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Synthesis of Alkylated Pyrimidines via Photoinduced Coupling Using Benzophenone as a Mediator

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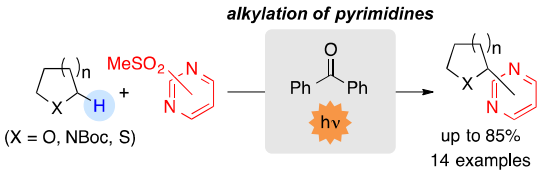
TOC



ABSTRACT: The synthesis of alkylated pyrimidines was achieved via benzophenone-mediated photoinduced coupling between saturated heterocycles and sulfonylpyrimidines. The pyrimidine ring was selectively introduced at the nonacidic C(sp^3)–H bond proximal to heteroatoms including oxygen, nitrogen, and sulfur. This is a coupling reaction mediated

solely by photoexcited benzophenone, an organic molecule, without the aid of any metallic catalysts or reagents.

INTRODUCTION

Molecules containing a pyrimidine ring are critically important for life since their derivatives, including cytosine, thymine, uracil, guanine, and adenine, are fundamental building blocks of DNA and RNA.[1] The pyrimidine core can also be found in a variety of biologically active compounds, so the pyrimidine ring is considered to be one of the most privileged scaffolds in the field of pharmaceutical sciences (Figure 1).[2] For example, Gleevec is a commercialized tyrosine kinase inhibitor for leukemia treatment, which works only for targeting cancer.[3] MK-0457 is another drug candidate for cancer that acts as an aurora kinase inhibitor.[4] Crestor is a well-known drug for dyslipidemia treatment, which inhibits the enzyme HMG-CoA reductase.[5] The recent advancements of medicinal chemistry have brought attention to pyrimidine derivatives attached with an alkyl side chain, such as Raltegravir and XL413. Raltegravir, containing the pyrimidine-based core, is an antiretroviral drug for treatment of HIV infection.[6] XL413 inhibits cell division and is thus considered as a potent anticancer agent.[7]

Most of these molecules contain a pyrimidine ring as the core structure, so contributions to the development of new synthetic methods for pyrimidine derivatives are of great importance.

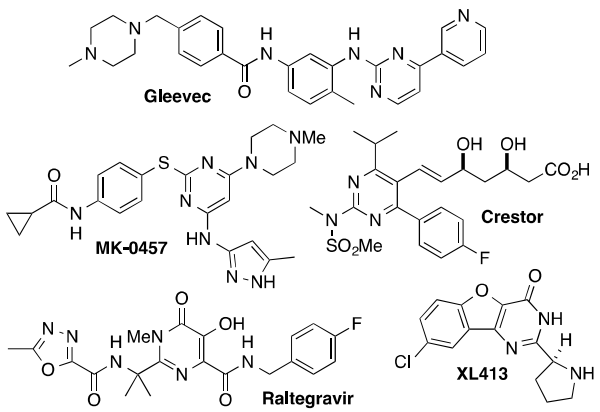


Figure 1. Representative Drugs and Drug Candidates Containing a Pyrimidine Core

Direct introduction of alkyl chains to nitrogen-containing six-membered heteroaromatics often poses a challenge. The Friedel–Crafts reaction, for instance, is a standard method for alkylation of benzene rings; however, this strategy is not suited for pyrimidines due to the lack of nucleophilicity caused by the high electronegativity of the nitrogen atoms. Additionally, the coordinating ability of the nitrogen atom generally deactivates Lewis acids. Nucleophilic aromatic substitution is a promising option for direct alkylation of such electron-deficient pyrimidines, although loss of regioselectivity can be a problem depending on substitution patterns of the starting pyrimidines (Figure 2).[8] To circumvent the regioselectivity issue, alkylated pyrimidines are often prepared by assembly of several fragments through the

formation of the pyrimidine ring itself, such as dehydrative condensation of 1,3-dicarbonyl derivatives and amidines.[9]

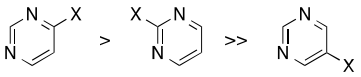


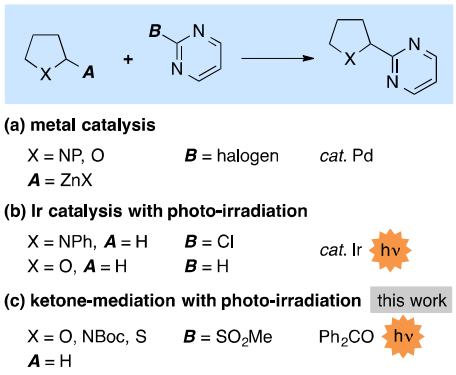
Figure 2. The General Reactivity Order of the Halogenated Pyrimidines for Nucleophilic Aromatic Substitution

Advancement of coupling strategies now allows the direct introduction of alkyl chains onto pyrimidine rings. The Negishi coupling is reported to be effective for synthesis of alkylated pyrimidines from alkylzinc species and halogenated pyrimidines (a, Scheme 1).[8b,10] Recently, the MacMillan group applied the photoredox Ir catalysis to introduce cyclic amine and ether moieties to pyrimidines (b, Scheme 1).[11] Despite that these reactions are efficiently promoted by a catalytic amount of an Ir complex (<2 mol %), there are several limitations. For instance, only electron-rich amines, such as *N*-phenyl pyrrolidine and *N*-phenyl morpholine, are suitable since the single electron transfer (SET) process plays an important role for introducing an amine moiety, and only two pyrimidine derivatives bearing tetrahydropyran moiety are prepared.

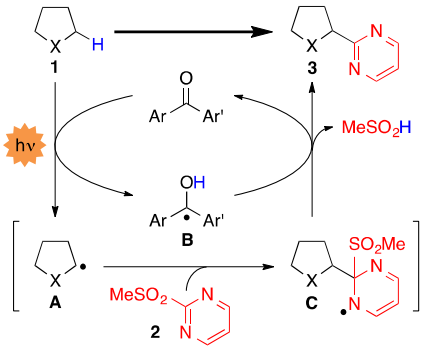
Our coupling strategy is based on a radical reaction, in which a carbon radical is generated via homolytic cleavage of a nonacidic C(sp^3)–H bond by making use of a highly reactive oxyl radical species derived from a photoexcited aryl ketone (c, Scheme 1).[12,13,14,15] Detailed

reaction pathway for the preparation of alkylated pyrimidines **3** was planned as illustrated in Scheme 2. The carbon radical **A**, generated via hydrogen abstraction from the starting substance **1** by the oxyl radical species of the photoexcited aryl ketone along with formation of the ketyl radical **B**, adds to sulfonylated pyrimidine **2** furnishing the radical **C**.[13a] Liberation of the sulfonyl radical from **C** completes rearomatization and provides the desired product **3**. The aryl ketone is regenerated when the hydrogen atom is transferred from **B** to the liberated sulfonyl radical.[16] In this communication, we report a novel method for direct alkylation of pyrimidines starting from saturated heterocycles, such as ethers, carbamates, amide, and sulfide, and sulfonylpyrimidines via photoinduced coupling using benzophenone (Ph_2CO), an organic molecule, as a mediator. The present transformation accomplishes direct substitutive introduction of a pyrimidine ring at the nonacidic C(sp^3)–H bonds proximal to heteroatoms, including oxygen, nitrogen and sulfur, under neutral conditions at ambient temperature without the aid of any metallic catalysts or reagents utilizing a unified protocol.

Scheme 1. Preparation of Alkylated Pyrimidines by Coupling Strategies



Scheme 2. A Proposed Reaction Pathway for Aryl Ketone-Mediated Photoinduced Preparation of Alkylated Pyrimidines

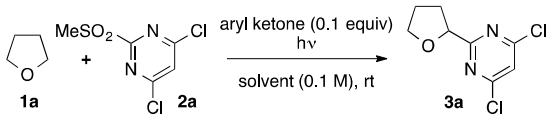


RESULTS AND DISCUSSION

Prior to optimizing the reaction conditions, we designed 2-methanesulfonylpyrimidine **2a** as a coupling partner due to the excellent leaving ability of the sulfonyl unit in our series of related substitutive functionalizations of nonacidic C(sp^3)–H bonds (Table 1).[13,17] Among the aryl ketones examined, benzophenone (Ph_2CO)[13,14] exhibited a higher catalytic activity compared to

4-benzoylpyridine (4-BzPy)[13a, 18] and 2-chloroanthraquinone (2-ClAQ)[13b] for the coupling between tetrahydrofuran (THF, **1a**) and **2a** (entries 1–3).[19] The pyrimidine ring was chemoselectively introduced at the C–H bond adjacent to the oxygen atom of the starting ether **1a**, and the 2-arylated adduct **3a** was formed. It is important to note that the coupling took place regioselectively at the sulfonylated carbon center to provide the 2-alkylated pyrimidine **3a** and no adduct derived via the substitution at the chlorinated carbon center was observed. It should be also emphasized that the coupling between THF **1a**, an inherently reactive substance, and highly electron-deficient 4,6-dichloro-2-methanesulfonylpyrimidine **2a** was smoothly promoted by a catalytic amount of Ph_2CO (0.1 equiv). The coupling took place in a range of solvents, including CH_2Cl_2, benzene, CH_3CN, and CH_3CN/H_2O (2:1),[14a,h] and the adduct **3a** was furnished in essentially the same yields (69–74%, entries 1 and 4–6). The solvent screening revealed that the present transformation proceeds even in the presence of water. When THF was employed as a solvent (123 equiv to **2a**), the reaction completed in a shorter reaction time and gave a higher yield of **3a** (entry 7).

Table 1. Optimization of Reaction Conditions[a]



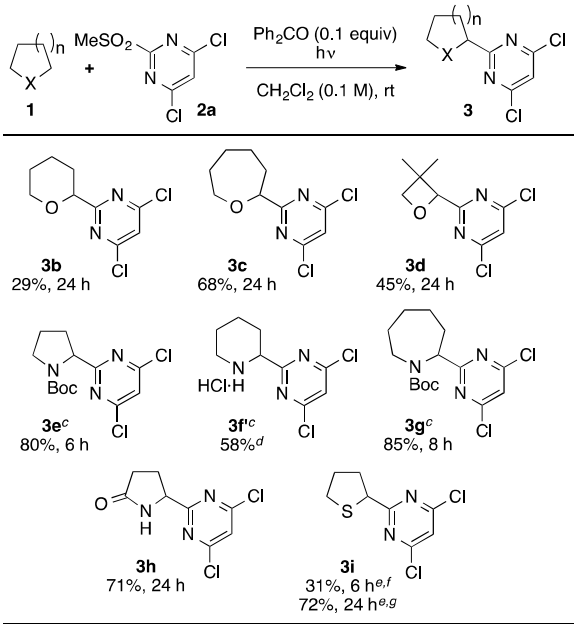
entry	aryl ketone	solvent	time, h	yield, %[b]
1	Ph_2CO	CH_2Cl_2	5	74[c]
2	4-BzPy	CH_2Cl_2	5	15[d]
3	2-ClAQ	CH_2Cl_2	24	57[e]
4	Ph_2CO	benzene	5	69
5	Ph_2CO	CH_3CN	5	73
6	Ph_2CO	CH_3CN/H_2O (2:1)	10	69
7	Ph_2CO	THF[f]	3.5	86

[a]Conditions: THF **1a** (10 equiv), sulfonylpyrimidine **2a** (1 equiv), Ph_2CO (0.1 equiv), CH_2Cl_2 (0.1 M), photo-irradiation under an Ar atmosphere using a medium-pressure Hg lamp at rt unless otherwise noted. [b]Yield determined by NMR analysis. [c]Isolated yield. [d]The sulfonylpyrimidine **2a** was recovered in 76% yield. [e]The sulfonylpyrimidine **2a** was recovered in 16% yield. [f]THF **1a** was employed as a solvent (123 equiv to **2a**).

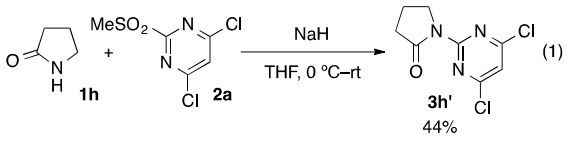
With the standard reaction conditions in hand, we investigated the generality of the Ph_2CO-catalyzed photoinduced coupling by utilizing a variety of saturated heterocycles **1b**–**i** and 4,6-dichloro-2-methanesulfonylpyrimidine **2a** (Scheme 3). The reactions employing tetrahydropyran **1b**, oxepane **1c**, and oxetane **1d** as starting substances gave rise to the corresponding adducts **3b**–**d** in 29% to 68% yields. Accordingly, the ethereal C–H bonds of 4- to 7-membered cyclic ethers were successfully arylated irrespective of the ring size.[20] The couplings of 5- to 7-membered azacycles **1e**–**g** took place selectively at the C–H bond adjacent to the nitrogen atom and the 2-arylated adducts **3e**–**g** were produced in good yields.[21,22] The

reaction employing pyrrolidone **1h** produced the adduct **3h** (71%) with the C–C bond formation at the carbon center next to the nitrogen atom as well. To highlight the synthetic versatility of 4,6-dichloro-2-methanesulfonylpyrimidine **2a** as a scaffold, we subjected pyrrolidone **1h** under anionic conditions (eq 1). The nucleophilic aromatic substitution took place regioselectively at the sulfonylated carbon center and the C–N bond was formed in 44% yield (**3h'**). This result clearly shows that pyrimidine isomers can be selectively prepared starting from the same combination of the substances merely by choosing the appropriate reaction conditions.[23] The coupling using tetrahydrothiophene **1i** under the catalytic conditions proceeded with similar selectivity but with a lower yield of the expected adduct **3i** (31%).[24] In this case, the employment of a stoichiometric amount of Ph_2CO improved the product yield up to 72%.[25,26,27]

Scheme 3. Coupling between Saturated Heterocycles and 4,6-Dichloro-2-methanesulfonylpyrimidine[a,b]



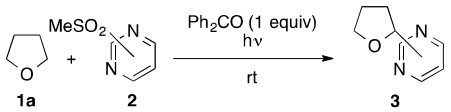
[a]Conditions as described in entry 1 of Table 1, unless otherwise noted. [b]Isolated yield. [c]The starting carbamates **1e**–**g** (5 equiv) was employed. [d]Isolated yield of **3f'** in two-step after Boc deprotection of the coupling adduct **3f**. [e]Irradiated with an LED lamp (365 nm). [f]The sulfonylpyrimidine **2a** was recovered in 65% yield. [g]Ph_2CO (1 equiv) was employed.

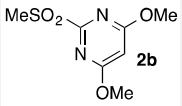
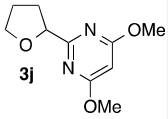
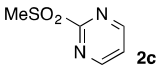
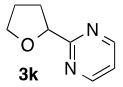
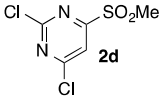
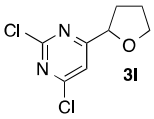
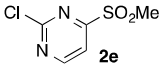
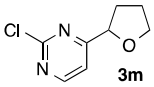
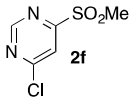
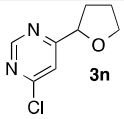


We next explored the applicability and reactivity of sulfonylpyrimidines **2b**–**f** to the present photoinduced coupling in combination with THF **1a** (Table 2). Electron-donating methoxy-substituted sulfonylpyrimidine **2b** and non-substituted sulfonylpyrimidine **2c** showed lower reactivity and the respective adducts **3j** and **3k** were formed in 48% and 42% yields when

the reaction was conducted with a stoichiometric amount of Ph_2CO in THF (entries 1 and 2). These results clearly indicated the superior reactivity of the electron-deficient chlorinated pyrimidine **2a** to the electron-rich methoxy and non-substituted pyrimidines **2b** and **2c**. Such reactivity difference was probably caused by the electron-rich nature of the carbon radical **A** generated from THF **1a** (*vide supra*, Scheme 2). Nevertheless, the low reactivity of pyrimidines **2b** and **2c** could be successfully made up by conducting the reaction with a stoichiometric amount of Ph_2CO in THF solvent to some extent, giving the corresponding adducts **3j** and **3k** in moderate yields (48% and 42%, respectively). On the other hand, the reaction of 2,6-dichloro-4-methanesulfonylpyrimidine **2d** was smoothly catalyzed by Ph_2CO (0.1 equiv) to provide the adduct **3l** in 75% yield (entry 3). It is important to note that the coupling took place regioselectively at the sulfonylated carbon center to give 4-substituted pyrimidine **3l** in this case. The mono-chlorinated sulfonylpyrimidines **2e** and **2f** again showed lower reactivities, and the expected adducts **3m** (72%) and **3n** (31%) were obtained after subjecting them to a stoichiometric amount of Ph_2CO in THF (entries 4 and 5).

Table 2. Coupling between THF and Sulfonylated Pyrimidines[a,b]



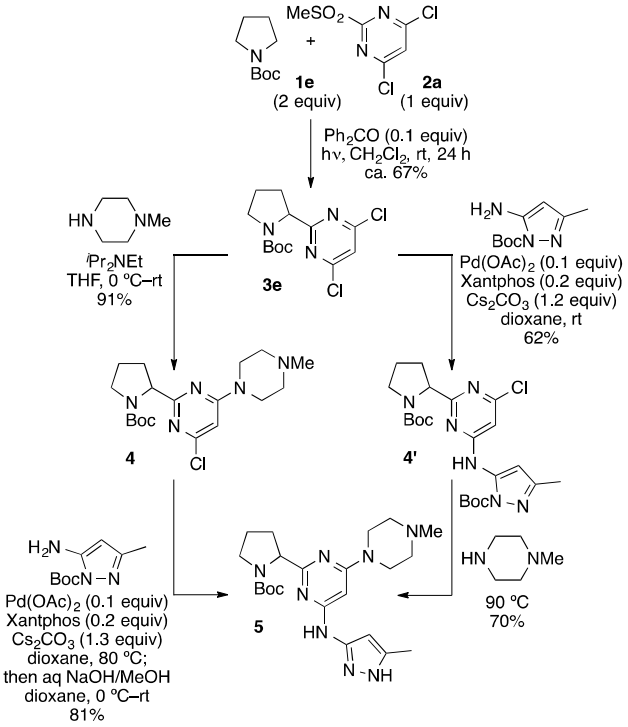
entry	pyrimidine **2**	time, h	product **3**	yield, %[b]
1	 **2b**	24	 **3j**	48
2	 **2c**	24	 **3k**	42
3[c]	 **2d**	24	 **3l**	75
4	 **2e**	4	 **3m**	72
5	 **2f**	3	 **3n**	31

[a]Conditions: THF **1a** (0.1 M, 123 equiv), sulfonylpyrimidines **2** (1 equiv), Ph_2CO (1 equiv), photo-irradiation under an Ar atmosphere using a medium-pressure Hg lamp at rt unless otherwise noted. [b]Isolated yield. [c]The reaction was conducted using THF **1a** (10 equiv), sulfonylated pyrimidine **2d** (1 equiv), and Ph_2CO (0.1 equiv) in CH_2Cl_2 (0.1 M) with photo-irradiation under an Ar atmosphere using a medium-pressure Hg lamp at rt.

To demonstrate the utility of the newly developed coupling reaction and to show the synthetic applicability of the derived coupling products, we prepared an analogue of the aurora kinase inhibitor, MK-0457 (Figure 1),[4] using the dichloropyrimidine substituted with the azacycle **3e** (Scheme 4). The Ph_2CO-catalyzed photoinduced coupling between the pyrrolidine derivative **1e** and sulfonylpyrimidine **2a** furnished the corresponding adduct **3e** in ca. 67% yield[28] even

when the amount of the starting substance **1e** was reduced to 2 equiv, although a longer reaction time was required (cf. 80% in 6 h, Scheme 3). The derived **3e** was then subjected to the reaction with methylpiperazine to furnish the adduct **4** in 91% yield. Subsequent coupling with the Boc-protected aminopyrazole[29] under a palladium catalyst and basic treatment for deprotection of the Boc group on the pyrazole ring gave rise to the target molecule **5** in 81% yield.[30] Alternatively, the coupling of **3e** with the Boc-protected aminopyrazole, then introduction of the methylpiperazine unit furnished the same product **5** as well. We thus achieved the synthesis of the MK-0457 analogue **5** in three steps starting from 4,6-dichloro-2-methanesulfonylpyrimidine **2a**, which clearly indicated its advantage as a scaffold leading to pyrimidine derivatives with a wide array of substituents.

Scheme 4. Preparation of an Analogue of the Aurora Kinase Inhibitor, MK-0457



CONCLUSION

In conclusion, we have developed a preparation method for alkylated pyrimidines via Ph_2CO-mediated photoinduced coupling starting from saturated heterocycles and sulfonylpyrimidines. This is a coupling reaction mediated solely by photoexcited benzophenone, an organic molecule, without the aid of any metallic catalysts or reagents. The present transformation allows direct substitutive introduction of pyrimidine rings at nonacidic C(sp^3)–H bonds proximal to heteroatoms, including oxygen, nitrogen and sulfur, under neutral reaction conditions at ambient temperature. Moreover, we disclosed that the catalytic coupling

is operative for highly electron-deficient dichlorinated sulfonylpyrimidines, which highlights their utility as a scaffold for the construction of molecules having a pyrimidine core.

EXPERIMENTAL SECTION

General Information. All reactions sensitive to air or moisture were carried out under an argon atmosphere with anhydrous conditions unless otherwise noted. Analytical TLC was performed on E. Merck silica gel 60 F254 pre-coated plates. Column chromatography was performed using silica gel (Fuji Silysia and KANTO), NH silica gel (Fuji Silysia), or a prepacked column using with a Biotage Isolera. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE III-400 or Bruker DRX500 spectrometer. Chemical shifts are reported in δ (ppm) relative to residual solvent signals [^{1}H NMR: $CHCl_3$ (7.26), DMSO-d_6 (TMS, 0.00); ^{13}C NMR: $CDCl_3$ (77.0), DMSO-d_6 (39.52)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer. HRMS were recorded on a Bruker Daltonics micrOTOF II. Melting points were measured on a Cornes MPA100 micro melting point apparatus. UV irradiation was carried out by using a Riko 100 W medium-pressure mercury lamp, an LED

lamp of KEYENCE UV-400 with UV-50A or UV-50H (365 nm). 4,6-Dichloro-2-methanesulfonylpyrimidine **2a** (Tokyo Chemical Industry Co., LTD.) and 4,6-dimethoxy-2-methanesulfonylpyrimidine **2b** (Wako Pure Chemical Industries, Ltd.) were commercially available.

Preparation of the starting sulfonylpyrimidines.

2-(Methylsulfonyl)pyrimidine (2c). To a CH_2Cl_2 solution (32 mL) of 2-methylthiopyrimidine (323 mg, 2.56 mmol) was added *m*-CPBA (~77 wt%, 1.26 g, 5.63 mmol) at 0 ºC. The solution was stirred at room temperature for 16 h and treated with sat. aq $Na_2S_2O_3$. The mixture was extracted with CH_2Cl_2, washed with sat. aq $NaHCO_3$, water, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 10% AcOEt in hexane to AcOEt) to provide the sulfonylpyrimidine **2c** in 70% yield (281 mg) as a colorless solid.[31]

[CAS: 14161-09-2]: colorless solid; mp 67.7-69.5 ºC; IR (ATR) 3081, 3074, 3026, 3004, 2925, 1564, 1549, 1387, 1306, 1214, 1126, 959, 824, 780, 730, 625 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.37 (3H, s), 7.59 (1H, t, J = 4.8 Hz), 8.95 (2H, d, J = 4.8 Hz)[31]; ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.2, 123.9, 158.6, 166.2; HRMS (APCI) calcd for $C_5H_7N_2O_2S$ $[M+H]^+$ 159.0223, found

159.0221.

2,4-Dichloro-6-(methylsulfonyl)pyrimidine (2d). To a THF solution (15 mL) of 2,4,6-trichloropyrimidine (1.08 g, 5.88 mmol) was added NaSMe (15% in water, 2.68 mL, 6.18 mmol) at 3 ºC (cooled with an ice bath). The solution was gradually warmed to room temperature for 4 h. The reaction was quenched with water and the mixture was extracted with ether, washed with brine, dried over Na_2SO_4, and concentrated.[32] The residue was directly used for the next step without further purification (white solid, 1.13 g; The purity of 2,6-dichloro-4-methylthiopyrimidine was ca. 77% and contaminated with dichloro(methylthio)pyrimidine regioisomer, two chloro(dimethylthio)pyrimidines, and starting 2,4,6-trichloropyrimidine.). The *m*-CPBA oxidation and the purification furnished the desired sulfonylpyrimidine **2d**[33] as a pure form in 69% yield in two steps (915 mg) as a colorless solid. [CAS: 1048389-45-2]: colorless solid; mp 101.5-102.3 ºC; IR (ATR) 3111, 3032, 3002, 2923, 1542, 1524, 1311, 1279, 1223, 1182, 1141, 961, 838, 747, 617 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.30 (3H, s), 7.96 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.3, 116.3, 161.4, 165.7, 168.5; HRMS (APCI) calcd for $C_5H_5Cl_2N_2O_2S$ $[M+H]^+$ 226.9443, found 226.9430.

2-Chloro-4-(methylsulfonyl)pyrimidine (2e). The compound **2e** was obtained in 84% yield in two steps (1.09 g) as a pure form from 2,4-dichloropyrimidine (1.00 g, 6.75 mmol) through 2-chloro-4-methylthiopyrimidine (ca. 91% purity with contamination of its regioisomer) followed by the procedures for preparation of the compounds **2c** and **2d**.[34,35]

[CAS: 1233026-31-7][35]; colorless solid; mp 91.3-92.1 ºC[36]; IR (ATR) 3116, 3019, 3003, 2921, 1552, 1540, 1412, 1347, 1315, 1188, 1160, 1129, 960, 818, 753, 683, 618 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.30 (3H, s), 7.95 (1H, d, J = 4.8 Hz), 9.00 (1H, d, J = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.1, 114.9, 161.9, 162.8, 168.0; HRMS (APCI) calcd for $C_5H_6ClN_2O_2S$ $[M+H]^+$ 192.9833, found 192.9835.

4-Chloro-6-(methylsulfonyl)pyrimidine (2f). The compound **2f** was obtained in 82% yield in two steps (1.59 g) as a pure form from 4,6-dichloropyrimidine (1.50 g, 10.0 mmol) through 4-chloro-6-methylthiopyrimidine (ca. 93% purity with contamination of (dimethylthio)pyrimidine and starting 4,6-trichloropyrimidine) followed by the procedures for preparation of the compounds **2c** and **2d**.[35,37]

[CAS: 89283-46-5][35]: colorless solid; mp 127.4-128.1 ºC; IR (ATR) 3103, 3081, 3018, 2932, 1547, 1534, 1442, 1308, 1284, 1135, 973, 903, 765, 746, 722, 610 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 3.28 (3H, s), 8.05 (1H, s), 9.15 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.4, 118.1, 159.2, 164.4, 166.6; HRMS (APCI) calcd for $C_5H_6ClN_2O_2S$ $[M+H]^+$ 192.9833, found 192.9829.

General Procedure for Benzophenone-catalyzed photoinduced coupling: (entry 1 in Table 1). A CH_2Cl_2 solution (2 mL, 0.1 M) of 4,6-dichloro-2-methanesulfonylpyrimidine **2a** (45.4 mg, 0.2 mmol, 1 equiv), THF **1a** (162 μL, 2.0 mmol, 10 equiv), and benzophenone (3.64 mg, 0.02 mmol, 0.1 equiv) was prepared in a Pyrex® test tube under an argon atmosphere. The test tube was placed at ca. 5 cm distance from a medium-pressure Hg lamp and was irradiated at room temperature for 5 h. The mixture was concentrated and the residue was purified by flash column chromatography (YMC Dispo-packAT SIL-25, hexane to 5% AcOEt in hexane) to provide the coupling adduct **3a** in 74% yield (32.2 mg) as a colorless oil.

4,6-Dichloro-2-(tetrahydrofuran-2-yl)pyrimidine (3a). [CAS: 1483355-82-3]: IR (ATR) 3094, 3042, 2978, 2951, 2875, 1523, 1376, 1308, 1227, 1114, 1064, 846, 808 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.93-2.13 (3H, m), 2.34-2.48 (1H, m), 3.96-4.03 (1H, m), 4.14-4.21 (1H, m), 5.03 (1H, dd, J = 7.6, 5.6 Hz), 7.28 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.7, 32.3, 69.7, 80.6, 119.6, 162.1, 172.9; HRMS (APCI) calcd for $C_8H_9Cl_2N_2O$ $[M+H]^+$ 219.0086, found

219.0101.

4,6-Dichloro-2-(tetrahydro-2H-pyran-2-yl)pyrimidine (3b). 29% yield (13.7 mg); colorless oil; IR (ATR) 3080, 3035, 2937, 2862, 2847, 1525, 1373, 1320, 1264, 1226, 1082, 1047, 807, 784, 711 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54-1.64 (1H, m), 1.64-1.84 (3H, m), 1.92-2.10 (2H, m), 3.62 (1H, ddd, *J* = 11.6, 11.6, 2.0 Hz), 4.20-4.26 (1H, m), 4.50-4.58 (1H, m), 7.30 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 25.2, 31.3, 69.0, 80.0, 119.8, 162.2, 171.2; HRMS (APCI) calcd for $C_9H_{11}Cl_2N_2O$ $[M+H]^+$ 233.0243, found 233.0245.

4,6-Dichloro-2-(oxepan-2-yl)pyrimidine (3c). 68% yield (33.6 mg); colorless oil; IR (ATR) 3092, 3040, 2926, 2856, 1541, 1524, 1375, 1226, 1130, 1106, 846, 809, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55-1.81 (4H, m), 1.83-1.99 (3H, m), 2.08-2.17 (1H, m), 3.76 (1H, ddd, *J* = 12.0, 6.4, 4.4 Hz), 4.09 (1H, ddd, *J* = 12.0, 7.6, 4.4 Hz), 4.71 (1H, dd, *J* = 10.4, 4.0 Hz), 7.27 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 26.6, 31.0, 35.1, 69.2, 81.5, 119.5, 162.0, 172.7; HRMS (APCI) calcd for $C_{10}H_{13}Cl_2N_2O$ $[M+H]^+$ 247.0399, found 247.0387.

4,6-Dichloro-2-(3,3-dimethyloxetan-2-yl)pyrimidine (3d). 45% yield (20.8 mg); colorless oil; IR (ATR) 3092, 3038, 2960, 2932, 2873, 1524, 1464, 1388, 1374, 1228, 1104, 993, 846, 811, 713 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, s), 1.52 (3H, s), 4.48 (1H, d, *J* = 5.6 Hz),

4.52 (1H, d, J = 5.6 Hz), 5.48 (1H, s), 7.30 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 27.0, 41.4, 82.1, 90.2, 119.6, 162.1, 170.4; HRMS (APCI) calcd for $C_9H_{11}Cl_2N_2O$ $[M+H]^+$ 233.0243, found 233.0251.

tert-Butyl 2-(4,6-dichloropyrimidin-2-yl)pyrrolidine-1-carboxylate (3e). 80% yield (51.0 mg), rotamer ratio = 62:38; colorless oil; IR (ATR) 3091, 2976, 2930, 2879, 1693, 1528, 1390, 1365, 1159, 1117, 844, 812, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (5.58H, s), 1.41 (3.42H, s), 1.79-2.07 (3H, m), 2.29-2.46 (1H, m), 3.44-3.53 (0.38H, m), 3.54-3.62 (0.62H, m), 3.62-3.71 (1H, m), 4.81 (0.62H, dd, J = 8.0, 4.8 Hz), 4.92 (0.38H, dd, J = 8.4, 3.6 Hz), 7.20 (0.38H, s), 7.25 (0.62H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.5, 23.9, 28.1, 28.4, 32.6, 33.5, 46.9, 47.1, 62.5, 62.7, 79.4, 79.6, 118.8, 119.1, 153.7, 154.5, 161.8, 161.9, 173.5, 174.1; HRMS (APCI) calcd for $C_{13}H_{18}Cl_2N_3O_2$ $[M+H]^+$ 318.0771, found 318.0755 (minor signal), calcd for $C_8H_{10}Cl_2N_3$ $[M–Boc+2H]^+$ 218.0246, found 218.0242 (major signal).

4,6-Dichloro-2-(piperidin-2-yl)pyrimidine hydrochloride (3f'). The benzophenone-catalyzed photoinduced coupling between *N*-Boc piperidine **1f** and 4,6-dichloro-2-methanesulfonylpyrimidine **2a** was carried out followed by the general procedure for preparation of the compound **3a**, and the yield of the expected adduct **3f** was

determined to be 72% based on the NMR analysis of the mixture after brief separated on silica gel column chromatography. The mixture was treated with HCl/dioxane (4 N, 3 mL) in dioxane (3 mL) at room temperature for 2 h. After volatiles were removed with evaporation, the residue was diluted with ether (~30 mL) and water then sat. aq $NaHCO_3$ was added. Then, the mixture was extracted with ether (~30 mL ×1, ~15 mL ×2) washed with water and brine, dried over K_2CO_3, and filtered. The filtrate was added HCl/dioxane (4 N, 6 mL) and evaporated; CAUTION: Concentration of the derived amine without salt formation causes undesired reactions. The obtained white solid was washed with ether and was dried under vacuum to provide the salt **3f'** in 58% yield (31.3 mg) in two steps as an off-white solid.

208.9 ºC (decomp.); IR (ATR) 3085, 3044, 2872 (br), 2706 (br), 2534 (br), 1537, 1423, 1389, 1312, 1234, 1121, 819 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.59-1.88 (5H, m), 2.17-2.28 (1H, m), 2.94-3.10 (1H, m), 3.29-3.38 (1H, m), 4.44-4.55 (1H, m), 8.15 (1H, s), 9.30 (1H, brs), 9.98 (1H, brs); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.2, 21.5, 28.4, 43.9, 58.5, 121.2, 161.6, 166.7; HRMS (APCI) calcd for $C_9H_{12}Cl_2N_3$ $[M–Cl]^+$ 232.0403, found 232.0400.

tert-Butyl 2-(4,6-dichloropyrimidin-2-yl)azepane-1-carboxylate (3g). 85% yield (58.6 mg), rotamer ratio = 53:47; colorless oil; IR (ATR) 3090, 2973, 2927, 2854, 1688, 1526, 1392, 1364,

1156, 1099, 986, 811, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18-1.88 (15H, m), 1.88-2.01 (1H, m), 2.31 (0.53H, ddd, *J* = 14.4, 8.8, 5.2 Hz), 2.41-2.52 (0.47H, m), 3.15 (0.47H, dd, *J* = 15.2, 11.6 Hz), 3.23 (0.53H, dd, *J* = 14.8, 11.6 Hz), 3.92-4.02 (0.47H, m), 4.08-4.17 (0.53H, m), 4.93 (0.53H, dd, *J* = 12.0, 5.2 Hz), 5.14 (0.47H, dd, *J* = 12.4, 6.0 Hz), 7.19 (0.47H, s), 7.23 (0.53H, s); detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 26.6, 28.3, 28.4, 29.37, 29.44, 30.0, 30.2, 33.6, 33.7, 43.5, 44.1, 61.4, 62.9, 79.68, 79.71, 118.8, 119.1, 155.5, 156.2, 161.8, 161.9, 173.8, 174.4; HRMS (APCI) calcd for $C_{10}H_{14}Cl_2N_3$ $[M–Boc+2H]^+$ 246.0559, found 246.0559.

5-(4,6-Dichloropyrimidin-2-yl)pyrrolidin-2-one (3h). 71% yield (32.8 mg); off-white solid; mp 147.7-149.0 ºC; IR (ATR) 3208, 3080, 3045, 3033, 2961, 2924, 1683, 1530, 1404, 1374, 1304, 1285, 1229, 1128, 814, 768, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.25-2.53 (3H, m), 2.60-2.71 (1H, m), 4.86 (1H, dd, *J* = 8.4, 4.8 Hz), 6.83 (1H, brs), 7.31 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 29.5, 58.5, 120.0, 162.4, 171.4, 178.2; HRMS (APCI) calcd for $C_8H_8Cl_2N_3O$ $[M+H]^+$ 232.0039, found 232.0031.

4,6-Dichloro-2-(tetrahydrothiophen-2-yl)pyrimidine (3i). [CAS: 1542343-51-0]: 31% yield (14.4 mg); colorless oil; IR (ATR) 3098, 3034, 2933, 2860, 1540, 1522, 1440, 1372, 1226, 1092,

842, 812 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.07-2.20 (1H, m), 2.28 (1H, ddddd, *J* = 6.0, 6.0, 6.0, 6.0, 6.0 Hz), 2.37-2.55 (2H, m), 2.93-3.02 (1H, m), 3.05-3.16 (1H, m), 4.64 (1H, dd, *J* = 6.4, 6.4 Hz), 7.22 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 34.0, 35.3, 52.7, 119.0, 161.9, 173.9; HRMS (APCI) calcd for $C_8H_9Cl_2N_2S$ $[M+H]^+$ 234.9858, found 234.9862.

4,6-Dimethoxy-2-(tetrahydrofuran-2-yl)pyrimidine (3j). 48% yield (50.5 mg) [0.5 mmol scale reaction]; colorless oil; IR (ATR) 3090, 2977, 2953, 2872, 1584, 1561, 1462, 1398, 1375, 1255, 1187, 1160, 1050, 986, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.93-2.03 (1H, m), 2.07-2.20 (2H, m), 2.25-2.34 (1H, m), 3.94 (6H, s), 3.96-4.03 (1H, m), 4.18 (1H, dd, *J* = 14.5, 7.0 Hz), 4.93 (1H, dd, *J* = 7.5, 5.0 Hz), 5.90 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.8, 31.5, 53.9, 69.4, 81.2, 87.8, 170.4, 171.6; HRMS (APCI) calcd for $C_{10}H_{15}N_2O_3$ $[M+H]^+$ 211.1077, found 211.1074.

2-(Tetrahydrofuran-2-yl)pyrimidine (3k). 42% yield (12.7 mg); colorless oil; IR (ATR) 3039, 2975, 2950, 2871, 1561, 1426, 1362, 1061, 923, 804, 631 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.95-2.14 (3H, m), 2.36-2.49 (1H, m), 3.95-4.05 (1H, m), 4.14-4.23 (1H, m), 5.06-5.12 (1H, m), 7.18 (1H, t, *J* = 5.2 Hz), 8.72 (2H, d, *J* = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 32.4, 69.4, 81.4, 119.5, 157.2, 171.0; HRMS (APCI) calcd for $C_8H_{11}N_2O$ $[M+H]^+$ 151.0866, found

151.0862.

2,4-dichloro-6-(tetrahydrofuran-2-yl)pyrimidine (3l). [CAS: 1878833-95-4]: 75% yield (33.0 mg); colorless oil; IR (ATR) 3126, 3087, 2981, 2952, 2875, 1556, 1523, 1299, 1237, 1073, 874, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.84-2.07 (3H, m), 2.42-2.55 (1H, m), 3.95-4.02 (1H, m), 4.02-4.10 (1H, m), 4.93 (1H, dd, *J* = 7.6, 5.6 Hz), 7.48 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 32.8, 69.6, 79.6, 115.9, 160.2, 163.1, 177.2; HRMS (APCI) calcd for $C_8H_9Cl_2N_2O$ $[M+H]^+$ 219.0086, found 219.0101.

2-Chloro-4-(tetrahydrofuran-2-yl)pyrimidine (3m). [CAS: 1850883-75-8]: 72% yield (26.5 mg); colorless oil; IR (ATR) 3145, 3115, 3078, 3039, 2979, 2952, 2874, 1570, 1541, 1430, 1341, 1193, 1179, 1071, 925, 851, 830, 739, 658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.83-2.06 (3H, m), 2.40-2.53 (1H, m), 3.94-4.00 (1H, m), 4.02-4.08 (1H, m), 4.93 (1H, dd, *J* = 8.0, 5.6 Hz), 7.43 (1H, dd, *J* = 4.8, 0.8 Hz), 8.56 (1H, d, *J* = 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 32.8, 69.4, 79.8, 115.4, 159.8, 160.9, 175.9; HRMS (APCI) calcd for $C_8H_{10}ClN_2O$ $[M+H]^+$ 185.0476, found 185.0484.

4-Chloro-6-(tetrahydrofuran-2-yl)pyrimidine (3n). [CAS: 1823913-80-9]: 31% yield (11.4 mg); colorless oil; IR (ATR) 3052, 2979, 2952, 2873, 1565, 1530, 1453, 1315, 1097, 1069, 927,

875, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.85-2.07 (3H, m), 2.41-2.54 (1H, m), 3.95-4.03 (1H, m), 4.05-4.11 (1H, m), 4.96 (1H, dd, *J* = 8.0, 5.6 Hz), 7.54 (1H, s), 8.89 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 32.7, 69.4, 79.8, 117.6, 158.3, 162.0, 174.0; HRMS (APCI) calcd for $C_8H_{10}ClN_2O$ $[M+H]^+$ 185.0476, found 185.0490.

Preparation of 1-(4,6-dichloropyrimidin-2-yl)pyrrolidin-2-one (3h', equation 1**)**: To a THF solution (2 mL) of pyrrolidinone **1h** (34.1 mg, 0.40 mmol, 1 equiv) was added NaH (60% in mineral oil, 16.0 mg, 0.40 mmol, 1 equiv) at 0 ºC under an argon atmosphere. After stirring ca. 40 min at 0 ºC, a THF solution (1 mL) of 4,6-dichloro-2-methanesulfonylpyrimidine **2a** (91.0 mg, 0.40 mmol, 1 equiv) was added. The solution was gradually warmed to room temperature and stirred for 3 h. The reaction was quenched with water at 0 ºC, and the mixture was extracted with AcOEt, washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (YMC Dispo-packAT SIL-25, 10% AcOEt in hexane to AcOEt) to provide the adduct **3h'** in 44% yield (40.5 mg) as a white solid. [CAS: 1289134-74-2]: mp 140.2-142.1 ºC; IR (ATR) 3126, 3117, 2993, 2923, 2902, 1746, 1557, 1515, 1440, 1420, 1265, 1183, 1146, 1092, 821, 809, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

2.13 (2H, quintet, J = 7.6 Hz), 2.67 (2H, t, J = 7.6 Hz), 4.04 (2H, t, J = 7.6 Hz), 7.09 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 33.4, 48.0, 115.8, 156.8, 162.1, 173.5; HRMS (APCI) calcd for $C_8H_8Cl_2N_3O$ $[M+H]^+$ 232.0039, found 232.0037.

A Route for Preparation of the aurora kinase inhibitor analogue (5, Scheme 4**)**: A CH_2Cl_2 solution (5 mL, 0.1 M) of 4,6-dichloro-2-methanesulfonylpyrimidine **2a** (113.5 mg, 0.5 mmol, 1 equiv), *N*-Boc pyrrolidine **1e** (171.2 mg, 1.0 mmol, 2 equiv), and benzophenone (9.11 mg, 0.05 mmol, 0.1 equiv) was prepared in a Pyrex® test tube under an argon atmosphere. The test tube was placed at ca. 5 cm distance from a medium-pressure Hg lamp and was irradiated at room temperature for 24 h. The mixture was concentrated and the residue was purified by flash column chromatography (silica gel, 5% AcOEt in hexane to AcOEt) to provide the coupling adduct **3e** in ca. 67% yield (105.9 mg, contaminated with a small amount of inseparable impurities) as a colorless oil.

To a THF solution (5 mL) of the dichloropyrimidine substituted with the azacycle **3e** (58.5 mg, ca. 0.183 mmol) and $^{i}Pr_2NEt$ (38.0 μL, 0.221 mmol) was added methylpiperazine (21.5 μL, 0.193 mmol) at 0 ºC under an argon atmosphere. The solution was warmed to room

temperature and stirred until the starting material **3e** was consumed. The mixture was extracted with AcOEt, washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (YMC Dispo-packAT NH2-25, 25% AcOEt in hexane to AcOEt) to provide the product **4** in 91% yield (64.3 mg, contaminated with 5% CH_2Cl_2) as a colorless syrup.

Compound 4. rotamer ratio = 71:29; IR (ATR) 3096, 2972, 2938, 2875, 2794, 1692, 1570, 1532, 1449, 1391, 1155, 998, 973, 917, 807, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (6.39H, s), 1.40 (2.61H, s), 1.74-1.99 (3H, m), 2.18-2.35 (1H, m), 2.28 (3H, s), 2.39 (4H, t, *J* = 5.2 Hz), 3.36-3.71 (6H, m), 4.65 (0.71H, dd, *J* = 8.4, 4.0 Hz), 4.77 (0.29H, dd, *J* = 8.4, 3.2 Hz), 6.27 (0.29H, s), 6.31 (0.71H, s); detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 23.6, 28.2, 28.5, 32.2, 33.0, 43.7, 43.8, 46.0, 46.7, 46.9, 54.38, 54.42, 62.2, 62.7, 78.8, 78.9, 98.6, 99.0, 154,3, 154.4, 160.0, 160.3, 162.6, 170.9, 171.9; HRMS (APCI) calcd for $C_{18}H_{29}ClN_5O_2$ $[M+H]^+$ 382.2004, found 382.2002 (minor signal), calcd for $C_{13}H_{21}ClN_5$ $[M–Boc+2H]^+$ 282.1480, found 282.1465 (major signal).

The starting substance **4** (63.0 mg, contaminated with 8% CH_2Cl_2, 0.162 mmol, 1 equiv), 5-amino-1-^{t}butoxycarbonyl-3-methylpyrazole (35.2 mg, 0.178 mmol, 1.1 equiv), $Pd(OAc)_2$

(3.64 mg, 0.0162 mmol, 0.1 equiv), Xantphos (18.8 mg, 0.0324 mmol, 0.2 equiv), and Cs_2CO_3 (68.7 mg, 0.211 mmol, 1.3 equiv) were dissolved in dioxane (2 mL, 0.08 M) under an argon atmosphere, and the solution was stirred at 80 ºC for 14.5 h. After cooling at 0 ºC, MeOH (2 mL) and 1 N NaOH aq (1 mL) were added and the solution was stirred at room temperature for 50 min. The mixture was extracted with CH_2Cl_2 and AcOEt, washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by PTLC (NH silica gel [WAKO], CH_2Cl_2/MeOH = 40:1) to provide the product **5** in 81% yield (61.3 mg, contaminated with 32% CH_2Cl_2) as a pale brown syrup.

Analogue of the Aurora Kinase Inhibitor, MK-0457 (5). rotamer ratio = 75:25 in $CDCl_3$ and rotamer ratio = 64:36 in DMSO-d_6; IR (ATR) 3253 (br), 2973, 2934, 2873, 2845, 2793, 1674, 1585, 1553, 1481, 1445, 1400, 1287, 1161, 1121, 1000, 769, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (6.75H, s), 1.42 (2.25H, s), 1.68-2.07 (3H, m), 2.15-2.34 (1H, m), 2.28 (3H, s), 2.29 (3H, s), 2.34-2.48 (4H, m), 3.39-3.78 (6H, m), 4.61 (0.75H, dd, *J* = 8.8, 3.6 Hz), 4.75 (0.25H, brd, *J* = 8.0 Hz), 5.81 (1H, brs), 6.34 (1H, brs), 7.81 (0.25H, brs), 8.22 (0.75H, brs), 11.2 (1H, brs); ^1H NMR (400 MHz, DMSO-d_6) δ 1.13 (5.76H, s), 1.37 (3.24H, s), 1.71-1.98 (3H, m), 2.12-2.29 (1H, m), 2.17 (3H, s), 2.19 (3H, s), 2.29-2.39 (4H, m), 3.29-3.59 (6H, m), 4.45

(0.64H, dd, J = 8.0, 4.0 Hz), 4.53 (0.36H, brd, J = 6.8 Hz), 5.94 (0.64H, brs), 6.06 (0.36H, brs), 6.41 (0.36H, brs), 6.59 (0.64H, brs), 9.12 (1H, brs), 11.8 (1H, brs); ^{13}C NMR (100 MHz, DMSO-d_6) δ 10.6 (br, x2), 22.8, 23.2, 27.9, 28.2, 31.8, 32.7, 43.45, 43.52, 45.8 (×2), 46.7 (×2), 54.2 (×2), 62.0, 62.7, 77.6, 77.9, 81.7 (br), 81.9 (br), 94.7 (br), 94.9 (br), 137.9 (br), 138.0 (br), 149.6 (br, ×2), 153.4, 153.7, 160.29, 160.34, 162.8, 162.9, 169.2, 169.9; HRMS (APCI) calcd for $C_{22}H_{35}N_8O_2$ $[M+H]^+$ 443.2877, found 443.2862, calcd for $C_{17}H_{27}N_8$ $[M–Boc+2H]^+$ 343.2353, found 343.2374.

Preparation of 5-amino-1-^{t}butoxycarbonyl-3-methylpyrazole[29]: To a CH_2Cl_2 solution (20 mL) of 3-amino-5-methylpyrazole (1.04 g, 10.7 mmol) were added 5 N NaOH aq (20 mL, 100 mmol) and $(Boc)_2O$ (2.58 mL, 11.2 mmol). After vigorous stirring at room temperature for 18 h, the mixture was extracted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (silica gel, 30% AcOEt in hexane to AcOEt) to provide the expected product, 5-amino-1-^{t}butoxycarbonyl-3-methylpyrazole, in 76% yield (1.61 g) as an off-white solid along with its regioisomer, 3-amino-1-^{t}butoxycarbonyl-5-methylpyrazole, in 6.7% (142 mg) as an off-white solid.

[CAS: 1065204-79-6]: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.54 (9H, s), 2.00 (3H, s), 5.15 (1H, s), 6.22 (2H, brs); ^{13}C NMR (100 MHz, DMSO-d_6) δ 13.8, 27.7, 83.4, 87.5, 150.0, 151.5, 151.7; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (9H, s), 2.16 (3H, s), 5.23 (1H, s), 5.26 (2H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 28.0, 84.9, 89.3, 150.6, 150.7, 153.2.

An Alternative Route for Preparation of the aurora kinase inhibitor analogue (5, Scheme 4**)**: The coupling adduct **3e** was prepared by following the above procedure.

The dichloropyrimidine substituted with the azacycle **3e** (72.9 mg, ca. 0.229 mmol, 1 equiv), 5-amino-1-^{t}butoxycarbonyl-3-methylpyrazole (45.2 mg, 0.229 mmol, 1 equiv), $Pd(OAc)_2$ (5.14 mg, 0.0229 mmol, 0.1 equiv), Xantphos (26.5 mg, 0.0458 mmol, 0.2 equiv), and Cs_2CO_3 (89.6 mg, 0.275 mmol, 1.2 equiv) were dissolved in dioxane (3 mL, 0.076 M) under an argon atmosphere, and the solution was stirred at room temperature for 2 d. The mixture was extracted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (YMC Dispo-packAT SIL-25, 50% AcOEt in hexane to AcOEt) and then PTLC (silica gel [Merck], hexane/AcOEt = 1:1) to provide the product **4'** in 62% yield (73.4 mg, contaminated with 42% CH_2Cl_2) as a colorless

syrup.

Compound 4'. rotamer ratio = 61:39; IR (ATR) 3276 (br), 2975, 2929, 2873, 1695, 1556, 1507, 1389, 1360, 1336, 1257, 1155, 1108, 971, 843, 767, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (5.49H, s), 1.39 (3.51H, s), 1.63 (9H, s), 1.77-2.05 (3H, m), 2.22-2.45 (1H, m), 2.27 (1.83H, s), 2.28 (1.17H, s), 3.47-3.74 (2H, m), 4.79 (0.61H, dd, *J* = 8.4, 4.0 Hz), 4.92 (0.39H, dd, *J* = 8.4, 2.8 Hz), 6.58 (0.39H, s), 6.62 (0.61H, s), 6.76 (0.61H, s), 6.77 (0.39H, s), 9.96 (0.39H, brs), 10.01 (0.61H, brs); detectable signals of ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 14.6, 23.3, 23.9, 27.9, 28.1, 28.4, 32.5, 33.4, 46.8, 47.2, 62.3, 62.6, 79.1, 79.3, 86.5, 97.6, 97.9, 104.0, 104.4, 141.8, 142.2, 151.16, 151.25, 153.1, 153.7, 154.0, 154.2, 158.2, 159.9, 160.1, 172.3, 173.0; HRMS (APCI) calcd for $C_{22}H_{32}ClN_6O_4$ $[M+H]^+$ 479.2168, found 479.2194 (minor peak), calcd for $C_{17}H_{24}ClN_6O_2$ $[M–Boc+2H]^+$ 379.1644, found 379.1665 (minor peak), calcd for $C_{12}H_{16}ClN_6$ $[M–2(Boc)+3H]^+$ 279.1119, found 279.1146 (major peak).

The starting substance **4'** (73.0 mg, contaminated with 42% CH_2Cl_2, 0.0142 mmol, 1 equiv) was dissolved in methylpiperazine (4 mL, 35.9 mmol) and the solution was stirred at 90 ºC for 2 h. The mixture was extracted with AcOEt, washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by PTLC (silica gel [Merck], $CHCl_3$/MeOH = 9:1)

to provide the product **5** in 70% yield (45.5 mg, contaminated with 19% CH_2Cl_2) as a colorless syrup.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

A plausible reaction mechanism and ^{1}H and ^{13}C NMR spectra for relevant compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(20) The coupling using the three-membered cyclic ether, 2,2-dimethyloxirane, did not give the expected adduct.

(21) The coupling between *N*-Boc piperidine **1f** and sulfonylpyrimidine **2a** was completed in 24 h and the yield of the adduct **3f** was determined to be 72% based on the NMR analysis of the mixture after brief separation on silica gel column chromatography. Deprotection of the Boc group from **3f** to derive the HCl salt **3f'** was essential to avoid the tedious separation of **1f** and **3f**.

(22) An acyclic substance, *N*-Boc butylamine, could be applied to the present coupling, however the yield of the expected adduct was rather low (<25% yield).

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(25) The catalytic reaction employing cyclooctane did not produce the expected adduct at all and the starting pyrimidine **2a** was recovered in 67% yield.

(26) We confirmed that the reaction between 4,6-dichloro-2-methanesulfonylpyrimidine **2a** and adamantane did not provide an appreciable amount of the coupling adduct even in the presence of a stoichiometric amount of Ph_2CO, indicating alkanes were not suitable substances for the present transformation.

(27) In the present photoinduced pyrimidination employing 5-membered heterocycles as a starting substance, the reactivity tendency seems to be N-substituted ≥ O-substituted > S-substituted C–H bonds.

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