor group (e.g., *p*-F, *p*-Cl, *p*-Br, and *m*-Cl) on the phenyl ring were obtained in a yield higher than that of their analogue (**1h**) containing an electron-rich group (e.g., CH_3) on the phenyl ring (Table 2). These results may indicate favorable fluorination with an electron-poor substituent at both C(4) and C(6) positions. 4,6-Di(thiophen-2-yl)-2-aminopyrimidine (**1j**) evidently worked well to afford **3j**[26] (Table 2). The heterocyclic compounds containing the 4,6-di(thiophen-2-yl)-2-aminopyrimidine moiety show their anti-HIV activity by inhibiting translation and interfering with the viral replication process.[27] It was found that a 2,6-dialiphatic substrate such as 4,6-dimethyl-2-aminopyrimidine (**1k**) failed to proceed with this fluorination reaction (Table 2).

A gram-scale fluorination of 4,6-substituted 2-aminopyrimidene such as **1d** (1.0 g, 4 mmol) with Selectfluor **2a** (1.6 g, 4.8 mmol) was performed under the optimal conditions. This reaction occurred smoothly, and **3d** (645 mg) was obtained with 60% yield (Scheme 1).

The introduction of a fluorine atom into drug molecules can enhance its lipophilicity and metabolic stability. According to the literature reports, it was concluded that sulfonamide derivatives showed anti-amoebic activity better than that of 4,6-disubstituted aminopyrimidines.[28] Therefore, the transformation of the fluorinated 2-aminopyrimidine **3d** into *N*-(4,6-diphenylpyrimidin-2-yl)-4-methylbenzenesulfonamide **4a** was also investigated (Scheme 1). The sulfonamidation of **3d** with 4-methylbenzene-1-sulfonyl chloride (TsCl) in pyridine at 80 °C gave the corresponding product **4a** in 60% yield (Scheme 1).[29]

Three controlled experiments were conducted under the optimized conditions: (1) *N*,*N*-dimethyl-4,6-diphenylpyrimidin-2-amine **1l** was examined, and no fluorinated product **3l** was obtained (eq-1 in Scheme 2); (2) the Ag(dppm)**1d**[30] complex (see the Supporting Information) was utilized, and it gave the corresponding product **3h** in a 24% yield (eq-2 in Scheme 2); and (3) TEMPO as a radical scavenger was applied, and no reaction was observed (eq-3 in Scheme 2).

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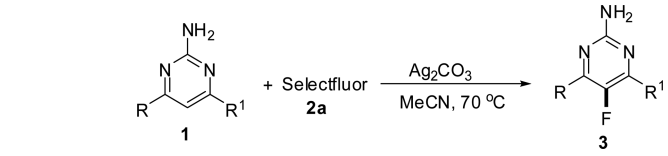
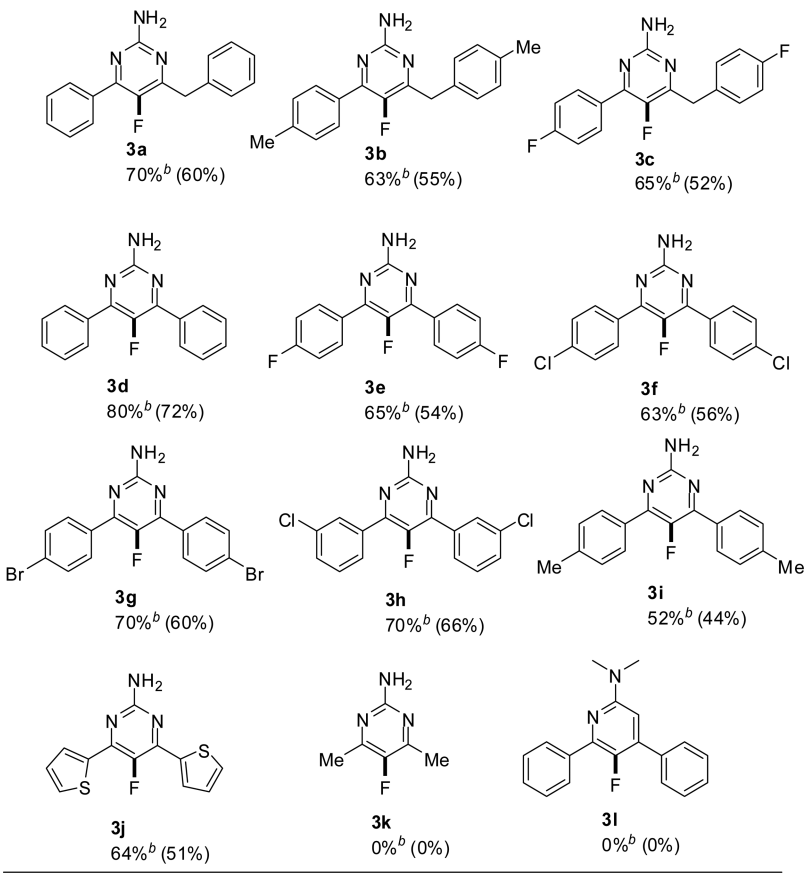
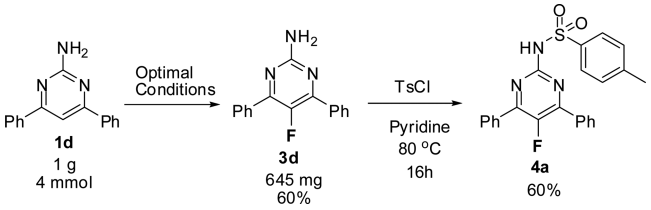
Table 2. Substrate Scope[a]



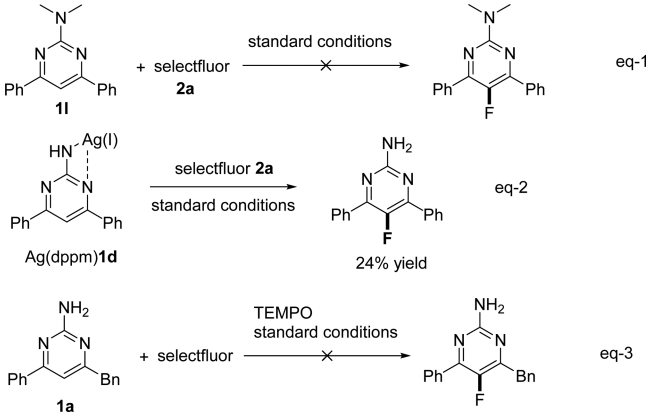


[a]Reactions were conducted at 0.1 mmol scale for 3 h. [b]^{19}F NMR yield with trifluoromethylbenzene as an internal standard. Isolated yield in parentheses.

Scheme 1. Gram-Scale Fluorination and Synthesis of 4a



Scheme 2. Three Controlled Experiments



On the basis of our observations, a possible mechanism is proposed in Scheme 3. The oxidation of ***Int* A**,[30] which is generated from a reaction of 2,4-disubstituted 2-aminopyrimidine **1** with Ag_2CO_3 in MeCN at 70 °C, with Selectfluor **2** produces ***Int* B**. Homolysis of ***Int* B** gives a radical of ***Int* C** along with the F−Ag(II) complex.[21] The radical of pyrimidin-2(5*H*)-imine ***Int* D**, a resonance tautomer of ***Int* C**, reacts with the F−Ag(II) species to afford the 5-fluoro-2-aminopyrimidine **3** and regenerates Ag(I).

In summary, we have developed a practical fluorination of 4,6-disubstituted 2-aminopyrimidines with Selectfluor in the presence of silver carbonate, which gives the 5-fluorinated 4,6-disubstituted 2-aminopyrimidine in fair to high yield. This method allows the use of unprotected aminopyrimidines, tolerates various aryl-substituted substrates, and provides a new way to synthesize 5-fluorinated 2-aminopyrimidines.

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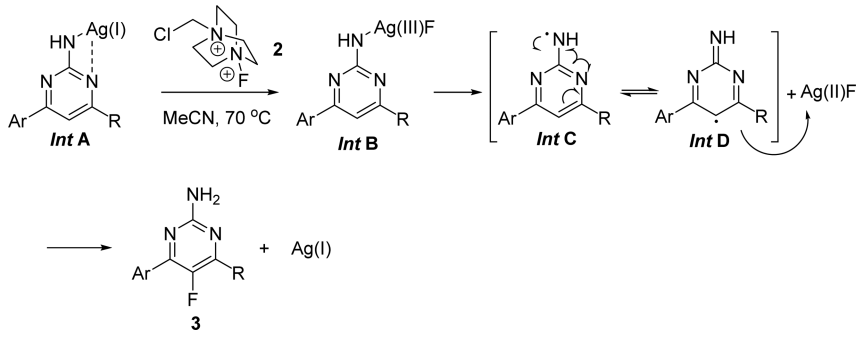
Scheme 3. Possible Mechanism for the Present Reaction



EXPERIMENTAL SECTION

General Information. All manipulations were carried out under air atmosphere using standard Schlenk techniques. All glassware was oven- or flame-dried immediately prior to use. All solvents were purified and dried according to standard methods prior to use, unless stated otherwise. All reagents were obtained from commercial sources, with most of them purchased from Adamas-beta and used without further purification; ^{1}H NMR spectra were obtained at 400 MHz and recorded relative to tetramethylsilane signal (0 ppm) or residual protio solvent. ^{13}C NMR spectra were obtained at 100 MHz, and chemical shifts were recorded relative to the solvent resonance ($CDCl_3$, 77.0 ppm; DMSO, 40.0). ^{19}F NMR spectra were obtained at 376 MHz with trifluoromethylbenezene as an internal standard. Infrared (IR) spectra were recorded on an IR spectrometer with KBr wafers or a film on a KBr plate. High-resolution mass spectra (HRMS) were recorded on a microTOF II mass spectrometer using electrospray ionization (ESI). Data collections for crystal structures were performed at room temperature (293 K) or 150 K using an X-ray single-crystal diffractometer (D8 VENTURE). Melting point temperatures were measured at a heating rate of 5 °C/min and are uncorrected. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad singlet, coupling constant(s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). The 4,6-disubstituted pyrimidin-2-amines were prepared according to the known procedures.[19]

General Procedure for the Synthesis of 3a–j. 4,6-Disubstituted pyrimidin-2-amine **1** (0.1 mmol), Selectfluor **2a** (42 mg, 0.12 mmol), and Ag_2CO_3 (55 mg, 0.2 mmol) were dissolved in MeCN (2.0 mL) in a sealed tube, and the reaction mixture was stirred at 70 °C for 3 h. After concentration of the filtrate to dryness and purification of the residue by silica gel column chromatography (petroleum ether/AcOEt = 60/10), the desired products **3a–j** were obtained.

*4-Benzyl-5-fluoro-6-phenylpyrimidin-2-amine (**3a**):* Canary yellow solid; mp 131–132 °C; 60% yield (16.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (2 H, s), 7.52 (3 H, s), 7.45–7.21 (5 H, m), 5.32 (2 H, s), 4.11 (2 H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.1 (d, J = 4.8 Hz), 158.5 (d, J = 17.9 Hz), 152.4 (d, J = 11.5 Hz), 150.0 (s), 147.6 (s), 137.2 (s), 133.7 (d, J = 4.8 Hz), 130.5 (s), 129.1 (s), 129.0 (d, J = 5.9 Hz), 128.6 (d, J = 16.6 Hz), 126.9 (s), 37.9 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −153.35; IR (KBr) ν_{max} (cm^{-1}) = 3438, 3318, 3191, 2923, 1575, 1391; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{15}FN_3$ 280.1245; found 280.1236.

*5-Fluoro-4-(4-methylbenzyl)-6-(p-tolyl)pyrimidin-2-amine (**3b**):* Yellow solid; mp 129–130 °C; 55% yield (16.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (d, J = 7.6 Hz, 2H), 7.29 (t, J = 7.3 Hz, 4H), 7.16 (d, J = 7.7 Hz, 2H), 5.13 (s, 2H), 4.04 (s, 2H), 2.44 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 158.9 (d, J = 4.8 Hz), 158.5 (d, J = 17.9 Hz), 152.3 (d, J = 11.3 Hz), 150.0 (s), 147.6 (s), 140.8 (s), 136.4 (s), 134.2 (s), 130.9 (d, J = 4.9 Hz), 129.4 (s), 129.3 (s), 129.0 (s), 128.9 (s), 37.5 (s), 21.4 (d, J = 41.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −153.14; IR (KBr) ν_{max} (cm^{-1}) = 3499, 3319, 3193, 2923, 1577, 1390; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{19}H_{18}FN_3Na$ 330.1377; found 330.1368.

*5-Fluoro-4-(4-fluorobenzyl)-6-(4-fluorophenyl)pyrimidin-2-amine (**3c**):* Yellow solid; mp 128–129 °C; 52% yield (17.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 7.9, 5.6 Hz, 2H), 7.30 (dd, J = 8.4, 5.5 Hz, 2H), 7.14 (t, J = 8.7 Hz, 2H), 6.99 (t, J = 8.7 Hz, 2H), 5.04 (s, 2H), 4.01 (d, J = 2.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 164.2 (d, J = 251.4 Hz), 161.8 (d, J = 245.1 Hz), 158.9 (d, J = 4.7 Hz), 158.4 (d, J = 17.9 Hz), 151.2 (d, J = 11.1 Hz), 148.7 (d, J = 250.8 Hz), 132.7 (d, J = 3.2 Hz), 131.2 (dd, J = 8.6, 6.8 Hz), 130.6 (d, J = 7.9 Hz), 130.1–129.5 (m), 115.6 (d, J = 21.7 Hz), 115.5 (d, J = 21.3 Hz), 37.0 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −109.39 (s), −116.03 (s), −153.33 (s); IR (KBr) ν_{max} (cm^{-1}) = 3495, 3327, 3190, 2926, 1578, 1391; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{12}F_3N_3$ 338.0876; found 338.0868.

*5-Fluoro-4,6-diphenylpyrimidin-2-amine (**3d**):* Yellow solid; mp 123–124 °C; 72% yield (19.2 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12–7.92 (m, 4H), 7.64–7.43 (m, 6H), 5.25 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.2 (d, J = 4.8 Hz), 154.2 (d, J = 13.1 Hz), 148.5 (d, J = 254.2 Hz), 134.0 (d, J = 4.4 Hz), 130.5 (s), 129.2 (d, J = 5.8 Hz), 128.6 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −152.24 (s); IR (KBr) ν_{max} (cm^{-1}) = 3494, 3318, 3200, 2925, 1583, 1387; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{13}FN_3$ 266.1088; found 266.1081.

*5-Fluoro-4,6-bis(4-fluorophenyl)pyrimidin-2-amine (**3e**):* White solid; mp 129–130 °C; 54% yield (16.3 mg); ^{1}H NMR (400 MHz, DMSO) δ = 8.03 (dd, J = 7.6, 5.6 Hz, 4H), 7.39 (t, J = 8.9 Hz, 4H), 6.80 (s, 2H); ^{13}C NMR (101 MHz, DMSO) δ = 163.8 (d, J = 248.4 Hz), 160.2 (s), 152.6 (d, J = 12.2 Hz), 147.5 (d, J = 257.6 Hz), 131.8 (dd, J = 8.7, 6.1 Hz), 130.7 (s), 116.0 (d, J = 21.7 Hz); ^{19}F NMR (377 MHz, DMSO) δ = −110.19 (s), −155.27 (s); IR (KBr) ν_{max} (cm^{-1}) = 3439, 3340, 3215, 2921, 1599, 1388; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{11}F_3N_3$ 302.0900; found 302.0873.

*4,6-Bis(4-chlorophenyl)-5-fluoropyrimidin-2-amine (**3f**):* Yellow solid; mp 237–238 °C; 56% yield (18.7 mg); ^{1}H NMR (400 MHz, DMSO) δ = 7.97 (d, J = 7.7 Hz, 4H), 7.61 (d, J = 8.6 Hz, 4H), 6.85 (s, 2H); ^{13}C NMR (101 MHz, DMSO) δ = 160.3 (d, J = 4.6 Hz), 152.5 (d, J = 12.3 Hz), 147.6 (d, J = 249.9 Hz), 135.8 (s), 133.0 (d, J = 4.5 Hz), 131.1 (d, J = 6.1 Hz), 129.1 (s); ^{19}F NMR (377 MHz, DMSO) δ = −154.59 (s); IR (KBr) ν_{max} (cm^{-1}) = 3442, 3347, 3050, 2923, 1595, 1361; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{11}Cl_2FN_3$ 334.0309; found 334.0336.

*4,6-Bis(4-bromophenyl)-5-fluoropyrimidin-2-amine (**3g**):* White solid; mp 143–144 °C; 60% yield (25.2 mg); ^{1}H NMR (400 MHz, DMSO) δ = 7.89 (d, J = 7.6 Hz, 4H), 7.75 (d, J = 8.6 Hz, 4H), 6.85 (s, 2H); ^{13}C NMR (101 MHz, DMSO) δ = 160.3 (d, J = 4.9 Hz), 152.6 (d, J = 12.3 Hz), 147.6 (d, J = 255.7 Hz), 133.4 (d, J = 4.9 Hz), 132.0 (s), 131.3 (d, J = 6.4 Hz), 124.7 (s); ^{19}F NMR (377 MHz, DMSO) δ = −154.50 (s); IR (KBr) ν_{max} (cm^{-1}) = 3439, 3327, 3194, 2921, 1563, 1383; IR (KBr) ν_{max} (cm^{-1}) = 3439, 3327, 3194, 2921, 1563, 1383; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{11}Br_2FN_3$ 421.9298; found 421.9271

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*4,6-Bis(3-chlorophenyl)-5-fluoropyrimidin-2-amine (**3h**):* White solid; mp 167−168 °C; 66% yield (21.9 mg); ^{1}H NMR (400 MHz, DMSO) δ = 7.99 (s, 2H), 7.92 (dd, J = 7.5, 1.3 Hz, 2H), 7.65−7.53 (m, 4H), 6.92 (s, 2H); ^{13}C NMR (101 MHz, DMSO) δ = 160.0 (d, J = 4.5 Hz), 152.0 (d, J = 12.2 Hz), 147.4 (d, J = 253.2 Hz), 135.9 (d, J = 4.5 Hz), 133.5 (s), 130.7 (s), 130.5 (s), 128.6 (d, J = 5.2 Hz), 127.8 (d, J = 6.9 Hz); ^{19}F NMR (377 MHz, DMSO) δ = −154.59 (s); IR (KBr) ν_{max} (cm^{-1}) = 3524, 3327, 3203, 2924, 1565, 1382; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{11}Cl_2FN_3$ 334.0309; found 334.0282.

*5-Fluoro-4,6-di-p-tolylpyrimidin-2-amine (**3i**):* Yellow solid; mp 136−137 °C; 44% yield (13.7 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, J = 7.0 Hz, 4H), 7.30 (d, J = 8.0 Hz, 4H), 5.28 (s, 2H), 2.43 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.1 (d, J = 4.8 Hz), 154.0 (d, J = 13.1 Hz), 148.5 (d, J = 253.8 Hz), 140.7 (s), 131.3 (d, J = 4.5 Hz), 129.3 (s), 129.1 (d, J = 6.1 Hz), 21.5 (s); ^{19}F NMR (377 MHz, $CDCl_3$) δ = −152.26 (dd, J = 6.7, 2.6 Hz); IR (KBr) ν_{max} (cm^{-1}) = 3498, 3317, 3198, 2922, 1581, 1388; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{18}H_{16}FN_3Na$ 316.1220; found 316.1202.

*5-Fluoro-4,6-di(naphthalen-2-yl)pyrimidin-2-amine (**3j**):* Brown solid; mp 168−169 °C; 51% yield (14.0 mg); ^{1}H NMR (400 MHz, DMSO) δ = 7.90 (ddd, J = 9.1, 5.2, 3.1 Hz, 4H), 7.29 (dd, J = 5.0, 3.8 Hz, 2H), 6.74 (s, 2H); ^{13}C NMR (101 MHz, DMSO) δ = 159.6 (d, J = 3.8 Hz, 1H), 147.5 (d, J = 11.9 Hz, 1H), 144.3 (d, J = 255.0 Hz, 1H), 138.2 (d, J = 6.7 Hz, 1H), 131.5 (d, J = 2.9 Hz, 3H), 131.3 (d, J = 12.9 Hz, 3H), 129.4 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −147.61 (s); IR (KBr) ν_{max} (cm^{-1}) = 3443, 3350, 3076, 2925, 1569, 1383; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_9FN_3S_2$ 278.0216; found 278.0245.

General Procedure for the Synthesis of 4a. *p*-Toluenesulfonyl chloride (0.3 mmol) in pyridine (1.0 mL) was slowly added to the mixture of **3d** (0.1 mmol) in pyridine (1.0 mL). The mixture was heated at 80 °C for 16 h and then was poured into H_2O and AcOEt. After extraction and concentration of the filtrate to dryness and purification of the residue by silica gel column chromatography (petroleum ether/AcOEt = 40/10), the desired product **4a** was obtained.

*N-(5-Fluoro-4,6-diphenylpyrimidin-2-yl)-4-methylbenzenesulfonamide (**4a**):* Yellow solid; mp 192−193 °C; 60% yield (25.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 (dd, J = 18.3, 7.9 Hz, 6H), 7.55 (d, J = 7.2 Hz, 6H), 7.30 (d, J = 6.2 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ = 154.0 (d, J = 13.0 Hz), 152.8 (d, J = 5.2 Hz), 150.3 (d, J = 261.2 Hz), 144.0 (s), 138.1 (s), 133.2 (d, J = 4.5 Hz), 129.8 (s), 129.6 (d, J = 6.0 Hz), 129.1 (s), 128.5 (d, J = 145.9 Hz), 128.0 (s), 21.5 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ = −144.71 (s); IR (KBr) ν_{max} (cm^{-1}) = 3054, 1545, 1030; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{19}FN_3O_2S$ 420.1177; found 420.1165.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02624.

X-ray data for **3a** (CIF)
X-ray data for **3j**(CIF)
X-ray data for Ag(dppm)**1d** (CIF)
^{1}H, ^{13}C, and ^{19}F NMR spectra for all isolated products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, Germany, 2013. (b) Grushin, V. *Acc. Chem. Res.* **2010**, *43*, 160−171. (c) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308−319. (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (e) Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 803−819. (f) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881−1886.

(2) (a) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160−171. (b) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 15−24.

(3) (a) Wang, J.; Sanchez-Roselló, M. S.; Aceña, J. L.; Del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432−2506. (b) Bohm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637−643. (c) Kirk, K. L. *Curr. Top. Med. Chem.* **2006**, *6*, 1447−1456. (d) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359−4369. (e) Bégué, J. P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992−1012. (f) Ismail, F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27−33. (g) Fried, J.; Sabo, E. F. *J. Am. Chem. Soc.* **1954**, *76*, 1455−1456. (h) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305−321.

(4) Jeschke, P. *ChemBioChem* **2004**, *5*, 570−589.

(5) (a) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. *Chem. Commun.* **2007**, 1003−1022. (b) Cametti, M.; Crousse, B.; Metrangolo, P.; Milani, R.; Resnati, G. *Chem. Soc. Rev.* **2012**, *41*, 31−42. (c) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.* **2011**, *40*, 3496−3508. (d) Dhara, M. G.; Banerjee, S. *Prog. Polym. Sci.* **2010**, *35*, 1022−1077. (e) Li, Y. F. *Acc. Chem. Res.* **2012**, *45*, 723−733.

(6) (a) Ametamey, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501−1506. (b) Cai, L.; Lu, S.; Pike, V. W. *Eur. J. Org. Chem.* **2008**, *2008*, 2841. (c) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8998−9033. (d) Littich, R.; Scott, P. J. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1106−1109.

(7) Zhang, W.; Bonnet, P.; Dubois, M.; Ewels, C. P.; Guérin, K.; Petit, E.; Mevellec, J.-Y. M.; Vidal, L.; Ivanov, D. A.; Hamwi, A. *Chem. Mater.* **2012**, *24*, 1744−1751.

(8) Roskoski, R. *Pharmacol. Res.* **2016**, *107*, 249−275.

(9) Johnson, G. A.; Barauhn, K. J.; Mccall, J. M. *Drug Metab. Dispos.* **1983**, *11*, 507−508.

(10) Piero, G.; Carlo, S.; Cesare, S. Eur. Patent Appl. EP73328A119830309, 1983.

(11) Herrera-Herrera, A. V.; Hernández-Borges, J.; Afonso, M. M.; Palenzuela, J. A.; Rodríguez-Delgado, M. A. *Talanta* **2013**, *116*, 695−703.

(12) Watanabe, M.; Koike, H.; Ishiba, T.; Okada, T.; Seo, S.; Hirai, K. *Bioorg. Med. Chem.* **1997**, *5*, 437−444.

(13) Lu, Z. H.; Li, Q. W.; Tang, M. H.; Jiang, P. P.; Zheng, H.; Yang, X. J. *Chem. Commun.* **2015**, *51*, 14852−14855.

(14) Hanthorn, J. J.; Valgimigli, L.; Pratt, D. A. *J. Org. Chem.* **2012**, *77*, 6908−6816.

(15) Nara, S. J.; Jha, M.; Brinkhorst, J.; Zemanek, T. J.; Pratt, D. A. *J. Org. Chem.* **2008**, *73*, 9326−9333.

(16) (a) Colonna, L.; Catalano, G.; Chew, C.; D'Agati, V.; Thomas, J. W.; Wong, F. S.; Schmitz, J.; Masuda, E. S.; Reizis, B.; Tarakhovsky, A.; Clynes, R. *J. Immunol.* **2010**, *185*, 1532−1543. (b) Padilla, F.; Bhagirath, N.; Chen, S.; Chiao, E.; Goldstein, D. M.; Hermann, J. C.; Hsu, J.; Kennedy-Smith, J. J.; Kuglstatter, A.; Liao,

DOI: 10.1021/acs.joc.6b02624
J. Org. Chem. 2017, 82, 1260−1265

C.; Liu, W.; Lowrie, L. E.; Luk, K. C.; Lynch, S. M.; Menke, J.; Niu, L.; Owens, T. D.; O-Yang, C.; Railkar, A.; Schoenfeld, R. C.; Slade, M.; Steiner, S.; Tan, Y. C.; Villasenor, A. G.; Wang, C.; Wanner, J.; Xie, W.; Xu, D.; Zhang, X.; Zhou, M.; Lucas, M. C. *J. Med. Chem.* **2013**, *56*, 1677−1692. (c) Berger, J. U.S. Patent 5952331, 1999.

(17) (a) Frederick, M. O.; Kjell, D. P. *Tetrahedron Lett.* **2015**, *56*, 949−951. (b) Funabiki, K.; Ohtsuki, T.; Ishihara, T.; Yamanaka, H. *Chem. Lett.* **1995**, *24*, 239−240.

(18) Liu, Y. F.; Wang, C. L.; Bai, Y. J.; Han, N.; Jiao, J. P.; Qi, X. L. *Org. Process Res. Dev.* **2008**, *12*, 490−495.

(19) Zhang, L.; Zhao, M. Z.; Zhao, X. M. *Chem. Commun.* **2015**, *51*, 9370−9373.

(20) SelectFluor as a fluorine agent was reported. See: (a) Banks, R. E.; Mohialdin-Khaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, 595−596. (b) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192−212. (c) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31−44.

(21) (a) Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662−1663. (b) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150−12154. (c) Dubbaka, S. R.; Narreddula, V. R.; Gadde, S.; Mathew, T. *Tetrahedron* **2014**, *70*, 9676−9681. (d) Zhao, H. J.; Fan, X. F.; Yu, J. J.; Zhu, C. *J. Am. Chem. Soc.* **2015**, *137*, 3490−3493.

(22) CCDC-1504983, **3a**, contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(23) Pd-catalyzed C−H fluorination of arenes with N-coordinating directing groups such as 2-phenylpyridine was reported. See: Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134−7135.

(24) (a) Lal, G. S. *J. Org. Chem.* **1993**, *58*, 2791−2796. (b) Zupan, M.; Iskra, J.; Stavber, S. *J. Fluorine Chem.* **1995**, *70*, 7−8. (c) Zupan, M.; Iskra, J.; Stavber, S. *Tetrahedron* **1996**, *52*, 11341−11348.

(25) AgF_2 was used as a fluorine source. See: Subramanian, M. A.; Manzer, L. E. *Science* **2002**, *297*, 1665.

(26) CCDC-1504984, **3j**, contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(27) (a) Schinazi, R. F.; Strekowski, L. PCT Int. Appl. WO1989011279 A1, 1989. (b) Mokrosz, M. J.; Strekowski, L.; Kozak, W. X.; Duszynska, B.; Bojarski, A. J.; et al. *Arch. Pharm. (Weinheim, Ger.)* **1995**, *328*, 659−666.

(28) Siddiqui, S. M.; Azam, A. *Med. Chem. Res.* **2014**, *23*, 2976−2984.

(29) (a) Roouf Bhat, A. R.; Arshad, M.; Lee, E. J.; Pokharel, S.; Choi, I.; Athar, F. *Chem. Biodiversity* **2013**, *10*, 2267−2277. (b) Acero-Alarcón, A.; Armero-Alarte, T.; Jorda-Gregori, J. M.; Rojas-Argudo, C.; Zaballos-García, E.; Server-Carrió, J.; Ahjyaje, F. Z.; Sepulveda-Arques, J. *Synthesis* **1999**, *1999*, 2124−2130.

(30) CCDC-1521003, Ag(dppm)**1d**, contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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