A Route to Alkenyl-Substituted 4-Hydroxypyridine and Pyrimidine Derivatives via Three-Component Access to β-Alkoxy-β-ketoenamides

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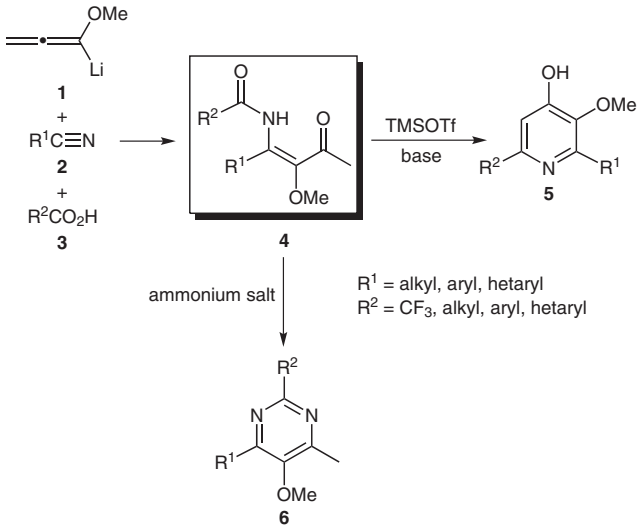
Dedicated to Professor Rolf Huisgen on the occasion of his 90th birthday

Abstract: β-Alkoxy-β-ketoenamides with an alkenylated side arm were prepared by three-component reaction of lithiated methoxyallene, nitriles, and α,β-unsaturated carboxylic acids. Their subsequent treatment with trimethylsilyl triflate and base provided 6-alkenyl-4-hydroxypyridine derivatives that were converted into the corresponding nonaflates. Alternatively, condensation of β-alkoxy-β-ketoenamides with an ammonium salt led to the smooth formation of alkenyl-substituted pyrimidine derivatives. The alkenyl group in pyridine or pyrimidine derivatives allows a wide scope of functional group modification. Moreover, the pyridin-4-yl nonaflates are excellent candidates for palladium-catalyzed coupling reactions and the 6-methyl group of the pyrimidine derivatives could also be employed for the introduction of functional groups and subsequent reactions. A variety of highly substituted pyridine and pyrimidine derivatives are available by this modular route to heterocycles.

Key words: alkoxyallenes, enamides, pyridines, nonaflates, pyrimidines, Suzuki couplings

Substituted pyridines are very common structural motifs in naturally occurring substances with promising biological properties and in the field of medicinal chemistry.[1] Appropriately functionalized pyridines have also been used as reagents in organic synthesis and for new materials.[2] For example, suitably substituted bipyridines and terpyridines are used as ligands in organocatalysis and as building blocks in supramolecular chemistry.[3] Pyrimidine derivatives are also a compound class with vast interest as they are often biologically active.[4] Compounds with a pyrimidine core have shown antiviral, antibacterial, antimicrobial, antifungal, or anticancer activity.[4] Therefore, substituted pyrimidine derivatives frequently constitute a crucial substructure in drug discovery. These heterocycles have been attractive targets for synthetic organic chemists for many years and as a consequence, various elegant strategies for the preparation of specifically functionalized pyridines[5] and pyrimidines[6] are well documented in the literature. Most of the routes towards pyrimidine derivatives employ the condensation reaction of 1,3-dicarbonyl compounds with amidines (Pinner synthesis),[7] or with aldehydes and urea (Biginelli synthesis).[8] Only a few utilized enamides as precursors for the preparation of substituted pyridine and pyrimidine derivatives.[9]

Recently, we became interested in the synthesis of substituted pyridines and pyrimidines employing alkoxyallenes as a crucial C3 building block.[10] We have already accomplished the syntheses of numerous pyridine[11] and pyrimidine[12] derivatives based upon the three-component access to β-alkoxy-β-ketoenamides **4** (Scheme 1).[11,12] The formation of these functionalized enamides occurs by a novel and mechanistically intriguing reaction using lithiated alkoxyallenes, such as lithiated methoxyallene **1**, nitriles **2**, and carboxylic acids **3** as precursors.[11a] The scope of this transformation with respect to all three components is remarkably broad. Subsequent Mukaiyama-type aldol condensation using trimethylsilyl trifluoromethanesulfonate and an amine provided highly substituted 4-hydroxypyridine derivatives **5** in good yields (Scheme 1), which were often converted into the corresponding pyridin-4-yl nonaflates ($OSO_2C_4F_9$ instead of OH). On the other hand, β-alkoxy-β-ketoenamides **4** could readily be transformed into pyrimidine derivatives **6** by heating with an ammonium salt in methanol (Scheme 1).[12] The possibility of synthesizing alkenyl-substituted pyridine and pyrimidine derivatives has not been explored to date. In this report we demonstrate that α,β-unsaturated carboxylic acids, including even acrylic acid, are also tolerated in these reactions and, thus, open a whole range of new op-



Scheme 1 Preparation of 4-hydroxypyridine derivatives **5** and 5-methoxypyrimidines **6** starting from lithiated methoxyallene **1**, nitriles **2**, and carboxylic acids **3** via β-alkoxy-β-ketoenamides **4**.

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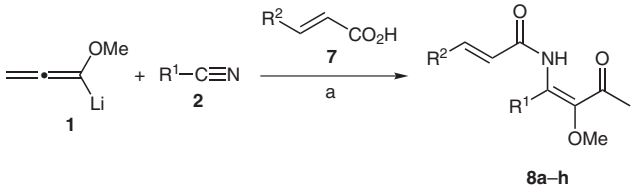
tions for subsequent synthetic elaboration of the two classes of heterocycles.

Reaction of lithiated methoxyallene **1** (in situ generated by deprotonation of methoxyallene with *n*-BuLi in Et_2O) with pivalonitrile followed by addition of the corresponding α,β-unsaturated carboxylic acids **7** provided the desired enamides **8a–e** in very good to excellent yields. As carboxylic acids we used acrylic, crotonic, cinnamic, 3-(thiophen-2-yl)acrylic, and 3-(furan-2-yl)acrylic acid (Scheme 2, Table 1, entries 1–5). To demonstrate that the formation of **8** is not restricted to *tert*-butyl-substituted derivatives we also examined other combinations (Table 1, entries 6–8). Benzonitrile or thiophene-2-carbonitrile also provided the expected enamides **8f–h** in moderate to good yields.



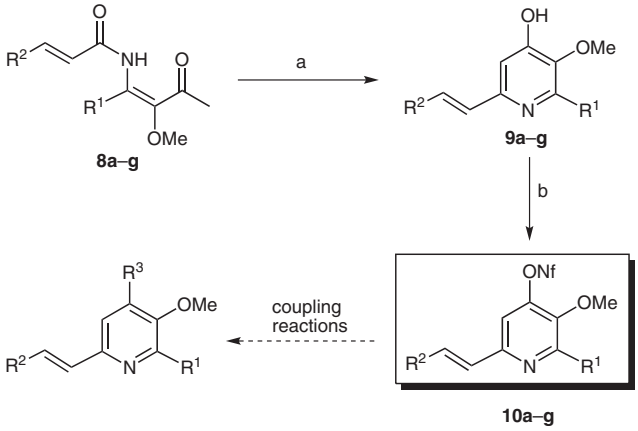
Scheme 2 Synthesis of alkenyl-substituted enamides **8a–h** (see Table 1) (a) (i) Et_2O, –50 °C, 4 h; (ii) carboxylic acid **7**, –78 °C to r.t., 12 h.

Table 1 Synthesis of Enamides **8a–h** Starting from Lithiated Methoxyallene **1**, Nitriles **2**, and α,β-Unsaturated Carboxylic Acids **7**

Entry	R^1	R^2	Product	Yield (%)
1	*t*-Bu	H	**8a**	91
2	*t*-Bu	Me	**8b**	93
3	*t*-Bu	Ph	**8c**	87
4	*t*-Bu	2-thienyl	**8d**	80
5	*t*-Bu	2-furyl	**8e**	89
6	Ph	Ph	**8f**	51
7	2-thienyl	Ph	**8g**	68
8	Ph	H	**8h**	45

We also wanted to explore the possibility of achieving the synthesis of dialkenyl-substituted pyridine and pyrimidine derivatives. Towards this end, we employed alkenylated carbonitriles such as acrylonitrile and cinnamonitrile along with α,β-unsaturated carboxylic acids in the above mentioned reaction, however, we have not, as yet, been able to obtain the corresponding dialkenyl-substituted enamides.

Following the standard cyclization protocol[11a] enamides **8a–g** were readily converted into the desired 4-hydroxypyridine derivatives **9a–g** in moderate to good yields (Scheme 3, Table 2); only phenyl-substituted derivative **8h** containing the acrylamide moiety failed to undergo this cyclization. None of these 4-hydroxypyridine derivatives gave reasonably good NMR spectra, which is very likely due to the equilibrium of the 4-hydroxypyridines with their corresponding pyridin-4-one tautomers. Therefore, in all cases, the purified 4-hydroxypyridine derivatives **9a–g** were treated with sodium hydride and nonafluorobutanesulfonyl fluoride (NfF) to provide the less polar, easily separable pyridin-4-yl nonaflates **10a–g** in good yields (Scheme 3, Table 2).

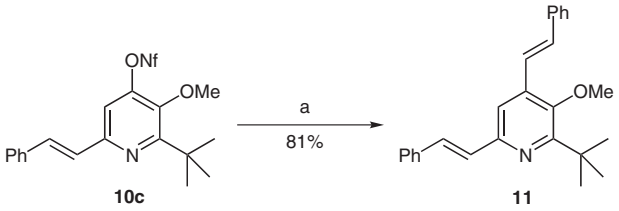


Scheme 3 Preparation of 6-alkenyl-substituted 4-hydroxypyridine derivatives **9** and conversion into pyridin-4-yl nonaflates **10** (see Table 2). *Reagents and conditions*: (a) TMSOTf, Et_3N, DCE, sealed tube, 90 °C, 3 d; (b) NaH, NfF, THF, r.t., 3–12 h.

Table 2 Synthesis of 6-Alkenyl-Substituted 4-Hydroxypyridine Derivatives **9a–g** and Subsequent Conversion into Pyridin-4-yl Nonaflates **10a–g**

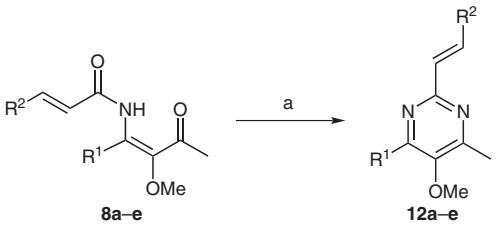
Entry	R^1	R^2	Product	Yield (%)	Product	Yield (%)
1	*t*-Bu	H	**9a**	63	**10a**	80
2	*t*-Bu	Me	**9b**	67	**10b**	79
3	*t*-Bu	Ph	**9c**	63	**10c**	76
4	*t*-Bu	2-thienyl	**9d**	55	**10d**	72
5	*t*-Bu	2-furyl	**9e**	53	**10e**	70
6	Ph	Ph	**9f**	82	**10f**	66
7	2-thienyl	Ph	**9g**	68	**10g**	81
8	Ph	H	**9h**	–	**10h**	–

All nonaflates **10a–g** have spectroscopic data that allow unambiguous characterization. More importantly, these nonaflates provide the option to perform different transition-metal-catalyzed cross-coupling reactions.[13] In order to test the feasibility of palladium-catalyzed coupling reactions we chose pyridin-4-yl nonaflate **10c** as a model substrate. Hence, this compound was treated with *trans*-styrylboronic acid under typical Suzuki coupling conditions[14] to furnish compound **11** bearing two styryl groups in 81% yield (Scheme 4).



Scheme 4 Synthesis of 4,6-distyryl-substituted pyridine derivative **11**. *Reagents and conditions*: (a) *trans*-styrylboronic acid, $Pd(OAc)_2$ (cat.), Ph_3P (cat.), K_2CO_3, DMF, 70 °C, 8 h.

After the successful synthesis of 2-alkenyl-substituted 4-hydroxypyridines **9** and their nonaflates **10**, we turned our attention to the preparation of the corresponding pyrimidine derivatives using enamides **8a–h**. First, ammonium hydrogen carbonate (16 equiv) dissolved in methanol at 70 °C was used to convert **8a** into **12a** in moderate yield (ca. 50%). By switching to ammonium acetate[12] the yield of pyrimidine derivative **12a** increased remarkably. With this modification lower amounts of ammonium salt (8 equiv) and shorter reaction times were sufficient. Therefore, we employed this method for the transformation of enamides **8a–h** into pyrimidine derivatives **12a–h**, which were smoothly obtained in good to very good yields (Scheme 5, Table 3). Here, enamide **8h** with the acrylamide moiety undergoes the condensation reaction without any problem, furnishing the desired pyrimidine derivative **12h** at least in moderate yield (entry 8).

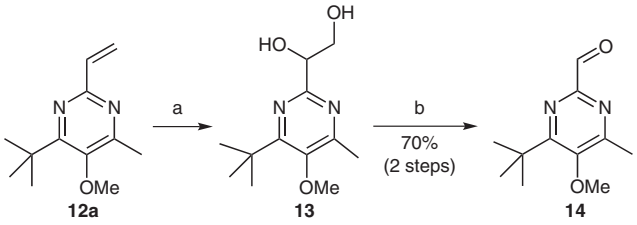


Scheme 5 Synthesis of alkenyl-substituted pyrimidine derivatives **12** starting from **8** (see Table 3). *Reagents and conditions*: (a) NH_4OAc, MeOH, sealed tube, 65 °C, 24 h.

Table 3 Synthesis of 2-Alkenyl-Substituted Pyrimidines **12a–h**

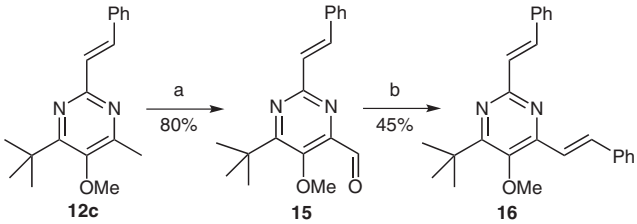
Entry	R^1	R^2	Product	Yield (%)
1	*t*-Bu	H	**12a**	77
2	*t*-Bu	Me	**12b**	75
3	*t*-Bu	Ph	**12c**	85
4	*t*-Bu	2-thienyl	**12d**	69
5	*t*-Bu	2-furyl	**12e**	67
6	Ph	Ph	**12f**	84
7	2-thienyl	Ph	**12g**	78
8	Ph	H	**12h**	55

The presence of an alkenyl subunit at C2 position of the prepared pyrimidine derivatives **12** is very advantageous, since this group allows smooth subsequent functionalizations. Compound **12a** was employed as a model compound to demonstrate the versatility of these intermediates. A standard osmium-promoted dihydroxylation protocol[15] converted **12a** into diol **13** which was subjected to oxidative cleavage by sodium periodate furnishing aldehyde **14** in very good overall yield (Scheme 6).



Scheme 6 Synthesis of pyrimidine-2-carbaldehyde **14**. *Reagents and conditions*: (a) $K_2OsO_4 \cdot 2H_2O$, NMO, acetone–H_2O (5:1), r.t., 6 h; (b) $NaIO_4$, THF–H_2O (25:1), 0 °C, 1 h.

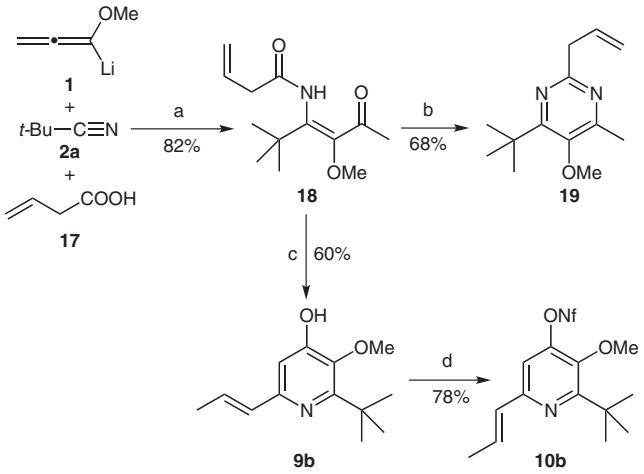
Moreover, the methyl group, which is present at C4 of all prepared pyrimidine derivatives **12a–h**, could also be a useful tool for further functionalization. Oxidation of the methyl group of **12c** was carried out under standard Riley conditions[16] to provide aldehyde **15** in good yield. This intermediate was subsequently subjected to Wittig reaction under standard conditions to give 2,6-distyryl-substituted pyrimidine **16** in reasonable overall yield (Scheme 7). It has to be mentioned here that in all compounds **12** it should also be possible to convert the methoxy group into a nonaflate group[12b] under fairly mild conditions, which obviously will allow transition-metal-catalyzed coupling reactions at C5 of the pyrimidine core.



Scheme 7 Preparation of pyrimidine-4-carbaldehyde **15** and olefination to **16**. *Reagents and conditions*: (a) SeO_2, 1,4-dioxane, sealed tube, 90 °C, 2 d; (b) Ph_3PCH_2PhBr, *n*-BuLi, Et_2O, 0 °C, 1 h.

After the successful synthesis of a set of alkenyl-substituted pyridine and pyrimidine derivatives, our next objective was to prepare the related allyl-substituted analogues. To realize our target, the required allylated enamide **18** was efficiently obtained by the three-component reaction involving lithiated methoxyallene **1**, pivalonitrile (**2a**), and but-3-enoic acid (**17**) (Scheme 8). β-Alkoxy-β-ketoenamide **18** was smoothly converted into the corresponding 2-allyl-substituted pyrimidine **19** in the presence of ammonium acetate in refluxing methanol. We expected that

the terminal double bond of enamide **18** or pyrimidine **19** might migrate to provide a conjugated system in the presence of an amine. This was apparently not the case under the fairly mild conditions required for pyrimidine generation. On the other hand, our expectation was found to be correct when harsher conditions for pyridine synthesis were applied. Instead of an allyl-substituted pyridine derivative the already known 4-hydroxypyridine derivative **9b** was obtained (Scheme 8). It was routinely transformed into pyridin-4-yl nonaflate **10b** whose spectroscopic data undoubtedly agree with the compound already discussed (Scheme 2, Table 1). This observation was further confirmed by carrying out an attempted cyclization reaction of enamide **18** at room temperature. After three days we found that compound **18** was transformed into enamide **8b** containing a crotonic acid moiety. Since we did not observe any pyridine derivative, we conclude that under these conditions allyl-substituted enamide **18** undergoes double bond migration considerably faster than the cyclization reaction.



Scheme 8 Conversion of allyl-substituted enamide **18** into 2-allylpyrimidine **19** and pyridine derivatives **9b** and **10b**. *Reagents and conditions*: (a) Et_2O, –78 °C to r.t., 12 h; (b) NH_4OAc, MeOH, sealed tube, 65 °C, 24 h; (c) TMSOTf, Et_3N, DCE, sealed tube, 90 °C, 3 d; (d) NaH, NfF, THF, r.t., 12 h.

The newly prepared pyridine and pyrimidine derivatives contain a system with at least one alkenyl unit conjugated with the heterocyclic core. Therefore, we were also interested in the physical properties of these compounds, in particular the optical properties.[2] Hence, a series of UV-Vis and fluorescence spectra were recorded and the results are summarized in Table 4. The cross-conjugated pyridine derivative **11** (Figure 1 and Table 4, entry 4) shows the largest Stokes shift, but pyrimidines **12e** and **16** have similar absorptions and emissions resulting in Stokes shifts in the range of 110 nm.

Table 4 UV-Vis and Fluorescence Spectra of Pyridine Derivatives **9d**, **9e**, **10d**, and **11**, and of Pyrimidine Derivatives **12e** and **16**

Entry	Compound	λ_{Abs} (nm)	λ_{Em} (nm)	Stokes shift (nm)
1	**9d**	348	393	45
2	**9e**	350	405	55
3	**10d**	340	404	64
4	**11**	309	423	114
5	**12e**	324	435	111
6	**16**	306	419	113

In conclusion, a variety of new 2-alkenyl-substituted 4-hydroxypyridine and pyrimidine derivatives have been synthesized by a two-step procedure employing first the three-component reaction of lithiated methoxyallene, nitriles, and a series of α,β-unsaturated carboxylic acids to β-alkoxy-β-ketoenamides followed by the appropriate cyclization steps. It should be mentioned here, that the crucial three-component reaction works with a broad range of nitriles although frequently with lower yields.[11] Instead of *tert*-butyl groups as presented in this report in most of our examples other alkyl or (hetero)aryl substituents are also possible. First examples in this report demonstrate that the enamide formation is smooth, however, that the cyclization to pyridine derivatives may require occasionally milder conditions.

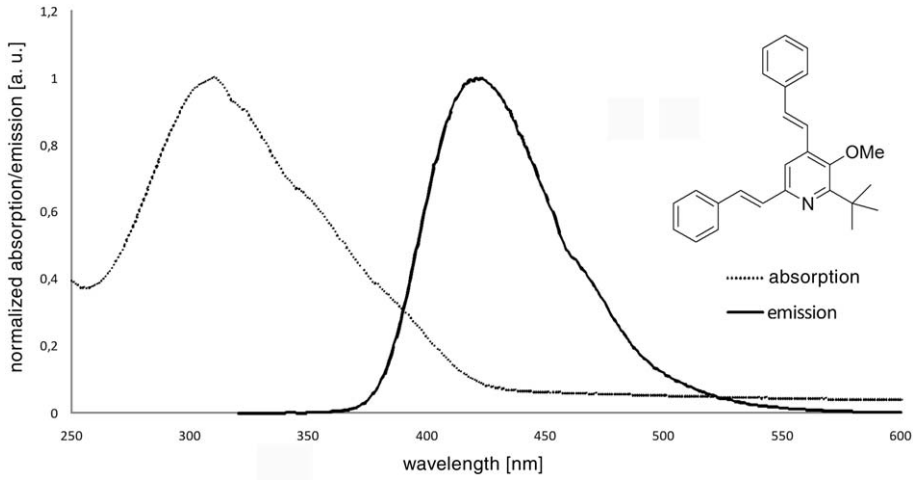


Figure 1 UV-Vis and fluorescence spectra of pyridine derivative **11**

The alkenyl group and the methyl group of the heterocycles could be employed for further functionalizations. In addition, the variety of highly substituted pyridine derivatives accessible can further be increased by employing palladium-catalyzed coupling reactions of the corresponding pyridin-4-yl nonaflates. Therefore our modular approach to specifically substituted pyridine and pyrimidine derivates will considerably increase the availability of these important heterocycles.

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). 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 Joel ECX 400 instruments in $CDCl_3$ solns. Integrals are in accordance with assignments. IR spectra were measured with an FT-IR spectrophotometer Nicolet 5 SXC. HRMS analyses were performed with Agilent 6210 (ESI-TOF, 4 μL/min, 1.0 bar, 4 kV) instrument. The elemental analyses were recorded with Elemental-Analyzers (Perkin-Elmer or Carlo Erba). UV/Vis spectra were measured with a UV-Vis spectrophotometer Scinco S-3150 PDA. Fluorescence spectra were measured with a spectrofluorometer Jasco FP-6500.

Methoxyallene was prepared according to the reported procedure.[10a] 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)acrylamide (8a); Typical Procedure 1

To a soln of methoxyallene (0.83 mL, 9.86 mmol) in anhyd Et_2O (25 mL) was added 2.5 M *n*-BuLi in hexanes (3.60 mL, 9.00 mmol) at –50 °C. The mixture was stirred at –50 °C for 30 min and then it was cooled to –78 °C and pivalonitrile (0.33 mL, 3.0 mmol) in anhyd Et_2O (5 mL) was added to the mixture, which was stirred at this temperature for 4 h. A soln of acrylic acid (1.25 mL, 18.2 mmol) in anhyd Et_2O (10 mL) was added to the mixture and the temperature was allowed to increase to r.t. and the mixture was stirred overnight. The reaction was quenched with sat. aq $NaHCO_3$ soln (20 mL) and the product was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (25 mL) and finally dried (Na_2SO_4). Solvent was removed on a rotary evaporator and the crude product was purified by column chromatography (silica gel, hexane–EtOAc, 1:1) to give **8a** (0.615 g, 91%) as pale yellow crystals; mp 140–144 °C.

IR (KBr): 3310 (NH), 3010–2835 (=CH, C–H), 1685–1510 cm^{-1} (C=O, C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s, 9 H, *t*-Bu), 2.25 (s, 3 H, COMe), 3.48 (s, 3 H, OMe), 5.59 (dd, *J* = 8.0, 1.8 Hz, 1 H, =CH_2), 6.11–6.26 (m, 2 H, CH_2=CH), 7.56 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.7 (q, Me), 28.5, 36.6 (s, q, *t*-Bu), 58.9 (q, OMe), 127.7 (t, =CH_2), 130.5, 132.9, 150.8 (2 s, d, C1, C2, =CH), 165.3 (s, C1′), 200.9 (s, C3).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{19}NNaO_3$: 248.1257; found: 248.1258.

Anal. Calcd for $C_{12}H_{19}NO_3$ (225.1): C, 63.98; H, 8.50; N, 6.22. Found: C, 63.85; H, 8.56; N, 6.23.

(*E*)-*N*-[(*E*)-4-Methoxy-2,2-dimethyl-5-oxohex-3-en-3-yl]but-2-enamide (8b)

According to typical procedure 1, a mixture of methoxyallene (1.00 mL, 11.9 mmol), 2.5 M *n*-BuLi in hexanes (4.32 mL, 10.8 mmol), pivalonitrile (0.40 mL, 3.61 mmol), and crotonic acid (1.90 g, 22.1 mmol) in anhyd Et_2O (50 mL) gave **8b** (0.810 g, 93%) as pale yellow crystals; mp 145–148 °C.

IR (KBr): 3335 (NH), 3020–2960 (=CH, C–H), 1685–1505 cm^{-1} (C=O, C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 9 H, *t*-Bu), 1.75 (dd, *J* = 3.7, 1.5 Hz, 3 H, =CHMe), 2.21 (s, 3 H, COMe), 3.44 (s, 3 H, OMe), 5.82 (dd, *J* = 15.2, 1.5 Hz, 1 H, =CH), 6.73–6.78 (m, 1 H, =CH), 7.47 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8 (q, =CH*Me*), 27.8 (q, Me), 28.4, 36.5 (s, q, *t*-Bu), 58.8 (q, OMe), 124.7, 133.2, 141.4, 150.7 (2 d, 2 s, C1, C2, HC=CH), 165.6 (s, C1′), 200.7 (s, C3).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{21}NNaO_3$: 262.1419; found: 262.1417.

Anal. Calcd for $C_{13}H_{21}NO_3$ (239.3): C, 65.25; H, 8.84; N, 5.85. Found: C, 65.05; H, 8.81; N, 5.84.

***N*-[(*E*)-4-Methoxy-2,2-dimethyl-5-oxohex-3-en-3-yl]cinnamamide (8c)**

According to typical procedure 1, a mixture of methoxyallene (1.10 mL, 13.0 mmol), 2.5 M *n*-BuLi in hexanes (5.00 mL, 12.5 mmol), pivalonitrile (0.70 mL, 6.33 mmol), and cinnamic acid (3.75 g, 25.3 mmol) in anhyd Et_2O (75 mL) gave **8c** (1.65 g, 87%) as a pale yellow solid; mp 125–128 °C.

IR (KBr): 3315 (NH), 3060–2835 (=CH, C–H), 1675–1575 cm^{-1} (C=O, C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (s, 9 H, *t*-Bu), 2.33 (s, 3 H, COMe), 3.49 (s, 3 H, OMe), 6.50 (d, *J* = 15.7 Hz, 1 H, =CHCO), 7.19–7.28 (m, 5 H, Ph), 7.46 (d, *J* = 15.7 Hz, 1 H, =CHPh), 7.90 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6 (q, Me), 28.4, 36.4 (s, q, *t*-Bu), 58.8 (q, OMe), 119.9, 134.5, 141.9, 150.5 (2 d, 2 s, C1, C2, HC=CH), 127.7, 128.4, 129.4, 132.5 (3 d, s, Ph), 165.5 (s, C1′), 201.0 (s, C3).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{23}NNaO_3$: 324.1576; found: 324.1574.

Anal. Calcd for $C_{18}H_{23}NO_3$ (301.4): C, 71.73; H, 7.69; N, 4.65. Found: C, 71.60; H, 7.75; N, 4.37.

(*E*)-*N*-[(*E*)-4-Methoxy-2,2-dimethyl-5-oxohex-3-en-3-yl]-3-(thiophen-2-yl)acrylamide (8d)

According to typical procedure 1, a mixture of methoxyallene (1.30 mL, 15.4 mmol), 2.5 M *n*-BuLi in hexanes (5.80 mL, 14.5 mmol), pivalonitrile (0.80 mL, 7.24 mmol), and (*E*)-3-(thiophen-2-yl)acrylic acid (4.45 g, 28.9 mmol) in anhyd Et_2O (75 mL) gave **8d** (1.77 g, 80%) as a pale yellow solid; mp 150–152 °C.

IR (KBr): 3290 (NH), 3100–2830 (=CH, C–H), 1700 (C=O), 1655–1425 cm^{-1} (C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (s, 9 H, *t*-Bu), 2.32 (s, 3 H, Me), 3.51 (s, 3 H, OMe), 6.26 (d, *J* = 15.2 Hz, 1 H, =CHCO), 6.91 (dd, *J* = 5.0, 3.5 Hz, 1 H, $H_{thienyl}$), 6.99 (d, *J* = 3.5 Hz, 1 H, $H_{thienyl}$), 7.23 (d, *J* = 5.0 Hz, 1 H, $H_{thienyl}$), 7.59 (d, *J* = 15.2 Hz, 1 H, =CH-thienyl), 7.60 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.7 (q, Me), 28.6, 36.6 (s, q, *t*-Bu), 59.1 (q, OMe), 119.1, 132.7, 134.8, 139.9, 150.6 (2 d, 3 s, C1, C2, HC=CH, $C_{thienyl}$), 127.7, 127.9, 130.2 (3 d, $C_{thienyl}$), 165.4 (s, C1′), 201.2 (s, C3).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{21}NNaO_3S$: 330.1140; found: 330.1138.

(*E*)-3-(Furan-2-yl)-*N*-[(*E*)-4-methoxy-2,2-dimethyl-5-oxohex-3-en-3-yl]acrylamide (8e)

According to typical procedure 1, a mixture of methoxyallene (1.10 mL, 13.0 mmol), 2.5 M *n*-BuLi in hexanes (5.00 mL, 12.5 mmol),

pivalonitrile (0.70 mL, 6.33 mmol), and (*E*)-3-(furan-2-yl)acrylic acid (3.50 g, 25.4 mmol) in anhyd Et_2O (75 mL) gave **8e** (1.63 g, 89%) as a pale yellow solid; mp 134–137 °C.

IR (KBr): 3260 (NH), 3150–2835 (=CH, C–H), 1695–1495 cm^{-1} (C=O, C=C).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (s, 9 H, *t*-Bu), 2.28 (s, 3 H, Me), 3.49 (s, 3 H, OMe), 6.33–6.35 (m, 1 H, H_{furyl}), 6.34 (d, *J* = 15.4 Hz, 1 H, =CHCO), 6.43–6.45 (m, 1 H, H_{furyl}), 7.31 (d, *J* = 15.4 Hz, 1 H, =CH-furyl), 7.29–7.33 (m, 1 H, H_{furyl}), 7.71 (br s, 1 H, NH).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{21}NNaO_4$: 314.1368; found: 314.1385.

Anal. Calcd for $C_{16}H_{21}NO_4$ (291.3): C, 65.96; H, 7.27; N, 4.81. Found: C, 65.32; H, 7.23; N, 4.58.

N-[(*E*)-2-Methoxy-3-oxo-1-phenylbut-1-enyl]cinnamamide (8f)

According to typical procedure 1, a mixture of methoxyallene (1.35 mL, 16.0 mmol), 2.5 M *n*-BuLi in hexanes (5.90 mL, 14.8 mmol), benzonitrile (0.75 mL, 7.35 mmol), and cinnamic acid (4.30 g, 29.0 mmol) in anhyd Et_2O (40 mL) gave **8f** (1.21 g, 51%) as a pale yellow solid; mp 115–120 °C.

IR (KBr): 3310 (NH), 3095–2950 (=CH, C–H), 1705–1630 cm^{-1} (C=O, C=C).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, Me), 3.20 (s, 3 H, OMe), 6.54 (d, *J* = 15.7 Hz, 1 H, =CHCO), 7.35–7.37 (m, 2 H, Ph), 7.39–7.42 (m, 3 H, Ph), 7.46–7.51 (m, 5 H, Ph), 7.61 (d, *J* = 15.7 Hz, 1 H, =CHPh), 11.65 (s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5 (q, Me), 60.7 (q, OMe), 120.9, 130.3, 132.3, 134.5, 138.5, 143.3 (2 d, 4 s, C1, C2, HC=CH, Ph), 127.9, 128.2, 128.4, 128.9, 129.0 (5 d, Ph), 164.4 (s, C1′), 202.7 (s, C3).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{19}NNaO_3$: 344.1263; found: 344.1251.

N-[(*E*)-2-Methoxy-3-oxo-1-(thiophen-2-yl)but-1-enyl]cinnamamide (8g)

According to typical procedure 1, a mixture of methoxyallene (1.00 mL, 12.1 mmol), 2.5 M *n*-BuLi in hexanes (4.40 mL, 11.0 mmol), thiophene-2-carbonitrile (0.50 mL, 5.37 mmol), and cinnamic acid (3.66 g, 24.7 mmol) in anhyd Et_2O (50 mL) gave **8g** (1.21 g, 68%) as a deep brownish solid; mp 108–110 °C.

IR (KBr): 3280 (NH), 3015–2860 (=CH, C–H), 1685–1570 cm^{-1} (C=O, C=C).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, Me), 3.50 (s, 3 H, OMe), 6.58 (d, *J* = 15.7 Hz, 1 H, =CHCO), 7.05–7.08 (m, 1 H, $H_{thienyl}$), 7.35–7.40 (m, 4 H, Ph, $H_{thienyl}$), 7.49–7.52 (m, 3 H, Ph), 7.65 (d, *J* = 15.7 Hz, 1 H, =CHPh), 10.44 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.8 (q, Me), 60.2 (q, OMe), 120.7, 130.0, 130.3, 131.3, 133.1, 133.7, 134.4, 143.4 (5 d, 3 s, C1, C2, HC=CH, $C_{thienyl}$), 126.8, 128.2, 128.9 (3 d, Ph), 165.7 (s, C1′), 200.8 (s, C3).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{17}NNaO_3S$: 350.0827; found: 350.0822.

(*E*)-*N*-(2-Methoxy-3-oxo-1-phenylbut-1-enyl)acrylamide (8h)

According to typical procedure 1, a mixture of methoxyallene (1.30 mL, 15.8 mmol), 2.5 M *n*-BuLi in hexanes (5.80 mL, 14.5 mmol), benzonitrile (0.50 mL, 4.90 mmol), and acrylic acid (2.00 mL, 29.1 mmol) in anhyd Et_2O (25 mL) gave **8h** (0.55 g, 45%) as a brownish solid; mp 135–138 °C.

IR (KBr): 3295 (NH), 3070–2835 (=CH, C–H), 1705–1570 cm^{-1} (C=O, C=C).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3 H, Me), 3.18 (s, 3 H, OMe), 5.73 (dd, *J* = 9.8, 1.6 Hz, 1 H, =CH), 6.17–6.32 (m, 2 H, $=CH_2$, =CH), 7.37–7.43 (m, 5 H, Ph), 11.54 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5 (q, Me), 60.7 (q, OMe), 127.9, 128.4, 128.9 (3 d, Ph), 128.7 (t, $=CH_2$), 131.4, 132.1, 138.6, 142.8 (2 d, 2 s, C1, C2, =CH, Ph), 163.9 (s, C1′), 202.3 (s, C3).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{15}NNaO_3$: 268.0950; found: 268.0951.

2-*tert*-Butyl-3-methoxy-6-vinylpyridin-4-ol (9a) and 2-*tert*-Butyl-3-methoxy-6-vinylpyridin-4-yl Nonaflate (10a); Typical Procedure 2

Enamide **8a** (0.225 g, 1.00 mmol) was dissolved in DCE (20 mL) and placed in a sealed tube. Then Et_3N (0.70 mL, 5.00 mmol) and TMSOTf (0.90 mL, 5.00 mmol) were added at r.t. The resulting mixture was heated at 90 °C for 3 d and quenched with sat. aq NH_4Cl soln (10 mL). After extraction with CH_2Cl_2 (3 × 25 mL), the combined organic layers were dried (Na_2SO_4) and evaporated to provide the crude product, which was purified by column chromatography (silica gel, EtOAc) affording **9a** (0.130 g, 63%) as a brown liquid.

Pyridinol **9a** (0.130 g, 0.628 mmol) was dissolved in THF (10 mL) and NaH (75 mg, 3.12 mmol) was added under an argon atmosphere. Nonafluorobutanesulfonyl fluoride (0.55 mL, 3.04 mmol) was added dropwise at r.t. The mixture was stirred at this temperature for 12 h and quenched by slow addition of H_2O. The resulting product was extracted with Et_2O (3 × 25 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was purified by column chromatography (silica gel, 2–5% EtOAc–hexane) to give **10a** (0.245 g, 80%) as a colorless oil.

IR (neat): 2960–2870 (C–H), 1585–1430 cm^{-1} (C=C).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, *t*-Bu), 3.91 (s, 3 H, OMe), 5.46 (dd, *J* = 10.5, 1.4 Hz, 1 H, $=CH_2$), 6.23 (dd, *J* = 17.2, 1.5 Hz, 1 H, $=CH_2$), 6.70 (dd, *J* = 17.2, 10.5 Hz, 1 H, =CH), 7.03 (s, 1 H, H_{Py}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.2, 38.9 (s, q, *t*-Bu), 61.8 (q, OMe), 112.6 (d, C5), 118.9 (t, $=CH_2$), 135.4 (d, =CH), 146.2, 149.9, 150.2, 164.3 (4 s, C2, C3, C4, C6).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –80.6, –109.5, –120.6, –125.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}F_9NO_4S$: 490.0735; found: 490.0737.

Anal. Calcd for $C_{16}H_{16}F_9NO_4S$ (489.4): C, 39.27; H, 3.30; N, 2.86; S, 6.55. Found: C, 39.67; H, 2.89; N, 2.86; S, 6.61.

(*E*)-2-*tert*-Butyl-3-methoxy-6-(prop-1-enyl)pyridin-4-ol (9b) and (*E*)-2-*tert*-Butyl-3-methoxy-6-(prop-1-enyl)pyridin-4-yl Nonaflate (10b)

According to typical procedure 2, a mixture of enamide **8b** (0.205 g, 0.858 mmol), Et_3N (0.60 mL, 4.30 mmol), and TMSOTf (0.80 mL, 4.30 mmol) in DCE (20 mL) gave **9b** (0.127 g, 67%) as a brown oil.

A mixture of pyridinol **9b** (0.127 g, 0.575 mmol), NaH (70 mg, 2.92 mmol), and NfF (0.500 mL, 2.78 mmol) in THF (10 mL) gave **10b** (0.228 g, 79%) as a colorless oil.

IR (neat): 2960–2870 (C–H), 1660–1400 cm^{-1} (C=C).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 9 H, *t*-Bu), 1.91 (dd, *J* = 6.8, 1.6 Hz, 3 H, =CH*Me*), 3.88 (s, 3 H, OMe), 6.40 (dd, *J* = 15.4, 1.6 Hz, 1 H, =C*H*Me), 6.77 (dd, *J* = 15.4, 6.8 Hz, 1 H, =CH-Py), 6.92 (s, 1 H, H_{Py}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2 (q, Me), 29.3, 38.9 (s, q, *t*-Bu), 61.8 (q, OMe), 111.8 (d, C5), 129.9, 131.7 (2 d, HC=CH), 145.4, 150.0, 150.8, 164.0 (4 s, C2, C3, C4, C6).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{19}F_9NO_4S$: 504.0891; found: 504.0885.

(*E*)-2-*tert*-Butyl-3-methoxy-6-styrylpyridin-4-ol (9c) and (*E*)-2-*tert*-Butyl-3-methoxy-6-styrylpyridin-4-yl Nonaflate (10c)

According to typical procedure 2, a mixture of enamide **8c** (0.219 g, 0.727 mmol), Et_3N (0.50 mL, 3.58 mmol), and TMSOTf (0.65 mL, 3.58 mmol) in DCE (14 mL) gave **9c** (0.130 g, 63%) as a brown oil.

A mixture of pyridinol **9c** (0.130 g, 0.459 mmol), NaH (55 mg, 2.29 mmol), and NfF (0.40 mL, 2.22 mmol) in THF (10 mL) gave **10c** (0.197 g, 76%) as a colorless oil.

IR (neat): 2960–2870 (C–H), 1580–1200 cm^{-1} (C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, *t*-Bu), 3.93 (s, 3 H, OMe), 7.07 (d, *J* = 15.9 Hz, 1 H, =CH-Py), 7.11 (s, 1 H, H_{Py}), 7.29–7.40 (m, 3 H, Ph), 7.56–7.59 (m, 2 H, Ph), 7.64 (d, *J* = 15.9 Hz, 1 H, =CHPh).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.3, 39.1 (s, q, *t*-Bu), 61.9 (q, OMe), 113.2 (d, C5), 126.7, 127.3, 128.5, 128.8, 133.6, 136.5 (5 d, s, Ph, HC=CH), 145.8, 150.0, 150.3, 164.4 (4 s, C2, C3, C4, C6).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –80.5, –109.4, –120.6, –125.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{21}F_9NO_4S$: 566.1048; found: 566.1057.

(*E*)-2-*tert*-Butyl-3-methoxy-6-[2-(thiophen-2-yl)vinyl]pyridin-4-ol (9d) and (*E*)-2-*tert*-Butyl-3-methoxy-6-[2-(thiophen-2-yl)vinyl]pyridin-4-yl Nonaflate (10d)

According to typical procedure 2, a mixture of enamide **8d** (0.220 g, 0.717 mmol), Et_3N (0.50 mL, 3.58 mmol), and TMSOTf (0.650 mL, 3.59 mmol) in DCE (15 mL) gave **9d** (0.115 g, 55%) as a brown oil.

A mixture of pyridinol **9d** (0.115 g, 0.398 mmol), NaH (47 mg, 1.96 mmol), and NfF (0.350 mL, 1.96 mmol) in THF (10 mL) gave **10d** (0.165 g, 72%) as a colorless oil.

IR (neat): 3115–2870 (=CH, C–H), 1630–1290 cm^{-1} (C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, *t*-Bu), 3.92 (s, 3 H, OMe), 6.86 (d, *J* = 15.5 Hz, 1 H, =CH-Py), 7.02–7.04 (m, 1 H, $H_{thienyl}$), 7.03 (s, 1 H, H_{Py}), 7.18 (d, *J* = 3.7 Hz, 1 H, $H_{thienyl}$), 7.26 (d, *J* = 3.7 Hz, 1 H, $H_{thienyl}$), 7.77 (d, *J* = 15.5 Hz, 1 H, =CH-thienyl).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.3, 39.1 (s, q, *t*-Bu), 61.9 (q, OMe), 113.1, 125.7, 125.9, 126.6, 127.9, 128.0, 142.0 (6 d, s, C5, HC=CH, $C_{thienyl}$), 145.8, 149.8, 149.9, 164.5 (4 s, C2, C3, C4, C6).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}F_9NO_4S_2$: 572.0612; found: 572.0612.

(*E*)-2-*tert*-Butyl-6-[2-(furan-2-yl)vinyl]-3-methoxypyridin-4-ol (9e) and (*E*)-2-*tert*-Butyl-6-[2-(furan-2-yl)vinyl]-3-methoxypyridin-4-yl Nonaflate (10e)

According to typical procedure 2, a mixture of enamide **8e** (0.185 g, 0.635 mmol), Et_3N (0.45 mL, 3.23 mmol), and TMSOTf (0.60 mL, 3.24 mmol) in DCE (13 mL) gave **9e** (92 mg, 53%) as a brownish oil.

A mixture of pyridinol **9e** (92 mg, 0.337 mmol), NaH (40 mg, 1.67 mmol), and NfF (0.30 mL, 1.67 mmol) in THF (8 mL) gave **10e** (0.130 g, 70%) as a colorless oil.

IR (neat): 2955–2855 (C–H), 1620–1350 cm^{-1} (C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, *t*-Bu), 3.91 (s, 3 H, OMe), 6.44–6.48 (m, 2 H, H_{furyl}), 6.95 (d, *J* = 15.5 Hz, 1 H, =CH-Py), 7.00 (s, 1 H, H_{Py}), 7.43 (s, 1 H, H_{furyl}), 7.45 (d, *J* = 15.5 Hz, 1 H, =CH-furyl).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.3, 39.1 (s, q, *t*-Bu), 61.9 (q, OMe), 111.0, 111.9, 113.4, 120.9, 124.6, 142.9, 145.7 (6 d, s, C5, HC=CH, C_{furyl}), 149.8, 149.9, 152.8, 164.4 (4 s, C2, C3, C4, C6).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}F_9NO_5S$: 556.0840; found: 556.0851.

(*E*)-3-Methoxy-2-phenyl-6-styrylpyridin-4-ol (9f) and (*E*)-3-Methoxy-2-phenyl-6-styrylpyridin-4-yl Nonaflate (10f)

According to typical procedure 2, a mixture of enamide **8f** (0.195 g, 0.607 mmol), Et_3N (0.425 mL, 3.04 mmol), and TMSOTf (0.55 mL, 3.04 mmol) in DCE (12 mL) gave **9f** (0.152 g, 82%) as a brownish foam.

A mixture of pyridinol **9f** (70 mg, 0.231 mmol), NaH (55 mg, 2.29 mmol), and NfF (0.40 mL, 2.22 mmol) in THF (5 mL) was stirred at r.t. for 3 h to give **10f** (90 mg, 66%) as a colorless oil.

IR (neat): 3010–2890 (C–H), 1575–1380 cm^{-1} (C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.64 (s, 3 H, OMe), 7.16 (d, *J* = 16.0 Hz, 1 H, =CH-Py), 7.22 (s, 1 H, H_{Py}), 7.30–7.41 (m, 3 H, Ph), 7.47–7.54 (m, 3 H, Ph), 7.57–7.59 (m, 2 H, Ph), 7.65 (d, *J* = 16.0 Hz, 1 H, =CHPh), 8.00–8.03 (m, 2 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.6 (q, OMe), 113.3 (d, C5), 126.3, 127.3, 128.6, 128.8, 128.9, 129.1, 129.6, 134.3 (8 d, Ph, HC=CH), 136.2, 136.6 (2 s, Ph), 145.1, 150.1, 152.6, 154.1 (4 s, C2, C3, C4, C6).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –80.4, –109.2, –120.5, –125.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{17}F_9NO_4S$: 586.0735; found: 586.0743.

Anal. Calcd for $C_{24}H_{16}F_9NO_4S$ (585.4): C, 49.24; H, 2.75; N, 2.39; S, 5.48. Found: C, 49.67; H, 2.85; N, 2.43; S, 5.21.

(*E*)-3-Methoxy-6-styryl-2-(thiophen-2-yl)pyridin-4-ol (9g) and (*E*)-3-Methoxy-6-styryl-2-(thiophen-2-yl)pyridin-4-yl Nonaflate (10g)

According to typical procedure 2, a mixture of enamide **8g** (0.210 g, 0.642 mmol), Et_3N (0.45 mL, 3.23 mmol), and TMSOTf (0.60 mL, 3.31 mmol) in DCE (10 mL) gave **9g** (0.135 g, 68%) as a brownish foam.

A mixture of pyridinol **9g** (62 mg, 0.201 mmol), NaH (24 mg, 1.00 mmol), and NfF (0.20 mL, 1.11 mmol) in THF (5 mL) was stirred at r.t. for 3 h to give **10g** (95 mg, 81%) as a pale yellow oil.

IR (neat): 3060–2945 (C–H), 1550–1425 cm^{-1} (C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 3 H, OMe), 7.09 (d, *J* = 16.0 Hz, 1 H, =CH-Py), 7.12 (s, 1 H, H_{Py}), 7.17–7.19 (m, 1 H, $H_{thienyl}$), 7.31–7.42 (m, 3 H, Ph), 7.51 (dd, *J* = 5.0, 1.0 Hz, 1 H, $H_{thienyl}$), 7.59–7.61 (m, 2 H, Ph), 7.68 (d, *J* = 16.0 Hz, 1 H, =CHPh), 8.06–8.07 (m, 1 H, $H_{thienyl}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 61.2 (q, OMe), 112.9 (d, C5), 126.0, 127.4, 128.2, 128.9, 129.1, 129.4, 134.6, 134.7, 136.2, 140.2 (8 d, 2 s, Ph, $C_{thienyl}$, HC=CH), 142.8, 148.5, 150.4, 152.6 (4 s, C2, C3, C4, C6).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –80.4, –109.2, –120.5, –125.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{15}F_9NO_4S_2$: 592.0298; found: 592.0324.

Anal. Calcd for $C_{22}H_{14}F_9NO_4S_2$ (591.5): C, 44.67; H, 2.39; N, 2.37; S, 10.84. Found: C, 44.94; H, 2.39; N, 2.39; S, 10.51.

2-*tert*-Butyl-3-methoxy-4,6-distyrylpyridine (11)

A mixture of pyridinyl nonaflate **10c** (85 mg, 0.150 mmol), $Pd(OAc)_2$ (4 mg, 0.020 mmol), Ph_3P (8 mg, 0.032 mmol), K_2CO_3 (25 mg, 0.181 mmol), and *trans*-styrylboronic acid (27 mg, 0.183 mmol) in DMF (5 mL) was heated at 70 °C for 8 h under an argon atmosphere. The mixture was cooled to r.t., diluted with brine (5 mL), and extracted with Et_2O (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated to dryness. The residue was purified by column chromatography (silica gel, 2% EtOAc–hexane) to give **11** (45 mg, 81%) as a colorless oil.

IR (neat): 3080–2865 (=CH, C–H), 1635–1355 cm^{-1} (C=C).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, *t*-Bu), 3.80 (s, 3 H, OMe), 7.16 (d, *J* = 16.0 Hz, 1 H, =CH-Py), 7.26–7.43 (m, 10 H, Ph), 7.57–7.59 (m, 3 H, Ph, H_{Py}), 7.64 (d, *J* = 16.0 Hz, 1 H, =CHPh).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.8, 38.4 (s, q, *t*-Bu), 62.5 (q, OMe), 117.6 (d, C5), 122.6, 126.9, 127.1, 127.9, 128.3, 128.6, 128.7, 128.8, 128.9, 131.5, 132.5, 136.9, 137.3, 138.5, 148.7, 152.4, 161.5 (10 d, 6 s, Ph, HC=CH, C2, C3, C4, C6).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{28}NO$: 370.2165; found: 370.2183.

Anal. Calcd for $C_{26}H_{27}NO$ (369.5): C, 84.51; H, 7.37; N, 3.79. Found: C, 83.70; H, 7.57; N, 3.63.

4-*tert*-Butyl-5-methoxy-6-methyl-2-vinylpyrimidine (12a); Typical Procedure 3

Enamide **8a** (0.285 g, 1.27 mmol) and NH_4OAc (0.780 g, 10.1 mmol) were placed in an ACE-sealed tube. The mixture was dissolved in MeOH (5 mL) and stirred at 65 °C for 1 d. After addition of H_2O and Et_2O (10 mL) the layers were separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. Column chromatography (silica gel, hexane–EtOAc, 10:1) provided **12a** (0.200 g, 77%) as a colorless oil.

IR (neat): 2955–2885 (C–H), 1555–1365 cm^{-1} (C=C, C=N).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9 H, *t*-Bu), 2.48 (s, 3 H, Me), 3.76 (s, 3 H, OMe), 5.58 (dd, *J* = 10.5, 2.1 Hz, 1 H, $=CH_2$), 6.49 (dd, *J* = 17.3, 2.1 Hz, 1 H, $=CH_2$), 6.78 (dd, *J* = 17.3, 10.5 Hz, 1 H, =CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7 (q, Me), 29.2, 38.0 (s, q, *t*-Bu), 61.1 (q, OMe), 121.9 (t, $=CH_2$), 136.6 (d, =CH), 150.9, 157.5, 159.9, 167.9 (4 s, C2, C4, C5, C6).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{19}N_2O$: 207.1497; found: 207.1496.

(*E*)-4-*tert*-Butyl-5-methoxy-6-methyl-2-(prop-1-enyl)pyrimidine (12b)

According to typical procedure 3, a mixture of enamide **8b** (0.210 g, 0.879 mmol) and NH_4OAc (0.540 g, 7.01 mmol) in MeOH (5 mL) gave **12b** (0.145 g, 75%) as a colorless oil.

IR (neat): 2955–2855 (C–H), 1660–1385 cm^{-1} (C=C, C=N).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 9 H, *t*-Bu), 1.92 (dd, *J* = 5.2, 1.7 Hz, 3 H, =CH*Me*), 2.46 (s, 3 H, Me), 3.74 (s, 3 H, OMe), 6.46–6.51 (m, 1 H, =C*H*Me), 6.97–7.07 (m, 1 H, =CH-Pyr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0 (q, Me), 19.7 (q, =CH*Me*), 29.2, 37.9 (s, q, *t*-Bu), 61.0 (q, OMe), 131.0, 134.9 (2 d, HC=CH), 150.3, 157.92, 159.8, 167.8 (4 s, C2, C4, C5, C6).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{21}N_2O$: 221.1654; found: 221.1680.

(*E*)-4-*tert*-Butyl-5-methoxy-6-methyl-2-styrylpyrimidine (12c)

According to typical procedure 3, a mixture of enamide **8c** (0.510 g, 1.69 mmol) and NH_4OAc (1.04 g, 13.5 mmol) in MeOH (10 mL) gave **12c** (0.405 g, 85%) as a colorless oil.

IR (neat): 3080–2865 (=CH, C–H), 1640–1380 cm^{-1} (C=C, C=N).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9 H, *t*-Bu), 2.52 (s, 3 H, Me), 3.77 (s, 3 H, OMe), 7.17 (d, *J* = 16.0 Hz, 1 H, =CHPh), 7.25–7.31 (m, 1 H, Ph), 7.34–7.38 (m, 2 H, Ph), 7.59–7.61 (m, 2 H, Ph), 7.85 (d, *J* = 16.0 Hz, 1 H, =CH-Pyr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8 (q, Me), 29.2, 38.1 (s, q, *t*-Bu), 61.1 (q, OMe), 127.5, 127.9, 128.6, 128.7 136.3, 136.7 (6 d, s, Ph, HC=CH), 150.5, 157.9, 159.9, 168.0 (4 s, C2, C4, C5, C6).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{23}N_2O$: 283.1810; found: 283.1766.

(*E*)-4-*tert*-Butyl-5-methoxy-6-methyl-2-[2-(thiophen-2-yl)vinyl]pyrimidine (12d)

According to typical procedure 3, a mixture of enamide **8d** (0.225 g, 0.733 mmol) and NH_4OAc (0.450 g, 5.84 mmol) in MeOH (5 mL) gave **12d** (0.145 g, 69%) as a colorless oil.

IR (neat): 2955–2865 (C–H), 1630–1360 cm^{-1} (C=C, C=N).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9 H, *t*-Bu), 2.49 (s, 3 H, Me), 3.76 (s, 3 H, OMe), 6.97 (d, *J* = 16.1 Hz, 1 H, =CH-Pyr), 6.96–7.02 (m, 1 H, $H_{thienyl}$), 7.18 (d, *J* = 3.6 Hz, 1 H, $H_{thienyl}$), 7.24 (d, *J* = 5.8 Hz, 1 H, $H_{thienyl}$), 7.94 (d, *J* = 16.1 Hz, 1 H, =CH-thienyl).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8 (q, Me), 29.2, 38.1 (s, q, *t*-Bu), 61.1 (q, OMe), 126.0, 127.3, 127.8 128.1, 129.1, 142.1 (5 d, s, $C_{thienyl}$, HC=CH), 150.4, 157.6, 159.9, 168.0 (4 s, C2, C4, C5, C6).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{21}N_2OS$: 289.1358; found: 289.1363.

(*E*)-4-*tert*-Butyl-2-[2-(furan-2-yl)vinyl]-5-methoxy-6-methylpyrimidine (12e)

According to typical procedure 3, a mixture of enamide **8e** (0.205 g, 0.704 mmol) and NH_4OAc (0.435 g, 5.64 mmol) in MeOH (5 mL) gave **12e** (0.128 g, 67%) as a colorless oil.

IR (neat): 3115–2870 (=CH, C–H), 1640–1360 cm^{-1} (C=C, C=N).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, *t*-Bu), 2.48 (s, 3 H, Me), 3.75 (s, 3 H, OMe), 6.41 (dd, *J* = 3.4, 1.8 Hz, 1 H, H_{furyl}), 6.48 (d, *J* = 3.4 Hz, 1 H, H_{furyl}), 7.05 (d, *J* = 15.8 Hz, 1 H, =CH-Pyr), 7.42 (d, *J* = 1.8 Hz, 1 H, H_{furyl}), 7.61 (d, *J* = 15.8 Hz, 1 H, =CH-furyl).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8 (q, Me), 29.2, 38.0 (s, q, *t*-Bu), 61.1 (q, OMe), 111.0 111.9, 123.6, 126.2, 143.2, 152.9 (5 d, s, Fu, HC=CH), 150.3, 157.8, 159.9, 167.9 (4 s, C2, C4, C5, C6).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{21}N_2O_2$: 273.1603; found: 273.1599.

(*E*)-5-Methoxy-4-methyl-6-phenyl-2-styrylpyrimidine (12f)

According to typical procedure 3, a mixture of enamide **8f** (0.124 g, 0.386 mmol) and NH_4OAc (0.237 g, 3.08 mmol) in MeOH (4 mL) gave **12f** (98 mg, 84%) as a colorless oil.

IR (neat): 3080–2845 (=CH, C–H), 1635–1390 cm^{-1} (C=C, C=N).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.59 (s, 3 H, Me), 3.53 (s, 3 H, OMe), 7.28 (d, *J* = 16.0 Hz, 1 H, =CHPh), 7.33–7.40 (m, 3 H, Ph), 7.47–7.53 (m, 3 H, Ph), 7.62–7.64 (m, 2 H, Ph), 7.96 (d, *J* = 16.0 Hz, 1 H, =CH-Pyr), 8.10–8.13 (m, 2 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.3 (q, Me), 60.4 (q, OMe), 127.6, 128.6, 128.7, 128.8, 129.2, 130.0, 136.0, 136.5, 136.9, 137.0 (8 d, 2 s, Ph, HC=CH), 149.0, 156.6, 159.5, 161.9 (4 s, C2, C4, C5, C6).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{19}N_2O$: 303.1497; found: 303.1499.

(*E*)-5-Methoxy-4-methyl-2-styryl-6-(thiophen-2-yl)pyrimidine (12g)

According to typical procedure 3, a mixture of enamide **8g** (0.104 g, 0.318 mmol) and NH_4OAc (0.196 g, 2.54 mmol) in MeOH (3 mL) gave **12g** (76 mg, 78%) as a colorless oil.

IR (neat): 3100–2855 (=CH, C–H), 1636–1380 cm^{-1} (C=C, C=N).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.58 (s, 3 H, Me), 3.81 (s, 3 H, OMe), 7.21 (d, *J* = 16.0 Hz, 1 H, =CHPh), 7.18–7.23 (m, 1 H, Ph), 7.29–7.40 (m, 3 H, Ph), 7.55 (dd, *J* = 5.0, 1.0 Hz, 1 H, $H_{thienyl}$), 7.62–7.65 (m, 2 H, Ph, $H_{thienyl}$), 7.93 (d, *J* = 16.0 Hz, 1 H, =CH-Pyr), 8.15–8.16 (m, 1 H, $H_{thienyl}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2 (q, Me), 60.2 (q, OMe), 127.3, 127.6, 128.3, 128.8, 130.4, 130.5, 136.4, 137.1, 137.2, 139.1 (8 d, 2 s, Ph, $C_{thienyl}$, HC=CH), 146.4, 150.9, 159.4, 161.8 (4 s, C2, C4, C5, C6).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}N_2OS$: 309.1062; found: 309.1062.

5-Methoxy-4-methyl-6-phenyl-2-vinylpyrimidine (12h)

According to typical procedure 3, a mixture of enamide **8h** (90 mg, 0.367 mmol), NH_4OAc (0.225 g, 2.92 mmol) in MeOH (3 mL) gave **12h** (45 mg, 55%) as a colorless oil.

IR (neat): 3060–2935 (=CH, C–H), 1560–1380 cm^{-1} (C=C, C=N).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56 (s, 3 H, Me), 3.52 (s, 3 H, OMe), 5.65 (dd, *J* = 10.6, 1.8 Hz, 1 H, =CH_2), 6.56 (dd, *J* = 17.3, 1.8 Hz, 1 H, =CH_2), 6.87 (dd, *J* = 17.3, 10.6 Hz, 1 H, =CH), 7.46–7.48 (m, 3 H, Ph), 8.06–8.08 (m, 2 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2 (q, Me), 60.3 (q, OMe), 122.6 (t, =CH_2), 128.6, 129.1, 129.9, 135.9, 136.4 (4 d, s, Ph, =CH), 149.4, 156.4, 159.0, 161.9 (4 s, C2, C4, C5, C6).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O$: 227.1184; found: 227.1199.

4-*tert*-Butyl-2-(1,2-dihydroxyethyl)-5-methoxy-6-methylpyrimidine (13) and 4-*tert*-Butyl-5-methoxy-6-methylpyrimidine-2-carbaldehyde (14)

To a soln of pyrimidine **12a** (92 mg, 0.447 mmol) in acetone–H_2O (6 mL, 5:1) was added $K_2OsO_4 \cdot 2H_2O$ (16 mg, 0.043 mmol) and solid NMO (0.180 g, 1.54 mmol) at r.t. and the resulting mixture was stirred at r.t. for 6 h. The reaction was quenched by addition of solid Na_2SO_3 (11 mg). Acetone was removed and the resulting product was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4) and evaporated to dryness to give crude diol **13** (69 mg).

Crude diol **13** (69 mg, 0.291 mmol) was dissolved in moist THF (4 mL) and $NaIO_4$ (99 mg, 0.463 mmol) was added at 0 °C; the mixture was stirred for 1 h. The product was extracted with Et_2O (3 × 10 mL) and the combined ether layers were washed with brine (10 mL) and dried (Na_2SO_4). Evaporation of solvent gave the crude product which was purified by column chromatography (silica gel, 10% EtOAc–hexane) to provide **14** (65 mg, 70% after 2 steps) as a pale yellow oil.

IR (neat): 2955–2870 (C–H), 1725 (CHO), 1555–1355 cm^{-1} (C=C, C=N).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, *t*-Bu), 2.58 (s, 3 H, Me), 3.83 (s, 3 H, OMe), 9.96 (s, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.2 (q, Me), 28.9, 38.2 (s, q, *t*-Bu), 61.2 (q, OMe), 153.0, 154.0, 161.6, 169.2 (4 s, C2, C4, C5, C6), 191.3 (d, CHO).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{16}N_2NaO_2$: 231.1109; found: 231.1097.

(*E*)-6-*tert*-Butyl-5-methoxy-2-styrylpyrimidine-4-carbaldehyde (15)

Pyrimidine **12c** (0.205 g, 0.727 mmol) and SeO_2 (0.240 g, 2.16 mmol) were placed in an ACE-sealed tube. The mixture was dissolved in 1,4-dioxane (5 mL) and stirred at 90 °C for 2 d. The black metal residue was filtered of by a small Celite pad and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 15% EtOAc–hexane) to afford **15** (0.174 g, 80%) as a pale yellow oil.

IR (neat): 3080–2830 (=CH, C–H), 1715 (C=O), 1635–1365 cm^{-1} (C=C, C=N).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*-Bu), 3.94 (s, 3 H, OMe), 7.24–7.39 (m, 4 H, Ph), 7.60–7.62 (m, 2 H, Ph, =CH), 7.93 (d, *J* = 16.0 Hz, 1 H, =CH), 10.14 (s, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.9, 38.9 (s, q, *t*-Bu), 67.1 (q, OMe), 126.8, 127.6, 128.8, 129.0, 136.2, 137.7 (5 d, s, Ph, HC=CH), 148.4, 151.7, 158.4, 172.8 (4 s, C2, C4, C5, C6), 192.1 (d, CHO).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{20}N_2NaO_2$: 319.1422; found: 319.1434.

4-*tert*-Butyl-5-methoxy-2,6-distyrylpyrimidine (16)

To a suspension of benzyl(triphenyl)phosphonium bromide (0.780 g, 1.88 mmol) in anhyd Et_2O (10 mL) was added 2.5 M *n*-BuLi in hexanes (0.65 mL, 1.64 mmol) at r.t. The mixture was stirred for 30 min and then the solid residue was allowed to precipitate. The orange-colored ylide soln was then transferred to a soln of aldehyde **15** (97 mg, 0.328 mmol) in anhyd Et_2O (5 mL) kept at 0 °C. The mixture was stirred at 0 °C for 1 h and then the reaction was quenched by addition of sat. aq NH_4Cl soln (5 mL). The aqueous phase was extracted with Et_2O (3 × 20 mL). The combined ether layers were washed with brine (15 mL), dried (Na_2SO_4), and evaporated to dryness. The crude product was subjected to column chromatography (silica gel, 5% EtOAc–hexane) to afford **16** (54 mg, 45%) as a colorless oil.

IR (neat): 3060–2850 (=CH, C–H), 1600–1355 cm^{-1} (C=C, C=N).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, *t*-Bu), 3.84 (s, 3 H, OMe), 7.25–7.43 (m, 8 H, Ph, =CHPh, =CH-Pyr), 7.64–7.69 (m, 4 H, Ph), 7.95 (d, *J* = 16.0 Hz, 1 H, =CHPh), 8.06 (d, *J* = 16.0 Hz, 1 H, =CH-Pyr).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.3, 38.3 (s, q, *t*-Bu), 62.9 (q, OMe), 120.9, 127.6, 127.8, 128.2, 128.6, 128.8, 128.9, 129.1, 136.5, 136.5, 136.5, 136.7 (10 d, 2 s, Ph, HC=CH), 149.3, 155.2, 158.2, 169.4 (4 s, C2, C4, C5, C6).

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{27}N_2O$: 371.2118; found: 371.2170.

(*E*)-*N*-(4-Methoxy-2,2-dimethyl-5-oxohex-3-en-3-yl)but-3-enamide (18)

According to typical procedure 1, a mixture of methoxyallene (2.60 mL, 30.8 mmol), 2.5 M *n*-BuLi in hexanes (11.6 mL, 29.0 mmol), pivalonitrile (1.60 mL, 14.5 mmol), and but-3-enoic acid **17** (4.90 mL, 57.5 mmol) in anhyd Et_2O (50 mL) gave **18** (2.83 g, 82%) as a pale yellow solid; mp 82–85 °C.

IR (KBr): 3320 (NH), 3010–2830 (=CH, C–H), 1685 (C=O), 1550–1380 cm^{-1} (C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 9 H, *t*-Bu), 2.26 (s, 3 H, Me), 2.97–2.99 (m, 2 H, $COCH_2$), 3.49 (s, 3 H, OMe), 5.22–5.27 (m, 2 H, =CH_2), 5.86–5.96 (m, 1 H, =CH), 6.88 (br s, 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5 (q, Me), 28.5, 36.5 (s, q, *t*-Bu), 42.1 (t, CO*C*H_2), 59.1 (q, OMe), 120.5 (t, *C*H_2=CH), 130.9 (d, =CH), 132.6, 150.5 (2 s, C1, C2), 169.9 (s, C1′), 200.7 (s, C3).

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{21}NNaO_3$: 262.1414; found: 262.1416.

2-Allyl-4-*tert*-butyl-5-methoxy-6-methylpyrimidine (19)

According to typical procedure 3, a mixture of enamide **18** (0.425 g, 1.78 mmol) and NH_4OAc (1.10 g, 14.3 mmol) in MeOH (10 mL) gave **19** (0.266 g, 68%) as a colorless oil.

IR (neat): 3080–2865 (=CH, C–H), 1550–1380 cm^{-1} (C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, *t*-Bu), 2.45 (s, 3 H, Me), 3.59–3.61 (m, 2 H, $COCH_2$), 3.72 (s, 3 H, OMe), 5.05–5.16 (m, 2 H, =CH_2), 6.12–6.23 (m, 1 H, =CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6 (q, Me), 29.3, 37.9 (s, q, *t*-Bu), 43.4 (t, CH_2-Pyr), 60.9 (q, OMe), 116.1, 135.6 (t, d, CH_2=CH), 150.3, 160.2, 162.0, 168.1 (4 s, C2, C4, C5, C6).

HRMS: *m/z* [M + H]$^+$ calcd for $C_{13}H_{21}N_2O$: 221.1654; found: 221.1668.

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