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Regioselective Amination

Highly Regioselective Organocatalytic S_NAr Amination of 2,4-Dichloropyrimidine and Related Heteroaryl Chlorides

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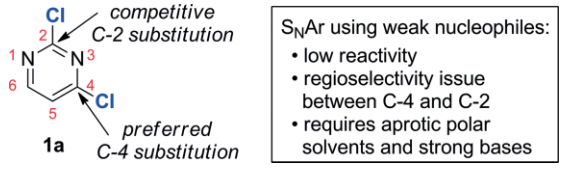
Abstract: A highly efficient and regioselective method for the S_NAr amination of 2,4-dichloropyrimidine with oxazolidin-2-one and related weakly nucleophilic amines, using sodium sulfinate and tetrabutylammonium bromide as catalysts, is disclosed. This strategy facilitates the synthesis of various aminopyrimidines in a regio- and chemoselective manner. This approach was successfully used for the amination of various activated N-heteroaromatic substrates.

Introduction

Substituted pyrimidines, and 2,4-aminopyrimidines in particular, are important structural motifs that are present in a wide variety of pharmaceuticals and biologically active substances.[1] A recent report shows that the pyrimidine scaffold is the second most common heteroaromatic ring present in pharmaceutically active compounds after the pyridine scaffold.[2] Consequently, efficient routes to this and related heteroaromatic moieties are urgently required for both drug discovery and process development. Conventional syntheses of aminopyrimidines rely on transition-metal-catalysed amination or nucleophilic aromatic substitution reactions of activated heteroaryl substrates.[3] Due to the importance of pyrimidines in pharmaceutical chemistry, a number of building blocks are now commercially available, with 2,4-dichloropyrimidine (**1a**, DCP; Scheme 1) a particularly notable example. The availability of this building block greatly simplifies synthetic considerations, but the development of efficient, regioselective methods for the direct amination of this common precursor remains a major challenge. Generally, amination reactions of DCP are highly sensitive to changes of reaction conditions, in particular to the combination of nucleophile and base.[4] The C-4 position of DCP tends to be more reactive towards nucleophilic substitution, but the exclusive formation of a single regioisomer remains challenging, and this is further complicated by separation issues and loss of product.[5–7] These challenges are further increased when weakly nucleophilic amines are used; most existing methods are limited to reactive primary and secondary amines. Only a handful of reports describe the use of weakly nucleophilic amines such as amides, carbamates, pyrroles, or imidazoles in such transformations.[8,9] To address this problem, we report a highly efficient, regioselective, and economical protocol for the selective C-4 amination of DCP with weakly nucleophilic oxazolidin-2-ones and related nucleophiles. The procedure was also successfully translated into a number of other activated heteroaryl chlorides.



Scheme 1. 2,4-Dichloropyrimidine.

Results and Discussion

For our initial investigations into an efficient and selective method for the amination of DCP (**1a**) with weakly nucleophilic amines, unsubstituted oxazolidin-2-one (**2a**) was selected as a model substrate. Aware of the possible formation of regioisomeric products, we began our study with the systematic alteration of reaction conditions. Specifically, time, solvent, base, and catalyst/additive combinations were investigated. We were particularly interested in the use of mild and environmentally friendly conditions that would be suitable for large-scale synthesis, and also for the synthesis of more complex structural motifs. Most of the preliminary control experiments carried out in the absence of catalyst or additive resulted in moderate yields and a significant amount of the unwanted regioisomer (Scheme 2a). Selected results using K_2CO_3 and NaH in THF are shown in Table 1 (entries 1 and 2). It is important to note that ethanol and other alcohol solvents that are often used in S_NAr amination reactions were found to be unsuitable in this case; they often led to the exclusive formation of the alcohol-addition products (Table 1, entry 3). From previous work,[10] it was known that replacement of the C-4 chloride with a sulfone differentiates the reactivity of the two electrophilic sites and

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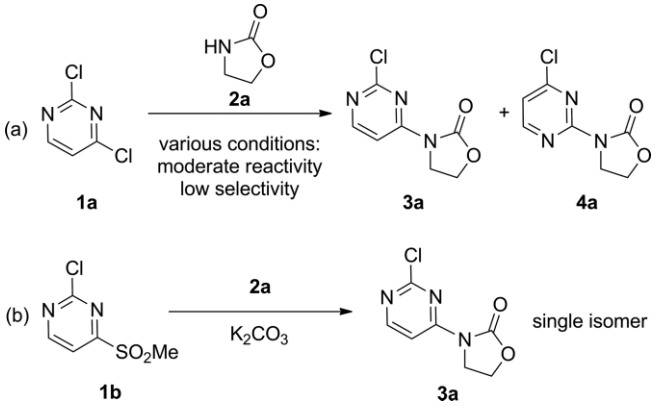
Table 1. Optimisation table.

Entry[a]	Solvent	Base (equiv.)	Ammonium salt (0.1 equiv.)	Sulfinate (0.03 equiv.)	Yield [%][c]	Ratio **3a**/**4a**[d]
1[b]	THF	NaH (1.1)	–	–	17	1:2
2	THF	K_2CO_3 (2)	–	–	20	1:0.8
3	EtOH	K_2CO_3 (2)	–	–	0[e]	–
4	THF	K_2CO_3 (2)	–	$NaSO_2Me$	22	1:0.8
5	THF	K_2CO_3 (2)	TBABr[g]	$NaSO_2Me$	91	42:1
6	THF	K_2CO_3 (2)	TBABr	–	72	8:1
7	THF	Li_2CO_3 (2)	TBABr	$NaSO_2Me$	<2[f]	1:2
8	THF	Na_2CO_3 (2)	TBABr	$NaSO_2Me$	<10[f]	1:1
9	THF	Cs_2CO_3 (2)	TBABr	$NaSO_2Me$	70	55:1
10	THF	K_3PO_4 (2)	TBABr	$NaSO_2Me$	67	21:1
11	THF	NEt_3 (2)	TBABr	$NaSO_2Me$	<20[f]	1:1.5
12	THF	2,6-lutidine (2)	TBABr	$NaSO_2Me$	<10[f]	10:1
13[b]	THF	NaH (1.1)	TBABr	$NaSO_2Me$	67	5:1
14	THF	K_2CO_3 (1)	TBABr	$NaSO_2Me$	74	12:1
15	THF	K_2CO_3 (3)	TBABr	$NaSO_2Me$	90	24:1
16	THF	K_2CO_3 (2)	$TBASO_3Me$	$NaSO_2Me$	79	70:1
17[b]	THF	Cs_2CO_3 (2)	$TBASO_3Me$	$NaSO_2Me$	71	30:1
18	THF	K_2CO_3 (2)	TMABr[h]	$NaSO_2Me$	53	3.5:1
19	THF	K_2CO_3 (2)	*n*BuPyBr[i]	$NaSO_2Me$	65	8:1
20	THF	K_2CO_3 (2)	TBABr	$NaSO_2Ph$	75	22:1
21	Me-THF	K_2CO_3 (2)	TBABr	$NaSO_2Me$	59	8:1
22	toluene	K_2CO_3 (2)	TBABr	$NaSO_2Me$	83	21:1
23	EtOAc	K_2CO_3 (2)	TBABr	$NaSO_2Me$	81	50:1
24	acetone	K_2CO_3 (2)	TBABr	$NaSO_2Me$	69	42:1
25	MeCN	K_2CO_3 (2)	TBABr	$NaSO_2Me$	83	65:1
26	CPME[j]	K_2CO_3 (2)	TBABr	$NaSO_2Me$	84	>100:1

[a] Reactions were carried out at 50 °C. [b] Carried out at room temperature. [c] Isolated yield of **3a**. [d] Determined by ^{1}H NMR spectroscopic analysis of the crude product after workup. [e] Only ethanol substitution. [f] Conversion determined by ^{1}H NMR spectroscopic analysis of the crude product after workup. [g] TBA: tetrabutylammonium. [h] TMA: trimethylammonium. [i] *n*BuPyBr: *n*-butylpyridinium bromide. [j] CPME: cyclopropyl methyl ether.

thereby enhances the selectivity, and that this can lead to the exclusive formation of the C-4 substituted pyrimidine **3a** (Scheme 2b).[4,7]

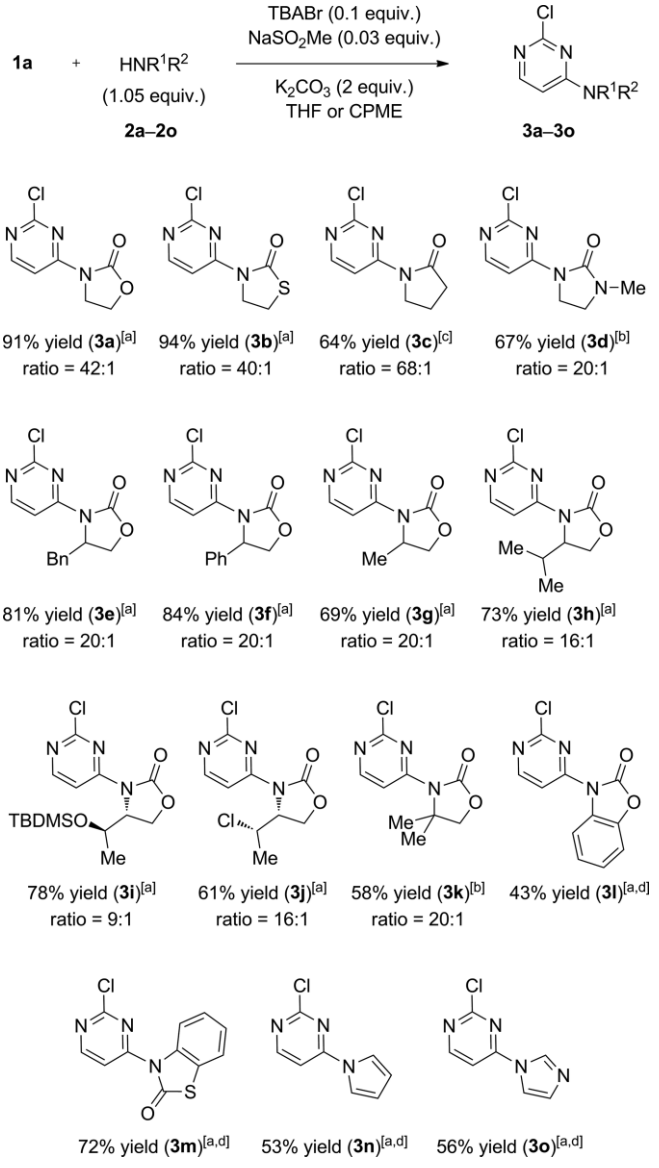


Scheme 2. Reactivity difference between DCP and 2-chloro-4-(methylsulfonyl)pyrimidine (**1b**).

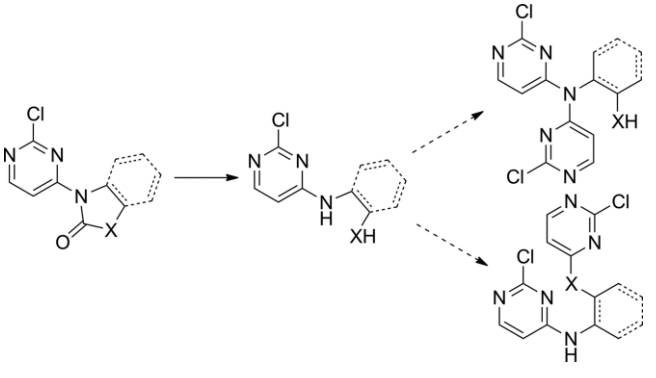
Based on these results, we envisioned a process in which the in-situ formation of the 2-chloro-4-(methylsulfonyl)pyrimidine (**1b**) might be realised through the addition of a sulfinate salt to **1a**.[11,12] This approach is extremely appealing, since the substitution of the SO_2Me group would regenerate the sulfinate salt needed to form **1b**, rendering the reaction catalytic in sulfinate. The substoichiometric use of sulfinates to promote the nucleophilic substitution of 2-chloro-4,6-dimethoxypyrimidine has already been described, which provided an encouraging precedent.[13] However, simply doping the reaction mixture with 0.03 equiv. of $NaSO_2Me$ did not lead to a noticeable improvement in terms of reactivity or selectivity compared to the uncatalysed control reaction (Table 1, Entries 2 and 4), which suggests that the desired sulfone **1b** was not formed. We suspected that this could be due to a problem of solubility, so a catalytic amount of tetrabutylammonium bromide (TBABr) was used to assist in solubilising the $NaSO_2Me$, and so promote the formation of the aryl sulfone.[14] Under these optimised catalysis conditions, the desired regioisomer was formed preferentially with a ratio of 42:1 in favour of product **3a**, as confirmed by ^{1}H NMR spectroscopy; product **3a** was isolated as a single compound in a synthetically useful 91 % yield (Table 1, Entry 5). The formation of a small quantity of **1b** was detected by HPLC and by ^{1}H NMR spectroscopy when the reaction was run in [D_8]THF. Interestingly, a control reaction in which only TBABr was used gave the desired product in 72 % yield (crude ratio **3a**/**4a** 8:1; Table 1, Entry 6). This result shows that the solubilisation of $NaSO_2Me$ is not the only effect of the ammonium salt.[15] Returning to the mixed-catalyst procedure, increasing the TBABr loading or introducing other tetrabutylammonium halide salts[16] did not lead to a measurable increase in the yield or selectivity. However, the use of higher loadings of $NaSO_2Me$ was found to result in partial substitution of the C-2 chloride

with sulfinate, resulting in the formation of an undesired product mixture of **3a** and 3-[2-(methylsulfonyl)pyrimidin-4-yl]-oxazolidin-2-one. Further attempts to optimise our catalytic system using quaternary ammonium salts, including tetrabutylammonium methanesulfonate ($TBASO_3Me$), tetramethylammonium bromide (TMABr), and *n*-butylpyridinium bromide (*n*BuPyBr) were unsuccessful (Table 1, Entries 16–19). The results were generally superior to those obtained in the absence of catalysts, but TBABr gave the best results. Furthermore, when $NaSO_2Me$ was replaced by $NaSO_2Ph$, a substantial drop in yield and selectivity was noted (Table 1, Entry 20). The choice of base proved to be critical, and no reaction was observed with either sodium or lithium carbonate, or with organic bases such as Et_3N or 2,6-lutidine. Although the use of Cs_2CO_3 and K_3PO_4 led to reasonable levels of conversion, the results were inferior to those obtained with K_2CO_3. To complete our investigation, a screen of commonly used green alternative solvents[17] such as methyl-THF, toluene, ethyl acetate, and acetone were evaluated. This screening revealed that the reaction performs satisfactorily in most solvents under the specified conditions (Table 1, Entries 21–26). Reactions were run at 50 °C, and complete conversion was obtained after only a few hours. The reactions also proceeded to completion at room temperature with no significant impact on the regioisomeric ratio, but required extended reaction times. Having optimised the catalyst system for the selective C-4 amination of 2,4-dichloropyrimidine with oxazolidin-2-one, a variety of other amines were evaluated (Scheme 3).

The method was found to work very well for various carbamates and similar weakly nucleophilic amines, giving yields from 53 to 91 %. In some cases, longer reaction times and higher temperatures were necessary to drive the reaction to completion (see the Experimental Section for full details). Our investigation of the substrate scope started with structurally similar cyclic amines. Thiazolidin-2-one, pyrrolidin-2-one, and 1-methylimidazolidin-2-one gave the corresponding products **3b**–**3d** in synthetically useful yields. The less nucleophilic 2-pyrrolidinone **2c** required slightly harsher conditions (cyclopentyl methyl ether at 100 °C) to obtain **3c** with full conversion. Aryl- and alkyl-substituted oxazolidin-2-ones proved to be viable substrates as well, and gave aminopyrimidines **3e**–**3h** in acceptable yields (69–81 %). Other substituted amines including (1-chloroethyl)- (**3j**), {1-[(*tert*-butyldimethylsilyl)oxy]ethyl}- (**2i**), and dimethyl- (**2k**) -oxazolidin-2-ones could also be used, and the corresponding products were formed in good yields. The unprotected 4-(1-hydroxyethyl)oxazolidin-2-one led to a complex mixture of products. We next examined different indoline-derived amines. When benzo[*d*]oxazol-2(3*H*)-one was used as substrate for the formation of **3l**, the reaction proceeded with the concomitant formation of increased levels of by-products, and the overall yield decreased to 43 %. These by-products were predominantly derived from opening of the oxazolidin-2-one ring (Scheme 4). Surprisingly, the formation of structural analogue **3m** was found to proceed more selectively. This may be due to the more electron-rich thiocarbamate being less susceptible to ring-opening. The final two substrates investigated were pyrrole (leading to **3n**) and imidazole (leading to **3o**) as heteroaromatic amines; the successful results obtained with these compounds demonstrate the versatility of the protocol with unreactive substrates. It should be noted that for the



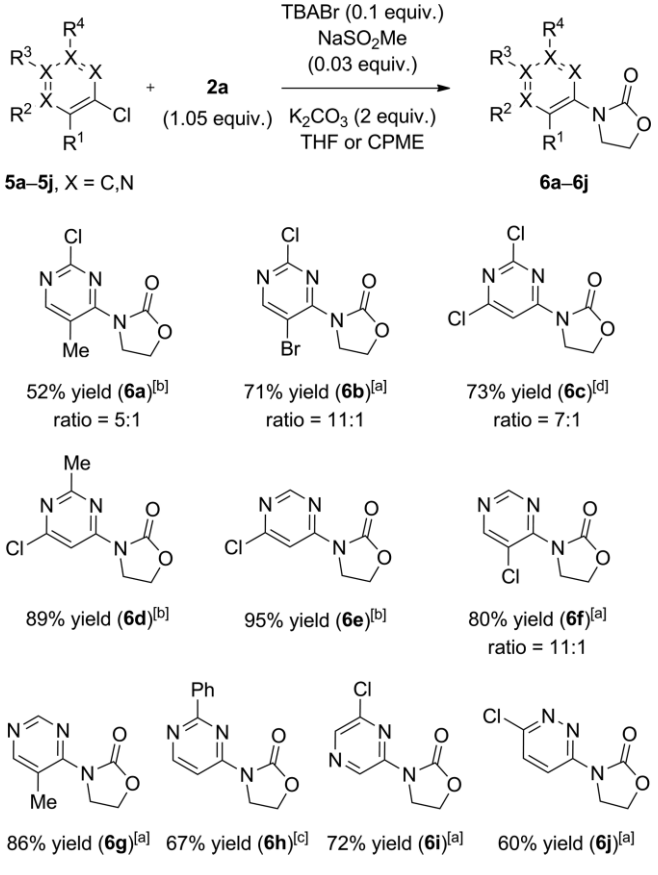
Scheme 3. Scope of the reaction in terms of nucleophiles. [a] Method A: THF, 50 °C. [b] Method B: THF, reflux. [c] Method C: CPME, 100 °C. [d] Regioisomeric ratio could not be determined due to side-product formation.



Scheme 4. Potential degradation pathways.

reactions with substrates **2l**–**2o**, the regioisomeric side-product could not be identified, and therefore no regioisomeric ratio could be determined. Also, no significant improvement in regioselectivity was observed when reactive primary and secondary amines were used under the described reaction conditions, and much lower conversions were observed for acyclic carbamates.

Following the study of different amines, the scope of activated heteroaryl chlorides that could undergo amination using our developed protocol was investigated (Scheme 5). Additional substitution on the C-5 position of 2,4-dichloropyrimidine with a methyl group (formation of **6a**) or a bromide (formation of **6b**) resulted in a drop of yield and selectivity. We presume that the decreased selectivity is due to an increased steric demand. 2,4,6-Trichloropyrimidine (TCP) showed a high reactivity, even at room temperature, but the selectivity dropped to a moderate 7:1 ratio. With symmetrical dichloropyrimidines such as 4,6-dichloro-2-methylpyrimidine (formation of **6d**) and 4,6-dichloropyrimidine (formation of **6e**), only the desired monoaddition adduct was formed. The reaction of 4,5-dichloropyrimidine gave the corresponding product **6f** in good yield with a selectivity of 11:1. Similarly, methyl substitution at C-5 delivered the product **6g** in 86 % yield.



Scheme 5. Scope of the reaction in terms of electrophiles. [a] Method A: THF, 50 °C. [b] Method B: THF, reflux. [c] Method C: CPME, 100 °C. [d] Method D: THF, room temperature.

When the chloride substituent at the C-2 position was replaced with a phenyl group, a higher reaction temperature was required (CPME, 100 °C) to obtain a good yield of **6h**. Finally, we found that the reaction was efficient with other activated heteroaryl scaffolds, such as the two symmetrical dichlorodiazines, which gave the corresponding products **6i** and **6j** in 72 and 60 % yields, respectively.

Conclusions

We have developed an efficient protocol for the catalytic regioselective S_NAr amination of 2,4-dichloropyrimidine with weakly nucleophilic oxazolidin-2-ones in yields ranging from 43 to 91 % and with high selectivities. This mild and environmentally friendly method works in a number of different solvents. The observed C-4 selectivity could be achieved by in-situ sulfone formation using sodium methanesulfinate, and promoted by the use of tetrabutylammonium bromide as a catalyst. The method also gives access to a number of different oxazolidin-2-one-substituted heteroaryl scaffolds in 52–95 % yield.

Experimental Section

General Reaction Procedure for the Amination of 2,4-Dichloropyrimidines and Heteroaryl Chlorides with Oxazolidin-2-ones: The heteroaryl chloride (2.00 mmol), amine (2.10 mmol), K_2CO_3 (551 mg, 3.99 mmol), TBABr (64.0 mg, 0.199 mmol), and $NaSO_2Me$ (6.1 mg, 0.060 mmol) were successively added to an oven-dried vial equipped with a magnetic stirrer bar. Then THF or CPME (1.5 mL) was added, and the reaction mixture was heated to the appropriate temperature while stirring. The reaction progress was monitored, and when the heteroaryl chloride was fully consumed, the mixture was cooled to 0 °C. The mixture was then added dropwise to ice-cold HCl (1 M aq.; 6 mL), and, if necessary, the pH was adjusted to pH 3–7 to prevent hydrolysis of the oxazolidinone. EtOAc (15 mL) and brine (5 mL) were added, the phases were separated, and the aqueous phase was further extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4, and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel using *n*-heptane and EtOAc.

3-(2-Chloropyrimidin-4-yl)oxazolidin-2-one (3a):[8] Prepared using 2,4-dichloropyrimidine (1.32 mmol) and oxazolidin-2-one according to the general procedure. The reaction mixture was stirred in THF at 50 °C for 3 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 3:1) gave **3a** (239 mg, 91 %) as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, J = 5.8 Hz, 1 H), 8.14 (d, J = 5.8 Hz, 1 H), 7.26 (s, 1 H), 4.57–4.52 (m, 2 H), 4.30–4.23 (m, 2 H), –0.02 (s, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.4, 159.5, 158.6, 154.1, 107.4, 62.7, 43.5 ppm.

3-(2-Chloropyrimidin-4-yl)thiazolidin-2-one (3b): Prepared using 2,4-dichloropyrimidine and thiazolidin-2-one according to the general procedure. The reaction mixture was stirred in THF at 50 °C for 5 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 10:1 to 2:1 over 30 min) gave **3b** (402 mg, 93 %) as fine, colourless needles. M.p. 149–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, J = 5.8 Hz, 1 H), 8.10 (d, J = 6.0 Hz, 1 H), 4.41 (t, J = 7.3 Hz, 2 H), 3.40 (t, J = 7.3 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.7, 160.0, 159.7, 158.7, 108.7, 48.0, 25.4 ppm. IR (neat): $\tilde{\nu}$ = 1705, 1683, 1562, 1535, 1459, 1429, 1378, 1332, 1280, 1280, 1237, 1206, 1172, 1142, 1098, 1088, 1018, 991, 924, 861, 839, 767, 748, 691, 664, 643, 628, 491, 439 cm^{-1}. HRMS (ES): calcd. for $C_7H_7ClN_3OS$ $[M + H]^+$ 215.99929; found 215.99930.

1-(2-Chloropyrimidin-4-yl)pyrrolidin-2-one (3c): Prepared using 2,4-dichloropyrimidine and pyrrolidin-2-one according to the general procedure. The reaction mixture was stirred in CPME at 90 °C for 2 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 5:1) gave **3c** (243 mg, 64 %) as a colourless solid. M.p. 163–164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, J = 5.8 Hz, 1 H), 8.33 (d, J = 5.8 Hz, 1 H), 4.10–4.05 (m, 2 H), 2.71–2.65 (m, 2 H), 2.20–2.12 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.1, 160.2, 159.5, 159.1, 108.6, 46.82, 33.6, 17.6 ppm. IR (neat): $\tilde{\nu}$ = 3117, 2900, 1723, 1565, 1537, 1427, 1381, 1341, 1246, 1205, 1183, 1090, 1001, 977, 873, 834, 787, 770 cm^{-1}. HRMS (ES): calcd. for $C_8H_9ClN_3O$ $[M + H]^+$ 198.04287; found 198.04288.

1-(2-Chloropyrimidin-4-yl)-3-methylimidazolidin-2-one (3d): Prepared using 2,4-dichloropyrimidine and 1-methylimidazolidin-2-one according to the general procedure, using THF at 68 °C for 18 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 10:1 to 1:1 over 40 min) gave **3d** (284 mg, 67 %) as colourless crystals. M.p. 178–179 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, J = 6.0 Hz, 1 H), 8.17 (d, J = 6.0 Hz, 1 H), 4.04–3.98 (m, 2 H), 3.55–3.48 (m, 2 H), 2.91 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.1, 159.6, 158.1, 155.8, 106.8, 43.7, 40.5, 30.9 ppm. IR (neat): $\tilde{\nu}$ = 2901, 1715, 1577, 1535, 154, 1488, 1466, 1433, 1406, 1382, 1333, 1294, 1265, 1226, 1203, 1154, 1122, 1079, 1040, 979, 848, 787, 769, 745, 721, 654, 544, 453, 410 cm^{-1}. HRMS (ES): calcd. for $C_8H_{10}ClN_4O$ $[M + H]^+$ 213.05377; found 213.05368.

4-Benzyl-3-(2-chloropyrimidin-4-yl)oxazolidin-2-one (3e): Prepared using 2,4-dichloropyrimidine and 4-benzyloxazolidin-2-one according to the general procedure, using THF at 50 °C for 6 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 19:1 to 3:1 over 25 min) gave **3e** (465 mg, 81 %) as a colourless solid. M.p. 79–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50 (d, J = 5.8 Hz, 1 H), 8.17 (d, J = 5.8 Hz, 1 H), 7.38–7.23 (m, 5 H), 5.06–4.95 (m, 1 H), 4.37–4.30 (m, 2 H), 3.45 (dd, J = 3.3, 13.3 Hz, 1 H), 2.85 (dd, J = 9.5, 13.3 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.4, 159.9, 158.2, 153.8, 135.3, 129.5, 129.1, 127.5, 107.7, 66.9, 55.9, 37.6 ppm. IR (neat): $\tilde{\nu}$ = 3030, 2984, 2917, 1764, 1567, 1541, 1442, 1393, 1347, 1288, 1170, 1119, 1087, 1034, 1002, 981, 841, 808, 763, 743, 702, 671, 658, 615, 571, 509 cm^{-1}. HRMS (ES): calcd. for $C_{14}H_{13}ClN_3O_2$ $[M + H]^+$ 290.06906; found 290.06908.

3-(2-Chloropyrimidin-4-yl)-4-phenyloxazolidin-2-one (3f): Prepared using 2,4-dichloropyrimidine and 4-phenyloxazolidin-2-one according to the general procedure, using THF at 50 °C for 19 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 20:1 to 4:1 over 25 min) gave **3f** (459 mg, 84 %) as colourless crystals. M.p. 99–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, J = 5.8 Hz, 1 H), 8.15 (d, J = 5.8 Hz, 1 H), 7.40–7.32 (m, 5 H), 5.78 (dd, J = 3.5, 8.8 Hz, 1 H), 4.83 (t, J = 8.8 Hz, 1 H), 4.45 (dd, J = 3.6, 8.9 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.1, 159.8, 158.0, 154.2, 138.6, 129.3, 129.0, 126.8, 108.1, 70.7, 58.1 ppm. IR (neat): $\tilde{\nu}$ = 3034, 2995, 1757, 1565, 1540, 1440, 1389, 1343, 1291, 1200, 1172, 1124, 1081, 1043, 981, 838, 787, 753, 711, 694, 672, 585, 525 cm^{-1}. HRMS (ES): calcd. for $C_{13}H_{11}ClN_3O_2$ $[M + H]^+$ 276.05341; found 276.05343.

3-(2-Chloropyrimidin-4-yl)-4-methyloxazolidin-2-one (3g): Prepared using 2,4-dichloropyrimidine and 4-methyloxazolidin-2-one according to the general procedure, using THF at 50 °C for 18 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 19:1 to 3:1 over 30 min) gave **3g** (292 mg, 69 %) as colourless crystals. M.p. 115–117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, J = 5.8 Hz, 1 H), 8.09 (d, J = 5.8 Hz, 1 H), 4.93–4.81 (m, 1 H), 4.54 (t, J = 8.4 Hz, 1 H), 4.12 (dd, J = 3.3, 8.8 Hz, 1 H), 1.51 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.2, 159.6, 158.3, 153.9, 107.9, 69.6, 51.2, 19.0 ppm. IR (neat): $\tilde{\nu}$ = 2990, 2973, 2934, 2912, 1756, 1650, 1571, 1543, 1437, 1388, 1372, 1343, 1307, 1177, 1142, 1125, 1085, 1049, 971, 841, 82, 764, 701, 665, 594, 459 cm^{-1}. HRMS (ES): calcd. for $C_8H_9ClN_3O_2$ $[M + H]^+$ 214.03778; found 214.03778.

3-(2-Chloropyrimidin-4-yl)-4-isopropyloxazolidin-2-one (3h): Prepared using 2,4-dichloropyrimidine and 4-isopropyloxazolidin-2-one according to the general procedure, using THF at 50 °C for 24 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 19:1 to 4:1 over 25 min) gave **3h** (349 mg, 73 %) as colourless crystals. M.p. 89–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, J = 6.0 Hz, 1 H), 8.14 (d, J = 6.0 Hz, 1 H), 4.76 (td, J = 3.5, 8.3 Hz, 1 H), 4.41–4.31 (m, 2 H), 2.63–2.51 (m, 1 H), 0.96 (d, J = 7.0 Hz, 3 H), 0.84 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.0, 159.6, 158.3, 154.2, 107.6, 63.5, 58.7, 27.5, 17.9, 14.3 ppm. IR (neat): $\tilde{\nu}$ = 3153, 2959, 2877, 1766, 1570, 1543, 1443, 1391, 1345, 1301, 1203, 1175, 1146, 1119, 1060, 982, 841, 791, 771, 676, 606, 455, 516 cm^{-1}. HRMS (ES): calcd. for $C_{10}H_{13}ClN_3O_2$ $[M + H]^+$ 242.06908; found 242.06917.

(*R*)-4-{(*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-3-(2-chloropyrimidin-4-yl)oxazolidin-2-one (3i): Prepared using 2,4-dichloropyrimidine and 4-(1-hydroxyethyl)oxazolidin-2-one according to the general procedure (0.80 mmol scale), using THF at 50 °C for 24 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 19:1 to 4:1 over 25 min) gave **3i** (227.3 mg, 78 %) as colourless crystals. M.p. 129–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, J = 5.77 Hz, 1 H), 8.00 (d, J = 5.77 Hz, 1 H), 4.64 (ddd, J = 8.53, 4.14, 2.89 Hz, 1 H), 4.47–4.55 (m, 2 H), 4.26 (t, J = 8.91 Hz, 1 H), 0.93 (d, J = 6.27 Hz, 3 H), 0.77 (s, 8 H), 0.03 (s, 3 H), 0.00 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.3, 159.8, 158.1, 154.2, 107.2, 64.7, 63.6, 57.8, 25.7 (3 C), 17.9, 16.1, –4.8, –4.9 ppm. IR (neat): $\tilde{\nu}$ = 2953, 2931, 2887, 2858, 1779, 1572, 1543, 1445, 1387, 1348, 1299, 1253, 1207, 1181, 1137, 1105, 1051, 1034, 982, 942, 830, 803, 777, 754, 717, 673 cm^{-1}. HRMS (ES): calcd. for $C_{15}H_{25}ClN_3O_3Si$ $[M + H]^+$ 358.1348; found 358.1355.

(±)-(*R*)-4-[(*S*)-1-Chloroethyl]-3-(2-chloropyrimidin-4-yl)oxazolidin-2-one (3j): Prepared using 2,4-dichloropyrimidine and 4-(1-chloroethyl)oxazolidin-2-one according to the general procedure (1.25 mmol scale), using THF at 50 °C for 4 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 19:1 to 4:1 over 25 min) gave **3i** (198 mg, 61 %) as white crystals. M.p. 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, J = 6.0 Hz, 1 H), 8.13 (d, J = 5.8 Hz, 1 H), 4.81–4.89 (m, 2 H), 4.53 (dd, J = 9.0, 3.5 Hz, 1 H), 4.44 (t, J = 9.3 Hz, 1 H), 1.49 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.1, 160.0, 158.0, 153.6, 107.9, 77.2, 62.9, 58.7, 55.3, 20.4 ppm. IR (neat): $\tilde{\nu}$ = 2988, 1748, 1568, 1546, 1477, 1442, 1403, 1348, 1186, 1144, 1121, 1047, 839, 753, 677 cm^{-1}. HRMS (ES): calcd. for $C_9H_9Cl_2N_3O_2$ $[M + H]^+$ 262.0145; found 262.0143.

3-(2-Chloropyrimidin-4-yl)-4,4-dimethyloxazolidin-2-one (3k): Prepared using 2,4-dichloropyrimidine and 4,4-dimethyloxazolidin-2-one according to the general procedure, using THF at 68 °C for 48 h. After 24 h, a second portion of 2,4-dichloropyrimidine (0.5 equiv.) was added. Purification by column chromatography (SiO_2; heptane/EtOAc, 19:1 to 3:1 over 30 min) gave **3k** (203 mg, 58 %) as colourless crystals. M.p. 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, J = 5.8 Hz, 1 H), 8.01 (d, J = 5.8 Hz, 1 H), 4.13 (s, 2 H), 1.73 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.6, 159.5, 159.2, 154.5, 109.7, 75.8, 61.7, 25.0 ppm. IR (neat): $\tilde{\nu}$ = 3156, 3005, 2977, 2928, 1754, 1572, 1538, 1463, 1438, 1396, 1382, 1340, 1282, 1216, 1167, 1091, 1037, 981, 948, 875, 841, 795, 762, 704, 677, 614, 585, 458 cm^{-1}. HRMS (ES): calcd. for $C_9H_{11}ClN_3O_2$ $[M + H]^+$ 228.05341; found 228.05343.

3-(2-Chloropyrimidin-4-yl)benzo[*d*]oxazol-2(3*H*)-one (3l): Prepared using 2,4-dichloropyrimidine and benzo[*d*]-oxazol-2-(3*H*)-one

according to the general procedure, using THF at 50 °C for 16 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 10:1 to 2:1 over 25 min) gave **3l** (212 mg, 43 %) as a colourless solid. M.p. 179–181 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (d, J = 5.8 Hz, 1 H), 8.40 (d, J = 7.1 Hz, 1 H), 8.42–8.38 (m, 1 H), 8.37–8.34 (m, 1 H), 8.35 (d, J = 5.7 Hz, 1 H), 7.35–7.25 (m, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.0, 160.4, 157.8, 151.4, 142.6, 127.7, 125.3, 125.0, 116.7, 110.3, 108.9 ppm. IR (neat): $\tilde{\nu}$ = 3062, 1785, 1627, 1563, 1550, 1476, 1439, 1378, 1357, 1329, 1249, 1223, 1197, 1158, 1137, 1099, 1086, 1042, 986, 967, 936, 882, 849, 799, 765, 752, 706, 676, 659, 615, 501, 459, 444, 426, 406 cm^{-1}. HRMS (ES): calcd. for $C_{11}H_7ClN_3O_2$ [M + H]$^+$ 248.02214; found 248.02213.

3-(2-Chloropyrimidin-4-yl)benzo[*d*]thiazol-2(3*H*)-one (3m): Prepared using benzo[*d*]thiazol-2(3*H*)-one according to the general procedure, using THF at 50 °C for 24 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 10:1 to 2:1 over 25 min) gave **3m** (381 mg, 72 %) as a colourless solid. M.p. 171–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.78 (d, J = 5.5 Hz, 1 H), 7.97 (d, J = 8.1 Hz, 1 H), 7.90 (d, J = 5.5 Hz, 1 H), 7.46 (dd, J = 1.3, 7.8 Hz, 1 H), 7.41–7.34 (m, 1 H), 7.31–7.26 (m, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.0, 161.4, 160.6, 157.8, 134.5, 127.1, 125.4, 122.6, 122.0, 115.4, 115.0 ppm. IR (neat): $\tilde{\nu}$ = 1684, 1586, 1548, 1467, 1423, 1343, 1311, 1213, 1151, 1088, 1070, 1030, 969, 910, 835, 771, 751, 735, 709, 687, 663, 635, 543 494, 440 422 cm^{-1}. HRMS (ES): calcd. for $C_{11}H_7ClN_3OS$ [M + H]$^+$ 263.99927; found 263.99929.

2-Chloro-4-(1*H*-pyrrol-1-yl)pyrimidine (3n): Prepared using 1*H*-pyrrole according to the general procedure, using THF at 68 °C for 24 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 20:1 to 3:1 over 30 min) gave **3n** (187 mg, 53 %) as a slightly yellowish/white solid. M.p. 108–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, J = 5.8 Hz, 1 H), 7.52–7.48 (m, 2 H), 7.13 (d, J = 5.8 Hz, 1 H), 6.41–6.37 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.4, 160.3, 158.3, 118.4, 114.0, 105.8 ppm. IR (neat): $\tilde{\nu}$ = 3146, 3073, 1562, 1477, 1450, 1398, 1347, 1301, 1211, 1181, 1113, 1061, 1031, 984, 938, 831, 784, 739, 687, 676, 583, 515, 422 cm^{-1}. HRMS (ES): calcd. for $C_8H_7ClN_3$ [M + H]$^+$ 180.03230; found 180.03230.

2-Chloro-4-(1*H*-imidazol-1-yl)pyrimidine (3o):[18] Prepared using 2,4-dichloropyrimidine and 1*H*-imidazole according to the general procedure, using THF at 50 °C for 16 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 10:1 to 0:1 over 40 min) gave **3o** (199 mg, 56 %) as a colourless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (d, J = 5.8 Hz, 1 H), 8.42 (s, 1 H), 7.64 (t, J = 1.4 Hz, 1 H), 7.26 (d, J = 5.5 Hz, 1 H), 7.20 (dd, J = 0.8, 1.5 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.7, 161.5, 156.4, 135.4, 132.1, 115.8, 106.8 ppm.

3-(2-Chloro-5-methylpyrimidin-4-yl)oxazolidin-2-one (6a): Prepared using 2,4-dichloro-5-methylpyrimidine and oxazolidin-2-one according to the general procedure, using THF at 68 °C for 28 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 20:1 to 1:1 over 35 min) gave **6a** (219 mg, 52 %) as colourless crystals. The remaining starting material could be removed by recrystallisation from CPME or TBME (*tert*-butyl methyl ether). M.p. 119–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (s, 1 H), 4.54 (t, J = 7.7 Hz, 2 H), 4.24 (t, J = 7.5 Hz, 2 H), 2.29 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.3, 158.4, 157.5, 154.0, 123.4, 63.3, 45.5, 15.6 ppm. IR (neat): $\tilde{\nu}$ = 3008, 2954, 2902, 1768, 1543, 1417, 1395, 1371, 1341, 1315, 1207, 1189, 1155, 1102, 1024, 1000, 946, 856, 773, 756, 744, 690, 653, 568, 452 cm^{-1}. HRMS (ES): calcd. for $C_8H_9ClN_3O_2$ [M + H]$^+$ 214.0378; found 214.0381.

3-(5-Bromo-2-chloropyrimidin-4-yl)oxazolidin-2-one (6b): Prepared using 5-bromo-2,4-dichloropyrimidine and oxazolidin-2-one according to the general procedure, using THF at 50 °C for 8 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 10:1 to 1:2 over 40 min) gave **6b** (390 mg, 71 %) as colourless crystals. M.p. 162–164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (s, 1 H), 4.57 (t, J = 7.7 Hz, 1 H), 4.25 (t, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.4, 158.6, 157.8, 152.7, 112.2, 63.4, 45.6 ppm. IR (neat): $\tilde{\nu}$ = 3065, 2950, 2901, 1764, 1659, 1537, 1520, 1469, 1426, 1392, 1337, 1283, 1220, 1175, 1133, 1113, 1060, 119, 974, 954, 833, 769, 753, 728, 679, 647, 601, 520, 446 cm^{-1}. HRMS (ES): calcd. for $C_7H_6BrClN_3O_2$ [M + H]$^+$ 277.9326; found 277.9332.

3-(2,6-Dichloropyrimidin-4-yl)oxazolidin-2-one (6c):[12] Prepared using 2,4,6-trichloropyrimidine and oxazolidin-2-one according to the general procedure, using THF at room temp. for 20 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 19:1 to 1:1 over 25 min) gave **6c** (462 mg, 73 %) as colourless crystals. M.p. 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (s, 1 H), 4.58–4.52 (m, 2 H), 4.28–4.22 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.5, 159.6, 159.1, 153.8, 106.9, 62.8, 43.7 ppm.

3-(6-Chloro-2-methylpyrimidin-4-yl)oxazolidin-2-one (6d): Prepared using 4,6-dichloro-2-methylpyrimidine and oxazolidin-2-one according to the general procedure, using THF at 68 °C for 19 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 19:1 to 1:1 over 30 min) gave **6d** (375 mg, 89 %) as colourless crystals. M.p. 115–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (s, 1 H), 4.51 (t, J = 8.0 Hz, 2 H), 4.23 (t, J = 8.0 Hz, 2 H), 2.59 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.5, 161.3, 157.7, 154.3, 105.5, 62.6, 43.7, 25.9 ppm. IR (neat): $\tilde{\nu}$ = 3168, 2988, 1926, 1765, 1559, 1540, 1440, 1384, 1534, 1221, 1205, 1152, 1114, 1092, 1038, 979, 896, 849, 813, 753, 703, 605, 583 cm^{-1}. HRMS (ES): calcd. for $C_8H_9ClN_3O_2$ [M + H]$^+$ 214.0378; found 214.0379.

3-(6-Chloropyrimidin-4-yl)oxazolidin-2-one (6e):[8] Prepared using 4,6-dichloropyrimidine and oxazolidin-2-one according to the general procedure, using THF at 68 °C for 24 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 5:1) gave **6e** (375 mg, 95 %) as colourless crystals. M.p. 143–145 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (s, 1 H), 8.23 (s, 1 H), 4.54 (t, J = 8.2 Hz, 1 H), 4.25 (t, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.6, 158.1, 157.7, 154.2, 108.8, 62.7, 43.6 ppm.

3-(5-Chloropyrimidin-4-yl)oxazolidin-2-one (6f): Prepared using 4,5-dichloropyrimidine and oxazolidin-2-one according to the general procedure, using THF at 50 °C for 5 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 19:1 to 1:1 over 40 min) gave **6f** (315 mg, 80 %) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (s, 1 H), 8.72 (s, 1 H), 4.57 (t, J = 7.5 Hz, 2 H), 4.25 (t, J = 7.7 Hz, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.8, 155.7, 154.7, 153.4, 124.9, 63.4, 45.4 ppm. IR (neat): $\tilde{\nu}$ = 2983, 2916, 1760, 1551, 1446, 1386, 1178, 1159, 1123, 1053, 1032, 969, 926, 771, 752, 723, 684, 651, 601 cm^{-1}. HRMS (ES): calcd. for $C_7H_7ClN_3O_2$ [M + H]$^+$ 200.0221; found 200.0226.

3-(5-Methylpyrimidin-4-yl)oxazolidin-2-one (6g): Prepared using 4-chloro-5-methylpyrimidine according to the general procedure, using THF at 50 °C for 20 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 1:1 to 0:1 over 25 min) gave **6g** (341 mg, 86 %) as a colourless solid. M.p. 84–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (s, 1 H), 8.52 (s, 1 H), 4.52 (t, J = 7.7 Hz, 2 H), 4.23 (t, J = 7.5 Hz, 2 H), 2.30 (s, 3 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.1, 156.5, 155.7, 154.6, 125.0, 63.2, 45.4, 16.0 ppm. IR (neat): $\tilde{\nu}$ = 2978, 2915, 1749, 1557, 1463, 1394, 1383, 1317, 1215, 1184, 1139, 1032, 1000, 966, 832, 780, 756, 693, 663, 585, 427 cm^{-1}. HRMS (ES): calcd. for $C_8H_{10}N_3O_2$ [M + H]$^+$ 180.0768; found 180.0769.

3-(2-Phenylpyrimidin-4-yl)oxazolidin-2-one (6h): Prepared using 4-chloro-2-phenylpyrimidine and oxazolidin-2-one according to the

general procedure, using CPME at 100 °C for 18 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 10:1 to 1:1 over 35 min) gave **6h** (321 mg, 67 %) as a colourless solid. M.p. 197–199 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (d, J = 5.8 Hz, 1 H), 8.42–8.37 (m, 2 H), 8.06 (d, J = 5.8 Hz, 1 H), 7.52–7.44 (m, 3 H), 4.58–4.50 (m, 2 H), 4.4–4.34 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.9, 157.8, 156.9, 154.6, 137.2, 131.1, 128.6, 128.2, 106.9, 62.6, 43.4 ppm. IR (neat): $\tilde{\nu}$ = 3050, 2992, 2910, 1767, 1588, 1555, 1484, 1459, 1431, 1388, 1359, 1211, 1136, 1114, 1048, 1029, 989, 840, 750, 695, 671, 645 cm^{-1}. HRMS (ES): calcd. for $C_{13}H_{12}N_3O_2$ $[M + H]^+$ 242.0924; found 242.0925.

3-(6-Chloropyrazin-2-yl)oxazolidin-2-one (6i): Prepared using 2,6-dichloropyrazine according to the general procedure, using THF at 50 °C for 24 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 19:1 to 4:1 over 35 min) gave **6i** (284 mg, 72 %) as colourless crystals. M.p. 150–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.42 (s, 1 H), 8.30 (s, 1 H), 7.26 (s, 1 H), 4.59–4.53 (m, 2 H), 4.26–4.19 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.2, 146.9, 146.2, 138.1, 133.4, 62.8, 43.5 ppm. IR (neat): $\tilde{\nu}$ = 3051, 2993, 2928, 1743, 1556, 1522, 1481, 1440, 1416, 1393, 1316, 1238, 1165, 1145, 1047, 997, 973, 882, 825, 752, 714, 469, 456 cm^{-1}. HRMS (ES): calcd. for $C_7H_7ClN_3O_2$ $[M + H]^+$ 200.0221; found 214.0221.

3-(6-Chloropyridazin-3-yl)oxazolidin-2-one (6j): Prepared using 3,6-dichloropyridazine according to the general procedure, using THF at 50 °C for 24 h. Purification by column chromatography (SiO_2; heptane/EtOAc, 20:1 to 0:1 over 35 min) gave **6j** (238 mg, 60 %) as colourless crystals. M.p. 173–174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (d, J = 9.3 Hz, 1 H), 7.48 (d, J = 9.5 Hz, 1 H), 4.62–4.53 (m, 2 H), 4.42–4.34 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.8, 153.2, 152.4, 129.6, 119.8, 62.7, 44.0 ppm. IR (neat): $\tilde{\nu}$ = 3091, 3055, 2981, 2919, 1756, 1571, 1540, 1477, 1423, 1399, 1290, 1226, 1131, 1102, 1305, 951, 865, 746, 717, 596, 495 cm^{-1}. HRMS (ES): calcd. for $C_7H_7ClN_3O_2$ $[M + H]^+$ 200.0221; found 214.0223.

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