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A simple method for the direct arylation of indoles

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Dedicated to Professor Justin DuBois on the occasion of his receipt of the Tetrahedron Young Investigator Award

ABSTRACT

The scope and limitations are described for a powerful new method to access indoles bearing a quaternary center at C-3 using easily accessible bisaryl λ^3-iodanes and a cheap organic base.

1. Introduction

Challenging chemical architectures of natural origin often point to gaps in synthetic methodology. For instance, there is a shortage of methods for C-3 quaternization of indoles with an aryl appendage. A number of natural products including haplophytine,[1] bipleiophylline,[2] hodgkinsine,[3] and leptosin D[4] (Fig. 1) contain a quaternary indole C-3 with an aryl appendage or a structure theoretically derived from such a motif as with haplophytine.[1h] Recent efforts by Nicolaou and co-workers,[5] and Fukuyama and co-workers[6] in the context of haplophytine have demonstrated the feasibility of the synthetic union of a substituted indole C-3 with an aryl nucleophile,[6] or a pseudo-aryl electrophile,[5] however, both approaches were highly substrate specific and proceed in less than 25% yield. In a much simpler context, Barton and co-workers have shown that treatment of skatole with *tert*-butyl tetramethylguanidine (BTMG) in the presence of 1.5 equiv of Ph_4BiOTs results in 95% conversion to the C-3 disubstituted indolenine **1** (Fig. 2).[7] This approach suffers from the required use of 4 equiv of aryl donor for each aryl group transfer. Additionally, extensive studies in these laboratories have shown that this bismuth mediated protocol does not have broad substrate scope and requires a tedious five-step reagent preparation.[8] In this article, we report the scope and limitations of a powerful method to access such structures using easily accessible bisaryl λ^3-iodanes and a cheap organic base.[9]

A priori, utilization of bisaryl λ^3-iodanes as an alternative to bismuth-V reagents for the arylation of indole was a logical choice based on their similar hypervalent nature and reactivity profile (see presumed intermediates [**2** and **3**] and mechanistic rationale in Fig. 2). Tri- and tetra-aryl bismuth-V reagents have been shown to be versatile arylating agents for heteroatoms and arenes,[7,10] similarly, bisaryl λ^3-iodanes have been employed in the α-arylation of ketones, esters, silyl enol ethers, 1,3-dicarbonyl compounds, and heteroatoms as well as alkylative dearomatization.[11] In a different context, Sanford and co-workers have utilized bisaryl λ^3-iodanes as both an oxidant and aryl transfer agent in the palladium mediated C-2 arylation of indole.[12]

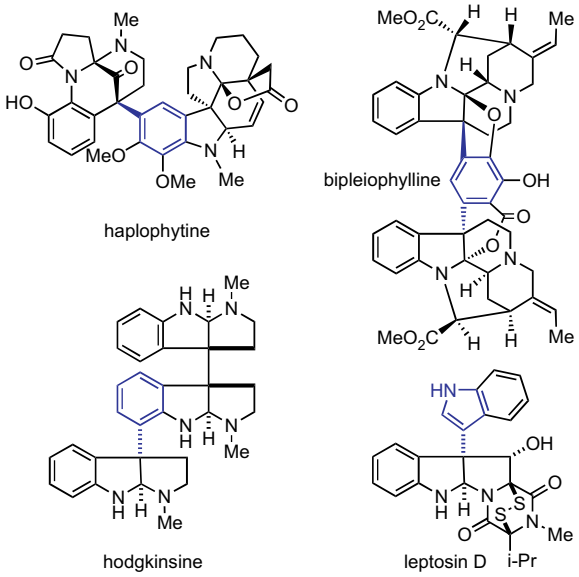

Figure 1. Natural products embodying the C-3 aryl indole motif.

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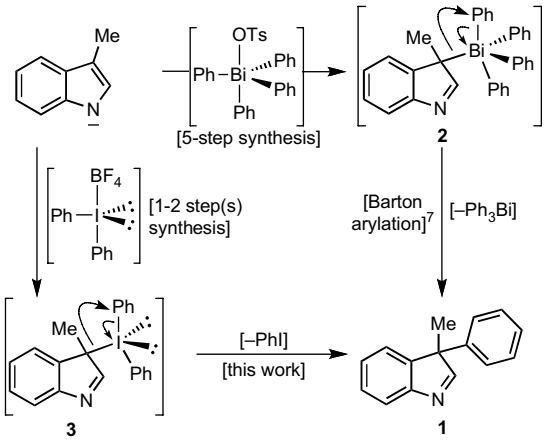


Figure 2. Speculative mechanism for the arylation of skatole with Ph_4BiOTs and Ph_2IBF_4.

Investigation probing the feasibility of the hypervalent iodine mediated arylation began with the simple one-step preparation of a host of differentially substituted bisaryl λ^3-iodane reagents from the requisite bisacetoxy iodoarene and commercially available arylboronic acid.[13] With the bisaryl λ^3-iodanes in hand, the scope of reactivity with skatole as a model indole was explored. Arylation experiments with skatole were effected via treatment of a mixture of skatole and the bisaryl λ^3-iodane with 1.5 equiv of *tert*-butyl tetramethylguanidine (BTMG) to give a relatively unstable indolenine, which was quantified in percent conversion based on crude ^{1}H NMR data. For purposes of characterization, all indolenines were reduced to the more stable indolines, and quantified in percent isolated yield from skatole. The results for these experiments are summarized in Table 1. The efficiency of the arylation of skatole[14] with a phenyl aryl substituent (entry 1) or more electron poor arene substituents (entries 2–5) is very good to excellent. The efficiency of the arylation, when electron rich arene substituents are employed, appears to be somewhat limited (entries 6–8). Gratifyingly, there appears to be little disadvantageous steric influence imparted by an *ortho* substituent (entries 5 and 8).

In an effort to demonstrate the scope of the indole partner, some of the more reactive arylating reagents were reacted with a several variably substituted indole substrates, these results are summarized in Table 2. *N*-Boc-β-carboline (**12**) undergoes excellent conversion to the C-3 arylation product with phenyl (entry 1), *p*-chlorophenyl (entry 2), and 1-naphthyl (entry 3) substituents, demonstrating a lack of sensitivity to having substitution at both C-2 and C-3 of the indole partner. Extension of this method to tryptamine was carried out with *N*-phthalimidyl tryptamine (**13**) as the indole model. Both phenyl (entry 4) and naphthyl (entry 6) were transferred with good efficiency, while *p*-chlorophenyl (entry 5) was transferred quantitatively to the desired C-3 arylated indolenine. It should be noted that tryptamine required double protection of the amine functionality. The presence of a secondary amine N–H or a carbamate N–H nearly shuts down the reaction sequence under the described conditions. Additionally, extension of these conditions to the fully protected tryptophan (**14**) with the bisphenyl λ^3-iodane (entry 7) gave 66% conversion to the desired C-3 arylated indolenine, while arylation with both chlorophenyl (entry 8) and naphthyl (entry 9) lead to quantitative and near quantitative conversion to the arylated indolines, respectively.[15]

Some preliminary optimization experiments employing skatole, BTMG, and Ph_2IBF_4, point to DCM or DCE as the solvent of choice, both of which can be used interchangeably. Experiments carried out in THF and toluene resulted in negligible transformation to the desired product. When a tertiary amine base other than BTMG (such as DBU or Et_3N) is used with skatole and Ph_2IBF_4 in DCM, the reaction proceeds at a greatly reduced rate producing negligible amounts of product after 24 h. All experiments that do not proceed to completion with 1.5 equiv of bisaryl iodide can be pushed to complete conversion by the addition of excess reagent (1.5–2.0 additional equivalents). Finally, the efficiency of this conversion is not diminished on gram scale, as demonstrated by the conversion of 1.0 g of skatole to the desired indolenine in 65% yield with 1.5 equiv of Ph_2IBF_4.

In summary, a powerful new method for the direct arylation of indole has been developed. The strategy has been generalized and performs well with a wide variety of substrate and reagent combinations. While this strategy is somewhat limited with respect to efficiency in appending very electron rich arene rings to C-3 of indole substrates, other than highly substrate dependent cases of Nicolaou[5] and Fukuyama,[6] there are no comparable methods in the literature that allow for the direct C-3 quaternization of indoles with an arene ring. It is anticipated that this work may aid in the rapid construction of the many known and yet to be discovered C-3 arylated indole alkaloids and medicinally relevant entities.

2. Experimental section

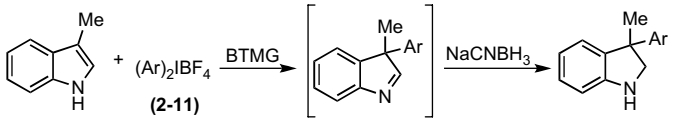
2.1. General information

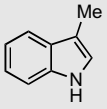
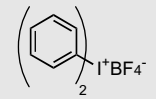
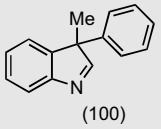
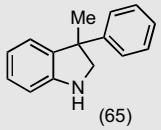
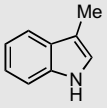
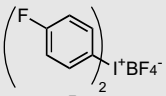
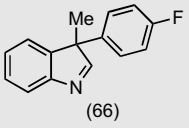
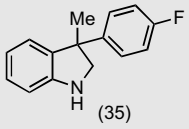
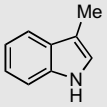
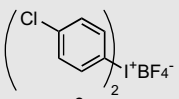
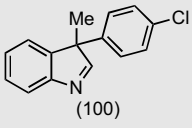
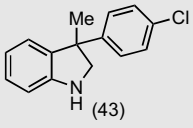
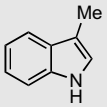
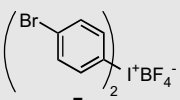
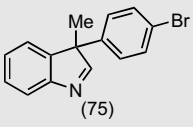
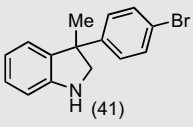
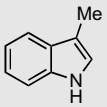
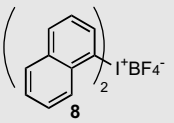
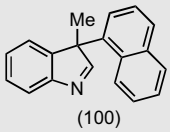
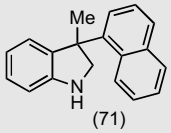
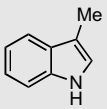
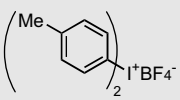
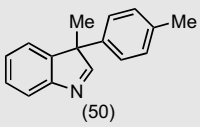
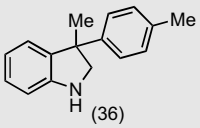
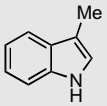
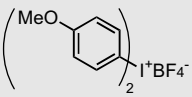
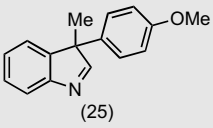
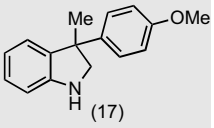
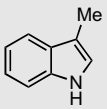
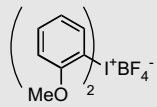
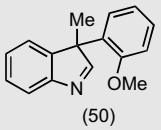
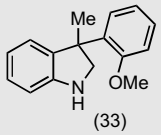
All reactions were carried out under an in inert nitrogen atmosphere with dry solvents under anhydrous conditions unless otherwise stated. Dry tetrahydrofuran (THF), toluene, and dichloromethane (CH_2Cl_2) were obtained by passing these previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless stated otherwise. Percent conversion is determined from the ratio of desired product to unreacted starting material. Due to the relatively unstable nature of the 3,3-disubstituted indolenines, products of the C-3 arylation were reduced to the indolines for purification and characterization. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merk silica gel plates ($60F_{254}$) using UV light as the visualizing agent and an acidic mixture of phophomolybdic acid and ceric ammonium molybdate and heat as the developing agent. E. Merk silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out on 0.25 or 0.5 mm E. Merk silica gel plates ($60F_{254}$). NMR spectra were recorded on Bruker DRX-600 or DRX-500 spectrometer and were calibrated using tetramethylsilane (TMS) as internal reference. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. IR spectra were recorded on a Perkin–Elmer Spetrum BX spectrometer. High resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight). Low resolution mass spectra (LRMS) were recorded on an Agilent LCMS. Azeotroping refers to dissolving or suspending the compound to be dried in toluene and removing the solvent by rotary evaporation.

2.2. General procedure

A mixture of the indole substrate (0.076 mmol, 1 equiv) and the bisaryl λ^3-iodane (0.114 mmol, 1.5 equiv) were combined and azeotroped with toluene 3×. The dry mixture was then dissolved in DCM (1.0 mL) under an atmosphere of N_2. Next, *tert*-butyl tetramethylguanidine (BTMG) (0.152 mmol, 2 equiv) was added with stirring, resulting in an immediate darkening of the reaction mixture from a colorless/pale yellow solution (or mixture) to a deep red/burgundy color. The dark mixture was stirred under N_2 until

Table 1
Arylation experiments with skatole



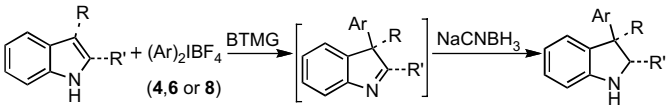
Entry	Indole	Reagent	Indolenine (% conversion)	Indoline (% yield)
1[a]		 **4**	 (100)	 (65)
2		 **5**	 (66)	 (35)
3		 **6**	 (100)	 (43)
4		 **7**	 (75)	 (41)
5		 **8**	 (100)	 (71)
6		 **9**	 (50)	 (36)
7		 **10**	 (25)	 (17)
8		 **11**	 (50)	 (33)

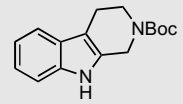
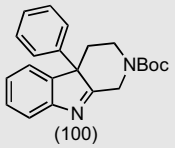
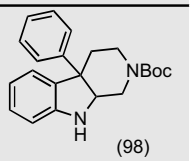
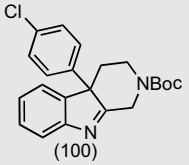
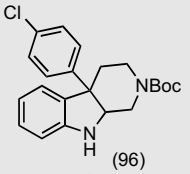
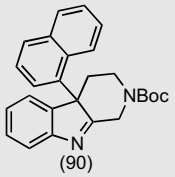
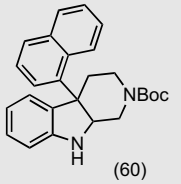
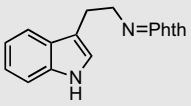
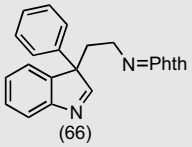
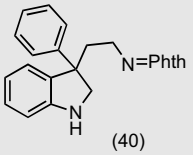
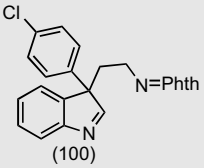
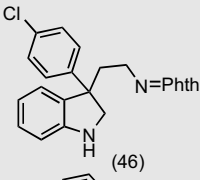
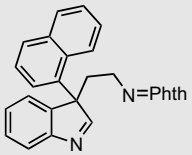
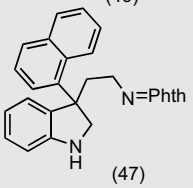
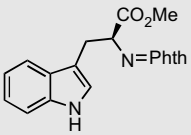
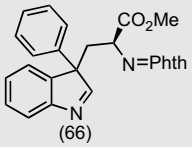
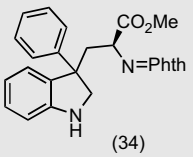
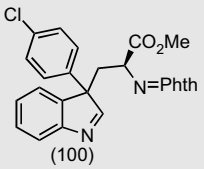
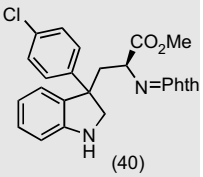
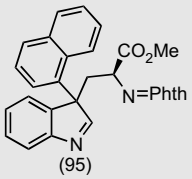
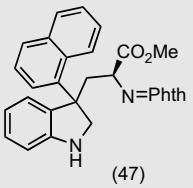
[a] Gram scale reaction.

the starting material was consumed or the reaction appeared not to be progressing any further (1–4 h). Completion of the reaction was, in nearly all cases, accompanied by lightening of the reaction mixture from dark red to a pale yellow/orange mixture. Upon completion of the reaction, the mixture was poured onto a plug of silica and rinsed with Et_2O. Concentration gave a crude residue containing only the desired unstable indolenine product, unreacted starting material, and aryl iodide by-product. The percent conversion of all reactions was determined by ^1H NMR as a measure of the ratio of desired product to unreacted starting material. After determination of the percent conversion, the mixture was reduced to obtain the more stable indoline product. Thus, the mixture from above was dissolved (or suspended) in 2 mL of DCM. Next, a solution of 10 equiv of $NaCNBH_3$ in MeOH (0.5 mL) was added to the stirring mixture in an open flask. After 30 min of stirring, 0.5 g of silica gel was added and stirring continued for an additional 30 min to ensure complete reduction.[16] The mixture was then concentrated and poured onto a silica gel column and eluted with the stated eluent to give the desired indoline.

Table 1 entry 1: prepared according to the general procedure. Purified on silica gel eluting with 9:1 hexanes/Et_2O. Yield: 9.0 mg, 57%. Gram scale yield: 1.0 g, 65%. Physical state: colorless oil. R_f: 0.55 (silica gel, 1:1 hexane/Et_2O). IR (film) ν_{max}: 3386 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.30 (m, 4H), 7.20 (t, J=7.0 Hz, 1H), 7.09 (t, J=7.6 Hz, 1H), 6.97 (d, J=7.4 Hz, 1H), 6.76 (t, J=7.4 Hz, 1H), 6.72 (d, J=7.8 Hz, 1H), 3.78 (br s, 1H), 3.72 (d, J=8.9 Hz, 1H), 3.57 (d, J=8.9 Hz, 1H), 1.72 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 150.7, 147.7, 137.0, 128.2, 127.7, 126.6, 126.2, 124.1, 119.0, 110.0, 63.7, 49.7, 26.2. HRMS (ESI-TOF): calcd for $C_{15}H_{15}N$ [M+H^+] 210.1277, found 210.1281.

Table 2
Arylation experiments with complex indole substrates



Entry	Indole	Reagent	Indolenine (% conversion)	Indoline (% yield)
1	 **12**	**4**	 (100)	 (98)
2	**12**	**6**	 (100)	 (96)
3	**12**	**8**	 (90)	 (60)
4	 **13**	**4**	 (66)	 (40)
5	**13**	**6**	 (100)	 (46)
6	**13**	**8**	 (65)	 (47)
7[a]	 **14**	**4**	 (66)	 (34)
8[a]	**14**	**6**	 (100)	 (40)
9[a]	**14**	**8**	 (95)	 (47)

[a] Bisaryl λ^3-iodane (2 equiv) was used.

Table 1 entry 2: prepared according to the general procedure. Purified on silica gel eluting with 9:1 hexanes/Et_2O. Yield: 6.0 mg, 35%. Physical state: colorless oil. R_f: 0.53 (silica gel, 1:1 hexane/Et_2O). IR (film) ν_{max}: 3374 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, J=8.9 Hz, 2H), 7.11 (t, J=7.6 Hz, 1H), 6.97 (d, J=8.7 Hz, 2H), 6.95 (d, J=7.8 Hz, 1H), 6.78 (t, J=7.4 Hz, 1H), 6.73 (d, J=7.7 Hz, 1H), 3.8 (br s, 1H), 3.67 (d, J=8.9 Hz, 1H), 3.57 (d, J=8.9 Hz, 1H), 1.7 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 161.4 (J=245 Hz), 150.6, 143.3 (J=3.3 Hz), 136.7, 128.1 (J=7.9 Hz), 127.8, 123.9, 119.1, 114.8 (J=20.8 Hz), 110.0, 63.7, 49.1, 26.2. HRMS (ESI-TOF): calcd for $C_{15}H_{14}FN$ [M+H^+] 228.1183, found 228.1188.

Table 1 entry 3: prepared according to the general procedure. Purified on silica gel eluting with 9/1 hexanes/Et_2O. Yield: 8.0 mg, 43%. Physical state: colorless oil. R_f: 0.53 (silica gel, 1:1 hexane/Et_2O). IR (film) ν_{max}: 3379 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.25 (d, J=9.1 Hz, 4H), 7.10 (t, J=7.7 Hz, 1H), 6.95 (d, J=7.5 Hz, 1H), 6.78 (t, J=7.4 Hz, 1H), 6.73 (d, J=7.7 Hz, 1H), 3.80 (br s, 1H), 3.67 (d, J=8.9 Hz, 1H), 3.57 (d, J=8.9 Hz, 1H), 1.70 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 150.6, 146.2, 136.4, 131.9, 128.2, 128.0, 127.9, 123.9, 119.1, 110.0, 63.6, 49.2, 26.0. HRMS (ESI-TOF): calcd for $C_{15}H_{14}ClN$ [M+H^+] 244.0887, found 244.0886.

Table 1 entry 4: prepared according to the general procedure. Purified on silica gel eluting with 9:1 hexanes/Et_2O. Yield: 9.0 mg, 41%. Physical state: colorless oil. R_f: 0.53 (silica gel, 1:1 hexane/Et_2O). IR (film) ν_{max}: 3378 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.40 (d, J=9.1 Hz, 2H), 7.19 (d, J=9.1 Hz, 2H), 7.11 (t, J=7.7 Hz, 1H), 6.95 (d, J=7.6 Hz, 1H), 6.77 (t, J=7.6 Hz, 1H), 6.73 (d, J=7.8 Hz, 1H), 3.67 (d, J=9.0 Hz, 1H), 3.57 (d, J=8.9 Hz, 1H), 1.70 (s, 3H) [NH—too broad to identify conclusively]. ^{13}C NMR (150 MHz, $CDCl_3$): δ 150.6, 146.7, 136.3, 131.2, 128.4, 127.9, 123.9, 120.1, 119.1, 110.0, 63.5, 49.3, 25.9. HRMS (ESI-TOF): calcd for $C_{15}H_{14}BrN$ [M+H^+] 288.0382, found 288.0377.

Table 1 entry 5: prepared according to the general procedure. Purified on silica gel eluting with 9:1 hexanes/Et_2O. Yield: 14 mg, 71%. Physical state: colorless semisolid. R_f: 0.62 (silica gel, 1:1 hexane/Et_2O). IR (film) ν_{max}: 3395 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.85 (d, J=8.2 Hz, 1H), 7.82 (d, J=8.7 Hz, 1H), 7.76 (d, J=8.2 Hz, 1H), 7.55 (d, J=7.5 Hz, 1H), 7.40 (t, J=8.2 Hz, 1H), 7.37 (t, J=7.4 Hz, 1H), 7.29 (t, J=7.9 Hz, 1H), 7.10 (t, J=7.9 Hz, 1H), 6.80 (d, J=7.7 Hz, 1H), 6.77 (d, J=7.7 Hz, 1H), 6.67 (t, J=7.4 Hz, 1H), 4.28 (d, J=9.4 Hz, 1H), 3.63 (d, J=9.4 Hz, 1H), 1.90 (s, 3H) [NH—too broad to identify conclusively]. ^{13}C NMR (150 MHz, $CDCl_3$): δ 149.7, 141.8, 138.2, 135.1, 131.2, 129.4, 128.2, 127.7, 126.2, 125.2, 124.9, 124.8 (2C's), 123.9, 118.8, 109.7, 61.6, 50.3, 29.4. HRMS (ESI-TOF): calcd for $C_{19}H_{17}N$ [M+H^+] 260.1434, found 260.1437.

Table 1 entry 6: prepared according to the general procedure. Purified on silica gel eluting with 9:1 hexanes/Et_2O. Yield: 6.0 mg, 36%. Physical state: colorless oil. R_f: 0.55 (silica gel, 1:1 hexane/Et_2O). IR (film) ν_{max}: 3382 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.21 (d, J=8.2 Hz, 2H), 7.10 (d, J=8.0 Hz, 2H), 7.09 (t, J=7.8 Hz, 1H), 6.96 (d, J=7.8 Hz, 1H), 6.76 (t, J=7.9 Hz, 1H), 6.72 (d, J=7.8 Hz, 1H), 3.77 (s, 1H), 3.70 (d, J=8.9 Hz, 1H), 3.55 (d, J=8.9 Hz, 1H), 2.31 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 150.7, 144.7, 137.2, 135.7, 128.9, 127.6, 126.5, 124.0, 119.0, 109.9, 63.8, 49.4, 26.2, 20.9. HRMS (ESI-TOF): calcd for $C_{16}H_{17}N$ [M+H^+] 224.1434, found 224.1438.

Table 1 entry 7: prepared according to the general procedure. Purified on silica gel eluting with 9:1 hexanes/Et_2O. Yield: 3.2 mg, 17%. Physical state: amber oil. R_f: 0.43 (silica gel, 1:1 hexane/Et_2O). IR (film) ν_{max}: 3382 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.71 (br s, 0.5H), 7.53 (br s, 0.5H), 7.23 (d, J=9.0 Hz, 2H), 7.08 (t, J=7.4 Hz, 1H), 6.96 (d, J=7.5 Hz, 1H), 6.82 (d, J=8.9 Hz, 2H), 6.76 (t, J=7.4 Hz, 1H), 6.72 (d, J=7.6 Hz, 1H), 3.78 (s, 3H), 3.68 (d, J=8.8 Hz, 1H), 3.54 (d, J=8.9 Hz, 1H), 1.69 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.9, 150.6, 139.8, 137.3, 130.9, 127.6, 124.0, 119.0, 113.5, 109.9, 63.8, 55.2, 49.1, 26.2. HRMS (ESI-TOF): calcd for $C_{16}H_{17}NO$ [M+H^+] 240.1383, found 240.1381.

Table 1 entry 8: prepared according to the general procedure. Purified on silica gel eluting with 9:1 hexanes/Et_2O. Yield: 6.0 mg, 32%. Physical state: colorless powder. R_f: 0.48 (silica gel, 1:1 hexane/Et_2O). IR (film) ν_{max}: 3380 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.72 (br s, 0.5H), 7.53 (br s, 0.5H), 7.20 (t, J=7.6 Hz, 1H), 7.09 (t, J=7.5 Hz, 1H), 7.08 (d, J=7.6 Hz, 1H), 6.99 (d, J=7.6 Hz, 1H), 6.90 (d, J=8.1 Hz, 1H), 6.81 (t, J=7.9 Hz, 1H), 6.79 (t, J=7.6 Hz, 1H), 6.70 (d, J=7.8 Hz, 1H), 3.99 (d, J=9.2 Hz, 1H), 3.77 (s, 3H), 3.55 (d, J=9.2 Hz, 1H), 1.76 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.7, 151.0, 136.6, 135.0, 127.9, 127.8, 127.5, 124.7, 120.2, 118.4, 111.8, 110.0, 60.8, 55.2, 49.0, 25.9. HRMS (ESI-TOF): calcd for $C_{16}H_{17}NO$ [M+H^+] 240.1383, found 240.1385.

Table 2 entry 1: prepared according to the general procedure. Purified on silica gel eluting with 9:1 hexanes/Et_2O. Yield: 26 mg, 98%. Physical state: colorless oil. R_f: 0.36 (silica gel, 1:1 hexane/Et_2O). IR (film) ν_{max}: 3346, 1683 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ mixture of rotomers (ratio: 2:1) 7.27–7.33 (m, 4H), 7.18–7.23 (m, 1H), 7.07 (t, J=7.4 Hz, 1H), 6.83–6.91 (m, 1H), 6.69–6.77 (m, 1H), 6.67 (d, J=7.6 Hz, 1H), 3.97–4.15 (m, 1H), 3.71–3.89 (m, 1H), 3.36–3.56 (m, 3H), 3.18–3.29 (m, 1H), 2.42–2.50 (m, 1H), 2.11–2.19 (m, 1H), 1.35–1.51 (m, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ major rotomer 156.1, 150.5, 147.1, 133.5, 128.4, 128.1, 126.8, 126.5, 124.3, 118.7, 109.6, 79.5, 66.5, 51.3, 43.4, 41.1, 31.3, 28.4. HRMS (ESI-TOF): calcd for $C_{22}H_{26}N_2O_2$ [M+H^+] 351.2067, found 351.2072.

Table 2 entry 2: prepared according to the general procedure. Purified on silica gel eluting with 9:1 hexanes/Et_2O. Yield: 28 mg, 96%. Physical state: colorless semisolid. R_f: 0.33 (silica gel, 1:1 hexane/Et_2O). IR (film) ν_{max}: 3346, 1684 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ mixture of rotomers (ratio: 2:1) 7.27 (d, J=8.6 Hz, 2H), 7.23 (d, J=8.5 Hz, 2H), 7.09 (t, J=7.5 Hz, 1H), 6.83–6.92 (m, 1H), 6.71–6.81 (m, 1H), 6.68 (d, J=7.5 Hz, 1H), 3.97–4.08 (m, 1H), 3.68–3.77 (m, 1H), 3.38–3.58 (m, 3H), 3.18–3.27 (m, 1H), 2.37–2.47 (m, 1H), 2.11–2.21 (m, 1H), 1.35–1.54 (m, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ major rotomer 156.0, 150.3, 145.8, 132.3, 128.5 (2C's), 128.4, 128.0, 124.1, 118.8, 109.7, 79.7, 66.4, 51.0, 43.4, 41.0, 31.2, 28.4. HRMS (ESI-TOF): calcd for $C_{22}H_{25}ClN_2O_2$ [M+H^+] 385.1677, found 385.1685.

Table 2 entry 3: prepared according to the general procedure. Purified on silica gel eluting with 9:1 hexanes/Et_2O. Yield: 18 mg, 60%. Physical state: white powder. R_f: 0.41 (silica gel, 1:1 hexane/Et_2O). IR (film) ν_{max}: 3350, 1684 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ mixture of rotomers (ratio: 2:1) 8.02 (d, J=8.6 Hz, 1H), 7.84 (d, J=8.0 Hz, 1H), 7.76 (d, J=8.3 Hz, 1H), 7.42–7.53 (m, 1H), 7.27–7.35 (m, 1H), 7.35–741 (m, 2H), 7.06–7.14 (m, 1H), 6.61–6.83 (m, 3H), 4.60–4.73 (m, 1H), 3.89–4.13 (m, 1H), 3.69–3.83 (m, 1H), 3.57–3.69 (m, 1H), 3.31–3.56 (m, 1H), 3.09–3.26 (m, 1H), 2.79–2.94 (m, 1H), 2.08–2.22 (m, 1H), 1.47–1.56 (m, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ major rotomer 156.1, 149.9, 141.2, 135.2, 131.3, 129.6, 128.6, 128.2, 125.5, 125.4, 125.3, 125.1, 124.7, 124.6, 124.1, 118.7, 109.3, 79.6, 63.9, 51.6, 43.0, 40.8, 33.3, 28.4. HRMS (ESI-TOF): calcd for $C_{26}H_{28}N_2O_2$ [M+H^+] 401.2223, found 401.2227.

Table 2 entry 4: prepared according to the general procedure. Purified on silica gel eluting with 1:1 hexanes/Et_2O. Yield: 11 mg, 40%. Physical state: colorless oil. R_f: 0.29 (silica gel, 1:1 hexane/Et_2O). IR (film) ν_{max}: 3370, 1708 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.76 (dd, J=5.4, 3.1 Hz, 2H), 7.66 (dd, J=5.4, 3.0 Hz, 2H), 7.39 (d, J=8.2 Hz, 2H), 7.23 (d, J=7.9 Hz, 1H), 7.21 (t, J=8.1 Hz, 2H), 7.08 (t, J=7.9 Hz, 1H), 7.07 (t, J=7.9 Hz, 1H), 6.78 (t, J=7.4 Hz, 1H), 6.70 (d, J=7.7 Hz, 1H), 3.82 (br s, 1H), 3.81 (s, 2H), 3.71–3.78 (m, 1H), 3.60–3.78 (m, 1H), 2.43–2.58 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.1, 150.9, 145.4, 133.7, 133.3, 132.1, 128.4, 128.1, 126.4, 126.3, 125.1, 123.0, 119.0, 110.2, 60.8, 52.3, 36.6, 34.8. HRMS (ESI-TOF): calcd for $C_{24}H_{20}N_2O_2$ [M+H^+] 369.1597, found 369.1592.

Table 2 entry 5: prepared according to the general procedure. Purified on silica gel eluting with 1:1 hexanes/Et_2O. Yield: 14 mg, 46%. Physical state: colorless oil. R_f: 0.29 (silica gel, 1:1 hexane/Et_2O). IR (film) ν_{max}: 3378, 1707 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.76 (dd, J=5.6, 3.0 Hz, 2H), 7.67 (dd, J=5.5, 3.1 Hz, 2H), 7.32 (d,

J=8.6 Hz, 2H), 7.19 (d, J=7.3 Hz, 1H), 7.16 (d, J=8.7 Hz, 2H), 7.07 (t, J=7.4 Hz, 1H), 6.78 (t, J=7.4 Hz, 1H), 6.69 (d, J=7.6 Hz, 1H), 3.83 (br s, 1H), 3.79 (d, J=9.2 Hz, 1H), 3.76 (d, J=9.2 Hz, 1H), 3.74 (ddd, J=15.6, 10.0, 5.5 Hz, 1H), 3.63 (ddd, J=15.6, 9.5, 6.1 Hz, 1H), 2.53 (ddd, J=15.6, 9.8, 5.7 Hz, 1H), 2.44 (ddd, J=15.6, 10.0, 5.8 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.1, 150.8, 143.9, 133.9, 132.8, 132.2, 132.0, 128.5, 128.3, 127.8, 124.8, 123.0, 119.2, 110.3, 60.7, 51.9, 36.4, 34.7. HRMS (ESI-TOF): calcd for $C_{24}H_{19}ClN_2O_2$ [M+H$^+$] 403.1208, found 403.1202.

Table 2 entry 6: prepared according to the general procedure. Purified on silica gel eluting with 1:1 hexanes/Et_2O. Yield: 17 mg, 47%. Physical state: white powder. R_f: 0.32 (silica gel, 1:1 hexane/Et_2O). IR (film) ν_{max}: 3386, 1707 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.93 (d, J=8.4 Hz, 1H), 7.81 (d, J=7.4 Hz, 1H), 7.76 (dd, J=5.4, 3.0 Hz, 2H), 7.71 (d, J=8.0 Hz, 1H), 7.66 (dd, J=5.3, 3.0 Hz, 2H), 7.58 (d, J=7.6 Hz, 1H), 7.33–7.41 (m, 3H), 7.14 (d, J=7.7 Hz, 1H), 7.10 (t, J=7.7 Hz, 1H), 6.77 (t, J=7.8 Hz, 1H), 6.74 (d, J=7.8 Hz, 1H), 4.26 (d, J=9.5 Hz, 1H), 4.12 (d, J=9.5 Hz, 1H), 4.00 (br s, 1H), 3.90 (ddd, J=15.1, 10.0 5.0 Hz, 1H), 3.64 (ddd, J=16.6, 10.1, 6.7 Hz, 1H), 2.64–2.77 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.1, 150.6, 141.1, 135.2, 133.7, 133.4, 132.1, 131.0, 129.5, 128.3, 128.2, 125.7, 125.6, 125.3, 125.2, 124.9, 124.8, 123.0, 118.9, 109.9, 58.8, 53.1, 38.7, 34.8. HRMS (ESI-TOF): calcd for $C_{28}H_{22}N_2O_2$ [M+H$^+$] 419.1754, found 419.1756.

Table 2 entry 7: prepared according to the general procedure. Purified on silica gel eluting with 5% Et_2O in DCM. Yield: 12 mg, 34%. Physical state: colorless semisolid. R_f: 0.38 (silica gel, 2:1 hexane/EtOAc). IR (film) ν_{max}: 3382, 1744, 1711 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ major diastereomer (ratio: 3:2) 7.60–7.66 (m, 4H), 7.42 (d, J=7.4 Hz, 1H), 7.30 (d, J=8.0 Hz, 2H), 7.04 (t, J=7.8 Hz, 2H), 6.91 (t, J=7.5 Hz, 1H), 6.82 (t, J=7.6 Hz, 1H), 6.63 (t, J=7.6 Hz, 1H), 6.61 (d, J=7.6 Hz, 1H), 5.09 (d, J=11.5 Hz, 1H), 3.83 (br s, 1H), 3.79 (d, J=9.2 Hz, 1H), 3.67 (s, 3H), 3.62 (d, J=9.2 Hz, 1H), 3.23 (dd, J=15.3, 11.6 Hz, 1H), 3.03 (d, J=15.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ mixture of diastereomers (ratio: 3:2) 169.9, 167.3, 151.2, 133.6, 131.7, 131.66. 131.3, 128.2, 128.16, 128.1, 128.0, 127.98, 126.1, 125.9, 125.6, 125.59, 123.6, 123.0, 122.9, 119.2, 118.7, 110.6, 110.3, 61.6, 57.8, 52.9, 52.6, 51.4, 49.3, 49.28, 36.7, 36.4. HRMS (ESI-TOF): calcd for $C_{26}H_{22}N_2O_4$ [M+H$^+$] 427.1652, found 427.1651.

Table 2 entry 8: prepared according to the general procedure. Purified on silica gel eluting with 5% Et_2O in DCM. Yield: 11 mg, 40%. Physical state: colorless semisolid. R_f: 0.41 (silica gel, 2:1 hexane/EtOAc). IR (film) ν_{max}: 3379, 1743, 1711 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ major diastereomer (ratio: 3:2) 7.63–7.70 (m, 4H), 7.44 (d, J=7.7 Hz, 1H), 7.23 (d, J=7.8 Hz, 2H), 6.98 (d, J=7.9 Hz, 2H), 6.94 (t, J=7.9 Hz, 1H), 6.65 (t, J=7.5 Hz, 1H), 6.64 (d, J=7.7 Hz, 1H), 5.06 (d, J=11.5 Hz, 1H), 3.83 (br s, 1H), 3.77 (d, J=9.5 Hz, 1H), 3.67 (s, 3H), 3.56 (d, J=9.4 Hz, 1H), 3.17 (dd, J=15.1, 11.7 Hz, 1H), 3.01 (d, J=15.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ mixture of diastereomers (ratio: 3:2) 169.7, 169.6, 167.3, 167.28, 151.1, 149.6, 143.3, 141.4, 134.0, 133.95, 132.0, 131.8, 131.6, 131.4, 130.7, 128.3, 128.24, 128.2, 127.7, 127.0, 123.2, 123.0, 119.4, 118.9, 110.7, 110.3, 61.2, 57.4, 53.0, 52.2, 50.9, 49.2, 49.0, 36.6, 36.4. HRMS (ESI-TOF): calcd for $C_{26}H_{21}ClN_2O_4$ [M+H$^+$] 461.1263, found 461.1260.

Table 2 entry 9: prepared according to the general procedure. Purified on silica gel eluting with 5% Et_2O in DCM. Yield: 13 mg, 47%. Physical state: yellow semisolid. R_f: 0.46 (silica gel, 2:1 hexane/EtOAc). IR (film) ν_{max}: 3389, 1741, 1711 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ major diastereomer (ratio: 2:1) 7.88 (d, J=8.3 Hz, 1H), 7.82–7.87 (m, 3H), 7.71–7.77 (m, 3H), 7.65 (d, J=7.4 Hz, 1H), 7.34–7.43 (m, 3H), 7.09 (d, J=7.4 Hz, 1H), 7.06 (t, J=7.6 Hz, 1H), 6.71 (t, J=7.4 Hz, 1H), 6.67 (d, J=7.8 Hz, 1H), 4.89 (d, J=10.5 Hz, 1H), 4.04 (d, J=10.0 Hz, 1H), 3.91 (dd, J=15.6, 10.4 Hz, 1H), 3.84 (d, J=10.0 Hz, 1H), 3.76 (br s, 1H), 3.63 (s, 3H), 3.13 (d, J=15.2 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ major diastereomer (ratio: 2:1) 193.8, 170.3, 167.7, 150.6, 135.3, 134.0, 132.0, 130.9, 129.5, 128.5, 128.4, 126.0, 125.9, 125.3, 125.0, 124.94, 124.9, 123.4, 118.8, 110.6, 105.2, 58.6, 54.0, 52.9, 50.3, 37.5 HRMS (ESI-TOF): calcd for $C_{30}H_{24}N_2O_4$ [M+H$^+$] 477.1809, found 477.1804.

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Supplementary data

Copies of all NMR spectra are included. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.09.028.

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16. Reduction to the indoline is aided by the addition of silica gel.