JOC The Journal of Organic Chemistry

Note

Synthesis of indolines by a Zn-mediated Mannich reaction / Pd-catalyzed amination sequence

Marc Presset, Antoine Pignon, Jérôme Paul, Erwan Le Gall, Eric Leonel, and Thierry Martens

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b00013 • Publication Date (Web): 24 Feb 2017

ACS Publications

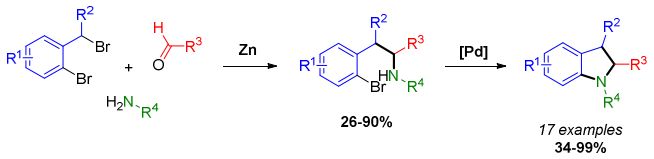
The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis of indolines by a Zn-mediated Mannich reaction / Pd-catalyzed amination sequence

Marc Presset, Antoine Pignon, Jérôme Paul, Erwan Le Gall,* Eric Léonel, Thierry Martens

Électrochimie et Synthèse Organique, Université Paris Est, ICMPE (UMR 7182), CNRS, UPEC, 2-8 rue Henri Dunant, F-94320 Thiais, France

legall@icmpe.cnrs.fr



Abstract

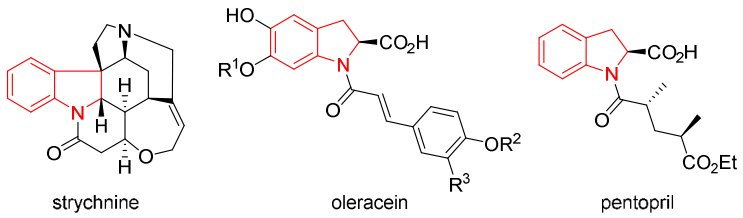
1,2-Disubstituted indolines have been prepared in fair to good yields by a Zn-mediated organometallic Mannich reaction followed by an intramolecular Pd-catalyzed aromatic amination. The reactions are easy to set up and compatible with a large variety of simple or commercially-available reagents. The method was further extended to the preparation of a 1,2,3-trisubstituted indoline.

The indoline scaffold is an important structural motif for medicinal chemists as it can be found in numerous naturally occurring alkaloids such as strychnine or oleracein A–D and in other bioactive compounds such as pentopril (**Figure 1**).[1,2,3] These attractive properties have made indolines relevant targets for the organic chemists' community.[4] Apart from the hydrogenation of indoles, main synthetic strategies towards indolines are based on the construction of the pyrrolidine ring system. For instance, the Pd-catalyzed heteroannulation of dienes with *o*-iodoanilines has been introduced by Larock in 1990.[5] This method has been recently improved by Jamison through extension to terminal alkenes using dual Ni/photoredox catalysis,[6] while Glorius developed the use

of alkenes in Rh(III)-catalyzed C–H activation/alkene insertion reactions.[7] A more general route has been pioneered by Buchwald, using a Pd-catalyzed intramolecular amination reaction between an aryl halide and an amine.[8,9,10] The main advantages of this strategy are the use of mild reaction conditions and a great functional group tolerance. However, it requires the preparation of *ortho*-halogenated β-arylethylamines bearing both reactive sites, usually by means of a multiple-step linear synthesis.

Although few of the usual synthetic methods could approach the high degree of modularity reached by multicomponent reactions (MCRs),[11] exploitation of this class of reactions for the preparation of indolines precursors has not been exploited so far. Based on our experience in MCRs involving organometallic species,[12,13] we anticipated that *ortho*-halogenated β-arylethylamines required for the preparation of indolines could be prepared by an organometallic Mannich reaction involving an *ortho*-brominated benzyl bromide.[14,15,16] Therefore, we describe herein a general two-step sequence involving a Zn-mediated Mannich reaction and a Pd-catalyzed intramolecular amination for the synthesis of 1,2-di- and even 1,2,3-trisubstituted indolines.

Figure 1. Selected bioactive indolines



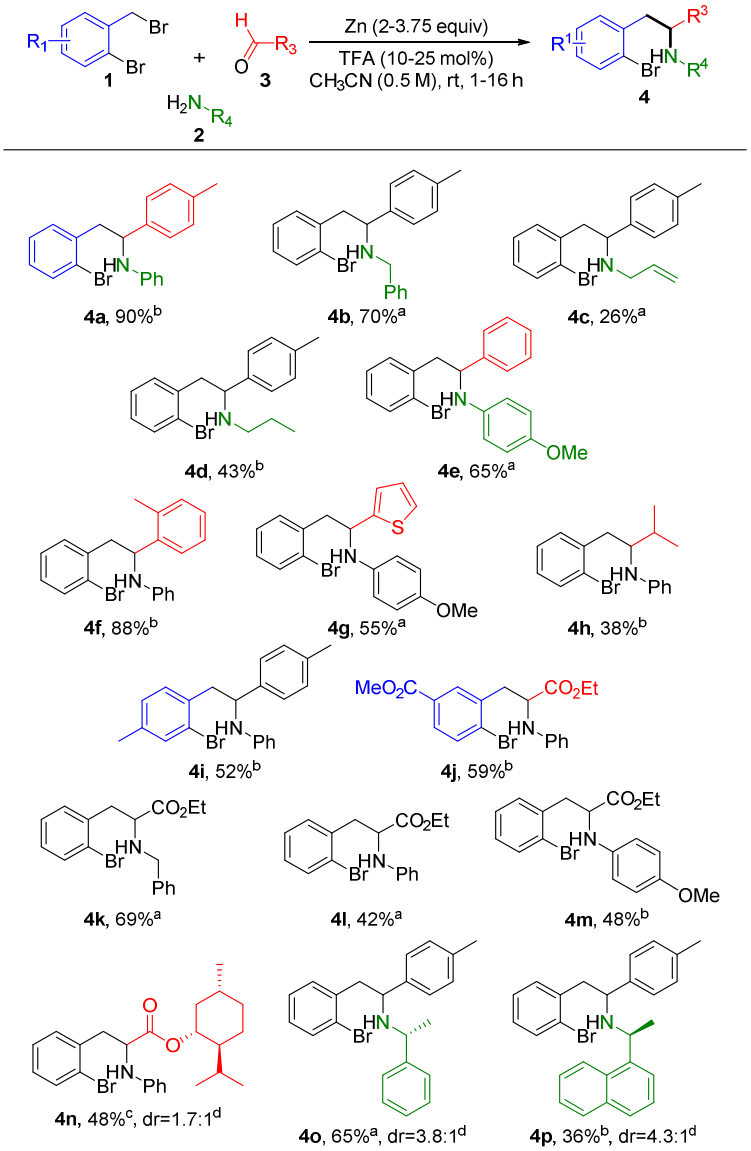
We began our study with the optimization of the organometallic Mannich reaction between commercial or easily accessible *ortho*-brominated benzyl bromides **1**, primary amines **2** and aldehydes **3**. Based on previous studies,[17,18,19] we turned our attention to Zn-mediated transformations as this metal proved efficient for the metalation of benzylic carbon-halogen bonds. A preliminary experiment using 2-bromobenzyl bromide **1a** (2.0 equiv), aniline **2a** (1.0 mmol) and 4-tolualdehyde **3a** (1.0 equiv) in the presence of zinc dust (2.0 equiv) in acetonitrile at ambient

temperature afforded the expected compound **4a** in 68%. This result revealed that **1a** was chemoselectively activated at the benzylic position without alteration of the aromatic C–Br bond. This information was consistent with previous reports by Gosmini indicating that zincation of aromatic carbon-halogen bonds requires the use of an additional cobalt catalyst.[20] We next found the addition of TFA to activate Zn was beneficial for the reaction with an increased yield of 90% whereas the use of THF as the solvent or Mn as the reductant were deleterious (59% yield and no reaction, respectively). The requirement of an excess (> 2.0 equiv) of the organozinc reagent to obtain the desired *ortho*-halogenated β-arylethylamine **4** in useful yields was confirmed by the decreased yield (58%) observed when the reaction was performed with only 1.5 equiv of **1a**.[21] We then turned our attention to the scope of the reaction and the results are reported in **Table 1**.

The Zn-mediated organometallic Mannich reaction proved general for the preparation of *ortho*-brominated β-arylamines **4**.[22] Using commercially available 2-bromobenzyl bromide (**1a**) as a starting material, a large variety of primary amines underwent the reaction even if small amines such as allylamine and *n*-propylamine afforded lower yields of coupling products (**4c** and **4d**), presumably due to their volatility under such exothermic conditions. The reaction also tolerated various aldehydes including aromatic (products **4a-f, 4i** and **4o-p**), heteroaromatic (product **4g**) or aliphatic aldehydes (product **4h**) in moderate to decent yields. However, the expected reaction was not observed with primary amides, ketones, pivaldehyde or methyl pyruvate. Substitution at the aromatic ring of the dibromide **1** with electron-neutral or electron-withdrawing groups was also possible (products **4i** and **4j**), but the introduction of an electron-donating group led only to traces of the desired product. Importantly, the present protocol was also compatible with the use of ethyl glyoxylate (**3f**) as the aldehyde partner, affording the corresponding α-aminoester derivatives in useful yields (products **4j-m**). The diastereoselectivity of the multicomponent reaction was also evaluated using commercial chiral substrates. Therefore, when (–)-menthyl glyoxylate (**3g**) was used, the expected product **4n** was obtained but only with moderate stereoinduction (dr=1.7:1). On

the other hand, when (*R*)-α-methylbenzylamine (**2f**) was used, the secondary β-arylethylamine **4o** was obtained in 65% yield with a fair diastereoselectivity (dr=3.8:1). The importance of the chiral group linked to the amine function was confirmed by the reaction performed with (*S*)-1-(1-naphthyl)ethylamine (**2g**) which displayed a slightly higher diastereoselectivity (dr=4.3:1).

Table 1. Multicomponent synthesis of *ortho*-brominated β-arylethylamine[a]

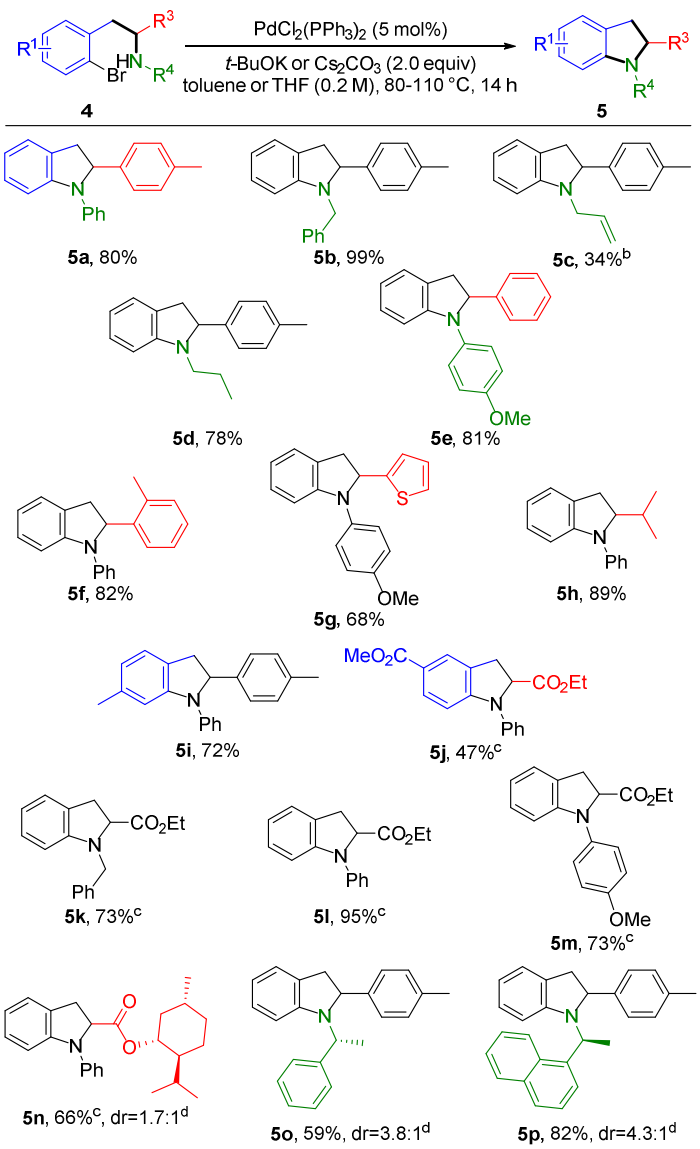


[a] Yields of isolated products. Reaction conditions: **1** (2.5 equiv), **2** (2.5 mmol), **3** (1.1 equiv), Zn (3.75 equiv), TFA (25 mol%), CH_3CN (C=0.5 M), 1 h; [b] Reaction conditions: **1** (2.0 equiv), **2** (1.0 mmol), **3** (1.0 equiv), Zn (2.0 equiv), TFA (10 mol%), CH_3CN (C=0.5 M), 16 h; [c] Reaction

performed under conditions b with **3a** (3.0 equiv) and Zn (3.0 equiv); [d] Diastereoisomeric ratio, determined by ^{1}H NMR analysis.

The cyclization of these β-arylethylamines **4** was undertaken by intramolecular aromatic amination. After a screening of diverse catalysts under varied conditions, the use of 5 mol% of $PdCl_2(PPh_3)_2$ with 2.0 equiv of potassium *tert*-butylate in refluxing toluene was identified as a very efficient catalytic system. The conversion of precursors **4** into the corresponding indolines was thus performed under such conditions and the results are reported in **Table 2**. These conditions proved to be general and afforded the desired indolines **5** in fair to good yields (products **5a-i**), regardless of the nature of the substituent of the pyrrolidine ring. However, although this set of conditions proved to efficiently deliver most of the target indolines, phenylalanine derivatives **4j-n** showed no conversion under standard conditions. Considering the presence of an enolizable ester group on the starting substrate, the base was thus changed to the less alkaline cesium carbonate and the solvent was switched from toluene to tetrahydrofuran. These modifications proved relevant, as the corresponding cyclization products **5j-n** were thus obtained in decent to good yields. Importantly, none of these conditions provoked either aromatization or erosion of diastereoisomeric ratios observed during the Mannich step (products **5n-p**).

Table 2. Pd-catalyzed cyclization of β-arylethylamines[a]

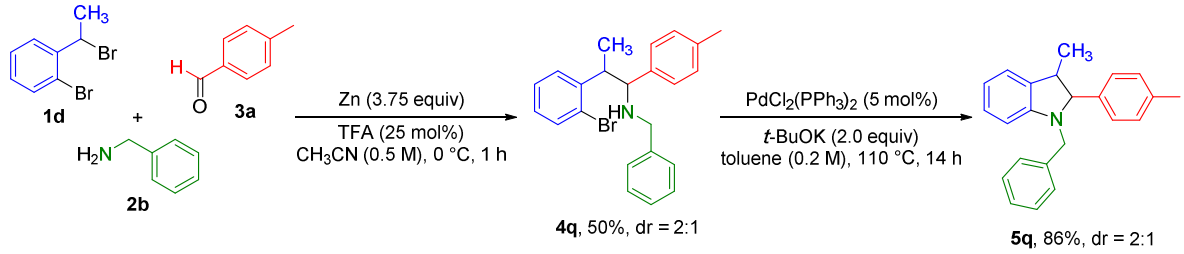


[a] Yields of isolated products. Reaction conditions: **4** (0.5 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), *t*-BuOK (2.0 equiv), toluene (C=0.2 M), 110 °C, 14 h; [b] The free indoline resulting from hydrodeallylation is concomitantly obtained in 19% yield; [c] Reactions performed using Cs_2CO_3 in THF at 80 °C for 24 h; [d] Diastereoisomeric ratio determined by ^1H NMR analysis.

Extension of this two-step strategy to the preparation of a 1,2,3-trisubstituted indoline required additional investigations. Indeed, the use of the above-mentioned conditions for the preparation of indolines precursors starting from secondary benzyl bromide **1d** only led to traces of the desired product together with major amounts of dimeric side-products. It was noticed that a decrease of the

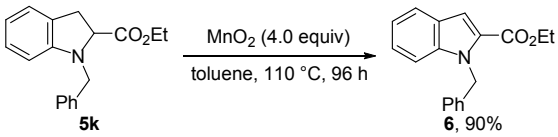
reaction temperature to 0 °C and dropwise addition of the dihalogenated starting material favors the desired multicomponent coupling. Under such conditions, the reaction between substrate **1d**, benzylamine (**2b**) and 4-tolualdehyde (**3a**) afforded a correct 50% isolated yield of **4q** with a moderate diastereoselectivity (**Scheme 1**).[23] The following intramolecular amination step, which was realized under the same above-mentioned conditions, led to the corresponding 1,2,3-trisubstituted indoline **5q** in very good yield (86%), without modification of the diastereoisomeric ratio.

Scheme 1. Synthesis of a 1,2,3-trisubstituted indoline



To ascertain that this method can represent a reliable route to substituted indoles, a tentative oxidation of indolinic α-amino ester **5k** to the corresponding indole **6** was undertaken using manganese oxide. The oxidized compound was obtained in an excellent 90% yield after 4 days in refluxing toluene (**Scheme 2**).

Scheme 2. Oxidation of indoline **5k** to indole **6**



In conclusion, we present herein a straightforward two-step procedure for the generation of diversely substituted indolines starting from commercial or easily accessible substrates. The tolerant and modular character of the method is ensured by an organometallic Mannich reaction followed by an intramolecular amination that allows the facile synthesis of 1,2-disubstituted indolines. The

present methodology was also demonstrated efficient for the preparation of indolinic α-amino esters and of a 1,2,3-trisubstituted indoline.

Experimental Section

General considerations: All commercially available reagents were used as received. In particular, zinc dust (<10 μm) was purchased from Sigma-Aldrich and 2-bromobenzyl bromide **1a** from Alfa-Aesar. Compound **1b** was prepared by $NaBH_4$ reduction and Appel's bromation of 2-bromo-4-methylbenzaldehyde. Compounds **1c** and **1d** were prepared by radical bromination of the corresponding toluene derivatives using NBS in the presence of a catalytic amount of AIBN. All 2-bromobenzyl bromides **1** are strong lachrymators and should be used under a well-ventilated fume hood. Acetonitrile (over calcium hydride) and THF (over sodium/benzophenone) were distilled prior to use. Unless other precision, reactions were performed under an argon atmosphere under magnetic stirring. Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude mixture. Analytical thin-layer chromatography (TLC) was performed on TLC silica gel plates (0.25 mm) precoated with a fluorescent indicator. Flash chromatography (FC) was performed on 40–63 μm silica gel with mixtures of ethyl acetate (EtOAc) and petroleum ether (PE), following Still's method. Visualization was effected with ultraviolet light and ethanolic $KMnO_4$. Melting point (mp) are uncorrected and were measured on a Büchi B-545 apparatus. NMR spectra were recorded on a Bruker 300 or 400 MHz spectrometer. ^{1}H NMR chemical shifts were referenced to the residual solvent signal; ^{13}C NMR chemical shifts were referenced to the deuterated solvent signal. Multiplicity was defined by DEPT 135 analysis. Data are presented as follows: chemical shift δ (ppm), multiplicity (*s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, *br* = broad), coupling constant *J* (Hz), integration. High-Resolution Mass Spectra were obtained at the ICOA of the Université of Orléans by electrospray ionization using a Q-TOF analyzer.

Preparation of *ortho*-bromo β-arylethylamines 4:

General procedure A: In air, a flame-dried 25 mL round-bottom flask equipped with a stir bar was charged with Zn (613 mg, 9.4 mmol, 3.75 equiv), closed with a septum and flushed with Ar. CH_3CN (5 mL, C=0.5 M), *o*-bromobenzyl bromide **1** (6.25 mmol, 2.5 equiv), aldehyde **3** (2.75 mmol, 1.1 equiv), amine **2** (2.5 mmol, 1.0 equiv) and TFA (48 µL, 0.62 mmol, 25 mol%) were successively added, and the reaction was stirred at rt for 1 h. Then, the reaction mixture was poured into sat aq NH_4Cl (50 mL) and the solution was extracted with EtOAc (2x25 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and evaporated. The crude material was purified either by FC or by an acid/base work-up: the residue was solubilized in Et_2O (50 mL) and concentrated H_2SO_4 (0.14 mL, 2.5 mmol, 1.0 equiv) was added dropwise under stirring. After 5 min, the ammonium salt was collected by gravity filtration on a fritted funnel and washed with Et_2O (2x20 mL). Then, the solid was poured into 50% aq NaOH (50 mL) and the solution was extracted with DCM (2x50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to afford the desired product **4**.

General procedure B: In air, a flame-dried 25 mL round-bottom flask equipped with a stir bar was charged with Zn (131 mg, 2.0 mmol, 2.0 equiv), closed with a septum and flushed with Ar. CH_3CN (2 mL, C=0.5 M), *o*-bromobenzyl bromide **1** (2.0 mmol, 2.0 equiv), aldehyde **3** (1.0 mmol, 1.0 equiv), amine **2** (1.0 mmol, 1.0 equiv) and TFA (8 µL, 0.10 mmol, 10 mol%) were successively added, and the reaction was stirred at rt for 16 h. Then, the reaction mixture was poured into sat aq NH_4Cl (20 mL) and the solution was extracted with EtOAc (2x10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and evaporated. The crude material was purified by FC to afford the desired product **4**.

Compound **4a**: Following the general procedure B, the reaction performed with 2-bromobenzyl bromide **1a** (500 mg, 2.0 mmol, 2.0 equiv), aniline **2a** (91 µL, 1.0 mmol, 1.0 equiv) and 4-tolualdehyde **3a** (118 µL, 1.0 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/EtOAc:99/1 then 97/3), the desired product **4a** (332 mg, 90%) as a yellow oil. **R_f (PE/EtOAc:95/5, UV+$KMnO_4$):** 0.39. **HRMS (ESI):** *m/z* calcd for $C_{21}H_{21}BrN$ $(M+H)^+$ 366.0851,

found 366.0849. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.61 (dd, *J*=7.9, 1.1 Hz, 1H), 7.34 (d, *J*=8.0 Hz, 2H), 7.23 (dd, *J*=7.3, 1.2 Hz, 1H), 7.19–7.14 (m, 3H), 7.12–7.058 (m, 3H), 6.66 (t, *J*=7.3 Hz, 1H), 6.53 (dd, *J*=8.6, 1.0 Hz, 2H), 4.74 (dd, *J*=8.4, 5.9 Hz, 1H), 4.31 (br s, 1H), 3.27–3.17 (m, 2H), 2.38 (s, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 147.4 (C), 140.5 (C), 137.8 (C), 136.8 (C), 133.1 (CH), 131.4 (CH), 129.4 (2 CH), 129.1 (2 CH), 128.5 (CH), 127.6 (CH), 126.3 (2 CH), 125.1 (C), 117.4 (CH), 113.6 (2 CH), 57.9 (CH), 45.4 (CH_2), 21.2 (CH_3).

Compound **4b**: Following the general procedure A, the reaction performed with 2-bromobenzyl bromide **1a** (1.6 g, 6.25 mmol, 2.5 equiv), benzylamine **2b** (0.27 mL, 2.5 mmol, 1.0 equiv) and 4-tolualdehyde **3a** (0.32 mL, 2.75 mmol, 1.1 equiv) afforded, after purification by FC (100 mL SiO_2, PE/Et_2O:95/5 then 90/10), the desired product **4b** (666 mg, 70%) as a yellow oil. **R_f (PE/Et_2O:90/10, UV+$KMnO_4$):** 0.17. **HRMS (ESI):** *m*/*z* calcd for $C_{22}H_{23}BrN$ $(M+H)^+$ 380.1008, found 380.1011.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (dd, *J*=7.9, 1.2 Hz, 1H), 7.16–7.12 (m, 4H), 7.10–7.08 (m, 1H), 7.04–7.02 (m, 4H), 7.00 (dd, *J*=7.4, 1.3 Hz, 1H), 6.92 (td, *J*=7.6, 1.8 Hz, 1H), 6.88 (dd, *J*=7.4, 1.7 Hz, 1H), 3.90 (dd, *J*=7.9–6.1 Hz, 1H), 3.58 (d, *J*=13.5 Hz, 1H), 3.39 (d, *J*=13.5 Hz, 1H), 3.01–2.90 (m, 2H), 3.07 (s, 3H), 1.67 (br s, 1H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 140.6 (C), 140.5 (C), 138.5 (C), 136.8 (C), 132.9 (CH), 131.8 (CH), 129.2 (2 CH), 128.3 (2 CH), 128.1 (CH), 127.9 (2 CH), 127.3 (2 CH), 127.2 (CH), 126.8 (CH), 125.0 (C), 61.5 (CH), 51.4 (CH_2), 45.4 (CH_2), 21.3 (CH_3).

Compound **4c**: Following the general procedure A, the reaction performed with 2-bromobenzyl bromide **1a** (1.6 g, 6.25 mmol, 2.5 equiv), allylamine **2c** (0.19 mL, 2.5 mmol, 1.0 equiv) and 4-tolualdehyde **3a** (0.32 mL, 2.75 mmol, 1.1 equiv) afforded, after purification by FC (100 mL SiO_2, CH/EtOAc:97.5/2.5 then 95/5), the desired product **4c** (217 mg, 26%) as a pale yellow oil. **R_f (CH/EtOAc:95/5, UV+$KMnO_4$):** 0.08. **HRMS (ESI):** *m*/*z* calcd for $C_{18}H_{21}BrN$ $(M+H)^+$ 330.0851, found 330.0850. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.56 (dd, *J*=7.9, 1.2 Hz, 1H), 7.23 (d, *J*=8.1 Hz, 2H), 7.17–7.12 (m, 3H), 7.08–7.01 (m, 2H), 5.82 (dddd, *J*=16.9, 10.3, 6.4, 5.3, 1H), 5.08–5.02 (m,

2H), 4.04 (dd, *J* = 7.5, 6.5 Hz, 1H), 3.18–3.10 (m, 2H), 3.07–3.00 (m, 2H), 2.35 (s, 3H) [NH not detected]. **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 140.2 (C), 138.4 (C), 136.8 (CH), 136.8 (C), 133.0 (CH), 131.8 (CH), 129.1 (2 CH), 128.1 (CH), 127.3 (2 CH), 127.2 (CH), 125.0 (C), 115.7 (CH_2), 61.5 (CH), 50.0 (CH_2), 45.2 (CH_2), 21.2 (CH_3).

Compound **4d**: Following the general procedure B, the reaction performed with 2-bromobenzyl bromide **1a** (1.0 g, 4.0 mmol, 2.0 equiv), propylamine **2d** (0.16 mL, 2.0 mmol, 1.0 equiv) and 4-tolualdehyde **3a** (0.24 mL, 2.0 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/EtOAc:9/1 then 8/2), the desired product **4d** (287 mg, 43%) as a yellow oil. **R_f (PE/EtOAc:8/2, UV+$KMnO_4$):** 0.31. **HRMS (ESI):** *m*/*z* calcd for $C_{18}H_{23}BrN$ $(M+H)^+$ 332.1008, found 332.1005. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.42 (dd, *J*=7.9, 1.2 Hz, 1H), 7.10 (d, *J*=8.0 Hz, 2H), 7.02–6.98 (m, 3H), 6.93–6.86 (m, 2H), 3.87–3.84 (m, 1H), 2.97 (dd, *J*=13.4, 7.7 Hz, 1H), 2.89 (dd, *J*=13.4, 6.3 Hz, 1H), 2.33–2.23 (m, 2H), 2.21 (s, 3H), 1.46 (br s, 1H), 1.35–1.24 (m, 2H), 0.68 (t, *J*=7.4 Hz, 3H). **^{13}C NMR {^{1}H}(100 MHz, $CDCl_3$):** δ 140.7 (C), 138.5 (C), 136.5 (C), 132.9 (CH), 131.8 (CH), 129.0 (2 CH), 128.0 (CH), 127.2 (2 CH), 127.1 (CH), 124.9 (C), 62.2 (CH), 49.6 (CH_2), 45.4 (CH_2), 23.2 (CH_2), 21.2 (CH_3), 11.7 (CH_3).

Compound **4e**: Following the general procedure A, the reaction performed with 2-bromobenzyl bromide **1a** (1.6 g, 6.25 mmol, 2.5 equiv), *p*-anisidine **2e** (308 mg, 2.5 mmol, 1.0 equiv) and benzaldehyde **3b** (0.28 mL, 2.75 mmol, 1.1 equiv) afforded, after purification by FC (100 mL SiO_2, PE/Et_2O:95/5 then 90/10), the desired product **4e** (620 mg, 65%) as a brown oil. **R_f (PE/Et_2O:90/10, UV+$KMnO_4$):** 0.26. **HRMS (ESI):** *m*/*z* calcd for $C_{21}H_{21}BrNO$ $(M+H)^+$ 382.0801, found 382.0799. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.62 (dd, *J*=8.1, 1.2 Hz, 1H), 7.46–7.44 (m, 2H), 7.39–7.35 (m, 2H), 7.32–7.28 (m, 1H), 7.26–7.22 (m, 1H), 7.15–7.11 (m, 2H), 6.71 (d, *J*=9.0 Hz, 2H), 6.50 (d, *J*=8.9 Hz, 2H), 4.71 (t, *J*=7.1 Hz, 1H), 4.08 (br s, 1H), 3.72 (s, 3H), 3.24–3.22 (m, 2H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 152.1 (C), 143.7 (C), 141.5 (C), 137.8 (C), 133.1 (CH), 131.4 (CH), 128.7 (2 CH), 128.5 (CH), 127.5 (CH), 127.2 (CH), 126.5 (2 CH), 125.1 (CH), 114.9 (2 CH), 114.7 (2 CH), 58.9 (CH), 55.8 (CH_3), 45.4 (CH_2).

Compound **4f**: Following the general procedure B, the reaction performed with 2-bromobenzyl bromide **1a** (500 g, 2.0 mmol, 2.0 equiv), aniline **2a** (91 μL, 1.0 mmol, 1.0 equiv) and 2-tolualdehyde **3c** (116 μL, 1.0 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/Et_2O:99/1 then 97.5/2.5), the desired product **4f** (323 mg, 88%) as a colorless oil. **R_f (PE/Et_2O:95/5, UV+$KMnO_4$):** 0.50. **HRMS (ESI):** *m*/*z* calcd for $C_{21}H_{21}BrN$ $(M+H)^+$ 366.0852, found 366.0853. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.73-7.69 (m, 2H), 7.38-7.29 (m, 4H), 7.25-7.19 (m, 4H), 6.80 (t, *J*=7.3 Hz, 1H), 6.61 (d, *J*=7.7 Hz, 2H), 5.13 (dd, *J*=8.5, 5.8 Hz, 1H), 4.45 (br s, 1H), 3.41 (dd, *J*=14.1, 8.5 Hz, 1H), 3.29 (dd, *J*=14.1, 5.8 Hz, 1H), 2.55 (s, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 147.2 (C), 141.2 (C), 137.5 (C), 135.1 (C), 133.0 (CH), 131.3 (CH), 130.6 (CH), 129.1 (2 CH), 128.5 (CH), 127.5 (CH), 127.0 (CH), 126.7 (CH), 125.6 (CH), 125.1 (C), 117.4 (CH), 113.3 (2 CH), 54.3 (CH), 43.6 (CH_2), 19.3 (CH_3).

Compound **4g**: Following the general procedure A, the reaction performed with 2-bromobenzyl bromide **1a** (1.6 g, 6.25 mmol, 2.5 equiv), *p*-anisidine **2e** (308 mg, 2.5 mmol, 1.0 equiv) and 2-thiophenecarboxaldehyde **3d** (0.26 mL, 2.75 mmol, 1.1 equiv) afforded, after purification by FC (100 mL SiO_2, PE/EtOAc:97.5/2.5 then 95/5), the desired product **4g** (532 mg, 55%) as an orange oil. **R_f (PE/EtOAc:95/5, UV+$KMnO_4$):** 0.19. **HRMS (ESI):** *m*/*z* calcd for $C_{19}H_{19}BrNOS$ $(M+H)^+$ 388.0365, found 388.0353. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.61 (dd, *J*=7.8, 1.0 Hz, 1H), 7.25–7.21 (m, 2H), 7.16–7.13 (m, 2H), 6.98–6.92 (m, 2H), 6.75 (d, *J*=9.0 Hz, 2H), 6.60 (d, *J*=9.0 Hz, 2H), 5.01 (t, *J*=6.8 Hz, 1H), 4.03 (br s, 1H), 3.74 (s, 3H), 3.36–3.34 (m, 2H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 152.5 (C), 148.9 (C), 141.1 (C), 137.3 (C), 133.0 (CH), 131.5 (CH), 128.5 (CH), 127.5 (CH), 126.8 (CH), 125.0 (C), 123.9 (CH), 123.7 (CH), 115.2 (2 CH), 114.7 (2 CH), 55.7 (CH_3), 55.3 (CH), 45.6 (CH_2).

Compound **4h**: Following the general procedure B, the reaction performed with 2-bromobenzyl bromide **1a** (1.0 g, 4.0 mmol, 2.0 equiv), aniline **2a** (0.18 mL, 2.0 mmol, 1.0 equiv) and iso-butyraldehyde **3e** (0.18 mL, 2.0 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/Et_2O:99/1 then 97.5/2.5), the desired product **4h** (246 mg, 38%) as a pale yellow oil. **R_f**

(PE/Et_2O:97.5/2.5, UV+$KMnO_4$): 0.43. **HRMS (ESI):** *m*/*z* calcd for $C_{17}H_{21}BrN$ $(M+H)^+$ 318.0852, found 318.0854. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38 (dd, *J*=8.0, 1.2 Hz, 1H), 7.10 (dd, *J*=7.6, 1.8 Hz, 1H), 7.03 (td, *J*=7.5, 1.3 Hz, 1H), 6.96–6.94 (m, 2H), 6.90–6.86 (m, 1H), 6.47 (tt, *J*=7.4, 1.0 Hz, 1H), 6.39–6.37 (m, 2H), 3.59–3.54 (m, 2H), 2.89 (dd, *J*=14.0, 4.6 Hz, 1H), 2.67 (dd, *J*=14.0, 9.3 Hz, 1H), 1.90–1.86 (m, 1H), 0.96 (d, *J*=6.9 Hz, 3H), 0.88 (d, *J*=6.8 Hz, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 148.2 (C), 139.1 (C), 132.8 (CH), 131.4 (CH), 129.2 (2 CH), 127.9 (CH), 127.4 (CH), 124.9 (C), 116.7 (CH), 113.0 (2 CH), 58.5 (CH), 38.2 (CH_2), 31.2 (CH), 18.6 (CH_3), 18.1 (CH_3).

Compound **4i**: Following the general procedure B, the reaction performed with α-bromobenzyl bromide **1b** (437 mg, 2.0 mmol, 2.0 equiv), aniline **2a** (91 µL, 1.0 mmol, 1.0 equiv) and 4-tolualdehyde **3a** (118 µL, 1.0 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/Et_2O:97.5/2.5 then 95/5), the desired product **4i** (197 mg, 52%) as a brown solid. **R_f (PE/Et_2O:95/5, UV+$KMnO_4$):** 0.43. **mp:** 75–78 °C. **HRMS (ESI):** *m*/*z* calcd for $C_{22}H_{23}BrN$ $(M+H)^+$ 380.1008, found 380.1010. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.53 (s, 1H), 7.44 (d, *J*=8.0 Hz, 2H), 7.29–7.26 (m, 2H), 7.21–7.27 (m, 2H), 7.13–7.12 (2H), 6.76 (t, *J*=7.3 Hz, 1H),6.63 (dd, *J*=8.6, 0.9 Hz, 2H), 4.81 (dd, *J*=8.8, 5.4 Hz, 1H), 4.40 (br s, 1H),3.33–3.22 (m, 2H), 2.47 (s, 3H), 2.41 (s, 3H). **^{13}C NMR {^{1}H}(100 MHz, $CDCl_3$):** δ 147.4 (C), 140.6 (C), 138.5 (C), 136.6 (C), 134.6 (C), 133.5 (CH), 131.0 (CH), 129.4 (2 CH), 129.0 (2 CH), 128.3 (CH), 126.3 (2 CH), 124.7 (C), 117.3 (CH), 113.6 (2 CH), 58.0 (CH), 44.9 (CH_2), 21.2 (CH_3), 20.7 (CH_3).

Compound **4j**: Following the general procedure B, the reaction performed with α-bromobenzyl bromide **1c** (1.2 g, purity=50%, 2.0 mmol, 2.0 equiv), aniline **2a** (91 µL, 1.0 mmol, 1.0 equiv) and ethyl glyoxylate **3f** (0.24 mL, 50% in toluene, 1.0 mmol, 1.0 equiv) afforded, after purification by FC (100 mL SiO_2, PE/Et_2O:8/2 then 6/4), the desired product **4j** (240 mg, 59%) as a brown solid.

R_f (PE/Et_2O:8/2, UV+$KMnO_4$): 0.23. **mp:** 75–78 °C. **HRMS (ESI):** *m*/*z* calcd for $C_{19}H_{21}BrNO_4$ $(M+H)^+$ 406.0648, found 406.0647. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.91 (d, *J*=2.1 Hz, 1H), 7.75 (dd, *J*=8.3, 2.1 Hz, 1H), 7.64 (d, *J*=8.3 Hz, 1H), 7.15 (dd, *J*=8.6, 7.4 Hz, 2H), 6.73 (t, *J*=7.3 Hz,

1H), 6.63 (dd, *J*=8.6, 1.0 Hz, 2H), 4.46 (t, *J*=7.2 Hz, 1H), 4.29 (br s, 1H) 4.14–4.08 (m, 2H), 3.90 (s, 3H), 3.32 (dd, *J*=13.7, 7.4 Hz, 1H), 3.25 -(dd, *J*=13.7, 7.0 Hz, 1H), 1.14 (t, *J*=7.1 Hz, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 173.0 (C), 166.3 (C), 146.4 (C), 137.1 (C), 133.2 (CH), 132.5 (CH), 130.3 (C), 129.6 (C), 129.5 (CH), 129.4 (2 CH), 118.7 (CH), 113.8 (2 CH), 61.4 (CH_2), 56.8 (CH), 52.4 (CH_3), 39.4 (CH_2), 14.1 (CH_2).

Compound **4k**: Following the general procedure A, the reaction performed with 2-bromobenzyl bromide **1a** (1.6 g, 6.25 mmol, 2.5 equiv), benzylamine **2b** (0.27 mL, 2.5 mmol, 1.0 equiv) and ethyl glyoxylate **3f** (0.56 mL, 50% in toluene, 2.75 mmol, 1.1 equiv) afforded, after purification by FC (100 mL SiO_2, PE/Et_2O:9/1 then 8/2), the desired product **4k** (625 mg, 69%) as a yellow oil. **R_f (PE/Et_2O:8/2, UV+$KMnO_4$):** 0.23. **HRMS (ESI):** *m*/*z* calcd for $C_{18}H_{21}BrNO_2$ $(M+H)^+$ 362.0750, found 362.0747. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.57 (d, *J*=8.2 Hz, 1H), 7.31–7.24 (m, 7H), 7.14–7.10 (m, 1H), 4.14 (q, *J*=7.1 Hz, 2H), 3.87 (d, *J*=13.2 Hz, 1H), 3.72–3.68 (m, 2H), 3.17 (dd, *J*=13.6, 7.5 Hz, 1H), 3.10 (dd, *J*=13.6, 7.4 Hz, 1H), 2.01 (br s, 1H), 1.19 (t, *J*=7.1 Hz, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 174.6 (C), 139.6 (C), 137.2 (C), 132.7 (CH), 131.5 (CH), 128.3 (2 CH), 128.3 (CH), 128.0 (2 CH), 127.1 (CH), 126.9 (CH), 124.9 (C), 60.6 (CH_2), 60.4 (CH), 51.9 (CH_2), 40.0 (CH_2), 14.1 (CH_3).

Compound **4l**: Following the general procedure A, the reaction performed with 2-bromobenzyl bromide **1a** (1.6 g, 6.25 mmol, 2.5 equiv), aniline **2a** (0.28 mL, 2.5 mmol, 1.0 equiv) and ethyl glyoxylate **3f** (0.56 mL, 50% in toluene, 2.75 mmol, 1.1 equiv) afforded, after purification by FC (100 mL SiO_2, PE/Et_2O:9/1 then 8/2), the desired product **4l** (365 mg, 42%) as a yellow paste. **R_f (PE/Et_2O:8/2, UV+$KMnO_4$):** 0.29. **HRMS (ESI):** *m*/*z* calcd for $C_{17}H_{19}BrNO_2$ $(M+H)^+$ 348.0593, found 348.0592. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.46 (dd, *J*=7.6, 0.9 Hz, 1H), 7.13–7.11 (m, 2H), 7.06 (dd, *J*=8.6, 7.4 Hz, 2H), 7.02–6.97 (m, 1H), 6.63 (tt, *J*=7.4, 1.0 Hz, 1H), 6.53 (dd, *J*=8.6, 1.0 Hz, 2H), 4.36 (t, *J*=7.3 Hz, 1H), 4.18 (br s, 1H), 4.03–3.94 (m, 2H), 3.20 (dd, *J*=13.6, 7.4 Hz, 1H), 3.08 (dd, *J*=13.6, 7.1 Hz, 1H), 1.01 (t, *J*=7.1 Hz, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 173.4

(C), 146.5 (C), 136.5 (C), 133.0 (CH), 131.5 (CH), 129.4 (2 CH), 128.7 (CH), 127.5 (CH), 124.9 (C), 118.5 (CH), 113.7 (2 CH), 61.2 (CH_2), 56.8 (CH), 39.5 (CH_2), 14.1 (CH_3).

Compound **4m**: Following the general procedure B, the reaction performed with 2-bromobenzyl bromide **1a** (1.0 g, 4.0 mmol, 2.0 equiv), *p*-anisidine **2e** (246 mg, 2.0 mmol, 1.0 equiv) and ethyl glyoxylate **3f** (0.48 mL, 50% in toluene, 2.0 mmol, 1.0 equiv) afforded, after purification by FC (100 mL SiO_2, PE/Et_2O:9/1 then 8/2), the desired product **4m** (363 mg, 48%) as a yellow oil. **R_f (PE/Et_2O:8/2, UV+$KMnO_4$):** 0.16. **HRMS (ESI):** *m*/*z* calcd for $C_{18}H_{20}BrNNaO_3$ $(M+Na)^+$ 400.0519, found 400.0518. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.56 (dd, *J*=7.6, 0.8 Hz, 1H), 7.24–7.22 (m, 2H), 7.12–7.08 (m, 1H), 6.75 (d, *J*=9.0 Hz, 2H), 6.61 (d, *J*=9.0 Hz, 2H), 4.37 (t, *J*=7.3 Hz, 1H), 4.12–4.03 (m, 2H), 3.72 (s, 3H), 3.28 (dd, *J*=13.6, 7.4 Hz, 1H), 3.16 (dd, *J*=13.6, 7.2 Hz, 1H), 1.11 (t, *J*=7.1 Hz, 3H) [NH not detected]. **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 173.7 (C), 152.9 (C), 140.6 (C), 136.6 (C), 133.0 (CH), 131.5 (CH), 128.6 (CH), 127.5 (CH), 124.9 (C), 115.4 (2 CH), 114.9 (2 CH), 61.1 (CH_2), 58.0 (CH), 55.7 (CH_3), 39.7 (CH_2), 14.1 (CH_3).

Compound **4n**: Following the general procedure B, the reaction performed with 2-bromobenzyl bromide **1a** (0.75 g, 3.0 mmol, 3.0 equiv), aniline **2a** (91 μL, 1.0 mmol, 1.0 equiv) and (–)-menthyl glyoxylate monohydrate **3g** (230 mg, 1.0 mmol, 1.0 equiv) with Zn (196 mg, 3.0 mmol, 3.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/Et_2O:97.5/2.5 then 95/5), the desired product **4n** (220 mg, dr=1.7:1, 48%) as a yellow oil. **R_f (PE/Et_2O:95/5, UV+$KMnO_4$):** 0.27. **HRMS (ESI):** *m*/*z* calcd for $C_{25}H_{33}BrNO_2$ $(M+H)^+$ 458.1689, found 458.1688. **^{1}H NMR (400 MHz, $CDCl_3$):** (2 diasteromers) δ 7.47 (dd, *J*=8.0, 1.2 Hz, 2H), 7.20–7.09 (m, 4H), 7.06–6.98 (m, 6H), 6.65–6.59 (m, 2H), 6.56–6.51 (m, 4H), 4.57–4.50 (m, 2H), 4.39–4.36 (m, 2H), 4.14 (br s, 2H), 3.22–3.06 (m, 4H), 1.87–1.81 (m, 1H), 1.72–1.50 (m, 7H), 1.34–1.18 (m, 5H), 0.93–0.85 (m, 4H), 0.80–0.73 (m, 9H), 0.63 (d, *J*=6.9 Hz, 3H), 0.54 (d, *J*=7.0 Hz, 3H), 0.45 (d, *J*=6.8 Hz, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** (2 diastereomers) δ 173.2 (C), 173.0 (C), 146.8 (C), 146.7 (C), 136.5 (C), 136.5 (C), 133.0 (CH), 133.0 (CH), 131.7 (CH), 131.5 (CH), 129.3 (2 CH), 129.2 (2 CH), 128.7 (CH), 128.7 (CH), 127.6 (CH), 127.6 (CH), 125.0 (C), 124.9 (C), 118.7 (CH), 118.6 (CH), 114.0 (2 CH), 113.8 (2

CH), 75.5 (CH), 75.2 (CH), 57.4 (CH), 57.0 (CH), 46.8 (CH), 46.8 (CH), 40.8 (CH_2), 40.4 (CH_2), 39.7 (CH_2), 39.6 (CH_2), 34.2 (CH_2), 34.1 (CH_2), 31.4 (CH), 31.3 (CH), 26.1 (CH), 25.5 (CH), 23.2 (CH_2), 23.0 (CH_2), 22.0 (CH_3), 22.0 (CH_3), 20.9 (CH_3), 20.9 (CH_3), 16.0 (CH_3), 15.9 (CH_3).

Compound **4o**: Following the general procedure A, the reaction performed with 2-bromobenzyl bromide **1a** (1.6 g, 6.25 mmol, 2.5 equiv), (R)-α-methylbenzylamine **2f** (0.32 mL, 2.5 mmol, 1.0 equiv) and 4-tolualdehyde **3a** (0.32 mL, 2.75 mmol, 1.1 equiv) afforded, after purification by FC (100 mL SiO_2, PE/Et_2O:95/5 then 90/10), the desired product **4o** (641 mg, dr=3.8:1, 65%) as a yellow paste. **R_f (PE/Et_2O:9/1, UV+$KMnO_4$):** 0.18. **HRMS (ESI):** *m*/*z* calcd for $C_{23}H_{25}BrN$ $(M+H)^+$ 394.1165, found 394.1164. **^{1}H NMR (400 MHz, $CDCl_3$):** (major diasteromer) δ 7.40 (dd, *J*=7.9, 1.3 Hz, 1H), 7.19–7.07 (m, 5H), 7.04–6.95 (m, 5H), 6.93–6.88 (m, 1H), 6.82–6.76 (m, 1H), 3.96 (t, *J*=7.0 Hz, 1H), 3.61 (q, *J*=6.5 Hz, 1H), 3.09 (dd, *J*=13.3, 7.0 Hz, 1H), 2.89 (dd, *J*=13.3, 7.1 Hz, 1H), 2.22 (s, 3H), 1.61 (br s, 1H), 1.15 (d, *J*=6.5 Hz, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** (major diasteromer) δ 146.3 (C), 140.7 (C), 138.7 (C), 136.6 (C), 132.8 (CH), 131.9 (CH), 129.1 (2 CH), 128.4 (2 CH), 127.9 (CH), 127.2 (2 CH), 127.0 (CH), 126.8 (CH), 126.7 (2 CH), 125.0 (C), 59.5 (CH), 54.8 (CH), 45.0 (CH_2), 22.6 (CH_3), 21.2 (CH_3).

Compound **4p**: Following the general procedure B, the reaction performed with 2-bromobenzyl bromide **1a** (500 mg, 2.0 mmol, 2.0 equiv), (S)-1-(1-naphthyl)ethylamine **2g** (160 µL, 1.0 mmol, 1.0 equiv) and 4-tolualdehyde **3a** (118 µL, 1.0 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/Et_2O:90/10 then 80/20), the desired product **4p** (162 mg, dr=4.3:1, 36%) as a pale yellow oil. **R_f (PE/Et_2O:80/20, UV+$KMnO_4$):** 0.42. **HRMS (ESI):** *m*/*z* calcd for $C_{27}H_{27}BrN$ $(M+H)^+$ 444.1321, found 444.1326. **^{1}H NMR (300 MHz, $CDCl_3$):** (major diasteromer) δ 7.93 (d, *J*=8.3 Hz, 1H), 7.89 (d, *J*=8.0 Hz, 1H), 7.78 (d, *J*=8.1 Hz, 1H), 7.59–7.52 (m, 2H), 7.50–7.41 (m, 3H), 7.25–7.14 (m, 4H), 7.12–6.98 (m, 3H), 4,61 (q, *J*=6.5 Hz, 1H), 4.23 (dd, *J*=7.1, 6.9 Hz, 1H), 3.27 (dd, *J*=13.3, 7.1 Hz, 1H), 3.10 (dd, *J*=13.3, 6.9 Hz, 1H), 2.41 (s, 3H), 1.90 (br s, 1H), 1.46 (d, *J*=6.5 Hz, 3H). **^{13}C NMR{^{1}H} (75 MHz, $CDCl_3$):** (major diasteromer) δ 142.0 (C), 140.7 (C), 138.8 (C), 136.7 (C), 134.0 (C), 132.8 (CH), 132.0 (CH), 131.2 (C), 129.2 (2 CH), 128.9 (2 CH),

127.9 (CH), 127.3 (2 CH), 127.0 (CH), 125.7 (2 CH), 125.4 (CH), 125.0 (C), 123.6 (CH), 123.0 (CH), 59.7 (CH), 50.5 (CH), 45.1 (CH_2), 22.1 (CH_3), 21.3 (CH_3).

Preparation of indolines 5:

General procedure A: In air, a flame-dried 25 mL Schlenk flask equipped with a stir bar was charged with β-arylethylamine **4** (0.5 mmol, 1.0 equiv) and toluene (2.5 mL, C=0.2 M). The solution was degassed by Ar bubbling for 5 min. *t*-BuOK (112 mg, 1.0 mmol, 2.0 equiv) and $PdCl_2(PPh_3)_2$ (18 mg, 0.025 mmol, 5 mol%) were successively added under an Ar flow and the flask was sealed (glass stopper). The reaction was heated at 110 °C overnight (14 h). Then, the reaction mixture was filtered through a pad of Celite (10 mL), thoroughly rinsed with EtOAc (ca. 50 mL), and the filtrate was evaporated. The crude material was purified by FC to afford the desired product **5**.

General procedure B (glyoxylate derivatives): In air, a flame-dried 25 mL Schlenk flask equipped with a stir bar was charged with β-arylethylamine **4** (0.5 mmol, 1.0 equiv) and THF (2.5 mL, C=0.2 M). The solution was degazed by Ar bubbling for 5 min. Cs_2CO_3 (326 mg, 1.0 mmol, 2.0 equiv) and $PdCl_2(PPh_3)_2$ (18 mg, 0.025 mmol, 5 mol%) were successively added under an Ar flow and the flask was sealed (glass stopper). The reaction was heated at 80 °C for 24 h. Then, the reaction mixture was filtered through a pad of Celite (10 mL), thoroughly rinsed with EtOAc (ca. 50 mL), and the filtrate was evaporated. The crude material was purified by FC to afford the desired product **5**.

Compound **5a**: Following the general procedure A, the reaction performed with **4a** (183 mg, 0.5 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE then PE/EtOAc:95/5), the desired product **5a** (114 mg, 80%) as a yellow solid. **R_f (PE/EtOAc:95/5, UV+$KMnO_4$):** 0.90. **mp:** 113–115 °C. **HRMS (ESI):** *m*/*z* calcd for $C_{21}H_{20}N$ $(M+H)^+$ 286.1590, found 286.1589. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.11–7.04 (m, 6H), 7.01–6.95 (m, 5H), 6.79 (t, *J*=7.1 Hz, 1H), 6.69–6.65 (m, 1H), 5.10 (dd, *J*=9.4, 6.3 Hz, 1H), 3.52 (dd, 15.6, 9.6 Hz, 1H), 2.84 (dd, *J*=15.6, 6.2 Hz, 1H), 2.17 (s, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 148.1 (C), 143.7 (C), 140.6 (C), 136.9 (C), 129.5 (2

CH), 129.3 (C), 129.1 (2 CH), 127.4 (CH), 126.2 (2 CH), 125.2 (CH), 121.8 (CH), 119.4 (2 CH), 108.8 (2 CH), 67.8 (CH), 39.8 (CH_2), 21.2 (CH_3).

Compound **5b**: Following the general procedure A, the reaction performed with **4b** (190 mg, 0.5 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE then PE/EtOAc:95/5), the desired product **5b** (149 mg, 99%) as a yellow oil. **R_f (PE, UV+KMnO$_4$):** 0.29. **HRMS (ESI):** *m*/*z* calcd for $C_{22}H_{22}N$ $(M+H)^+$ 300.1747, found 300.1747. **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.22 (d, *J*=8.0 Hz, 2H), 7.15–7.09 (m, 5H), 7.04 (d, *J*=7.8 Hz, 2H), 6.96–6.90 (m, 2H), 6.57 (t, *J*=7.3 Hz, 1H), 6.28 (d, *J*=7.8 Hz, 1H), 4.49 (t, *J*=9.7 Hz, 1H), 4.25 (d, *J*=15.8 Hz, 1H), 3.82 (d, *J*=15.8 Hz, 1H), 3.24 (dd, *J*=15.7, 9.0 Hz, 1H), 2.90 (dd, *J*=15.7, 10.4 Hz, 1H), 2.23 (s, 3H). **^{13}C NMR{^{1}H} (100 MHz, CDCl$_3$):** δ 152.5 (C), 139.5 (C), 138.5 (C), 137.4 (C), 129.4 (2 CH), 128.6 (C), 128.5 (2 CH), 127.7 (3 CH), 127.6 (2 CH), 126.9 (CH), 124.2 (CH), 117.9 (CH), 107.5 (CH), 69.2 (CH), 50.9 (CH_2), 39.6 (CH_2), 21.3 (CH_3).

Compound **5c**: Following the general procedure A, the reaction performed with **4c** (165 mg, 0.5 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/EtOAc:97.5/2.5 then 95/5), the desired product **5c** (44 mg, 34%) as a yellow oil. **R_f (PE/EtOAc:95/5, UV+KMnO$_4$):** 0.72. **HRMS (ESI):** *m*/*z* calcd for $C_{18}H_{20}N$ $(M+H)^+$ 250.1590, found 250.1585. **^{1}H NMR (400 MHz, CDCl$_3$):** δ 7.36 (d, *J*=7.9 Hz, 2H), 7.20 (d, *J*=7.9 Hz, 2H), 7.15–7.07 (m, 2H), 6.72 (td, *J*=7.4, 0.9 Hz, 1H), 6.57 (d, *J*=7.8 Hz, 1H), 5.82 (dddd, *J*=17.2, 10.3, 7.0, 4.5 Hz, 1H), 5.22–5.16 (m, 2H), 4.65 (dd, *J*=10.8, 9.0 Hz, 1H), 3.84–3.78 (m, 1H), 3.47–3.40 (m, 1H), 3.35 (dd, *J*=15.6, 8.9 Hz, 1H), 2.96 (dd, *J*=15.6, 10.9 Hz, 1H), 2.39 (s, 3H). **^{13}C NMR{^{1}H} (100 MHz, CDCl$_3$):** δ 152.2 (C), 139.7 (C), 137.4 (C), 133.6 (CH), 129.4 (2 CH), 128.7 (C), 127.7 (CH), 127.6 (2 CH), 124.2 (CH), 117.9 (CH), 117.4 (CH_2), 107.4 (CH), 68.7 (CH), 49.2 (CH_2), 39.6 (CH_2), 21.3 (CH_3).

Compound **5d**: Following the general procedure A, the reaction performed with **4d** (166 mg, 0.5 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/EtOAc:97.5/2.5 then 95/5), the desired product **5d** (98 mg, 78%) as a pale yellow oil. **R_f (PE/EtOAc:95/5, UV+KMnO$_4$):** 0.69. **HRMS (ESI):** *m*/*z* calcd for $C_{18}H_{22}N$ $(M+H)^+$ 252.1747, found 252.1747. **^{1}H NMR (400**

MHz, $CDCl_3$): δ 7.43 (d, *J*=7.9 Hz, 2H), 7.28 (d, *J*=7.9 Hz, 2H), 7.23 (t, *J*=7.7 Hz, 1H), 7.15 (d, *J*=7.1 Hz, 1H), 6.77 (td, *J*=7.5, 0.8 Hz, 1H), 6.59 (d, *J*=7.8 Hz, 1H), 4.74 (t, *J*=9.6 Hz, 1H), 3.45 (dd, *J*=15.7, 9.1 Hz, 1H), 3.15 (ddd, *J*=14.5, 8.6, 7.1 Hz, 1H), 3.07–2.95 (m, 2H), 2.48 (s, 3H), 1.63–1.57 (m, 2H), 0.94 (t, *J*=7.4 Hz, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 152.5 (C), 140.2 (C), 137.2 (C), 129.3 (2 CH), 128.3 (C), 127.7 (CH), 127.4 (2 CH), 124.1 (CH), 117.1 (CH), 106.3 (CH), 68.8 (CH), 48.5 (CH_2), 39.8 (CH_2), 21.2 (CH_3), 19.6 (CH_2), 11.8 (CH_3).

Compound **5e**: Following the general procedure A, the reaction performed with **4e** (191 mg, 0.5 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/EtOAc:95/5 then 90/10), the desired product **5e** (122 mg, 81%) as a yellow oil. **R_f (PE/EtOAc:90/10, UV+$KMnO_4$):** 0.50. **HRMS (ESI):** *m*/*z* calcd for $C_{21}H_{20}NO$ $(M+H)^+$ 302.1539, found 302.1538. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.27 (d, *J*=7.1 Hz, 2H), 7.20–7.16 (m, 2H), 7.13 (d, *J*=7.2 Hz, 1H), 7.02–6.96 (m, 4H), 6.69–6.64 (m, 4H), 5.06 (t, *J*=8.9 Hz, 1H), 3.63 (s, 3H), 3.49 (dd, *J*=15.7, 9.5 Hz, 1H), 2.93 (dd, *J*=15.7, 8.4 Hz, 1H). **^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$):** δ 155.7 (C), 150.2 (C), 143.4 (C), 137.1 (C), 128.7 (2 CH), 128.6 (C), 127.5 (CH), 127.4 (CH), 126.9 (2 CH), 124.8 (CH), 123.5 (2 CH), 118.8 (CH), 114.5 (2 CH), 108.0 (CH), 69.4 (CH), 55.5 (CH_3), 39.8 (CH_2).

Compound **5f**: Following the general procedure A, the reaction performed with **4f** (183 mg, 0.5 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE then PE/Et_2O:97.5/2.5), the desired product **5f** (117 mg, 82%) as a yellow oil. **R_f (PE/Et_2O:95/5, UV+$KMnO_4$):** 0.61. **HRMS (ESI):** *m*/*z* calcd for $C_{21}H_{20}N$ $(M+H)^+$ 286.1590, found 286.1588. **^{1}H NMR (300 MHz, $CDCl_3$):** δ 7.37 (d, *J*=7.3 Hz, 1H), 7.32–7.25 (m, 4H), 7.22–7.11 (m, 6H), 6.98 (t, *J*=7.2 Hz, 1H), 6.87 (t, *J*=7.3 Hz, 1H), 5.50 (dd, *J*=9.9, 5.3 Hz, 1H), 3.82 (dd, *J*=15.5, 9.9 Hz, 1H), 2.92 (dd, *J*=15.5, 5.3 Hz, 1H), 2.50 (s, 3H). **^{13}C NMR{^{1}H} (75 MHz, $CDCl_3$):** δ 147.6 (C), 143.9 (C), 141.4 (C), 134.1 (C), 130.9 (CH), 129.4 (C), 129.2 (2 CH), 127.4 (CH), 127.1 (CH), 126.5 (CH), 125.8 (CH), 125.5 (CH), 121.4 (CH), 119.6 (CH), 118.3 (2 CH), 109.4 (CH), 65.1 (CH), 37.9 (CH_2), 19.4 (CH_3).

Compound **5g**: Following the general procedure A, the reaction performed with **4g** (194 mg, 0.5 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/EtOAc:97.5/2.5 then 95/5),

the desired product **5g** (105 mg, 68%) as a yellow solid. **R_f (PE/EtOAc:95/5, UV+$KMnO_4$):** 0.27. **mp:** 120–125 °C. **HRMS (ESI):** *m*/*z* calcd for $C_{19}H_{18}NOS$ $(M+H)^+$ 308.1104, found 308.1099. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.21–7.15 (m, 4H), 7.11 (t, *J*=7.7 Hz, 1H), 6.95 (dd, *J*=3.4, 0.7 Hz, 1H), 6.92–6.86 (m, 3H), 6.83–6.79 (m, 1H), 6.66 (d, *J*=7.9 Hz, 1H), 5.41 (t, *J*=9.0 Hz, 1H), 3.80 (s, 3H), 3.63 (dd, *J*=15.6, 9.0 Hz, 1H), 3.24 (dd, *J*=15.6, 9.0 Hz, 1H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 156.5 (C), 150.2 (C), 147.1 (C), 136.9 (C), 128.2 (C), 127.6 (CH), 126.5 (CH), 125.3 (CH), 125.1 (2 CH), 124.7 (CH), 124.6 (CH), 119.0 (CH), 114.5 (2 CH), 108.4 (CH), 65.8 (CH), 55.4 (CH_3), 40.3 (CH_2).

Compound **5h**: Following the general procedure A, the reaction performed with **4h** (159 mg, 0.5 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/Et_2O:95/5), the desired product **5h** (105 mg, 89%) as a yellow oil. **R_f (PE/Et_2O:95/5, UV+$KMnO_4$):** 0.88. **HRMS (ESI):** *m*/*z* calcd for $C_{17}H_{20}N$ $(M+H)^+$ 238.1590, found 238.1590. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.45 (dd, *J*=8.5, 7.3 Hz, 2H), 7.35 (dd, *J*=8.5, 1.2 Hz, 2H), 7.20 (dd, *J*=7.2, 0.8 Hz, 1H), 7.16 (ddd, *J*=7.5, 4.2, 1.2 Hz, 1H), 7.08 (ddd, *J*=8.0, 1.2, 0.6 Hz, 1H), 6.83 (d, *J*=7.8 Hz, 1H), 6.78 (td, *J*=7.3, 0.9 Hz, 1H), 4.44 (ddd, *J*=9.6, 8.6, 3.9 Hz, 1H), 3.13 (dd, *J*=16.0, 9.6 Hz, 1H), 3.04 (dd, *J*=16.0, 8.6 Hz, 1H), 2.28–2.24 (m, 1H), 1.02 (d, *J*=7.0 Hz, 3H), 0.90 (d, *J*=6.8 Hz, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 150.0 (C), 143.6 (C), 129.5 (C), 129.3 (2 CH), 127.1 (CH), 124.8 (CH), 123.3 (CH), 122.9 (2 CH), 118.4 (CH), 107.4 (CH), 68.3 (CH), 28.7 (CH_2), 28.4 (CH), 19.1 (CH_3), 15.0 (CH_3).

Compound **5i**: Following the general procedure A, the reaction performed with **4i** (190 mg, 0.5 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/EtOAc:97.5/2.5 then 95/5), the desired product **5i** (108 mg, 72%) as a colorless oil. **R_f (PE/EtOAc:95/5, UV+$KMnO_4$):** 0.39. **HRMS (ESI):** *m*/*z* calcd for $C_{22}H_{20}N$ $(M-H)^+$ 298.1590, found 298.1593. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.40 (s, 1H), 7.30 (d, *J*=8.0 Hz, 2H), 7.14 (d, *J*=7.8 Hz, 2H), 7.05 (dd, *J*=8.5, 7.3 Hz, 2H), 7.01 (s, 2H), 6.62 (t, *J*=7.3 Hz, 1H), 6.48 (t, *J*=7.7 Hz, 2H), 4.66 (dd, *J*=8.9, 5.4 Hz, 1H), 3.17 (dd, *J*=14.2, 5.3 Hz, 1H), 3.11 (dd, *J*=14.2, 9.0 Hz, 1H), 2.34 (s, 3H), 2.30 (s, 3H). **^{13}C NMR{^{1}H}**

(100 MHz, $CDCl_3$): δ 147.4 (C), 140.6 (C), 138.5 (C), 136.8 (C), 134.6 (C), 133.6 (CH), 131.1 (CH), 129.4 (3 CH), 129.1 (3 CH), 128.4 (CH), 126.3 (2 CH), 124.8 (C), 113.7 (CH), 58.1 (CH), 45.0 (CH_2), 21.2 (CH_3), 20.7 (CH_3).

Compound **5j**: Following the general procedure B, the reaction performed with **4j** (203 mg, 0.5 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/EtOAc:90/10 then 80/20), the desired product **5j** (76 mg, 47%) as a yellow oil. **R_f (PE/EtOAc:90/10, UV+$KMnO_4$):** 0.26. **HRMS (ESI):** *m*/*z* calcd for $C_{19}H_{20}NO_4$ $(M+H)^+$ 326.1387, found 326.1385. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.74 (d, *J*=8.4 Hz, 1H), 7.71 (s, 1H), 7.31–7.27 (m, 2H), 7.18 (d, *J*=7.6 Hz, 2H), 7.03 (t, *J*=7.4 Hz, 1H), 6.84 (d, *J*=8.4 Hz, 1H), 4.82 (dd, *J*=10.7, 5.9 Hz, 1H), 4.12–4.02 (m, 2H), 3.78 (s, 3H), 3.50 (dd, *J*=16.1, 10.7 Hz, 1H), 3.16 (dd, *J*=16.1, 5.9 Hz, 1H), 1.09 (t, *J*=7.1 Hz, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 172.1 (C), 167.2 (C), 151.8 (C), 141.9 (C), 131.0 (CH), 129.5 (2 CH), 128.1 (C), 126.3 (CH), 124.1 (CH), 120.9 (2 CH), 120.8 (C), 107.4 (CH), 65.9 (CH), 61.6 (CH_2), 51.8 (CH_3), 33.2 (CH_2), 14.1 (CH_3).

Compound **5k**:[24] Following the general procedure B, the reaction performed with **4k** (181 mg, 0.5 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/EtOAc:97.5/2.5 then 95/5), the desired product **5k** (103 mg, 73%) as a pale yellow solid. **R_f (PE/EtOAc:95/5, UV+$KMnO_4$):** 0.27. **mp:** 56–58 °C. **HRMS (ESI):** *m*/*z* calcd for $C_{18}H_{20}NO_2$ $(M+H)^+$ 282.1489, found 282.1490. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.41–7.39 (m, 2H), 7.38–7.34 (m, 2H), 7.31–7.29 (m, 1H), 7.11–7.06 (m, 2H), 6.72 (ddd, *J*=7.5, 0.9 Hz, 1H), 6.48 (d, *J*=7.8 Hz, 1H), 4.56 (d, *J*=15.6 Hz, 1H), 4.36 (d, *J*=15.6 Hz, 1H), 4.29 (dd, *J*=10.3, 8.3 Hz, 1H), 4.21–4.13 (m, 2H), 3.42 (dd, *J*=15.9, 10.3 Hz, 1H), 3.24 (dd, *J*=15.9, 8.3 Hz, 1H), 1.26 (t, *J*=7.1 Hz, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 172.9 (C), 151.5 (C), 138.0 (C), 128.6 (2 CH), 127.9 (2 CH), 127.8 (CH), 127.3 (CH), 127.0 (C), 124.2 (CH), 118.2 (CH), 107.3 (CH), 65.6 (CH), 61.1 (CH_2), 52.3 (CH_2), 33.6 (CH_2), 14.2 (CH_3).

Compound **5l**:[23] Following the general procedure B, the reaction performed with **4l** (174 mg, 0.5 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/EtOAc:97.5/2.5 then 95/5), the desired product **5l** (127 mg, 95%) as a yellow solid. **R_f (PE/EtOAc:95/5, UV+$KMnO_4$):** 0.64.

mp: 55–57 °C. **HRMS (ESI):** *m/z* calcd for $C_{17}H_{18}NO_2$ $(M+H)^+$ 268.1332, found 268.1327. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.26–7.22 (m, 2H), 7.16–7.14 (m, 2H), 7.04 (d, *J*=7.3 Hz, 1H), 6.99 (d, *J*=7.3 Hz, 1H), 6.96–6.91 (m, 2H), 6.68 (td, *J*=7.2, 1.0 Hz, 1H), 4.71 (dd, *J*=10.5, 5.8 Hz, 1H), 4.12–4.02 (m, 2H), 3.47 (dd, *J*=15.9, 10.5 Hz, 1H), 3.12 (dd, *J*=15.9, 5.8 Hz, 1H), 1.09 (t, *J*=7.1 Hz, 3H). **^{13}C NMR {^{1}H}(100 MHz, $CDCl_3$):** δ 172.8 (C), 147.3 (C), 143.4 (C), 129.3 (2 CH), 128.3 (C), 127.5 (CH), 124.9 (CH), 122.5 (CH), 119.5 (CH), 119.4 (2 CH), 109.2 (CH), 65.6 (CH), 61.3 (CH_2), 33.8 (CH_2), 14.2 (CH_3).

Compound **5m**: Following the general procedure B, the reaction performed with **4m** (189 mg, 0.5 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/Et_2O:90/10 then 80/20), the desired product **5m** (109 mg, 73%) as a pale yellow paste. **R_f (PE/EtOAc:80/20, UV+$KMnO_4$):** 0.43. **HRMS (ESI):** *m/z* calcd for $C_{18}H_{20}NO_3$ $(M+H)^+$ 298.1438, found 2981436. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.28 (d, *J*=9.1 Hz, 2H), 7.16 (ddd, *J*=7.2, 1.2, 0.5, 1H), 7.11–7.07 (m, 1H), 6.95 (d, *J*=9.1 Hz, 2H), 6.79–6.75 (m, 2H), 4.77 (dd, *J*=10.4, 7.4 Hz, 1H), 4.26–4.16 (m, 2H), 3.85 (s, 3H), 3.58 (dd, *J*=15.9, 10.4 Hz, 1H), 3.28 (dd, *J*=15.9, 7.4 Hz, 1H), 1.24 (t, *J*=7.1 Hz, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 172.8 (C), 156.3 (C), 149.3 (C), 136.9 (C), 127.6 (CH), 127.5 (C), 124.6 (CH), 123.8 (2 CH), 118.9 (CH), 114.7 (2 CH), 108.3 (CH), 66.8 (CH), 61.2 (CH_2), 55.5 (CH_3), 33.9 (CH_2), 14.2 (CH_3).

Compound **5n**: Following the general procedure B, the reaction performed with **4n** (236 mg, 0.5 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/Et_2O:97.5/2.5 then 95/5), the desired product **5n** (125 mg, 66%, dr=1.7:1) as a white solid. **R_f (PE/Et_2O:95/5, UV+$KMnO_4$):** 0.47. **mp:** 48–58 °C. **HRMS (ESI):** *m/z* calcd for $C_{25}H_{31}NNaO_2$ $(M+Na)^+$ 400.2247, found 400.2248. **^{1}H NMR (400 MHz, $CDCl_3$):** (2 diastereomers) δ 7.25–7.21 (m, 4H), 7.15–7.11 (m, 4H), 7.05–7.03 (m, 2H), 6.99–6.96 (m, 4H), 6.93–6.89 (m, 2H), 6.69–6.65 (m, 2H), 4.81 (dd, *J*=10.3, 7.6 Hz, 1H), 4.68 (dd, *J*=10.4, 5.5 Hz, 1H), 4.60–4.52 (m, 2H), 3.49–3.38 (m, 2H), 3.15–3.04 (m, 2H), 1.83–1.78 (m, 2H), 1.56–1.48 (m, 6H), 1.40–1.20 (m, 4H), 1.22–1.12 (m, 2H), 0.94–0.84 (m, 4H), 0.79 (d, *J*=6.6 Hz, 3H), 0.77 (d, *J*=6.6 Hz, 3H), 0.68 (d, *J*=7.0 Hz, 3H), 0.63 (d, *J*=7.0

Hz, 3H), 0.55 (d, *J*=7.0 Hz, 3H), 0.44 (d, *J*=6.9 Hz, 3H). **^{13}C NMR {^{1}H} (100 MHz, $CDCl_3$):** (2 diastereomers) δ 172.6 (C), 172.3 (C), 147.4 (C), 147.2 (C), 143.2 (C), 143.1 (C), 129.3 (2 CH), 129.3 (2 CH), 128.4 (C), 128.2 (C), 127.6 (CH), 127.5 (CH), 124.8 (2 CH), 122.4 (CH), 122.2 (CH), 119.4 (CH), 119.4 (CH), 119.3 (2 CH), 119.0 (2 CH), 108.8 (CH), 108.4 (CH), 75.3 (CH), 75.3 (CH), 65.7 (CH), 65.6 (CH), 46.9 (CH), 46.8 (CH), 40.5 (CH_2), 40.4 (CH_2), 34.2 (2 CH_2), 34.1 (CH_2), 33.8 (CH_2), 31.4 (CH), 31.4 (CH), 26.0 (CH), 25.5 (CH), 23.2 (CH_2), 23.0 (CH_2), 22.1 (CH_3), 22.0 (CH_3), 20.9 (CH_3), 20.8 (CH_3), 16.0 (CH_3), 15.7 (CH_3).

Compound **5o**: Following the general procedure A, the reaction performed with **4o** (197 mg, 0.5 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE then PE/EtOAc:95/5), the desired product **5o** (92 mg, 59%, dr=3.8:1) as a pale yellow solid. **R_f (PE/EtOAc:90/10, UV+$KMnO_4$):** 0.95. **mp:** 110–112 °C. **HRMS (ESI):** *m*/*z* calcd for $C_{23}H_{24}N$ $(M+H)^+$ 314.1903, found 314.1903. **^{1}H NMR (400 MHz, $CDCl_3$):** (major diastereomer) δ 7.35 (d, *J*=8.1 Hz, 2H), 7.32 (d, *J*=8.0 Hz, 2H), 7.21 (t, *J*=7.6 Hz, 2H), 7.14–7.08 (m, 1H), 7.07 (d, *J*=6.1 Hz, 2H), 6.94 (d, *J*=7.3 Hz, 1H), 6.77 (t, *J*=7.7 Hz, 1H), 6.54 (t, *J*=7.3 Hz, 1H), 5.99 (d, *J*=7.9 Hz, 1H), 4.62 (dd, *J*=10.6, 9.0 Hz, 1H), 4.33–4.25 (m, 1H), 3.28 (dd, *J*=15.6, 9.0 Hz, 1H), 2.91 (dd, *J*=15.6, 10.6 Hz, 1H), 2.24 (s, 3H), 1.37 (d, *J*=6.9 Hz, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** (major diastereomer) δ 149.9 (C), 142.7 (C), 140.6 (C), 137.4 (C), 129.4 (2 CH), 129.3 (C), 128.4 (2 CH), 127.6 (2 CH), 127.1 (CH), 126.9 (2 CH), 126.7 (CH), 124.2 (CH), 117.8 (CH), 109.7 (CH), 67.9 (CH), 53.7 (CH), 39.8 (CH_2), 21.3 (CH_3), 12.8 (CH_3).

Compound **5p**: Following the general procedure A, the reaction performed with **4p** (110 mg, 0.25 mmol, 1.0 equiv) afforded, after purification by FC (50 mL SiO_2, PE/Et_2O:99/1 then 97.5/2.5), the desired product **5p** (74 mg, 82%, dr=4.3:1) as a colorless oil. **R_f (PE/Et_2O:95/5, UV+$KMnO_4$):** 0.74. **HRMS (ESI):** *m*/*z* calcd for $C_{27}H_{26}N$ $(M+H)^+$ 364.2060, found 364.2055. **^{1}H NMR (300 MHz, $CDCl_3$):** (major diastereomer) δ 7.95–7.84 (m, 3H), 7.53–7.38 (m, 4H), 7.14–7.01 (m, 6H), 6.71 (t, *J*=7.7 Hz, 1H), 6.51 (d, *J*=7.8 Hz, 1H), 5.39 (q, *J*=6.8 Hz, 1H), 4.42 (dd, *J*=10.1, 5.6 Hz, 1H), 3.45 (dd, *J*=15.9, 10.1 Hz, 1H), 2.91 (dd, *J*=15.9, 5.6 Hz, 1H), 2.40 (s, 3H), 1.55 (d, *J*=6.8 Hz,

3H). **^{13}C NMR{^{1}H} (75 MHz, $CDCl_3$):** (major diastereomer) δ 151.0 (C), 142.6 (C), 137.1 (C), 137.0 (C), 133.8 (C), 132.0 (C), 129.1 (2 CH), 128.9 (CH), 128.2 (C), 128.1 (CH), 127.6 (CH), 126.8 (2 CH), 126.4 (CH), 125.6 (CH), 125.2 (CH), 124.8 (CH), 124.4 (CH), 123.8 (CH), 116.7 (CH), 105.8 (CH), 64.9 (CH), 51.4 (CH), 39.5 (CH_2), 21.3 (CH_3), 17.9 (CH_3).

Synthesis of 1,2,3-trisubstituted indoline 5q:

Compound **4q**: In air, a flame-dried 25 mL round-bottom flask equipped with a stir bar was charged with Zn (368 mg, 5.6 mmol, 3.75 equiv), closed with a septum and flushed with Ar. CH_3CN (1 mL) and TFA (29 µL, 0.37 mmol, 25 mol%) were successively added and the mixture was stirred at room temperature for 5 min. The mixture was cooled down to 0 °C (ice/water bath) and 4-tolualdehyde **3a** (0.2 mL, 1.65 mmol, 1.1 equiv) and benzylamine **2b** (163 µL, 1.5 mmol, 1.0 equiv) were added in one portion. *o*-bromobenzyl bromide **1d** (1.0 g, 3.75 mmol, 2.5 equiv) in solution in CH_3CN (2 mL, C=0.5 M) was added dropwise (1 drop/s) at 0 °C, and the reaction was stirred for 1 h at 0 °C. Then, the reaction mixture was poured into sat aq NH_4Cl (50 mL) and the solution was extracted with EtOAc (2x25 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and evaporated. The crude material was purified by FC (100 mL SiO_2, PE/EtOAc:97.5/2.5 then 95/5) to afford the desired product **4q** (296 mg, 50%, dr=2:1) as a pale yellow oil. **R_f (PE/EtOAc:90/10, UV+$KMnO_4$):** 0.52 & 0.57. **HRMS (ESI):** *m*/*z* calcd for $C_{23}H_{25}BrN$ $(M+H)^+$ 394.1165, found 394.1164. **^{1}H NMR (400 MHz, $CDCl_3$):** (2 diastereomers) δ 7.70 (dd, *J*=7.9, 1.1 Hz, 1H), 7.60 (dd, *J*=8.0, 1.0 Hz, 1H), 7.43–7.29 (m, 18H), 7.25–7.23 (m, 2H), 7.20–7.14 (m, 4H), 4.09 (d, *J*=5.5 Hz, 1H), 3.83–3.80 (m, 2H), 3.76–3.73 (m, 5H), 3.52–3.46 (m, 2H), 2.50 (s, 3H), 2.44 (s, 3H), 1.86 (br s, 2H), 1.40 (d, *J*=7.1 Hz, 3H), 1.04 (d, *J*=6.8 Hz, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** (2 diastereomers) δ 144.0 (C), 143.7 (C), 140.8 (C), 140.5 (C), 139.2 (C), 138.9 (C), 136.9 (C), 136.3 (C), 133.0 (CH), 133.0 (CH), 129.0 (3 CH), 128.9 (CH), 128.8 (2 CH), 128.5 (2 CH), 128.3 (CH), 128.2 (4 CH), 128.2 (4 CH), 127.9 (CH), 127.8 (2 CH), 127.7 (2 CH), 127.2 (CH), 126.7 (CH), 125.8 (C), 125.1 (C), 66.5 (CH), 64.6 (CH), 51.5 (CH_2), 51.0 (CH_2), 44.8 (CH), 44.6 (CH), 21.3 (CH_3), 21.2 (CH_3), 18.7 (CH_3), 15.1 (CH_3).

Compound **5q**: In air, a flame-dried 25 mL Schlenk flask equipped with a stir bar was charged with β-arylethylamine **4q** (192 mg, 0.5 mmol, 1.0 equiv) and toluene (2.5 mL, C=0.2 M). The solution was degazed by Ar bubbling for 5 min. *t*-BuOK (112 mg, 1.0 mmol, 2.0 equiv) and $PdCl_2(PPh_3)_2$ (18 mg, 0.025 mmol, 5 mol%) were successively added under an Ar flow and the flask was sealed (glass stopper). The reaction was heated at 110 °C overnight (14 h). Then, the reaction mixture was filtered through a pad of Celite (10 mL), thoroughly rinsed with EtOAc (ca. 50 mL), and the filtrate was evaporated. The crude material was purified by FC (50 mL SiO_2, PE/EtOAc:97.5/2.5 then 95/5) to afford the desired product **5q** (131 mg, 86%, dr=2:1) as a pale yellow solid. **R_f (PE/EtOAc:95/5, UV+$KMnO_4$):** 0.70 & 0.80. **mp:** 68–70 °C. **HRMS (ESI):** *m*/*z* calcd for $C_{23}H_{24}N$ $(M+H)^+$ 314.1903, found 314.1900. **^{1}H NMR (400 MHz, $CDCl_3$):** (2 diastereomers) δ 7.55 (d, *J*=8.0 Hz, 2H), 7.45–7.42 (m, 8H), 7.38–7.27 (m, 8H), 7.24–7.19 (m, 4H), 6.93–6.88 (m, 2H), 6.61–6.57 (m, 2H), 4.89 (d, *J*=8.9 Hz, 1H), 4.60 (d, *J*=15.8 Hz, 1H), 4.50 (d, *J*=15.7 Hz, 1H), 4.22 (d, *J*=10.4 Hz, 1H), 4.14–4.10 (m, 2H), 3.70–3.63 (m, 1H), 3.43–3.39 (dq, *J*=13.4, 6.7 Hz, 1H), 2.52 (s, 3H), 2.50 (s, 3H), 1.48 (d, *J*=6.7 Hz, 3H), 1.03 (d, *J*=7.2 Hz, 3H). **^{13}C NMR {^{1}H}(100 MHz, $CDCl_3$):** (2 diastereomers) δ 152.0 (C), 151.9 (C), 138.6 (2 C), 138.5 (2 C), 137.5 (C), 137.0 (C), 135.1 (C), 134.6 (C), 133.5 (CH), 130.5 (CH), 129.4 (2 CH), 129.0 (2 CH), 128.5 (2 CH), 128.4 (2 CH), 128.0 (2 CH), 127.7 (2 CH), 127.6 (2 CH), 127.6 (2 CH), 126.9 (CH), 126.9 (CH), 123.7 (CH), 122.7 (CH), 118.2 (CH), 118.0 (CH), 107.9 (CH), 107.4 (CH), 78.4 (CH), 72.4 (CH), 51.4 (CH_2), 50.7 (CH_2), 45.8 (CH), 40.7 (CH), 21.3 (CH_3), 21.0 (CH_3), 16.7 (CH_3), 16.5 (CH_3).

Oxidation of indoline 5k to indole 6:[25] In air, a flame-dried 25 mL round-bottom flask equipped with a stir bar was charged with **5k** (100 mg, 0.35 mmol, 1.0 equiv), toluene (4 mL, C=0.1 M) and MnO_2 (124 mg, 1.4 mmol, 4.0 equiv). The flask was equipped with a condenser closed by a septum opened to air by a needle. The reaction was heated at reflux for 96 h. Then, the reaction mixture was filtered through a pad of Celite (10 mL), thoroughly rinsed with CH_2Cl_2 (ca. 50 mL), and the filtrate was evaporated. The crude material was purified by FC (50 mL SiO_2, PE/Et_2O:95/5 then 90/10) to afford the desired product **6** (90 mg, 90%) as a white solid. **R_f (PE/Et_2O:90/10, UV+$KMnO_4$):**

0.43. **mp:** 57–58 °C (litt. 55–56 °C). **HRMS (ESI):** *m/z* calcd for $C_{18}H_{18}NO_2$ $(M+H)^+$ 280.1332, found 280.1332. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.59 (d, *J*=8.0 Hz, 1H), 7.29 (d, *J*=0.7 Hz, 1H), 7.22 (dd, *J*=8.4, 0.7 Hz, 1H), 7.18 (dd, *J*=6.8, 1.2 Hz, 1H), 7.15–7.02 (m, 4H), 6.93 (d, *J*=6.8 Hz, 2H), 5.72 (s, 2H), 4.20 (q, *J*=7.1 Hz, 2H), 1.23 (t, *J*=7.1 Hz, 3H). **^{13}C NMR{^{1}H} (100 MHz, $CDCl_3$):** δ 162.0 (C), 139.6 (C), 138.4 (C), 128.6 (2 CH), 127.8 (C), 127.2 (CH), 126.3 (2 CH), 126.2 (C), 125.3 (CH), 122.7 (CH), 120.9 (CH), 111.1 (CH), 110.9 (CH), 60.7 (CH_2), 47.9 (CH_2), 14.4 (CH_3).

Acknowledgments

The financial support of this work by the CNRS and the University Paris-Est (PhD grants to A. P. and J. P.) is gratefully acknowledged.

Supporting Information

Copies of NMR spectra for all compounds.

References

[1] *Modern Alkaloids*; Fattorusso, E., Taglialatela-Scafati, O., Eds.; Wiley-VCH: Weinheim, 2008.
[2] Xiang, L.; Xing, D.; Wang, W.; Wang, R.; Ding, Y.; Du, L. *Phytochemistry* **2005**, *66*, 2595–2601.
[3] Rakhit, A.; Hurley, M. E.; Tipnis, V.; Coleman, J.; Rommel, A.; Brunner, H. R. *J. Clin. Pharmacol.* **1986**, *26*, 156–164.
[4] Liu, D.; Zhao, G.; Xiang, L. *Eur. J. Org. Chem.* **2010**, 3975–3984.
[5] Larock, R. C.; Berrios-Pena, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447–3450.
[6] Tasker, S. Z.; Jamison, T. F. *J. Am. Chem. Soc.* **2015**, *137*, 9531–9534.
[7] Zhao, D.; Vasquez-Cespedes, S.; Glorius, F. *Angew. Chem. Int. Ed.* **2015**, *54*, 1657–1661.
[8] Wolfe, P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525–7546.
[9] Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451–8458.
[10] Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35–38.
[11] *Multicomponent Reaction in Organic Synthesis*; Zhu, J.; Wang, Q.; Wang, M.-X., Eds.; Wiley-VCH: Weinheim, 2015.
[12] Le Gall, E.; Léonel, E. *Chem. Eur. J.* **2013**, *19*, 5238–5241.
[13] Paul, J.; Presset, M.; Cantagrel, F.; Le Gall, E.; Léonel, E. *Chem. Eur. J.* **2017**, *23*, 402–406.
[14] Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1044–1070.
[15] Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094.
[16] Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626–2704.
[17] Le Gall, E.; Haurena, C.; Sengmany, S.; Martens, T.; Troupel, M. *J. Org. Chem*. **2009**, *74*, 7970–7973.
[18] Haurena, C.; Le Gall, E.; Sengmany, S.; Martens, T.; Troupel, M. *J. Org. Chem*. **2010**, *75*, 2645–2650.
[19] Fan, R.; Pu, D.; Qin, L.; Wen, F.; Yao, G.; Wu, J. *J. Org. Chem.* **2007**, *72*, 3149–3151.
[20] Fillon, H.; Gosmini, C.; Périchon, J. *J. Am. Chem. Soc*. **2003**, *125*, 3867–3870.
[21] One equivalent of the organometallic reagent is required to trap the water generated by the imine formation.

[22] When the reaction was performed on a larger scale (2.5 mmol), increased amounts of **1** (2.5 equiv) and Zn (3.75 equiv) were necessary to balance the dimerization of the organozinc reagent.

[23] Other attempts carried out by changing the nature of halogen atom (benzylic chloride in spite of bromide) or the reducing metal (Mn in spite of Zn) gave only lower amounts of the expected product. Moreover, the introduction of a phenyl substituent in the benzylic position has also been evaluated but this modification resulted in almost exclusive dimerization of this starting material.

[24] Hlasta, D. J.; Luttinger, D.; Perrone, M. H.; Silbernagel, M. J.; Ward, S. J.; Haubrich, D. R. *J. Med. Chem.* **1987**, *30*, 1555–1562.

[25] Sechi, M.; Derudas, M.; Dallocchio, R. Dessì, A.; Bacchi, A.; Sannia, L.; Carta, F.; Palomba, M.; Ragab, O.; Chan, C.; Shoemaker, R.; Sei, S.; Dayam, R.; Neamati, N. *J. Med. Chem.* **2004**, *47*, 5298–5310.