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Access to Highly Substituted Pyrimidine *N*-Oxides and 4-Acetoxymethyl-Substituted Pyrimidines via the LANCA Three-Component Reaction–Cyclocondensation Sequence

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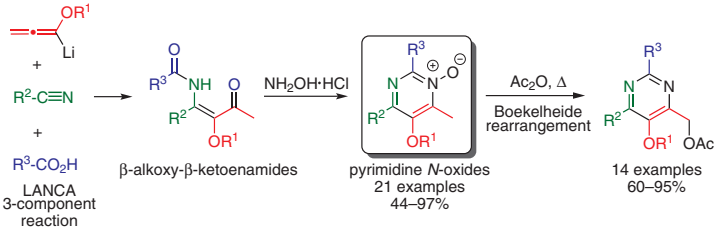
Dedicated to Professor Heinz Heimgartner on the occasion of his 80th birthday



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Abstract The LANCA three-component reaction of lithiated alkoxyallenes (LA), nitriles (N), and carboxylic acids (CA) smoothly provides β-alkoxy-β-ketoenamides in broad structural variety. The subsequent cyclocondensation of these compounds with hydroxylamine hydrochloride afforded a large library of pyrimidine *N*-oxides under mild conditions and in good yields. Their synthetic utility was further increased by the Boekelheide rearrangement leading to 4-acetoxymethyl-substituted pyrimidines. With trifluoroacetic anhydride the rearrangement proceeds even at room temperature and directly furnishes 4-hydroxymethyl-substituted pyrimidine derivatives. The key reactions are very robust and work well even in the presence of sterically demanding substituents.

Key words alkoxyallene, β-alkoxy-β-ketoenamide, pyrimidine *N*-oxide, Boekelheide rearrangement, oxidation

Pyrimidines constitute one of the most important classes of nitrogen-containing heterocycles and play a prominent role in organic synthesis as well as in medicinal and agrochemistry.[1] The pyrimidine core is for instance present in pharmacologically interesting compounds possessing antitubercular,[2] antiproliferative,[3] and CYP1A2 inhibitory activities.[4] Derivatives of pyrimidines are identified as potent dual M3 antagonists and PDE4 inhibitors[5] and more recently they have been tested in multiple phase I/II trials for treatment of cancer.[6] In addition, pyrimidine derivatives have also received a great attention from material science. Numerous research groups have investigated their photophysical, electrochemical, and optoelectronic properties (Figure 1).[7] Due to this high importance, the synthesis of pyrimidines has attracted considerable attention and a number of strategies for their synthesis are reported.[1a–c] To date, beside cyclocondensations of β-keto esters and various nitrogen-containing C1-building blocks as the conventional procedure, pyrimidines are also accessible using different approaches developed only recently,[8] including cycloaddition of alkynes and nitriles,[9] gold-catalyzed cyclizations of ynals and amidines,[10] inverse electron demand Diels–Alder reactions of heterocyclic aza-dienes,[11] domino processes starting from activated skipped diynes

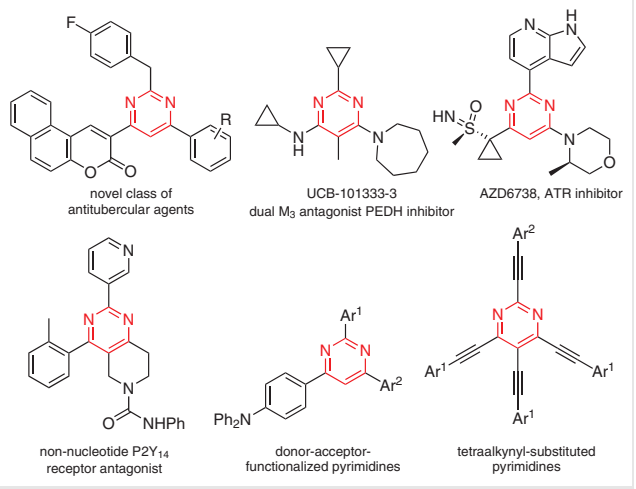

Figure 1 Typical examples of highly functionalized pyrimidine derivatives investigated as drug candidates or novel materials

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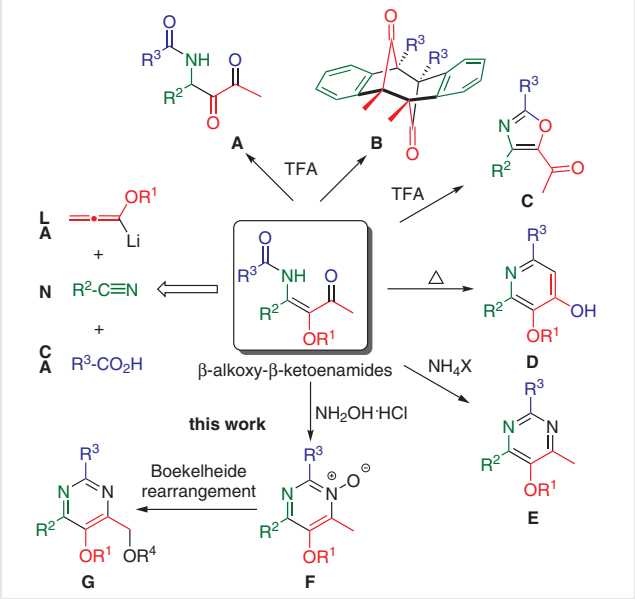
and amidines as nitrogen source[12] as well as numerous multicomponent reactions either metal-promoted[13] or metal-free[14] versions.[1g,15]

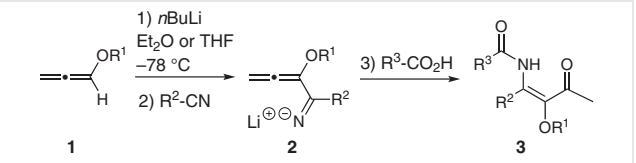
Among the many possible starting materials, compounds with enamide and enamine substructure are efficient precursors for the synthesis of pyrimidines.[13b,f,14a] Enamides are generally very versatile polyfunctional building blocks frequently employed in organic synthesis.[16] Our group serendipitously found a new route to β-alkoxy-β-ketoenamides (Scheme 1) by an intriguing one-pot three-component reaction of lithiated alkoxyallenes (LA), nitriles (N), and carboxylic acids (CA),[17] subsequently explored this LANCA process[18,19] and established it as a versatile and broadly applicable method. Its mechanism has been described in detail in earlier publications.[17]



Scheme 1 The LANCA three-component approach to β-alkoxy-β-ketoenamides and subsequent products **A**–**F** derived from these polyfunctionalized compounds

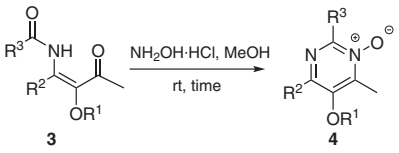
In a series of reports, we explored the high synthetic potential of the β-alkoxy-β-ketoenamides as versatile precursors of 1,2-diketones **A** and (certain substitution patterns given) for intriguing polycyclic compounds **B**.[20] However, the major synthetic importance of β-alkoxy-β-ketoenamides lies in cyclocondensation reactions leading to different nitrogen-containing heterocycles, such as oxazoles **C**,[21] pyridines **D**[17,22] (including bipyridine derivatives[17e]), or pyrimidines **E** (Scheme 1).[17f,i,23] While the synthesis and chemistry of pyrimidines has attracted widespread interest, the synthesis and application of pyrimidine *N*-oxides is much less explored.[24] We have already reported preliminary results demonstrating that the cyclocondensation of β-alkoxy-β-ketoenamides with hydroxylamine hydrochloride smoothly furnishes pyrimidine *N*-oxides **F** under mild conditions.[25] In this account full details are reported exploring scope and limitations of the method as well as the application of the subsequent Boekelheide rearrangement leading to 4-acetoxymethyl-substituted pyrimidines.

Most of the studied β-alkoxy-β-ketoenamides **3** are known in the literature, but a few derivatives were newly prepared for this study applying the known standard procedure (see Supporting Information). Alkoxyallene **1** was treated with *n*-butyllithium at low temperature and to the generated lithiated alkoxyallene was subsequently added the nitrile R^2-CN providing the intermediate **2** (Scheme 2). By addition of excess of the corresponding carboxylic acid a reaction cascade was initiated[17] that finally led to the desired β-alkoxy-β-ketoenamides **3**. The LANCA three-component reactions generally proceed in good to very good yields, even in gram scale.



Scheme 2 Synthesis of β-alkoxy-β-ketoenamides **3** by the LANCA three-component reaction of lithiated alkoxyallenes, nitriles, and carboxylic acids

The cyclocondensation of the β-alkoxy-β-ketoenamides **3** with hydroxylamine hydrochloride occurs in most cases at room temperature using methanol as solvent providing the desired pyrimidine *N*-oxides **4** in good to excellent yields (Scheme 3, Table 1). The conceivable formation of oxazepine derivatives, the seven-membered isomers of **4**, was not observed. Most of the examples collected in Table 1 bear the methoxy group as alkoxy substituent OR^1 (entries 1–12) since the parent compound methoxyallene is most easily available and usually serves as a component to explore new reactions. Other alkoxy groups such as benzyloxy or 2-(trimethylsilyl)ethoxy are also possible (entries 13–17). With respect to the nitrile component and the carboxylic acid simple or functionalized alkyl groups as well as aryl or heteroaryl groups are compatible with the reaction conditions and provide the product generally in satisfying to excellent yields. The precursor β-alkoxy-β-ketoenamides **3** are available in high yields if the components bear bulky substituents R^2 and R^3.[17,18] For this reason, many examples can be found in Table 1 with sterically quite demanding substituents such as *tert*-butyl or 1-adamantyl [see for instance, compounds **4g** (entry 7), **4j** (entry 10), or **4q** (entry 17)].



Scheme 3 Cyclocondensation of β-alkoxy-β-ketoenamides **3** with hydroxylamine hydrochloride affording pyrimidine *N*-oxides **4**

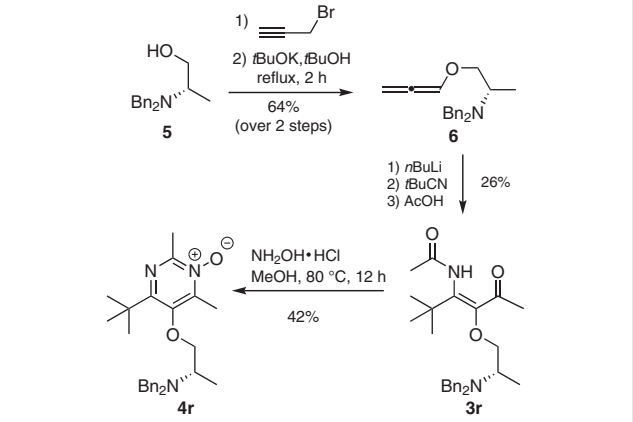
Table 1 Preparation of Pyrimidine *N*-Oxides **4** from β-Alkoxy-β-ketoenamides **3** (according to Scheme 3)[a]

Entry	Precursor	R^1	R^2	R^3	Time	Product	Yield
1	**3a**	Me	*i*-Pr	Ph	1 d	**4a**	61%
2	**3b**	Me	*c*-Pr	*c*-Pr	2 d	**4b**	68%
3	**3c**	Me	*c*-Pr	4-BrC_6H_4	1 d	**4c**	69%
4	**3d**	Me	*t*-Bu	TMSE	1 d	**4d**	46%
5	**3e**	Me	*t*-Bu	Bn	1.5 d	**4e**	81%
6	**3f**	Me	*t*-Bu	*c*-Pr	2 d	**4f**	71%
7	**3g**	Me	*t*-Bu	*t*-Bu	1 d	**4g**	65%
8	**3h**	Me	*t*-Bu	CH_2Cl	1 d	**4h**	44%
9	**3i**	Me	*t*-Bu	Ph	1 d	**4i**	97%
10	**3j**	Me	Ad	*c*-Pr	1 d	**4j**	67%
11	**3k**	Me	Ph	Ph	1 d	**4k**	58%
12	**3l**	Me	2-Th	2-Th	1 d	**4l**	59%
13	**3m**	Bn	*t*-Bu	*c*-Pr	2 d	**4m**	38%
14	**3n**	TMSE	*c*-Pr	*c*-Pr	1 d	**4n**	65%
15	**3o**	TMSE	*t*-Bu	Me	1.5 d	**4o**	50%
16	**3p**	TMSE	*t*-Bu	Ph	2 d	**4p**	quant.
17	**3q**	TMSE	Ad	*c*-Pr	1 d	**4q**	84%

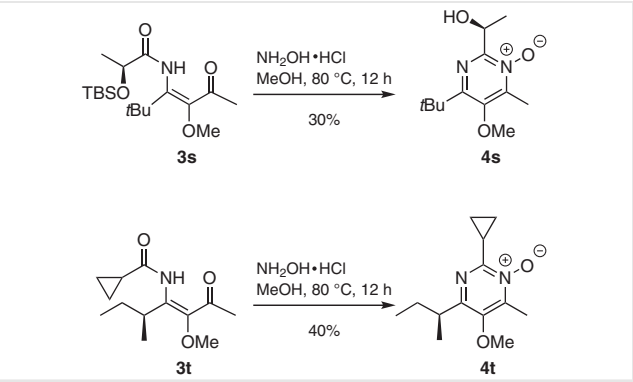
[a] Ad = 1-adamantyl, 2-Th = 2-thienyl, TMSE = 2-(trimethylsilyl)ethyl.

We also studied the applicability of the cyclocondensation protocol for the synthesis of pyrimidine *N*-oxides with chiral substituents in different positions. The enantiopure alkoxyallene **6** was readily accessible from *N*,*N*-dibenzyl-protected (*S*)-alaninol **5** by O-alkylation with propargyl bromide followed by base-promoted isomerization (Scheme 4). After lithiation the LANCA reaction of this allene with pivalonitrile and acetic acid provided the desired β-alkoxy-β-ketoenamide **3r** in low yield. The reaction with hydroxylamine hydrochloride required heating to 80 °C to afford the pyrimidine *N*-oxide **4r** in 42% yield. Both steps were not optimized and may probably be improved.

The synthesis of β-alkoxy-β-ketoenamides **3s** and **3t** bearing the chirality at the amido group at the α-position was already described earlier.[17g] Their cyclocondensations with hydroxylamine hydrochloride proceeded in methanol under reflux and gave the pyrimidine *N*-oxides **4s** and **4t**, respectively, in moderate yields (Scheme 5).

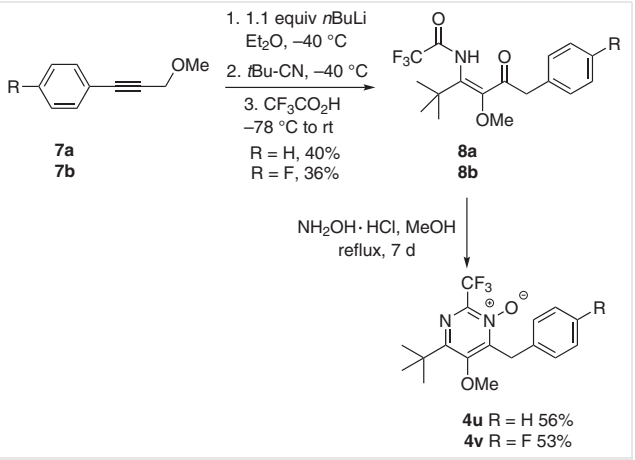


Scheme 4 Synthesis of enantiopure alkoxyallene **6** and its conversion into β-alkoxy-β-ketoenamide **3r** and subsequent cyclocondensation to pyrimidine *N*-oxide **4r**



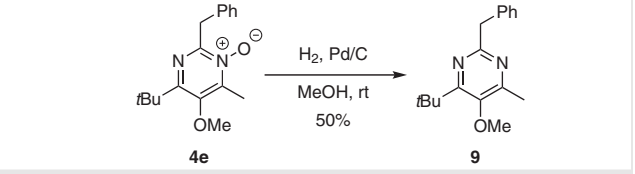
Scheme 5 Conversion of enantiopure β-alkoxy-β-ketoenamides **3s** and **3t**, respectively, into chiral pyrimidine *N*-oxides **4s** and **4t**

Finally, we included β-alkoxy-β-ketoenamides without the methyl ketone moiety in our investigations in order to prepare pyrimidine *N*-oxides with different substituents in the 6-position. Remarkably, precursor compounds with an arylmethylcarbonyl group are directly available from aryl-substituted propargylic ethers. Their deprotonation and reaction with nitriles and carboxylic acids also provided the desired target compounds although the exact mechanism (requiring an intermediate proton transfer from the α-position to the γ-position) is not known.[17d,21b,26] The reaction of aryl-substituted propargyl ethers **7a** and **7b** with *n*-butyllithium in diethyl ether followed by addition of pivalonitrile and then trifluoroacetic acid afforded the desired β-alkoxy-β-ketoenamides **8a** and **8b** in 40% and 36% yield, respectively (Scheme 6). Their cyclocondensation reaction with hydroxylamine hydrochloride proceeded relatively slowly and in both cases unconsumed starting material was re-isolated (35% of **8a** and 41% of **8b**). The pyrimidine *N*-oxides **4u** and **4v** were obtained in 56% and 53% yield, showing that 6-benzyl-substituted pyrimidine derivatives are smoothly accessible via this route.



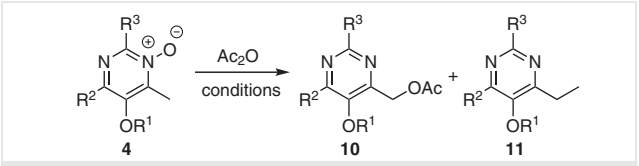
Scheme 6 Conversion of aryl-substituted propargyl ethers **7a** and **7b**, respectively, into β-alkoxy-β-ketoenamides **8a** and **8b** and subsequent cyclocondensations leading to pyrimidine *N*-oxides **4u** and **4v**

An obvious synthetic use of pyrimidine *N*-oxides is their reductive deoxygenation which was demonstrated by subjecting compound **4e** to hydrogen in the presence of palladium on carbon affording the expected pyrimidine derivative **9** in 50% yield (Scheme 7). Pyrimidines such as **9** can be directly prepared from β-alkoxy-β-ketoenamides and ammonia sources.[18b,23] The 'detour' via pyrimidine *N*-oxides may have advantages in singular cases because the condensation and the reduction step proceed at room temperature.



Scheme 7 Deoxygenation of pyrimidine *N*-oxide **4e** leading to compound **9**

However, the focus of this study was to employ the *N*-oxide unit for the functionalization of the adjacent alkyl group in order to also allow variations at this position. This objective could be smoothly accomplished by employing the Boekelheide rearrangement, an elegant and synthetically valuable method to functionalize N-heterocycles such as pyridine, pyrimidine, pyrazine, tetrahydroquinoline, or thiazole derivatives.[27] Heating of typically substituted pyrimidine *N*-oxides **4** with acetic anhydride at 120 °C for 3 hours (method A) afforded the 4-acetoxymethyl-substituted pyrimidine derivatives **10** generally in very good yields (Scheme 8, Table 2, entries 1–5, 7, 8). Alternatively, the transformation can also be achieved in refluxing benzene as solvent at 80 °C and an excess of acetic anhydride (method B, entries 6, 9). In two cases the ethyl-substituted pyrimidine derivatives **11** were isolated as byproducts in 3% and 5% yield, respectively (entries 4, 7). The formation of this type of compounds can be regarded as evidence of the participation of radical intermediates during the rearrangement process. The mechanism of the Boekelheide rearrangement is still controversially discussed and a study with an emphasis on this aspect will be published separately.[28]



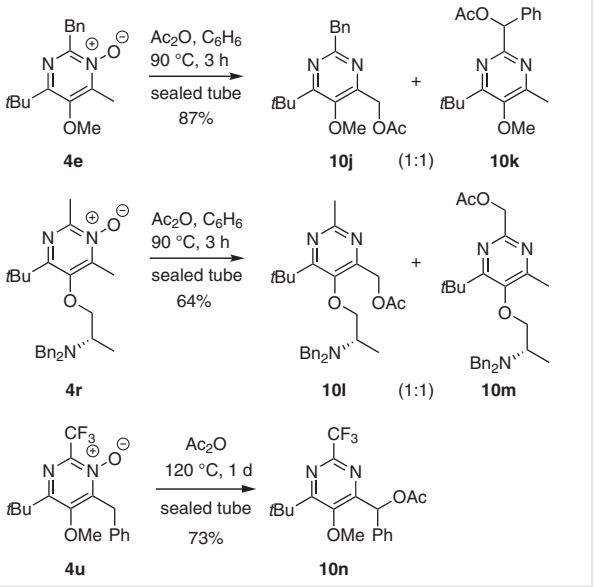
Scheme 8 Boekelheide rearrangement of pyrimidine *N*-oxides **4** leading to 4-acetoxymethyl-substituted pyrimidine derivatives **10** and byproducts **11** (for details see Table 2)

Table 2 Conversion of Pyrimidine *N*-Oxides **4** into Acetoxymethyl-Substituted Pyrimidines **10** (according to Scheme 8)[a]

Entry	Precursor	R^1	R^2	R^3	Method	Product Yield
1	**4c**	Me	*c*-Pr	4-BrC_6H_4	A: 120 °C, 3 h	**10a** 66%
2	**4f**	Me	*t*-Bu	*c*-Pr	A: 120 °C, 3 h	**10b** 78%
3	**4g**	Me	*t*-Bu	*t*-Bu	A: 120 °C, 3 h	**10c** 87%
4	**4i**	Me	*t*-Bu	Ph	A: 120 °C, 3 h	**10d** 69%[b]
5	**4j**	Me	Ad	*c*-Pr	A: 120 °C, 3 h	**10e** 89%
6	**4l**	Me	2-Th	2-Th	B: C_6H_6, 80 °C, 4 h	**10f** 67%
7	**4m**	Bn	*t*-Bu	*c*-Pr	A: 120 °C, 3 h	**10g** 60%[c]
8	**4p**	TMSE	*t*-Bu	Ph	A: 120 °C, 3 h	**10h** 94%
9	**4q**	TMSE	Ad	*c*-Pr	B: C_6H_6, 80 °C, 3 h	**10i** 95%

[a] Ad = 1-adamantyl, 2-Th = 2-thienyl, TMSE = 2-(trimethylsilyl)ethyl.
[b] + 3% of **11d**.
[c] + 5% of **11g**.

In Scheme 9 we have collected examples of pyrimidine *N*-oxides with special substitution patterns needing separate discussion. In the case of **4e** the Boekelheide rearrangement can either provide the 'normal' product **10j** with an acetoxymethyl group or pyrimidine derivative **10k** where the benzyl group was involved in the transformation. Actually, both compounds were formed in a ca. 1:1 ratio. The missing regioselectivity of the rearrangement indicates that the (assumed) electronic activation by the phenyl group and the steric effect exhibited by this substituent are

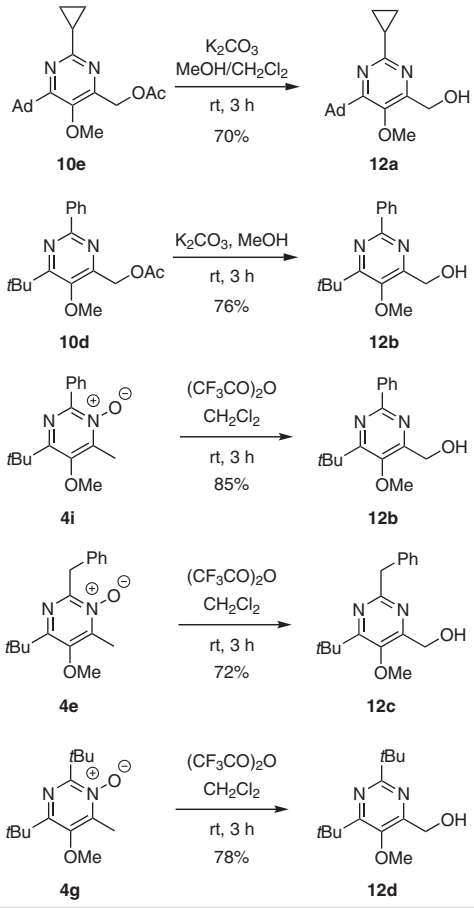


Scheme 9 Boekelheide rearrangements of pyrimidine *N*-oxides **4e**, **4r**, and **4u** leading to the acetoxy-substituted pyrimidine derivatives **10j–10n**

roughly in the same order. In the second case of Scheme 9, two methyl groups in different positions of **4r** compete during the rearrangement process. Again a 1:1 mixture of the two possible products **10l** and **10m** was isolated. The last example of trifluoromethyl-substituted compound **4u** shows that the rearrangement is apparently retarded by this electron-withdrawing substituent. After one day at 120 °C product **10n** was isolated in 73% yield.

The acetoxymethyl group of compounds **10a–10n** allows further transformations in this position which will be the content of a separated report. The most trivial reaction is the saponification of the acetic ester moiety which could be smoothly achieved with potassium carbonate in methanol as demonstrated by the conversion of **10e** and **10d**, respectively, into the 4-hydroxymethyl-substituted compounds **12a** and **12b** (Scheme 10). Remarkably, pyrimidine derivatives of this type could be directly obtained by performing the Boekelheide rearrangement of *N*-oxides **4** using trifluoroacetic anhydride.[29] The primarily formed trifluoroacetic esters undergo hydrolysis to the alcohols during work-up and/or purification and therefore the saponification step is not required. The three examples of Scheme 10 demonstrate that with the more electrophilic trifluoroacetic anhydride the Boekelheide rearrangement occurs already at room temperature, delivering the 4-hydroxymethyl-substituted pyrimidine derivatives **12b–12d** under mild conditions and in very good yield.

Our results clearly demonstrate that the LANCA approach to highly functionalized pyrimidine derivatives is simple and very flexible. The required starting materials, β-alkoxy-β-ketoenamides **3**, are available in large variety and



Scheme 10 Synthesis of 4-hydroxymethyl-substituted pyrimidine derivatives **12a–12d** either by saponification of 4-acetoxymethyl-substituted compounds **10e** and **10d**, respectively, or by Boekelheide rearrangement of pyrimidine *N*-oxides **4e**, **4g**, and **4i** with trifluoroacetic anhydride

their cyclocondensation with hydroxylamine hydrochloride works smoothly providing the desired pyrimidine *N*-oxides **4** generally in high yields. A subsequent Boekelheide rearrangement of **4** with acetic anhydride under heating allows a functionalization of the methyl group adjacent to the *N*-oxide moiety delivering 4-acetoxymethyl-substituted pyrimidines **10** in good yield. With trifluoroacetic anhydride the rearrangement proceeds even at room temperature and directly furnishes 4-hydroxymethyl-substituted pyrimidine derivatives **12.** Bulky substituents do not lead to diminished efficiency of the key reactions. The alkoxy substituent (introduced via the allene component) also allows further substitutions at C-5 of the pyrimidine derivatives, in particular, if benzyloxy or 2-(trimethylsilyl)ethoxy groups are employed. These subsequent transformations and other typical reactions of the prepared pyrimidine derivatives **4**, **10**, or **12** will be presented in an upcoming report.

Reactions were generally performed under argon in flame-dried flasks, and the components were added by syringe. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck or Macherey & Nagel). Unless otherwise stated, yields refer to analytically pure samples. ^{1}H NMR [$CHCl_3$ (δ = 7.26), TMS (δ = 0.00) as internal standard] and ^{13}C NMR spectra [$CDCl_3$ (δ = 77.0) as internal standard] were recorded with Bruker AC 250, DRX 500, AV 700 or Jeol ECX 400 and Eclipse 500 instruments in $CDCl_3$ solutions. Integrals are in accordance with assignments; coupling constants are given in Hz. ^{13}C NMR spectra are proton-decoupled and the multiplicity of signals was determined by DEPT spectra. IR spectra were measured with an FTIR spectrophotometer Nicolet 5 SXC FTIR or a Nicolet Smart DuraSamplIR ATR spectrophotometer. MS and HRMS analyses were performed with Finnigan MAT 711 (EI, 80 eV, 8 kV), MAT 95 (EI, 70 eV), MAT CH7A (EI, 80 eV, 3 kV), or Agilent ESI-TOF 6210 (4 µL/min, 1 bar, 4000 V) instruments. Optical rotations ($[\alpha]_D$) were measured with a Perkin Elmer 241 polarimeter in a 1 mL microcuvette at the temperature given. The elemental analyses were recorded with 'Elemental-Analyzers' (Perkin–Elmer or Carlo Erba).

The preparation of starting materials **3a**,[17e] **3b**,[23b] **3e**,[17f] **3i**,[17e] **3j**,[25] **3k**,[23] **3l**,[17h] **3m**,[21b] **3o**,[21b] **3q**,[21b] **3s**,[17g] **8a**,[17d] and alkoxyallenes[30] has been reported earlier. The synthesis of other β-alkoxy-β-ketoenamides is described in the Supporting Information. All other chemicals are commercially available and were used without further purification.

(*E*)-*N*-(4-Methoxy-2,2-dimethyl-5-oxohex-3-en-3-yl)cyclopropanecarboxamide (3f); Typical Procedure for the Synthesis of β-Alkoxy-β-ketoenamides 3

Methoxyallene (2.00 g, 28.5 mmol) was dissolved in Et_2O (60 mL) and *n*-BuLi (12.5 mL, 31.3 mmol, 2.5 M in hexanes) was added at –40 °C. After 25 min at –50 °C to –40 °C pivalonitrile (4.70 mL, 43.0 mmol) was added. The solution was stirred at –40 °C for 30 min and then cooled to –78 °C. After stirring for 4 h at this temperature cyclopropanecarboxylic acid (3.40 mL, 43.0 mmol) was added and the mixture was warmed up overnight to rt. The mixture was quenched with sat. aq $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Column chromatography (silica gel, hexane/EtOAc, 4:1, 1:1 to 1:3) provided **1f** (2.68 g, 39%) as a pale yellow solid; mp 150 °C.

IR (ATR): 3285 (N–H), 2965–2840 (C–H), 1695 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.69–0.79, 0.90–0.97 (m, 4 H each, *c*Pr), 1.22 (s, 9 H, *t*Bu), 1.40–1.51 (m, 1 H, *c*Pr), 2.25 (s, 3 H, Me), 3.51 (s, 3 H, OMe), 7.12 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 7.6 (t, CH_2), 14.3 (d, CH), 27.9 (q, Me), 28.3, 36.5 (q, s, *t*Bu), 58.8 (q, OMe), 134.1, 150.5 (2 s, C=C), 178.8 (s, CONH), 200.4 (s, C=O).

HRMS (ESI-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{21}NNaO_3$: 262.1419; found: 262.1421.

Anal. Calcd for $C_{13}H_{21}NO_3$ (239.3): C, 65.25; H, 8.84; N, 5.85. Found: C, 65.22; H, 8.83; N, 5.84.

5-Methoxy-6-methylpyrimidine 1-Oxides 4; General Procedure (GP 1)

β-Alkoxy-β-ketoenamide **3** (1 equiv) was dissolved in MeOH (12–24 mL/mmol) and NH_2OH·HCl (3–10 equiv) was added. The mixture was stirred at rt (or under reflux) for the time indicated in the individual experiment. After addition of water (20 mL/mmol), the mixture was extracted with CH_2Cl_2 (5 × 10 mL/mmol). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Column chromatography (silica gel, hexanes/EtOAc) provided the corresponding pyrimidine *N*-oxide **4**.

4-Isopropyl-5-methoxy-6-methyl-2-phenylpyrimidine 1-Oxide (4a)

According to general procedure (GP 1), β-ketoenamide **4a** (0.260 g, 0.821 mmol) and NH_2OH·HCl (0.571 g, 8.21 mmol) in MeOH (15 mL) were used; reaction time: 1 d. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 3:1 to 1:1) to give **4a** (0.158 g, 61%) as a colorless oil.

IR (ATR): 3060–2870 (C–H), 1715–1570 cm^{-1} (C=C, C=N).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.41 (d, *J* = 6.9 Hz, 6 H, *i*Pr), 2.63 (s, 3 H, Me), 3.44 (sept, *J* = 6.9 Hz, 1 H, *i*Pr), 3.91 (s, 3 H, OMe), 7.53–7.55, 8.58–8.60 (2 m, 2 H, 3 H, Ph).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 11.9 (q, Me), 21.4, 29.1 (q, d, *i*Pr), 62.0 (q, OMe), 127.8, 130.0, 130.4, 132.6 (3 d, s, Ph), 148.3, 151.5, 151.6, 155.5 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}N_2O_2$: 259.1441; found: 259.1444.

Anal. Calcd for $C_{15}H_{18}N_2O_2$ (258.3): C, 69.74; H, 7.02; N, 10.84. Found: C, 69.39; H, 7.40; N, 10.12.

2,4-Dicyclopropyl-5-methoxy-6-methylpyrimidine 1-Oxide (4b)

According to general procedure (GP1), β-ketoenamide **3b** (0.679 g, 3.04 mmol) and NH_2OH·HCl (1.09 g, 15.6 mmol) in MeOH (10 mL) were used; reaction time: 2 d. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 3:1 to 1:1) to give **4b** (0.454 g, 68%) as a colorless oil.

IR (ATR): 3000–2880 (C–H), 1560 (C=C), 1475 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.92–1.15 (m, 8 H, *c*Pr), 2.16–2.19, 3.01–3.06 (2 m, 1 H each, *c*Pr), 2.49 (s, 3 H, Me), 3.77 (s, 3 H, OMe).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 10.0, 10.2 (2 t, CH_2), 10.3, 10.8 (2 d, CH), 11.5 (q, Me), 61.7 (q, OMe), 147.6, 149.5, 152.2, 158.1 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{16}N_2NaO_2$: 243.1104; found: 243.1115.

2-(4-Bromophenyl)-4-cyclopropyl-5-methoxy-6-methylpyrimidine 1-Oxide (4c)

According to general procedure (GP 1), β-ketoenamide **3c** (1.42 g, 4.20 mmol) and NH_2OH·HCl (1.17 g, 16.8 mmol) in MeOH (30 mL) were used; reaction time: 1 d. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 2:1) to give **4c** (0.965 g, 69%) as colorless crystals; mp 118 °C.

IR (ATR): 3085–2835 (=C–H, C–H), 1585 (C=C), 1460 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.07–1.11, 1.17–1.20 (2 m, 2 H each, CH_2), 2.27–2.34 (m, 1 H, CH), 2.52 (s, 3 H, Me), 3.85 (s, 3 H, OMe), 7.53–7.58, 8.32–8.39 (2 m, 2 H each, Aryl).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 10.4 (t, CH_2), 11.0, 11.5 (d/q, CH, Me), 61.7 (q, OMe), 124.9, 130.9, 131.2, 131.5 (s, d, s, d, Aryl), 149.1, 150.2, 151.0, 152.2 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}BrN_2O_2$: 335.0390, 337.0268; found: 335.0395, 337.0219.

Anal. Calcd for $C_{15}H_{15}BrN_2O_2$ (335.2): C, 53.75; H, 4.51; N, 8.36. Found: C, 53.76; H, 4.40; N, 8.33.

4-*tert*-Butyl-5-methoxy-6-methyl-2-[2-(trimethylsilyl)ethyl]-pyrimidine 1-Oxide (4d)

According to general procedure (GP1), β-ketoenamide **3d** (0.245 g, 0.810 mmol) and $NH_2OH{\cdot}HCl$ (0.285 g, 4.10 mmol) in MeOH (3 mL) were used; reaction time: 1 d. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 3:1 to 1:1) to give **4d** (0.123 g, 46%) as a colorless oil.

IR (ATR): 2955–2870 (C–H), 1525 (C=C), 1475 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 500 MHz): δ = –0.01 (s, 9 H, $SiMe_3$), 0.98–1.04 (m, 2 H, CH_2Si), 1.36 (s, 9 H, *t*Bu), 2.48 (s, 3 H, Me), 3.00–3.05 (m, 2 H, CH_2), 3.75 (s, 3 H, OMe).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = –1.84 (q, $SiMe_3$), 11.4 (t, $SiCH_2$), 12.3 (q, Me), 26.7 (t, CH_2), 29.1, 37.9 (q, s, *t*Bu), 61.8 (q, OMe), 149.7, 150.2, 155.9, 156.5 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{28}N_2NaO_2Si$: 319.1812; found: 319.1810.

2-Benzyl-4-*tert*-butyl-5-methoxy-6-methylpyrimidine 1-Oxide (4e)

According to general procedure (GP1), β-ketoenamide **3e** (0.340 g, 1.18 mmol) and $NH_2OH{\cdot}HCl$ (0.408 g, 5.88 mmol) in MeOH (5 mL) were used; reaction time: 1.5 d. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 2:1 to 1:2) to give **4e** (0.275 g, 81%) as a colorless oil.

IR (ATR): 3065–2865 (=CH, C–H), 1470–1350 cm^{-1} (C=N).

^1H NMR (CD_3OD, 400 MHz): δ = 1.32 (s, 9 H, *t*Bu), 2.48 (s, 3 H, Me), 3.74 (s, 3 H, OMe), 4.37 (s, 2 H, CH_2Ph), 7.17–7.21, 7.25–7.29, 7.40–7.42 (3 m, 1 H, 2 H, 2 H, Ph).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 12.5 (q, Me), 29.2, 37.9 (q, s, *t*Bu), 38.4 (t, CH_2Ph), 61.9 (q, OMe), 126.6, 128.3, 129.9, 136.2 (3 d, s, Ph), 150.2, 150.6, 153.6, 156.0 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{22}N_2NaO_2$: 309.1579; found: 309.1584.

4-*tert*-Butyl-2-cyclopropyl-5-methoxy-6-methylpyrimidine 1-Oxide (4f)

According to general procedure (GP1), β-ketoenamide **3f** (0.998 g, 4.17 mmol) and $NH_2OH{\cdot}HCl$ (0.733 g, 10.5 mmol) in MeOH (16 mL) were used; reaction time: 2 d. The crude product was purified by chromatography (silica gel, pentane/EtOAc, 2:1 to 1:1) to give **4f** (0.697 g, 71%) as a colorless oil.

IR (ATR): 2960–2870 (C–H), 1530 (C=C), 1475 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.03–1.15 (m, 4 H, *c*Pr), 1.32 (s, 9 H, *t*Bu), 2.51 (s, 3 H, Me), 3.04–3.23 (m, 1 H, *c*Pr), 3.74 (s, 3 H, OMe).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 10.1, 10.4 (t, d, *c*Pr), 12.8 (q, Me), 29.5, 37.6 (q, s, *t*Bu), 62.7 (q, OMe), 149.4, 150.1, 155.6, 156.4 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{20}N_2NaO_2$: 259.1417; found: 259.1421.

2,4-Di-*tert*-butyl-5-methoxy-6-methylpyrimidine 1-Oxide (4g)

According to general procedure (GP 1), β-ketoenamide **3g** (0.960 g, 4.00 mmol) and $NH_2OH{\cdot}HCl$ (0.830 g, 12.0 mmol) in MeOH (16 mL) were used; reaction time: 1 d. The crude product was purified by chromatography (silica gel, pentane/EtOAc, 5:1 to 2:1) to give **4g** (0.650 g, 65%) as a colorless oil.

IR (ATR): 2865–2870 (C–H), 1575 (C=C), 1460 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.36, 1.50 (2 s, 9 H each, *t*Bu), 2.50 (s, 3 H, Me), 3.76 (s, 3 H, OMe).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 12.4 (q, Me), 29.2, 29.7, 38.2, 38.9 (2 q, 2 s, *t*Bu), 61.7 (q, OMe), 149.9, 151.7, 154.7, 158.9 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{25}N_2O_2$: 253.1911; found: 253.1919.

4-*tert*-Butyl-2-(chloromethyl)-5-methoxy-6-methylpyrimidine 1-Oxide (4h)

According to general procedure (GP1), β-ketoenamide **3h** (0.330 g, 1.33 mmol) and $NH_2OH{\cdot}HCl$ (0.278 g, 4.00 mmol) in MeOH (5 mL) were used; reaction time: 1 d. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 3:1 to 1:1) to give **4h** (0.144 g, 44%) as a pale yellow oil.

IR (ATR): 2960–2865 (C–H), 1520 (C=C), 1480 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.37 (s, 9 H, *t*Bu), 2.51 (s, 3 H, Me), 3.80 (s, 3 H, OMe), 4.85 (s, 2 H, CH_2Cl).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 12.2 (q, Me), 28.9, 37.9 (q, s, *t*Bu), 40.8 (t, CH_2Cl), 61.9 (q, OMe), 149.3, 151.1, 151.5, 156.9 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{17}ClN_2NaO_2$: 267.0871; found: 267.0867.

4-*tert*-Butyl-5-methoxy-6-methyl-2-phenylpyrimidine 1-Oxide (4i)

According to general procedure (GP 1), β-ketoenamide **3i** (1.70 g, 6.17 mmol) and $NH_2OH{\cdot}HCl$ (1.35 g, 19.4 mmol) in MeOH (20 mL) were used; reaction time: 1 d. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 3:1 to 1:1) to give **4i** (1.63 g, 97%) as a colorless oil.

IR (ATR): 2960–2870 (C–H), 1600 (C=C), 1460 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.42 (s, 9 H, *t*Bu), 2.57 (s, 3 H, Me), 3.86 (s, 3 H, OMe), 7.45–7.48, 8.54–8.58 (2 m, 2 H, 3 H, Ph).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 12.6 (q, Me), 29.0, 38.0 (q, s, *t*Bu), 61.8 (q, OMe), 127.7, 129.8, 130.3, 132.5 (3 d, s, Ph), 149.1, 150.0, 151.8, 156.4 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{20}N_2NaO_2$: 295.1417; found: 295.1431.

4-(1-Adamantyl)-2-cyclopropyl-5-methoxy-6-methylpyrimidine 1-Oxide (4j)

According to general procedure (GP 1), β-ketoenamide **3j** (0.260 g, 0.820 mmol) and $NH_2OH{\cdot}HCl$ (0.171 g, 2.46 mmol) in MeOH (3 mL) were used; reaction time: 1 d. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 2:1) to give **4j** (0.172 g, 67%) as a pale yellow oil.

IR (ATR): 2870–2870 (C–H), 1570 (C=C), 1460 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.08–1.18 (m, 4 H, *c*Pr), 1.63–1.88, 1.95–2.11 (2 m, 6 H, 9 H, adamantyl-CH, -CH_2), 2.51 (s, 3 H, Me), 3.05–3.16 (m, 1 H, *c*Pr), 3.75 (s, 3 H, OMe).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 10.0, 10.5 (t, d, *c*Pr), 12.5 (q, Me), 28.7, 36.8, 40.2, 40.3 (d, 2 t, s, adamantyl), 62.2 (q, OMe), 149.2, 150.3, 155.8, 156.2 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_2$: 315.2072; found: 315.2081.

5-Methoxy-6-methyl-2,4-diphenylpyrimidine 1-Oxide (4k)

According to general procedure (GP1), β-ketoenamide **3k** (0.257 g, 0.870 mmol) and $NH_2OH·HCl$ (0.182 g, 2.61 mmol) in MeOH (5 mL) were used; reaction time: 1 d. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 3:1 to 1:1) to give **4k** (0.148 g, 58%) as a colorless oil.

IR (ATR): 2990–2870 (C–H), 1590 (C=C), 1450 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 250 MHz): δ = 2.53 (s, 3 H, Me), 3.89 (s, 3 H, OMe), 7.35–7.50, 8.41–8.60 (2 m, 4 H, 6 H, Ph).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 12.8 (q, Me), 61.5 (q, OMe), 127.6, 127.7, 129.7, 129.8, 130.3, 130.5, 132.5, 133.0 (6 d, 2 s, Ph), 149.5, 150.8, 151.7, 156.7 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_2$: 293.1263; found: 293.1285.

5-Methoxy-6-methyl-2,4-di(2-thienyl)pyrimidine 1-Oxide (4l)

According to general procedure (GP1), β-ketoenamide **3l** (0.120 g, 0.391 mmol) and $NH_2OH·HCl$ (0.081 g, 1.17 mmol) in MeOH (3 mL) were used; reaction time: 1 d. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 1:1 to 1:2) to give **4l** (0.070 g, 59%) as a colorless oil.

IR (Neat): 3065–2995 (=C–H, C–H), 1570–1465 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.63 (s, 3 H, Me), 3.84 (s, 3 H, OMe), 7.17 (dd, *J* = 5.1, 3.8 Hz, 1 H, Thio), 7.23 (dd, *J* = 5.1, 4.0 Hz, 1 H, Thio), 7.54 (dd, *J* = 5.1, 1.2 Hz, 1 H, Thio), 7.59 (dd, *J* = 5.1, 1.3 Hz, 1 H, Thio), 8.06 (dd, *J* = 3.8, 1.2 Hz, 1 H, Thio), 8.45 (dd, *J* = 4.0, 1.3 Hz, 1 H, Thio).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 11.8 (q, Me), 61.2 (q, OMe), 126.6, 128.4, 129.5, 130.3, 131.9, 132.1, 132.2, 138.5 (2 s, 6 d, Thio), 141.2, 145.2, 147.5, 151.3 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{12}N_2NaO_2S_2$: 327.0238; found: 327.0244.

5-(Benzyloxy)-4-*tert*-butyl-2-cyclopropyl-6-methylpyrimidine 1-Oxide (4m)

According to general procedure (GP1), β-ketoenamide **3m** (1.37 g, 4.35 mmol) and $NH_2OH·HCl$ (0.907 g, 13.1 mmol) in MeOH (20 mL) were used; reaction time: 2 d. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 3:1 to 1:1) to give **4m** (0.520 g, 38%) as a pale yellow oil.

IR (ATR): 3090–2865 (C–H), 1525 (C=C), 1455 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.05–1.15 (m, 4 H, *c*Pr), 1.33 (s, 9 H, *t*Bu), 2.53 (s, 3 H, Me), 3.06–3.16 (m, 1 H, *c*Pr), 4.84 (s, 2 H, OCH_2), 7.30–7.50 (m, 5 H, Ph).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 9.8 (t, CH_2), 10.2 (d, CH), 12.6 (q, Me), 29.0, 37.8 (q, s, *t*Bu), 75.7 (t, OCH_2), 126.9, 128.2, 128.5, 135.6 (3 d, s, Ph), 147.0, 150.3, 155.9, 156.1 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{24}N_2NaO_2$: 335.1730; found: 335.1747.

2,4-Dicyclopropyl-6-methyl-5-[2-(trimethylsilyl)ethoxy]pyrimidine 1-Oxide (4n)

According to general procedure (GP 1), β-ketoenamide **3n** (0.618 g, 2.00 mmol) and $NH_2OH·HCl$ (0.278 g, 4.00 mmol) in MeOH (5 mL) were used; reaction time: 1 d. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 3:1 to 1:1) to give **4n** (0.398 g, 65%) as a colorless oil.

IR (ATR): 3000–2850 (C–H), 1560 (C=C), 1480 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 250 MHz): δ = –0.01 (s, 9 H, $SiMe_3$), 0.93–1.23 (m, 10 H, *c*Pr, CH_2Si), 2.14–2.24, 3.03–3.13 (2 m, 1 H each, *c*Pr), 2.49 (s, 3 H, Me), 3.92–4.00 (m, 2 H, OCH_2).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 1.6 (q, $SiMe_3$), 9.8, 10.0 (2 t, CH_2), 10.1, 10.9 (2 d, CH), 11.8 (q, Me), 18.9 (t, CH_2Si), 72.7 (t, OCH_2), 146.5, 149.5, 152.0, 157.5 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{27}N_2O_2Si$: 307.1842; found: 307.1845.

4-*tert*-Butyl-2,6-dimethyl-5-[2-(trimethylsilyl)ethoxy]pyrimidine 1-Oxide (4o)

According to general procedure (GP1), β-ketoenamide **3o** (0.302 g, 1.02 mmol) and $NH_2OH·HCl$ (0.213 g, 3.06 mmol) in MeOH (20 mL) were used; reaction time: 1.5 d. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 3:1 to 1:1) to give **4o** (0.152 g, 50%) as a pale yellow oil.

IR (ATR): 3050–2890 (C–H), 1570 (C=C), 1490 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.06 (s, 9 H, $SiMe_3$), 1.22–1.29 (m, 2 H, CH_2Si), 1.43 (s, 9 H, *t*Bu), 2.45, 2.64 (2 s, 3 H each, 2 Me), 3.79–3.89 (m, 2 H, OCH_2).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = –1.4 (q, $SiMe_3$), 12.7 (q, Me), 18.9 (t, CH_2Si), 20.0 (q, Me), 29.3, 37.8 (q, s, *t*Bu), 72.7 (t, OCH_2), 148.9, 150.7, 152.4, 156.5 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{29}N_2O_2Si$: 297.1993; found: 297.1991.

4-*tert*-Butyl-6-methyl-2-phenyl-5-[2-(trimethylsilyl)ethoxy]pyrimidine 1-Oxide (4p)

According to general procedure (GP1), β-ketoenamide **3p** (3.00 g, 8.27 mmol) and $NH_2OH·HCl$ (1.73 g, 24.9 mmol) in MeOH (200 mL) were used; reaction time: 2 d. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 3:1 to 1:1) to give **4p** (3.01 g, quant.) as a pale yellow oil.

IR (ATR): 3060–2850 (C–H), 1570 (C=C), 1485 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.03 (s, 9 H, $SiMe_3$), 1.19–1.24 (m, 2 H, CH_2Si), 1.35 (s, 9 H, *t*Bu), 2.52 (s, 3 H, Me), 3.87–3.96 (m, 2 H, OCH_2), 7.38–7.49, 8.48–8.56 (2 m, 3 H, 2 H, Ph).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = –1.3 (q, $SiMe_3$), 12.8 (q, Me), 18.8 (t, CH_2Si), 29.1, 38.1 (q, s, *t*Bu), 72.7 (t, OCH_2), 127.7, 129.8, 130.2, 132.6 (3 d, s, Ph), 148.8, 148.9, 152.1, 156.5 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{31}N_2O_2Si$: 359.2149; found: 359.2164.

4-(1-Adamantyl)-2-cyclopropyl-6-methyl-5-[2-(trimethylsilyl)-ethoxy]pyrimidine 1-Oxide (4q)

According to general procedure (GP1), β-ketoenamide **3q** (0.379 g, 0.940 mmol) and $NH_2OH·HCl$ (0.196 g, 2.82 mmol) in MeOH (3 mL) were used; reaction time: 1 d. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 3:1 to 1:1) to give **4q** (0.313 g, 84%) as a pale yellow oil.

IR (ATR): 2950–2850 (C–H), 1530, 1465 cm^{-1} (C=C, C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.01 (s, 9 H, $SiMe_3$), 1.02–1.11 (m, 4 H, *c*Pr), 1.17–1.25 (m, 2 H, CH_2Si), 1.65–1.83, 1.93–2.12 (2 m, 6 H, 9 H, adamantyl-CH, CH_2), 2.51 (s, 3 H, Me), 3.06–3.16 (m, 1 H, *c*Pr), 3.79–3.89 (m, 2 H, OCH_2).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = –1.5 (q, $SiMe_3$), 9.8, 10.4 (t, d, *c*Pr), 12.6 (q, Me), 18.7 (t, CH_2Si), 28.6, 36.7, 40.0, 40.2 (d, 2 t, s, adamantyl), 72.8 (t, OCH_2), 147.6, 150.6, 155.9, 156.0 (4 s, C-4, C-5, C-6, C-2).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{36}N_2O_2SiNa$: 423.2438; found: 423.2467.

(*S*)-4-*tert*-Butyl-5-[2-(dibenzylamino)propoxy]-2,6-dimethylpyrimidine 1-Oxide (4r)

According to general procedure (GP1), β-ketoenamide **3r** (0.116 g, 0.265 mmol) and $NH_2OH{\cdot}HCl$ (0.184 g, 2.65 mmol) in MeOH (5 mL) were used; reaction time: 12 h at 80 °C. The crude product was purified by chromatography (silica gel, EtOAc/MeOH, 20:1) to give **4r** (0.045 g, 42%) as a yellow oil.

$[\alpha]_D^{22}$ –38.4 (*c* 0.31, $CHCl_3$).

IR (ATR): 3080–2890 (C–H), 1570 (C=C), 1475 cm^{-1} (C=N).

^{1}H NMR (CD_3OD, 250 MHz): δ = 1.22 (d, *J* = 6.3 Hz, 3 H, Me), 1.28 (s, 9 H, *t*Bu), 2.31, 2.58 (2 s, 3 H each, Me), 3.24–3.39 (m, 1 H, CHN), 3.60 (d, *J* = 14.3 Hz, 2 H, C*H*$_2$Ph), 3.65–3.73 (m, 1 H, OCH_2), 3.77 (d, *J* = 14.3 Hz, 2 H, C*H*$_2$Ph), 3.90 (dd, *J* = 5.5, 8.7 Hz, 1 H, OCH_2), 7.17–7.32, 7.37–7.44 (2 m, 6 H, 4 H, Ph).

^{13}C NMR (CD_3OD, 100.5 MHz): δ = 11.3, 23.5, 27.7 (3 q, Me), 29.1, 37.6 (q, s, *t*Bu), 52.8 (t, CHN), 54.4 (t, *C*H$_2$Ph), 76.9 (t, OCH_2), 127.0, 128.3, 128.8, 140.2 (3 d, s, Ph), 148.8, 150.4, 152.3, 155.8 (4 s, C-2, C-3. C-4, C-5).

HRMS (ESI-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{36}N_3O_2$: 434.2802; found: 437.2827.

(*S*)-4-*tert*-Butyl-2-(1-hydroxyethyl)-5-methoxy-6-methylpyrimidine 1-Oxide (4s)

According to general procedure (GP 1), β-ketoenamide **3s** (0.068 g, 0.190 mmol) and $NH_2OH{\cdot}HCl$ (0.066 g, 0.949 mmol) in MeOH (3 mL) were used; reaction time: 12 h. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 2:1) to give **4s** (0.013 g, 30%) as a colorless oil.

$[\alpha]_D^{22}$ +6.0 (*c* 0.43, $CHCl_3$).

IR (neat): 3335 (O–H), 2965–2880 (C–H), 1625–1465 cm^{-1} (C=C, C=N).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.38 (s, 9 H, *t*Bu), 1.62 (d, *J* = 6.6 Hz, 3 H, *Me*CH), 2.52 (s, 3 H, Me), 3.80 (s, 3 H, OMe), 5.15–5.41 (m, 1 H, *CH*Me).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 12.1 (q, Me), 18.7 (q, *Me*CH), 29.0, 38.1 (q, s, *t*Bu), 62.0 (q, OMe), 67.1 (d, *CH*Me), 150.8, 151.3, 154.3, 157.4 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{20}N_2O_2SiNa$: 263.1376; found: 263.1377.

(*S*)-4-Butan-2-yl-2-cyclopropyl-5-methoxy-6-methylpyrimidine 1-Oxide (4t)

According to general procedure (GP1), β-ketoenamide **3t** (0.182 g, 0.762 mmol) and $NH_2OH{\cdot}HCl$ (0.530 g, 7.62 mmol) in MeOH (20 mL) were used; reaction time: 12 h at 80 °C. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 4:1 to 1:1) to give **4t** (0.072 g, 40%) as a colorless oil.

IR (neat): 2995–2885 (C–H), 1615–1495 cm^{-1} (C=C, C=N).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.77 (t, *J* = 7 Hz, 3 H, Me), 1.05–1.17, 1.48–1.56, 1.63–1.72 (3 m, 7 H, 1 H, 1 H, Me, 3xCH_2), 2.51 (s, 3 H, Me), 2.99 (sext, *J* = 6.8 Hz, 1 H, CH), 3.10–3.15 (m, 1 H, *C*H), 3.72 (s, 3 H, OMe).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 10.1, 10.2, 10.4 (3 t, CH_2), 11.9, 12.1 (2 d, CH), 19.5 (q, Me), 29.6 (q, Me), 35.6 (q, *Me*CH), 62.1 (q, OMe), 147.5, 150.0, 155.0, 158.3 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{22}N_2O_2$: 237.1598; found: 237.1591.

6-Benzyl-4-*tert*-butyl-5-methoxy-2-(trifluoromethyl)pyrimidine 1-Oxide (4u)

According to general procedure (GP 1), β-ketoenamide **8a** (0.036 g, 0.105 mmol) and $NH_2OH{\cdot}HCl$ (0.073 g, 1.05 mmol) in MeOH (10 mL) were used; reaction time: 7 d at 60 °C. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 10:1 to 4:1) to give **4u** (0.020 g, 56%) as a yellow oil and precursor **8a** (0.013 g, 35%).

IR (ATR): 3090–2870 (C–H), 1600 (C=C), 1480 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.41 (s, 9 H, *t*Bu), 3.82 (s, 3 H, OMe), 4.37 (s, 2 H, CH_2), 7.20–7.24, 7.27–7.28 (2 m, 1 H, 4 H, Ph).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 29.1 (q, *t*Bu), 30.8 (t, CH_2), 38.3 (s, *t*Bu), 63.5 (q, OMe), 127.2, 128.7, 128.9, 135.1 (3 d, s, Ph), 153.9, 155.2, 156.9 (3 s, C-4, C-5, C-6); the signals of CF_3 and C-2 cannot be assigned unambiguously due to CF couplings.

^{19}F NMR (471 MHz, $CDCl_3$): δ = –70.28 (s, 3 F, CF_3).

HRMS (ESI-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}F_3N_2NaO_2$: 363.1296; found: 363.1309.

N-[(*E*)-1-*tert*-Butyl-2-methoxy-3-oxo-4-(4-fluorophenyl)but-1-enyl]-2,2,2-trifluoroacetamide (8b)

In a flame-dried flask under argon atmosphere, propargyl ether **7b** (0.300 g, 1.83 mmol) was dissolved in Et_2O (14 mL) and treated with *n*-BuLi (0.77 mL, 1.92 mmol) at –40 °C for 30 min. Pivalonitrile (0.228 g, 2.74 mmol) was added and after 15 min the mixture was cooled to –78 °C. Trifluoroacetic acid (0.32 mL, 4.20 mmol) was added and the mixture was allowed to warm up to rt within 19 h. Sat. aq $NaHCO_3$ solution was added (15 mL), the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, hexanes/EtOAc, 10:1 to 4:1) to furnish **8b** (0.239 g, 36%) as a colorless solid.

IR (ATR): 3285 (N–H), 3045–2845 (=C–H, C–H), 1720, 1700, 1535, 1510 cm^{-1} (C=O, C=C, C–N).

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.20 (s, 9 H, *t*Bu), 3.53 (s, 3 H, OMe), 3.90 (s, 2 H, CH_2), 6.96–7.01, 7.12–7.16 (2 m, 2 H each, Ar), 7.56 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 28.4, 36.6 (q, s, *t*Bu), 45.6 (t, CH_2), 59.4 (q, OMe), 115.4 (dd, J_{CF} = 21.7 Hz, Ar), 115.8 (q, J_{CF} = 288.6 Hz, CF_3), 128.9 (d, J_{CF} = 3.1 Hz, Ar), 130.2 (s, C-1), 131.4 (dd, J_{CF} = 8.1 Hz, Ar), 151.8 (s, C-2), 156.7 (q, J_{CF} = 37.1 Hz, CF_3CO), 162.1 (d, J_{CF} = 245.5 Hz, Ar), 200.0 (d, J_{CF} = 1.0 Hz, C-3).

^{19}F NMR ($CDCl_3$, 471 MHz): δ = –115.7 (m_c, 1 F, Ar-F), –75.9 (s, 3 F, CF_3).

HRMS (ESI-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{19}F_4NO_3Na$: 384.1193; found: 384.1206.

Anal. Calcd for $C_{17}H_{19}F_4NO_3$ (361.3): C, 56.51; H, 5.30; N, 3.88. Found: C, 56.48; H, 5.28; N, 3.79.

4-*tert*-Butyl-6-(4-fluorobenzyl)-5-methoxy-2-(trifluoromethyl)-pyrimidine 1-Oxide (4v)

According to general procedure (GP1), β-ketoenamide **8b** (0.100 g, 0.291 mmol) and $NH_2OH{\cdot}HCl$ (0.202 g, 2.91 mmol) were dissolved in MeOH (25 mL); reaction time: 7 d at 60 °C. The crude product was purified by chromatography (silica gel, hexanes/EtOAc, 10:1 to 4:1) to give **4v** (0.052 g, 53%) as a yellow oil and precursor **8b** (0.041 g, 41%).

IR (KBr): 3075–2875 (=C–H, C–H), 1605, 1580, 1510, 1480, 1460 cm^{-1} (C=C, C=N).

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.41 (s, 9 H, *t*Bu), 3.84 (s, 3 H, OMe), 4.32 (s, 2 H, CH_2), 6.93–6.98, 7.25–7.30 (2 m, 2 H each, Ar).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 29.1 (q, *t*Bu), 30.0 (t, CH_2), 38.4 (s, *t*Bu), 63.5 (q, OMe), 115.7 (dd, J_{CF} = 21.7 Hz, Ar), 130.4 (dd, J_{CF} = 8.0 Hz, Ar), 130.7 (d, J_{CF} = 3.1 Hz, Ar), 153.8, 155.1, 157.1 (3 s, C-4, C-5, C-6), 162.0 (d, J_{CF} = 245.7 Hz, Ar); the signals of CF_3 and C-2 cannot be assigned unambiguously due to CF couplings.

^{19}F NMR ($CDCl_3$, 471 MHz): δ = –115.3 (m_c, 1 F, Ar-F), –70.3 (s, 3 F, CF_3).

HRMS (ESI-ToF): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{18}F_4N_2O_2Na$: 381.1197; found: 381.1218.

2-Benzyl-4-*tert*-butyl-5-methoxy-6-methylpyrimidine (9)

To a solution of pyrimidine *N*-oxide **4e** (0.045 g, 0.167 mmol) in MeOH (2 mL) was added Pd/C (0.017 g, 0.042 mmol, 25% on charcoal) and the resulting mixture was bubbled with H_2 gas for 15 min. After that the mixture was stirred for 24 h under H_2 atmosphere. Metal residue was filtered with a small silica gel pad and concentrated to give pyrimidine **9** (0.024 g, 50%) as a colorless oil.

IR (ATR): 3065–2870 (=C–H, C–H), 1555–1375 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.38 (s, 9 H, *t*Bu), 2.46 (s, 3 H, Me), 3.73 (s, 3 H, OMe), 4.16 (s, 2 H, CH_2Ph), 7.17–7.21 (m, 1 H, Ph), 7.26–7.30 (m, 2 H, Ph), 7.43–7.45 (m, 2 H, Ph).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 19.7 (q, Me), 29.3, 38.0 (q, s, *t*Bu), 45.4 (t, CH_2Ph), 60.9 (q, OMe), 126.2, 128.2, 129.3, 139.2 (3 d, s, Ph), 150.3, 160.2, 162.4, 168.1 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{23}N_2O$: 271.1810; found: 271.1810.

General Procedure for the Reaction of Pyrimidine *N*-Oxides 4 with Acetic Anhydride (GP 2)

Method A: In an ACE sealed tube, pyrimidine *N*-oxide **4** was dissolved in Ac_2O and the solution was heated at reflux at 120 °C for 3 h. After cooling to rt, the excess Ac_2O was removed under reduced pressure. Purification of the crude product by column chromatography (silica gel, hexanes/EtOAc) provided the rearranged product **10**.

Method B: In an ACE sealed tube, pyrimidine *N*-oxide **4** (1 equiv) was dissolved in benzene and Ac_2O (3 equiv) was added. The solution was heated at reflux at 90 °C for 3 h. After cooling to rt, Ac_2O and benzene were removed under reduced pressure. Purification of the crude product by column chromatography (silica gel, hexanes/EtOAc) provided the rearranged product **10**.

[2-(4-Bromophenyl)-6-cyclopropyl-5-methoxypyrimidin-4-yl]-methyl Acetate (10a)

According to general procedure (GP 2, method A), pyrimidine *N*-oxide **4c** (0.071 g, 0.212 mmol), and Ac_2O (2 mL) afforded after purification by flash chromatography (silica gel, hexanes/EtOAc, 4:1) compound **10a** (0.053 g, 66%) as a pale yellow oil.

IR (ATR): 3085–2870 (=C–H, C–H), 1755 (C=O), 1560 (C=C), 1455 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.05–1.15, 1.20–1.33 (2 m, 2 H each, CH_2), 2.18 (s, 3 H, Me), 2.31–2.44 (m, 1 H, CH), 3.89 (s, 3 H, OMe), 5.26 (s, 2 H, OCH_2), 7.46–7.61, 8.12–8.28 (2 m, 2 H each, Aryl).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 11.1, 11.15 (2 t, CH_2), 20.9 (q, Me), 61.8 (t, OCH_2), 62.0 (q, OMe), 124.7, 129.6, 131.4, 136.5 (s, 2 d, s, Aryl), 149.4, 154.9, 158.2, 165.2 (4 s, C-2, C-4, C-5, C-6), 170.6 (s, CO_2).

HRMS (ESI-ToF): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{17}BrN_2NaO_3$: 399.0315; found: 399.0326.

(6-*tert*-Butyl-2-cyclopropyl-5-methoxypyrimidin-4-yl)methyl Acetate (10b)

According to general procedure (GP 2, method A), pyrimidine *N*-oxide **4f** (1.00 g, 4.23 mmol), and Ac_2O (10 mL) afforded after purification by flash chromatography (silica gel, hexanes/EtOAc, 8:1) compound **10b** (0.920 g, 78%) as a colorless oil.

IR (ATR): 3090–2870 (=C–H, C–H), 1560 (C=C), 1450 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.92–0.97, 0.99–1.05 (2 m, 2 H each, CH_2), 1.32 (s, 9 H, *t*Bu), 2.12–2.20 (m, 4 H, CH, Me), 3.73 (s, 3 H, OMe), 5.15 (s, 2 H, OCH_2).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 10.4 (t, CH_2), 17.7 (d, CH), 20.9 (q, Me), 29.2, 38.2 (q, s, *t*Bu), 61.8 (t, OCH_2), 62.7 (q, OMe), 149.6, 155.9, 165.2, 169.2 (4 s, C-2, C-4, C-5, C-6), 170.8 (s, CO_2).

HRMS (ESI-ToF): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{22}N_2NaO_3$: 301.1523; found: 301.1534.

Anal. Calcd for $C_{15}H_{22}N_2O_3$ (278.4): C, 64.73; H, 7.97; N, 10.06. Found: C, 64.82; H, 7.78; N, 9.97.

(2,6-Di-*tert*-butyl-5-methoxypyrimidin-4-yl)methyl Acetate (10c)

According to general procedure (GP 2, method A), pyrimidine *N*-oxide **4g** (0.320 g, 1.29 mmol), and Ac_2O (10 mL) afforded after purification by flash chromatography (silica gel, hexanes/EtOAc, 10:1) compound **10c** (0.330 g, 87%) as pale yellow crystals; mp 69.5–72 °C.

IR (ATR): 3020–2870 (=C–H, C–H), 1750 (C=O), 1545 (C=C), 1450 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.34 (s, 9 H, *t*Bu), 1.38 (s, 9 H, *t*Bu), 2.18 (s, 3 H, Me), 3.78 (s, 3 H, OMe), 5.28 (s, 2 H, OCH_2).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 20.9 (q, Me), 29.4, 29.8, 38.4, 39.2 (2 q, 2 s, *t*Bu), 61.8 (q, OMe), 62.3 (t, OCH_2), 149.0, 155.7, 168.0, 170.3 (4 s, C-2, C-4, C-5, C-6), 170.9 (s, C=O).

HRMS (ESI-ToF): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{26}N_2NaO_3$: 317.1835; found: 317.1829.

(6-*tert*-Butyl-5-methoxy-2-phenylpyrimidin-4-yl)methyl Acetate (10d)

According to general procedure (GP 2, method A), pyrimidine *N*-oxide **4i** (0.878 g, 3.22 mmol), and Ac_2O (10 mL) afforded after purification by flash chromatography (silica gel, hexanes/EtOAc, 8:1) compound **10d** (0.699 g, 69%) as colorless crystals and compound **11d** (0.028 g, 3%) as a colorless oil.

Compound 10d

Mp 59–61 °C.

IR (ATR): 2960–2865 (=C–H, C–H), 1750 (C=O), 1550 (C=C), 1450 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.48 (s, 9 H, *t*Bu), 2.22 (s, 3 H, Me), 3.84 (s, 3 H, OMe), 5.32 (s, 2 H, OCH_2), 7.43–7.62, 8.40–8.43 (2 m, 2 H, 3 H, Ph).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 20.9 (q, Me), 29.2, 38.4 (q, s, *t*Bu), 61.7 (t, OCH_2), 62.6 (q, OMe), 128.0, 128.3, 129.9, 137.7 (3 d, s, Ph), 150.4, 156.6, 157.8, 169.2 (4 s, C-2, C-4, C-5, C-6), 170.8 (s, C=O).

HRMS (ESI-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{22}N_2NaO_3$: 337.1528; found: 337.1540.

4-*tert*-Butyl-6-ethyl-5-methoxy-2-phenylpyrimidine (11d)

IR (ATR): 3090–2870 (=C–H, C–H), 1545 (C=C), 1445 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.55 (t, *J* = 7.5 Hz, 3 H, Me), 1.58 (s, 9 H, *t*Bu), 2.93 (q, *J* = 7.5 Hz, 2 H, CH_2), 3.80 (s, 3 H, OMe), 7.45–7.56, 8.58–8.62 (2 m, 2 H, 3 H, Ph).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 12.3 (q, Me), 25.2 (t, CH_2), 29.6, 38.3 (q, s, *t*Bu), 61.8 (q, OMe), 128.2, 128.5, 129.8, 138.5 (3 d, s, Ph), 150.6, 157.6, 164.7, 167.9 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}N_2O$: 271.1810; found: 271.1791.

[6-(1-Adamantyl)-2-cyclopropyl-5-methoxypyrimidin-4-yl]methyl Acetate (10e)

According to general procedure (GP 2, method A), pyrimidine *N*-oxide **4j** (0.520 g, 1.66 mmol), and Ac_2O (3 mL) afforded after purification by flash chromatography (silica gel, hexanes/EtOAc, 3:1) compound **10e** (0.527 g, 89%) as pale yellow crystals; mp 98 °C.

IR (ATR): 2940–2850 (=C–H, C–H), 1750 (C=O), 1555 (C=C), 1430 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.91–1.10 (m, 4 H, *c*Pr), 1.70–1.80, 2.03–2.10 (2 m, 6 H, 9 H, adamantyl-CH, -CH_2), 2.12–2.21 (m, 4 H, *c*Pr, Me), 3.73 (s, 3 H, OMe), 5.15 (s, 2 H, OCH_2).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 10.3, 17.7 (t, d, *c*Pr), 20.9 (q, Me), 28.6, 36.8, 40.0, 40.6 (d, 2 t, s, adamantyl), 61.7 (t, CH_2O), 62.9 (q, OMe), 149.9, 156.0, 165.2, 168.4 (4 s, C-2, C-4, C-5, C-6), 170.7 (s, C=O).

HRMS (ESI-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{29}N_2O_3$: 357.2178; found: 357.2195.

Anal. Calcd for $C_{21}H_{28}N_2O_3$ (356.5): C, 70.76; H, 7.92; N, 7.86. Found: C, 70.76; H, 7.91; N, 7.86.

[5-Methoxy-2,6-di(2-thienyl)pyrimidin-4-yl]methyl Acetate (10f)

According to general procedure (GP 2, method B), pyrimidine *N*-oxide **4l** (0.052 g, 0.171 mmol) and Ac_2O (0.1 mL) in benzene (2 mL) afforded after purification by flash chromatography (silica gel, hexanes/EtOAc, 4:1 to 3:1) compound **10f** (0.040 g, 67%) as a colorless oil.

IR (Neat): 3020–2990 (=C–H, C–H), 1740 (C=O), 1550–1750 cm^{-1} (C=C).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.24 (s, 3 H, Me), 3.85 (s, 3 H, OMe), 5.33 (s, 2 H, OCH_2), 7.12 (dd, *J* = 5.0, 3.6 Hz, 1 H, Thio), 7.19 (dd, *J* = 5.0, 3.8 Hz, 1 H, Thio), 7.43 (dd, *J* = 5.0, 1.2 Hz, 1 H, Thio), 7.58 (dd, *J* = 5.0, 1.2 Hz, 1 H, Thio), 7.95 (dd, *J* = 3.6, 1.2 Hz, 1 H, Thio), 8.14 (dd, *J* = 3.8, 1.2 Hz, 1 H, Thio).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 20.9 (q, Me), 61.2 (q, OMe), 61.5 (t, OCH_2), 128.2, 128.4, 128.8, 129.6, 131.0, 131.1, 138.5, 142.9 (2 s, 6 d, Thio), 145.7, 152.2, 156.5, 158.3 (4 s, C-2, C-4, C-5, C-6), 170.8 (s, CO_2).

HRMS (ESI-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{14}N_2NaO_3S_2$: 369.0338; found: 369.0334.

Anal. Calcd for $C_{16}H_{14}N_2O_3S_2$ (346.4): C, 55.47; H, 4.07; N, 8.09; S, 18.51. Found: C, 55.06; H, 4.00; N, 7.94; S, 18.44.

[5-(Benzyloxy)-6-*tert*-butyl-2-cyclopropylpyrimidin-4-yl]methyl Acetate (10g)

According to general procedure (GP 2, method A), pyrimidine *N*-oxide **4m** (0.507 g, 1.62 mmol), and Ac_2O (5 mL) afforded after purification by flash chromatography (silica gel, hexanes/EtOAc, 6:1) compound **10g** (0.363 g, 60%) and **11g** (0.028 g, 5%) as pale yellow oils.

Compound 10g

IR (ATR): 3085–2845 (=C–H, C–H), 1740 (C=O), 1570 (C=C), 1455 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.97–1.01, 1.05–1.08 (2 m, 2 H each, CH_2), 1.38 (s, 9 H, *t*Bu), 2.14 (s, 3 H, Me), 2.16–2.23 (m, 1 H, CH), 4.89, 5.18 (2 s, 2 H each, OCH_2), 7.33–7.48 (m, 5 H, Ph).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 10.3 (t, CH_2), 17.6 (d, CH), 20.7 (q, Me), 29.3, 38.2 (q, s, *t*Bu), 61.7 (t, OCH_2), 76.7 (t, OCH_2), 127.1, 128.2, 128.6, 136.2 (3 d, s, Ph), 148.0, 156.3, 165.2, 169.2 (4 s, C-2, C-4, C-5, C-6), 170.6 (s, CO_2).

HRMS (ESI-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{26}N_2NaO_3$: 377.1836; found: 377.1826.

5-(Benzyloxy)-4-*tert*-butyl-2-cyclopropyl-6-ethylpyrimidine (11g)

IR (ATR): 3070–2860 (=C–H, C–H), 1570 (C=C), 1460 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.94–0.98, 1.06–1.10 (2 m, 2 H each, CH_2), 1.30 (t, *J* = 7 Hz, 3 H, Me), 1.38 (s, 9 H, *t*Bu), 2.12–2.19 (m, 1 H, CH), 2.78 (q, *J* = 7 Hz, 2 H, CH_2), 4.82 (s, 2 H, OCH_2), 7.34–7.49 (m, 5 H, Ph).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 10.2 (t, CH_2), 12.2 (q, Me), 17.0 (d, CH), 25.8 (t, CH_2), 29.5, 37.3 (q, s, *t*Bu), 75.8 (t, OCH_2), 127.1, 128.2, 128.7, 136.2 (3 d, s, Ph), 147.5, 164.6, 164.8, 168.1 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{26}N_2NaO$: 333.1937; found: 333.1920.

{6-*tert*-Butyl-2-phenyl-5-[2-(trimethylsilyl)ethoxy]pyrimidin-4-yl}methyl Acetate (10h)

According to general procedure (GP 2, method A), pyrimidine *N*-oxide **4p** (0.132 g, 0.368 mmol), and Ac_2O (1 mL) afforded after purification by flash chromatography (silica gel, hexanes/EtOAc, 4:1) compound **10h** (0.139 g, 94%) as a pale yellow oil.

IR (ATR): 3070–2920 (=C–H, C–H), 1755 (C=O), 1560 (C=C), 1460 cm^{-1} (C=N).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.05 (s, 9 H, $SiMe_3$), 1.21–1.28 (m, 2 H, CH_2Si), 1.47 (s, 9 H, *t*Bu), 2.21 (s, 3 H, Me), 3.87–3.96 (m, 2 H, OCH_2), 5.27 (s, 2 H, OCH_2), 7.40–7.47, 8.37–8.43 (2 m, 3 H, 2 H, Ph).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = –1.5 (q, $SiMe_3$), 18.9 (t, CH_2Si), 20.9 (q, Me), 29.2, 38.4 (q, s, *t*Bu), 61.8 (t, OCH_2), 73.5 (t, OCH_2), 128.0, 128.3, 129.8, 137.8 (3 d, s, Ph), 149.1, 156.8, 157.6, 169.3 (4 s, C-2, C-4, C-5, C-6), 170.7 (s, CO_2).

HRMS (ESI-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{32}N_2NaO_3Si$: 423.2074; found: 423.2080.

{6-(1-Adamantyl)-2-cyclopropyl-5-[2-(trimethylsilyl)ethoxy]-pyrimidin-4-yl}methyl Acetate (10i)

According to general procedure (GP 2, method B), pyrimidine *N*-oxide **4q** (0.041 g, 0.102 mmol), and Ac_2O (0.5 mL) dissolved in benzene (2 mL) afforded after purification by flash chromatography (silica gel, hexanes/EtOAc, 6:1) compound **10i** (0.043 g, 95%) as a colorless oil.

IR (ATR): 3010–2845 (=C–H, C–H), 1750 (C=O), 1560 (C=C), 1430 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.04 (s, 9 H, $SiMe_3$), 0.91–1.08, 1.18–1.27 (2 m, 4 H, 2 H each, *c*Pr, CH_2Si), 1.70–1.78, 2.03–2.10 (2 m, 6 H, 9 H, adamantyl-CH, CH_2), 2.04–2.20 (m, 4 H, *c*Pr, Me), 3.78–3.88 (s, 2 H, CH_2O), 5.11 (s, 2 H, OCH_2).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = –1.5 (q, $SiMe_3$), 10.3, 17.6 (t, d, *c*Pr), 28.6, 36.8, 40.0, 40.6 (d, 2 t, s, adamantyl), 61.8 (t, CH_2O), 73.8 (t, CH_2O), 148.6, 156.2, 165.0, 168.6 (4 s, C-2, C-4, C-5, C-6), 170.7 (s, C=O).

HRMS (ESI-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{39}N_2O_3Si$: 443.2724; found: 443.2739.

(2-Benzyl-6-*tert*-butyl-5-methoxypyrimidin-4-yl)methyl Acetate (10j) and (4-*tert*-Butyl-5-methoxy-6-methylpyrimidin-2-yl)(phenyl)methyl Acetate (10k)

According to general procedure (GP 2, method B), pyrimidine *N*-oxide **4e** (0.200 g, 1.00 mmol), and Ac_2O (0.66 mL) in benzene (5 mL) afforded after purification by flash chromatography (silica gel, hexanes/EtOAc, 4:1) compound **10j** and **10k** (0.201 g, 87%, 2 isomers = 1:1) as a pale yellow oil. A sample of the mixture was separated by a second flash chromatography.

Compound 10j

IR (ATR): 2995–2870 (C–H), 1735 (C=O), 1560 (C=C), 1440 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.37 (s, 9 H, *t*Bu), 2.11 (s, 3 H, Me), 3.77 (s, 3 H, OMe), 4.19 (s, 2 H, CH_2), 5.18 (s, 2 H, OCH_2), 7.17–7.30, 7.37–7.40 (2 m, 3 H, 2 H, Ph).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 20.9 (q, Me), 29.3, 38.3 (q, s, *t*Bu), 45.3 (t, CH_2), 61.7 (t, OCH_2), 62.7 (q, OMe), 126.3, 128.2, 129.4, 138.9 (3 d, s, Ph), 150.1, 156.4, 163.1, 169.6 (4 s, C-2, C-4, C-5, C-6), 170.8 (s, CO_2).

HRMS (ESI-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{25}N_2O_3$: 329.1860; found: 329.1879.

Compound 10k

IR (ATR): 3030–2870 (C–H), 1745 (C=O), 1545 (C=C), 1460 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.37 (s, 9 H, *t*Bu), 2.20 (s, 3 H, Me), 2.45 (s, 3 H, Me), 3.73 (s, 3 H, OMe), 6.67 (s, 1 H, OCH), 7.25–7.35, 7.56–7.58 (2 m, 3 H, 2 H, Ph).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 19.8, 21.3 (2 q, 2 Me), 29.3, 38.1 (q, s, *t*Bu), 61.0 (q, OMe), 78.3 (d, OCH), 127.9, 128.3, 128.4, 138.3 (3 d, s, Ph), 150.8, 159.8, 160.8, 168.2 (4 s, C-2, C-4, C-5, C-6), 170.6 (s, CO_2).

HRMS (ESI-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{25}N_2O_3$: 329.1860; found: 329.1900.

{(*S*)-6-*tert*-Butyl-5-[2-(dibenzylamino)propoxy]-2-methylpyrimidin-4-yl}methyl Acetate (10l) and {(*S*)-6-*tert*-Butyl-5-[2-(dibenzylamino)propoxy]-4-methylpyrimidin-2-yl}methyl Acetate (10m)

According to general procedure (GP 2, , method B), pyrimidine *N*-oxide **4r** (0.520 g, 1.51 mmol), and Ac_2O (1 mL) in benzene (5 mL) afforded after purification by flash chromatography (silica gel, hexanes/EtOAc, 4:1) an inseparable mixture of compounds **10l** and **10m** (0.463 g, 64%; 1:1) as a pale yellow oil.

IR (ATR): 3030–2850 (C–H), 1740 (C=O), 1560 (C=C), 1450 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.24, 1.25 (2 d, *J* = 6.3 Hz, 3 H, Me), 1.29, 1.30 (2 s, 9 H, *t*Bu), 2.14, 2.19 (2 s, 3 H, Me), 2.34, 2.63 (2 s, 3 H, Me), 3.26–3.38 (m, 1 H, CHN), 3.62 (d, *J* = 14.0 Hz, 2 H, CH_2Ph), 3.68–3.99 (m, 4 H, OCH_2, CH_2Ph), 5.01, 5.08 (AB system, J_{AB} = 12.7 Hz, 1 H, OCH_2), 5.19 (s, 1 H, OCH_2), 7.17–7.43 (m, 10 H, Ph).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 11.6, 11.7, 19.7, 20.8, 20.9, 25.5 (6 q, Me), 29.1, 29.2, 37.9, 38.0 (2 q, 2 s, *t*Bu), 52.6 (d, CHN), 54.2, 54.3 (2 t, CH_2Ph), 61.6, 66.0 (2 t, OCH_2), 75.8, 78.0 (2 t, OCH_2), 126.9, 128.3, 128.4, 128.7, 139.9, 140.0 (4 d, 2 s, Ph), 148.5, 149.8, 156.2, 157.0, 160.8, 161.5, 168.3, 169.4 (8 s, C-2, C-4, C-5, C-6), 170.5, 170.8 (2 s, CO_2).

HRMS (ESI-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{36}N_3O_3$: 476.2908; found: 476.2912.

[6-*tert*-Butyl-5-methoxy-2-(trifluoromethyl)pyrimidin-4-yl](phenyl)methyl Acetate (10n)

According to general procedure (GP 2, method A, reaction time: 1 d), pyrimidine *N*-oxide **4u** (0.236 g, 0.693 mmol), and Ac_2O (2 mL) afforded after purification by flash chromatography (silica gel, hexanes/EtOAc, 10:1) compound **10n** (0.192 g, 73%) as a pale yellow oil.

IR (ATR): 3030–2855 (=C–H, C–H), 1545–1520 cm^{-1} (C=C, C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (s, 9 H, *t*Bu), 2.19 (s, 3 H, Me), 3.95 (s, 3 H, OMe), 6.95 (s, 1 H, OCH), 7.33–7.39, 7.52–7.56 (2 m, 3 H, 2 H, Ph).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 21.1 (q, Me), 29.3, 38.7 (q, s, *t*Bu), 63.0 (q, OMe), 72.3 (d, 6-CH), 119.7 (q, $^1J_{CF}$ = 275 Hz, CF_3), 128.1, 128.8, 129.2, 136.2 (3 d, s, Ph), 150.2 (q, $^2J_{CF}$ = 36.7 Hz, C-2), 152.1, 161.5, 171.0 (3 s, C-4, C-5, C-6), 171.9 (s, C=O).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –69.5 (s, CF_3).

HRMS (ESI-ToF): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{21}F_3N_2NaO_3$: 405.1396; found: 405.1404.

[6-(1-Adamantyl)-2-cyclopropyl-5-methoxypyrimidin-4-yl]methanol (12a)

To a solution of **10e** (0.456 g, 1.28 mmol) in MeOH/CH_2Cl_2 (10:1 mL) was added K_2CO_3 (0.708 g, 5.12 mmol) at rt and the mixture was stirred for 3 h. After filtration, the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, hexanes/EtOAc, 3:1) to afford **12a** (0.280 g, 70%) as colorless crystals; mp 127 °C.

IR (ATR): 3175 (O–H), 2930–2845 (C–H), 1565 (C=C), 1455 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.94–1.00, 1.03–1.10 (2 m, 2 H each, *c*Pr), 1.69–1.79, 1.98–2.10 (2 m, 6 H, 9 H, adamantyl-CH, -CH_2), 2.14–2.23 (m, 1 H, *c*Pr), 3.68 (s, 3 H, OMe), 4.19 (br s, 1 H, OH), 4.69 (s, 2 H, CH_2O).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 10.3, 17.6 (t, d, *c*Pr), 28.6, 36.8, 40.0, 40.4 (d, 2 t, s, adamantyl), 59.3 (q, OMe), 61.8 (t, CH_2O), 148.3, 159.5, 164.4, 167.5 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{27}N_2O_2$: 315.2072; found: 315.2082.

Anal. Calcd for $C_{19}H_{26}N_2O_2$ (314.4): C, 72.58; H, 8.33; N, 8.91. Found: C, 72.56; H, 8.23; N, 8.95.

(6-*tert*-Butyl-5-methoxy-2-phenylpyrimidin-4-yl)methanol (12b)

Method A: To a solution of **10d** (0.716 g, 2.25 mmol) in MeOH (15 mL) was added K_2CO_3 (1.18 g, 8.53 mmol) at rt and the mixture was stirred for 3 h. After filtration, the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/EtOAc, 3:1) to afford **12b** (0.465 g, 76%) as a colorless oil.

Method B: To a solution of pyrimidine *N*-oxide **4i** (0.430 g, 1.58 mmol) in CH_2Cl_2 (10 mL) was added TFAA (1 mL) and the solution was stirred at rt for 3 h. The excess TFAA and the solvent were removed under reduced pressure. Purification of the crude product by column chromatography (silica gel, hexanes/EtOAc, 5:1) provided **12b** (0.364 g, 85%) as a colorless oil.

IR (ATR): 3450 (O–H), 3090–2865 (=CH, C–H), 1555–1450 cm^{-1} (C=C).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.44 (s, 9 H, *t*Bu), 3.78 (s, 3 H, OMe), 4.30 (br s, 1 H, OH), 4.82 (s, 2 H, OCH_2), 7.38–7.50, 8.41–8.50 (2 m, 2 H, 3 H, Ph).

^{13}C NMR ($CDCl_3$, 100.5 MHz): δ = 29.3, 38.3 (q, s, *t*Bu), 59.5 (t, OCH_2), 61.5 (q, OMe), 127.9, 128.4, 130.1, 137.1 (3 d, s, Ph), 148.9, 156.9, 159.8, 168.5 (4 s, C-2, C-4, C-5, C-6),

HRMS (ESI-ToF): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{20}N_2NaO_2$: 295.1418; found: 295.1420.

(2-Benzyl-6-*tert*-butyl-5-methoxypyrimidin-4-yl)methanol (12c)

Pyrimidine *N*-oxide **4e** (0.130 g, 0.488 mmol) and TFAA (0.190 g, 1.36 mmol) were dissolved in CH_2Cl_2 (4 mL) and the solution was stirred at rt for 3 h. Then the solvent and the excess TFAA were removed under reduced pressure. Purification of the crude product by column chromatography (silica gel, hexanes/EtOAc, 6:1 to 1:1) provided **12c** (0.094 g, 72%) as a colorless oil.

IR (ATR): 3185 (O–H), 2980–2880 (C–H), 1560 (C=C), 1460 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.37 (s, 9 H, *t*Bu), 3.77 (s, 3 H, OMe), 4.15 (br s, 1 H, OH), 4.25 (s, 2 H, CH_2), 4.72 (s, 2 H, OCH_2), 7.20–7.31, 7.37–7.42 (2 m, 3 H, 2 H, Ph).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 29.1, 38.1 (q, s, *t*Bu), 45.0 (t, CH_2), 59.2 (t, OCH_2), 61.4 (q, OMe), 126.3, 128.2, 129.2, 138.5 (3 d, s, Ph), 148.4, 159.7, 161.9, 168.8 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{23}N_2O_2$: 287.1754; found: 287.1728.

(2,6-Di-*tert*-butyl-5-methoxypyrimidin-4-yl)methanol (12d)

Pyrimidine *N*-oxide **4g** (0.320 g, 1.29 mmol) and TFAA (0.810 g, 3.87 mmol) were dissolved in CH_2Cl_2 (10 mL) and the solution was stirred at rt for 3 h. Then the solvent and the excess TFAA were removed under reduced pressure. Purification of the crude product by column chromatography (silica gel, hexanes/EtOAc, 20:1 to 15:1) provided **12d** (0.260 g, 78%) as a colorless oil.

IR (ATR): 3150 (O–H), 2950–2860 (C–H), 1560 (C=C), 1455 cm^{-1} (C=N).

^1H NMR ($CDCl_3$, 500 MHz): δ = 1.37, 1.38 (2 s, 9 H each, *t*Bu), 3.74 (s, 3 H, OMe), 4.20 (very br s, 1 H, OH), 4.74 (s, 2 H, OCH_2).

^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 29.3, 29.7, 38.4, 39.2 (2 q, 2 s, *t*Bu), 59.5 (t, OCH_2), 61.4 (q, OMe), 127.1, 128.2, 128.6, 136.2 (3 d, s, Ph), 147.7, 158.8, 167.6, 169.4 (4 s, C-2, C-4, C-5, C-6).

HRMS (ESI-ToF): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{25}N_2O_2$: 253.1911; found: 253.1932.

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Supporting Information

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