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Synthesis of Acrylamides via the Doebner-Knoevenagel Condensation

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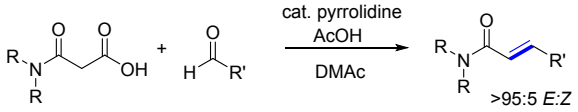
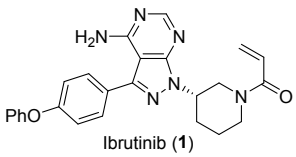
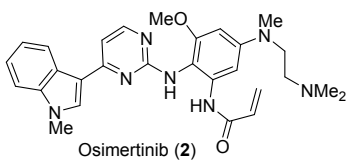
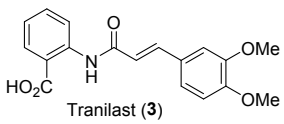


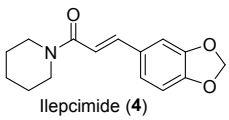
Abstract: A selective synthesis of acrylamides had been developed using the Doebner-Knoevenagel condensation. The reaction occurs under mild conditions at ambient temperatures, tolerates a wide array of functional groups, and affords the *E*-isomer with high selectivity. The reported method expands the scope of this classic reaction to a class of industrially important products, and as well as to the use of aliphatic aldehydes. An organocatalytic mechanism has been proposed, and the ability to scale the process has been demonstrated.

Acrylamides are important pharmaceutical moieties, present in the active pharmaceutical ingredient (API) of oncology products Ibrutinib (**1**) and Osimertinib (**2**),[1] antiallergenic Tranilast (**3**)[2] and the anticonvulsant Ilepcimide (**4**).[3] Ibrutinib and Osimertinib are thought to covalently bind cellular targets via conjugate addition of heteroatom-containing amino acids in the active site.[1]


Ibrutinib (**1**)


Osimertinib (**2**)


Tranilast (**3**)


Ilepcimide (**4**)

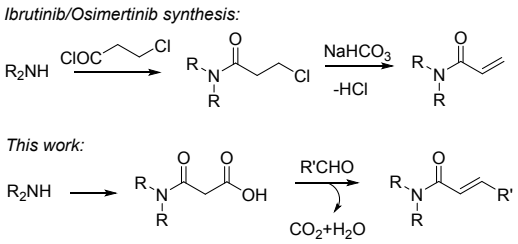
Due to their sensitivity towards conjugate addition, acrylamides are often installed late in a synthesis. This typically involves advanced amine intermediates, and therefore impurities from side reactions divert valuable material and yield away from the desired product. Impurity control is critical to meeting the high purity standards required for pharmaceuticals, and opportunities to reject impurities formed late in a synthesis become scarce. In this context, simple and clean reactions are highly valuable.

Accordingly, there has been recent interest in acrylamide synthesis.[4] Many of the newer contributions are transition metal- catalyzed reactions, whereas metal- free processes are favorable for large- scale pharmaceutical applications due to concerns of cost and the toxicity of heavy metal residues. The commercial syntheses of Ibrutinib[5] and possibly Osimertinib,[6] for example, employ a two- step procedure involving acylation with 3-chloropropionyl chloride, followed by elimination of HCl in a second step.[7] This approach bypasses formation of the acrylamide in the presence of the reacting amine to suppress double addition impurities from conjugate addition of the nucleophilic amine to the electrophilic acrylamide product.[6b, 8] While 3-chloropropionyl chloride is readily available, substituted analogs are not easily obtained, limiting the generality of this approach.[9] Furthermore, this sequence generates a potential genotoxic impurity- the β-chloro-propanamide- whose levels need to be tightly controlled in the final API.[10]

To expand the toolkit for late stage acrylamide formation, we envisioned use of the Doebner-Knoevenagel reaction to form the C=C bond (Scheme 1). Adaptation of this classic reaction to the synthesis of acrylamides has received little attention. Most known examples focus primarily on the formation of secondary cinnamide analogs of tranilast and require high temperatures (refluxing piperidine or toluene).[11] The use of aliphatic aldehydes is rarer still, and the high temperatures employed lead to nearly equal amounts of α,β-and β,γ- unsaturated

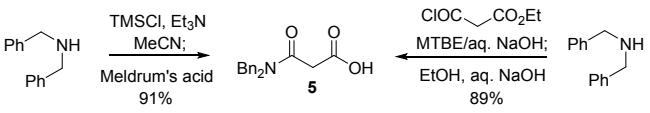
amides.[12,13] The preparation of tertiary acrylamides is essentially unexplored,[13,14] and use of formaldehyde to prepare unsubstituted acrylamides is unknown. For our studies, we focused on mild conditions applicable to challenging aliphatic amine substrates such as that in Ibrutinib, using both aromatic and aliphatic aldehydes.

Scheme 1. Approaches to acrylamide synthesis.



The practicality of this approach relies on the ability to prepare and cleanly isolate the required β-amido acids. To illustrate this feasibility, we prepared **5** as a surrogate for synthetically relevant analogs to the Ibrunitib system.[15] Dibenzylamine was treated with Meldrum's acid, TMSCl and Et_3N[16] to afford **5**, which was isolated as its stable *tert*-butylamine salt (Scheme 2). Alternatively, **5** could be prepared under Schotten-Baumann conditions.

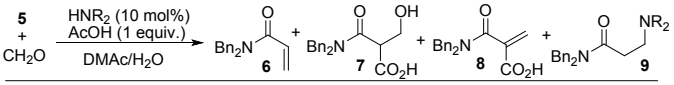
Scheme 2



Screening conditions were inspired by a malonic acid precedent with an aliphatic aldehyde, catalyzed by pyrrolidine in DMAc.[17] Accordingly, we subjected a mixture of **5** and aqueous formaldehyde with secondary amine catalysts in DMAc (Table 1). The results revealed that aldol (**7**) and aldol condensation products (**8**) were possible, along with the catalyst-product adduct (**9**).

We have found that impurities such as **7-9** are readily separated from the desired products, often via extraction into an aqueous phase.

Table 1. Screen of secondary amines for acrylamide formation with aqueous formaldehyde[a]

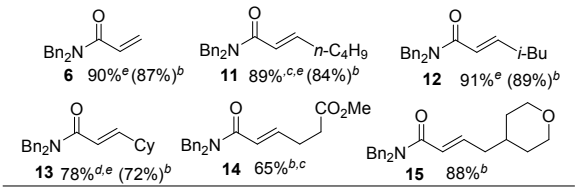


entry	R_2NH	%**5**[a]	%**6**[a]	%**7**[a]	%**8**[a]	%**9**[a]	% yield **6**[b]
1	pyrrolidine	0.3	91.0	0.8	0.2	7.1	86%
2	dibenzylamine	5.3	32.7		49.3	11.6	37%
3	*L*-proline	17.6	28.4		46.2	5.3	28%
4	piperidine	25.0	23.3	25.5		15.0	28%
5	morpholine	4.4	23.3	3.4	25.6	45.6	47%
6	dimethylamine		92.5			7.5	84%

[a] HPLC % area under curve. [b] Assay yields were determined by quantitative dilution of the crude reaction and comparison of the area under the curve to that of an analytically pure authentic product (see Experimental Section)

AcOH (1 equiv.) was included to screening runs to impart robust reactivity, as stalled reactions without this additive reactivated upon addition of AcOH. Of the secondary amines screened, we selected pyrrolidine (**10**) for further development. Application of these conditions to other aliphatic aldehydes was explored (Table 2). Branching at the α- and β- positions of the aldehyde (**6-13**) was tolerated, with little impact on yield. **11** and **14** required slow addition of the aldehyde to minimize self aldol-condensation. In each case, the *E/Z* ratio was determined by HPLC assay of the crude reaction to be ≥95:5.

Table 2. Acrylamide formation from aliphatic aldehydes[a]

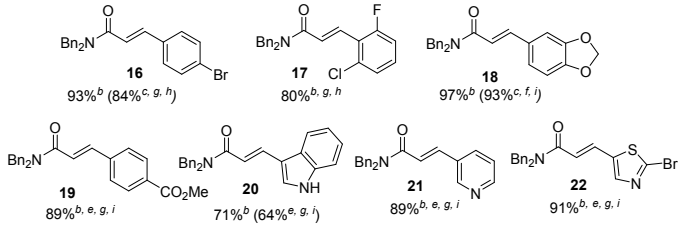


[a] Conditions: 1.0 equiv. of **5** (free acid), 1.5 equiv. aldehyde, 0.15 equiv. pyrrolidine, 1.0 equiv. AcOH, DMAc. [b] Isolated yield after chromatography. [c] Slow addition of aldehyde . [d] 0.3 equiv. of pyrrolidine was utilized. [e] Assay yield from crude reaction (see Experimental Section).

Aldehydes bearing *O*- and *N*- heteroatoms at the α- position afforded the desired products[18] as part of complex mixtures, though these reactions are not synthetically useful.[19] Use of 3-(benzyloxy)-propanal afforded 60% of benzyl alcohol, resulting from elimination of BnOH via an iminium species. Chloral, trifluoroacetaldehyde, pivaldehyde and ethyl glyoxate were unreactive, perhaps due to unfavorable iminium formation.[20]

Aromatic aldehydes were excellent substrates, with high conversion and *E/Z* selectivity (≥95:5) over a wide range of aldehydes (Table 3). Halogen substituents (**16**-**17**, **22**), heterocycles (**18**, **20**-**22**), and electronically diverse motifs were tolerated. The moderate yield of **20** may reflect the iminium stability, as this species was water-stable. Impurities analogous to **7**-**9** were not observed at significant levels.

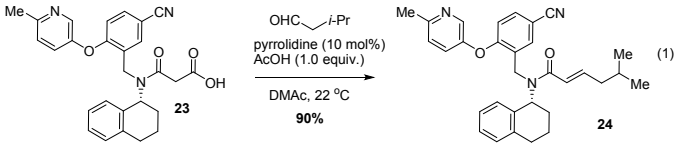
Table 3. Acrylamide formation from aromatic aldehydes[a]

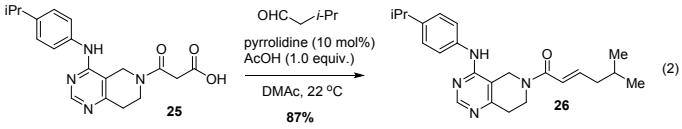


[a] Conditions: 1.0 equiv. of **5** (free acid), 1.2-1.5 equiv. aldehyde, 0.15-0.20 equiv. pyrrolidine, 1.0 equiv. AcOH, DMAc. [b] Assay yields were calculated by addition of the isolated yield (obtained from the unoptimized product crystallization) and the measured losses to the liquors (see Experimental Section) [c] Crystallization from EtOAc/*n*-heptane (unoptimized). [d] Isolated yield after chromatography. [e] Crystallization from DMAc/H_2O during reaction quench (unoptimized). [f] 1.5 equiv. of aldehyde. [g] 1.2 equiv. of aldehyde. [h] 0.15 equiv. pyrrolidine. [i] 0.20 equiv. pyrrolidine.

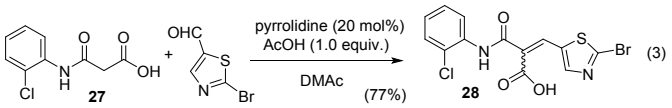
We investigated complex β-amido acids and observed a high degree of functional group compatibility. **23** represents an advanced substrate (eq. 1), and formation of **26** demonstrates the compatibility of the reaction conditions with aminopyrimidine moieties found in Osimertinib. The reaction to form **24** (as a crude 96:4 *E:Z* mixture) contained only one detectable impurity at 0.45

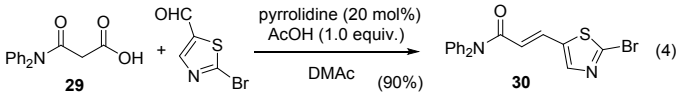
HPLC area % - identified as the pyrrolidine adduct (analogous to **9**)- that was easily extracted from **24** during the workup.[21]





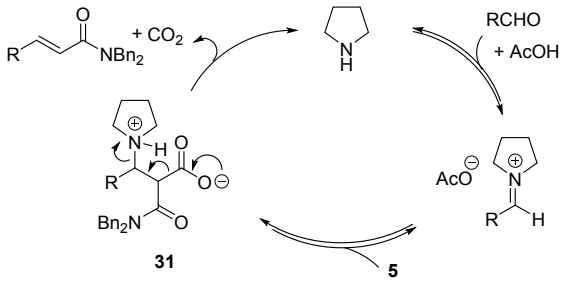
Attempted formation of secondary acrylamides was unsuccessful. For example, **27** reacted with 2-bromo-4-formylthiazole to form a 4:1 mixture of aldol condensation products **28** (eq. 3).[22] Control experiments confirmed that catalytic pyrrolidine was necessary, implying elimination from a Mannich-type intermediate without decarboxylation. By contrast, **29** gave the acrylamide **30** in 90% yield (eq. 4).[23] These results suggest the *N*-H moiety in **27** disrupted the decarboxylation mechanism.



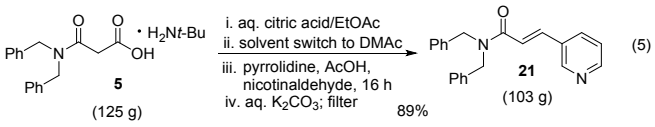


The proposed mechanism involves iminium formation, Mannich-type addition, and a decarboxylative-elimination of **31** (Scheme 3).[24] An intriguing feature is the proposed connection between the stereochemistry of **31** and the resulting double bond geometry. The high selectivity suggests either high diastereoselectivity of **31**, or selective elimination of one of two equilibrating diastereomers.[25, 26]

Scheme 3. Proposed mechanism



The potential to scale this process was explored through a 100 g demonstration (eq. 5). Salt break of **5** (125 g) was followed by a solvent- switch into DMAc. Acetic acid and pyrrolidine were added, followed by nicontinaldehyde. After 16 h, quench with aqueous K_2CO_3 [27] affected product crystallization. Filtration afforded **21** in 89% isolated yield and 99.2% HPLC purity.[28]



In conclusion, we have developed a mild process to prepare acrylamides using the Doebner-Knoevenagel reaction. The method expands the scope of this classic reaction to industrially important acrylamides, and the benign conditions are compatible with highly functionalized substrates, aliphatic aldehydes, and tertiary amides. A decarboxylative elimination mechanism has been proposed, and the potential to scale the reaction demonstrated. This method represents an attractive alternative to existing protocols and offers promise for clean reaction profiles.

Experimental Section:

General. Reagents and solvents were obtained from commercial sources and were used as received. Chromatography was performed using silica gel (70−230 mesh), using reagent grade solvents which were used as received. ^{1}H NMR spectra were recorded using a 300 MHz Bruker Avance spectrometer, using either the $CDCl_3$ resonance (7.26 ppm) or the d_6-dmso resonance (2.50 ppm) as an internal standard. ^{13}C NMR spectra were recorded on a 75 MHz Bruker spectrometer using either the $CDCl_3$ resonance (77.0 ppm) or the d_6-dmso resonance (39.5) ppm as an internal standard measured. High-resolution mass spectrometry (HRMS) was performed using a HPLC-TOFMS mass spectrometer in electrospray ionization (ESI) mode. Melting points were recorded on a TA Instruments Q1000 system which applied a heating ramp of 10 ˚C/min from 30 to 320 ˚C. Melting points are recorded as peak temperatures.

All manipulations were carried out under an inert atmosphere of nitrogen using standard Schlenk techniques unless otherwise noted. All aldehydes and other reagents (dibenzylamine, Meldrum's acid, ethyl malonyl chloride, and solvents) were purchased from commercial sources. HPLC assays were performed using a method with the following conditions: Ascentis Express C18 column; 4.6 mm × 100 mm, 2.7 μm particle size, 40 °C, flow rate of 1.5 mL/min consisting of a mobile phase comprised of MeCN and 0.1% by volume aqueous H_3PO_4; gradient 10% MeCN ramp to 95% MeCN over 5 min, then isocratic 95% MeCN for 2 min, with integration based on spectra recorded at the 210 nm wavelength. Assay yields were determined by quantitative dilution of the crude product stream to a known volume, followed by subjection to HPLC analysis. Comparison of the area under the curve of the diluted sample to that of a sample of known concentration prepared from the analytically pure authentic product allowed calculation of the total amount of the desired product. Alternatively, when the product was isolated via crystallization, the assay yield was determined by combining the mass of the analytically pure isolate with the desired

product lost to the combined liquors (filtered supernatant plus washes). The loss was determined as described above for the assay yield, utilizing a standard prepared from the isolate. An example of assay yield determination is provided for acrylamide **13** and further discussed in the Supporting Information.

2-methylpropan-2-aminium 3-(dibenzylamino)-3-oxopropanoate (5•t-BuNH$_2$) via Meldrum's acid. A flask equipped with an N_2 inlet and a reflux condenser was charged with dibenzylamine (100.0 mmol, 19.7 g, 19.2 mL) and CH_2Cl_2 (300 mL). Et_3N (140.0 mmol, 14.2 g, 19.5 mL) was added, followed by TMSCl (150.0 mL, 16.3 g, 19.0 mL) and the resulting thin slurry was heated to reflux for 30 min. The resulting solution was cooled to T_i = 30-35 °C, and Meldrum's acid (110.0 mmol, 15.8 g) was added in a single portion. After an additional 1 h of stirring at ambient temperature, HPLC assay showed full conversion to the desired product. The reaction was quenched with 1N HCl (180 mL) and the contents were transferred to a separatory funnel. The phases were split and the organic phase was washed with 15% aq. NaCl (100 mL). The phases were split and the organic phase was dried over $MgSO_4$, filtered, and concentrated to an oil under reduced pressure. IPAc (100 mL) was added, and the resulting solution was concentrated to an oil under reduced pressure. The resulting oil was diluted with IPAc (250 mL) and transferred to a flask equipped with an overhead stirrer and an N_2 inlet, with overhead stirring. *t*-BuNH$_2$ (110 mmol, 11.6 mL) was added via syringe pump over 30 min., maintaining T_i = 20-30 °C. The resulting slurry was aged 12 h and was filtered. The wetcake was displaced with IPAc (100 mL). Drying via vacuum suction/N_2 tent afforded 32.54 g (91%) of **5•*t*-BuNH$_2$** as a white solid. Mp = 124.8 ˚C (DSC). ^{1}H NMR (300 MHz, d_6-dmso): δ 7.92 (br s,2H), 7.39-7.16 (m, 10H), 4.54 (s, 2H), 4.44 (s, 2H), 3.12 (s, 2H), 1.22 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, d_6-dmso): δ 170.2, 169.8, 137.8,

137.5, 128.7, 128.2, 127.3, 127.2, 126.7, 126.6, 50.4, 50.2, 47.0, 45.7, 27.4; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{17}H_{18}NO_3$ (free acid) 284.1281; found 284.1281. The combined liquors were adjusted to a volume of 400 mL, and using the isolated product as a reference standard the liquors were assayed to contain 1.25 g of the desired product.

2-methylpropan-2-aminium 3-(dibenzylamino)-3-oxopropanoate (5•t-BuNH$_2$) under Schotten-Baumann conditions. A flask was charged with dibenzylamine (25.35 mmol, 5.0 g, 4.9 mL), MTBE (25.0 mL) and 3N NaOH (25.0 mL), and the resulting stirred solution was cooled to 0-5 ˚C with an external ice bath. Ethyl malonyl chloride (technical grade 5.35 g, 4.55 mL) was added over 1 h via syringe pump. The resulting solution was aged 30 min. at which time HPLC assay showed full conversion of Bn_2NH. The reaction mixture was warmed to ambient temperature and diluted with EtOH (15 mL) and 5N NaOH (20 mL) and stirred for 5 h. After HPLC confirmed full conversion of the intermediate ester, 6N HCl (25 mL) was added so as to adjust the reaction pH to 2.5. The biphasic mixture was transferred to a separatory funnel and the phases were split. The organic phase was washed with 15% aq. NaCl (10 mL), then dried over $MgSO_4$. The MTBE stream was filtered and concentrated under reduced pressure. IPAc (50 mL) was added, and the resulting solution was concentrated under reduced pressure. The resulting oil was diluted with IPAc (50 mL) and transferred to a 100 mL three neck flask equipped with overhead stirring and seeded with **5**•*t*-BuNH$_2$ (20 mg). *t*-BuNH$_2$ (27.5 mmol, 2.9 mL) was added via syringe pump over 1.5 h and the resulting slurry was aged for 16 h. The slurry was filtered, and the cake was displaced with IPAc (20 mL). Drying via vacuum suction/N_2 tent afforded 7.98 g of **5**•*t*-BuNH$_2$ (89%).

Representative procedure for acrylamide formation utilizing slow addition of the aldehyde (Table 1, entries 2 and 5). The *t*-BuNH$_2$ salt of **5** (1.07 g, 3.0 mmol) was slurried in EtOAc (10 mL), to which was added 15 wt% aqueous citric acid (8 mL). After stirring for 0.5-1 h, the biphasic

mixture was transferred to a separatory funnel. The phases were separated, and the aqueous phase was back extracted with EtOAc (5 mL). The combined organic phases were washed with 15 wt% aq. NaCl (5 mL), then dried over $MgSO_4$, filtered, and concentrated to an oil. The oil was dissolved in DMAc (4 mL), to which was added pyrrolidine (25 μL, 0.3 mmol) and AcOH (171 μL, 3.0 mmol). The resulting solution was stirred at T_i = 22 ˚C while a solution of the aldehyde (4.5 mmol) in DMAc (1-2 mL) was added over 6-10 h via syringe pump. Upon completion of the addition, the solution was aged for 16-18 hours, at which point HPLC assay confirmed >95% conversion of **5**. The reaction was quenched by the addition of H_2O (8 mL), and the product was extracted with EtOAc (8 mL). The mixture was transferred to a separatory funnel and the phases were separated. The aqueous phase was back extracted with EtOAc (6 mL). The combined organic phases were washed with 10 wt% aq. LiCl (4 mL), then dried over $MgSO_4$, and subsequently filtered. The solution was diluted to a specified volume with EtOAc in a volumetric flask for assay yield determination, and/or was concentrated to an oil and purified by silica gel chromatography.

Representative procedure for acrylamide formation with aldehydes under standard batch conditions (Table 1, entries 1, 3, 4, and 6). The *t*-$BuNH_2$ salt of **5** (1.07 g, 3.0 mmol) was slurried in EtOAc (10 mL), to which was added 15 wt% aqueous citric acid (8 mL). After stirring for 0.5-1 h, the biphasic mixture was transferred to a separatory funnel. The phases were separated and the aqueous phase was back extracted with EtOAc (5 mL). The combined organic phases were washed with 15 wt% aq. NaCl (5 mL), then dried over $MgSO_4$, filtered, and concentrated to an oil. The oil was dissolved in DMAc (4 mL), to which was added pyrrolidine (38 μL, 0.45 mmol), AcOH (171 μL, 3.0 mmol), and the aldehyde (4.5 mmol). The resulting solution was stirred at T_i = 22 ˚C while a solution of the aldehyde (4.5 mmol) in DMAc (1 mL) was added over 6-10 h via syringe pump. Upon completion of the addition, the solution was aged for 12-16 hours, at which

point HPLC assay confirmed >95% conversion of **5**. The reaction was quenched by the addition of H_2O (8 mL), and the product was extracted with EtOAc (8 mL). The mixture was transferred to a separatory funnel and the phases were separated. The aqueous phase was back extracted with EtOAc (6 mL). The combined organic phases were washed with 10 wt% aq. LiCl (4 mL), then dried over $MgSO_4$, filtered, and concentrated to an oil. The solution was diluted to a specified volume with EtOAc in a volumetric flask for assay yield determination, and/or was concentrated to an oil and purified by silica gel chromatography.

***N,N*-dibenzylacrylamide (6).** Performed according to the standard batch mode procedure. The final solution was diluted to 25 mL total in a volumetric flask, and a 100 μL aliquot was diluted to 10 mL total in a volumetric flask and injected onto the HPLC method. The area count (1903151) was compared to that of a previously prepared standard from material isolated by silica gel chromatography (1713322 area counts, corresponding to 12.36 mg/50 mL) to show 675 mg of **6** (90% assay yield). The EtOAc solution was concentrated to an oil and purified via silica gel chromatography (eluting with EtOAc/hexanes, 0 to 20% EtOAc/hexanes gradient) to afford **6** as a clear, colorless oil (656 mg). ^{1}HNMR (300 MHz, d_6-dmso): δ 7.40 (m, 10 H), 6.79 (dd, J_1 = 16.6 Hz, J_2 = 10.3 Hz, 1 H), 6.26 (dd, J_1 = 16.6 Hz, J_2 = 2.5 Hz, 1 H), 5.72 (dd, J_1 = 10.3 Hz, J_2 = 2.5 Hz, 1 H), 4.62 (s, 2H), 4.56 (s, 2H). ^{13}C{^{1}H} NMR (75 MHz, d_6-dmso): δ 165.9, 137.5, 137.5, 128.6, 128.4, 128.4, 128.2, 127.7, 127.3, 127.1, 126.5, 49.8, 48.5. This was consistent with published data.[29]

***(E)-N,N*-dibenzylhept-2-enamide (11).** Performed under the slow aldehyde addition procedure conditions. A solution of the aldehyde in DMAc (2 mL) was added over 10 h via syringe pump. The final solution was diluted to 50 mL total in a volumetric flask, and a 200 μL aliquot was diluted to 10 mL total in a volumetric flask and injected onto the HPLC method. The area count (2198687 for the *E* isomer, 65807 for the *Z* isomer) was compared to that of a previously prepared standard from material isolated by silica gel chromatography (1,979,577 area counts as a 99.8:0.2 HPLC ratio, corresponding to 16.80 mg/50 mL) to show 825 mg of **11** *E* isomer as part of a 97:3 HPLC ratio of isomers (89% assay yield). The EtOAc solution was concentrated to an oil and purified via silica gel chromatography (eluting with EtOAc/hexanes, 0 to 15% EtOAc/hexanes gradient) to afford **11** as a clear, colorless oil (770 mg). ^{1}H NMR (300 MHz, d_6-dmso): δ 7.41-7.13 (m, 10H), 6.81 (dt, J_1 = 15.1 Hz, J_2 = 7.3 Hz, 1H), 6.44 (dt, J_1 = 15.1 Hz, J_2 = 1.5 Hz, 1H), 4.60 (2, 2H), 4.54 (s, 2H), 2.15 (dd, $J_1 = J_2$ = 7.3 Hz, 2H), 1.41-1.16 (m, 4H), 0.83 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, d_6-dmso): δ 166.5, 146.8, 138.3, 138.2, 129.1, 128.9, 128.2, 127.7, 127.5, 127.0, 121.2, 50.3, 48.9, 31.7, 30.4, 22.1, 14.1; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{21}H_{26}NO$ 308.2009; found 308.2020.

***(E)-N,N*-dibenzyl-5-methylhex-2-enamide (12).** Performed on a 2.0 mmol scale according to the standard batch mode procedure. The final solution was diluted to 25 mL total in a volumetric flask, and a 150 μL aliquot was diluted to 10 mL total in a volumetric flask and injected onto the HPLC method. The area count (2316148 for the *E* isomer, 77631 for the *Z* isomer) was compared to that of a previously prepared standard from material isolated by silica gel chromatography (2128251 area counts, corresponding to 15.50 mg/50 mL) to show 562 mg of **12** *E* isomer as part of a 97:3 HPLC ratio of isomers (90% assay yield). The EtOAc solution was concentrated to an oil and purified via silica gel chromatography (eluting with EtOAc/hexanes, 0 to 20%

EtOAc/hexanes gradient) to afford **12** as a clear, colorless oil (544 mg). ^{1}H NMR (300 MHz, d_6-dmso): δ 7.42-7.14 9 (m, 10H), 6.79 (dt, J_1 = 14.9 Hz, J_2 = 7.5 Hz, 1H), 6.44 (dt, J_1 = 14.9 Hz, J_2 = 1.4 Hz, 1H), 4.60 (s, 2H), 4.54 (s, 2H), 2.04 (dd, $J_1 = J_2$ = 7.4 Hz, 2H), 1.67 (sept., J = 6.7 Hz, 1H), 0.82 (d, J = 6.7 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, d_6-dmso): δ 166.5, 145.4, 138.3, 138.2, 129.1, 128.9, 128.2, 127.7, 127.5, 127.2, 127.0, 122.3, 50.3, 48.9, 41.3, 27.8, 22.6; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{21}H_{26}NO$ 308.2009; found 308.2022.

***(E)-N,N*-dibenzyl-3-cyclohexylacrylamide (13). 5•*t*-BuNH$_2$** (2.0 mmol, 713 mg) was slurried in EtOAc (8 mL), to which was added 15% aq. citric acid (6 mL). After 20 min., the biphasic mixture was transferred to a separatory funnel and the phases were split and both were retained. The aqueous was extracted with EtOAc (4 mL) and the aqueous phase was discarded. The combined organic phases were washed with 15% aq. NaCl (5 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to an oil. The oil was dissolved in DMAc (3.5 mL), to which was added pyrrolidine (0.6 mmol, 50 μL) followed by AcOH (2.0 mmol, 114 μL) and cyclohexanecarboxaldehyde (3.0 mmol, 364 μL). After 36 h, H_2O (7 mL) was added, followed by EtOAc (6 mL). The biphasic mixture was transferred to a separatory funnel and the phases were split and both were retained. The aqueous phase was extracted with EtOAc (4 mL) and the aqueous phase was discarded. The combined org phases were washed with 10 wt% aq. LiCl (2 x 4 mL). The organic phase was dried over $MgSO_4$, filtered, then diluted (with EtOAc) to 25 mL total in a volumetric flask. A 150 μL aliquot was diluted to 10 mL in a volumetric flask and injected onto the described HPLC assay. Comparison of the area under the curve (1,934,035 area counts as a 97:3 HPLC ratio of olefin isomers) to that of a previously prepared standard from material isolated by silica gel chromatography (2,145,831 area counts as a 99.8:0.2 HPLC ratio, corresponding to 16.80 mg/50 mL) showed 20.76 mg/mL, or 519 mg total of **13** (78% AY) which, after purification

via silica gel chromatography (eluting with EtOAc/hexanes, 0 to 20% EtOAc/hexanes gradient) was isolated as a white solid (478 mg). Mp = 81.6 ˚C (DSC); ^{1}H NMR (300 MHz, d_6-dmso): δ 7.42-7.13 (m, 10H), 6.75 (dd, J_1 = 15.2 Hz, J_2 = 7.0 Hz, 1H), 6.36 (d, J = 15.2 Hz, 1H), 4.60 (s, 2H), 4.54 (s, 2H), 2.20-2.01 (m, 1H), 1.72-1.54 (m, 5H), 1.31-0.98 (m, 5H); ^{13}C{^{1}H} NMR (75 MHz, d_6-dmso): δ 166.7, 151.7, 138.3, 138.2, 129.1, 128.9, 128.3, 127.7, 127.5, 127.0, 118.9, 50.3, 48.9, 40.3, 32.0, 25.6; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{23}H_{28}NO$ 334.2165; found 334.2177.

Methyl *(E)*-6-(dibenzylamino)-6-oxohex-4-enoate (14). Performed under the slow aldehyde addition procedure conditions. A solution of the aldehyde in DMAc (2 mL) was added over 10 h via syringe pump. Following silica gel chromatography (eluting with EtOAc/hexanes, 0 to 20% EtOAc/hexanes gradient), the product was isolated as an oil (650 mg, 65% yield). ^{1}H NMR (300 MHz, d_6-dmso): δ 7.41-7.14 (m, 10H), 6.81 (dt, J_1 = 15.2 Hz, J_2 = 6.3 Hz, 1H), 6.50 (d, J = 15.2 Hz, 1H), 4.49 (s, 2H), 4.52 (s, 2H), 3.54 (s, 3H), 2.47-2.36 (m, 4H); ^{13}C{^{1}H} NMR (75 MHz, d6-dmso): δ 172.4, 165.8, 144.5, 137.7, 137.5, 128.6, 128.4, 127.7, 127.2, 127.0, 126.6, 121.2, 51.3, 49.7, 48.3, 31.9, 26.8; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{21}H_{24}NO_3$ 338.1751; found 338.1759.

***(E)*-*N*,*N*-dibenzyl-4-(tetrahydro-2H-pyran-4-yl)but-2-enamide (15).** Performed according to the standard batch mode procedure. Following silica gel chromatography (eluting with EtOAc/hexanes, 0 to 20% EtOAc/hexanes gradient), the product was isolated as an oil (926 mg). ^{1}H NMR (300 MHz, d_6-dmso): δ 7.39-7.13 (m, 10H), 6.76 (dt, J_1 = 15.0 Hz, J_2 = 7.4 Hz, 1H), 6.45 (d, J = 15.0 Hz, 1H), 4.60 (s, 2H), 4.56 (s, 2H), 6.76 (dd, J_1 = 11.6 Hz, J_2 = 4.3 Hz, 2H,), 3.21 (dt, J_1 = 11.6 Hz, J_2 = 1.9 Hz, 2H), 2.08 (dd, J_1 = J_2 = 7.1 Hz, 2H), 1.64-1.50 (m, 1H), 1.48-1.38 (m,

1H), 1.07 (ddd, J_1 = , J_2 = 7.1 Hz, J_3 = 7.1 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, d_6-dmso): δ 166.4, 144.4, 138.3, 129.1, 128.9, 128.2, 127.6, 127.6, 127.0, 122.8, 67.3, 50.4, 49.1, 34.4, 32.8 ; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{23}H_{28}NO_2$ 350.2115; found 350.2125.

Representative procedure for acrylamide formation with aromatic aldehydes (Table 2). The same procedure was utilized as that for standard batch mode in Table 1. **5**•*t*-$BuNH_2$ (3.0 mmol, 1.07 g) was slurried in EtOAc (10 mL), to which was added 15% aq. citric acid (8 mL). After 30 min., the biphasic mixture was transferred to a separatory funnel and the phases were split and both were retained. The aqueous was extracted with EtOAc (2 mL) and the aqueous phase was discarded. The combined organic phases were washed with 15% aq. NaCl (5 mL), then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to an oil. The oil was dissolved in DMAc (5.0 mL), to which was added pyrrolidine (0.45-0.60 mmol) and AcOH (3.0 mmol, 171 μL), followed by the aldehyde (3.6-4.5 mmol). A combination of chromatography and crystallization was applied for product isolation depending on the substrate, as illustrated below.

***(E)*-*N*,*N*-dibenzyl-3-(4-bromophenyl)acrylamide (16).** The standard procedure was implemented with pyrrolidine (0.45 mmol, 38 μL) and and 4-bromobenzaldehyde (3.6 mmol, 555 mg). After 16 h, H_2O (10 mL) was added, followed by MTBE (12 mL). The biphasic mixture was transferred to a separatory funnel and the phases were split and both were retained. The aqueous phase was extracted with MTBE (3 mL) and the resulting aqueous phase was discarded. The combined organic phases were diluted with EtOAc (10 mL) in order to dissolve product solids, and the resulting organic phase was washed with 10% aq. LiCl (2 x 5 mL), followed by 15% aq. NaCl (5 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a solid. MTBE (2 mL) was added and the resulting slurry was stirred magnetically for 30 min. *n*-Heptane (10 mL) was then added via syringe pump over 1 h. After an additional 1 h, the

slurry was filtered. The cake was displaced with 5:1 *n*-heptane:MTBE (3 mL), then *n*-heptane (3 mL). Drying via vacuum suction/N_2 tent afforded 1.02 g of **17** (83.7%) as a white solid. Mp = 124.7 ˚C (DSC); ^{1}H NMR (300 MHz, d_6-dmso): δ 7.69-7.54 (m, 5H), 7.42-7.18 (m, 11H), 4.77 (s, 2H), 4.59 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, d_6-dmso): δ 165.9, 141.1, 137.8, 137.6, 134.3, 131.7, 130.0, 128.7, 128.4, 127.7, 127.3, 127.1, 126.8, 122.9, 119.1, 49.9, 48.5; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{23}H_{21}BrNO$ 406.0801; found 406.0797. Using the isolated product as a standard, the combined liquors were diluted to 25 mL in a volumetric flask and assayed for loss of 4.453 mg/mL (111 mg total, 9.1%). Thus, assay yield was 1.131g (92.8%).

***(E)-N,N*-dibenzyl-3-(2-chloro-6-fluorophenyl)acrylamide (17).** The standard procedure was implemented with pyrrolidine (0.45 mmol, 38 μL) and AcOH (3.0 mmol, 171 μL) and 2-chloro-6-fluorobenzaldehyde (3.6 mmol, 571 mg). After 48 h, H_2O (10 mL) was added, followed by EtOAc (8 mL). The biphasic mixture was transferred to a separatory funnel and the phases were split and both were retained. The aqueous phase was extracted with EtOAc (4 mL) and the resulting aqueous phase was discarded. The combined organic phases were washed with 10% aq. LiCl (2 x 5 mL), followed by 15% aq. NaCl (5 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to an oil. The oil was purified via silica gel chromatography (0 to 15% EtOAc/Hexanes) afforded 915 mg of **17** as an oil (80.3%) that solidified to a white solid upon standing. Mp = 83.9 ˚C (DSC); ^{1}H NMR (300 MHz, d_6-dmso): δ 7.71 (d, J = 15.8 Hz, 1H), 7.46-7.21 (m, 13H), 7.20 (d, J = 15.8 Hz, 1H), 4.70 (s, 2H), 4.67 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, d_6-dmso): δ 165.6, 160.8 (d, $J_{C\text{-}F}$ = 254 Hz), 137.5 (d, $J_{C\text{-}F}$ = 2.5 Hz), 134.4 (d, $J_{C\text{-}F}$ = 5.0 Hz), 131.6, 131.3, 131.1, 128.7, 128.5, 127.9, 127.3, 127.2, 126.5, 126.1 (d, $J_{C\text{-}F}$ = 2.6 Hz), 125.4 (d, $J_{C\text{-}F}$ = 12.0 Hz), 121.5 (d, $J_{C\text{-}F}$ = 14.3 Hz), 115.3 (d, $J_{C\text{-}F}$ = 23.5 Hz), 50.1, 49.2; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{23}H_{20}ClFNO$ 380.1212; found 380.1218.

***(E)-3*-(benzo[d][1,3]dioxol-5-yl)-N,N-dibenzylacrylamide (18).** The standard procedure was implemented with pyrrolidine (0.60 mmol, 50 μL) and AcOH (3.0 mmol, 171 μL) and piperonal (4.5 mmol, 676 mg). After 16 h, H_2O (10 mL) was added, followed by EtOAc (8 mL). The biphasic mixture was transferred to a separatory funnel and the phases were split and both were retained. The aqueous phase was extracted with EtOAc (4 mL) and the resulting aqueous phase was discarded. The combined organic phases were washed with 10% aq. LiCl (2 x 5 mL), followed by 15% aq. NaCl (5 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to 3 mL total volume (containing ~ 2 mL EtOAc). The resulting solution was stirred and *n*-heptane (2 mL) was added, resulting in the formation of a seed bed. Additional *n*-heptane (10 mL) was added via syringe pump over 1 h, followed by an additional 1 h of stirring. The slurry was filtered, and the cake was displaced with 1:6 EtOAc:*n*-heptane (3.5 mL), then *n*-heptane (3.5 mL). Drying via vacuum suction/N_2 tent afforded 1.03 g of **18** (93%). Mp = 123.6 ˚C (DSC); ^{1}H NMR (300 MHz, d_6-dmso): δ 7.56 (d, J = 15.5 Hz, 1H), 7.42-7.10 (m, 13H), 6.92 (d, J = 8.0 Hz, 1H), 6.05 (s, 2H), 4.75 (s, 2H), 4.58 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, d_6-dmso): δ 166.3, 148.6, 147.9, 142.3, 138.0, 137.8, 129.5, 128.6, 128.4, 127.7, 127.2, 127.0, 126.8, 124.3, 116.0, 108.3, 106.6, 101.4, 49.7, 48.4; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{24}H_{22}NO_3$ 372.1594; found 372.1594. Using the isolated product as a standard, the combined liquors were diluted to 25 mL in a volumetric flask and assayed for loss of 46 mg total, (4.1%). Thus, assay yield was 1.076 g (97%).

Methyl *(E)*-4-(3-(dibenzylamino)-3-oxoprop-1-en-1-yl)benzoate (19). The standard procedure was implemented with pyrrolidine (0.60 mmol, 50 μL) and AcOH (3.0 mmol, 171 μL) and methyl-4-formylbenzoate (3.6 mmol, 591 mg). After 16 h, HPLC assay showed full conversion of **5**. H_2O (3 mL) was added, resulting in crystallization of the product. After stirring

for an additional 3.5 h, the slurry was filtered and the cake was displaced with 1:1 DMAc:H_2O (3 mL), followed by H_2O (3 mL). Drying via vacuum suction/N_2 tent afforded 1.02 g of **19** (88.5%). Mp = 119.4 ˚C (DSC); ^{1}H NMR (300 MHz, d_6-dmso): δ 7.94 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 15.4 Hz, 1H), 7.47-7.20 (m, 11H), 4.79 (s, 2H), 4.59 (s, 2H), 3.85 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, d_6-dmso): δ 165.8, 141.0, 139.6, 137.8, 137.6, 130.1, 129.5, 128.7, 128.5, 128.3, 127.8, 127.3, 127.1, 126.8, 120.9, 52.2, 49.9, 48.6; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{25}H_{24}NO_3$ 386.1751; found 386.1748. Using the isolated product as a standard, the combined liquors were diluted to 25 mL in a volumetric flask and assayed for loss of 4.4 mg total, (0.4%). Thus, assay yield was 1.024 g (89%).

***(E)-N,N*-dibenzyl-3-(1H-indol-3-yl)acrylamide (20).** The standard procedure was implemented with pyrrolidine (0.60 mmol, 50 μL) and AcOH (3.0 mmol, 171 μL) and Indole-3-carboxaldehyde (3.6 mmol, 540 mg of 97% reagent). After 8 days, H_2O (10 mL) was added, followed by EtOAc (8 mL). The biphasic mixture was transferred to a separatory funnel and the phases were split and both were retained. The aqueous phase was extracted with EtOAc (4 mL) and the resulting aqueous phase was discarded. The combined organic phases were washed with 10% aq. LiCl (2 x 5 mL), followed by 15% aq. NaCl (5 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to 2 mL total volume (containing ~ 1 mL EtOAc), which resulted in the formation of a slurry. MTBE (10 mL) was added over several minutes, and the resulting slurry was stirred for 2 h. The slurry was filtered, and the cake was displaced with MTBE (3 mL). Drying via vacuum suction/N_2 tent afforded 700 mg of **20** (63.7%). Mp = 202.0 ˚C (DSC); ^{1}H NMR (300 MHz, d_6-dmso): δ 11.61 (s, 1H), 7.85 (d, J = 15.3 Hz, 1H), 7.84 (d, J = 2.8 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.44-7.23 (m, 11H), 7.15 (dd, $J_1 = J_2$ = 7.5 Hz, 1H), 7.04 (dd, $J_1 = J_2$ = 7.5 Hz, 1H), 6.86 (d, J = 15.3 Hz, 1H), 4.75 (s, 2H), 4.69 (s, 2H); ^{13}C{^{1}H}

NMR (75 MHz, d_6-dmso): δ 167.2, 138.5, 138.3, 137.3, 136.7, 130.6, 128.7, 128.4, 127.8, 127.2, 127.0, 126.6, 124.9, 122.2, 120.5, 119.8, 112.4, 112.2, 111.6, 50.3, 49.1; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{25}H_{23}N_2O$ 367.1805; found 367.1801. Using the isolated product as a standard, the combined liquors were diluted to 25 mL in a volumetric flask and assayed for loss of 81 mg total, (7.4%). Thus, assay yield was 781 mg (71%).

***(E)-N,N*-dibenzyl-3-(pyridin-3-yl)acrylamide (21).** The standard procedure was implemented with pyrrolidine (0.60 mmol, 50 μL) and AcOH (3.0 mmol, 171 μL) and Indole-3-carboxaldehyde (3.6 mmol, 386 mg, 338 μL). After 16 h, a solution of K_2CO_3 (3.0 mmol, 415 mg) dissolved in H_2O (10 mL) was added via syringe pump over 1 h, resulting in crystallization of the product. After stirring for an additional 12 h, the slurry was filtered and the cake was displaced with 1:2 DMAc:H_2O (3 mL), followed by H_2O (2 mL). Drying via vacuum suction/N_2 tent afforded 880 mg of **21** (89.3%). Mp = 167.7 ˚C (DSC); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, J = 15.5 Hz, 1H), 7.73 (dt, J_1 = 8.0 Hz, J_2 = 2.0 Hz, 1H), 7.44-7.17 (m, 11H), 6.95 (d, J = 15.5 Hz, 1H), 4.73 (s, 2H), 4.61 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.3, 150.2, 149.2, 139.9, 136.9, 136.3, 134.1, 130.7, 128.9, 128.5, 128.2, 127.7, 127.4, 126.3, 123.4, 119.3, 50.0, 48.8; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{22}H_{21}N_2O$ 329.1648; found 329.1651. No product was detected in the filtrates.

***(E)-N,N*-dibenzyl-3-(2-bromothiazol-5-yl)acrylamide (22)**: The standard procedure was implemented with pyrrolidine (0.60 mmol, 50 μL) and AcOH (3.0 mmol, 171 μL) and 2-bromo-4-formylthiazole (3.6 mmol, 691 mg). After 16 h, HPLC assay showed full conversion of **5**. H_2O (1 mL) was added, resulting in crystallization of the product. Additional H_2O (4 mL) over 30 min.,

followed by 2 h of stirring. The slurry was filtered and the cake was displaced with 1:1 DMAc:H_2O (4 mL), followed by H_2O (4 mL). Drying via vacuum suction/N_2 tent afforded 1.13 g of **22** (91%). Mp = 138.6 ˚C (DSC); ^{1}H NMR (300 MHz, d_6-dmso): δ 8.06 (s, 1H), 7.60 (d, J = 15.0 Hz, 1H), 7.42-7.18 (m, 10H), 7.17 (d, J = 15.0 Hz, 1H), 4.70 (s, 2H), 4.6 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, d_6-dmso): δ 165.9, 151.9, 137.6, 137.4, 137.2, 133.9, 128.8, 128.5, 127.7, 127.3, 127.1, 126.6, 126.5, 120.1, 49.9, 48.7; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{20}H_{18}BrN_2OS$ 413.0318; found 413.0315. No product was detected in the filtrates.

***(R)*-3-((5-cyano-2-((6-methylpyridin-3-yl)oxy)benzyl)(1,2,3,4-tetrahydronaphthalen-1-yl)amino)-3-oxopropanoic acid (23).** A mixture of 3-formyl-4-((6-methylpyridin-3-yl)oxy)benzonitrile[30] (1.4 mmol, 335 mg) and DMAc (2.0 mL) was treated with (R)-1,2,3,4-tetrahydronaphthalen-1-amine (1.68 mmol, 255 mg), followed by AcOH (2.80 mmol, 160 μL). After stirring at ambient temperature for 1 h, $NaBH(OAc)_3$ (4.2 mmol, 900 mg) was added as a solid. The resulting slurry was aged 16 h at ambient temperature. The reaction was quenched with H_2O (4 mL), and the pH of the resulting solution was adjusted from 4.5 to 8.5 with NH_4OH. The product was extracted with CH_2Cl_2 (2 x 5 mL). The resulting organic solution was washed with saturated aqueous NaCl (3 mL), then dried over $MgSO_4$, filtered, and concentrated to an oil. Silica gel chromatography (gradient 0 to 55% EtOAc/Heptane) afforded 373 mg of (*R*)-4-((6-methylpyridin-3-yl)oxy)-3-(((1,2,3,4-tetrahydronaphthalen-1-yl)amino)methyl)benzonitrile as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, J = 2.8 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.47 (dd, J_1 = 8.5 Hz, J_2 = 2.1 Hz, 1H), 7.35-7.28 (m, 1H), 7.25-7.06 (m, 5H), 6.76 (d, J = 8.5 Hz, 1H), 4.05 (d, J = 14.6 Hz, 1H), 3.97 (d, J = 14.6 Hz, 1H), 3.84 (dd, $J_1 = J_2$ = 4.8 Hz, 1H), 2.89-2.67 (m, 2H), 2.59 (s, 3H), 2.06-1.87 (m, 3H), 1.81-1.69 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 159.0,

155.2, 149.8, 141.6, 138.9, 137.7, 134.1, 132.9, 132.5, 129.3, 128.8, 127.7, 127.0, 126.0, 124.2, 118.9, 116.5, 106.9, 77.6, 77.1, 76.7, 55.4, 45.3, 29.4, 28.4, 23.9, 19.1; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{24}H_{23}N_3O$ 370.1914; found 370.1901.

The intermediate amine- (*R*)-4-((6-methylpyridin-3-yl)oxy)-3-(((1,2,3,4-tetrahydronaphthalen-1-yl)amino)methyl)benzonitrile- (0.5 mol, 185 mg) was dissolved in CH_2Cl_2 (3 mL). Et_3N (100 μL, 0.7 mmol) was added, followed by TMSCl (95 μL, 0.75 mmol) and the resulting solution was heated to reflux for 45 min. The solution was cooled to T_i = 22 °C, and then was charged with Meldrum's acid (79 mg. 0.55 mmol) in a single portion. After 2 h, an additional charge of Meldrum's acid (0.25 equiv., 18 mg) was made. After an additional 16 h age, the reaction was quenched with 15% aq. citric acid (1 mL). The resulting mixture was transferred to a separatory funnel and the phases were separated. The organic phase was extracted with 15% aq. citric acid (1 mL), followed by saturated brine (1 mL). The resulting organic phase was dried over $MgSO_4$, then filtered and subjected to a solvent switch into *n*-heptane which resulted in the formation of a white slurry. The *n*-heptane volume was reduced to 4 mL, and EtOAc (1 mL) was added to the resulting slurry. After stirring for 0.5 h, the slurry was filtered and displacement- washed with *n*-heptane (1 mL). Drying afforded 155 mg of **23** as a white solid. Mp = 270 ˚C (decomp., DSC); ^{1}H NMR showed desired product as rotamers (~2:1 ratio by ^{1}H NMR). ^{1}H NMR (300 MHz, $CDCl_3$): major rotamer δ 8.20 (s, 1H), 7.64 (s, 1H), 7.49-7.42 (m, 1H), 7.31-7.10 (m, 5H), 6.99-6.92 (m, 1H), 6.67 (d, *J* = 8.7 Hz, 1H), 5.23-5.11 (m, 1H), 4.89 (d, *J* = 16.5 Hz, 1H), 4.20 (d, *J* = 16.5 Hz, 1H), 3.69-3.60 (m, 2H), 2.86-2.72 (m, 2H), 2.57 (s, 3H), 2.26-2.13 (m, 1H), 2.11-1.95 (m, 1H), 1.91-1.56 (m, 2H); minor rotamer δ 8.29 (s, 1H), 7.56-7.48 (m, 1H), 7.44 (s, 1H), 7.31-7.10 (m, 5H), 7.06-7.00 (m, 1H), 6.71 (d, J = 8.8 Hz, 1H), 6.20-6.09 (m, 1H), 4.66 (d, *J* = 18.2 Hz, 1H), 4.26 (d, *J* =

18.2 Hz, 1H), 3.54 (d, *J* = 18.8 Hz, 1H), 3.30 (d, *J* = 18.8 Hz, 1H), 2.86 (m, 2H), 2.60 (s, 3H), 2.26-2.13 (m, 1H), 2.11-1.95 (m, 1H), 1.91-1.56 (m, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) combined rotamers δ; 171.3, 170.3, 168.6, 168.0, 158.5, 158.0, 155.9, 155.1, 149.5, 148.6, 141.6, 141.2, 138.9, 138.5, 133.7, 133.6, 133.5, 132.7, 131.1, 130.1, 129.8, 129.4, 129.2, 128.6, 128.1, 127.9, 127.7, 127.0, 126.8, 126.7, 126.1, 124.9, 124.6, 118.8, 118.2, 116.1, 115.5, 107.0, 107.0, 58.9, 54.9, 43.8, 42.4, 38.9, 37.9, 29.6, 29.3, 29.2, 28.6, 27.7, 23.4, 22.2, 22.0; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{27}H_{26}N_3O_4$ 456.1918; found 456.1894.

***(R,E)-N*-(5-cyano-2-((6-methylpyridin-3-yl)oxy)benzyl)-5-methyl-N-(1,2,3,4-tetrahydro-naphthalen-1-yl)hex-2-enamide (24).** A vial was charged with **23** (39 mg, 0.086 mmol), DMAc (1.0 mL), pyrrolidine (0.02 mmol, 1.7 μL) and AcOH (0.1 mmol, 60 μL). Isovaleraldehyde (0.15 mmol, 16 μL) was added. After 25 h, HP LC assay showed ~50% conversion. An additional charge of isovaleraldehyde (0.15 mmol, 16 μL) was performed, and HPLC assay showed full conversion after an additional 15 h. H_2O (2 mL) was added, followed by EtOAc (2 mL). The biphasic mixture was transferred to a separatory funnel and the phases were separated with retention of each. The aqueous phase was extracted with EtOAc (1 mL) and the resulting aqueous phase was discarded. The combined organic phases were washed with 10% aq. LiCl (3 x 1 mL). The organic phase was separated and dried over $MgSO_4$, then filtered and concentrated under reduced pressure. Silica gel chromatography (0 to 100% EtOAc/Hexanes) afforded 37 mg of **24** as a viscous oil (90%). ^{1}H NMR (300 MHz, $CDCl_3$): (major rotamer) δ 8.20 (s, 1H), 7.60 (s, 1H), 7.40 (dd, J_1 = 8.5 Hz, J_2 = 1.8 Hz, 1H), 7.22-7.00 (m, 7H), 6.64 (d, *J* = 8.5 Hz, 1H), 6.42 (d, *J* = 15.0 Hz, 1H), 5.41-5.30 (m, 1H), 4.87 (d, *J* = 16.9 Hz, 1H), 4.07 (d, *J* = 16.9 Hz, 1H), 2.85-2.70 (m, 2H), 2.55 (s, 3H), 2.24-1.43 (m, 7H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H) (minor rotamer) δ 8.20 (s, 1H),

7.60 (s, 1H), 7.46 (dd, J_1 = 8.5 Hz, J_2 = 1.8 Hz, 1H),, 7.22-7.00 (m, 7H), 6.69 (d, J = 8.6 Hz, 1H), 6.27-6.17 (m, 1H), 5.98 (d, J = 15.0 Hz, 1H), 4.68 (d, J = 19.1 Hz, 1H), 4.22 (d, J = 19.1 Hz, 1H), 2.85-2.70 (m, 2H), 2.57 (s, 3H), 2.24-1.43 (m, 7H), 0.87 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H); : $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): (combined rotamers) δ 168.4, 168.0, 158.0, 157.8, 155.6, 155.0, 149.3, 148.8, 148.1, 147.3, 141.6, 138.7, 138.2, 135.1, 135.0, 132.7, 132.5, 132.0, 132.0, 130.5, 130.2, 129.5, 129.3, 128.1, 128.0, 127.9, 127.5, 127.1, 127.0, 126.6, 126.5, 126.2, 124.1, 124.0, 121.1, 121.0, 118.9, 118.3, 115.9, 115.5, 106.7, 106.6, 58.0, 53.6, 42.9, 42.1, 41.9, 41.9, 30.0, 29.4, 29.2, 28.7, 27.9, 27.8, 23.8, 23.7, 22.4, 22.4, 22.2, 22.0; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{31}H_{34}N_3O_2$ 480.2646; found 480.2648.

3-(4-((4-isopropylphenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-3-oxopropanoic acid (25). A solution of *tert*-butyl 4-chloro-5H,6H,7H,8H-pyrido[4,3-d]pyrimidine-6-carboxylate (2.9 g, 10.0 mmol) and 4-isopropylaniline (1.50 mL, 11.0 mmol) in isopropanol (8 mL) and H_2O (8 mL) was heated to T_i = 75 ˚C, after which HPLC assay showed full conversion to the N-Boc protected intermediate. The solution was cooled to T_i = 50 ˚C and 3N HCl (5 mL) was added. After 8 h, the solution was cooled to T_i = 22 ˚C, followed by the addition of NH_4OH (2.0 mL). Isopropanol was removed via distillation under reduced pressure, resulting in the precipitation of dark solids. Addition of IPAc (20 mL) to a stirring solution of the dark solids resulted in the formation of a triphasic slurry containing a dark organic phase, a clear aqueous phase, and lightly colored solids. The solids were filtered and displacement-washed with IPAc. The solids were dried via vacuum suction under a N_2 tent, affording 2.01 g of the desired product as a pale beige solid (75% yield). Mp = 199.7 ˚C (DSC); ^1H NMR (300 MHz, d_6-dmso): δ 8.53 (s, 1H), 8.37 (s, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.191 (d, J = 8.5 Hz, 2H), 4.01 (s, 2H), 3.28 (t, J = 6.2 Hz, 2H), 2.92-2.77 (m, 3H), 1.20 (d, J = 6.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, d_6-dmso): δ 159.1,

156.8, 155.4, 143.4, 137.0, 126.0, 122.5, 109.3, 40.6, 40.4, 32.9, 29.0, 24.0; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{16}H_{21}N_4$ 269.1761; found 269.1766.

The intermediate amine *N*-(4-isopropylphenyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine (268 mg, 1.0 mmol) was dissolved in a biphasic mixture of MeTHF (3 mL) and saturated aq. $NaHCO_3$ (3 mL). Ethyl malonyl chloride (191 μL, 1.5 mmol) was added via syringe pump over 1 h. After 10 h, an additional charge of saturated aq. $NaHCO_3$ (3 mL) was followed by ethyl malonyl chloride (600 μL) over 1 h. After an additional 12 h, HPLC assay revealed high conversion. The biphasic mixture was transferred to a separatory funnel and the organic phase was discarded. The organic phase was washed with 1N glycolic acid (3 mL), followed by saturated aq. NaCl (3 mL). The resulting organic phase was concentrated under reduced pressure to an oil.

The resulting oil was dissolved in EtOH, to which was added 1 N NaOH (1 mL). After 1 h, HPLC assay showed full consumption of the starting ester. 1N glycolic acid (2.5 mL) was added, forming an initially homogeneous solution that spontaneously began to crystallize a white solid. After stirring for 3 h, the slurry was filtered. The wetcake was displacement-washed with 1:3.5 EtOH:H_2O (1.5 mL), then dried to afford **25** (186 mg of a white solid) as a ~2:1 mixture of rotamers. Mp = 153.6 ˚C (DSC); ^{1}H NMR (300 MHz, CD_3OD): major rotamer δ 8.31 (s, 1H), 7.49-7.40 (m, 2H), 7.29-7.20 (m, 2H), 4.66 (s, 2H), 3.87 (t, *J* = 5.8 Hz, 2H), 3.66 (s, 1H), 2.97-2.79 (m, 3H), 1.26 (d, *J* = 6.9 Hz, 6H): minor rotamer δ 8.33 (s, 1H), 7.49-7.40 (m, 2H), 7.29-7.20 (m, 2H), 4.61 (s, 2H), 3.94 (t, *J* = 5.9 Hz, 2H), 3.65 (s, 1H), 2.97-2.79 (m, 3H), 1.26 (d, *J* = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, CD_3OD) combined rotamers δ 171.5, 171.4, 168.8, 168.6, 160.2, 159.6, 159.2, 158.9, 156.0, 155.8, 146.9, 137.4, 137.4, 127.7, 127.1, 125.0, 124.8, 111.8, 111.6,

44.2, 44.1, 40.4, 39.6, 35.0, 31.9, 31.1, 24.5; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{19}H_{23}N_4O_3$ 355.1765; found 355.1765.

***(E)*-1-(4-((4-isopropylphenyl)amino)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)-5-methylhex-2-en-1-one (26).** A solution of **25** (0.282 mmol, 100 mg) in DMAc (2 mL) was treated with pyrrolidine (0.042 mmol, 3.5 µL) and AcOH (0.282 mmol, 16 µL). Isovaleraldehyde (0.423 mmol, 45 µL). The resulting solution was stirred for 5 h, at which point HPLC assay showed full conversion of **25**. H_2O (4 mL) was added, followed by MTBE (4 mL). The biphasic mixture was transferred to a separatory funnel and the phases were separated with retention of each. The aqueous phase was extracted with MTBE (2 mL) and the resulting aqueous phase was discarded. The combined organic phases were washed with 10% aq. LiCl (3 x 1 mL). The organic phase was separated and dried over $MgSO_4$, then filtered and concentrated under reduced pressure. Silica gel chromatography (50 to 100% EtOAc/Hexanes) afforded 93 mg of **26** as a viscous oil (87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (s, 1H), 7.46 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 7.01-6.84 (m, 1H), 6.33 (d, J = 15.0 Hz, 1H), 4.65 (s, 2H), 3.94-3.82 (m, 2H), 3.03-2.83 (m, 3H), 2.13 (dd, $J_1 = J_2$ = 7.1 Hz, 2H), 1.84-1.69 (m, 1H), 1.26 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.3, 158.3, 157.4, 155.3, 147.2, 145.3, 135.6, 126.8, 122.9, 120.2, 110.2, 42.5, 41.9, 39.6, 33.6, 31.6, 27.8, 24.0, 22.4; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{23}H_{31}N_4O$ 379.2492; found 379.2495.

3-((2-chlorophenyl)amino)-3-oxopropanoic acid (27). A flask was charged with 2-chloroaniline (10.0 mmol, 1.27 g) and CH_2Cl_2 (30 mL). Et_3N (14.0 mmol, 1.42 g) was added, followed by TMSCl (15.0 mmol, 1.63 g) and the resulting thin slurry was heated to reflux for 30 min. The solution was cooled to T_i = 30 °C, then Meldrum's acid (11.0 mmol, 1.58 g) was added in a single portion. After 4 h, the reaction was quenched with 1N HCl (18 mL), which resulted in a triphasic

system in which the product had solidified. The slurry was filtered, and the collected product was washed with water (10 mL), followed by DCM (10 mL). Drying via suction/N_2 tent afforded 1.69 g (94%) of **27** as a white solid. Mp = 140.3 ˚C (DSC);: ^{1}H NMR (300 MHz, d_6-dmso): δ 12.73 (s, 1H), 9.83 (s, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.34 (dd, $J_1 = J_2 = 7.8$ Hz, 1H), 7.18 (dd, $J_1 = J_2 = 7.8$ Hz, 1H), 3.49 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, d_6-dmso): δ 169.7, 165.1, 134.8, 129.5, 127.5, 126.1, 125.4, 125.1, 43.0; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_9H_9ClNO_3$ 214.0265; found 214.0252.

3-(2-bromothiazol-5-yl)-2-((2-chlorophenyl)carbamoyl)acrylic acid (28) control experiment without AcOH. A flask was charged with **27** (1.0 mmol, 214 mg), DMAc (1.0 mL), pyrrolidine (0.2 mmol, 17 μL) and 2-bromo-4-formylthiazole (1.2 mmol, 230 mg). After 1.5 h, LC showed full conversion. H_2O (2 mL) was added, followed by EtOAc (1 mL) which resulted in the formation of a triphasic slurry (solid product and a biphasic supernatant). The slurry was filtered, and the cake was displaced with EtOAc (1 mL). Drying via suction/N_2 tent afforded 183 mg of the major isomer of **28**. Mp = 175.5 ˚C (DSC); ^{1}H NMR (300 MHz, d_6-dmso): δ 13.04 (br S, 1H), 9.87 (s, 1H), 8.19 (s, 1H), 7.95 (dd, $J_1 = 8.1$ Hz, $J_2 = 1.4$ Hz, 1H), 7.56 (s, 1H), 7.48 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.3$ Hz, 1H), 7.37 (ddd, $J_1 = J_2 = 7.9$ Hz, $J_3 = 1.4$ Hz, 1H), 7.20 (ddd, $J_1 = J_2 = 7.8$ Hz, $J_3 = 1.5$ Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, d_6-dmso): δ 165.8, 164.4, 149.9, 136.9, 134.9, 130.7, 130.3, 129.7, 129.4, 127.1, 126.9, 126.7, 126.3; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{13}H_9BrClN_2O_3S$ 386.9200; found 386.9203. Using the isolated product as a standard, loss to the EtOAc phase (diluted to 10 mL) was 82 mg as a mixture of isomers. Therefore, the assay yield was 77%.

3-(diphenylamino)-3-oxopropanoic acid (29). A flask was charged with Ph_2NH (10.0 mmol, 1.69 g) and DCM (20 mL). Et_3N (14 mmol, 1.42 g) was added, followed by TMSCl (15 mmol, 1.63 g) and the resulting thin slurry was heated to reflux for 30 min. The solution was cooled to T_i = 27 °C, then Meldrum's acid (11.0 mmol, 1.58 g) was added in a single portion. After 1 h, the heterogeneous reaction was quenched with 15% aq. citric acid (11 mL), and the biphasic mixture was transferred to a separatory funnel and the layers were separated. The product- containing organic phase was washed with sat. aq. NaCl (6 mL), and the phases were separated. The organic phase was solvent-switched into IPAc and diluted to 40 mL total volume, resulting in the formation of a slurry. IPAc was removed via distillation to form a slurry (~15 mL total volume). The heterogeneous mixture was filtered and displaced with IPAc (10 mL). Drying via suction/N_2 tent afforded 1.81 g of a solid that was shown by ^{1}H NMR to be **29** contaminated with 5 mol% of Et_3NHCl.

A portion of the initially isolated solid (550 mg) was dissolved in CH_2Cl_2 (10 mL) and stirred, to which was added 1N HCl (5 mL). After 10 min., the biphasic solution was transferred to a separatory funnel and the phases were split. The resulting organic phase was washed with 15% aq. NaCl (5 mL), then dried over $MgSO_4$, filtered, and concentrated to a thin slurry (~2 mL total volume). IPAc (8 mL) was added over 1 h via syringe pump. The resulting slurry was aged 1 h, then filtered. The cake was displaced with IPAc (5 mL) and dried via suction/N_2 tent to afford clean **29** as a white solid. Mp = 115.5 ˚C (DSC); ^{1}H NMR (300 MHz, d_6-dmso): δ 12.57 (s, 1H), 7.52-7.12 (m, 10H), 3.25 (s, 2H); ^{13}C{^{1}H} NMR (75 MHz, d_6-dmso): δ 168.8, 166.0, 142.6, 129.9, 129.0, 128.7, 128.2, 126.9, 126.4, 126.4, 42.4; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{15}H_{14}NO_3$ 256.0968; found 256.0976.

***(E)*-3-(2-bromothiazol-5-yl)-N,N-diphenylacrylamide (30).** A flask was charged with **29** (1.0 mmol, 255 mg) and DMAc (2.5 mL). Pyrrolidine (0.12 mmol, 10 μL) and AcOH (1.0 mmol, 57 μL) were subsequently added to the DMAc solution. A solution of 2-bromo-4-formylthiazole (1.2 mmol, 230 mg) dissolved in DMAc (1.5 mL) was then added over 10 h via syringe pump. After addition was complete, the reaction was aged an additional 24 h. H_2O (2 mL) was charged via syringe pump over 1 h, followed by 2 h of stirring. The slurry was filtered, and the cake was displaced with 1:1 DMAc:H_2O (0.5 mL), followed by H_2O (0.5 mL). Drying via vacuum suction/N_2 tent afforded 346 mg of **30** (90%) as a white solid. Mp = 187.0 ˚C (DSC); ^{1}H NMR (300 MHz, d_6-dmso): δ 8.04 (s, 1H), 7.56 (d, J = 15.0 Hz, 1H), 7.50-7.23 (m, 10H), 6.59 (d, J = 15.0 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, d_6-dmso): δ 164.7, 151.6, 142.6, 142.6, 137.5, 133.2, 129.4, 129.4, 129.4, 129.4 127.8, 127.8, 127.3, 121.6; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calc'd for $C_{18}H_{14}BrN_2OS$ 385.0005; found 385.0000.

100 g demonstration of the synthesis of **(21)**: **5**•*t*-BuNH_2 (125 g, 351 mmol) was charged to a 2 L flask equipped with overhead stirring and a drop valve. EtOAc (700 mL) was added, followed by 15 wt% aq. citric acid (700 mL). The resulting biphasic mixture was stirred for 30 min., after which agitation was stopped and the phases were allowed to settle. The lower aqueous phase was drained and discarded. 15 wt% aq. NaCl (150 mL) was added to the vessel and the resulting biphasic mixture was stirred for 30 min., after which agitation was stopped and the phases were allowed to settle. The lower aqueous phase was drained and discarded. The retained organic phase then concentrated under reduced pressure (40-50 mm Hg partial pressure and 30-35 ˚C) to a final volume of 300 mL. A solvent switch was performed under the conditions of constant volume

distillation[31] with 300 mL of DMAc. The resulting solution was transferred to a 2L flask via in-line filtration (to filter inorganic solids), followed by a rinse with DMAc (100 mL).

Pyrrolidine (52.65 mmol, 3.74 g, 4.4 mL) was charged to the DMAc solution, followed by AcOH (351 mmol, 21.1 g, 20.0 mL) and nicotinaldehyde (421 mmol, 45.1 g, 39.5 mL) and the resulting solution was agitated at 22 ˚C for 16 h, at which point HPLC assay indicated >99.5% conversion of the aldehyde. 1N K_2CO_3 (200 mL) was added over 30 minutes, resulting in a heterogeneous seed bed (pH = 8). Additional water (200 mL) was charged over 1 h. The resulting slurry was heated to 60 ˚C over 1 h, then cooled to 22 ˚C over 1 h. The slurry was subsequently filtered. The cake was displaced with 1:1 DMAc:H_2O (v:v, 150 mL), followed by H_2O (150 mL). Drying via vacuum suction/N_2 tent afforded 102.6 g of **21** (99.2 LCAP).

An analytically pure sample was obtained by heating a slurry of **21** in EtOAc (15 x volumes) to reflux, followed by gradual cooling to ambient temperature. The resulting slurry was filtered, and the resulting cake was displaced with EtOAc. Drying as above afforded **21** with no detectable impurities.

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Supporting Information:

^{1}H and ^{13}C spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References:

[1] Jackson, P. A.; Widen, J. C.; Harki, D. A.; Brummond, K. M. Covalent Modifiers: A Chemical Perspective on the Reactivity of α,β-Unsaturated Carbonyls with Thiols via Hetero-Michael Addition Reactions. *J. Med. Chem.* **2017**, *60*, 839.

[2] Rogosnitzky, M.; Danks, R.; Kardash, E. Therapeutic Potential of Tranilast, an Anti-allergy Drug, in Proliferative Disorders. *Anticancer Res.* **2012**, *32*, 2471.

[3] Yan, Q. S.; Mishra, P. K.; Burger, R. L.; Bettendorf, A. F.; Jobe, P. C.; Dailey, J. W. Evidence that carbamazepine and antiepilepsirine may produce a component of their anticonvulsant effects by activating serotonergic neurons in genetically epilepsy-prone rats. *J. Pharmacol. Exp. Ther.* **1992**, *261*, 652.

[4] (a) Chang, S-J. Scale Up of a Ritter Reaction. *Org. Proc. Res. Dev.* **1999**, *3*, 232. (b) Cvetovich, R. J.; DiMichele, L. Formation of Acrylanilides, Acrylamides, and Amides Directly from Carboxylic Acids Using Thionyl Chloride in Dimethylacetamide in the Absence of Bases. *Org. Proc. Res. Dev.* **2006**, *10*, 944. For transition-metal catalyzed reactions, see: (c) Nagarsenkar, A.; Prajapti, S. K.; Guggilapu, S. D.; Babu, B. N. Aldehyde-Promoted One-Pot Regiospecific Synthesis of Acrylamides Using an in Situ Generated Molybdenum Tetracarbonyl Amine $[Mo(CO)_4(amine)_2]$ Complex. *Org. Lett.* **2015**, *17*, 4592. (d) Driller, K. M.; Prateeptongkum, S.; Jackstell, R.; Beller, M. A General and Selective Iron-Catalyzed Aminocarbonylation of Alkynes: Synthesis of Acryl- and Cinnamides. *Angew. Chem. Int. Ed. Eng.* **2011**, *50*, 537. (e) Schleicher, K. D.; Jamison, T. F. Nickel-Catalyzed Synthesis of Acrylamides from α-Olefins and Isocyanates. *Org. Lett.* **2007**, *9*, 875. (f) Chen, Y; Turlik, A,; Newhouse, T. R. Amide α,β-Dehydrogenation Using Allyl-Palladium Catalysis and a Hindered Monodentate Anilide. *J. Am. Chem. Soc.* **2016**, *138*, 1166. (g) Teskey, C. J.; Adler, P. Gonçalves, C. R.; Maulide, N. Chemoselective α,β-Dehydrogenation of Saturated Amides. *Angew. Chem. Int. Ed.* **2019**, *58*, 447 (disclosed during the preparation of our manuscript).

[5] Benhaim, C.; Chen, W.; Goldman, E.; Horvath, A.; Pye, P.; Smythe, M. S.; Verner, E. J. Synthesis of a Bruton's Tyrosine Kinase Inhibitor WO 2016115356 (2016).

[6] (a) Butterworth, S.; Finlay, M. R. V.; Ward, R. A.; Kadambar, V. K.; Chintakuntla, C. R.; Murugan, A.; Redfearn, H. M.; Chuaqui, C. E. 2-(2,4,5-Substituted-anilino)pyrimidine Derivatives as EGRF Modulators Useful for Treating Cancer WO 2013014448 (2013). (b) Hughes, D. L. Highlights of the Recent U.S. Patent Literature. *Org. Proc. Res. Dev.* **2016**, *20*, 2028.

[7] For additional examples, see (a) Roberts, C.; Zhang, Y.; Beaumier, F.; Lepissier, L.; Marineau, J. J.; Rahl, P. B.; Sprott, K.; Ciblat, S.; Sow, B.; Larouche-Gauther, R.; Berstler, L. Compounds for the Modulation of Myc Activity. WO 2016196910 (2016). (b) Ito, F.; Koike, H.; Sudo, M.; Yamagishi, T.; Ando, K. Preparation of Spiropiperidine Compounds as Ligands for the ORL-1 Receptor. WO 2003000677 (2003). (c) Juchum, M.; Günther, M.; Döring, E.; Sievers-Engler, A.; Lämmerhofer, M.; Laufer, S. Trisubstituted Imidazoles with a Rigidized Hinge Binding Motif Act as Single Digit nM Inhibitors of Clinically Relevant EGFR L858R/T790M and L858R/T790M/C797S Mutants: An Example of Target Hopping. *J. Med. Chem.* **2017**, *60*, 4636.

[8] (a) Clark, W. M.; Bender, C. A Practical and Efficient Large-Scale Preparation of (4R,5S)-N-Propenoyl-1,5-dimethyl-4-phenylimidazolidin-2-one. A Simple Procedure for the Preparation of N-Acylimidazolidin-2-ones and N-Acylbornane 2,10-Sultams. *J. Org. Chem.* **1998**, *63*, 6732. (b) Merce-Vidal, R.; Díaz-Fernández, J. L.; Almansa Rosales, C. Preparation of Pyrazinoindole Derivatives for Use as Analgesics WO 2014173901 (2014). (c) Laursen, J. S.; Harris, P.; Fristup, P.; Olsen, C. A. Triangular Prism-Shaped β-Peptoid Helices as Unique Biomimetic Scaffolds. *Nature Commun.* **2015**, *6*, 7013.

[9] A SciFinder search revealed limited number and quantities of 3-Cl-substituted analogues; fewer than ten β-Cl acids or acid chlorides available from ≥5 suppliers were identified.

[10] Teasdale, A.; Fenner, S.; Ray, A.; Ford, A.; Phillips, A. A Tool for the Semiquantitative Assessment of Potentially Genotoxic Impurity (PGI) Carryover into API Using Physicochemical Parameters and Process Conditions. *Org. Proc. Res. Dev.* **2010**, *14*, 943.

[11] Anthanilic acid-derived (secondary) cinnamides: (a) Iizuka. K.; Kamijo, T.; Yamamoto, R.; Harada, H. A Method for the Production of Nuclear Substituted Cinnamoylanthranilic Acid Derivatives and Intermediates Thereof. EP 0074725B1 (1983). (b) Williams, S. J.; Stapleton, D.; Kelly, D. J.; Gilbert, R. E.; Krum, H. Treatment of Mesangioproliferative Diseases. WO-2008003141-A1 (2008). (c) Mierina, I.; Zaharova, M.; Jure, M.; Neibolte, I. The Role of Carboxylic Group Position on the Antiradical Activity of Synthetic Analogues of Oat Antioxidants. *J. Chem. Pharm. Res.* **2015**, *7 (6)*, 416. (d) Zammit, S.C.; Cox, A. J.; Gow, R. M.; Zhang, Y.; Gilbert, R. E.; Krum, Kelly, D. J.; Williams, S. J. Evaluation and Optimization of Antifibrotic Activity of Cinnamoyl Anthranilates. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 7003. (e) Kamat, S. P.; Parab, S. J. A Simple Two-Step Synthesis of Avenanthramides, Constituents of Oats (Avena Sativa L). *Indian J. Chem. Section B* **2007**, *46B*, 2074. Related secondary cinnamides: (f) Freudenberg, K.; Gehrke, G. *p*-Coumaryl Alcohol [3-(p-hydroxyphenyl)-2-propen-1-ol] and its Dehydrogenation Polymers. *Chem. Ber.* **1951**, *84*, 443. (g) Ghosh, K.; Chaudhari, A.; Seth, D. S. Synthesis, Characterization and Fluorescence Study of Certain Cinnamamide Derivatives and α,β-Uunsaturated Acids. *J. Pharm. Sci. Res.* **2010**, *2 (8)*, 445. (h) Pareek, A. K.; Joseph, P. E.; Seth, D. S. A Mild Synthesis, Characterization and Spectral Properties of Some New Substituted Cinnamamides and Substituted α-β Unsaturated Acids. *Oriental J. Chem.* **2010**, *26*, 155. (i) Mierina, I.; Stikute, A.; Jure, M. Synthesis and Antiradical Properties of 4-Aryl-3,4-Dihydroquinolin-2-(1H)-Ones, Aza Analogs of Neoflavonoids. *Chem. Het. Cmpds.* **2014**, *50*, 1137. (j) Reddy, M. V. R.; Reddy, E. P. Aryl and Heteroaryl Propene Amides, Derivatives Thereof and Therapeutic Uses Thereof. WO 2004037751 (2004).

[12] Tanaka, S.; Yagi, K.; Ujihara, H.; Ishida, K. Method for Production of (2e,6z,8e)-*N*-isobutyl-2,6,8-Decatrienamide (Spilanthol), and Foods, Beverages, Cosmetics and Pharmaceutical Preparations Each Comprising the Compound WO 2009091040 (2009). In these studies towards the preparation of spilanthol, equilibration of such mixtures to the acrylamides has been demonstrated but required an added step.

[13] One example using an aldehyde to form a tertiary amide has been reported: Fernández, M. V.; Durante-Lanes, P.; López-Herrera, F. J. Reaction of aldehydes with stabilized sulfur ylides. Highly stereoselective synthesis of 2,3-epoxy-amides. *Tetrahedron* **1990**, *46*, 7911. Under these conditions (catalytic piperidine and pyridine as solvent at ambient temperature), low yields of acrylamide were formed, along with aldol products.

[14] Kitazawa, M.; Akahane, M.; Nakano, Y.; Hayakawa, K.; Sato, K.; Kobayashi, M. Studies on the Synthesis of Antiulcer Agents. VI. Synthesis and Antiulcer Activity of Dihydrobenzofuranone Derivatives. *J. Pharm. Soc. Jpn. (Yakugaka Zasshi)* **1989**, *109*, 718. In these examples, only aromatic aldehydes were examined.

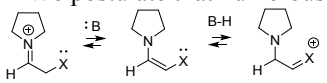
[15] Specifically that bear nucleophilic secondary amines. This substrate also benefited from the equivalence of its rotamers, which aided spectroscopic analysis of derived acrylamide products (for example, E/Z isomer determination)

[16] Rigo, B.; Fasseur, D.; Caulier, P.; Couturier, D. Reaction of Trimethylsilyl Derivatives with Meldrum's Acid: A New and Easy Monofunctionalization of Malonic Acid. *Tetrahedron Lett.* **1989**, *30*, 3073.

[17] Xu, F.; Zacuto, M. J.; Yoshikawa, N.; Desmond, R. Hoerrner, S.; Itoh, T.; Journet, M.; Humphrey, G. R.; Cowden, C.; Strotman, N.; Devine, P. Asymmetric Synthesis of Telcagepant, a CGRP Receptor Antagonist for the Treatment of Migraine. *J. Org. Chem.* **2010**, *75*, 7829. The use of DMAc as solvent allows for dissolution of a wide variety of β-amido acids.

[18] As determined by HPLC-MS data. In the case of *N*-Boc-2-aminoacetaldehyde and 2-(benzyloxy)acetaldehyde, the major products had an observed [M + H] = 381.29 and 372.26, respectively. This data was consistent with the desired acrylamides.

[19] We postulate that numerous side reactions are due to heteroatom-lone pair overlap with enamine π-system:



[20] Likely due to steric or electronic factors. In the case of chloral and triflouroacetaldehyde, the use of aquueous hydrate solutions was not necessarily inhibitive, as the use of aqueous formaldehyde has been successfully demonstrated. Instead, we postulate that destabilizing dipole-dipole interactions of an iminium α- to and electron withdrawing group contributed to the observed lack of reactivity.

[21] From LCMS data we observed [M + H] = 551.42, which was consistent with the adduct of pyrrolidine and **27** (via conjugate addition of pyrrolidine). In this case, the presence of a basic amine afforded the possibility of extraction of this impurity under acidic conditions (pH = 2-4, resulting from the acetic acid in the reaction was sufficient to protonate this moiety but not the pyridine moiety).

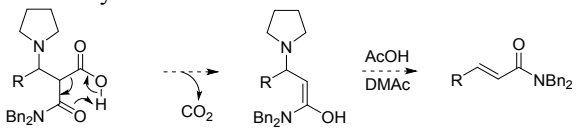
[22] While the assignment of olefin geometry was not undertaken, the major product was cleanly isolated through crystallization. At 210 nm, the HPLC ratio (LCAP) of olefin isomers was 4:1. In addition, UPLC-MS data,

combined with HPLC data, suggested 0.4 HPLC area % of the desired Knoevenagel condensation product. Analogous reactivity was observed between **27** and methyl-4-formylbenzoate.

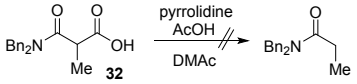
[23] The typical procedure was modified to incorporate slow addition of the aldehyde. Under standard batch mode, **29** was formed in 50% assay yield, with the mass balance consisting of aldol products (assigned by UPLC-MS data). Slow addition of the aldehyde to **27** did not alter the product distribution.

[24] The proposed mechanism follows the outlines proposed in ref. 17 . Further support for this elimination is the lack of observed β,γ-unsaturated amide products.

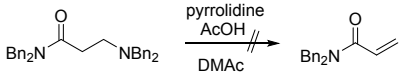
[25] An alternative mechanism can be proposed whereby the initial Mannich adduct **31** undergoes spontaneous decarboxylation to afford an intermediate amino- enol which then undergoes elimination:



However, the available data does not support this pathway: β-amido acid **32** was stable (no decarboxylation observed) under the reaction conditions in the absence of an aldehyde:



[26] Experimental data is not consistent with amine-catalyzed olefin isomerization (see: Nozaki, K. cis-trans Isomerizations. II. The Mechanism of the Amine Catalyzed Isomerization of Diethyl Maleate. *J. Am. Chem. Soc.* **1941**, *63,* 2681). The *E/Z* isomer ratio does not change over the course of the reaction, and an isolated amine-acrylamide adduct was unreactive when re-subjected to the reaction conditions:



[27] Neutralization of the acetic acid was required for the crystallization of **21**. By contrast, addition of neutral water was sufficient to crystallize **20** under otherwise identical conditions.

[28] Recrystallization from EtOAc afforded analytically pure **21** (see Experimental Section).

[29] Cheung, W-H.; Zheng, S-L.; Yu, W-Y.; Zhou, C-G.; Che, C-M. Ruthenium Porphyrin Catalyzed Intramolecular Carbenoid C−H Insertion. Stereoselective Synthesis of Cis-Disubstituted Oxygen and Nitrogen Heterocycles. *Org. Lett.* **2003**, 5, 2535.

[30] Nielsen, M. K.; Shields, B. J.; Liu, J.; Williams, M. J.; Zacuto, M. J.; Doyle, A. G. Mild, Redox-Neutral Formylation of Aryl Chlorides via Photocatalytic Generation of Chlorine radicals. *Angew. Chem. Int. Ed.* **2017**, *56*, 7191.

[31] Li, Y-E.; Yang, Y; Kalthod, V.; Tyler, S. M. Optimization of Solvent Chasing in API Manufacturing Process: Constant Volume Distillation. *Org. Proc. Res. Dev.* **2009**, *13*, 73.