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Heumann Indole Flow Chemistry Process

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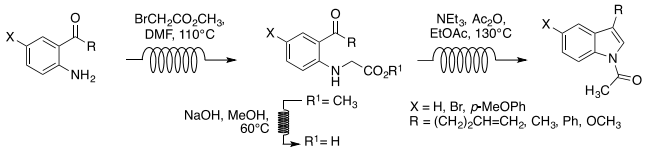


ABSTRACT: Continuous flow chemistry has improved efficiency in the Heumann indole process. 3-Substituted indoles were prepared by three flow steps performed in succession in better overall yield and shorter reaction times relative to their batch counterparts. Novel 3-alkyl and 3-methoxyindoles were synthesized from their corresponding amino ketone and ester precursors by flow sequences featuring base-free alkylation with methyl bromoacetate in DMF, saponification, and cyclization with acetic anhydride and Et_3N.

INTRODUCTION

Indole is ubiquitous among heterocycle ring systems in natural products, agrochemicals, medicines, dyes and materials.[1] Indoles are frequently used as pharmaceutical components, and found in anti-inflammatory, antihypertensive, anti-tumour, anti-HIV, and antimigraine agents.[2-3] Intense worldwide use of indoles, particularly 3-substituted derivatives (e.g., tryptophan), dictates need for effective synthetic methods.

Strategies for indole synthesis are usually categorized according to the aromatic precursors.[4-5] For example, the Fisher protocol employs aryl hydrazine derivatives and is a mainstay for indole synthesis in spite issues of regiocontrol,[6-8] which have been addressed by alternative methods which use *o*-iodo aniline[9-10] and *o*-nitro toluene precursors.[11] The spectrum of indole products impels continued search for safe cost-effective methods employing alternative starting materials and mild conditions with minimal waste.[1, 12-15]

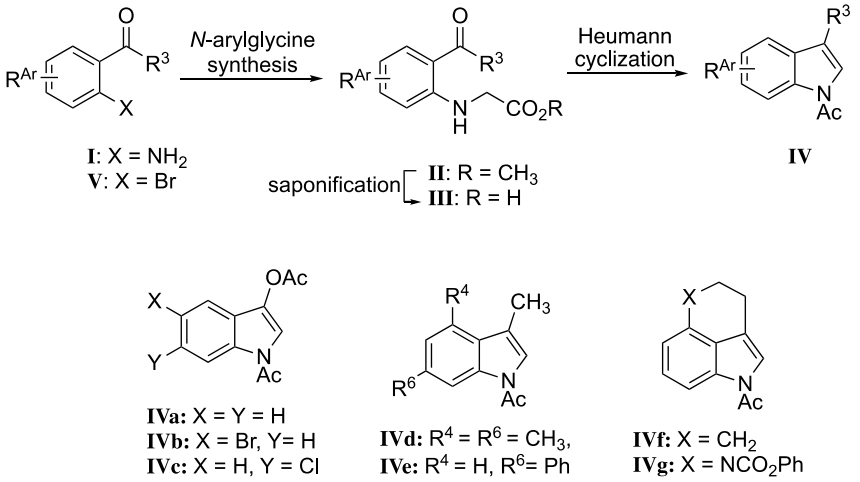


Figure 1. Heumann indole process general reaction sequence and representative products.

Lessons in the challenges of indole derivative synthesis are epitomized in research towards an industrial process to make the important dyestuff, indigo. In spite the harsh conditions of heating *N*-phenylglycine and sodium amide at ca. 200 °C,[16] the Heumann–Pfleger process supplanted a relatively milder reaction sequence from anthranilic acid and remains viable today. The discarded process, the so-called Heumann indole process consisted of heating *N*-(2-carboxyphenyl)glycine **III** with acetic anhydride and sodium acetate to provide indoxyl after work-up and hydrolysis of acetate **IV** (R^{Ar} = H, R^3 = OAc).[17-18] Nearly forgotten, due likely in part to challenges in preparing *N*-arylglycine precursors (e.g., **II** and **III**), the Heumann indole process has been occasionally used to prepare substituted indoles (e.g., **IVa-g**) with regiocontrol (Figure 1).[4, 19-24] For example, employing 2-acyl arylglycines **III**, indoles with 2-, 4-, and 6-position substituents were synthesized in 50-78% yields.[4, 22, 25]

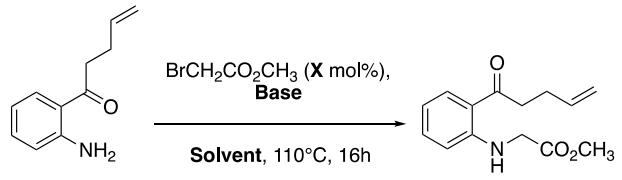
In our research oriented on homologues of tryptophan,[26-27] 3-(but-3'-enyl)indole (**5a**) was considered as a versatile precursor from which different analogs could be obtained from olefin diversification chemistry.

Substituted 3-(but-3'-enyl)indoles have been used in carbazole synthesis, and prepared by conjugate additions of indole onto vinyl ketones and subsequent Wittig reaction with methyl triphenylphosphonium bromide.[28] The parent 3-(but-3'-enyl)indole has also been obtained from indole precursors. For example, treatment of indole with methyl magnesium chloride and 4-bromobutene in benzene gave **5a** in 41% yield.[29] Moreover, indole-3-carbaldehyde reacted in an indium-mediated allylation with allyl bromide in the presence of Hantzsch's ester to provide **5a** in 77% yield.[30] Notably, 3-(but-3'-enyl)indole has been employed as substrate in cross-metathesis chemistry,[31] as well as starting material for the synthesis of 3-substituted indole fluoroalkanes,[32] pyrroloindolines,[33] a pentacyclic *strychons* alkaloid skeleton,[34] and hexahydrocarbazole alanine.[29] To the best of our knowledge, 3-(but-3'-enyl)indole has however never been synthesized from an aromatic precursor. Previously, 1-[2-aminophenyl]pent-4-en-1-one (**1a**, R^{Ar} = H, R^3 = $CH_2CH_2CH{=}CH_2$) has been prepared quantitatively from methyl anthranilate using a copper catalyzed cascade addition of vinyl Grignard reagent,[35] and used as an effective starting material for syntheses of pyrroles,[36] quinazolinones,[36] quinolines,[35] benzodia- and triazepinones,[37-39] and pyrrolobenzodi- and trizepinones.[40] The Heumann indole process from amino ketone **1a** was thus pursued to effectively prepare 3-(but-3'-enyl)indole (**5a**).

In exploring the Heumann indole process to make 1-acetyl-3-(but-3'-enyl)indole (**4a**), the use of flow chemistry was found to give significant enhancements in reaction rates and yields relative to the corresponding batch processes. Continuous flow chemistry is known to improve specific synthetic processes through controlled reagent mixing, enabling safer and more reliable scale-up.[41] Moreover, effective Fisher and Hemetsberger-Knittel syntheses have been adapted to flow processes to give convenient access to certain indole products.[42-49] In the flow Heumann indole process, the yields of the aniline alkylation and Heumann cyclization steps, both were significantly augmented compared to the batch counterparts likely due to better substrate mixing. Examining the flow method on a set of other substrates, certain 3-substituted indoles as well as 3-methoxy indole were effectively synthesized.

RESULTS AND DISCUSSION

In the Heumann indole process,[18] the construction of the arylglycine component has been a traditional challenge, often plagued by low yields, and pursued using various protocols: e.g., alkylation of anthranilate with haloacetates,[25] reductive amination with ethylglyoxalate,[21] copper-catalyzed cross-couplings of halobenzoates (e.g., **V**) with glycine derivatives,[20, 50] as well as *ipso*-displacement of fluorobenzonitrile with glycinates.[51] In our hands, attempts at *N*-alkylation of aniline **1a** using bromoacetic acid caused product degradation as detected by thin-layer chromatography. On the contrary, methyl bromoacetate reacted with **1a** at 110°C under various conditions (Table 1).[4, 52] In the presence of potassium carbonate in DMF, alkylation with methyl bromoacetate (6 eq.) gave arylglycine **2a** in only 20% yield (entry 1).[4] In the absence of base, the reaction improved to 57% yield (entry 2), which was also obtained using stoichiometric amounts of alkyl halide (entry 3). Alternative solvents (MeCN and MePh) were less effective (entries 4 and 5), and use of Hünig's base gave no improvement in yield (entry 6).



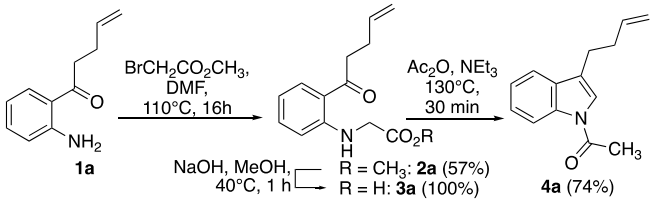
1a **2a**

Entry	Solvent	Base	$BrCH_2CO_2Me$ (eq)	Yield (%)
1	DMF	K_2CO_3	6	20
2	DMF	None	6	57
3	DMF	None	1.1	57
4	Acetonitrile	None	1.1	no rxn
5	Toluene	None	1.1	37
6	DMF	DIPEA	1.1	56

Table 1. Alkylation of aniline 1a in batch

Saponification gave quantitatively arylglycine **3a** from heating *N*-arylglycinate **2a** in 4N NaOH at 40°C for 1h (Scheme 1). The Heumann cyclization performed best in batch using acetic anhydride (100 eq.) and triethylamine at 130°C for 30 min to afford indole **4a** in 74% yield.[4] Increasing the amount of acetic

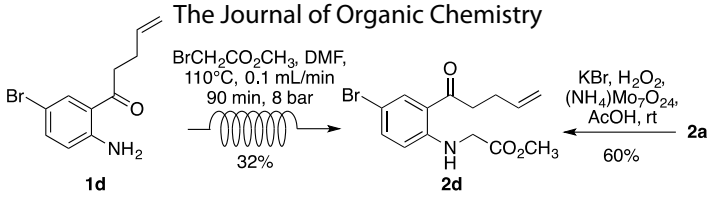
anhydride in the batch cyclization process from 1 to 10 to 100 equivalents improved the yield from 33 to 41 to 74%.



Scheme 1. Batch synthesis of N-acetyl-3-(but-3-enyl)indole (4a)

The synthesis of 1-acetyl-3-(but-3-enyl)indole (**4a**) from aniline **1a** gave 42% overall yield using a route featuring three batch reactions: amine alkylation with methyl bromoacetate, saponification and annulation (Scheme 1). In batch, the alkylation and cyclization steps gave moderate yields, and required relatively long reaction times, high temperature and purification of the reaction mixture using column chromatography. To overcome these obstacles, we reasoned that efficient heat transfer and rapid mixing in a continuous flow microreactor may enable shorter residence times to improve product purity and yields.

Initially, the alkylation of aniline **1a** was examined by adopting the batch conditions. Aniline **1a** and methyl bromoacetate were safely mixed in DMF at room temperature, introduced into a Vapourtec system through an injection loop and flowed through and heated in a perfluoroalkoxy alkane (PFA, 110 °C) reactor equipped with a back-pressure regulator. After 90 min, glycine **2a** was obtained quantitatively without chromatography (Table 2). Lower conversion was obtained using a shorter residence time. A longer residence time gave poorer yields of **2a** due in part to formation of dialkylated and degradation products. Poorer yields were also obtained in attempts to replace DMF with more environmentally benign solvents such as ethyl acetate and *tert*-butyl methyl ether (Table 2, entries 4 and 5).



Entry	Solvent	Residence Time (min)	Temp.	% Yield (%)
1	DMF	120	110	61
2	DMF	90	110	100
3	DMF	60	110	80
4	EtOAc	90	110	12
5	*t*-BuOMe	90	110	no rxn

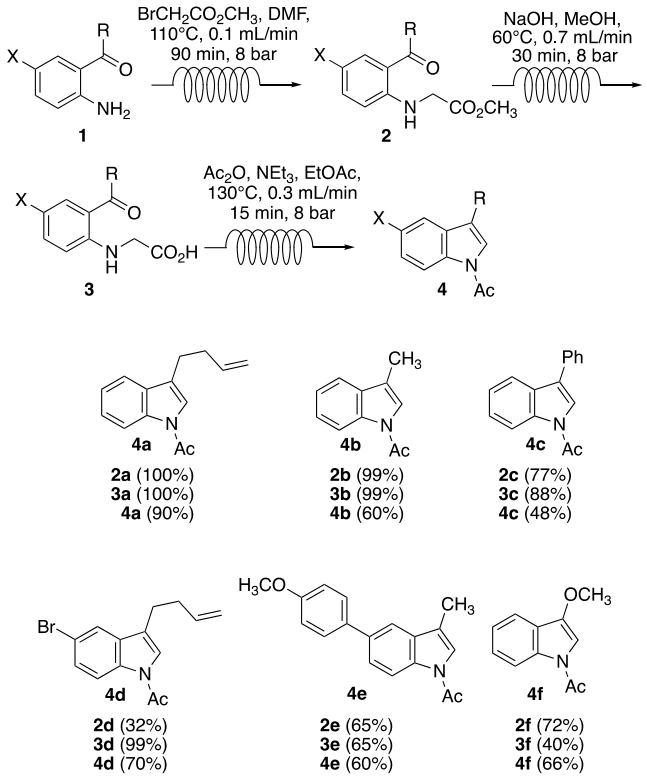
Table 2. Alkylation of aniline 1a in flow

Saponification of ester **2a** was accomplished quantitatively using both the batch and flow conditions; however, the latter were more expedient. *N*-Arylglycinate **2a** was dissolved in methanol and treated with sodium hydroxide (10 N) at rt, introduced into the injection loop and heated in the PFA reactor at 60°C for a residence time of 15 min. Acid **3a** was quantitatively afforded as a white solid by quenching the excess of NaOH with 2N HCl (4.1 eq.) followed by extraction into DCM, and evaporation of the volatiles under vacuum (Scheme 2).

The Heumann cyclization was performed in flow by passing the reaction mixture through a 5-mL stainless-steel reactor. The relatively viscous acetic anhydride was diluted with ethyl acetate to avoid reactor clogging. Indole **4a** was obtained in 90% yield by reacting *N*-arylglycine **3a** with excess acetic anhydride and triethylamine in ethyl acetate for 15 min at 130°C in the stainless-steel reactor. The final indole was isolated as a yellow oil after co-evaporation of the excess acetic anhydride with methanol. Compared to the batch reaction sequence, the three flow-step synthesis of indole **4a** was achieved in shorter reaction times with more than twofold improvement in overall yield.

The best flow conditions for the Heumann indole flow chemistry process to synthesize 3-(but-3'-enyl)indole **4a** were subsequently examined on the corresponding *o*-aminophenyl methyl and phenyl

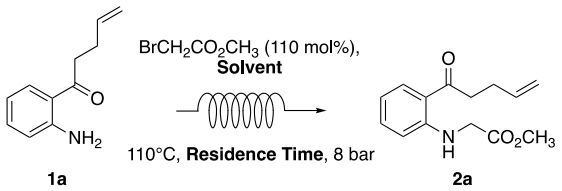
ketones **1b** and **1c**, and provided the corresponding 3-methyl and 3-phenyl indoles **4b** and **4c** in 59% and 33% overall yields (Scheme 2, isolated individual yields are shown for glycinates **2** and **3**, and indole **4**).



Scheme 2. Heumann indole flow chemistry process.

The influence of aromatic ring substituents in the flow protocol for Heumann indole synthesis was examined using 1-[2-amino-5-bromophenyl]pent-4-en-1-one (**1d**) and methyl 2-amino-5-(*p*-methoxyphenyl)phenyl ketone (**1e**). The latter was synthesized from 1-(2-amino-5-bromophenyl)ethan-1-one in 62% yield by Suzuki cross-coupling with methoxyphenylboronate using catalytic $Pd(PPh_3)_4$ and sodium carbonate in 4:1 toluene/methanol at 120°C.[53]

Attempts to use continuous flow chemistry to alkylate 5-bromo-aniline **1d** gave only 32% yield of bromophenylglycinate **2d**, likely due to diminished aniline nucleophilicity from the electron withdrawing bromide. Improved access to ester **2d** resulted on bromination of *N*-arylgycinate **2a** using potassium bromide (1 eq.) hydrogen peroxide (2 eq.) and ammonium molybdate tetrahydrate (0.01 eq.) which gave **2d** in 60% yield (Scheme 3).



Scheme 3. Synthesis of 4-bromophenyl)glycinate 2d

Saponification of bromophenylglycinate **2d** and Heumann cyclization under flow conditions gave 1-acetyl-5-bromo-3-(but-3-enyl)indole (**4d**) in 70% yield over two steps. Employing conditions optimized for the flow synthesis of **4a**, alkylation of aniline **1e** (65%), saponification of ester **2e** (65%) and Heumann cyclization of acid **3e** (60%) provided 3,5-disubstituted indole **4e**. Notably, Suzuki cross-coupling of 5-bromoindole **4d** with *p*-methoxyphenylboronate using the same conditions mentioned above gave *N*-acetyl 3-(but-3-en-1-yl)-5-(4-methoxyphenyl)-1H-indole **4g** in 76% yield.

The flow process gave consistently better yields than the batch counterpart likely due to multiple factors. For example, the small dimensions of the flow reactor have been shown to enhance heat transfer and to accelerate mixing, diminishing diffusion times and variations in temperature, which may avoid side reactions encountered in batch chemistry.[41] A set of experiments were performed to analyze further the differences between the flow and batch processes in the alkylation and indole synthesis steps. The yields for the synthesis of glycinates **2b** and **2c** in batch and flow were respectively 70% and 63% vs 99% and 77%. The batch alkylation failed to go to completion after 16 h, such that chromatography was essential to obtain pure glycinate **2b**. Notably, batch mixing influenced the rate at which starting aniline **1b** was consumed, which varied from 70% to 90% to 99% after 1.5 h as the stirring speed changed from 0 to ca. 750 rpm to 1500 rpm. In the batch alkylation reaction to **2b**, a molecular ion corresponding to a dimer (m/z = 368) was observed to increase in aliquots removed over time and analyzed by mass spectrometry.[54] After the batch reaction, glycinate **2b** was separated from decomposition products by elution on a medium-pressure liquid chromatography column using a gradient of 0-100% ethyl acetate in hexanes. Glycinate **2b** was shown however to be unstable to the purification conditions on silica gel by reinjection of pure sample, which was recovered in 60% yield. In the corresponding flow reaction, enhanced heat

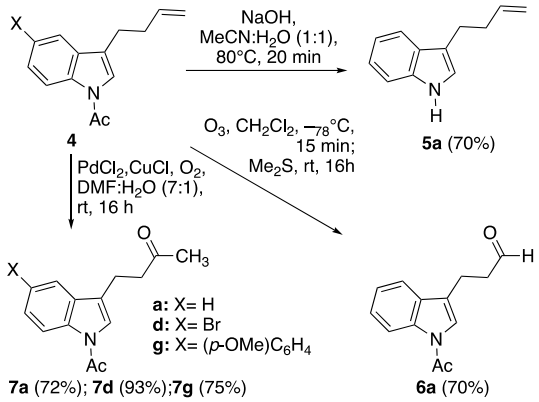
transfer and rapid mixing accelerate likely the alkylation reaction, such that after a shorter reaction time, pure sample was obtained after aqueous work-up without chromatography.

Although consumption of starting material was observed and pure indole **4** was isolated from the flow Heumann cyclization after aqueous work-up, the mass balance was not 100%. After the flow reaction and elution of indole **4b**, washing of the stainless-steel reactor using methanol acidified with 1% concentrated HCl eluded a colored impurity, which exhibited a molecular ion (m/z = 392) consistent with the bis-sodium salt of a dimer of the starting glycine **3b** in the mass spectrometric analysis.[54] Slow elution of this impurity may account for the high purity of the indole products. Notably, attempts failed to prepare indole **4b** by cyclization of glycinate **3b** in batch; instead, a colored residue was obtained likely due to the formation of similar bi-products. In addition, attempts to perform the Heumann cyclization in batch failed to provide indoles **4c** and **4f**, but gave **4d** using a 1 h reaction time in 70% yield after chromatography.

3-Methoxyindole **4f** was synthesized by employing methyl anthranilate **1f** in the 3-step flow Heumann synthesis. Alkylation of **1f** was significantly more effective using flow compared to batch conditions (72% vs 6% yield). Saponification of glycinate **2f** gave selectively acid **3f**, which was difficult to isolate due to its aqueous solubility (40%). Although longer reactions times were necessary, Heumann cyclization of acid **3f** under the flow conditions gave 3-methoxyindole **4f** in 66% yield (vs 26% in batch, Scheme 2). 3-Alkoxy indoles have previously been pursued due to their wide range of biological activities; however, their synthesis has generally required multiple steps and expensive metal catalysis.[55-57] The ability to obtain 3-alkoxy indoles directly from the corresponding anthranilates enriches the utility of the flow Heumann chemistry.

In addition to arylation of indole bromide **4d**, the utility of 3-(but-3'-enyl)indoles **4a**, **4d** and **4g** was demonstrated by modification of the amine and olefin groups (Scheme 4). Liberation of the indole nitrogen by acetamide removal was achieved by flowing **4a** together with sodium hydroxide in acetonitrile for 20 min at 80°C to afford 3-(but-3'-enyl)indole (**5a)** in 70% yield; similar yield was obtained in batch in 1h. Olefin oxidation was examined to provide the corresponding aldehyde **6** and ketone **7**. Aldehyde

6a was obtained quantitatively by treating olefin **4a** with ozone in DCM. Ketones **7** were respectively obtained in 72-93% yields by Wacker oxidation of indoles **4a**, **4d** and **4g** using palladium dichloride and copper chloride under 1 atm of oxygen in DCM/water. Applications of aldehyde **6a** and ketones **7** in syntheses of other 3-substituted indole products are under investigation and will be presented in due time.



Scheme 4. Diversification of 3-(but-3'enyl)indoles 4

Flow chemistry has enhanced the utility of the Heumann indole process. A set of 3-substituted indoles were synthesized by three successive flow steps in typically higher yields and shorter reaction times compared to the corresponding batch processes. Products were obtained in high purity without silica gel purification. Novel 3-alkyl and 3-methoxyindoles were prepared effectively for the first time. Considering the need for effective means to prepare substituted indoles and the potential to diversify groups such as the bromide and olefin of 3-(but-3'enyl)indoles **4**, this novel flow method offers interesting utility for procuring this important class of heterocycle structures.

EXPERIMENTAL SECTION

General Methods. Anhydrous conditions refer to reactions performed in flame-dried glassware under a positive pressure of argon using dry solvent transferred by syringe. Methyl bromoacetate was purchased from Sigma- Aldrich and filtered on a silica plug prior to use. 1-[2-Aminophenyl]pent-4-en-1-one (**1a**) was synthesized according to the literature.[35] Anhydrous THF and DMF were obtained by passage through solvent filtration systems (GlassContour, Irvine, CA). Flash column chromatography was performed using 230-400 mesh silica gel.[58] Thin layer chromatography (TLC) was performed on silica gel-coated

glass-backed plates (Merck 60 F254). Batch processes were performed on an IKA RCT Basic stirring plate with a speed range from 50 to 1500 rpm. The stir bar sized was 12.7 x 8mm.

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were measured in $CDCl_3$ (7.27 and 77.2 ppm) at 400 MHz and 75 MHz, respectively. The Mass Spectrometry Facility at the Université de Montréal performed HRMS measurements on a LC-MSD TOF (Agilent) mass analyzer.

Methyl (2-(pent-4-enoyl)phenyl)glycinate (2a). In a 20 mL-vial, aminoketone **1a** (175.3 mg, 1.0 mmol) and methyl bromoacetate (0.1 mL, 1.1 mmol) were premixed in DMF (1.4 mL, 0.71M). The mixture was injected into a 2 mL-loop that flowed into a 10 mL PFA reactor preheated at 110°C with a back-pressure regulator at 8 bar. The reaction was run with a residence time of 90 min (flow rate of 111 µL/min) and DMF was used as the elution solvent. The crude mixture was collected in an opened flask and co-evaporated with toluene. The reduced volume was partitioned between water (5 mL) and DCM (5 mL). The aqueous layer was extracted with DCM (4 × 5 mL). The combined organic layers were washed with water (3 × 5 mL) and brine, dried over $MgSO_4$, filtered, evaporated and dried under vacuum to afford glycinate **2a** as yellow oil (247 mg, 99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.82 (dd, J = 6.3, 1.4 Hz, 1H), 7.36 (td, J = 6.3, 1.4 Hz, 1H), 6.67 (t, J = 7.7 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 5.95- 5.89 (m, 1H), 5.11 (m, 1H), 5.06 (m, 1H), 4.02 (d, J = 5.6 Hz, 2H), 3.78 (s, 3H), 3.07 (t, J = 7.5 Hz, 2H), 2.49 (q, J = 6.6 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 202.2, 170.9, 150.1, 137.8, 135.1, 131.9, 118.2, 115.3, 111.8, 52.5, 44.9, 38.5, 29.8, 28.8; HRMS (ESI) Calcd *m/z* for $C_{14}H_{18}NO_3$ $[M+H^+]$ 248.1280, found 248.1272.

Methyl (2-acetylphenyl)glycinate (2b). Glycinate **2b** was synthesized from 2'-aminoacetophenone (**1b**, 500 mg, 3.7 mmol) following the protocol for the synthesis of ester **2a**, which afforded a yellow oil (767 mg, 99%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 7.8 Hz 1H), 6.68 (t, J = 8.1 Hz, 1H), 6.55 (d, J = 8.5 Hz, 1H), 4.03 (d, J = 5.6 Hz, 2H), 3.79 (s, 3H), 2.60 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 201.1, 170.8, 150.0, 135.2, 132.9, 118.6, 115.3, 111.6, 52.5, 44.8, 28.1; HRMS (ESI) Calcd *m/z* for $C_{11}H_{13}NO_3$ $[M+H^+]$ 208.0968, found 208.0972.

Methyl (2-benzoylphenyl)glycinate (2c). Glycinate **2c** was synthesized from 2'-aminobenzophenone (**1c**, 546.5 mg, 2.8 mmol) following the protocol for the synthesis of ester **2a**, which afforded an orange oil (574.4 mg, 77%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.67- 7.61 (m, 2H), 7.56- 7.50 (m, 2H), 7.49- 7.38 (m, 3H), 6.67- 6.60 (m, 2H), 4.09 (d, *J* = 3.2 Hz, 2H), 3.82 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 199.5, 170.8, 150.6, 140.3, 135.6, 135.1, 131.1, 129.3, 128.2, 118.3, 115.1, 111.6, 52.5, 45.0; HRMS (ESI) Calcd *m/z* for $C_{16}H_{16}NO_3$ [M+H$^+$] 270.1125, found 270.1121.

Methyl (4-bromo-2-(pent-4-enoyl)phenyl)glycinate (2d). Glycinate **2d** was synthesized from 1-(2-amino-5-bromophenyl)pent-4-en-1-one (**1d**, 384.0 mg, 1.51 mmol) following the protocol for the synthesis of ester **2a**, which afforded a dark brown oil (147.0 mg, 32%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.91 (d, *J* = 2.3 Hz, 1H), 7.43 (dd, *J* = 9.0, 2.3 Hz, 1H), 6.46 (d, *J* = 9.0 Hz, 1H), 5.91 (m, 1H), 5.10 (m, 1H), 5.03 (m, 1H), 4.01 (d, *J* = 5.6 Hz, 2H), 3.80 (s, 3H), 3.05 (dt, *J* = 8.6, 6.3 Hz, 2H), 2.56-2.42 (dt, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 201.1, 170.4, 148.9, 137.5, 137.4, 134.1, 119.5, 115.5, 113.7, 106.7, 52.6, 44.8, 38.5, 28.5; HRMS (ESI) Calcd *m/z* for $C_{14}H_{17}BrNO_3$ [M+H$^+$] 326.0386, found 326.0396.

Methyl (3-acetyl-4'-methoxy-1,1'-biphen-4-yl)glycinate (2e). Glycinate **2e** was synthesized from 1-(4-amino-4'-methoxy-1,1'-biphen-3-yl)ethan-1-one (**1e**, 173.3 mg, 0.72 mmol) following the protocol for the synthesis of ester **2a**, which afforded a dark brown oil (146.6 mg, 65%); δ 9.23 (br s, 1H), 7.95 (d, *J* = 2.2 Hz, 1H), 7.59 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.46 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H) , 6.63 (d, *J* = 8.8 Hz, 1H), 4.08 (d, *J* = 5.1 Hz, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 2.67 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 201.2, 170.8, 158.8, 148.9, 133.7, 133.2, 130.8, 128.3, 127.5, 118.7, 114.4, 112.1, 55.5, 52.5, 44.9, 28.1; HRMS (ESI) Calcd *m/z* for $C_{18}H_{20}NO_4$ [M+H$^+$] 314.1387, found 314.1395.

Methyl 2-((2-methoxy-2-oxoethyl)amino)benzoate (2f). Glycinate **2f** was synthesized from methyl 2-aminobenzoate (**1f**, 1 g, 6.61 mmol) following the protocol for the synthesis of ester **2a**, which afforded a yellow solid (1.06 g, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 8.8 Hz,

1H), 6.66 (t, J = 8.1 Hz, 1H), 6.52 (d, J = 8.5, 0.7 Hz, 1H), 4.02 (s, 2H), 3.87 (s, 3H), 2.79 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 171.0, 168.9, 149.9, 134.7, 131.8, 115.7, 111.2, 111.0, 52.4, 51.7, 44.9; HRMS (ESI) Calcd *m/z* for $C_{11}H_{14}NO_4$ $[M+H^+]$ 224.0917, found 224.0923.

(2-(Pent-4-enoyl)phenyl)glycine (3a). In a 20 mL-vial, glycinate **2a** (500 mg, 2.02 mmol) and a 10N aqueous NaOH (0.8 mL, 8.09 mmol) solution were mixed in MeOH (9 mL, 0.22M). The reaction mixture was injected into a 10 mL-loop and flowed into a 10 mL PFA reactor preheated at 60°C maintaining a regulated back-pressure of 8 bar. The reaction was run with a residence time of 15 min (flow rate of 667 μL/min) using MeOH as elution solvent. The mixture was collected in an opened flask, acidified with 2M HCl (4.1 mL, 8.3 mmol) and extracted with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to afford the carboxylic acid **3a** as yellow solid (466.6 mg, 99%), which was employed in the next step without further purification: HRMS (ESI) Calcd *m/z* for $C_{13}H_{15}NO_3$ $[M+H^+]$ 234.1125, found 234.1122.

1-Acetyl-3-(but-3'-enyl)indole (4a). In a 20 mL-vial, glycine **3a** (150 mg, 0.64 mmol), acetic anhydride (6 mL, 64.3 mmol) and triethylamine (1 mL, 7.04 mmol) were premixed in EtOAc (3 mL, 0.21 M). The reaction mixture was injected into a 10 mL-loop and flowed through a 5 mL-stainless steel reactor preheated at 130°C maintaining a back-pressure regulated at 8 bar. The reaction was run with a residence time of 15 min (flow rate of 333 μL/min) using EtOAc as the elution solvent. The mixture was collected in an opened flask and co-evaporated with MeOH to afford **4a** as yellow oil (123 mg, 90%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (brs, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.37 (t, J = 7.9, Hz, 1H), 7.30 (t, J = 7.6, 1.1 Hz, 1H), 7.21 (s, 1H), 5.99-5.87 (m, 1H), 5.11 (m, 1H), 5.05 (m, 1H), 2.82 (t, J = 7.6 Hz, 2H), 2.62 (s, 3H), 2.50 (dt, J = 14.0, 7.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 168.3, 137.9, 136.0, 130.7, 125.2, 123.4, 122.5, 121.8, 118.9, 116.7, 115.3, 33.1, 24.4, 24.0; HRMS (ESI) Calcd m/z for $C_{14}H_{16}NO$ $[M+H^+]$ 214.1235, found 214.1226.

1-Acetyl-3-(methyl)indole (4b). Indole **4b** was synthesized from glycinate **2b** (767 mg, 3.67 mmol) following the protocols for the saponification to prepare glycine **3a** (99% yield of **3b**) and the Heumann reaction to prepare **4a** (60% yield of **4b**), which afforded a dark brown oil (39 mg, 59% from glycine **2b**); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 8.3 Hz,1H), 7.37 (t, J = 9.5 Hz, 1H), 7.30 (t, J = 7.4Hz 1H), 7.20 (s, 1H), 2.61 (s, 3H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.4, 136.0, 131.6, 125.3,123.5, 122.3, 119.0, 118.5, 116.7, 24.1, 9.8; HRMS (ESI) Calcd *m/z* for $C_{11}H_{12}NO$ [M+H$^+$] 174.0913, found 174.0920.

1-Acetyl-3-(phenyl)indole (4c). Indole **4c** was synthesized from glycinate **2c** (574.4 mg, 2.2 mmol) following the protocols for the saponification to prepare glycine **3a** (88% yield of **3c**) and the Heumann reaction to prepare **4a** (48% yield of **4c**), which afforded a dark brown oil (28 mg, 42% from glycine **2c**); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 7.0 Hz 2H), 7.44-7.32 (m, 6H), 2.71 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.6, 136.3, 133.3, 129.0, 128.9, 128.0, 127.6, 125.5, 124.1, 123.9, 122.0, 119.9, 116.8, 24.1; HRMS (ESI) Calcd *m/z* for $C_{16}H_{16}NO_3$ [M+H$^+$] 270.1125, found 270.1121.

1-Acetyl-3-(but-3'-enyl)-5-bromoindole (4d). Indole **4d** was synthesized from glycinate **2d** (147.0 mg, 0.48 mmol) following the protocols for the saponification to prepare glycine **3a** (99% yield of **3d**) and the Heumann reaction to prepare **4a** (70% yield of **4d**), which afforded a light yellow oil (110 mg, 69% from glycine **2d**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 1.8 Hz, 1H), 7.44 (dd, J = 8.8, 1.9 Hz, 1H), 7.19 (s, 1H), 5.97- 5.83 (m, 1H), 5.11 (m, 1H), 5.05 (m, 1H), 2.76 (d, J = 7.8 Hz, 2H), 2.61 (s, 3H), 2.47 (dt, J = 13.9, 6.8 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.4, 137.7, 134.7, 132.6, 128.1, 123.0, 121.9, 121.8, 118.2, 116.9, 115.7, 33.1, 24.4, 24.0; HRMS (ESI) Calcd *m/z* for $C_{14}H_{15}BrNO$ [M+H$^+$] 292.0332, found 292.0319.

1-Acetyl-3-methyl-5-(4-methoxy)phenylindole (4e). Indole **4e** was synthesized from glycinate **2e** (146.6 mg, 0.47 mmol) following the protocols for the saponification to prepare glycine **3a** (65% yield of

3e) and the Heumann reaction to prepare **4a** (60% yield of **4e**). Indole **4e** was obtained as a yellow oil (20 mg, 40% from glycine **2e**); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (br s, 1H), 7.64 (d, *J* = 1.3 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.56 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.22 (br s, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H), 2.62 (s, 3H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.3, 159.1, 136.6, 135.0, 134.3, 132.1, 128.5, 124.4, 122.9, 120.9, 118.7, 117.0, 114.4, 55.5, 29.8, 24.1, 9.9. HRMS (ESI) Calcd *m/z* for $C_{18}H_{17}NO_2$ [M+H$^+$] 280.1332, found 280.1329

1-Acetyl-3-methoxyindole (4f). Indole **4f** was synthesized from glycinate **2f** (1.06 g, 4.76 mmol) following the protocols for the saponification to prepare glycine **3a** (40% yield of **3f**) and the Heumann reaction to prepare **4a** (66% yield of **4f**) with residence time of 30 min. Indole **4f** was obtained as light translucent oil (60 mg, 26% from glycine **2f**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 7.9 Hz, 1H), 7.73 (s, 1H), 7.55 (d, *J* = 7.0 Hz, 1H), 7.44-7.38 (t, 1H), 7.36-7.28 (t, 1H), 2.62 (s, 3H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.9, 168.0, 134.8, 133.0 126.4, 123.9, 117.6, 116.8, 113.4, 24.1, 21.2. HRMS (ESI) Calcd *m/z* for $C_{11}H_{12}NO_2$ [M+H+] 190.0863, found 190.0869.

3-(But-3'-enyl)indole (5a). In a 20 mL vial, NaOH pellets (56.4 mg, 1.41 mmol) were dissolved in 1 mL of water and treated with indole **4a** (100 mg, 0.47 mmol) in MeCN (1.6 mL, 0.88M). The heterogenous reaction mixture was injected into a 2 mL-loop and flowed into a 10 mL PFA reactor preheated at 80°C maintaining a back-pressure regulated at 8 bar. The reaction was run with a residence time of 20 min (flow rate of 500 μL/min) using MeCN as the elution solvent. The mixture was collected in an opened flask, treated with 1M NaH_2PO_4 (5 mL,) and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to afford the indole **5a** as a yellow oil (57.1 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.01 (s, 1H), 6.01-5.91 (m, 1H), 5.10 (m, 1H), 5.01 (m, 1H), 2.88 (t, *J* = 5.9 Hz, 2H), 2.50 (dt, *J* = 14.9, 7.1 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$)

□□138.9, 136.4, 122.0, 121.3, 119.3, 119.1, 116.4, 114.8, 111.2, 34.4, 29.8, 24.9. HRMS (ESI) Calcd *m/z* for $C_{12}H_{13}N$ [M+H$^+$] 172.1121, found 172.1124.

Batch Processes

1-(2-Amino-5-bromophenyl)pent-4-en-1-one (1d). Aniline **1d** was synthesized according to the procedure used to make bromide **2d** described below using 1-(2-aminophenyl)pent-4-en-1-one **1a** (1 g, 7.4 mmol). After silica gel column chromatography (5% EtOAc/hexanes), **1d** was isolated as orange oil (1.33 g, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 2.3 Hz, 1H), 7.32 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.56 (d, *J* = 8.8 Hz, 1H), 6.30 (s, 2H), 5.90 (m, 1H), 5.10 (m, 1H), 5.03 (m, 1H), 3.02 (t, *J* = 5.6 Hz, 2H), 2.48 (dt, *J* = 6.6, 1.2 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 200.9, 149.3, 137.4, 137.0, 133.3, 119.3, 119.2, 115.5, 106.9, 38.4, 28.5. HRMS (ESI) Calcd *m/z* for $C_{11}H_{13}BrNO$ [M+H$^+$] 254.0175, found 254.0167.

1-(2-Amino-5-bromophenyl)ethan-1-one (1h). Aniline **1h** was synthesized according to the procedure used to make bromide **2d** described below using 1-(2-aminophenyl)ethan-1-one (**1b**, 1 g, 7.4 mmol). After silica gel column chromatography (30% EtOAc/hexanes), **1h** was isolated as brown solid (1.31 g, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 1H), 6.72- 6.60 (m, 2H), 2.58 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 200.9, 150.4, 134.5, 132.2, 118.4, 117.3, 115.9, 28.0. The spectral corresponded to that previously reported.[59]

1-(2-Amino-5-(4-methoxyphenyl)phenyl)ethan-1-one (1e). In a 25-mL round bottom flask, a solution of 4-methoxyphenylboronic acid (297.4 mg, 1.96 mmol) in dry MeOH (1.1 mL) was added to a suspension of aniline **1h** (300 mg, 1.40 mmol), $Pd(PPh_3)_4$ (48.5 mg, 42 μmol) and Na_2CO_3 (sat.) (1.6 mL) in toluene (4.3 mL). The reaction mixture was heated to reflux for 4 h, cooled to room temperature and diluted with water (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water, sodium carbonate and brine, dried over $MgSO_4$, filtered and concentrated to a residue, which was purified on silica gel column chromatography (40%

EtOAc/hexanes). Aniline **1e** was obtained as orange solid (207 mg, 61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 2.1 Hz, 1H), 7.51 (dd, *J* = 5.2, 2.6 Hz, 2H), 7.46 (d, *J* = 9 Hz, 1H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 1H), 6.28 (s, 2H), 3.86 (s, 3H), 2.65 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 201.0, 158.8, 149.3, 133.3, 133.2, 130.0, 128.9, 127.5, 118.5, 117.9, 114.4, 55.5, 28.1; HRMS (ESI) Calcd *m/z* for $C_{15}H_{16}NO_2$ [M+H$^+$] 242.1176, found 242.1180.

Methyl (2-(pent-4-enoyl)phenyl)glycinate (2a). Aminoketone **1a** (500 mg, 2.85 mmol) and methyl bromoacetate (300 μL, 3.14 mmol) were heated in DMF (1 mL, 2.85M) at 110°C overnight, in a 20-mL sealed vial. After cooling to room temperature, DMF was co-evaporated three times with toluene and the reduced volume was partitioned between water (5 mL) and DCM (5 mL). The aqueous layer was extracted with DCM (4 × 5 mL). The combined organic layers were washed with water (3 × 5 mL) and brine, dried over $MgSO_4$, filtered and evaporated to a residue, that was purified by silica gel column chromatography (10-20% EtOAc/hexanes) to afford **2a** as yellow oil (409 mg, 57%), which exhibited identical physical and spectral characterization as material that was obtained from the corresponding flow chemistry protocol above.

Methyl (2-acetylphenyl)glycinate (2b). Employing 2-aminoacetophenone (500 mg, 3.7 mmol) and methyl bromoacetate (390 μL, 4.07 mmol) in DMF (2 mL, 1.85M) in the batch protocol described above for **2a**, followed by silica gel column chromatography (10-20% EtOAc/hexanes), glycinate **2b** was obtained as brown oil (537 mg, 70%), which exhibited identical physical and spectral characterization as material that was obtained from the corresponding flow chemistry protocol above.

Methyl (2-benzoylphenyl)glycinate (2c). Employing 2-aminobenzophenone (200 mg, 1.01 mmol) and methyl bromoacetate (110 μL, 1.12 mmol) in DMF (2 mL, 0.51 M) in the batch protocol described above for **2a** followed by silica gel column chromatography (10-20% EtOAc/hexanes), glycinate **2c** was obtained as a pale yellow oil (173 mg, 63%), which exhibited identical physical and spectral characterization as material that was obtained from the corresponding flow chemistry protocol above.

Methyl (2-(pent-4-enoyl)-4-bromophenyl)glycinate (2d). In a 50-mL round bottom flask, potassium bromide (341 mg, 2.87 mmol) and $(NH_4)_6Mo_7O_{24}$•4 H_2O (36 mg, 28.7 μmol) were added to a solution of homo-allylic ketone **2a** (500 mg, 2.87 mmol) in acetic acid (8 mL), followed dropwise with 30% hydrogen peroxide (440 μL, 4.31 mmol) at room temperature. The solution was stirred overnight, treated with saturated sodium carbonate, and extracted with EtOAc. The organic layer was washed with Na_2CO_3 (sat.) and dried over $MgSO_4$. After chromatography (95:5 hexane:EtOAc), bromide **2d** was obtained as orange oil (439 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 7.91 (s, 1H), 7.43 (dd, *J* = 9.0, 2.3 Hz, 1H), 6.46 (d, *J* = 9.0 Hz, 1H), 5.91 (m, 1H), 5.07 (m, 2H), 4.01 (d, *J* = 5.6 Hz, 2H), 3.80 (s, 3H), 3.05 (dd, *J* = 8.6, 6.3 Hz, 2H), 2.54- 2.43 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 201.1, 170.4, 148.9, 137.5, 137.4, 134.1, 119.5, 115.5, 113.7, 106.7, 52.6, 44.8, 38.5, 28.5; HRMS (ESI) Calcd *m/z* for $C_{14}H_{17}BrNO_3$ [M+H$^+$] 326.0386, found 326.0396.

(2-(Pent-4-enoyl)phenyl)glycine (3a). To a solution of glycinate **2a** (200 mg, 0.81 mmol) in MeOH (5 mL, 0.16M), 4M aqueous NaOH (0.81 mL, 3.24 mmol) was added. The mixture was stirred at 40°C for an hour, in a 20-mL sealed vial. The resulting solution was acidified with 2M HCl (1.66 mL, 3.32 mmol) and extracted with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to afford the crude carboxylic acid as a yellow solid (189 mg, 100%), which exhibited identical physical and spectral characterization as material that was obtained from the corresponding flow chemistry protocol above, and was used without further purification.

1-Acetyl-3-(but-3'-enyl)indole (4a). Carboxylic acid **3a** (200 mg, 0.85 mmol) was added to a solution of acetic anhydride (8.02 mL, 85 mmol) and triethylamine (1.30 mL, 9.35 mmol), and heated to 130°C for 30 min, in a 20-mL sealed vial. The mixture was co-evaporated with MeOH to a residue, that was partitioned between EtOAc (2 mL) and 1M NaH_2PO_4 (2 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water (3 × 5 mL) and brine, dried over $MgSO_4$, filtered and evaporated to a residue, that was purified by silica gel column chromatography

(10% EtOAc/hexanes) to afford **4a** as yellow oil (134 mg, 74%), which exhibited identical physical and spectral characterization as material that was obtained from the corresponding flow chemistry protocol above.

1-Acetyl-3-(but-3'-enyl)-5-bromoindole (4d). Carboxylic acid **3d** (167 mg, 0.54 mmol) was dissolved in acetic anhydride (3 mL) and triethylamine (1.3 mL, 0.59 mmol), in a 20-mL sealed vial, and the solution was heated at reflux (130°C bath temperature) for 1 h. The reaction mixture was cooled to room temperature, the volatiles were evaporated and the residue was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford **4d** as light-yellow oil (110 mg, 70%), which exhibited identical physical and spectral characterization as material that was obtained from the corresponding flow chemistry protocol above.

1-Acetyl-3-methoxyindole (4f). Indole **4f** was synthesized from glycinate **2f** (100 mg, 0.48 mmol) following the batch protocols for the saponification to prepare glycine **3a** and the Heumann reaction to prepare **4a**. Indole **4f** was obtained as light translucent oil (24 mg, 26% from the glycine **2f**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 7.9 Hz, 1H), 7.73 (s, 1H), 7.55 (d, J = 7.0 Hz, 1H), 7.44-7.38 (t, 1H), 7.36-7.28 (t, 1H), 2.62 (s, 3H), 2.40 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 168.9, 168.0, 134.8, 133.0 126.4, 123.9, 117.6, 116.8, 113.4, 24.1, 21.2. HRMS (ESI) Calcd *m/z* for $C_{11}H_{12}NO_2$ [M+H$^+$] 189.0790, found 189.0767.

1-Acetyl-3-(but-3'-enyl)-5-(4-methoxy)phenylindole (4g). Indole **4g** was synthesized according to the cross-coupling procedure used to make biphenyl **1e** using 1-acetyl-3-(but-3'-enyl)-5-bromoindole **(4d**, 40 mg, 0.14 mmol), and obtained after purification by silica gel column chromatography (5 to 10% EtOAc/hexanes) as yellow oil (33 mg, 76%). In the proton-NMR spectrum, a mixture of amide isomers was observed. The signals of the major isomers are as follows. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 1.3 Hz, 1H), 7.59 (d, J = 8.8 Hz, 3H), 7.40 (d, J = 1.2 Hz, 1H), 7.23 (s, 1H), 7.01 (d, J = 8.8 Hz, 2H), 6.01- 5.87 (m, 1H), 5.16- 5.00 (m, 2H), 3.87 (s, 3H), 2.85 (t, J = 8.0 Hz, 2H),

2.63 (s, 3H), 2.52 (dt, J = 13.9, 6.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.1, 138.0, 136.6, 134.3, 128.5, 124.5, 122.9, 122.5, 122.0, 121.8, 117.0, 115.5, 114.4, 114.2, 55.5, 44.8, 34.4, 33.3, 24.6, 24.1; HRMS (ESI) Calcd *m/z* for $C_{21}H_{22}NO_2$ $[M+H^+]$ 320.1645, found 320.1646.

3-(1-Acetyl-1H-indol-3-yl)propanal (6a). A solution of indole **4a** (84.3mg, 0.39 mmol) in DCM (4 mL) in a 20-mL sealed vial was treated with ozone bubbles at –78°C until a blue color persisted, purged with a stream of argon bubbles, treated with dimethyl sulfide (144 μL, 1.95 mmol), and stirred overnight, after which time, the bath had warmed to room temperature. Removal of the volatiles by rotary evaporation gave a residue, which was purified by column chromatography on silica gel (2% MeOH/DCM) to provide aldehyde **6a** as yellow oil (84 mg, 100%); ^1H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.43 (d, J = 1.2 Hz, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.38 (t, J = 1.5 Hz, 1H), 7.31 (t, J = 1.5 Hz, 1H), 7.22 (s, 1H), 3.06 (t, J = 7.1 Hz, 2H), 2.89 (t, J = 7.1 Hz, 2H), 2.62 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 210.2, 168.3, 135.9, 130.1, 125.4, 123.5, 122.2, 121.1 118.6, 116.8, 43.0, 24.0, 17.4; HRMS (ESI) Calcd *m/z* for $C_{13}H_{14}NO_2$ $[M+H^+]$ 216.1019, found 216.1024.

4-(1-Acetyl-1H-indol-3-yl)butan-2-one (7a). In a 25-mL round bottom flask containing 2 mL of a 7:1 DMF/H_2O solution, $PdCl_2$ (24.8 mg, 0.14 mmol) and CuCl (71.3 mg, 0.72 mmol) were dissolved. The vessel was evacuated and filled three times with oxygen before stirring under O_2 (1 atm) for 1 h. Indole **4a** (102.4 mg, 0.48 mmol) in 2 mL of a 7:1 DMF/H_2O solution was then added to the reaction mixture and stirred under oxygen atmosphere overnight at room temperature. The vessel was purged with nitrogen and treated with a solution of 10% aq. HCl (4 mL). The aqueous layer was separated and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water and brine, filtered over Celite™, dried over $MgSO_4$, filtered and evaporated to a residue, that was purified by silica gel column chromatography (40% EtOAc/hexanes) to afford ketone **7a** as a dark oil (79 mg, 72%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (br d, J = 8.0 Hz, 1H), 7.53 (d, J = 7.2 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.31 (t, J = 7.1 Hz, 1H), 7.22 (s, 1H), 3.00 (t, J = 7.6 Hz, 2H), 2.88 (t, J = 7.6 Hz, 2H), 2.62 (s, 3H), 2.18 (s,

3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 207.8, 168.5, 136.1, 130.4, 125.5, 123.6, 122.4, 121.8, 118.8, 116.9, 43.0, 30.2, 24.2, 19.0; HRMS (ESI) Calcd *m/z* for $C_{14}H_{16}NO_2$ $[M+H^+]$ 230.117, found 230.1176.

4-(1-Acetyl-5-bromo-1H-indol-3-yl)butan-2-one (7d). Bromoindole **7d** was synthesized according to the protocol described to prepare ketone **7a** using 1-(5-bromo-3-(but-3-en-1-yl)-1*H*-indol-1-yl)ethan-1-one **4d** (85 mg, 0.29 mmol). After purification by silica gel column chromatography (50% EtOAc/hexanes), ketone **7d** was isolated as white solid (83 mg, 93%): mp 118-125°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.9 Hz, 1H), 7.64 (d, *J* = 1.9 Hz, 1H), 7.45 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.22 (s, 1H), 2.95 (t, *J* = 7.0 Hz, 2H), 2.84 (t, *J* = 7.0 Hz, 2H), 2.60 (s, 3H), 2.18 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 207.4, 168.4, 132.2, 128.3, 123.6, 121.6, 121.0, 117.0, 104.0, 42.8, 30.2, 24.0, 18.7; HRMS (ESI) Calcd *m/z* for $C_{14}H_{15}BrNO_2$ $[M+H^+]$ 308.0281, found 308.0275.

4-(1-acetyl-5-(4-methoxyphenyl)-1H-indol-3-yl)butan-2-one (7g). Indole **7g** was synthesized according to the protocol described to prepare ketone **7a** using 1-(3-(but-3-en-1-yl)-5-(4-methoxyphenyl)-1*H*-indol-1-yl)ethan-1-one **4g** (40 mg, 0.13 mmol). After purification by silica gel column chromatography (50% EtOAc/hexanes) ketone **7g** was isolated as white oil (33 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (br d, *J* = 7.9 Hz, 1H), 7.65 (m, 4H), 7.24 (s, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 3.88 (s, 3H), 3.88 (t, *J* = 7.2 Hz, 2H), 2.89 (t, *J* = 7.0 Hz, 2H), 2.63 (s, 3H), 2.19 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 207.8, 168.4,159.2, 136.7, 135.1, 134.1, 131.0, 128.5, 127.8, 124.6, 122.9, 121.9, 116.7, 114.4, 55.5, 43.0, 30.2, 24.1, 18.9; HRMS (ESI) Calcd *m/z* for $C_{21}H_{22}NO_3$ $[M+H^+]$ 336.1594, found 336.1597.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

Characterization data and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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