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Direct C-H arylation of indole-3-acetic acid derivatives enabled by an autonomous self-optimizing flow reactor

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Abstract. Described herein is a continuous-flow strategy for the palladium-catalyzed direct C-H arylation of indole-3-acetic acid derivatives with arenediazonium salts. A fully autonomous self-optimizing flow platform was used to efficiently optimize the coupling reaction in a 3-dimensional space. The flow methodology developed is experimentally simple, mild, broad in scope and safer than traditional batch approaches. Our continuous-flow approach is particularly convenient to prepare precursors of pharmaceutically relevant compounds.

Keywords: Self-Optimizing flow reactor; Flow chemistry; Direct C-H arylation; Autonomous synthesis; Indole

Introduction

The 2-aryl-3-carbonylmethyl indole skeleton is a ubiquitous moiety in compounds of pharmaceutical relevance (Figure 1). For instance, paullone **1** and kenpaullone **2** exhibit potent biological activities as ATP-competitive inhibitors of cyclin-dependent kinases (CDKs), glycogen-synthase kinases-3 (GSKs 3) and mitochondrial malate dehydrogenase (mMDH).^[1] FS-554 **3** is a potent trypanothione synthetase inhibitor with promising activity against parasites.^[2] Compound **4** is the most active member of a large family of farnesyl pyrophosphate-competitive inhibitors of farnesyl protein transferase.^[3] FGIN-1-27 **5** is a well-known potent and selective ligand for mitochondrial diazodiazepine receptors, producing anxiolytic effects.^[4] Because these compounds are frequently used by biologists as biochemical tools and references in drug discovery, they are occasionally commercially available from specialized sellers but only on milligram scale and at a very prohibitive cost. Therefore, the development of methodologies allowing a straightforward and efficient access to 2-aryl-3-carbonylmethyl indole derivatives is of huge interest for biologists and medicinal chemists.

The traditional approach to access the 2-arylindole-3-acetic acid motif involves the arylation of indole acetic acid derivatives through Suzuki-Miyaura or Stille cross-coupling reactions.^[5, 6] While versatile and efficient, these strategies suffer from the

necessity to pre-functionalize the indole moiety at the C2 position with either a halogen atom or a metal (Sn or B). A more step- and atom-efficient approach consists of the direct C-H arylation of indole acetic acids with aryl halides using palladium-catalyzed coupling reactions.^[7] While generally high yielding, this batch approach suffers from extensive reaction times and high temperatures. Our long standing experience in diazonium chemistry associated with pioneering works from Correia,^[8] Noël^[9] and Fairlamb^[10] describing the arylations of indoles with arenediazonium salts in batch, prompted us to propose our own flow-based strategy. Indeed, with the objective of developing an efficient arylation strategy of indole acetic acid derivatives, we acknowledged that the use of arenediazonium salts as highly reactive aryl halides surrogates would allow mild experimental conditions and fast reaction rates. However, considering the high reactivity and hazardous behavior of arenediazonium salts, we envisioned the development of a flow-based strategy to mitigate the safety concerns. In this contribution, we describe our efforts toward the development of an efficient, safe and operationally simple palladium-catalyzed direct C-H arylation strategy of indole acetic acid derivatives, assisted by an autonomous self-optimizing flow reactor. The methodology shows a broad substrate scope and is applied to the preparation of a key intermediate of farnesyl pyrophosphate-competitive inhibitors of farnesyl protein transferase **4**.

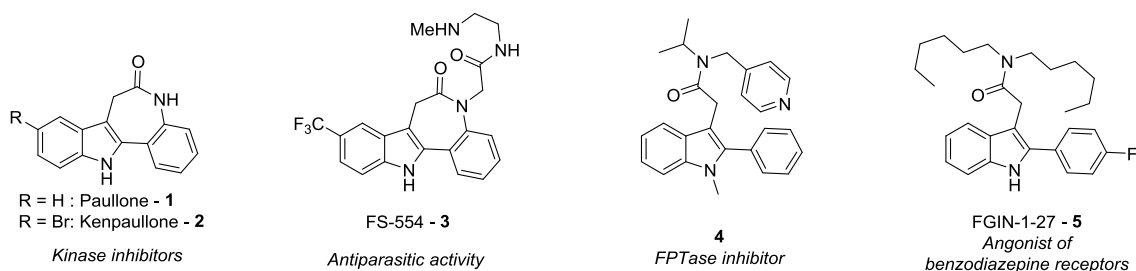
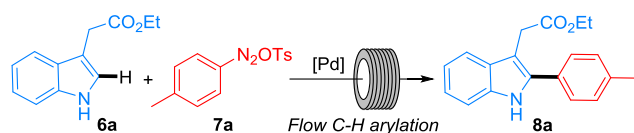


Figure 1. Pharmaceutically relevant 2-aryl-3-carbonylmethyl indoles.

Results and Discussion

The arylation of indole **6** with tolyldiazonium tosylate **7a**, in the presence of Pd(OAc)₂ as catalyst, was selected as benchmark transformation to be optimized for the development of a continuous flow strategy (Scheme 1).



Scheme 1. Benchmark reaction for the direct C-H arylation of 2-arylindole-3-acetic acid derivatives with arenediazonium salts in flow.

As our objective was to develop a simple, robust and environmentally acceptable methodology, we excluded the use of additives such as ligand, base, oxidant and stabilizing agent (ammonium salt). Traditionally, the optimizations of chemical transformations conducted either in batch or in flow, are mainly based on the (often biased) know-how of chemists through one-variable-at-a-time optimizations. Whilst this popular optimization method is easily set up, it is generally poorly efficient for multi-dimensional optimizations as it neglects interactions between variables. The use of design-of-experiment (DoE) methods partially addresses these drawbacks, but the high number of experiments required to locate a satisfactory optimum associated to the absence of feedback are strong handicaps to develop efficient automations. The development and optimization of continuous flow processes can be greatly speeded-up with the use of autonomous self-optimizing flow reactors.^[11-26] These powerful automated devices combine flow reactors with process control instrumentations, in-line/online analyses and optimization algorithms to assist the decision-making process of chemists.^[27-34] Our lab also recently contributed to this emerging field of research with the development of a reconfigurable flow platform for the screening of reagents and the autonomous optimization of chemical

transformations including natural product synthesis.^[35-37]

Based on our experience in autonomous self-optimizing reactors, we designed an automated two-stream flow setup integrating an online HPLC unit for the benchmark arylation of indole **6a** with tolyldiazonium tosylate **7a** under palladium catalysis (Figure 2). Before starting an optimization campaign with the flow platform, a careful assessment of the solubility profile of all known chemicals involved in the reaction is an important pre-requisite as any precipitate formed during the process would inevitably clog the flow reactor. This is particularly true when using arenediazonium tosylates which are poorly soluble in many organic solvents and generate inorganic salts. Arenediazonium tosylates are often ideally handled in MeOH or EtOH in which they are generally well soluble and stable over hours.^[38] By contrast, Pd(OAc)₂ is rapidly reduced by MeOH and EtOH into Pd nanoparticles which precipitate within minutes. Considering these features, we used a solution of diazonium **7a** in MeOH in the first stream while in the second stream indole **6a**, Pd(OAc)₂ and naphthalene **9** (used as internal standard for HPLC analysis) were solubilized in DMF. Therefore, a solution of diazonium salt **7a** was continuously pumped (0.1 M) and meet, in a T-shaped mixer, a DMF solution of indole **6a** (0.1 M), Pd(OAc)₂ (5 × 10⁻³ M) and naphthalene **9** (0.1 M). The reaction occurred in a stainless steel reactor coil (0.75 mm i.d., 10 mL) placed in an oven. The outlet of the reactor was connected to an automatic 2-way 6-port switch valve which injected an aliquot of the crude mixture into the HPLC line. An automated data processing allowed to integrate the chromatogram and to calculate the reaction yield. The value was automatically sent to the algorithm which proposed a new set of experimental conditions and the process control software modified the variables accordingly. The machine autonomously continues this iterative process until it reaches an optimum. The reaction yield was optimized in a 3-dimensional space where three variables, i.e., equivalent of **7a**, residence time and temperature, were considered in the range of 1-2 equiv, 15-90 min, and 25-60 °C, respectively. The temperature was limited to 60 °C to preserve the diazonium salt integrity. The initial experiment X₀ was fixed at 1 equiv of **7a**, 15 min of residence time

and 25 °C with *d* value of 0.2 equiv, 15 min and 7 °C, respectively.

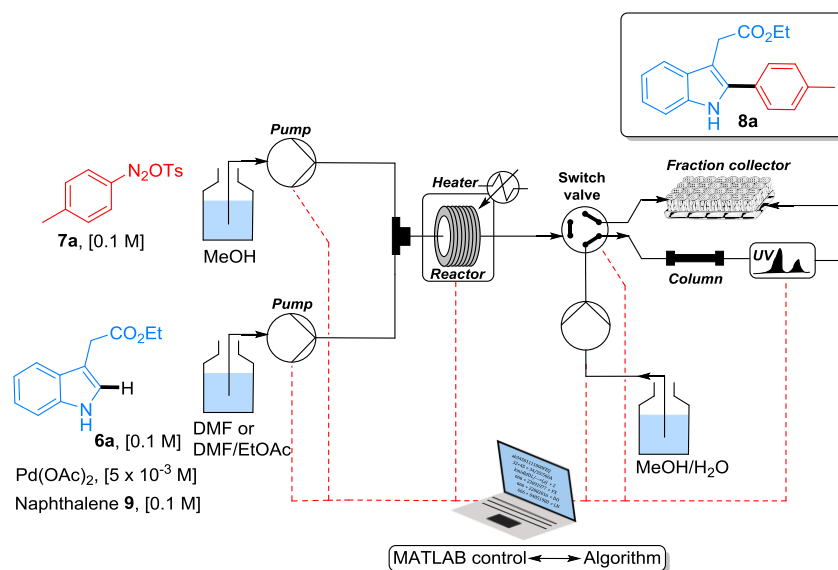


Figure 2. Autonomous self-optimizing flow reactor for the optimization of **8a**. The red dashed lines indicate the units controlled by the computer via MATLAB.

The optimization progressed rapidly until reaching a maximum reaction yield of 62% after 17 experiments at 1.2 equiv of **7a**, 65 min of residence time and 48 °C (Figure 3a, blue curve). The algorithm reached a stopping criteria in experiment 20 after 5 consecutive simplexes without improvement (see Table S1 in Supporting Information for details on experimental conditions). A close examination of the crude mixture showed the presence of a significant amount of toluene which likely arose from a rapid proto-diazotization of **7a**. We suspected that this unwanted behavior was, at least partially, favored in DMF which has been reported to promote proto-diazotization of arenediazonium salts.^[39] We, therefore, reconsidered the selection of solvents and reasoned that the volume of DMF, which is required to solubilize Pd species, should be significantly reduced through the use of a co-solvent. After having evaluated various combinations of DMF/co-solvent in different ratios, we selected a mixture of DMF/EtOAc in a 1/4 ratio. This choice was justified by the fact that tolyldiazonium tosylate **7a** is stable in EtOAc (no degradation observed after 30 min at room temperature) which is, in turn, considered as a sustainable solvent. The DMF/EtOAc ratio (1/4, respectively) was adjusted in order to reduce the volume of DMF to a minimum while keeping a clear solution with a complete dissolution of Pd species. We re-started the optimization process with this new solvent system while conserving the same search space and starting parameters. A spectacular effect was observed on the initial simplex since the reaction yields, ranging from 5 to 14% in MeOH/DMF, increased from 19 to 41% in MeOH/DMF/EtOAc (Figure 3b, red curve).

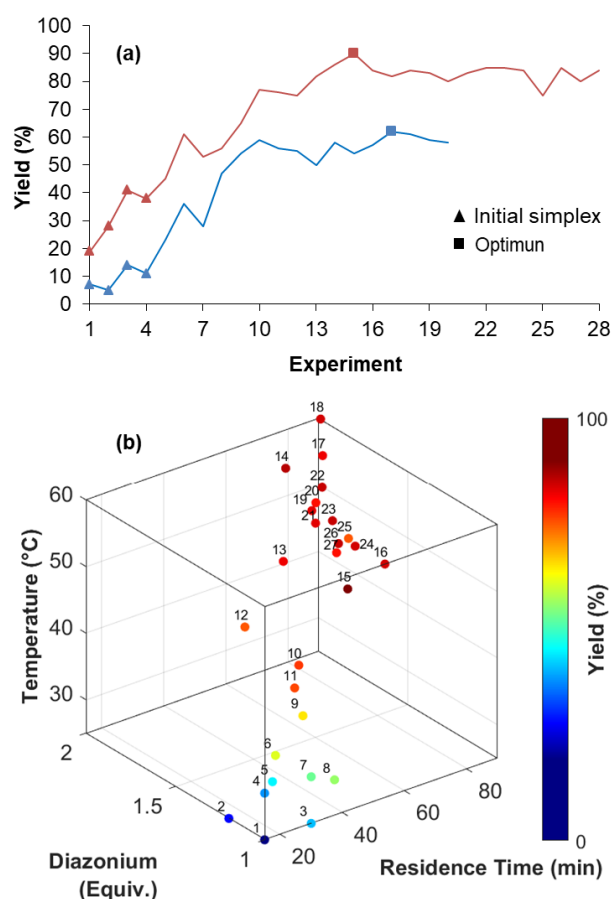
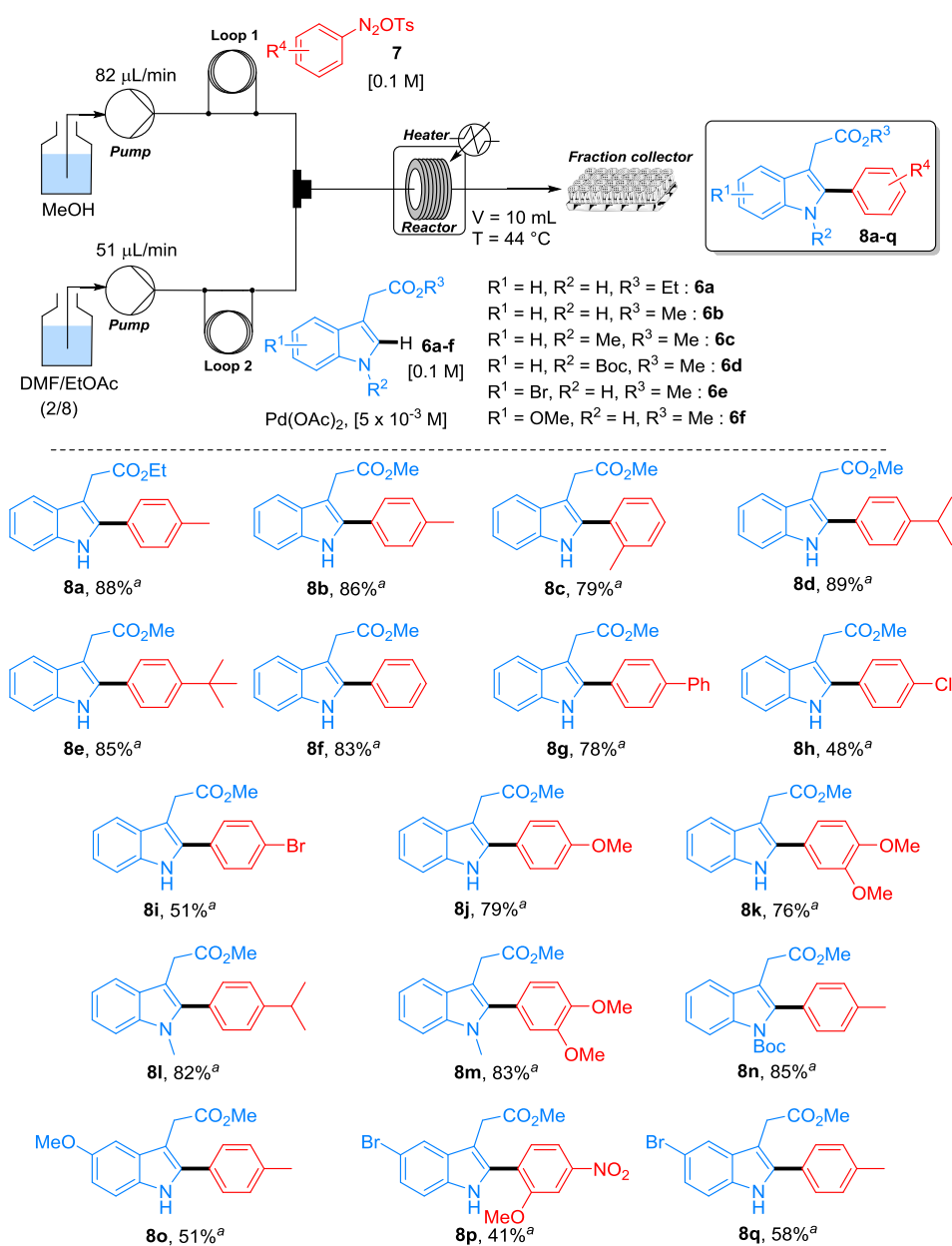


Figure 3. (a) Maximization of the yield of indole **8a**. The blue curve corresponds to the MeOH/DMF solvent system while the red curve corresponds to the MeOH/DMF/EtOAc solvent system. (b) Representation of the three-dimensional experimental conditions for the maximization

of the yield for indole **8a** in the MeOH/DMF/EtOAc solvent system.

After the initial simplex, the algorithm smoothly progressed by increasing the value of all variables until reaching an optimum in the 15th experiment at 44 °C, 74 min of residence time and 1.6 equivalents of **7a**, corresponding to 90% HPLC yield (88% isolated yield, see Figure S1 in supporting information for the HPLC chromatogram). The algorithm was unable to improve the reaction yield in the subsequent 5 simplexes and, therefore, reached a stopping criterion after experiment 28 (see Table S2 in Supporting Information for details on experimental conditions).

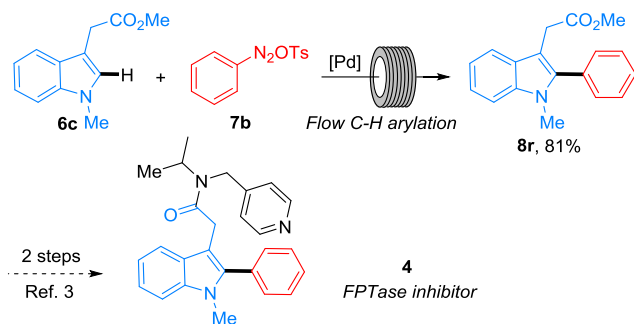
With the optimized conditions in hand, the reaction scope was examined with various arenediazonium salts and indoles, using the continuous flow setup depicted in Figure 4. The first stream, equipped with a 5 mL injection loop 1 and loaded with a solution of arenediazonium salts in MeOH (0.1 M, 82 $\mu\text{L}/\text{min}$), met in a T-shaped piece a second stream equipped with a 2 mL injection loop 2 and loaded with a solution of indole (0.1 M) and Pd(OAc)₂ (5×10^{-3} M) in DMF/EtOAc (1/4, 51 $\mu\text{L}/\text{min}$). The merged streams (133 $\mu\text{L}/\text{min}$) entered in a stainless steel reactor coil (0.75 mm id, 10 mL, 74 min residence time) heated at 44 °C, and the resulting 2-arylidole-3-acetic acid derivatives **8a-8q** were collected in vials.



^a Isolated yields

Figure 4. Scope of the C2-arylation of indole-3-acetic acid derivatives.

The arylation of indole-3-acetic acid alkyl esters was explored with a broad set of arenediazonium salts. While the optimization was conducted with indole-3-acetic acid ethyl ester **6a**, the reaction scope was extended to the methyl ester derivative **6b-f** to avoid any unwanted transesterification process with MeOH. The arylation of indoles **6a-b** was found to be compatible with arenediazonium salts bearing alkyl substituents at either *para*- or *ortho*-positions (**8a-e**). The excellent yield obtained for the *ortho*, *ortho*'-substituted indole **8c** suggests that the transformation was poorly sensitive to steric hindrance. Switching an alkyl group for an aryl substituent on the diazonium salt, did not significantly affect the reaction outcome (compounds **8g**). One of the salient advantages of using arenediazonium salts as super-electrophile is the possibility to introduce very electron-rich substituents such as methoxy groups which usually significantly deactivate aryl halides and compromise the C-H arylation efficiency. Another unique advantage of arenediazonium salts is the possibility to work without any base, resulting in a high chemoselectivity at the diazonium group in the presence of halogen positions and the compatibility of base-sensitive functional groups such as esters. For instance the coupling of 4-chloro- and 4-bromophenyl diazonium tosylates provided indoles **8h-i** with no evidence for a competing electrophilic reactivity of the halide atoms. Interestingly, we did not observe any significant difference in reactivity of 1-methylindole **6c** and N-Boc indole **6d** which behaved similarly than free NH-indoles (see **8l-n** versus **8d**, **8k** and **8b**, respectively). Decorating the indole skeleton with substituents (OMe and Br) significantly extended the reaction scope of the process (**8o-q**). Despite the lower yields observed with bromo-indoles, no evidence for a competing electrophilic reactivity of the bromine atom was observed and the drop in reactivity was instead attributed to a lower solubility of the starting indole **6e**. The inertness of halogen atoms in the reaction conditions might allow further chemical functionalizations through standard transition-metal catalyzed reactions.



Scheme 2. Synthesis of the key intermediate **8r** of FPTase inhibitor **4**.

To further confirm the efficiency of the methodology developed herein and, if this should

prove necessary, highlight the importance of such transformations, we applied our process to the synthesis of Methyl 2-(2-phenyl-1-methyl-1H-indol-3-yl)acetate **8r** which was isolated with 81% yield (Scheme 2). A continuous use of the flow platform over a period of 10 hours allowed to isolate *ca.* 0.5 g of indole **8r** (79%), showing the facile scalability of our methodology in flow. Indole **8r** is a key intermediate in the synthesis of farnesyl pyrophosphate-competitive inhibitor of farnesyl protein transferase **4**.^[3]

Conclusion

In summary, we developed a mild, base-free, ligand-free and safe continuous-flow protocol for the palladium-catalyzed direct C-H arylation of indole-3-acetic acid derivatives with arenediazonium salts. Highlights of this work include (i) the development of a fully autonomous self-optimizing flow platform, (ii) the use of arenediazonium salts as super-electrophiles, and (iii) the synthesis of a key intermediate in the synthesis of a farnesyl pyrophosphate-competitive inhibitor of farnesyl protein transferase. The capability of our autonomous self-optimizing flow platform to simultaneously screen several continuous variables without a priori knowledge of the optimal objective function is an indisputable attractive feature to optimize chemical transformations in a short time frame and reliable experimental conditions. While arenediazonium salts are often considered as hazardous reagents, our continuous-flow approach mitigates the risk associated with these attractive electrophiles which allow high reaction rates and mild experimental conditions. We believe that this work is a representative contribution in the area of machine-assisted chemistry which should become the standard of chemical laboratories 4.0.

Experimental Section

General Information. All commercially available chemicals were used as received unless otherwise noted. High-field ¹H and ¹³C NMR spectra were recorded at 300 or 400 and 75 or 100 MHz, respectively. ¹H and ¹³C NMR spectra were referenced to the residual signal of the internal deuterated solvent (CDCl₃) at 7.26 and 77.16 ppm, respectively, and coupling constants were measured in Hertz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. FT-IR spectra were recorded in the ATR mode. Wavelengths of maximum absorbance (ν_{max}) are quoted in wave numbers (cm⁻¹). High resolution mass spectrometry (HRMS) was recorded on a microTOF spectrometer equipped with orthogonal electrospray interface (ESI). Reactions were monitored by thin layer chromatography (TLC) with pre-coated silica gel plates (60 F₂₅₄), and visualization was accomplished with either a UV lamp at 254 nm or by immersion in ethanolic solution of phosphomolybdic acid (PMA). Flash column chromatography was performed using silica gel 60 (40–63 μm). In order to remove any trace of waste (Pd particles, inorganic salts...) which progressively deposits on the wall of the reactor coil, the tubing was washed every 100 hours of use with an aqueous solution of nitric acid (1M,

50 mL) followed by a thorough washing with water (100 mL) and CH₃CN (100 mL).

Details of the experimental setup of the self-optimizing reactor. HPLC pumps (JASCO PU2080 and JASCO PU4185) equipped with a RS-232 port were employed to flow the solution through the system. The reactor coil was heated with a heating plate (Heidolph, MR Hei-Connect) equipped with a RS-232 port. A 2-way 6-port valve (VICI, Cheminert C2-3006D) equipped with a RS-232 port was used to inject an aliquot of the crude mixture within the on-line HPLC unit. The HPLC column (Agela Promosil C18, 3.5 mm × 150mm, 5 μm) outlet was connected to a UV detector (JASCO, UV 2075) equipped with a RS-232 port. The flow outlet was connected to a programmable fraction collector (Advantec, CHF 1225C). All units equipped with a RS-232 port were autonomously controlled with MATLAB[®] through the use of communication protocols provided by the manufacturers.

Experimental procedure of the self-optimization for compound 8a. The experimental setup consisted of two streams as depicted in Figure 2. The first stream contained a solution of tolyldiazonium tosylate **7a** (0.1 M) in MeOH while the second stream contained a solution of indole **6a** (0.1 M), Pd(OAc)₂ (5 × 10⁻³ M) and naphthalene **9** (0.1 M) as the internal standard in DMF. Each solution was continuously pumped with two independent pumps at the required flow rate, and met in a stainless steel T-shaped piece (internal volume: 0.57 μL). The resulting mixture was introduced in a PEEK reactor coil (10 mL, 0.75 mm i.d.) heated at the desired temperature. The reactor outlet was connected to an automatic 2-way 6-port switch valve which injected 0.2 μL of the crude mixture in the HPLC unit while the remaining stream was collected in a fraction collector. A mixture of MeOH/H₂O (60/40, v/v) was used as mobile phase for the HPLC analysis at a flow rate of 0.4 mL/min. A UV detector was connected to the outlet of the HPLC column (Agela Promosil C18, 3.5 mm × 150 mm, 5 μm) to follow the absorbance at a wavelength of 254 nm. Peak integration and yield calculation were under full MATLAB automation. The calculated yield was automatically sent to the algorithm which set new experimental conditions to the units via RS-232 ports. A 3-D optimization of the reaction yield was conducted using the temperature, residence time and stoichiometry as the variables. The initial experiment of the simplex was: 25 °C, 15 min and 1 equivalent of diazonium salt **7a**. The *d* values were 7 °C, 15 min and 0.2 equivalent. The lower and upper boundaries of the research space were the following: 25-70 °C, 10-90 min and 1-2 equiv for the temperature, residence time and stoichiometry, respectively. The details of the 28 experiments carried out with the autonomous flow reactor are given in supporting information (Table S2). An optimum giving 90% HPLC yield was found in experiment 15 at 44 °C, 74 min of residence time and 1.60 equiv. of diazonium salt **7a**. An analytical sample of ethyl 2-(2-(p-tolyl)-1H-indol-3-yl)acetate **8a** was obtained by flash chromatography (10% AcOEt-petroleum ether) as a white solid (51.6 mg, 88%). mp 97 °C. IR (ATR) ν 3346, 1719, 764 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 8.10 (brs, 1H), 7.67 (dd, 1H, *J* = 0.7, 7.6 Hz), 7.56 (d, 2H, *J* = 8.1 Hz), 7.37 (dm, 1H, *J* = 6.4 Hz), 7.32 (d, 2H, *J* = 7.8 Hz), 7.22 (dt, 1H, *J* = 1.3, 7.1 Hz), 7.15 (dt, 1H, *J* = 1.2, 7.1 Hz), 4.18 (q, 2H, *J* = 7.2 Hz),

3.82 (s, 2H), 2.42 (s, 3H), 1.26 (t, 3H, *J* = 7.1 Hz). ¹³C NMR (CDCl₃, 75 MHz) δ 172.3, 137.9, 136.3, 135.6, 130.0, 129.6, 129.5, 129.1, 128.1, 122.3, 119.9, 119.2, 115.0, 110.8, 105.3, 60.8, 31.2, 21.3, 14.2. HRMS (ESI) *m/z* [M + H]⁺ Calcd for C₁₉H₂₀O₂N 294.1494; Found 294.1493.

General experimental setup for the synthesis of indoles 8b-r. The experimental setup consisted of two streams as depicted in Figure 4. The first stream (flow rate: 82 μL/min), equipped with a PEEK injection loop (5 mL) loaded with a solution of arenediazonium tosylate in MeOH (0.1 M), meet in a stainless steel T-shaped piece (internal volume 0.57 μL) a second stream (flow rate: 51 μL/min) consisting of a solution of indoles (0.1 M) and Pd(OAc)₂ (5 × 10⁻³ M) in DMF/EtOAc (1/4) loaded in a second PEEK loop (2 mL). The merged streams entered in a PEEK reactor coil (10 or 15 mL, 0.75 mm id, 44 °C) at a flow rate of 0.133 mL/min and the resulting indoles **8b-r** were collected in vials. Volatiles were removed under reduced pressure and the crude indoles **8b-r** were purified by flash chromatography on silica gel.

Methyl 2-(2-(p-tolyl)-1H-indol-3-yl)acetate 8b. Purification by flash chromatography on silica gel (5% EtOAc-petroleum ether) gave **8b** as a colorless oil (48 mg, 86%). IR (ATR) ν 3373, 1723, 1456, 740 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ 8.14 (br s, 1H), 7.66 (d, 1H, *J* = 7.7 Hz), 7.54 (d, 2H, *J* = 8.1 Hz), 7.36 (d, 1H, *J* = 8.0 Hz), 7.30 (d, 2H, *J* = 8.2 Hz), 7.22 (dt, 1H, *J* = 1.1, 7.1 Hz), 7.17 (dt, 1H, *J* = 0.9, 7.0 Hz), 3.85 (s, 2H), 3.72 (s, 3H), 2.43 (s, 3H). ¹³C NMR (CDCl₃, 100 MHz) δ 172.7, 138.0, 136.3, 135.6, 129.6, 129.5, 129.1, 128.1, 122.4, 120.0, 119.1, 110.8, 105.2, 52.0, 30.9, 21.3. HRMS (ESI) *m/z* [M + H]⁺ Calcd for C₁₈H₁₈O₂N 280.1338; Found 280.1336.

Methyl 2-(2-(o-tolyl)-1H-indol-3-yl)acetate 8c. Purification by flash chromatography on silica gel (5% EtOAc-petroleum ether) gave **8c** as a white solid (44.1 mg, 79%). mp 98 °C [Lit.^[40] 102 °C]. IR (ATR) ν 3362, 1719, 1167, 694 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 8.03 (br s, 1H), 7.66 (dd, 1H, *J* = 0.9, 8.0 Hz), 7.42 - 7.28 (m, 5H), 7.24 (dt, 1H, *J* = 1.4, 7.0 Hz), 7.18 (dt, 1H, *J* = 1.2, 7.1 Hz), 3.65 (s, 2H), 3.63 (s, 3H), 2.27 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ 172.4, 137.8, 136.0, 135.5, 131.6, 131.1, 130.3, 128.8, 128.1, 125.7, 122.2, 119.8, 119.0, 110.8, 106.3, 51.8, 30.6, 19.9. HRMS (ESI) *m/z* [M + H]⁺ Calcd for C₁₈H₁₈O₂N 280.1338; Found 280.1341.

Methyl 2-(2-(4-isopropylphenyl)-1H-indol-3-yl)acetate 8d. Purification by flash chromatography on silica gel (5% EtOAc-petroleum ether) gave **8d** as a white solid (54.6 mg, 89%). mp 124 °C. IR (ATR) ν 3309, 1703, 1343, 738 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 8.10 (br s, 1H), 7.66 (dt, 1H, *J* = 0.6, 7.7 Hz), 7.58 (dt, 2H, *J* = 2.0, 8.3 Hz), 7.40-7.34 (m, 3H), 7.22 (dt, 1H, *J* = 1.4, 7.1 Hz), 7.16 (dt, 1H, *J* = 1.2, 7.1 Hz), 3.85 (s, 2H), 3.72 (s, 3H), 2.98 (sept, 1H, *J* = 6.9 Hz), 1.30 (d, 6H, *J* = 6.9 Hz). ¹³C NMR (CDCl₃, 75 MHz) δ 172.8, 148.9, 136.3, 135.6, 129.8, 129.0, 128.2, 127.0, 122.4, 120.0, 119.1, 110.8, 105.1, 52.0, 33.9, 31.0, 23.9. HRMS (ESI) *m/z* [M + H]⁺ Calcd for C₂₁H₂₄O₂N 308.1651; Found 308.1663.

Methyl 2-(2-(4-(tert-butyl)phenyl)-1H-indol-3-yl)acetate 8e. Purification by flash chromatography on silica gel (5% EtOAc-petroleum ether) gave **8e** as a white solid (54.6 mg, 85%). mp 138 °C. IR (ATR) ν 3316, 1704,

1008, 700 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 8.15 (br s, 1H), 7.67 (dm, 1H, $J = 7.6$ Hz), 7.59 (app dt, 2H, $J = 1.6$, 8.1 Hz), 7.52 (app dt, 2H, $J = 2.1$, 8.7 Hz), 7.37 (dm, 1H, $J = 7.6$ Hz), 7.23 (dt, 1H, $J = 1.4$, 7.1 Hz), 7.17 (dt, 1H, $J = 1.2$, 7.1 Hz), 3.87 (s, 2H), 3.73 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.7, 151.1, 136.2, 135.6, 129.4, 129.1, 127.9, 125.9, 122.4, 120.0, 119.2, 110.8, 105.2, 52.0, 34.7, 31.3, 31.0. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{24}\text{O}_2\text{N}$ 322.1807; Found 322.1807.

Methyl 2-(2-phenyl-1H-indol-3-yl)acetate 8f. Purification by flash chromatography on silica gel (5% EtOAc-petroleum ether) gave **8f** as a white solid (44.1 mg, 83%). mp 108 $^\circ\text{C}$ [Lit.^[40] 106 $^\circ\text{C}$]. IR (ATR) ν 3326, 1703, 1274, 740 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 8.18 (br s, 1H), 7.70-7.63 (m, 3H), 7.52-7.47 (m, 2H), 7.43-7.36 (m, 2H), 7.24-7.15 (m, 2H), 3.87 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.7, 136.2, 135.7, 132.3, 129.0, 128.9, 128.2, 128.1, 122.6, 120.1, 119.2, 110.9, 105.5, 52.0, 30.9. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{16}\text{O}_2\text{N}$ 266.1181; Found 266.1185.

Methyl 2-(2-([1,1'-biphenyl]-4-yl)-1H-indol-3-yl)acetate 8g. Purification by flash chromatography on silica gel (5% EtOAc-petroleum ether) gave **8g** as a white solid (53.4 mg, 78%). mp 126 $^\circ\text{C}$. IR (ATR) ν 3359, 1723, 1168, 733 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 8.22 (s, 1H), 7.72-7.64 (m, 7H), 7.48 (app tm, 2H, $J = 7.1$ Hz), 7.43-7.36 (m, 2H), 7.25 (dt, 1H, $J = 1.4$, 7.1 Hz), 7.19 (dt, 1H, $J = 1.2$, 7.1 Hz), 3.92 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.7, 140.7, 140.4, 135.8, 131.2, 129.1, 128.9, 128.5, 127.6, 127.0, 122.6, 120.1, 119.2, 110.9, 105.7, 52.0, 31.0. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{24}\text{O}_2\text{N}$ 342.1492; Found 342.1494.

Methyl 2-(2-(4-chlorophenyl)-1H-indol-3-yl)acetate 8h. Purification by flash chromatography on silica gel (5% EtOAc-petroleum ether) gave **8h** as a white solid (28.7 mg, 48%). mp 94 $^\circ\text{C}$. IR (ATR) ν 3364, 1716, 1435, 749 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 8.18 (br s, 1H), 7.66 (dt, 1H, $J = 0.6$, 7.7 Hz), 7.57 (dt, 2H, $J = 2.4$, 8.7 Hz), 7.44 (dt, 2H, $J = 2.4$, 8.7 Hz), 7.35 (dm, 1H, $J = 8.1$ Hz), 7.23 (dt, 1H, $J = 1.4$, 7.0 Hz), 7.17 (dt, 1H, $J = 1.2$, 7.1 Hz), 3.82 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.6, 135.8, 135.0, 134.1, 130.8, 129.4, 129.2, 128.9, 122.9, 120.3, 119.3, 116.6, 110.9, 106.0, 52.1, 30.8. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{15}\text{O}_2\text{NCl}$ 300.0791; Found 300.0793.

Methyl 2-(2-(4-bromophenyl)-1H-indol-3-yl)acetate 8i. Purification by flash chromatography on silica gel (5% EtOAc-petroleum ether) gave **8i** as a white solid (35.0 mg, 51%). mp 119 $^\circ\text{C}$ [Lit.^[40] 121 $^\circ\text{C}$]. IR (ATR) ν 3360, 1721, 1168, 639 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 8.14 (br s, 1H), 7.65 (dd, 1H, $J = 0.7$, 7.7 Hz), 7.60 (dt, 2H, $J = 2.1$, 8.7 Hz), 7.51 (dt, 2H, $J = 2.2$, 8.6 Hz), 7.35 (d, 1H, $J = 7.6$ Hz), 7.24 (dt, 1H, $J = 1.2$, 7.7 Hz), 7.17 (dt, 1H, $J = 1.1$, 7.1 Hz), 3.82 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.5, 135.8, 134.9, 132.1, 131.2, 129.7, 128.9, 122.9, 122.3, 120.3, 119.3, 110.9, 106.1, 52.1, 30.8. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{15}\text{O}_2\text{NBr}$ 344.0286; Found 344.0285.

Methyl 2-(2-(4-methoxyphenyl)-1H-indol-3-yl)acetate 8j. Purification by flash chromatography on silica gel (20% EtOAc-petroleum ether) gave **8j** as a pale yellow solid (46.6 mg, 79%). mp 89 $^\circ\text{C}$. IR (ATR) ν 3334,

1705, 1241, 741 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 8.11 (br s, 1H), 7.65 (d, 1H, $J = 7.3$ Hz), 7.58 (dt, 2H, $J = 2.9$, 8.8 Hz), 7.35 (dm, 1H, $J = 7.3$ Hz), 7.19 (app dq, 2H, $J = 1.4$, 7.1 Hz), 7.01 (dt, 2H, $J = 2.9$, 8.8 Hz), 3.87 (s, 3H), 3.83 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.8, 159.6, 136.2, 135.6, 129.5, 129.0, 124.8, 122.3, 120.0, 119.0, 114.4, 110.7, 104.8, 55.3, 52.0, 30.9. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{18}\text{O}_3\text{N}$ 296.1287; Found 296.1291.

Methyl 2-(2-(3,4-dimethoxyphenyl)-1H-indol-3-yl)acetate 8k. Purification by flash chromatography on silica gel (30% EtOAc-petroleum ether) gave **8k** as a pale yellow solid (49.4 mg, 76%). mp 128 $^\circ\text{C}$. IR (ATR) ν 3324, 1722, 1010, 738 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 8.20 (s, 1H), 7.68 (dm, 1H, $J = 7.2$ Hz), 7.36 (dd, 1H, $J = 1.2$, 6.6 Hz), 7.32 (d, 1H, $J = 2.1$ Hz), 7.24-7.14 (m, 3H), 6.97 (d, 1H, $J = 8.4$ Hz), 3.95 (s, 3H), 3.93 (s, 3H), 3.84 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 172.8, 149.2, 149.0, 136.3, 135.5, 129.1, 125.1, 122.3, 120.5, 120.0, 119.1, 111.8, 111.5, 110.7, 104.8, 56.0, 55.9, 52.0, 31.0. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{20}\text{O}_4\text{N}$ 326.1406; Found 326.1392.

Methyl 2-(2-(4-isopropylphenyl)-1-methyl-1H-indol-3-yl)acetate 8l. Purification by flash chromatography on silica gel (5% EtOAc-petroleum ether) gave **8l** as a colorless oil (52.6 mg, 82%). IR (ATR) ν 1733, 1506, 1148, 739 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 7.65 (d, 1H, $J = 7.8$ Hz), 7.42-7.34 (m, 5H), 7.27 (app dt, 1H, $J = 1.1$, 6.9 Hz), 7.18 (app dt, 1H, $J = 1.1$, 7.9 Hz), 3.70 (s, 2H), 3.69 (s, 3H), 3.64 (s, 3H), 3.01 (quin, 1H, $J = 7.0$ Hz), 1.34 (d, 6H, $J = 7.0$ Hz). ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.9, 149.0, 139.5, 137.1, 130.6, 128.5, 127.6, 126.5, 121.8, 119.6, 119.0, 109.4, 105.5, 51.9, 34.0, 31.0, 31.0, 23.9. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{24}\text{O}_2\text{N}$ 322.1807; Found 322.1819.

Methyl 2-(2-(3,4-dimethoxyphenyl)-1-methyl-1H-indol-3-yl)acetate 8m. Purification by flash chromatography on silica gel (30% EtOAc-petroleum ether) gave **8m** as a colorless oil (56.3 mg, 83%). IR (ATR) ν 3002, 2941, 1727, 1509, 1465, 1247, 1025 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 7.67 (dt, 1H, $J = 1.0$, 7.7 Hz), 7.35 (d, 1H, $J = 8.0$ Hz), 7.27 (ddd, 1H, $J = 1.0$, 1.2, 6.9 Hz), 7.18 (ddd, 1H, $J = 1.0$, 1.2, 7.0 Hz), 7.10 (brs, 1H), 7.02 (m, 2H), 3.97 (s, 3H), 3.93 (s, 3H), 3.70 (s, 2H), 3.70 (s, 3H), 3.65 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.8, 149.1, 148.7, 139.3, 137.0, 127.5, 123.6, 123.2, 121.9, 119.7, 118.9, 114.0, 111.0, 109.4, 105.4, 55.9, 55.9, 51.8, 31.0, 30.9. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_2\text{H}_{22}\text{O}_4\text{N}$ 340.1549; Found 34

tert-Butyl 3-(2-methoxy-2-oxoethyl)-2-(p-tolyl)-1H-indole-1-carboxylate 8n. Purification by flash chromatography on silica gel (10% EtOAc-petroleum ether) gave **8n** as a colorless oil (75.8 mg, 85%). IR (ATR) ν 2979, 2950, 1726, 1454, 1358, 1322, 1144, 1071, 748 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz) δ 8.23 (d, 1H, $J = 8.2$ Hz), 7.55 (dm, 1H, $J = 7.6$ Hz), 7.35 (ddd, 1H, $J = 1.3$, 7.2, 8.5 Hz), 7.30-7.23 (m, 5H), 3.68 (s, 3H), 3.54 (s, 2H), 2.42 (s, 3H), 1.27 (s, 9H). ^{13}C NMR (CDCl_3 , 100 MHz) δ 171.9, 150.1, 137.8, 137.6, 136.4, 130.5, 129.7, 129.2, 128.6, 124.5, 122.8, 118.8, 115.3, 113.2, 83.1, 52.0, 30.6, 27.5, 21.3. HRMS (ESI) m/z $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_4\text{Na}$ 402.1681; Found 402.1671.

Methyl 2-(5-methoxy-2-(p-tolyl)-1H-indol-3-yl)acetate 8o. Purification by flash chromatography on silica gel (10% EtOAc-petroleum ether) gave **8o** as a yellow oil (31.5 mg, 51%). IR (ATR) ν 3367, 2949, 2830, 1729, 1624, 1485, 1452, 1434, 1216, 1197, 1169, 1113, 1022, 821 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 7.97 (br s, 1H), 7.43 (d, 2H, $J = 8.1$ Hz), 7.20 (d, 2H, $J = 7.9$ Hz), 7.16 (d, 1H, $J = 9.2$ Hz), 7.02 (d, 1H, $J = 2.4$ Hz), 6.78 (dd, 1H, $J = 2.5, 8.8$ Hz), 3.80 (s, 3H), 3.73 (s, 2H), 3.64 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.7, 154.4, 137.9, 137.1, 130.7, 129.6, 129.5, 128.0, 112.4, 111.6, 104.9, 101.0, 55.9, 52.0, 31.0, 21.2. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{20}\text{NO}_3$ 310.1443; Found 310.1437.

Methyl 2-(5-bromo-2-(2-methoxy-4-nitrophenyl)-1H-indol-3-yl)acetate 8p. Purification by flash chromatography on silica gel (10% EtOAc-petroleum ether) gave **8p** as an orange solid (34.1 mg, 41%). mp 185 °C. IR (ATR) ν 3373, 3112, 2920, 2850, 1714, 1588, 1509, 1437, 1337, 1237, 1170, 1058, 1023, 790 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 8.80 (br s, 1H), 7.99 (dd, 1H, $J = 2.2, 8.4$ Hz), 7.88 (d, 1H, $J = 2.1$ Hz), 7.86 (d, 1H, $J = 8.5$ Hz), 7.81-7.80 (m, 1H), 7.34 (dd, 1H, $J = 1.8, 8.7$ Hz), 7.27 (dd, 1H, $J = 0.5, 8.6$ Hz), 3.99 (s, 3H), 3.77 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 171.9, 156.9, 148.4, 134.4, 131.9, 131.4, 129.8, 126.7, 126.3, 122.0, 116.5, 113.4, 112.5, 108.1, 106.5, 56.4, 52.3, 31.0. HRMS (ESI) m/z $[\text{M} - \text{H}]^-$ Calcd for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_5\text{Br}$ 417.0086; Found 417.0083.

Methyl 2-(5-bromo-2-(p-tolyl)-1H-indol-3-yl)acetate 8q. Purification by flash chromatography on silica gel (10% EtOAc-petroleum ether) gave **8q** as a beige solid (41.2 mg, 58%). mp 133 °C. IR (ATR) ν 3339, 2954, 2916, 1715, 1510, 1464, 1436, 1332, 1317, 1197, 1170, 991, 888, 791 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 8.24 (br s, 1H), 7.74 (d, 1H, $J = 1.8$ Hz), 7.49 (d, 2H, $J = 6.5$ Hz), 7.27-7.23 (m, 3H), 7.15 (d, 1H, $J = 8.6$ Hz), 3.78 (s, 2H), 3.74 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.6, 138.3, 137.5, 134.2, 130.7, 129.7, 128.8, 128.0, 125.1, 121.5, 113.2, 112.3, 104.6, 52.1, 30.6, 21.3. HRMS (ESI) m/z $[\text{M} - \text{H}]^-$ Calcd for $\text{C}_{18}\text{H}_{15}\text{NO}_2\text{Br}$ 356.0286; Found 356.0286.

Methyl 2-(2-phenyl-1-methyl-1H-indol-3-yl)acetate 8r. Purification by flash chromatography on silica gel (10% EtOAc-petroleum ether) gave **8r** as a colorless oil (45.2 mg, 81%). IR (ATR) ν 1730, 1466, 1148, 738 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 7.64 (dt, 1H, $J = 1.0, 7.7$ Hz), 7.53-7.41 (m, 5H), 7.35 (d, 1H, $J = 7.2$ Hz), 7.27 (app dt, 1H, $J = 1.2, 6.9$ Hz), 7.17 (ddd, 1H, $J = 1.0, 1.1, 6.8$ Hz), 3.68 (s, 2H), 3.66 (s, 3H), 3.61 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 172.7, 139.3, 137.2, 131.2, 130.7, 128.5, 128.3, 127.5, 122.0, 119.7, 119.0, 109.5, 105.7, 51.9, 30.9. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{18}\text{O}_2\text{N}$ 280.1338; Found 280.1331.

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Direct C-H arylation of indole-3-acetic acid derivatives enabled by an autonomous self-optimizing flow reactor

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