Chemoselective Reactions of 4,6-Dichloro-2-(methylsulfonyl)pyrimidine and Related Electrophiles with Amines

Ramil Baiazitov, Wu Du, Chang-Sun Lee, Seongwoo Hwang, Neil G. Almstead, Young-Choon Moon*

PTC Therapeutics, Inc., 100 Corporate Ct, South Plainfield, NJ 07080, USA
Fax +1(908)2220567; E-mail: ymoon@ptcbio.com

Received: 30.03.2013; Accepted: 15.04.2013

Dedicated to Prof. Scott E. Denmark on the occasion of his 60th birthday

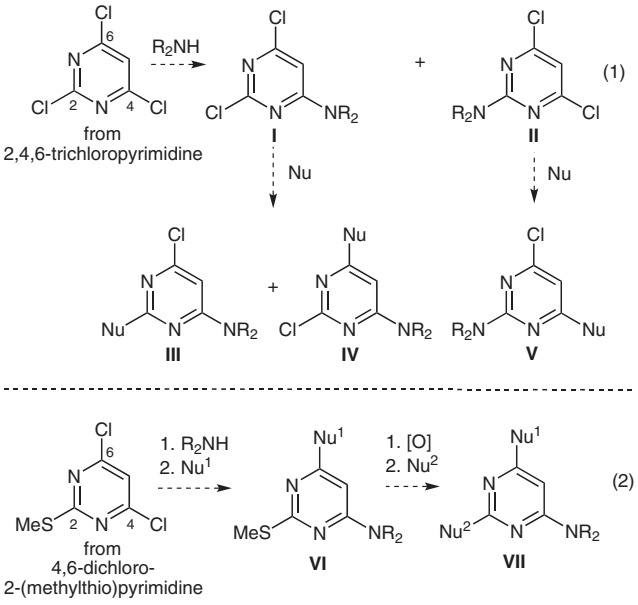
Abstract: Chemoselective S_{NAr} reactions of 4,6-dichloro-2-(methylsulfonyl)pyrimidine and several related electrophiles with amines and their derivatives are described. In the presence of weak bases anilines and secondary aliphatic amines selectively displace the chloride group. Deprotonated anilines and their carbonyl derivatives displace the sulfone group. Sterically and electronically unbiased primary aliphatic amines selectively displace the sulfone group in 4,6-dichloro-2-(methylsulfonyl)pyrimidine; however, their reactions with other electrophiles generally are less selective. Steric-driven selectivity explanation was proposed.

Key words: pyrimidine, sulfone, chloride, heterocycles, chemoselectivity

Aminopyrimidines are privileged structures for drug discovery and have received much attention as highlighted by the FDA approved anti-HIV drugs Rilpivirine[1a] and Etravirine,[1b] and the anticancer drug Pazopanib.[2] Compounds from these scaffolds have shown diverse bioactivity. For example, they were recently reported to be inhibitors of various kinases,[3] GalR2 ligands,[4] antimalarial agents,[5] γ-secrerase modulators,[6] CRF1 receptor antagonists,[7] and anti-HIV agents.[8]

Recently we were interested in the preparation of a series of 2,4,6-trisubstututed aminopyrimidines. A literature review revealed that there are two principal methods for the preparation of such compounds as shown in Scheme 1. The first method involves the sequential substitution of the chlorine atoms of 2,4,6-trichloropyrimidine with amines or other nucleophiles [Scheme 1, (1)]. This electrophile, while inexpensive, suffers from poor selectivity in its reaction with nucleophiles.[9] Moreover, separation and identification of isomers **I** and **II** may be difficult. Further selective functionalization of **I** to form either **III** or **IV** may be similarly complicated.

Alternatively, 4,6-dichloro-2-(methylthio)pyrimidine has been used to prepare polysubstituted pyrimidines through nucleophilic substitution of one or both chlorine atoms, followed by oxidation of the 2-sulfane to form a 2-sulfone, which can then undergo a substitution reaction at C2 [Scheme 1 (2)].[10] Although this method does not have selectivity issues with regard to the site of the nucleophilic substitution, the need for oxidation of the 2-sulfane introduces an extra step that may not be compatible with sensitive substrates.



Scheme 1 Typical methods for preparation of aminopyrimidines

The reactions of commercially available 4,6-dichloro-2-(methylsulfonyl)pyrimidine (**1**) have been much less explored than the comparative reactions with 2,4,6-trichloropyrimidine.[11] There are only a few examples of the reactions of **1** with various nucleophiles. For example, alkoxides,[12] thiolates,[13] Grignard reagents,[14] aziridine,[11] and methylamine,[15] as well as deprotonated N(H)-heterocycles[16] and a formamide,[17] react selectively with **1** at C2. In contrast, there is only one report of a selective, albeit low yielding, displacement of the chloride group at C4 of **1**, using heteroaromatic amines.[18] Herein, we disclose our findings that **1** can serve as a common starting material to selectively provide either C2- or C4-displacement products by applying different reaction conditions. The course of the reaction can be readily monitored by LC-MS, and the isolation of the desired products is facile. This finding leads to the efficient and divergent syntheses of polysubstituted 2- and 4-aminopyrimidines.

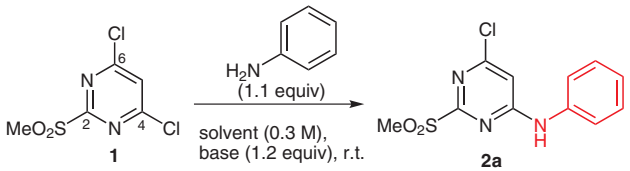
SYNTHESIS 2013, 45, 1764–1784
Advanced online publication: 11.06.2013
DOI: 10.1055/s-0033-1338853; Art ID: SS-2013-C0253-OP

Chemoselective Displacement of Chloride in 1 with Anilines in the Presence of Weak Base

We determined that aniline selectively displaced the chloride at C4 from **1** (Table 1). For example, in acetonitrile when sodium hydrogen carbonate was used as the base, the isolated yield of **2a** was 95% after 48 hours (entry 1). In the presence of stronger bases, such as potassium carbonate (entry 2) or Hünig's base (entry 3), the electrophile was consumed within five to eight hours; however, the yield was lower due to byproduct formation.[19] The use of pyridine led to rapid and extensive decomposition (entry 4);[20] we could not identify or isolate the byproducts.

The non-nucleophilic and mild base 2,6-lutidine, on the other hand, served as an excellent acid scavenger (entry 5). Alternative solvents, such as tetrahydrofuran, *N*,*N*-dimethylformamide, or dimethyl sulfoxide (entries 6–8), led to an equally high yield of product **2a**. The reaction proceeded most efficiently in dimethyl sulfoxide (entry 8). An extra equivalent of inexpensive aniline can serve as an equally competent acid scavenger (entry 9).

Table 1 Selective Substitution at C4 with Aniline: Solvent and Base Screening



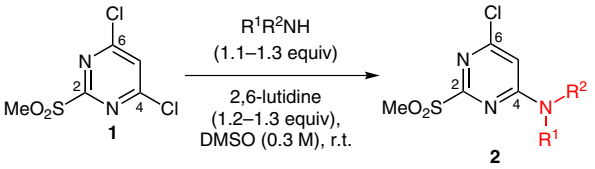
Entry	Solvent	Base	Time (h)	Yield[a] (%) of **2a**
1	MeCN	$NaHCO_3$	48	95
2	MeCN	K_2CO_3	5	59
3	MeCN	*i*-Pr_2NEt	8	67
4	MeCN	pyridine	2	15
5	MeCN	2,6-lutidine	8	95
6	THF	2,6-lutidine	6	96
7	DMF	2,6-lutidine	2	98
8	DMSO	2,6-lutidine	1	97
9	DMSO	$PhNH_2$	0.25	99

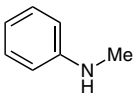
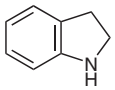
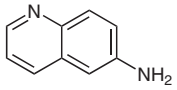
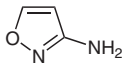
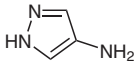
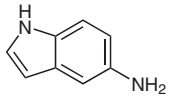
[a] Isolated yield.

These initial screening experiments identified dimethyl sulfoxide and 2,6-lutidine (Table 1, entry 8) as the optimal combination of solvent and base that provided the shortest reaction time and a high yield. For consistency, these conditions were also used to study the reaction scope. As data in Table 2 show, this reaction is quite general. Reactions with sterically hindered 2-substituted anilines (entries 2 and 3) were much slower, but they still provided the product in high to excellent yields. Both electron-rich (entry 4) and electron-poor (entries 5 and 6) 3-substituted anilines produced **2** in high yield. As expected, in the latter case the reaction was slower. The same trend was observed for both electron-rich (entries 7 and 8) and electron-poor (entries 9–11) 4-substituted anilines. The reaction with sterically hindered 2,6-dimethylaniline was slow but high-yielding (entry 12). *N*-Alkylanilines also demonstrated high selectivity for reaction at C4 (entries 13 and 14).

Several heteroaromatic amines were employed and these amines cleanly displaced the chloride in **1** (entries 15–

Table 2 Chemoselective Substitution of C4–Cl in **1** with Anilines



Entry	R^1R^2NH	Time (h)	Product	Yield[a] (%)
1	$PhNH_2$	1	**2a**	95
2	2-$MeC_6H_4NH_2$	15	**2b**	95
3	2-$ClC_6H_4NH_2$	36	**2c**	82
4	3-$MeC_6H_4NH_2$	1	**2d**	98
5	3-$ClC_6H_4NH_2$	2	**2e**	94
6	3-$O_2NC_6H_4NH_2$	6	**2f**	97
7	4-$MeC_6H_4NH_2$	1	**2g**	96
8	4-$MeOC_6H_4NH_2$	0.5	**2h**	99
9	4-$ClC_6H_4NH_2$	3	**2i**	94
10	4-$MeO_2CC_6H_4NH_2$	20	**2j**	91
11	4-$NCC_6H_4NH_2$	48	**2k**	92
12	2,6-$Me_2C_6H_3NH_2$	20	**2l**	95
13		1	**2m**	98
14		1	**2n**	98
15		0.5	**2o**	93
16		2	**2p**	90
17		0.2	**2q**	99
18[b]		1	**2r**	98

[a] Isolated yield.
[b] **1** (1 mmol), 1*H*-indol-5-amine (1 mmol), $NaHCO_3$ (1.5 equiv), DMF), r.t., 1 h.

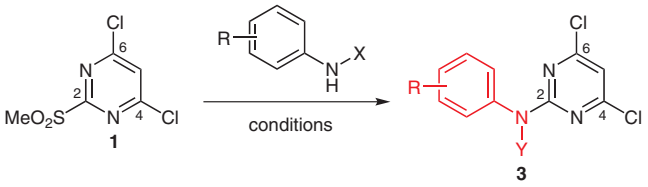
18).[21] ^{1}H NMR spectra of products **2o–r** show broad signals of rotamers, which makes NMR analysis less useful for identification of these compounds. For the product **2q** (entry 17) the existence of rotamers was confirmed by the collapse of the ^{1}H NMR signals upon heating to 350 K in DMSO-d_6.[22] Although the structure of product **2r** (entry 18) could not be unambiguously established by NMR spectroscopy, we believe that reaction of the 5-aminoindole with **1** proceeded via its NH_2 group and not the indole NH, because indole itself did not react with **1** at these conditions (data not shown).[23]

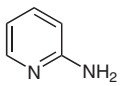
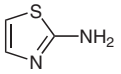
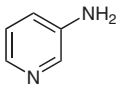
Although the reactions with anilines and some heteroaromatic amines were clean and followed the same general trends, we were surprised to determine that the reactions with many aromatic heterocyclic amines proceeded quite different. For example, the reaction of amines such as pyrazole, 3,5-dimethylpyrazole, 2-aminopyridine, 2-aminothiazole, and 5-aminobenzimidazole proceeded unselectively, displacing both the chloride and the sulfone, as well as forming bis-substituted and other unidentified byproducts.[24] Reaction of the 5-aminopyrimidine and 3-aminopyridine proceeded selectively with the chloride at the early stages of the reaction (according to LC-MS analysis of the reaction mixtures). However, the reactions were slow, and multiple byproducts were formed at completion. Some amines react not only unselectively but also very slowly (such as indole).[23] Additionally, LC-MS analysis of the reaction mixtures suggested that the released sulfinate byproduct often was also capable of reaction with **1**, leading to the formation of additional byproducts through a process described previously.[36b]

Chemoselective Displacement of Sulfone in 1 with Anionic Nucleophiles

As demonstrated above, in the presence of a weak base anilines and some heteroaromatic amines attack **1** at C4 with selective displacement of the chloride moiety (Table 2). This reactivity trend was unexpected, because previously **1** was mainly used to provide the C2-sulfone displacement products.[25] Because many of these examples[25] involve anionic nucleophiles, we reasoned that upon changing the nature of the nucleophile from a neutral aniline to its deprotonated form, the reaction selectivity may be reversed. Indeed, we found that aniline deprotonation completely changed the selectivity, leading to exclusive reaction at C2 with displacement of methylsulfone and the formation of product **3a** (Table 3, entry 1). The reaction with sterically and electronically deactivated 2-chloroaniline had been slow in the presence of 2,6-lutidine (Table 2, entry 3); however, a sodium hexamethyldisilazanide[26] promoted reaction was fast and high yielding (Table 3, entry 2). The yield was equally high with both electron-poor (entry 3) and electron-rich (entry 4) 4-substituted anilines. Product **3e** (entry 5) was isolated in lower yield. This could be a result of the decreased acidity of *p*-anisidine due to the strongly electron-donating nature of the 4-OMe group. In the absence of a sufficient concentration of deprotonated aniline, side reactions take place instead.[27]

Table 3 Chemoselective Substitution of C2–SO_2Me in **1** with Anionic Nucleophiles



Entry	R or amine	X	Y	Product	Yield[a,b] (%)
1[c]	H	H	H	**3a**	79
2[c]	2-Cl	H	H	**3b**	76
3[c]	4-Cl	H	H	**3c**	84
4[c]	4-Me	H	H	**3d**	85
5[c]	4-OMe	H	H	**3e**	67
6[d]	H	CHO	H	**3a**	93
7[d]	2-OMe	CHO	H	**3f**	75
8[d]	3-OMe	CHO	H	**3g**	78
9[d]	4-OMe	CHO	H	**3e**	91
10[d]	4-Cl	CHO	H	**3c**	85
11[e]	2-Br	Boc	Boc	**3h**	87
12[e]	3-Br	Boc	Boc	**3i**	75
13[e]	4-Cl	Boc	Boc	**3j**	95
14[c]		H	H	**3k**	84
15[c]		H	H	**3l**	75[f]
16[c]		H	H	**3m**	38

[a] Isolated yield.
[b] Reactions were not optimized.
[c] NaHMDS, THF, –70 °C, 15–30 min.
[d] 1. NaO*t*-Am, THF, 0 °C–r.t., 30 min; 2. aq NaOH.
[e] NaH, DMF–THF, –60 °C–0 °C, 1–2 h.
[f] Impure, contains ~10% of the bis-adduct $[M + H]^+$ 395.[30]

As a potentially milder variant of this process, reactions of **1** with formamides in the presence of sodium *tert*-amylate provided the same C2-displacement products (entries 6–10).[28] The intermediate formamide products (**3**, Y = CHO) were partially hydrolyzed during the reactions. This hydrolysis could be completed by treatment with aqueous sodium hydroxide to form the corresponding amines **3a**,**c**,**e–g**. The yields of the process were high and independent of the steric or electronic properties of the nucleophile. Products of the C4-chloride displacement of **1** were

not observed under these reaction conditions. Instead of the amide-protected anilines, Boc-protected anilines can be used (entries 11–13).[29] The products **3h–j** were stable and isolated unchanged. Several deprotonated heteroaromatic amines displaced the sulfone selectively. For example, the reaction with 2-aminopyridine provided product **3k** in 84% isolated yield (entry 14). The reaction with 2-aminothiazole proceeded, but was complicated by further arylation of the product **3l** with **1** and its poor solubility, which prevented its isolation (entry 15).[30] Even though the reaction with 3-aminopyridine was clean according to LC-MS analysis of the reaction mixture, the product **3m** was isolated in only 38% yield, perhaps due to its instability (entry 16).[31]

Selective Displacement of Sulfone in 1 with Primary Aliphatic Amines and Selective Displacement of Chloride in 1 with Secondary Aliphatic Amines

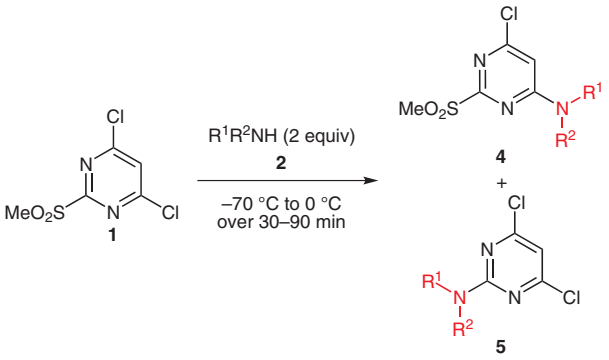
Next, we examined the selectivity of the reaction between **1** and various aliphatic amines (Table 4). Because most aliphatic amines are more reactive than anilines, the reactants were mixed at –70 °C, followed by slow warming to ~0 °C over one to two hours. However, data shown in entry 4 suggests that use of low temperature may be unnecessary and ambient temperature may be acceptable. Reactions with some substrates at –70 °C were too slow and required higher (ambient) temperature (entries 8–11). An extra equivalent of the amine was used as the external base for all of these reactions.

Interestingly, unlike the similar reactions with anilines (Table 2), the chemoselectivity of the reactions with aliphatic amines depended upon the nature of the amine. Thus, the reaction of several primary aliphatic amines with **1** proceeded highly selectively at C2, with the formation of products **5a–d** (entries 1–4).[32] In contrast, several secondary aliphatic amines preferentially displaced the chloride at C4, forming products **4e–g** (entries 5–7). The less sterically hindered piperidine was less selective in displacing the C4–Cl (69% vs. 29%, entry 7) compared to highly selective diethylamine (entry 6) or *N*-methylethylamine (entry 5). The sterically hindered primary amines *tert*-butylamine and 1-adamantylamine did not displace the sulfone as selectively as ethylamine (**5**/**4** ~2:1, entries 8 and 9 vs. entry 1). It appears that the steric interactions between **1** and the amine nucleophile are important in determining the reaction selectivity.

We also demonstrated that the electronic properties of the amine affect the selectivity. For example, replacement of the methyl group in ethylamine with an inductively electron-withdrawing difluoromethyl or trifluoromethyl group provides less basic[33] and less nucleophilic[34] amines, which were also combined with **1** (entries 10 and 11). Whereas ethylamine displaced the sulfone group very selectively (entry 1), the less electron-rich 2,2-difluoroethylamine was less discriminating (entry 10). The even less electron-rich 2,2,2-trifluoroethylamine did not displace the sulfone at all, but it did displace the chloride instead, albeit slowly (entry 11).

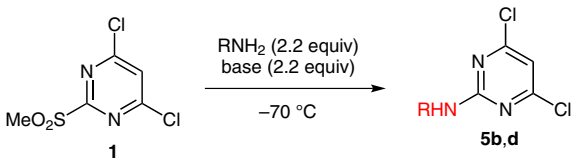
Attempted reactions between deprotonated secondary aliphatic amines and **1** were unsuccessful, and mixtures of multiple products were formed instead as judged by LC-MS analysis.[35] However, deprotonated primary aliphatic amines did displace the sulfone group selectively. For example, when phenethylamine deprotonated with butyllithium was combined with **1**, the SO_2Me-displacement product was produced, although in only 42% isolated yield (Scheme 2). Cyclohexylamine deprotonated with isopropylmagnesium chloride–lithium chloride complex similarly formed the sulfone displacement product in 65% isolated yield.

Table 4 Substitution of C4–Cl or C2–SO_2Me in **1** with Aliphatic Amines



Entry	R^1R^2NH	Product	Yield (%)	Product	Yield (%)
1	$EtNH_2$	**4a**	trace	**5a**	82
2	$Ph(CH_2)_2NH_2$	**4b**	trace	**5b**	92
3	$BnNH_2$	**4c**	trace	**5c**	96
4[a]	$CyNH_2$	**4d**	2	**5d**	77
5	MeEtNH	**4e**	77	**5e**	trace
6	Et_2NH	**4f**	86	**5f**	4
7	piperidine	**4g**	69	**5g**	27
8[a]	*t*-$BuNH_2$	**4h**	16[b]	**5h**	32
9[a]	1-adamantylNH_2	**4i**	27[b]	**5i**	58
10[a]	$CHF_2CH_2NH_2$	**4j**	36	**5j**	48
11[a,c]	$CF_3CH_2NH_2$	**4k**	58[d]	**5k**	0

[a] Reaction run at r.t., 0.3–2.5 h.
[b] Impure.
[c] 1.3 equiv of amine used.
[d] 13% of 2,4-(dimethylsulfonyl)-6-(2,2,2-trifluoroethylamino)pyrimidine or its isomer was also isolated.



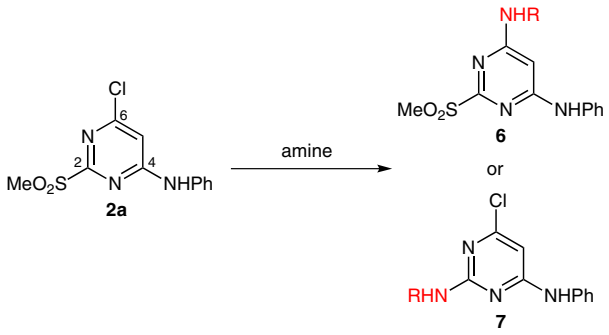
a. **5b**, R = C_2H_4Ph, base = *n*-BuLi, 42%
b. **5d**, R = Cy, base = *i*-PrMgCl·LiCl, 65%

Scheme 2 Reactions of **1** with deprotonated primary aliphatic amines

Further Chemoselective Functionalizations of 2a

Additionally, we studied the selectivity of the reaction between **2a** and various nucleophiles. We found that either the sulfone or the chloride in **2a** can be selectively displaced. For example, heating **2a** with anilines and 2,6-lutidine in dimethyl sulfoxide led to chloride displacement and formation of products **6a–e** (Table 5). Sterically hindered (entry 2) or electronically deactivated (entry 5) anilines required higher temperatures (100 °C) than did the other anilines (80 °C). The reaction was highly chemoselective, and only trace amounts of the sulfone-displacement product were observed by LC-MS analysis of the reaction mixtures. These selective displacements by anilines of the chloride and not of the sulfone are consistent with the data presented in Table 2.

Table 5 Substitution of C6–Cl or C2–SO_2Me in **2a** with Amines



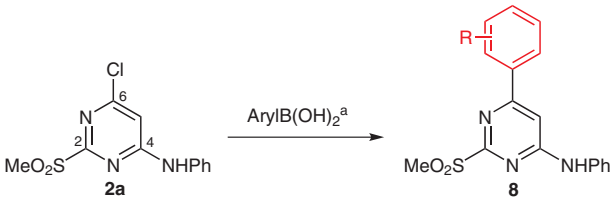
Entry	RNH_2	Product	Yield[a] (%)	Product	Yield[a] (%)
1[b]	$PhNH_2$	**6a**	87	–	–
2[b]	2-$MeC_6H_4NH_2$	**6b**	76	–	–
3[b]	3-$MeC_6H_4NH_2$	**6c**	78	–	–
4[b]	4-$MeC_6H_4NH_2$	**6d**	95	–	–
5[b]	4-$ClC_6H_4NH_2$	**6e**	95	–	–
6[c]	$CyNH_2$	–	–	**7a**	94
7[c]	$HOCH_2CH_2NH_2$	–	–	**7b**	98
8[c]	$BnNH_2$	**6f**	4	**7c**	87

[a] Isolated yield.
[b] $RC_6H_4NH_2$ (2–4 equiv), 2,6-lutidine (1.2 equiv), DMSO, 80–100 °C, 24–48 h.
[c] RNH_2 (3 equiv), DMSO, r.t., 24 h.

On the other hand, primary aliphatic amines selectively displaced the sulfone group in **2a** (entries 6–8). This observation is consistent with the selective displacement by similar amines of sulfone and not chloride in **1** (Table 4). Formation of the alternative products (such as **6f**) was observed by LC-MS analysis; however, these minor products could not be isolated in pure form.

We also found that the C6-position in **2a** could be selectively functionalized by Suzuki reaction, providing arylated products **8a–d** (Table 6). The reactions could be run at relatively low temperatures (60 °C), which avoided competitive hydrolysis of **2a** or formation of other byproducts.

Table 6 Substitution of C6–Cl in **2a** with Arylboronates[a]



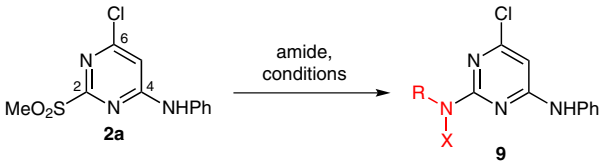
Entry	R	Product	Yield[b] (%)
1	H	**8a**	90
2	3-Me	**8b**	93
3	4-OMe	**8c**	90
4	4-F	**8d**	94

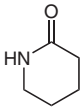
[a] Ar-$B(OH)_2$ (1.5 equiv), $PdCl_2$dppf (5 mol%), K_2CO_3 (2 equiv), aq DME, 60 °C, 4 h.
[b] Isolated yield.

Data presented in Table 3 illustrate that certain anionic nucleophiles can selectively displace the sulfone group in **1**. Similarly, the C2-position of **2a** can also be selectively functionalized. For example, deprotonated amides exclusively displaced the sulfone from **2a** (Table 7), forming products **9**. The reaction of aromatic formamides with different steric and electronic properties proceeded uneventfully (entries 1–5). The intermediate formamide products (**9**, X = CHO) were partially hydrolyzed during the reactions, which could be observed by LC-MS analysis of the reaction mixtures. This hydrolysis could be completed by treatment with aqueous sodium hydroxide to form the corresponding amines **9a–e**. The reaction of aliphatic phenethylformamide proceeded in a similar fashion (entry 6), providing product **9f** in 91% yield upon hydrolysis. A cyclic amide piperidone upon deprotonation also dis-

placed the methylsulfone group, providing amide product **9g** in 68% yield (entry 7).

Table 7 Substitution of C2–SO_2Me in **2a** with Deprotonated Amides[a]

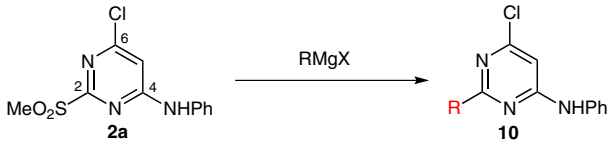


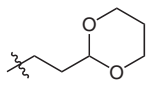
Entry	R	Product	X	Yield[b] (%)
1	2-ClC_6H_4	**9a**	H	92
2	3-ClC_6H_4	**9b**	H	87
3	4-ClC_6H_4	**9c**	H	95
4	4-$MeOC_6H_4$	**9d**	H	99
5	4-$O_2NC_6H_4$	**9e**	H	96
6	$Ph(CH_2)_2$	**9f**	H	91
7[c]		**9g**	–	68

[a] Reaction conditions: 1. RNHCHO, NaO*t*-Am (2 equiv), THF, 0 °C–r.t., 30 min; 2. aq NaOH, r.t., 30 min.
[b] Isolated yield.
[c] The hydrolysis step was omitted.

Finally, we demonstrated that organomagnesium reagents also preferentially displace the sulfone over the chloride (Table 8). At least two equivalents of the nucleophile were required for this reaction, as one equivalent was consumed to deprotonate the acidic N–H present in **2a**. As the data illustrates, both arylmagnesium reagents (entries 1–3) and alkylmagnesium reagents (entry 4) provided the desired products **10a–d** in high yield.

Table 8 Substitution of C2–SO_2Me in **2a** with Organomagnesium Reagents[a]



Entry	R	Product	Yield[b] (%)
1	Ph	**10a**	95
2	3-$F_3COC_6H_4$	**10b**	97
3	4-FC_6H_4	**10c**	93
4		**10d**	96

[a] Reaction conditions: RMgBr (2.5 equiv), THF, 0 °C–r.t., 1 h.
[b] Isolated yield.

Analysis of the Reaction Selectivity

The selectivity trends described in Table 2 and Table 4 are intriguing and deserve an explanation. A literature review of the reactions of heterocyclic electrophiles bearing both chloride and sulfone leaving groups reveals that chloride is always selectively displaced by aniline or secondary aliphatic amine nucleophiles (neutral, not deprotonated).

For example, both aniline and dimethylamine displace chloride from 3-chloro-6-(methylsulfonyl)pyridazine (**11b**, Table 9, entry 2) to provide products **13b-1** and **13b-2**.[36a] Similar selectivity was observed for 4-chloro-6-(methylsulfonyl)pyrimidine (**11c**, entry 3), which provided products **13c-1** and **13c-2**.[36a]

Additional examples include 4-chloro-2-(ethylsulfonyl)pyrimidine,[36b] 4-chloro-2-(ethylsulfonyl)-6-phenylpyrimidine,[36b] and 2,4-dichloro-6-(methylsulfonyl)pyrimidine.[6] The reaction of these electrophiles with anilines or secondary aliphatic amines proceeded by chloride displacement.

As the further confirmation of this trend, we found[37] that reaction of 2-chloro-6-(methylsulfonyl)pyrazine (**11d**, entry 4) and 4-chloro-2-(methylsulfonyl)pyrimidine (**11e**, entry 5), proceeded in a similar fashion, with selective displacement of chloride by either aniline or diethylamine, providing products **13d-1**, **13d-2**, **13e-1**, and **13e-2**. 2-Chloro-4-(methylsulfonyl)pyrimidine (**11f**, entry 10) behaved anomalously because the reaction with aniline was not clean. In addition to the major product **13f-1**, the sulfone displacement product could also be observed by LC-MS analysis. In comparison, when **11f** was combined with diethylamine, a clean and selective chloride displacement was observed with formation of **13f-2**.

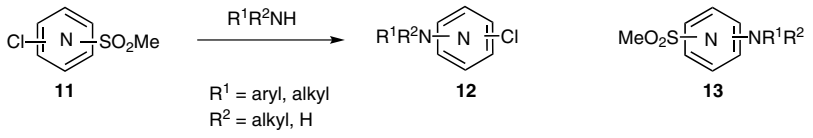
In contrast, reactions of primary aliphatic amines are less consistent and may proceed according to one of the three scenarios.

(1) Selective chloride displacement was observed when primary aliphatic amines were combined with 3-chloro-6-(methylsulfonyl)pyridazine **11b** to provide **13b-3** (entry 2),[36a] or with 2-chloro-6-(methylsulfonyl)pyrazine **11d** to provide **13d-3** (entry 4).

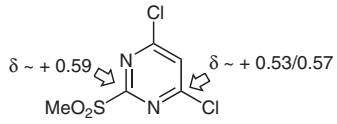
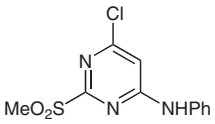
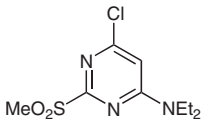
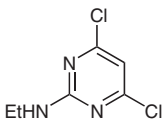
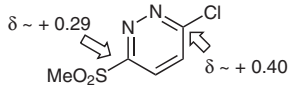
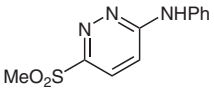
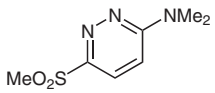
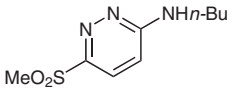
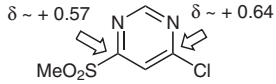
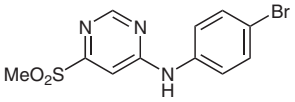
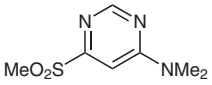
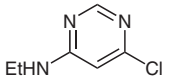
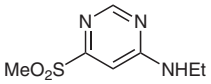
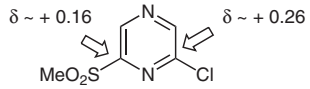
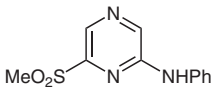
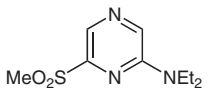
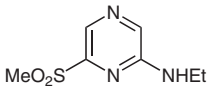
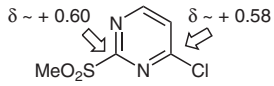
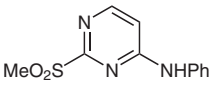
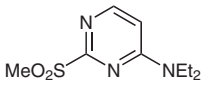
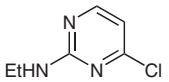
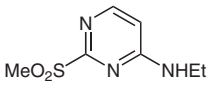
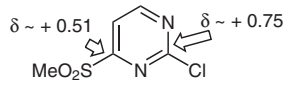
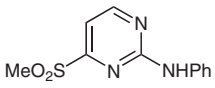
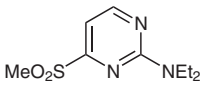
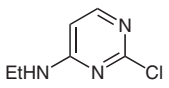
(2) Selective sulfone displacement was observed when primary aliphatic amines were combined with 4,6-dichloro-2-(methylsulfonyl)pyrimidine (**1**) to provide **12a** (entry 1).

(3) In general, primary aliphatic amines react with heterocyclic electrophiles less selectively. Examples include reactions with: (a) 4-chloro-6-(methylsulfonyl)pyrimidine (**11c**, entry 3), with the formation of both products **12c-1** and **13c-3**; (b) 4-chloro-2-(methylsulfonyl)pyrimidine (**11e**, entry 5), with formation of both **12e-1** and **13e-3**. In each case, the sulfone displacement was preferred. Additional examples of unselective reactions include 4-chloro-2-(ethylsulfonyl)pyrimidine,[36b] and 4-chloro-2-(ethylsulfonyl)-6-phenylpyrimidine.[36b,38] In both reactions sulfone

Table 9 Selected Data on the Chemoselectivity of Reactions between Electrophiles **11a–f** Containing Both Chloride and Sulfone Leaving Groups and the Three Types of Amines: Anilines, Secondary Aliphatic Amines, and Primary Aliphatic Amines



11 **12** **13**

Entry	Heterocycle **5**[a]	Product of reaction with: Anilines	Secondary aliphatic amines	Primary aliphatic amines
1	 **11a** (same as **1**)	 **13a-1**, 97% (same as **2a**) this work	 **13a-2**, 86% (same as **4f**) this work	 **12a**, 82% (same as **5a**) this work
2	 **11b**	 **13b-1**, 77% ref. 36a	 **13b-2**, 86% ref. 36a	 **13b-3**, 92% ref. 36a
3	 **11c**	 **13c-1**, 77% ref. 36a	 **13c-2**, 72% ref. 36a	 **12c-1**, 83%  **13c-3**, 14% this work
4	 **11d**	 **13d-1**, 73% this work	 **13d-2**, 92% this work	 **13d-3**, 78% this work
5	 **11e**	 **13e-1**, 97% this work	 **13e-2**, 93% this work	 **12e-1**, 67%  **13e-3**, 19% this work
6	 **11f**	 **13f-1**[b] this work	 **13f-2**, 94% this work	 **12f-1**, 79% this work

[a] Partial atomic charges are shown on the S- and Cl-bound carbon atoms.
[b] The product could not be isolated clean. Ratio of the chloride-substitution product to the sulfone-substitution product is ~3.5:1 by LC, detection with UV 254 nm.

displacement was also slightly favored over chloride displacement (sulfone displacement/chloride displacement ~2:1 or 4:1)

To summarize, heterocyclic electrophiles bearing both chloride and sulfone leaving groups react with anilines and secondary aliphatic amines by selective chloride displacement. Reactions with primary aliphatic amines in general favor sulfone displacement, although selective chloride displacement is sometimes observed instead.

In order to understand what dictates the observed selectivity, we analyzed: (1) frontier molecular orbitals (FMO) of the electrophiles; (2) partial atomic charges on the S- and Cl-bound carbon atoms in the electrophiles;[39] and (3) the steric factors. We consider that the SO_2Me group has more steric bulk the corresponding Cl; and anilines[40] and secondary aliphatic amines will have more steric bulk than primary aliphatic amines.

First, we calculated lowest unoccupied molecular orbitals (LUMO) in these electrophiles and determined that no correlation exists between the atomic LUMO coefficients and the reaction selectivity. For example, in 3-chloro-6-(methylsulfonyl)pyridazine (**11b**) the LUMO is concentrated on the C(S); however, it is the chloride that is being displaced from this electrophile. On the other hand, the atomic LUMO coefficients at C(Cl) and C(S) in **1** are very similar. Nevertheless, either carbon atom may be selectively attacked by different nucleophiles.

The calculated partial atomic charges on the chlorine- and sulfur-bound carbon atoms in these electrophiles are shown in Table 9. We found that anilines and secondary aliphatic amines always displace the chloride atom independent of the position of the more positively charged carbon atom. For example, in 3-chloro-6-(methylsulfonyl)pyridazine (**11b**) the partial atomic charge on the C(Cl) atom is larger than on the C(S) carbon (+0.40 vs. +0.29). On the other hand, in **1** the charge on C(Cl) is lower than on C(S) (+0.53/+0.57 vs. +0.59). Nevertheless, both electrophiles react with anilines or dialkylamines by selective attack at C(Cl).

Because the selectivity of reactions with anilines or secondary aliphatic amines is not FMO- or charge-controlled, we propose that it is governed by steric factors; and the less sterically hindered C(Cl) is always attacked by these bulkier amines.[41]

However, primary aliphatic amines preferentially attack the most positively charged atom, although often unselectively. Thus, in **1** the more positive C(S) is attacked by ethylamine (entry 1), while in **11b** and **11d** the amines attack the more positive C(Cl). However, frequently the reactions with primary aliphatic amines are less selective (such as with **11c** and **11e**). It appears that when a primary aliphatic amine reacts, the steric bulk may be as important as the electrostatic attraction. In some cases (such as entries 2 and 4) both steric and electronic factors match and highly selective chloride displacement is possible. When electronic factors predominate, selective sulfone displacement is possible, such as observed with **1**.

This steric-driven selectivity explanation is also consistent with the less selective chloride displacement from **1** by the less hindered piperidine (Table 4, entry 7) compared to diethylamine (Table 4, entry 6). Further support for the steric origins of selectivity comes from data of Table 4, entries 8 and 9. The sulfone displacement with these bulky primary amines from **1** is not as selective as with the less sterically biased ethylamine (Table 4, entry 1).

Reaction of 2-chloro-4-(methylsulfonyl)pyrimidine (**11f**) with ethylamine was anomalous. The less positively charged C(S) was attacked with formation of **12f-1**. Similarly, in **11c** the less positively charged C(S) was preferentially attacked by ethylamine. This anomalous behavior suggests that there must be additional factors affecting the selectivity of these reactions.

To summarize, we have demonstrated that **1** is a versatile intermediate that can be used for selective synthesis of polysubstituted pyrimidines. In the absence of a strong external base, anilines, some heteroaromatic amines, and sterically unbiased secondary aliphatic amines selectively displace the chloride group. In contrast, under the same conditions electronically and sterically unbiased primary aliphatic amines preferentially displace the sulfone group. We proposed a steric-driven selectivity explanation for the selective chloride displacement in **1** and similar electrophiles (**11b**–**f**). Further, we proposed that for the reactions of primary aliphatic amines, electrostatic attraction may be equally important for the selectivity. In contrast, anionic nucleophiles always selectively displace the sulfone group. The same reactivity trends apply for the reactions of the advanced intermediate **2a**.

^{1}H and ^{13}C NMR spectra were recorded on Bruker 500 MHz NMR spectrometer (500 MHz ^{1}H, 126 MHz ^{13}C) in $CDCl_3$, acetone-d_6, or DMSO-d_6. ^{1}H and ^{13}C NMR assignments are corroborated by 2D experiments (COSY, HMQC, HMBC, and NOESY) when relevant. HRMS analysis (ESI+) was performed on an LTQ Orbitrap Discovery mass spectrometer. Analytical TLC was performed on silica gel plates with F-254 indicator. Visualization was accomplished by UV light. Column chromatography was performed with silica gel. Melting points were determined in open capillary tubes on an OptiMelt MPA100 Automated Melting Point System. Anhydrous solvents were purchased from Acros and used without further purification. All commercially available reagents were purchased and used without further purification unless otherwise noted. 4,6-Dichloro-2-(methylsulfonyl)pyrimidine (**1**) was purchased from Accela ChemBio and used without further purification.

6-Chloro-2-(methylsulfonyl)-*N*-phenylpyrimidin-4-amine (2a); Typical Procedure

Compound **1** (227 mg, 1 mmol), 2,6-lutidine (150 μL, 1.3 mmol), and aniline (118 μL, 1.3 mmol) were dissolved in DMSO (3 mL) and the soln was stirred for 1 h under N_2 at r.t. The reaction was quenched with 0.1 M aq HCl (3 mL), and the resulting suspension was stirred at 1 h at r.t. The solid product was filtered and washed with H_2O. The wet product was dried at 50 °C under high vacuum to give **2a** as an off-white solid material; yield 270 mg (95%); mp 196–198 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.54 (br s, 1 H), 7.62 (br s, 2 H), 7.42 (t, J = 8.04 Hz, 2 H), 7.18 (t, J = 7.09 Hz, 1 H), 6.96 (s, 1 H), 3.36 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 165.10, 161.44, 158.17, 137.85, 129.11, 124.34, 120.87, 107.32, 38.80.

MS (ESI): *m*/*z* (%) = 288 (1), 287 (4), 286 (36), 285 (11), 284 (100, $[M + H]^+$), 222 (2), 204 (2).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{11}ClN_3O_2S$: 284.0255; found: 284.0248.

6-Chloro-2-(methylsulfonyl)-*N*-(*o*-tolyl)pyrimidin-4-amine (2b)
Prepared according to the typical procedure for **2a** as a white solid material; yield: 140 mg (95%); mp 129–130 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48 (br s, 1 H), 7.34–7.33 (br m, 1 H), 7.28 (br m, 3 H), 6.44 (br s, 1 H), 3.31 (s, 3 H), 2.26 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.3, 163.4, 161.0, 134.3, 134.0, 131.5, 128.1, 127.3, 125.9, 104.1, 38.8, 17.7.

MS (ESI): *m*/*z* (%) = 298 (100, $[M + H]^+$), 300 (32).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{13}ClN_3O_2S$: 298.0417; found 298.0427.

6-Chloro-*N*-(2-chlorophenyl)-2-(methylsulfonyl)pyrimidin-4-amine (2c)
Prepared according to the typical procedure for **2a** as an off-white solid material; yield: 260 mg (82%); mp 123–126 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.34 (br s, 1 H), 7.70 (d, *J* = 7.57 Hz, 1 H), 7.61 (dd, *J* = 8.04, 1.42 Hz, 1 H), 7.44 (td, *J* = 7.65, 1.42 Hz, 1 H), 7.34 (t, *J* = 7.09 Hz, 1 H), 6.92 (br s, 1 H), 3.28 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 170.38, 165.05, 162.54, 158.92, 133.94, 130.06, 127.95, 127.83, 127.28, 106.40, 38.68.

MS (ESI): *m*/*z* (%) = 323 (1), 322 (13), 321 (8), 320 (71), 319 (10), 318 (100, $[M + H]^+$), 258 (1), 256 (1).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}Cl_2N_3O_2S$: 317.9865; found: 317.9858.

6-Chloro-2-(methylsulfonyl)-*N*-(*m*-tolyl)pyrimidin-4-amine (2d)
Prepared according to the typical procedure for **2a** as a yellow solid material; yield: 291 mg (98%); mp 129–140 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.27–10.56 (m, 1 H), 7.37–7.54 (m, 2 H), 7.20–7.36 (m, 1 H), 6.97–7.04 (m, 1 H), 6.91–6.96 (m, 1 H), 3.36 (s, 3 H), 2.33 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 165.07, 161.39, 158.24, 138.39, 137.72, 128.88, 124.82, 121.05, 117.90, 107.47, 38.75, 21.06.

MS (ESI): *m*/*z* (%) = 302 (2), 301 (4), 300 (36), 299 (11), 298 (100, $[M + H]^+$), 238 (1), 236 (3), 218 (2).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{13}ClN_3O_2S$: 298.0417; found: 298.0424.

6-Chloro-*N*-(3-chlorophenyl)-2-(methylsulfonyl)pyrimidin-4-amine (2e)
Prepared according to the typical procedure for **2a** as a yellow solid material; yield: 298 mg (94%); mp 134–136 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.72 (s, 1 H), 7.85 (br s, 1 H), 7.54 (d, *J* = 9.14 Hz, 1 H), 7.44 (t, *J* = 8.04 Hz, 1 H), 7.16–7.27 (m, 1 H), 7.03 (s, 1 H), 3.37 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 164.95, 161.24, 158.38, 139.50, 133.30, 130.65, 123.76, 120.18, 118.99, 107.93, 38.80.

MS (ESI): *m*/*z* (%) = 322 (12), 321 (7), 320 (71), 319 (11), 318 (100, $[M + H]^+$), 281 (2), 267 (6), 256 (2).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}Cl_2N_3O_2S$: 317.9865; found: 317.9857.

6-Chloro-2-(methylsulfonyl)-*N*-(3-nitrophenyl)pyrimidin-4-amine (2f)
Prepared according to the typical procedure for **2a**, as a yellow solid material; yield: 319 mg (97%); mp 245–246 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.92 (s, 1 H), 8.72 (br s, 1 H), 7.99–7.94 (m, 2 H), 7.70 (t, *J* = 8.2 Hz, 1 H), 7.06 (s, 1 H), 3.43 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 164.9, 161.2, 158.7, 148.1, 139.3, 130.5, 126.3, 118.3, 114.6, 108.4, 38.8.

MS (ESI): *m*/*z* (%) = 329 (100, $[M + H]^+$), 331 (32).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}ClN_4O_4S$: 329.0111; found: 329.0122.

6-Chloro-2-(methylsulfonyl)-*N*-(*p*-tolyl)pyrimidin-4-amine (2g)
Prepared according to the typical procedure for **2a** as a yellow solid material; yield: 285 mg (96%); mp 164–168 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.46 (br s, 1 H), 7.50 (br s, 2 H), 7.23 (d, *J* = 8.20 Hz, 2 H), 6.91 (br s, 1 H), 3.34 (s, 3 H), 2.30 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.07, 161.29, 157.61, 135.43, 133.08, 129.34, 120.43, 107.62, 38.79, 20.44.

MS (ESI): *m*/*z* (%) = 302 (2), 301 (4), 300 (37), 299 (13), 298 (100, $[M + H]^+$), 267 (1), 218 (2).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{13}ClN_3O_2S$: 298.0412; found: 298.0403.

6-Chloro-*N*-(4-methoxyphenyl)-2-(methylsulfonyl)pyrimidin-4-amine (2h)
Prepared according to the typical procedure for **2a** as an off-white solid material; yield: 310 mg (99%); mp 199–201 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.39 (br s, 1 H), 7.55–7.52 (br m, 2 H), 7.01 (d, *J* = 8.6 Hz, 2 H), 6.89 (br, 1 H), 3.78 (s, 3 H), 3.34 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 165.2, 161.1, 157.5, 156.0, 130.9, 122.1, 114.2, 107.5, 55.2, 38.8.

MS (ESI): *m*/*z* (%) = 314 (100, $[M + H]^+$), 316 (32).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{13}ClN_3O_3S$: 314.0366; found: 314.0377.

6-Chloro-*N*-(4-chlorophenyl)-2-(methylsulfonyl)pyrimidin-4-amine (2i)
Prepared according to the typical procedure for **2a** as a white solid material; yield: 301 mg (94%); mp 178–179 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.60 (br s, 1 H), 7.65 (br m, 2 H), 7.47 (d, *J* = 8.9 Hz, 2 H), 6.98 (s, 1 H), 3.36 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 165.0, 161.3, 158.3, 136.9, 129.0, 128.0, 122.9, 122.4, 38.8.

MS (ESI): *m*/*z* (%) = 318 (100, $[M + H]^+$), 320 (63).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}Cl_2N_3O_2S$: 317.9871; found: 317.9881.

Methyl 4-[6-Chloro-2-(methylsulfonyl)pyrimidin-4-ylamino]benzoate (2j)
Prepared according to the typical procedure for **2a** as a yellow solid material; yield: 310 mg (91%); mp 127–129 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.84 (s, 1 H), 8.01 (d, *J* = 9.14 Hz, 2 H), 7.80 (d, *J* = 8.51 Hz, 2 H), 7.08 (s, 1 H), 3.85 (s, 3 H), 3.41 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 165.65, 164.98, 161.11, 158.57, 142.49, 130.41, 124.46, 119.72, 108.43, 51.95, 38.87.

MS (ESI): *m*/*z* (%) = 346 (1), 345 (4), 344 (36), 343 (14), 342 (100, $[M + H]^+$), 312 (2), 310 (7).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}ClN_3O_4S$: 342.0310; found: 342.0301.

4-[6-Chloro-2-(methylsulfonyl)pyrimidin-4-ylamino]benzonitrile (2k)
Prepared according to the typical procedure for **2a** as an off-white solid material; yield: 283 mg (92%); mp 219–229 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.90 (s, 1 H), 7.92–7.82 (m, 4 H), 7.10 (s, 1 H), 3.40 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ =165.07, 161.26, 158.83, 142.60, 133.63, 120.44, 119.07, 108.80, 105.61, 39.05.

MS (ESI): *m*/*z* (%) = 313 (2), 312 (4), 311 (34), 310 (12), 309 (100, [M + H]$^+$), 247 (2), 229 (2), 215 (2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{10}ClN_4O_2S$: 309.0208; found: 309.0199.

6-Chloro-*N*-(2,6-dimethylphenyl)-2-(methylsulfonyl)pyrimidin-4-amine (2l)
Prepared according to the typical procedure for **2a** as a yellow solid material; yield: 295 mg (95%); mp 163–169 °C.

^{1}H NMR (500 MHz, DMSO-d_6, mixture of two rotamers ~0.4:0.6): δ = 10.24 (s, 0.6 H), 9.87 (s, 0.4 H), 7.20–7.29 (m, *J* = 3.50 Hz, 1.8 H), 7.11–7.18 (m, 1.2 H), 7.02 (s, 0.4 H), 5.88 (s, 0.6 H), 3.37 (s, 1.8 H), 3.11 (s, 1.2 H), 2.16 (s, 3.5 H), 2.14 (s, 2.5 H); see the Supporting Information for the spectrum.

^{13}C NMR (126 MHz, acetone-d_6, signals for both rotamers): δ = 166.9, 164.9, 164.1, 164.1, 161.6, 159.8, 137.2, 136.5, 135.2, 134.1, 129.8, 129.3, 128.9, 128.2, 125.8, 107.4, 103.2, 39.7, 39.3, 38.9, 18.7, 18.2.

MS (ESI): *m*/*z* (%) = 316 (3), 315 (7), 314 (65), 312 (100, [M + H]$^+$), 115 (9).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}ClN_3O_2S$: 312.0568; found: 312.0561.

6-Chloro-*N*-methyl-2-(methylsulfonyl)-*N*-phenylpyrimidin-4-amine (2m)
Prepared according to the typical procedure for **2a** as a white solid material; yield: 292 mg (98%); mp 184–185 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (s, 1 H), 7.53 (t, *J* = 7.5 Hz, 2 H), 7.43 (t, *J* = 7.5 Hz, 1 H), 7.24 (dd, *J* = 8.3, 1.3 Hz, 2 H), 3.55 (s, 3 H), 3.38 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 164.8, 162.8, 158.6, 142.4, 130.2, 128.1, 126.4, 104.7, 38.69, 38.66.

MS (ESI): *m*/*z* (%) = 191 (100), 298 (100, [M + H]$^+$), 300 (36), 320 (28).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}ClN_3O_2S$: 298.0417; found: 298.0403.

1-[6-Chloro-2-(methylsulfonyl)pyrimidin-4-yl]indoline (2n)
Prepared according to the typical procedure for **2a** as an off-white solid material; yield: 304 mg (98%); mp 222–223 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.40 (br s, 1 H), 7.32 (d, *J* = 7.3 Hz, 1 H), 7.29 (t, *J* = 7.8 Hz, 1 H), 7.19 (s, 1 H), 7.09 (td, *J* = 7.5, 0.6 Hz, 1 H), 4.14 (t, *J* = 8.4 Hz, 2 H), 3.42 (s, 3 H), 3.27 (t, *J* = 8.4 Hz, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 164.3, 159.02, 158.98, 141.8, 133.1, 127.3, 125.2, 123.0, 116.7, 106.7, 48.8, 39.0, 26.8.

MS (ESI): *m*/*z* (%) = 310 (100, [M + H]$^+$), 312 (36).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{13}ClN_3O_2S$: 310.0417; found: 310.0404.

***N*-[6-Chloro-2-(methylsulfonyl)pyrimidin-4-yl]isoquinolin-6-amine (2o)**
Prepared according to the typical procedure for **2a** as a white amorphous solid; yield: 618 mg (93%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.83 (s, 1 H), 8.83 (dd, *J* = 1.6, 4.1 Hz, 1 H), 8.30 (br d, *J* = 7.9 Hz, 2 H), 8.05 (d, *J* = 9.1 Hz, 1 H), 7.89 (app. br d, *J* = 8.8 Hz, 1 H), 7.52 (dd, *J* = 4.3, 8.4 Hz, 1 H), 7.08 (s, 1 H), 3.43 (s, 3 H).

^{13}C NMR (126MHz, DMSO-d_6): δ = 165.1, 161.4, 158.5, 149.6, 145.0, 135.9, 135.6, 129.9, 128.2, 124.4, 122.0, 117.0, 107.7, 38.9.

MS (ESI): *m*/*z* (%) = 337 (37), 336 (15), 335 (100, [M + H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C1_4H_{12}ClN_4O_2S$: 335.0364; found: 335.0357.

***N*-[6-Chloro-2-(methylsulfonyl)pyrimidin-4-yl]isoxazol-3-amine (2p)**
Prepared according to the typical procedure for **2a** as an off-white solid material; yield: 247 mg (90%); mp 219–220 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.6 (s, 1 H), 8.89 (s, 1 H), 7.53 (br s, 1 H), 6.82 (br s, 1 H), 3.40 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 164.9, 160.52, 160.47, 157.7, 108.3, 99.3, 39.0.

MS (ESI): *m*/*z* (%) = 255 (18), 267 (100), 275 (40, [M + H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_8ClN_4O_3S$: 275.0006; found: 274.9992.

6-Chloro-2-(methylsulfonyl)-*N*-(1*H*-pyrazol-4-yl)pyrimidin-4-amine (2q)
Prepared according to the typical procedure for **2a** as a pink amorphous solid; yield: 269 mg (99%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.68–13.12 (m, 1 H), 10.57 (br s, 0.8 H), 10.20 (br s, 0.2 H), 7.88–8.11 (m, 1 H), 7.50–7.82 (m, 1 H), 6.87 (br s, 0.8 H), 6.68 (br s, 0.2 H), 3.35 (s, 3 H); see VT NMR experiments in the Supporting Information.

^{13}C NMR (126 MHz, DMSO-d_6): δ = 165.4, 160.0, 157.1, 120.4, 120.4, 106.9, 38.8.

LC-MS (ESI): *m*/*z* = 274 [M + H]$^+$.

***N*-[6-Chloro-2-(methylsulfonyl)pyrimidin-4-yl]-1*H*-indol-5-amine (2r)**
To **1** (227 mg, 1 mmol) was added 1*H*-indol-5-amine (132 mg, 1 mmol), $NaHCO_3$ (130 mg, 1.5 equiv), DMF (1 mL) and the mixture was stirred at r.t. under N_2 for 1 h. LC-MS analysis of the mixture showed complete conversion of **1** and clean formation of the major product (M + H = 323). AcOH (3 drops) was added, then the mixture was diluted with H_2O, filtered, washed with more H_2O, then hexane, and Et_2O, and dried in vacuo to provide **2r** as a yellow amorphous solid material; yield: 314 mg (98%).

^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers): δ = 11.00–11.39 (m, 1 H), 10.29–10.58 (m, 1 H), 7.85 (br s, 0.54 H), 7.32–7.56 (m, 2.55 H), 7.27 (br s, 0.6 H), 7.02 (br s, 0.42 H), 6.91 (br s, 0.57 H), 6.59 (br s, 0.41 H), 6.44 (br s, 1.1 H), 3.35 (s, 3 H); see the Supporting Information for the ^{1}H NMR spectrum.

^{13}C NMR not available due to signals being too weak/broad, see HSQC spectrum in the Supporting Information for information on some signals.

LC-MS (ESI): *m*/*z* = 323 [M + H]$^+$.

4,6-Dichloro-*N*-phenylpyrimidin-2-amine (3a); Typical Procedure
To aniline (279 mg, 3 mmol) in a tube with septum, stirbar, and needle for N_2 was added THF (3 mL) and the soln was cooled to –70 °C (external temperature). 1 M NaHMDS in THF (5 mL, 5 mmol) was added by syringe, followed by slow addition by cannula of a soln of **1** [454 mg, 2 mmol in THF (3 mL)] over 2 min. UPLC analysis after 10 min showed complete conversion and after 40 min of total reaction time the mixture was quenched with AcOH, then partitioned between brine and EtOAc–hexane (~1:1) mixture. The organic layer was concentrated and purified by chromatography

(silica gel, EtOAc–hexanes, gradient 0:1 to 1:5) to provide **3a** as glassy material (404 mg, 85%). The analytically pure material was prepared through crystallization (heptane) to provide **3a** as a solid material; yield: 381 mg (79%); mp 115–117 °C (heptane).

^{1}H NMR (500 MHz, acetone-d_6): δ = 9.25 (br s, 1 H), 7.82–7.72 (m, 2 H), 7.41–7.31 (m, 2 H), 7.10 (tt, *J* = 1.1, 7.4 Hz, 1 H), 6.98 (s, 1 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 162.8, 160.8, 140.3, 130.1, 124.8, 121.4, 111.7.

MS (ESI): *m*/*z* (%) = 244 (9), 243 (8), 242 (65), 241 (12), 240 (100, $[M + H]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_8Cl_2N_3$: 240.0090; found: 240.0085.

4,6-Dichloro-*N*-(2-chlorophenyl)pyrimidin-2-amine (3b)
Prepared according to the typical procedure for **3a** as a white solid material upon crystallization (heptane); yield: 416 mg (76%); mp 112–114 °C (heptane).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.65 (br s, 1 H), 7.95 (dd, *J* = 1.7, 8.0 Hz, 1 H), 7.53 (dd, *J* = 1.6, 8.2 Hz, 1 H), 7.40 (dt, *J* = 1.6, 7.7 Hz, 1 H), 7.24 (dt, *J* = 1.6, 7.7 Hz, 1 H), 7.05 (s, 1 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 163.2, 161.4, 136.4, 131.0, 129.0, 128.7, 127.7, 127.0, 112.5.

MS (ESI): *m*/*z* (%) = 278 (31), 277 (8), 276 (100), 275 (11), 274 (94, $[M + H]^+$), 238 (10).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_7Cl_3N_3$: 273.9700; found: 273.9694.

4,6-Dichloro-*N*-(4-chlorophenyl)pyrimidin-2-amine (3c)
Prepared according to the typical procedure for **3a** as a white solid material; yield: 229 mg (84%); mp 172–174 °C (EtOAc–hexane).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.53 (s, 1 H), 7.72–7.62 (m, 2 H), 7.44–7.36 (m, 2 H), 7.23 (s, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 160.9, 158.6, 137.7, 128.6, 126.7, 121.1, 110.6.

MS (ESI): *m*/*z* (%) = 278 (31), 277 (13), 276 (97), 275 (10), 274 (100, $[M + H]^+$), 238 (7).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_7Cl_3N_3$: 273.9700; found: 273.9695.

4,6-Dichloro-*N*-(*p*-tolyl)pyrimidin-2-amine (3d)
Prepared according to the typical procedure for **3a** as a light yellow solid material; yield: 215 mg (85%); mp 114–116 °C (EtOAc–hexane).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.29 (s, 1 H), 7.54–7.48 (m, 2 H), 7.13 (s, 1 H), 7.19–7.08 (m, 2 H), 2.26 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 160.8, 158.9, 136.1, 132.2, 129.1, 120.0, 109.8, 20.4.

MS (ESI): *m*/*z* (%) = 258 (8), 257 (7), 256 (65), 255 (12), 254 (100, $[M + H]^+$), 218 (9).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}Cl_2N_3$: 254.0246; found: 254.0239.

4,6-Dichloro-*N*-(4-methoxyphenyl)pyrimidin-2-amine (3e)
Prepared according to the typical procedure for **3a** as an off-white amorphous solid material; yield: 181 mg (67%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.22 (s, 1 H), 7.45–7.55 (m, 2 H), 7.09 (s, 1 H), 6.88–6.97 (m, 2 H), 3.73 (s, 3 H)

^{13}C NMR (126 MHz, DMSO-d_6): δ = 160.9, 159.1, 155.5, 131.6, 121.8, 113.9, 109.4, 55.2

MS (ESI): *m*/*z* (%) = 274 (11), 273 (8), 272 (65), 271 (12), 270 (100, $[M + H]^+$), 234 (7), 102 (8).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}Cl_2N_3O$: 270.0195; found: 270.0218.

4,6-Dichloro-*N*-phenylpyrimidin-2-amine (3a); Alternate Typical Procedure
Compound **1** (227 mg, 1 mmol) and *N*-phenylformamide (1.1 mmol) were dissolved in THF (3 mL) and the soln was cooled under N_2 to 0 °C using an ice bath. To this soln was added dropwise a soln of 1.4 M NaO*t*-Am in THF (0.9 mL, 1.2 mmol). The mixture was stirred at 0 °C for 30 min. LC-MS analysis showed consumption of the starting material **1**. Then 1 M aq NaOH (1.5 mL, 1.5 mmol) was added and the mixture was stirred at r.t. for 30 min. LC-MS analysis showed clean formation of the desired product **3a**. The material was extracted with EtOAc. The organic layer was collected, dried, and evaporated. The crude product was purified by flash chromatography to provide the **3a** as white solid material; yield: 224 mg (93%). Based on NMR and LC-MS analysis the material is identical to **3a** prepared from aniline in the presence of NaHMDS.

4,6-Dichloro-*N*-(2-methoxyphenyl)pyrimidin-2-amine (3f)
Prepared according to the alternate typical procedure for **3a** as a white solid material; yield: 201 mg (75%); mp 83–85 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29 (dd, *J* = 7.6, 2.2 Hz, 1 H), 7.86 (br s, 1 H), 6.94–6.88 (m, 2 H), 6.77 (dd, *J* = 7.4, 2.2 Hz, 1 H), 6.63 (s, 1 H), 3.77 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.5, 158.6, 147.9, 127.5, 123.0, 120.9, 118.8, 110.8, 109.9, 55.6.

MS (ESI): *m*/*z* (%) = 270 (100, $[M + H]^+$), 272 (64).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}Cl_2N_3O$: 270.0201; found: 270.0188.

4,6-Dichloro-*N*-(3-methoxyphenyl)pyrimidin-2-amine (3g)
Prepared according to the alternate typical procedure for **3a** as a white solid material; yield: 207 mg (78%); mp 107–108 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45 (br s, 1 H), 7.36 (t, *J* = 2.3 Hz, 1 H), 7.26 (t, *J* = 8.2 Hz, 1 H), 7.06 (ddd, *J* = 8.2, 2.3, 0.7 Hz, 1 H), 6.80 (s, 1 H), 6.69 (ddd, *J* = 8.2, 2.3, 0.7 Hz, 1 H), 3.85 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.7, 160.1, 158.8, 138.9, 129.7, 112.0, 111.2, 109.3, 105.6, 55.2. MS (ESI): *m*/*z* (%) = 270 (100, $[M + H]^+$), 272 (64).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}Cl_2N_3O$: 270.0201; found: 270.0188.

4,6-Dichloro-*N*-(4-methoxyphenyl)pyrimidin-2-amine (3e)
Prepared according to the alternate typical procedure for **3a** as a white solid material; yield: 245 mg (91%); mp 139–140 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 9 Hz, 2 H), 7.29 (br s, 1 H), 6.92 (d, *J* = 9 Hz, 2 H), 6.75 (s, 1 H), 3.83 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.8, 159.3, 156.4, 130.6, 122.1, 114.2, 110.6, 55.5.

MS (ESI): *m*/*z* (%) = 115 (100), 270 (70, $[M + H]^+$), 272 (47).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}Cl_2N_3O$: 270.0201; found: 270.0220.

4,6-Dichloro-*N*-(4-chlorophenyl)pyrimidin-2-amine (3c)
Prepared according to the alternate typical procedure for **3a** as a white solid material; yield: 232 mg (85%); mp 173–175 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.43 (m, 2 H), 7.25–7.19 (m, 2 H), 6.74 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.9, 158.8, 136.3, 129.1, 129.0, 121.0, 111.6.

MS (ESI): *m*/*z* (%) = 274 (100, $[M + H]^+$), 276 (100).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_7Cl_3N_3$: 273.9706; found: 273.9693.

***tert*-Butyl 2-Bromophenyl(4,6-dichloropyrimidin-2-yl)carbamate (3h); Typical Procedure**

To 2-bromo-*N*-(*tert*-butoxycarbonyl)aniline (272 mg, 1 mmol) in a reaction tube with a septum, a stirbar, and a needle for N_2 was added DMF (1 mL) and THF (1.5 mL), followed by NaH (60% suspension in oil, 80 mg, 2 mmol, GAS EVOLUTION!). After stirring at r.t. for 5 min, the mixture was cooled to –60 °C (external temperature). To the resulting suspension was added a soln of **1** (341 mg, 1.5 mmol) in THF (1.5 mL). The mixture quickly turned into an unstirrable suspension, which was warmed to 0 °C over 1 h. The mixture was quenched with AcOH (GAS EVOLUTION!) and H_2O, and extracted with a mixture EtOAc–hexanes (~1:1). Upon purification by chromatography (silica gel, gradient EtOAc–hexanes from 0:1 to 1:6) **3h** was obtained as an oily viscous material, which solidified in vacuo; yield: 365 mg (87%); mp 98–101 °C (EtOAc–hexanes).

^{1}H NMR (500 MHz, acetone-d_6): δ = 7.73 (dd, *J* = 1.6, 8.2 Hz, 1 H), 7.50–7.43 (m, 2 H), 7.43 (s, 1 H), 7.35 (ddd, *J* = 0.9, 1.9, 6.9 Hz, 1 H), 1.47 (s, 9 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 163.0, 161.1, 152.2, 140.9, 134.6, 132.3, 131.2, 130.1, 124.8, 117.3, 84.1, 28.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}BrCl_2N_3NaO_2$: 439.9539; found: 439.9534.

***tert*-Butyl 3-Bromophenyl(4,6-dichloropyrimidin-2-yl)carbamate (3i)**

Prepared according to the typical procedure for **3h** as a white solid material; yield: 313 mg (75%); mp 81–85 °C (EtOAc–hexanes).

^{1}H NMR (500 MHz, acetone-d_6): δ = 7.55–7.52 (m, 2 H), 7.51 (s, 1 H), 7.42–7.37 (m, 1 H), 7.33–7.28 (m, 1 H), 1.49 (s, 9 H)

^{13}C NMR (126 MHz, acetone-d_6): δ = 163.2, 161.7, 153.4, 143.3, 132.1, 132.1, 131.7, 128.2, 123.0, 118.2, 84.3, 28.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}BrCl_2N_3NaO_2$: 439.9539; found: 439.9527.

***tert*-Butyl 4-Chlorophenyl(4,6-dichloropyrimidin-2-yl)carbamate (3j)**

Prepared according to the typical procedure for **3h** as a white solid material; yield: 712 mg (95%); mp 98–101 °C (EtOAc–hexanes).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.77 (s, 1 H), 7.50–7.45 (m, 2 H), 7.32–7.27 (m, 2 H), 1.42 (s, 9 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 161.3, 159.6, 151.8, 138.9, 131.7, 129.4, 129.2, 117.0, 82.9, 27.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}Cl_3N_3NaO_2$: 396.0044; found: 396.0039.

4,6-Dichloro-*N*-(pyridin-2-yl)pyrimidin-2-amine (3k)

Prepared according to the typical procedure for **3a** as an amorphous white solid material; yield: 201 mg (84%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.70 (s, 1 H), 8.33 (dd, *J* = 1.89, 5.04 Hz, 1 H), 8.02 (d, *J* = 8.20 Hz, 1 H), 7.76–7.88 (m, 1 H), 7.27–7.34 (m, 1 H), 7.03–7.14 (m, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 161.0, 158.4, 151.7, 148.1, 138.1, 119.1, 113.9, 111.6.

MS (ESI): *m*/*z* (%) = 245 (11), 244 (6), 243 (65), 242 (1), 241 (100, [M + H]$^+$), 207 (7), 206 (2), 205 (22).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_7Cl_2N_4$: 241.0061; found: 241.0042.

***N*-(4,6-Dichloropyrimidin-2-yl)thiazol-2-amine (3l)**

Prepared according to the typical procedure for **3a** as a white amorphous solid material, ~90% pure according to ^{1}H NMR analysis; yield: 384 mg (starting with 2.2 mmol of **1** as the limiting reagent).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.70 (s, 1 H), 8.33 (dd, *J* = 1.89, 5.04 Hz, 1 H), 8.02 (d, *J* = 8.20 Hz, 1 H), 7.76–7.88 (m, 1 H), 7.27–7.34 (m, 1 H), 7.03–7.14 (m, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6, major signals): δ = 164.4, 162.4, 160.9, 160.4, 158.7, 156.6, 137.7, 113.8, 112.1.

MS (ESI): *m*/*z* (%) = 251 (13), 250 (4), 249 (69), 248 (7), 247 (100, [M + H]$^+$), 213 94), 211 (9), 102 (4).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_5Cl_2N_4S$: 246.9606; found: 246.9626.

4,6-Dichloro-*N*-(pyridin-3-yl)pyrimidin-2-amine (3m)

Prepared according to the typical procedure for **3a** as an amorphous white solid material after column chromatography (silica gel, EtOAc–hexanes, gradient from 1:4 to 1:0, then to EtOAc–MeOH, ~20:1); yield: 184 mg (38%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.82 (s, 1 H), 8.94 (d, *J* = 2.52 Hz, 1 H), 8.38 (dd, *J* = 1.42, 4.89 Hz, 1 H), 8.25 (ddd, *J* = 1.42, 2.68, 8.51 Hz, 1 H), 7.62 (dd, *J* = 5.04, 8.51 Hz, 1 H), 7.35 (s, 1 H).

APT NMR (126 MHz, DMSO-d_6): δ = 161.1, 158.6, 141.1, 138.2, 136.6, 129.2, 124.8, 111.7.

MS (ESI): *m*/*z* (%) = 245 (10), 244 (6), 243 (63), 242 (9), 241 (100, [M + H]$^+$), 207 (4), 206 (1), 205 (12), 102 (3).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_7Cl_2N_4$: 241.0061; found: 241.0063.

4,6-Dichloro-*N*-ethylpyrimidin-2-amine (5a); Typical Procedure

To **1** (454 mg, 2 mmol) was added THF (3 mL) under N_2, the mixture was cooled to –70 °C (*i*-PrOH/CO_2 bath), 2 M $EtNH_2$ in THF (2 mL, 4 mmol) was added by syringe. The white suspension was stirred for 1.5 h, during which time the bath temperature reached 0 °C. The mixture was diluted with hexane–EtOAc (~1:1), washed with H_2O, and the organic layer was purified by chromatography (silica gel, EtOAc–hexanes, gradient from 0:1 to 1:10) to provide **5a** as a white solid material; yield: 314 mg (82%); mp 96–100 °C (EtOAc–hexane).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.14 (t, *J* = 5.2 Hz, 1 H), 6.84 (s, 1 H), 3.25 (dq, *J* = 5.5, 7.2 Hz, 2 H), 1.10 (t, *J* = 7.3 Hz, 3 H)).

APT NMR (126 MHz, DMSO-d_6): δ = 161.3, 161.1, 160.7, 107.1, 14.1.

MS (ESI): *m*/*z* (%) = 196 (10), 195 (4), 194 (65), 193 (6), 192 (100, [M + H]$^+$), 166 915), 164 (22), 102 (23).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_6H_8Cl_2N_3$: 192.0104; found: 192.0090.

4,6-Dichloro-*N*-phenethylpyrimidin-2-amine (5b)

Prepared according to the typical procedure for **5a** as a white solid material; yield: 490 mg (92%); mp 131–135 °C (EtOAc–hexane).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.24 (t, *J* = 5.7 Hz, 1 H), 7.32–7.26 (m, 2 H), 7.25–7.17 (m, 3 H), 6.86 (s, 1 H), 3.50–3.42 (m, 2 H), 2.82 (t, *J* = 7.4 Hz, 2 H).

APT NMR (126 MHz, DMSO-d_6): δ = 161.4, 161.1, 160.7, 139.2, 128.7, 128.3, 126.1, 107.4, 42.5, 34.4.

MS (ESI): *m*/*z* (%) = 272 (11), 271 (8), 270 (64), 269 (13), 268 (100, [M + H]$^+$), 105 (77), 102 (12).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{12}Cl_2N_3$: 240.0090; found: 240.0424.

4,6-Dichloro-*N*-phenethylpyrimidin-2-amine (5b); Alternate Typical Procedure

To 2-phenylethanamine (0.754 mL, 6 mmol) was added THF (12 mL) and the soln was cooled under N_2 to –70 °C. Then 2.6 M *n*-BuLi in hexane (2.1 mL, 5.5 mmol) was added by syringe. After 15 min at this temperature, to the mixture was slowly added a soln of **1** [454 mg, 2 mmol, in THF (3 mL)] by cannula. After 15 min at this temperature, the mixture was quenched with AcOH, partitioned between H_2O and EtOAc–hexane (~1:1), and the organic layer was concentrated and purified by chromatography (silica gel, EtOAc–

hexanes, gradient 0:1–1:10) and recrystallized (heptane) to provide **5b** as an off-white solid material; yield: 226 mg (42%). The ^{1}H NMR, ^{13}C NMR, and MS data match with the material prepared without use of *n*-BuLi.

_N_-Benzyl-4,6-dichloropyrimidin-2-amine (5c)
Prepared according to typical procedure for **5a** as a white solid material; yield: 487 mg (96%); mp 130–133 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.67 (t, *J* = 6.3 Hz, 1 H), 7.35–7.27 (m, 4 H), 7.27–7.21 (m, 1 H), 6.90 (s, 1 H), 4.47 (d, *J* = 6.3 Hz, 2 H).

APT NMR (126 MHz, DMSO-d_6): δ = 161.5, 161.1, 161.0, 138.8, 128.3, 127.1, 126.9, 107.6, 44.1.

MS (ESI): *m*/*z* (%) = 258 (9), 257 (7), 256 (67), 255 (11), 254 (100, $[M + H]^+$), 178 (12), 176 (19), 102 (15).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}Cl_2N_3$: 254.0246; found: 240.0262.

6-Chloro-_N_-cyclohexyl-2-(methylsulfonyl)pyrimidin-4-amine (4d) and 4,6-Dichloro-_N_-cyclohexylpyrimidin-2-amine (5d)
To **1** (313 mg, 1.38 mmol) was added THF (3 mL) then at r.t. under N_2 $CyNH_2$ (0.32 mL, 2.8 mmol, 2 equiv) was added; after 20 min a white precipitate formed. The mixture was diluted with CH_2Cl_2, filtered through a short plug of silica gel, concentrated, and purified by chromatography (silica gel, EtOAc–hexanes, gradient 1:50 to 1:1). Concentration of the less polar fractions provided **5d** as a white solid material; yield: 259 mg (77%). Concentration of the more polar fractions provided **4d** as a colorless oily material; yield: 8 mg (2%).

2-Cyclohexylamino Product 5d
^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.09 (d, *J* = 7.9 Hz, 1 H), 6.75–6.68 (m, 1 H), 3.68–3.54 (m, 1 H), 1.88–1.74 (m, 2 H), 1.74–1.60 (m, 2 H), 1.54 (td, *J* = 3.8, 13.2 Hz, 1 H), 1.32–1.15 (m, 4 H), 1.15–0.99 (m, 1 H).

APT NMR (126 MHz, DMSO-d_6): δ = 161.1, 160.7, 160.6, 106.8, 49.6, 31.9, 25.2, 24.6

LC-MS (ESI): *m*/*z* = 246 $[M + H]^+$.

2-Methylsulfonyl Product 4d
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16–7.11 (m, 1 H), 5.59–5.43 (m, 1 H), 3.97–3.77 (m, 1 H), 3.15 (m, 3 H), 2.01 (br s, 2 H), 1.81–1.71 (m, 2 H), 1.52–1.34 (m, 2 H), 1.34–1.19 (m, 4 H).

LC-MS (ESI): *m*/*z* = 290 $[M + H]^+$.

4,6-Dichloro-_N_-cyclohexylpyrimidin-2-amine (5d); Alternate Preparation
To $CyNH_2$ (0.23 mL, 2 mmol) was added THF (3 mL) and the soln was cooled under N_2 in an ice bath (0 °C). Then 1 M *i*-PrMgCl·LiCl in THF (2 mL, 2 mmol) was added by syringe and after 5 min at this temperature, the mixture was cooled to –60 °C. A soln of **1** [227 mg, 1 mmol, in THF (2 mL)] was added slowly by cannula. After 15 min at this temperature, the reaction was continued in an ice bath for 10 min, then the mixture was quenched with AcOH, partitioned between H_2O and EtOAc–hexane, (~1:1). The organic layer was concentrated and purified by chromatography (silica gel, EtOAc–hexanes, gradient 0:1–1:5) to provide **5d** as a light yellow solid material; yield: 161 mg (65%). The ^{1}H NMR and MS data match with the material prepared without use of *i*-PrMgCl·LiCl.

6-Chloro-_N_-ethyl-_N_-methyl-2-(methylsulfonyl)pyrimidin-4-amine (4e)
To **1** (454 mg, 2 mmol) was added THF (3 mL) then the mixture was cooled to –70 °C under N_2 and MeEtNH (0.36 mL, 4.2 mmol) was added by syringe. After 1.5 h the bath temperature reached 0 °C, the mixture was quenched with AcOH, partitioned between H_2O and EtOAc, and the organic layer was concentrated and purified by chromatography (silica gel, EtOAc–hexanes, gradient 1:50 to 1:1) to provide **4e** as a white solid material; yield: 383 mg (77%); mp 118–121 °C (EtOAc–hexane).

^{1}H NMR (500 MHz, DMSO-d_6, mixture of two rotamers ~0.44:0.55): δ = 7.10 (br s, 0.44 H), 6.97 (s, 0.53 H), 3.67 (q, *J* = 6.1 Hz, 1.1 H), 3.53 (q, *J* = 6.9 Hz, 0.9 H), 3.32 (s, 3 H), 3.14 (br s, 1.3 H), 3.07 (s, 1.7 H), 1.11 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6, signals for both rotamers): δ = 164.8, 164.6, 162.0, 161.8, 158.8, 103.7, 103.5, 44.4, 44.3, 38.7, 35.4, 34.9, 11.7, 11.2.

MS (ESI): *m*/*z* (%) = 272 (4, $[M + Na]^+$), 254 (1), 253 (3), 252 (37), 251 (8), 250 (100, $[M + H]^+$), 190 (2), 188 (6), 102 (8).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{13}ClN_3O_2S$: 250.0412; found: 250.0431.

6-Chloro-_N_,_N_-diethyl-2-(methylsulfonyl)pyrimidin-4-amine (4f) and 4,6-Dichloro-_N_,_N_-diethylpyrimidin-2-amine (5f); Typical Procedure
To **1** (454 mg, 2 mmol) was added THF (6 mL), cooled to –70 °C under N_2 and Et_2NH (0.42 mL, 4 mmol, 2 equiv) was added by syringe. After 55 min the bath temperature reached +8 °C, the mixture was quenched with AcOH, diluted with EtOAc–toluene (~1:1), and washed with H_2O. The organic layer was filtered through a short plug of silica gel, concentrated, and purified by chromatography (silica gel, EtOAc–hexanes, gradient 0:1 to 1:0). Concentration of the less polar fractions provided **5f** as a colorless oily material; yield: 19 mg (4%). Concentration of the more polar fractions provided **4f** as a white solid material; yield: 453 mg (86%).

2-Diethylamino Product 5f
^{1}H NMR (500 MHz, acetone-d_6): δ = 6.66 (s, 1 H), 3.62 (q, *J* = 7.3 Hz, 4 H), 1.17 (t, *J* = 7.1 Hz, 6 H).

APT NMR (126 MHz, acetone-d_6): δ = 162.8, 108.0, 43.6, 13.5; one signal could not be found

2-Methylsulfonyl Product 4f
Mp 109–112 °C (EtOAc–hexanes).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.02 (s, 1 H), 3.62 (q, *J* = 6.7 Hz, 2 H), 3.51 (q, *J* = 6.8 Hz, 2 H), 3.32 (s, 3 H), 1.17–1.08 (m, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 164.8, 161.2, 158.8, 103.4, 42.6, 42.5, 38.6, 12.3, 12.0.

MS (ESI): *m*/*z* (%) = 286 (4, $[M + Na]^+$), 268 (1), 267 (3), 266 (36), 265 (9), 264 (100, $[M + H]^+$), 202 (5), 102 (5).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{15}ClN_3O_2S$: 264.0568; found: 264.0590.

4-Chloro-2-(methylsulfonyl)-6-(piperidin-1-yl)pyrimidine (4g) and 4,6-Dichloro-2-(piperidin-1-yl)pyrimidine (5g)
Prepared according to the typical procedure for **4f** and **5f**. The less polar fractions provided **5g** as a white solid material; yield: 123 mg (27%). Concentration of the more polar fractions provided **4g** as a white solid material; yield: 378 mg (69%).

2-Piperidin-1-yl Product 5g
Mp 73–79 °C (EtOAc–hexanes).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 6.84 (s, 1 H), 3.69 (t, *J* = 5.7 Hz, 4 H), 1.67–1.58 (m, 2 H), 1.56–1.45 (m, 4 H).

APT NMR (126 MHz, acetone-d_6): δ = 162.8, 108.0, 43.6, 13.5; one signal could not be found

MS (ESI): *m*/*z* (%) = 236 (10), 235 (5), 234 (64), 233 (9), 232 (100, $[M + H]^+$), 102 (15).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_9H_{12}Cl_2N_3$: 232.0403; found: 232.0417.

2-Methylsulfonyl Product 4g
Mp 140–145 °C (EtOAc–hexanes).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.20 (s, 1 H), 3.79 (br s, 2 H), 3.62 (br s, 2 H), 3.30 (s, 3 H), 1.69–1.61 (m, 2 H), 1.61–1.49 (m, 4 H).

^{13}C NMR (126 MHz, DMSO-d_6, signals for the two rotamers): δ = 164.8, 161.6, 159.2, 103.7, 38.7, 25.1, 23.7; additionally, two signals for the C-atoms on the piperidine, α to the N-atom are found from HSQC (45.0, 46.2, see Supporting Information for the spectrum).

MS (ESI): *m*/*z* (%) = 298 (100, [M + Na]$^+$), 280 (1), 279 (4), 278 (36), 277 (10), 276 (100, [M + H]$^+$), 136 (2).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{15}ClN_3O_2S$: 276.0568; found: 276.0591.

_N_-*tert*-Butyl-6-chloro-2-(methylsulfonyl)pyrimidin-4-amine (4h) and _N_-*tert*-Butyl-4,6-dichloropyrimidin-2-amine (5h)

To **1** (454 mg, 2 mmol) was added THF (3 mL) and the mixture was cooled to –70 °C under N_2. *t*-BuNH_2 (0.42 mL, 4 mmol, 2 equiv) was added by syringe. After 1 h the bath temperature reached 0 °C. The mixture was kept at this temperature for additional 30 min; the LC-MS analysis of the mixture showed that the reaction had stalled with ~7% of **1** remaining. The mixture was quenched with AcOH, partitioned between H_2O and mixture EtOAc–hexane (~1:1), and the organic layer was purified by chromatography (silica gel, EtOAc–hexanes, gradient 1:20–1:1). The less polar fractions provided **5h** as a white solid material; yield: 142 mg (32%). Concentration of the more polar fractions provided still impure **4h** as a colorless oily material; yield: 83 mg (16%).

2-*tert*-Butylamino Product 5h

Mp 112–114 °C (EtOAc–hexanes).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.90 (s, 1 H), 6.84 (s, 1 H), 1.34 (s, 9 H).

APT NMR (126 MHz, DMSO-d_6): δ = 160.7, 107.0, 50.9, 28.1; one signal could not be found. It may be the broad signal around δ = 160.0–160.7, see the Supporting Information for the spectrum.

LC-MS (ESI): *m*/*z* (%) = 220 [M + H]$^+$.

2-Methylsulfonyl Product 4h

^{1}H NMR (500 MHz, acetone-d_6): δ = 7.29 (br s, 1 H), 6.70 (s, 1 H), 3.27 (s, 3 H), 1.49 (s, 9 H).

LC-MS (ESI): *m*/*z* (%) = 264 [M + H]$^+$.

_N_-(1-Adamantyl)-6-chloro-2-(methylsulfonyl)pyrimidin-4-amine (4i) and _N_-(1-Adamantyl)-4,6-dichloropyrimidin-2-amine (5i)

To **1** (145 mg, 0.64 mmol) was added THF (1.5 mL), adamantan-1-amine (193 mg, 1.28 mmol, 2 equiv), and the mixture was stirred at r.t. under N_2 for 40 min. An unstirrable thick suspension was formed and LC-MS analysis of the mixture showed that the reaction had stalled with ~3% of **1** remaining. The mixture was diluted with EtOAc and CH_2Cl_2, filtered through a short plug of silica gel, and purified by chromatography (silica gel, EtOAc–hexanes, gradient 0:1–1:1). The less polar fractions provided **5i** as a white solid material; yield: 111 mg (58%). Concentration of the more polar fractions provided still impure **4i** as a white solid material; yield: 58 mg (27%).

2-(1-Adamantyl)amino Product 5i

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.82 (s, 1 H), 6.83 (s, 1 H), 2.07–1.97 (m, 9 H), 1.67–1.57 (m, 6 H).

APT NMR (126 MHz, DMSO-d_6): δ = 160.5, 107.0, 51.4, 40.3, 35.9, 28.7; one more signal may be the broad peak around δ = 160.0–160.7, see the Supporting Information for the spectrum.

LC-MS (ESI): *m*/*z* = 298 [M + H]$^+$.

2-Methylsulfonyl Product 4i

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.06 (s, 1 H), 6.70 (s, 1 H), 3.30 (s, 3 H), 2.06 (s, 9 H), 1.65 (br s, 6 H).

LC-MS (ESI): *m*/*z* = 342 [M + H]$^+$.

6-Chloro-_N_-(2,2-difluoroethyl)-2-(methylsulfonyl)pyrimidin-4-amine (4j) and 4,6-Dichloro-_N_-(2,2-difluoroethyl)pyrimidin-2-amine (5j)

To **1** (297 mg, 1.31 mmol) was added THF (3 mL), then at r.t. under N_2 was added 2,2-difluoroethylamine (0.21 mL, 3 mmol, 2.2 equiv), and the mixture was stirred at r.t. under N_2 for 2.5 h. The mixture was diluted with CH_2Cl_2, filtered through a short plug of silica gel, which was washed with EtOAc, and the combined material was purified by chromatography (silica gel, EtOAc–hexanes, gradient 0:1–1:0). The less polar fractions provided **5j** as a white solid material; yield: 143 mg (48%). Concentration of the more polar fractions provided **4j** as a white solid material; yield: 129 mg (36%).

2-(2,2-Difluoroethyl)amino Product 5j

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.49 (t, *J* = 6.1 Hz, 1 H), 7.01 (s, 1 H), 6.10 (tt, *J* = 4.1, 55.5 Hz, 1 H), 3.68 (ddt, *J* = 3.9, 6.1, 15.4 Hz, 2 H).

APT NMR (126 MHz, DMSO-d_6): δ = 161.6, 161.1, 114.3 (t, *J* = 244.3 Hz), 108.8, 43.0 (t, *J* = 26.3 Hz).

LC-MS (ESI): *m*/*z* = 226, 228 [M – H]$^+$.

2-Methylsulfonyl Product 4j

^{1}H NMR (500 MHz, DMSO-d_6, mixture of two rotamers ~4:1): δ = 8.85 (t, *J* = 5.4 Hz, 0.2 H), 8.77 (t, *J* = 4.7 Hz, 0.8 H), 7.15 (s, 0.2 H), 6.84 (s, 0.8 H), 6.20 (tt, *J* = 4.1, 55.8 Hz, 0.8 H), 6.17 (t, *J* = 55.8 Hz, 0.2 H), 3.88 (tt, *J* = 4.7, 15.4 Hz, 1.6 H), 3.78 (t, *J* = 15.1 Hz, 0.4 H), 3.33 (s, 3 H).

APT NMR (126 MHz, DMSO-d_6, only signals of the major rotamer are shown): δ = 165.2, 164.0, 157.8, 114.2 (t, *J* = 240.7 Hz), 106.4, 42.6 (t, *J* = 26.3 Hz), 38.6.

LC-MS (ESI): *m*/*z* = 272 [M + H]$^+$.

6-Chloro-2-(methylsulfonyl)-_N_-(2,2,2-trifluoroethyl)pyrimidin-4-amine (4k)

To **1** (297 mg, 1.31 mmol) was added THF (3 mL), then at r.t. under N_2 was added 2,2,2-trifluoroethylamine (0.21 mL, 1.6 mmol, 1.3 equiv), and the mixture was stirred at r.t. under N_2 for 2.5 h. The mixture was diluted with CH_2Cl_2, filtered through a short plug of silica gel, which was washed with EtOAc, and the combined material was purified by chromatography (silica gel, EtOAc–hexanes, gradient 1:2–1:0) to provide **4k** as a white solid material; yield: 220 mg (58%).

^{1}H NMR (500 MHz, DMSO-d_6, mixture of rotamers ~4:1): δ = 9.14 (br s, 0.2 H), 8.98 (t, *J* = 5.8 Hz, 0.8 H), 7.32 (br s, 0.2 H), 6.89 (s, 0.8 H), 4.39–4.29 (m, 1.6 H), 4.26 (br s, 0.4 H), 3.34 (s, 3 H).

APT NMR (126 MHz, DMSO-d_6, major isomer): δ = 165.0, 164.0, 158.3 (q, *J* = 279.7 Hz), 106.7, 41.09 (q, *J* = 33.6 Hz), 38.6.

LC-MS (ESI): *m*/*z* = 290 [M + H]$^+$.

2-(Methylsulfonyl)-N^4,N^6-diphenylpyrimidine-4,6-diamine (6a); Typical Procedure

To a soln of **2a** (142 mg, 0.50 mmol) and aniline (186 mg, 2.0 mmol) in DMSO (1 mL) in a capped tube was added 2,6-lutidine (0.087 mL, 0.75 mmol) at r.t. The mixture was stirred for 24 h at 90 °C. The mixture was cooled down to r.t. and then H_2O (10 mL) was added to precipitate the product. The product was dried over N_2 to provide **6a** as an off-white amorphous solid material; yield: 148 mg (87%)

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.69 (s, 2 H), 7.47–7.56 (m, 4 H), 7.31–7.38 (m, 4 H), 7.00–7.10 (m, 2 H), 6.25 (d, *J* = 2.5 Hz, 1 H), 3.33 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 164.9, 160.8, 139.4, 129.0, 122.9, 120.4, 120.3, 38.7.

MS (ESI): *m*/*z* (%) = 409 (5), 388 (2), 387 (9), 363 (8), 342 (19), 341 (100, [M + H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}N_4O_2S$: 341.1067; found: 341.1059.

2-(Methylsulfonyl)-*N*^{4}-phenyl-*N*^{6}-(*o*-tolyl)pyrimidine-4,6-diamine (6b)

Prepared according to the typical procedure for **6a** as pale yellow viscous oily material; yield: 135 mg (76%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.69 (s, 1 H), 8.22 (s, 1 H), 7.56–7.61 (m, 2 H), 7.41–7.46 (m, 1 H), 7.31–7.37 (m, 3 H), 7.28 (td, *J* = 7.6, 1.6 Hz, 1 H), 7.18–7.23 (m, 1 H), 7.07 (tt, *J* = 7.4, 1.1 Hz, 1 H), 5.88 (s, 1 H), 3.24 (s, 3 H), 2.31 (s, 3 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 166.8, 163.7, 162.6, 140.5, 137.6, 134.7, 132.0, 129.9, 127.7, 127.2, 126.9, 124.1, 121.5, 85.7, 38.3, 18.2.

MS (ESI): *m*/*z* (%) = 377 (11), 357 (4), 356 (20), 355 (100, [M + H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}N_4O_2S$: 355.1229; found: 355.1215.

2-(Methylsulfonyl)-*N*^{4}-phenyl-*N*^{6}-(*m*-tolyl)pyrimidine-4,6-diamine (6c)

Prepared according to the typical procedure for **6a** as pale yellow viscous oily material; yield: 138 mg (78%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.70 (s, 1 H), 8.64 (s, 1 H), 7.58 (dd, *J* = 8.5, 0.9 Hz, 2 H), 7.34–7.40 (m, 4 H), 7.21–7.28 (m, 1 H), 7.10 (tt, *J* = 7.4, 1.1 Hz, 1 H), 6.93 (dd, *J* = 7.3, 0.6 Hz, 1 H), 6.30 (s, 1 H), 3.28 (s, 3 H), 2.33 (s, 3 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 166.8, 162.7, 140.5, 140.3, 139.8, 130.1, 130.0, 125.4, 124.6, 122.8, 122.1, 122.1, 119.3, 87.0, 39.5, 21.7.

MS (ESI): *m*/*z* (%) = 377 (9), 357 (3), 356 (19), 355 (100, [M + H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}N_4O_2S$: 355.1229; found: 355.1216.

2-(Methylsulfonyl)-*N*^{4}-phenyl-*N*^{6}-(*p*-tolyl)pyrimidine-4,6-diamine (6d)

Prepared according to the typical procedure for **6a** as an off-white amorphous solid material; yield: 168 mg (95%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.69 (br s, 1 H), 8.60 (br s, 1 H), 7.58 (d, *J* = 6.9 Hz, 2 H), 7.40–7.46 (m, 2 H), 7.36 (t, *J* = 7.4 Hz, 2 H), 7.18 (d, *J* = 7.6 Hz, 2 H), 7.06–7.12 (m, 1 H), 6.24 (s, 1 H), 3.27 (s, 3 H), 2.31 (s, 3 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 166.7, 162.7, 162.5, 140.4, 137.6, 134.2, 130.5, 129.9, 124.3, 122.5, 121.9, 121.7, 86.6, 39.4, 20.9.

MS (ESI): *m*/*z* (%) = 377 (8), 357 (4), 356 (19), 355 (100, [M + H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}N_4O_2S$: 355.1229; found: 355.1216.

***N*^{4}-(4-Chlorophenyl)-2-(methylsulfonyl)-*N*^{6}-phenylpyrimidine-4,6-diamine (6e)**

Prepared according to the typical procedure for **6a** as an off-white amorphous solid material; yield: 177 mg (95%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.88 (s, 1 H), 8.79 (s, 1 H), 7.62–7.68 (m, 2 H), 7.54–7.60 (m, 2 H), 7.35–7.41 (m, 4 H), 7.08–7.16 (m, 1 H), 6.29 (s, 1 H), 3.29 (s, 3 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 166.6, 162.5, 162.2, 140.2, 139.4, 130.0, 129.8, 128.4, 124.6, 123.0, 122.1, 39.3.

MS (ESI): *m*/*z* (%) = 399 (3), 398 (1), 397 (8), 378 (7), 377 (36), 376 (19), 375 (100, [M + H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}ClN_4O_2S$: 375.0682; found: 375.0668.

6-Chloro-*N*^{2}-cyclohexyl-*N*^{4}-phenylpyrimidine-2,4-diamine (7a); Typical Procedure

A soln of **2a** (142 mg, 0.50 mmol) and $CyNH_2$ (297 mg, 3.0 mmol) in DMSO (3 mL) in a capped tube was stirred for 24 h at r.t. The mixture was diluted with EtOAc (50 mL) and washed with H_2O (30 mL) and then 1 M $KHSO_4$ soln (30 mL). The organic layer was separated and concentrated under the reduced pressure. The product was isolated by column chromatography to provide **7a** as a pale yellow viscous oily material; yield: 142 mg (94%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.38 (br s, 1 H), 7.70 (br s, 2 H), 7.20–7.34 (m, 3 H), 6.92–7.03 (m, 1 H), 5.98 (br s, 1 H), 3.58–3.70 (m, 1 H), 1.55–1.96 (m, 5 H), 1.21–1.35 (m, 4 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 161.6, 160.9, 158.0, 140.1, 128.6, 122.0, 119.5, 92.8, 50.1, 32.3, 25.4, 24.9.

MS (ESI): *m*/*z* (%) = 306 (5), 305 (33), 304 (17), 303 (100, [M + H]$^+$), 223 (2), 221 (7).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{20}ClN_4^+$: 303.1371; found: 303.1399.

2-[4-Chloro-6-(phenylamino)pyrimidin-2-ylamino]ethanol (7b)

Prepared according to the typical procedure for **7a** as pale yellow viscous oily material; yield: 129 mg (98%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.26–9.45 (m, 1 H), 7.67 (br s, 2 H), 7.30 (t, *J* = 7.7 Hz, 2 H), 7.15 (br s, 1 H), 6.93–7.03 (m, 1 H), 6.01 (br s, 1 H), 4.68 (br s, 1 H), 3.54 (br s, 2 H), 3.25–3.38 (m, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 161.8, 161.6, 158.1, 140.0, 128.7, 122.2, 119.7, 119.6, 58.7, 43.6.

MS (ESI): *m*/*z* (%) = 268 (4), 267 (32), 266 (13), 265 (100, [M + H]$^+$), 249 (4), 247 (11).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}ClN_4O^+$: 265.0851; found: 265.0872.

***N*^{2}-Benzyl-6-chloro-*N*^{4}-phenylpyrimidine-2,4-diamine (7c)**

Prepared according to the typical procedure for **7a** as pale yellow viscous oily material; yield: 135 mg (87%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.37 (s, 1 H), 7.93 (br s, 1 H), 7.74 (br s, 1 H), 7.48 (d, *J* = 3.8 Hz, 1 H), 7.26–7.35 (m, 5 H), 7.21 (br s, 2 H), 6.01 (br s, 1 H), 4.47 (d, *J* = 6.0 Hz, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 161.7, 161.6, 140.2, 139.7, 128.6, 128.2, 126.5, 122.1, 119.7, 44.2.

MS (ESI): *m*/*z* (%) = 314 (6), 313 (33), 311 (100, [M + H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}ClN_4^+$: 311.1058; found: 311.1081.

2-(Methylsulfonyl)-*N*,6-diphenylpyrimidin-4-amine (8a); Typical Procedure

A mixture of **2a** (142 mg, 0.50 mmol), phenylboronic acid (91 mg, 0.75 mmol), $PdCl_2$(dppf) (18 mg, 5 mol%), and K_2CO_3 (276 mg, 2.0 mmol) in DME (3 mL) and H_2O (0.8 mL) in a capped tube was stirred for 4 h under N_2 at 60 °C. The mixture was cooled to r.t. and purified by column chromatography to provide **8a** as an off-white amorphous solid material; yield: 146 mg (90%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.33 (s, 1 H), 8.02–8.11 (m, 2 H), 7.72 (d, *J* = 7.9 Hz, 2 H), 7.55–7.61 (m, 3 H), 7.42 (dd, *J* = 8.5, 7.6 Hz, 2 H), 7.38 (s, 1 H), 7.13 (s, 1 H), 3.43 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 165.5, 161.9, 161.5, 138.7, 135.4, 131.2, 129.1, 129.1, 126.7, 123.6, 120.4, 38.8.

MS (ESI): *m*/*z* (%) = 349 (2), 348 (13), 328 (4), 327 (18), 326 (100, [M + H]$^+$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}N_3O_2S$: 326.0958; found: 326.0949.

2-(Methylsulfonyl)-*N*-phenyl-6-(*m*-tolyl)pyrimidin-4-amine (8b)

Prepared according to the typical procedure used **8a** as an off-white amorphous solid material; yield: 157 mg (93%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 9.30 (br s, 1 H), 7.95 (s, 1 H), 7.88–7.93 (m, 1 H), 7.74–7.81 (m, 2 H), 7.34–7.46 (m, 5 H), 7.12–7.19 (m, 1 H), 3.38 (s, 3 H), 2.42 (s, 3 H).

^{1}H NMR (500 MHz, DMSO-d_6) δ = 10.30 (s, 1 H), 7.83–7.91 (m, 2 H), 7.72 (d, J = 7.9 Hz, 2 H), 7.32–7.49 (m, 5 H), 7.13 (t, J = 7.3 Hz, 1 H), 3.44 (s, 3 H), 2.42 (s, 3 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 165.5, 162.0, 161.5, 138.8, 138.4, 135.4, 131.8, 129.1, 129.0, 127.2, 123.9, 123.6, 120.3, 103.8, 38.8, 21.0.

MS (ESI): *m*/*z* (%) = 363 (3), 362 (13), 342 (4), 341 (20), 340 (100, $[M + H]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{18}N_3O_2S^+$: 340.1120; found: 340.1105.

6-(4-Methoxyphenyl)-2-(methylsulfonyl)-*N*-phenylpyrimidin-4-amine (8c)

Prepared according to the typical procedure used **8a** as an off-white amorphous solid material; yield: 160 mg (90%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.22 (s, 1 H), 8.00–8.06 (m, 2 H), 7.70 (d, J = 7.9 Hz, 2 H), 7.40 (dd, J = 8.5, 7.6 Hz, 2 H), 7.28 (s, 1 H), 7.08–7.14 (m, 3 H), 3.83 (s, 3 H), 3.42 (s, 3 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 165.4, 161.8, 161.6, 161.4, 138.9, 129.0, 128.4, 127.6, 123.4, 120.2, 114.4, 102.4, 55.4, 38.8.

MS (ESI): *m*/*z* (%) = 378 (8), 358 (3), 357 (19), 356 (100, $[M + H]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{18}N_3O_3S$: 356.1069; found: 356.1054.

6-(4-Fluorophenyl)-2-(methylsulfonyl)-*N*-phenylpyrimidin-4-amine (8d)

Prepared according to the typical procedure used **8a** as an off-white amorphous solid material; yield: 161 mg (94%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.34 (s, 1 H), 8.10–8.18 (m, 2 H), 7.71 (d, J = 7.9 Hz, 2 H), 7.39–7.45 (m, 4 H), 7.35 (s, 1 H), 7.14 (t, J = 7.4 Hz, 1 H), 3.43 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 165.5, 164.9, 163.0, 161.5, 160.8, 138.7, 131.9, 129.3, 129.2, 129.1, 123.7, 120.4, 116.2, 116.0, 38.8.

MS (ESI): *m*/*z* (%) = 367 (2), 366 (12), 346 (4), 345 (19), 344 (100, $[M + H]^+$).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{15}FN_3O_2S$: 344.0869; found: 344.0855.

6-Chloro-N^2-(2-chlorophenyl)-N^4-phenylpyrimidine-2,4-diamine (9a); Typical Procedure

2-Chloro-*N*-phenylformamide (155 mg, 1 mmol) and **2a** (142 mg, 0.5 mmol) were dissolved in THF (3 mL) under N_2, and the soln was cooled to 0 °C using an ice bath. To this soln was added dropwise 1.4 M NaO*t*-Am in THF (0.7 mL, 1 mmol). The mixture was stirred at 0 °C for 30 min. LC-MS analysis showed consumption of the starting material **2a**. Aq 1 M NaOH (2 mL, 2 mmol) was added and the mixture was stirred at r.t. for 30 min. LC-MS analysis showed clean formation of the desired product **9a**. The mixture was extracted with EtOAc. The organic layer was collected, dried, and concentrated. The product was purified by flash chromatography to provide **9a** as a white solid material; yield: 152 mg (92%); mp 108–110 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.35 (dd, J = 8.4, 1.5 Hz, 1 H), 7.37 (br s, 1 H), 7.32–7.27 (m, 3 H), 7.23 (d, J = 8.4 Hz, 2 H), 7.17–7.11 (m, 2 H), 6.75 (br s, 1 H), 6.14 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.4, 160.4, 159.0, 137.5, 135.7, 129.4, 129.1, 127.2, 125.4, 123.04, 122.99, 122.8, 121.1, 95.2.

MS (ESI): *m*/*z* (%) = 331 (100, $[M + H]^+$), 333 (63).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{13}Cl_2N_4$: 331.0517; found: 331.0507.

6-Chloro-N^2-(3-chlorophenyl)-N^4-phenylpyrimidine-2,4-diamine (9b)

Prepared according to the typical procedure for **9a** as a white solid material; yield: 144 mg (87%); mp 147–148 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77 (t, J = 2.1 Hz, 1 H), 7.45–7.39 (m, 2 H), 7.34 (d, J =7.6 Hz, 2 H), 7.29 (dd, J = 8.2, 1.3 Hz, 1 H), 7.25–7.15 (m, 3 H), 7.04–6.98 (ddd, J = 8.0, 2.0, 1.0 Hz, 1 H), 6.93 (br s, 1 H), 6.21 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.4, 160.3, 159.0, 140.2, 137.4, 134.5, 129.7, 129.5, 125.4, 123.0, 122.7, 119.4, 117.5, 95.1.

MS (ESI): *m*/*z* (%) = 331 (100, $[M + H]^+$), 333 (61).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{13}Cl_2N_4$: 331.0517; found:331.0507.

6-Chloro-N^2-(4-chlorophenyl)-N^4-phenylpyrimidine-2,4-diamine (9c)

Prepared according to the typical procedure for **9a** as a white solid material; yield: 126 mg (95%); mp 180–182 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55–7.49 (m, 2 H), 7.45–7.38 (m, 2 H), 7.37–7.31 (m, 2 H), 7.29–7.25 (m, 2 H), 7.23 (tt, J = 7.3, 1.2 Hz, 1 H), 7.00 (br s, 1 H), 6.72 (br s, 1 H), 6.20 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.4, 160.3, 159.1, 137.6, 137.5, 129.5, 128.8, 127.7, 125.4, 123.1, 120.8, 94.9.

MS (ESI): *m*/*z* (%) = 331 (100, $[M + H]^+$), 333 (63).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{13}Cl_2N_4$: 331.0517; found:331.0508.

6-Chloro-N^2-(4-methoxyphenyl)-N^4-phenylpyrimidine-2,4-diamine (9d)

Prepared according to the typical procedure for **9a** as a white solid material; yield: 161 mg (99%); mp 148–150 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.42 (m, 2 H), 7.39–7.36 (m, 2 H), 7.32 (d, J = 7.3 Hz, 2 H), 7.19 (tt, J = 7.5, 0.9 Hz, 1 H), 6.67 (br s, 1 H), 6.94–6.83 (m, 2 H), 6.80 (br s, 1 H), 6.15 (s, 1 H), 3.81 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.4, 160.3, 159.8, 155.9, 137.8, 132.0, 129.4, 125.1, 122.8, 122.3, 114.1, 94.1, 55.6.

MS (ESI): *m*/*z* (%) = 327 (100, $[M + H]^+$), 329 (32).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{16}ClN_4O$: 327.1013; found:327.1004.

6-Chloro-N^2-(4-nitrophenyl)-N^4-phenylpyrimidine-2,4-diamine (9e)

Prepared according to the typical procedure for **9a** as a pale yellow solid material; yield: 131 mg (96%); mp 221–223 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.36 (br s, 1 H), 9.79 (br s, 1 H), 8.14 (d, J = 9.1 Hz, 2 H), 7.95 (d, J = 9.5 Hz, 2 H), 7.61 (d, J = 7.9 Hz, 2 H), 7.41 (t, J = 7.9 Hz, 2 H), 7.15 (t, J = 7.4 Hz, 1 H), 6.37 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.7, 158.4, 157.8, 146.7, 140.6, 138.8, 128.9, 124.7, 123.6, 121.3, 118.1, 97.4.

MS (ESI): *m*/*z* (%) = 342 (100, $[M + H]^+$), 344 (32).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{13}ClN_5O_2$: 342.0758; found: 342.0747.

6-Chloro-N^2-phenethyl-N^4-phenylpyrimidin-2,4-diamine (9f)

Prepared according to the typical procedure for **9a** as an amorphous solid material; yield: 147 mg (91%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.35 (m, 4 H), 7.32–7.29 (m, 2 H), 7.24–7.21 (m, 3 H), 7.18–7.15 (m, 1 H), 6.77 (br s, 1 H), 6.02 (s, 1 H), 5.39 (br, 1 H), 3.66 (q, *J* = 6.7 Hz, 2 H), 2.89 (t, *J* = 6.7 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 162.3, 161.8, 160.3, 139.1, 138.1, 129.3, 128.8, 128.5, 126.3, 124.6, 122.3, 92.8, 42.6, 35.8.

MS (ESI): *m*/*z* (%) = 325 (100, $[M + H]^+$), 327 (32).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{18}ClN_4^+$: 325.1215; found: 325.1240.

1-[4-Chloro-6-(phenylamino)pyrimidin-2-yl]piperidin-2-one (9g)

Prepared according to the typical procedure for **9a** as an amorphous solid material; yield: 103 mg (68%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (br s, 1 H), 7.36–7.31 (m, 4 H,), 7.16–7.13 (m, 1 H), 6.45 (s, 1 H), 3.82–3.80 (m, 2 H), 2.55 (t, *J* = 6.5 Hz, 2 H), 1.93–1.85 (m, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.2, 162.6, 160.3, 137.6, 129.4, 125.1, 122.3, 100.7, 48.7, 33.7, 22.9, 21.0.

MS (ESI): *m*/*z* (%) = 303 (100, $[M + H]^+$), 305 (32).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{16}ClN_4O$: 303.1013; found: 303.1031.

6-Chloro-*N*,2-diphenylpyrimidin-4-amine (10a); Typical Procedure

Compound **2a** (115 mg, 0.4 mmol) was dissolved in THF (2 mL) under N_2 and cooled to 0 °C. A 2 M soln of PhMgCl in THF (0.5 mL, 1 mmol) was added and the mixture was stirred at 0 °C for 1 h. LC-MS analysis showed consumption of the starting material. The mixture was quenched with brine and extracted with EtOAc. The organic layer was dried and concentrated in vacuo. The residue was purified by chromatography to provide **10a** as a white solid material; yield: 109 mg (95%); mp 136–137 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.41–8.39 (m, 2 H), 7.51–7.42 (m, 5 H), 7.37 (d, *J* = 7.4 Hz, 2 H), 7.24 (tt, *J* = 7.4, 1.0 Hz, 1 H), 7.04 (br s, 1 H), 6.61 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.0, 162.2, 161.0, 137.6, 136.6, 131.1, 129.6, 128.45, 128.42, 125.5, 122.8, 100.6.

MS (ESI): *m*/*z* (%) = 282 (100, $[M + H]^+$), 284 (33).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{13}ClN_3$: 282.0798; found: 282.0787.

6-Chloro-*N*-phenyl-2-[3-(trifluoromethoxy)phenyl]pyrimidin-4-amine (10b)

Prepared according to the typical procedure for **10a** as an amorphous solid material; yield: 71 mg (97%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.36 (dt, *J* = 7.9, 1.3 Hz, 1 H), 8.29 (s, 1 H), 7.51 (t, *J* = 8 Hz, 1 H), 7.46–7.45 (m, 2 H), 7.39–7.35 (m, 3 H), 7.29–7.26 (m, 1 H), 7.05 (br s, 1 H), 6.65 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.5, 162.2, 161.0, 149.5, 138.8, 137.3, 129.8, 129.7, 126.7, 125.7, 123.4, 122.9, 121.6, 120.9, 101.1.

MS (ESI): *m*/*z* (%) = 366 (100, $[M + H]^+$), 368 (31).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{12}ClF_3N_3O$: 366.0621; found: 366.0609.

6-Chloro-2-(4-fluorophenyl)-*N*-phenylpyrimidin-4-amine (10c)

Prepared according to the typical procedure for **10a** as a white solid material; yield: 56 mg (93%); mp 122–123 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.41–8.38 (m, 2 H), 7.45–7.41 (m, 2 H), 7.36 (d, *J* = 7.5 Hz, 2 H), 7.25 (tt, *J* = 7.4, 0.9 Hz, 1 H), 7.15–7.12 (m, 2 H), 7.01 (br s, 1 H), 6.59 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 165.9, 164.0, 163.9, 162.1, 160.9, 137.4, 132.74, 132.71, 130.6, 129.6, 125.5, 122.8, 115.4, 115.3, 100.4.

MS (ESI): *m*/*z* (%) = 300 (100, $[M + H]^+$), 302 (32).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{12}ClFN_3$: 300.0704; found: 300.0692.

6-Chloro-2-[2-(1,3-dioxan-2-yl)ethyl]-*N*-phenylpyrimidin-4-amine (10d)

Prepared according to the typical procedure for **10a** as an amorphous solid material; yield: 154 mg (96%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.36 (m, 2 H), 7.33–7.31 (m, 2 H), 7.20–7.17 (m, 2 H), 6.51 (s, 1 H), 4.6 (t, *J* = 5 Hz, 1 H), 4.08 (ddd, *J* = 11.8, 4.9, 0.9 Hz, 2 H), 3.76–3.71 (m, 2 H), 2.86–2.83 (m, 2 H), 2.11–2.02 (m, 3 H), 1.33–1.29 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.3, 162.1, 160.3, 137.6, 129.6, 125.4, 122.7, 101.5, 100.0, 66.9, 33.4, 33.0, 25.8.

MS (ESI): *m*/*z* (%) = 320 (100, $[M + H]^+$), 322 (31).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{19}ClN_3O_2$: 320.1166; found: 320.1186.

4-Chloro-6-(methylsulfonyl)pyrimidine (11c)

To 4-chloro-6-(methylthio)pyrimidine (1 g, 6.2 mmol) was added CH_2Cl_2 (20 mL), and the mixture was cooled in an ice bath. MCPBA (77% pure, 3.1 g, 13.6 mmol, 2.2 equiv) was added and the mixture was stirred for 20 h with slow warming to r.t. To the material was added $MgSO_4$, the mixture was filtered, the filtrate was concentrated, dissolved in EtOAc, and washed with aq $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered through a plug of silica gel, concentrated, and washed with a mixture of hexane and Et_2O to provide **11c** as an off-white solid material; yield: 855 mg (71%); mp 125–127 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.34 (d, *J* = 0.9 Hz, 1 H), 8.30 (d, *J* = 0.9 Hz, 1 H), 3.40 (s, 3 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 168.1, 164.7, 160.3, 119.3, 39.9

LC-MS (ESI): *m*/*z* = 193, 195 $[M + H]^+$.

6-Chloro-*N*-ethylpyrimidin-4-amine (12c-1) and *N*-Ethyl-6-(methylsulfonyl)pyrimidin-4-amine (13c-3)

To 4-chloro-6-(methylsulfonyl)pyrimidine (**11c**, 297 mg, 1.54 mmol) was added THF (2 mL), then under N_2 the mixture was cooled to –70 °C. 2 M $EtNH_2$ in THF (1.9 mL, 3.9 mmol, 2.5 equiv) was added by syringe, and the mixture was stirred with slow warming to r.t. under N_2 for 70 min. The mixture was filtered through a plug of silica gel, concentrated, and purified by chromatography (silica gel, EtOAc–hexanes, gradient 1:4–1:0). The less polar fractions upon concentration provided **12c-1** as a white solid material; yield: 198 mg (83%). The more polar fractions upon concentration provided **13c-3** as an off-white solid material; yield: 43 mg (14%).

6-Chloro Product 12c-1

Mp 124–126 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.25 (br s, 1 H), 7.70 (br s, 1 H, NH), 6.47 (br s, 1 H), 3.38–3.09 (m, 2 H, CH_2), 1.11 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.0, 158.5, 156.8, 103.5, 35.0, 14.3.

LC-MS (ESI): *m*/*z* = 158, 160 $[M + H]^+$.

6-Methylsulfonyl Product 13c-3

Mp 72–75 °C.

^{1}H NMR (500 MHz, acetone-d_6, mixture of rotamers ~10:1): δ = 8.55 (distorted br s, 1 H), 7.26 (distorted br s, 1 H), 7.11–6.88 (m, 1 H), 3.47 (distorted t, *J* = 6.6 Hz, 2 H), 3.15 (s, 3 H), 1.22 (distorted t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 164.7, 164.6, 160.4, 103.4, 39.8, 36.9, 15.0.

LC-MS (ESI): m/z = 202 $[M + H]^+$.

2-Chloro-6-(methylsulfonyl)pyrazine (11d)

To 2,6-dichloropyrazine (4.811 g, 32.3 mmol) was added MeCN (30 mL), then NaSMe (5.19 g, 74 mmol, 2.3 equiv), the mixture was stirred at r.t. under N_2 for 1 h, then more NaSMe was added (~1 g). After 30 min the mixture was heated to 60 °C for 30 min, then cooled, diluted with a mixture of hexanes and CH_2Cl_2, filtered through a plug of silica gel, and concentrated to provide crude **11d** as a yellow oily material (~50% pure according to ^{1}H NMR analysis, 4.27 g). This material was dissolved in CH_2Cl_2 (100 mL), cooled in an ice bath, then MCPBA (77% pure, 13.5 g, 60 mmol) was added in 2 portions. The mixture was stirred for 15 h with slow warming to r.t., then concentrated, purified by chromatography (silica gel, EtOAc–hexane, gradient 1:10 to 1:1, poor separation, streaking), and crystallization (EtOAc–hexanes) to provide **11d** as a white solid material; yield: 2.19 g (35%); mp 112–117 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.22 (s, 1 H), 9.19 (s, 1 H), 3.38 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 151.9, 149.3, 148.0, 140.3, 40.7.

LC-MS (ESI): m/z = 193 $[M + H]^+$.

6-(Methylsulfonyl)-*N*-phenylpyrazin-2-amine (13d-1)

To 2-chloro-6-(methylsulfonyl)pyrazine (**11d**, 291 mg, 1.51 mmol) was added aniline (0.17 mL, 1.8 mmol, 1.2 equiv), 2,6-lutidine (0.21 mL, 1.8 mmol, 1.2 equiv), and DMSO (1.5 mL), and the mixture was heated under N_2 at 80 °C for 26 h. Additional aniline (0.1 mL, ~0.7 equiv) was added and the mixture was heated for additional 25 h. At this point LC-MS analysis of the mixture showed complete consumption of **11d**. The mixture was cooled to r.t., diluted with H_2O, filtered, washed with H_2O, then Et_2O. The solid material was dissolved in hot mixture of EtOAc–MeOH, dried ($MgSO_4$), filtered through a plug of silica gel, concentrated, then washed with EtOAc and then Et_2O to provide **13d-1** as a light brown amorphous solid material; yield: 275 mg (73%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.14 (s, 1 H), 8.48 (s, 1 H), 8.40 (s, 1 H), 7.71 (dd, J = 1.1, 8.7 Hz, 2 H), 7.38 (dd, J = 7.3, 8.5 Hz, 2 H), 7.06 (tt, J = 1.3, 7.3 Hz, 1 H), 3.30 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 151.1, 149.5, 139.9, 139.4, 129.0, 128.9, 122.7, 118.8, 40.1.

MS (ESI): m/z (%) = 252 (4), 251 (11), 250 (100, $[M + H]^+$), 102 (4).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{12}N_3O_2S$: 250.0645; found: 250.0655.

***N*,*N*-Diethyl-6-(methylsulfonyl)pyrazin-2-amine (13d-2)**

To 2-chloro-6-(methylsulfonyl)pyrazine (**11d**, 193 mg, 1 mmol) was added THF (1 mL), then the mixture was cooled under N_2 to –60 °C. Et_2NH (0.23 mL, 2.2 mmol) was added by syringe and the mixture was warmed to r.t. over 3 h. After 1.5 h at r.t. the mixture was heated to 40 °C for 3 h, then additional Et_2NH (0.11 mL, 1 mmol) was added and the mixture was left at r.t. for 28 h. At this point the LC-MS analysis of the mixture showed complete consumption of **11d**. The mixture was concentrated and purified by chromatography (silica gel, EtOAc–hexane, gradient 1:2 to 1:0) to provide **13d-2** as a light yellow waxy material that partly solidified on drying; yield: 210 mg (92%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.36 (s, 1 H), 8.21 (s, 1 H), 3.67 (q, J = 7.3 Hz, 4 H), 3.18 (s, 3 H), 1.24 (t, J = 6.9 Hz, 6 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 153.8, 152.5, 135.9, 127.5, 44.0, 40.6, 13.4.

MS (ESI): m/z (%) = 232 (5), 231 (10), 230 (100, $[M + H]^+$), 136 (2), 102 (2).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_9H_{16}N_3O_2S$: 230.0958; found: 230.0975.

***N*-Ethyl-6-(methylsulfonyl)pyrazin-2-amine (13d-3)**

To 2-chloro-6-(methylsulfonyl)pyrazine (**11d**, 193 mg, 1 mmol) was added THF (1 mL), then the mixture was cooled under N_2 to –60 °C. 2 M $EtNH_2$ in THF (1.1 mL, 2.2 mmol) was added by syringe and the mixture was warmed to r.t. over 3 h. After 1.5 h at r.t. the mixture was heated to 40 °C for 3 h. At this point the LC-MS analysis of the mixture showed only small amounts of **11d** remaining. The mixture was concentrated and purified by chromatography (silica gel, EtOAc–hexane, gradient 1:2 to 1:0, then EtOAc–MeOH ~20:1) to provide **13d-3** as a white solid material; yield: 157 mg (78%); mp 126–130 °C.

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.18 (m, 2 H), 6.97 (br s, 1 H), 3.45 (dq, J = 5.4, 7.3 Hz, 2 H), 3.17 (s, 3 H), 1.25 (t, J = 7.3 Hz, 3 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 155.7, 152.4, 139.4, 128.3, 40.6, 36.9, 14.9.

MS (ESI): m/z (%) = 204 (5), 203 (7), 202 (100, $[M + H]^+$), 140 (1), 108 (3), 102 (9).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_7H_{12}N_3O_2S$: 202.0645; found: 202.0658.

2-(Methylsulfonyl)-*N*-phenylpyrimidin-4-amine (13e-1)

To 4-chloro-2-(methylsulfonyl)pyrimidine (**11e**, 192 mg, 1 mmol) was added aniline (0.11 mL, 1.2 mmol, 1.2 equiv), 2,6-lutidine (0.14 mL, 1.2 mmol, 1.2 equiv), and DMSO (1 mL), and the mixture was stirred under N_2 at r.t. for 7 h. At this point LC-MS analysis of the mixture showed complete consumption of **11e**. The mixture was diluted with H_2O, extracted with CH_2Cl_2, dried ($MgSO_4$), concentrated, then purified by chromatography (silica gel, EtOAc–hexanes, gradient 1:2 to 1:0) to provide **13e-1** as a light yellow amorphous solid material; yield: 242 mg (97%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 9.31 (br s, 1 H), 8.38 (d, J = 6.0 Hz, 1 H), 7.72 (d, J = 8.2 Hz, 2 H), 7.45–7.36 (m, 2 H), 7.16 (t, J = 7.4 Hz, 1 H), 6.99 (d, J = 6.0 Hz, 1 H), 3.28 (s, 3 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 167.5, 162.6, 157.4, 140.1, 130.5, 125.6, 122.4, 110.1, 39.9.

MS (ESI): m/z (%) = 252 (4), 251 (11), 250 (100, $[M + H]^+$), 171 (1), 170 (3), 102 (4).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{12}N_3O_2S$: 250.0645; found: 250.0665.

***N*,*N*-Diethyl-2-(methylsulfonyl)pyrimidin-4-amine (13e-2)**

To 4-chloro-2-(methylsulfonyl)pyrimidine (**11e**, 192 mg, 1 mmol) was added THF (1 mL), then the mixture was cooled under N_2 to 0 °C (ice bath). Et_2NH (0.23 mL, 2.2 mmol) was added by syringe and the mixture was stirred at this temperature for 1 h. At this point the LC-MS analysis of the mixture showed almost complete consumption of **11e**. The mixture was diluted with EtOAc, filtered through a plug of silica gel, concentrated, and purified by chromatography (silica gel, EtOAc–hexane, gradient 1:2 to 1:0, then EtOAc–$CHCl_3$–MeOH ~50:50:3 to 50:50:5) to provide **13e-2** as a colorless oily material; yield: 213 mg (93%).

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.23 (d, J = 6.3 Hz, 1 H), 6.80 (d, J = 6.3 Hz, 1 H), 3.68 (br s, 2 H), 3.59 (br s, 2 H), 3.23 (s, 3 H), 1.21 (t, J = 7.1 Hz, 6 H).

^{13}C NMR (126 MHz, acetone-d_6): δ = 167.5, 162.2, 156.8, 106.4, 43.8, 39.7, 13.2.

LC-MS (ESI): m/z = 230 $[M + H]^+$.

4-Chloro-*N*-ethylpyrimidin-2-amine (12e-1) and *N*-Ethyl-2-(methylsulfonyl)pyrimidin-4-amine (13e-3)

To 4-chloro-2-(methylsulfonyl)pyrimidine (**11e**, 192 mg, 1 mmol) was added THF (1 mL), then under N_2 the mixture was cooled to 0 °C (ice bath). 2 M $EtNH_2$ in THF (1.1 mL, 2.2 mmol, 2.2 equiv) was added by syringe, and the mixture was stirred in an ice bath under N_2 for 1 h. The mixture was diluted with EtOAc, filtered through a plug of silica gel, concentrated, and purified by chromatography

(silica gel, EtOAc–hexanes, gradient 0:1–1:0). The less polar fractions upon concentration provided **12e-1** as a white solid material; yield: 105 mg (67%). The more polar fractions upon concentration provided **13e-3** as a colorless oily material; yield: 38 mg (19%).

2-Ethylamino Product 12e-1
Mp 87–89 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.21 (br s, 1 H), 7.64 (t, J = 5.8 Hz, 1 H), 6.63 (d, J = 5.0 Hz, 1 H), 3.26 (br s, 2 H), 1.10 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 162.1, 159.9 (br, probably 2 signals), 108.5, 35.4, 14.3.

LC-MS (ESI): m/z = 158 $[M + H]^+$.

2-Methylsulfonyl Product 13e-3
^{1}H NMR (500 MHz, acetone-d_6, mixture of rotamers ~3:1): δ = 8.30 (br s, 0.25 H), 8.13 (br s, 0.75 H), 7.26 (br s, 0.75 H), 7.14 (br s, 0.25 H), 6.67 (d, J = 6.0 Hz, 1 H), 3.50 (br s, 1.5 H), 3.38 (br s, 0.5 H), 3.23 (br s, 3 H), 1.22 (br s, 3 H).

LC-MS (ESI): m/z = 202 $[M + H]^+$.

2-Chloro-4-(methylsulfonyl)pyrimidine (11f)
To 2-chloro-4-(methylthio)pyrimidine (1 g, 6.2 mmol) was added CH_2Cl_2 (10 mL), and the mixture was cooled in an ice bath. MCPBA (77% pure, 3.15 g, 14 mmol, 2.2 equiv) was added and the mixture was stirred for 18 h with slow warming to r.t. The mixture was filtered, and the filtrate was washed with aq $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, concentrated, and washed with hexane to provide **11f** as a white solid material; yield: 1.02 g (86%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.34 (d, J = 0.9 Hz, 1 H), 8.30 (d, J = 0.9 Hz, 1 H), 3.40 (s, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 167.3, 164.7, 160.2, 116.4, 39.5.

4-(Methylsulfonyl)-*N*-phenylpyrimidin-2-amine (13f-1)
To 2-chloro-4-(methylsulfonyl)pyrimidine (**11f**, 221 mg, 1.15 mmol) was added DMSO (1.1 mL), aniline (0.13 mL, 1.4 mmol, 1.2 equiv), and 2,6-lutidine (0.16 mL, 1.4 mmol, 1.2 equiv), and the mixture was stirred under N_2 at r.t. for 21 h. At this point LC-MS analysis of the mixture still showed presence of **11f**. Additional aniline (0.1 mL, 1 equiv) was added, after 5 h the starting material did not disappear; however, side-product formation became profound. The mixture was diluted with H_2O, extracted with EtOAc–hexanes (~1:1), dried ($MgSO_4$), concentrated, then purified by chromatography (silica gel, gradient EtOAc–hexanes 1:10 to 1:1) to provide **13f-1** as a light yellow heterogeneous oily material; yield: 204 mg, ~70% pure by UPLC–MS analysis (see below).

^{1}H NMR (500 MHz, acetone-d_6, major component, **13f-1**): δ = 9.21 (br s, 1 H), 8.81 (d, J = 4.7 Hz, 1 H), 7.81 (dd, J = 1.1, 8.7 Hz, 2 H), 7.40–7.32 (m, 2 H), 7.31 (d, J = 4.7 Hz, 1 H), 7.07 (tt, J = 1.3, 7.3 Hz, 1 H), 3.25 (s, 3 H).

LC-MS (UV 254 nm): 9% of **11f**, 70% of **13f-1** (M = 250 $[M + H]^+$), 21% of 2-chloro-***N***-phenylpyrimidin-4-amine[42] (M = 206 $[M + H]^+$).

***N*,*N*-Diethyl-4-(methylsulfonyl)pyrimidin-2-amine (13f-2)**
To 2-chloro-4-(methylsulfonyl)pyrimidine (**11f**, 227 mg, 1.18 mmol) was added THF (1.2 mL), then the mixture was cooled under N_2 to –60 °C. Et_2NH (0.27 mL, 2.6 mmol, 2.2 equiv) was added by syringe and the mixture was stirred with slow warming to r.t. over 1.5 h. At this point the LC-MS analysis of the mixture showed almost complete consumption of **11e**. The mixture was diluted with EtOAc, filtered through a plug of silica gel, concentrated, and purified by chromatography (silica gel, EtOAc–hexane, gradient 1:10 to 1:2 to provide **13f-2** as a light yellow viscous oily material that partly solidified upon standing; yield: 254 mg (94%); mp 52–56 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.70 (d, J = 5.0 Hz, 1 H), 7.03 (d, J = 4.7 Hz, 1 H), 3.61 (br s, 4 H), 3.27 (s, 3 H), 1.14 (t, J = 7.1 Hz, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 165.9, 161.7, 160.0, 102.4, 41.8, 38.4, 12.6.

MS (ESI): m/z (%) = 231 (9), 230 (100, $[M + H]^+$), 202 (2), 186 (3), 169 (1), 168 915), 150 (5), 140 92), 138 (2), 122 91), 102 (1).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_9H_{16}N_3O_2S$: 230.0958; found: 230.0976.

2-Chloro-*N*-ethylpyrimidin-4-amine (12f-1)
To 2-chloro-4-(methylsulfonyl)pyrimidine (**11f**, 260 mg, 1.35 mmol) was added THF (2 mL), then the mixture was cooled under N_2 to –70 °C. 2 M $EtNH_2$ in THF (1.5 mL, 2.2 mmol) was added by syringe and the mixture was warmed to r.t. over 3 h. The mixture was concentrated and purified by chromatography (silica gel, EtOAc–hexane, gradient 1:4 to 1:0) to provide **12f-1** as a white solid material; yield: 165 mg (79%); mp 63–66 °C.

^{1}H NMR (500 MHz, acetone-d_6, mixture of rotamers ~4:1): δ = 8.11–7.79 (m, 2 H), 6.52–6.36 (m, 1 H), 3.31–3.10 (m, 2 H), 1.11 (t, J = 7.3 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.2, 159.9, 155.2, 105.0, 34.8, 14.1.

MS (ESI): m/z (%) = 161 (2), 160 (34), 159 (6), 158 (100, $[M + H]^+$), 130 (11), 122 (4), 112 (3), 102 (2).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_6H_9ClN_3$: 158.0480; found: 158.0491.

Acknowledgment

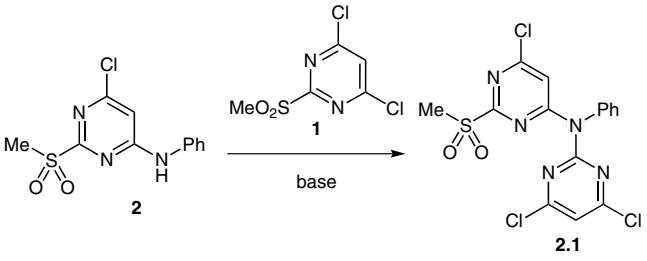
The authors wish to thank Dr. Joseph M. Colacino, Dr. Christie Morrill, and Prof. Scott E. Denmark, University of Illinois at Urbana-Champaign, for helpful discussions and Jane Yang for analytical support.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) (a) Sanford, M. *Drugs* **2012**, *72*, 525. (b) Croxtall, J. D. *Drugs* **2012**, *72*, 847.
(2) Sonpavde, G.; Hutson, T. E.; Sternberg, C. N. *Drugs Today* **2009**, *45*, 651.
(3) (a) Sabat, M.; VanRens, J. C.; Laufersweiler, M. J.; Brugel, T. A.; Maier, J.; Golebiowski, A.; De , B.; Easwaran, V.; Hsieh, L. C.; Walter, R. L.; Mekel, M. J.; Evdokimov, A.; Janusz, M. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5973. (b) Gong, B.; Hong, F.; Kohm, C.; Jenkins, S.; Tulinsky, J.; Bhatt, R.; de Vries, P.; Singer, J. S.; Klein, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2303. (c) Yang, W.; AbdulHameed, M. D. M.; Hamza, A.; Zhan, C.-G. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1629.
(4) Sagi, V. N.; Liu, T.; Lu, X.; Bartfai, T.; Roberts, E. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7210.
(5) Deng, X.; Nagle, A.; Wu, T.; Sakata, T.; Henson, K.; Chen, Z.; Kuhen, K.; Plouffe, D.; Winzeler, E.; Adrian, F.; Tuntland, T.; Chang, J.; Simerson, S.; Howard, S.; Ek, J.; Isbell, J.; Tully, D. C.; Chatterjee, A. K.; Gray, N. S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4027.
(6) Rivkin, A.; Ahearn, S. P.; Chichetti, S. M.; Kim, Y. R.; Li, C.; Rosenau, A.; Kattar, S. D.; Jung, J.; Shah, S.; Hughes, B. L.; Crispino, J. L.; Middleton, R. E.; Szewczak, A. A.;

Munoz, B.; Shearman, M. S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1269.
(7) Kumagai, T.; Okubo, T.; Kataoka-Okubo, H.; Chaki, S.; Okuyama, S.; Nakazato, A. *Bioorg. Med. Chem.* **2001**, *9*, 1349.
(8) Gu, S.; Yang, S.; He, Q.; Ma, X.; Chen, F.; Dai, H.; De Clercq, E.; Balzarini, J.; Pannecouque, C. *Bioorg. Med. Chem.* **2011**, *19*, 7093.
(9) (a) Delia, T. J.; Meltsner, B. R.; Schomaker, J. M. *J. Heterocycl. Chem.* **2000**, *37*, 1457. (b) Matsuno, T.; Kato, M.; Sasahara, H.; Watanabe, T.; Inaba, M.; Takahashi, M.; Yaguchi, S.; Yoshioka, K.; Sakato, M.; Kawaseima, S. *Chem. Pharm. Bull.* **2000**, *48*, 1778. (c) Delia, T. J.; Meltsner, B. R.; Schomaker, J. M. *J. Heterocyl. Chem.* **1999**, *36*, 1259. (d) Montebugnoli, D.; Bravo, P.; Corradi, E.; Dettori, G.; Mioskowski, C.; Volonterio, A.; Wagner, A.; Zanda, M. *Tetrahedron* **2002**, *58*, 2147. (e) Zanda, M.; Talaga, P.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 1757.
(10) (a) D'Atri, G.; Gomarasca, P.; Resnati, G.; Tronconi, G.; Scolastico, C.; Sirtori, C. R. *J. Med. Chem.* **1984**, *27*, 1621. (b) Wernert, G. T.; Winkler, D. A.; Holan, G.; Nicoletti, G. *Aust. J. Chem.* **2004**, *57*, 77.
(11) Kopell, H. C.; Springer, R. H.; Cheng, C. C. *J. Org. Chem.* **1961**, *26*, 1884.
(12) (a) Martin, R. E.; Morawitz, F.; Kuratli, C.; Alker, A. M.; Alanine, A. I. *Eur. J. Org. Chem.* **2012**, 47. (b) Huang, T.-H.; Tu, H.-Y.; Aibibu, Z.; Hou, C.-J.; Zhang, A.-D. *ARKIVOC* **2011**, *(ii)*, 1.
(13) Bebbington, D.; Binch, H.; Charrier, J.-D.; Everitt, S.; Fraysse, D.; Golec, J.; Kay, D.; Knegtel, R.; Mak, C.; Mazzei, F.; Miller, A.; Mortimore, A.; O'Donnell, M.; Patel, S.; Pierard, F.; Pinder, J.; Pollard, J.; Ramaya, S.; Robinson, D.; Rutherford, A.; Studley, J.; Westcott, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3586.
(14) Xiao, X.-Y.; Patel, D. V.; Ward, J. S.; Bray, M. R.; Agoston, G. E.; Treston, A. M. WO 2007041358, **2007**.
(15) Medina, J. R.; Becker, C. J.; Blackledge, C. W.; Duquenne, C.; Feng, Y.; Grant, S. W.; Heerding, D.; Li, W. H.; Miller, W. H.; Romeril, S. P.; Scherzer, D.; Shu, A.; Bobko, M. A.; Chadderton, A. R.; Dumble, M.; Gardiner, C. M.; Gilbert, S.; Liu, Q.; Rabindran, S. K.; Sudakin, S.; Xiang, H.; Brady, P. G.; Campobasso, N.; Ward, P.; Axten, J. M. *J. Med. Chem.* **2011**, *54*, 1871.
(16) Eriksen, B. L.; Hougaard, C.; Peters, D.; Christophersen, P. WO 2010026087, **2010**.
(17) Nagata, T.; Masuda, K.; Maeno, S.; Miura, I. *Pest Manage. Sci.* **2004**, *60*, 399.
(18) Ji, M.; Zheng, Y.; Zheng, M. CN 101857589, **2010**.
(19) One such byproduct was identified using LC-MS analysis as **2.1** ([M + H]$^+$ 430, see Scheme 3). It seems that the N–H in **2a** is acidic enough to be deprotonated by stronger bases (such as aliphatic amines or K_2CO_3) and displaces the sulfone in **1**, which seems to be the preferred site of displacement by anionic nucleophiles (*vide infra*).



Scheme 3

(20) A ^{1}H NMR experiment (data not shown) demonstrated that pyridine reacts with **1** within minutes at r.t. in DMSO-d_6 to provide a complex mixture of products.
(21) The reaction is less general with these amines. Many heteroaromatic and all heterocyclic amines that we tested reacted unselectively, with substitution occurring at both C2 and C4, as well as forming multiple other byproducts. Unselective examples include 2-, 3-, or 4-aminopyridine, 2-aminothiazole, etc. Imidazole and benzimidazole preferentially react at C2.
(22) See Supporting Information for details.
(23) When indole was combined with **1** in DMSO in the presence of 2,6-lutidine (1.2 equiv), after 3 d at r.t. side products started forming according to LC-MS analysis of the reaction mixture. At that point LC-MS analysis failed to demonstrate formation of either the C4–Cl or the C2–SO_2Me displacement products.
(24) Preliminary data suggests that the higher acidity of heterocyclic aromatic amines may be a reason for some of these reactions being unselective. Both neutral and deprotonated species may coexist and react with **1** via different pathways.
(25) (a) With aziridine: see ref. 11. (b) With methylamine: see ref. 15. (c) With alkoxide: see ref. 12a. (d) With thiolate: see ref. 13. (e) With RMgX: see ref. 14. (f) With deprotonated formamide: see ref. 17. (g) With deprotonated heterocyclic amine: see ref. 16.
(26) Slightly lower yields were generally obtained when PhLi/Et_2O or *i*-PrMgCl·LiCl/THF were used instead of NaHMDS.
(27) One such side product was isolated and identified as **V** (see Scheme 4). Its formation may be explained by the mechanism shown in the scheme that starts with the deprotonation of **1**. Product **V** was the major product (38%) isolated when cyclohexylamine was combined with NaHMDS and **1**. Analytical data for **V**: white solid, LC-MS (ESI) [M + H]$^+$ 311 (4 Cl atoms pattern); ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.00 (s, 2 H), 4.57 (s, 2 H); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 167.5, 161.3, 120.0, 47.3.
(28) Similar reaction has been reported in ref. 8f.
(29) Reaction with Boc-protected pyridin-3-ylmethanamine did not provide the clean product even though the reaction was moderately clean according to the LC-MS analysis of the reaction mixture. The product seems to be unstable.
(30) The byproduct (Figure 1) was identified as the product of bis-arylation of the amine with **1** based on LC-MS analysis. This reaction was not optimized.

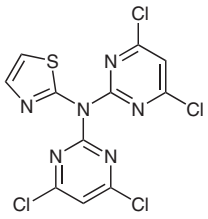
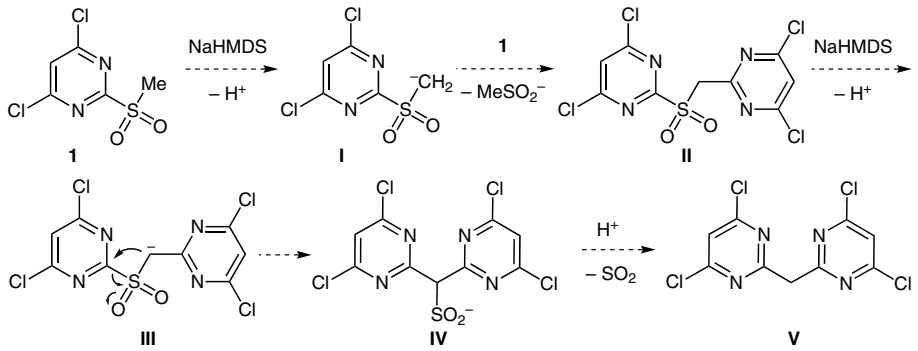


Figure 1

(31) Unfortunately, reactions with deprotonated *N*-alkylanilines, such as *N*-methylaniline or indoline (NaHMDS, TMPMgCl·LiCl, *n*-BuLi; various modes of addition) were not clean. These reactions produced mixtures of products, with displacements at C2, C4 and double C2 and C4 displacement, as well as other unidentified byproducts.



Scheme 4

(32) The alternate products **4a–c** or **5e**,**f** could be detected by LC-MS or ^{1}H NMR analysis of the reaction mixtures. However, these minor products could be isolated only in impure form and negligible amounts.

(33) Henne, A. L.; Stewart, J. J. *J. Am. Chem. Soc.* **1955**, *77*, 1901.

(34) Kanzian, T.; Nigst, T. A.; Maier, A.; Pilch, S.; Mayr, H. *Eur. J. Org. Chem.* **2009**, 6379.

(35) Various modes of addition and stoichiometries were tried unsuccessfully.

(36) (a) With 3-chloro-6-(methylsulfonyl)-1,2-diazine and 4-chloro-6-(methylsulfonyl)pyrimidine: Nyberg, W. H.; Cheng, C. C. *J. Heterocyl. Chem.* **1964**, *1*, 1. (b) With 4-chloro-2-(ethylsulfonyl)-6-phenylpyrimidine and 4-chloro-2-(ethylsulfonyl)pyrimidine: Sawayama, T.; Yamamoto, R.; Kinugasa, H.; Nishimura, H. *Heterocycles* **1977**, *8*, 299.

(37) See experimental section for details.

(38) Some limited information is also available on reactions with 4-chloro-6-(ethylsulfonyl)pyrimidine (see ref. 19b) and 4-chloro-6-(propylsulfonyl)pyrimidine, see: Porter, J. R.; Archibald, S. C.; Brown, J. A.; Childs, K.; Critchley, D.; Head, J. C.; Hutchinson, B.; Parton, T. A. H.; Robinson, M. K.; Shock, A.; Warrellow, G. J.; Zomaya, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1595.

(39) Calculations were conducted using Spartan software, B3LYP 6-31G* in DMSO.

(40) In anilines the NH_2-group is planarized. This may lead to anilines being effectively bulkier compared to, for example, $CyNH_2$.

(41) This conclusion is similar to the one made earlier; see ref. 19b.

(42) Assigned based on the LC-MS data.

