Research on Chemical Intermediates
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Efficient base-free asymmetric one-pot synthesis of spiro[indoline-3,3′-pyrrolizin]-2-one derivatives catalyzed by chiral organocatalyst

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Abstract

A 1,3-dipolar cycloaddition reaction has been performed under organocatalytic conditions with high enantioselectivity by the utilization of bipyridine-based chiral quaternary ammonium bromide as an organocatalyst. Here, the reaction of 1,3-dipolar cycloaddition of azomethine ylide generated *in situ* from the decarboxylative condensation of α-amino acids and non-enolizable 1,2-diketones to the above dipolarophiles takes place.

Keywords Organocatalyst · Indoline derivatives · Bipyridine · Cinchona alkaloid · Cycloaddition

Introduction

The 1,3-dipolar cycloaddition is a chemical reaction between a 1,3-dipole and a dipolarophile to form a five-membered ring system. Mechanistic investigation and synthetic applications were established in the 1960s, primarily through the work of Rolf Huisgen [1, 2]. 1,3-Dipolar cycloaddition is an efficient method for the synthesis of spiro pyrrolizidines with multiple stereogenic centers in a one-pot reaction [3, 4]. This reaction proceeded the HOMO of azomethine ylide directly interacted with LUMO of the alkene [5]. Further, this reaction of azomethine ylide to dipolarophile

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with exocyclic double bond affords the spiro-heterocycles [6–10] like pyrrolizines, pyrrolizidines, pyrazolidines, etc., and they have important biological activities [11].

Generally, 1,3-dipolar reactions are extremely useful in biological valuable product synthesis, because they are stereospecific, diastereoselective and regioselective reaction. Previously reported procedures for the synthesis of spiro compounds have some limitations, such as multi-step reactions, use of toxic solvents under refluxed conditions and the formation of unwanted byproducts [12, 13]. In order to overcome these problems, here, we report a simple modified procedure for the synthesis of spiro[indoline-3,3′-pyrrolizin]-2-one derivatives between the chalcone (dipolarophile) and a dipole (azomethine ylide) from isatin and secondary amino acids like L-proline provided an excellent yield of desired products. Chalcones itself have enormous biological properties such as anti-inflammatory, antimicrobial, antifungal, antioxidant, cytotoxic, antitumor and anticancer activities [14–16]. Further, the addition of chalcone moiety with the isatin molecule can enhance its biological activities. Hence, most of the researchers concentrated on the synthesis of spiro derivatives in the presence of metal catalysts [17–22] and chiral organocatalysts [23–31] (Fig. 1).

To the best of our knowledge, there are few reports available for the asymmetric dipolar cycloaddition reaction involving chiral organocatalyst. The synthesized new Chiral phase transfer catalysts (CPTC) **4** (Fig. 2) was showing its excellent catalytic reactivity in the asymmetric Michael addition of chalcones with diethylmalonate; within two hours, these catalysts result in high chemical yield (up to 98%) and enantiomeric excess (up to 99%) [32]. In connection with these, previous successes led us to envision that CPTC **4** might be highly enantioselective catalyst for the asymmetric one-pot 1,3-dipolar cycloaddition cascade sequence of chalcone, isatin and proline. But, here this CPTC acts as an organocatalyst due to no need for biphasic medium (aqueous/organic). Herein, we present our preliminary results on this subject; a wide range of spiro[indoline-3,3′-pyrrolizin]-2-one derivatives was obtained in high yields (up to 99%) and excellent enantioselectivities (up to 96%).

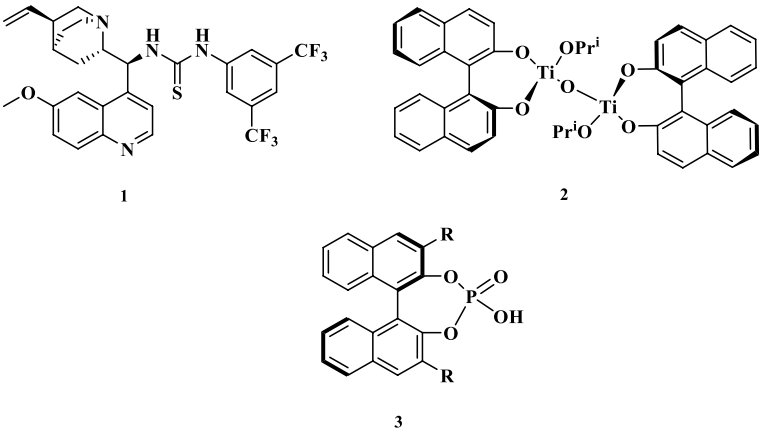
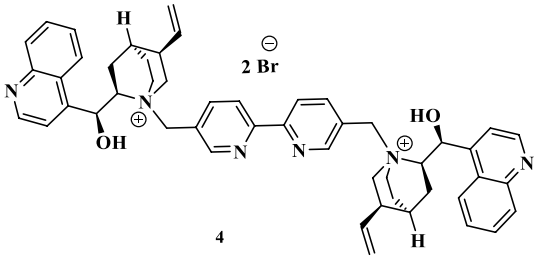


Fig. 1 Previously reported chiral organo/organometallic catalysts for 1,3-dipolar cycloaddition reaction

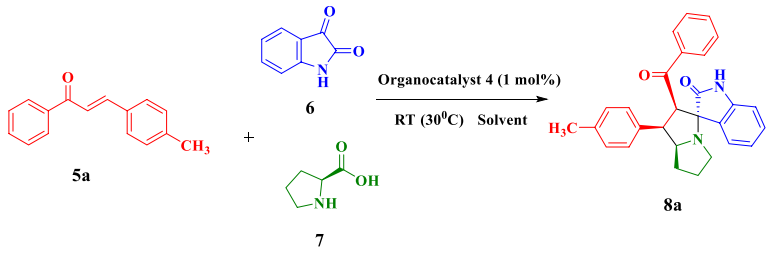
Fig. 2 Chiral organocatalyst for one-pot reaction of 1,3-dipolar cycloaddition



Results and discussion

Initially, we concentrated on the solvent optimization for the 1,3-dipolar cycloaddition of azomethine ylide generated in situ from the decarboxylative condensation of α-amino acids and non-enolizable 1,2-diketones to the above dipolarophiles. In this connection, we selected the reaction of chalcone **5a**, isatin **6** and proline 7 that presumably affords 2′-benzoyl-1′-(*p*-tolyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro [indoline-3,3′-pyrrolizin]-2-one **8a**, as a model reaction, under room temperature in various solvents (Table 1). From the data in Table 1, we observed superior yield in less time in methanol when compared to other solvent system for this cycloaddition reaction, wherein quantitative yield of **8a** was obtained (97%). Further, we carried out the cycloaddition reaction; without the addition of organocatalyst **4**, we got only less than 10% of product at 48 h.

Table 1 Screening the solvent for the one-pot synthesis of spiro[indoline-3,3′-pyrrolizin]-2-one derivatives catalyzed by chiral organocatalyst.



Entry	Solvent	Time	Yield (%)[a]
1	Methanol	10 min	97
2	Ethanol	12 h	65
3	*i*- PrOH	18 h	42[b]
4	1,4-Dioxane	24 h	56[b]
5	Acetonitrile	24 h	44[b]
6	Methanol	48 h	< 10[c]

[a]Isolated yield, [b]yield after column chromatography, [c]without addition of organocatalyst

Further, from Table 1 it is evident that methanol is the optimum solvent for further investigation. After completion of the reaction as evident from the TLC, the reaction mixture was poured into ice cold water and the resultant precipitate was filtered and dried to obtain the product **8a**. It is remarkable that the crude reaction product was clean enough to be purified just by crystallization, thereby eliminating the need for column chromatography, which is the main source of waste.

A series of spiro[indoline-3,3′-pyrrolizin]-2-one derivatives have been synthesized with the optimized reaction conditions in hand; the 1,3-dipolar cycloaddition reaction of a wide range of chalcone **5(a–t)** was investigated for the substrate scope. As shown in Table 2, chalcone bearing both electron-donating and electron-withdrawing substituents on phenyl group did not affect the reaction, and the corresponding reactions proceeded smoothly to afford the desired products **8(a–t)** with excellent yield (up to 99%) as well as ee's (or de's) (up to 96%) in lesser reaction time. The formation of single selective compound has also been evidenced from the crystal data. In addition to that, the structure of compounds **8a** and **8p** was confirmed by the ORTEP diagram for a single crystal structure (Fig. 3). Hence, we inveterated all the products of isatin derivatives are similar structure remains irrespective of the substituent present in the molecules.

Initially, Isatin and L-proline have ion pair interaction very closely with R_4N^+ of the organocatalyst which leads to the formation of carboxylative cyclic ester (**iv**); at the same time, decarboxylation may occur to form an azomethine ylide (**v**). The formation of dipole is shown in Fig. 4. Then, the dipolarophile chalcone directly interacts with the ylide in a concerted manner to give the cycloadduct product of spirrolizidine (**vi**) and the catalyst (**vii**) removed from the reaction mixture.

Conclusion

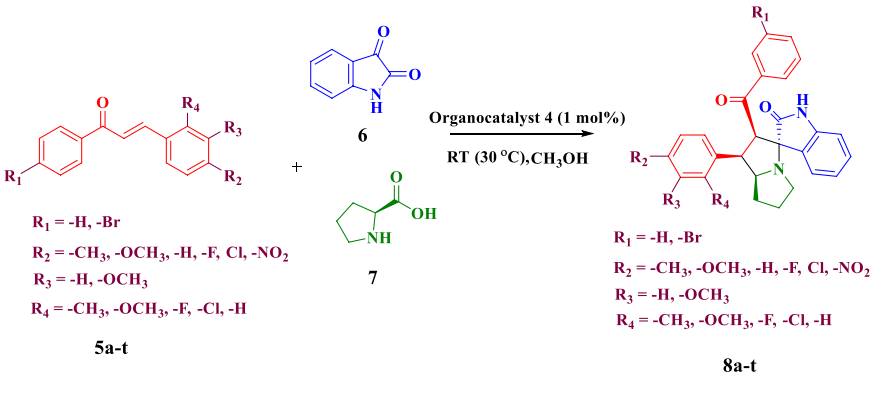
In conclusion, we have developed an efficient and practical protocol to synthesize optically active spiro[indoline-3,3′-pyrrolizin]-2-one derivatives with many stereogenic centers by chiral organocatalyzed enantioselective one-pot reaction of 1,3-dipolar cycloaddition reaction. Based on this methodology, a series of spiro[indoline-3,3′-pyrrolizin]-2-one were obtained in excellent yields (up to 99%) with excellent ee's (up to 96%) at room temperature.

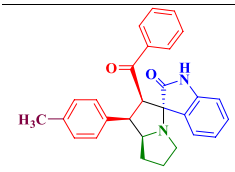
Experimental section

Materials and methods

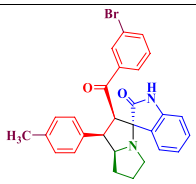
All the chemicals and reagents were used in this work as an analytical grade. *p*-Tolualdehyde, veratraldehyde, 4-chlorobenzaldehyde, 2-chlorobenzaldehyde, 4-nitrobenzaldehyde, 2,4-dichlorobenzaldehyde, 2,4-diflurobenzaldehyde, 4-flurobenzaldehyde, acetophenone and 4-bromo acetophenone were purchased from Sigma-Aldrich. Benzaldehyde, 2-methylbenzaldehyde, 4-methoxybenzaldehyde and 2-methoxybenzaldehyde were purchased from Alfa Aesar, and sodium hydroxide was obtained from

Table 2 Substrate scope

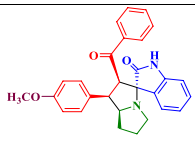



8a

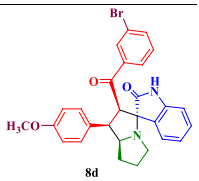
Yield 97%, ee's 84%


8b

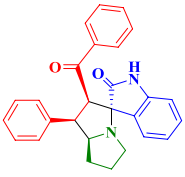
Yield 98%, ee's 93%


8c

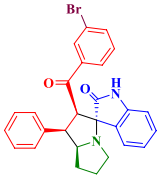
Yield 96%, ee's 92%


8d

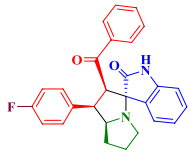
Yield 97%, ee's 94%


8e

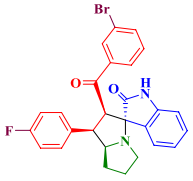
Yield 99%, ee's 93%


8f

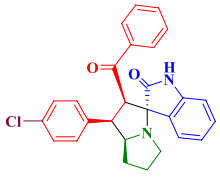
Yield 99%, ee's 89%


8g

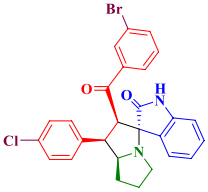
Yield 98%, ee's 83%


8h

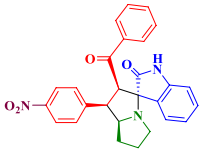
Yield 97%, ee's 92%


8i

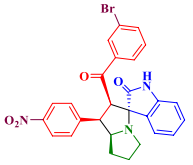
Yield 97%, ee's 91%


8j

Yield 99%, ee's 87%


8k

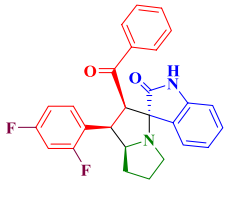
Yield 96%, ee's 86%


8l

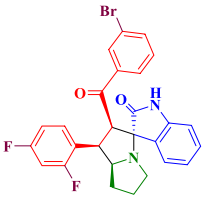
Yield 95%, ee's 88%

Merck, and all the solvents were obtained from laboratory grade. The melting points were measured in open capillary tubes and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as an internal standard and $CDCl_3$ as a solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale), and the coupling

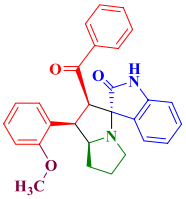
Table 2 (continued)



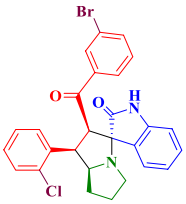
8m
Yield 98%,
ee's 72%



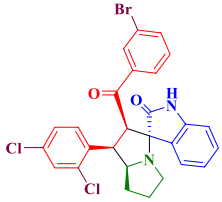
8n
Yield 99%,
ee's 75%



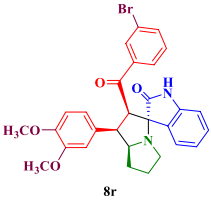
8o
Yield 94%,
ee's 96%



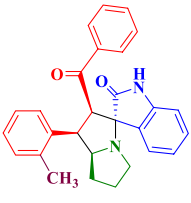
8p
Yield 95%,
ee's 94%



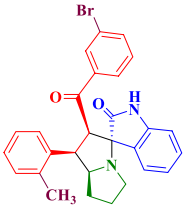
8q
Yield 97%,
ee's 76%



8r
Yield 98%,
ee's 94%



8s
Yield 97%,
ee's 93%



8t
Yield 98%,
ee's 94%

The 1,3-dipolar cycloaddition reaction of various chalcone 5(a-t) (0.4 mmol), isatin 6 (0.4 mmol), proline 7 (0.4 mmol), and MCPTC 4 (1 mol%), with 5 ml of methanol at room temperature (30ºC). Isolated yield. Enantiopurity was determined by HPLC analysis using a chiral column (Chiralcel OD-H) with hexane–IPA as the eluent.

constants are given in Hertz. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of n-hexane and ethyl acetate as an eluent. The HPLC was recorded in SHIMADZU LC-6AD with a chiral column (Chiralcel OD-H), using HPLC grade n-hexane and isopropanol as solvents. Optical rotations were measured on Rudolph Research Analytical AUTOPOL-II (readability $\pm 0.01°$) and AUTOPOL-IV (readability $\pm 0.001°$) automatic polarimeters.

General method for synthesis of chalcones 5(a–t) [34, 35]

Acetophenone or 4-bromo acetophenone (5 mmol) and aromatic aldehydes (5 mmol) were dissolved in 5 mL of ethanol, and then 10% sodium hydroxide was added; the mixture was stirred for about 5 min. After completion of the reaction, the mixture was poured into ice; the precipitate was filtered and recrystallized with ethanol, to get pure chalcone.

General method for one-pot synthesis of spiro[indoline-3,3′-pyrrolizin]-2-one derivatives (8a–t)

To the mixture of chalcone (0.4 mmol), isatin (0.4 mmol) and L-proline (0.4 mmol), 5 ml of methanol was dissolved, and 1 mol% of chiral organocatalysts **4** was added

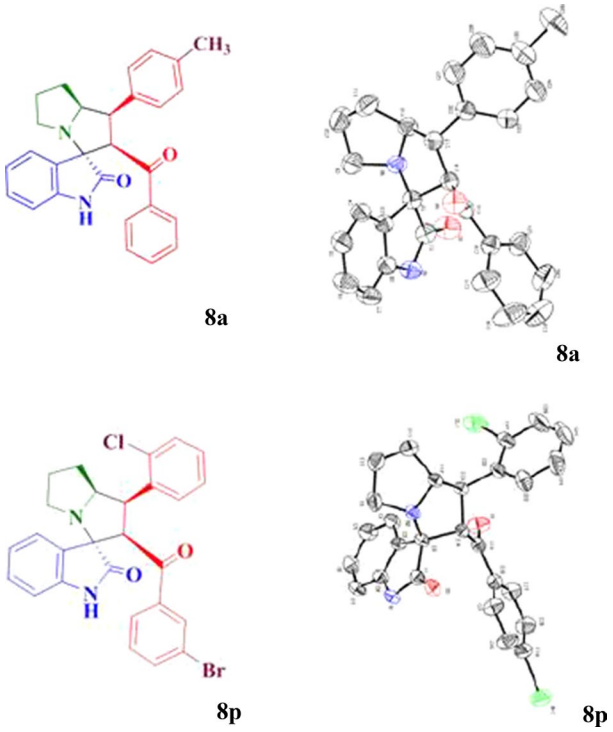


Fig. 3 ORTEP representation of the crystal structure of compound **8a** and **8p** [33]

and stirred at room temperature until the completion of reaction as indicated by TLC. After completion of the reaction, the mixture was poured into ice; the precipitate was filtered and recrystallized with ethanol, to get pure product without column chromatography.

Spectral data for the synthesized spiro[indoline-3,3′-pyrrolizin]-2-one derivatives (8)

2′-Benzoyl-1′-(*p*-tolyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (8a)

White solid (97% yield). m.p. 118–120 °C; 84% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, $\lambda = 254$ nm, t (major) = 4.38 min, t (minor) = 15.34 min]. $[\alpha]_D^{25} = -31.4°$ ($c = 0.98$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.06 (*s*, 1H), 7.43 (*d*, 2H, $J = 7.77$ Hz), 7.40 (*d*, 2H, $J = 1.08$ Hz), 7.33 (*t*, 1H, $J = 4.15$ Hz), 7.24 (*d*, 1H, $J = 18.78$ Hz), 7.20–7.11 (*m*, 5H), 7.14 (*t*, 1H, $J = 19.17$ Hz), 6.58 (*d*, 1H, $J = 7.71$ Hz), 4.94 (*d*, 1H, $J = 11.46$ Hz), 4.28–4.21 (*m*, 1H), 3.90 (*t*, 1H, $J = 10.63$ Hz), 2.75–2.00 (*m*, 2H), 2.31 (*s*, 3H), 2.10–2.00 (*m*, 2H), 1.95–1.71 (*m*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 197.43, 181.80, 141.17, 137.47, 137.12, 136.91,

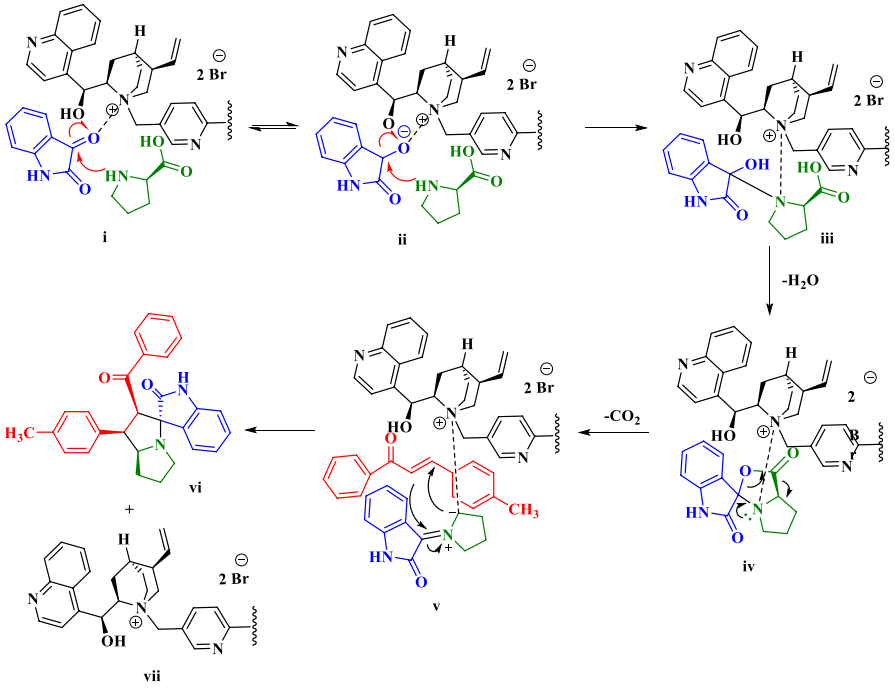


Fig. 4 Plausible mechanism for the formation of spirrolizidine from chalcone in the presence of chiral organocatalyst

133.24, 129.76, 128.43, 128.35, 128.25, 127.87, 125.54, 122.62, 110.64, 74.25, 72.50, 64.81, 53.02, 48.67, 31.17, 27.71, 21.43; ESI Mass: *m/z* [M + H^+]: 424.58.

2′-(3-Bromobenzoyl)-1′-(*p*-tolyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (8b)

White solid (98% yield). m.p. 130–132 °C; 93% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, λ = 254 nm, *t* (major) = 5.55 min, *t* (minor) = 18.90 min]. $[\alpha]_D^{25} = -42.3°$ (*c* = 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.83 (*s*, 1H), 7.39 (*d*, 2H, *J* = 7.71 Hz), 7.33–7.23 (*m*, 6H), 7.13 (*d*, 2H, *J* = 7.47 Hz), 7.02 (*t*, 1H, *J* = 7.33 Hz), 6.59 (*d*, 1H, *J* = 7.62 Hz), 4.86 (*d*, 1H, *J* = 11.34 Hz), 4.25–4.18 (*m*, 1H), 3.851 (*t*, 1H, *J* = 10.6 Hz), 2.67–2.59 (*m*, 2H), 2.297 (*s*, 3H), 2.05–1.87 (*m*, 2H), 1.75–1.70 (*m*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 195.98, 181.03, 140.46, 136.58, 136.38, 135.70, 131.30, 129.43, 129.34, 127.99, 127.83, 127.43, 124.89, 122.26, 110.23, 73.64, 72.00, 64.30, 52.56, 48.20, 30.62, 27.20, 20.95; ESI Mass: *m/z* [M + H^+]: 503.16.

2′-Benzoyl-1′-(4-methoxyphenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (8c)

White solid (96% yield). m.p. 154–156 °C; 92% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, $\lambda = 254$ nm, t (major) = 4.69 min, t (minor) = 16.38 min]. $[\alpha]_D^{25} = -50.07°$ ($c = 1.05$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.90 (s, 1H), 7.44–7.37 (*m*, 4H), 7.31 (*d*, 1H, $J = 7.35$ Hz), 7.24 (*d*, 1H, $J = 6.18$ Hz), 7.17–7.13 (*m*, 3H), 7.03 (*t*, 1H, $J = 11.07$ Hz), 6.84 (*d*, 2H, $J = 8.67$ Hz), 6.54 (*d*, 1H, $J = 7.65$ Hz), 4.87 (*d*, 1H, $J = 11.49$ Hz), 4.24–4.17 (*m*, 1H), 3.85 (*t*, 1H, $J = 10.69$ Hz), 3.75 (*s*, 3H), 2.71–2.56 (*m*, 2H), 2.05–1.69 (*m*, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 197.49, 181.68, 158.92, 141.11, 137.46, 133.25, 132.14, 129.76, 129.43, 128.44, 128.24, 127.88, 125.54, 122.61, 114.48, 110.57, 74.18, 72.39, 64.92, 55.61, 52.63, 48.66, 31.15, 27.69; ESI Mass: m/z [M + H$^+$]: 440.56.

2′-(3-Bromobenzoyl)-1′-(4-methoxyphenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro [indoline-3,3′-pyrrolizin]-2-one (8d)

White solid (97% yield). m.p. 210–212 °C; 94% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, $\lambda = 254$ nm, t (major) = 5.90 min, t (minor) = 9.67 min]. $[\alpha]_D^{25} = -60.4°$ ($c = 1.57$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.05 (*s*, 1H), 7.41 (*d*, 2H, $J = 8.43$ Hz), 7.33–7.23 (*m*, 4H), 7.14 (*t*, 2H, $J = 7.65$ Hz), 7.02 (*t*, 1H, $J = 7.30$ Hz), 6.85 (*d*, 2H, $J = 7.26$ Hz), 4.82 (*d*, 1H, $J = 11.46$ Hz), 4.24–4.16 (*m*, 1H), 3.84 (*t*, 1H, $J = 10.30$ Hz), 3.76 (*s*, 3H), 2.68–2.61 (*m*, 2H), 2.05–1.97 (*m*, 2H), 1.94–1.68 (*m*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 196.51, 181.59, 158.97, 141.03, 136.15, 131.88, 131.80, 129.92, 129.80, 129.40, 128.51, 127.88, 125.38, 122.72, 114.53, 110.77, 74.14, 72.37, 64.85, 55.62, 52.66, 48.69, 31.11, 27.70; ESI Mass: m/z [M + H$^+$]: 519.23.

2′-Benzoyl-1′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (8e)

White solid (99% yield). m.p. 104–106 °C; 93% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, $\lambda = 254$ nm, t (major) = 3.23 min, t (minor) = 11.01 min]. $[\alpha]_D^{25} = -66.7°$ ($c = 2.73$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.05 (*s*, 1H), 7.51 (*d*, 2H, $J = 7.44$ Hz), 7.38 (*d*, 3H, $J = 7.11$ Hz), 7.29 (*d*, 3H, $J = 7.68$ Hz), 7.24 (*d*, 1H, $J = 4.86$ Hz), 7.21 (*d*, 1H, $J = 7.41$ Hz), 7.16 (*d*, 2H, $J = 7.47$ Hz), 7.10 (*d*, 1H, $J = 7.8$ Hz), 7.01 (*t*, 1H, $J = 6.96$ Hz), 6.56 (*d*, 1H, $J = 7.53$ Hz), 4.93 (*d*, 1H, $J = 11.46$ Hz), 4.27–4.20 (*m*, 1H), 3.90 (*t*, 1H, $J = 10.60$ Hz), 2.77–2.57 (*m*, 2H), 2.08–1.71 (*m*, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 196.86, 180.89, 140.44, 139.61, 136.87, 132.67, 129.21, 128.48, 127.92, 127.67, 127.35, 126.76, 124.92, 122.08, 109.91, 73.54, 71.93, 64.30, 52.75, 48.08, 30.57, 27.10; ESI Mass: m/z [M + H$^+$]: 410.19.

2′-(3-Bromobenzoyl)-1′-phenyl-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (8f)

White solid (99% yield). m.p. 110–112 °C; 89% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, $\lambda = 254$ nm, *t* (major) = 3.10 min, *t* (minor) = 9.24 min]. $[\alpha]_D^{25} = -60.1°$ ($c = 1.82$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.22 (*s*, 1H), 7.50 (*d*, 2H, $J = 7.20$ Hz), 7.34–7.26 (*m*, 6H), 7.22 (*d*, 2H, $J = 8.31$ Hz), 7.13 (*d*, 1H, $J = 7.59$ Hz), 7.03 (*t*, 1H, $J = 7.24$ Hz), 6.62 (*d*, 1H, $J = 7.59$ Hz), 4.88 (*d*, 1H, $J = 11.46$ Hz), 4.27–4.20 (*m*, 1H), 3.89 (*t*, 1H, $J = 10.63$ Hz), 2.72–2.59 (*m*, 2H), 2.06–1.71 (*m*, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 196.51, 181.59, 158.97, 141.03, 136.15, 131.88, 131.80, 129.92, 129.80, 129.40, 128.51, 127.88, 125.38, 122.72, 114.53, 110.77, 74.14, 72.37, 64.85, 52.66, 48.69, 31.11, 27.70; ESI Mass: *m/z* [M + H$^+$]: 489.20.

2′-Benzoyl-1′-(4-fluorophenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (8g)

White solid (98% yield). m.p. 118–120 °C; 83% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, $\lambda = 254$ nm, *t* (major) = 4.29 min, *t* (minor) = 14.83 min]. $[\alpha]_D^{25} = -27.3°$ ($c = 1.73$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.04 (*s*, 1H), 7.50–7.46 (*m*, 3H), 7.38 (*d*, 2H, $J = 8.28$ Hz), 7.33 (*d*, 1H, $J = 7.26$ Hz), 7.24 (*d*, 1H, $J = 7.41$ Hz), 7.18 (*d*, 2H, $J = 19.77$ Hz), 7.11 (*d*, 1H, $J = 7.59$ Hz), 7.04–6.97 (*m*, 3H), 4.86 (*d*, 1H, $J = 11.46$ Hz), 4.25–4.17 (*m*, 1H), 3.89 (*t*, 1H, $J = 10.65$ Hz), 2.73–2.58 (*m*, 2H), 2.08–1.69 (*m*, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 197.41, 181.66, 141.16, 137.32, 135.88, 133.37, 130.00, 129.89, 128.50, 128.22, 127.81, 125.39, 122.68, 116.05, 115.77, 110.68, 74.14, 72.38, 64.99, 52.62, 48.65, 31.08, 27.67; ESI Mass: *m/z* [M + H$^+$]: 428.23.

2′-(3-Bromobenzoyl)-1′-(4-fluorophenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro [indoline-3,3′-pyrrolizin]-2-one (8h)

White solid (97% yield). m.p. 120–122 °C; 92% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, $\lambda = 254$ nm, *t* (major) = 8.19 min, *t* (minor) = 10.53 min]. $[\alpha]_D^{25} = -60.0°$ ($c = 1.89$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.44 (*s*, 1H), 7.46 (*t*, 2H, $J = 6.54$ Hz), 7.32–7.21 (*m*, 5H), 7.13 (*t*, 2H, $J = 7.57$ Hz), 7.00 (*t*, 3H, $J = 8.34$ Hz), 6.62 (*d*, 1H, $J = 7.68$ Hz), 4.80 (*d*, 1H, $J = 11.40$ Hz), 4.23–4.16 (*m*, 1H), 3.87 (*t*, 1H, $J = 10.63$ Hz), 2.68–2.61 (*m*, 2H), 2.04–1.94 (*m*, 2H), 1.91–1.65 (*m*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 196.04, 181.32, 163.50, 160.26, 140.81, 135.61, 131.45, 129.65, 129.50, 129.39, 128.26, 127.42, 122.38, 115.46, 110.54, 73.74, 71.95, 64.49, 52.25, 48.29, 30.63, 27.25; ESI Mass: *m/z* [M + H$^+$]: 507.09.

2′-Benzoyl-1′-(4-chlorophenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (8i)

White solid (97% yield). m.p. 126–128 °C; 91% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, $\lambda = 254$ nm, *t* (major) = 3.61 min, *t* (minor) = 5.97 min]. $[\alpha]_D^{25} = -88.3°$ ($c = 3.17$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.91 (*s*, 1H), 7.45 (*d*, 2H, $J = 8.40$ Hz), 7.38 (*d*, 2H, $J = 7.20$ Hz), 7.32 (*d*, 2H, $J = 12.60$ Hz), 7.26 (*d*, 1H, $J = 2.10$ Hz), 7.22 (*d*, 2H, $J = 7.50$ Hz), 7.17 (*d*, 1H, $J = 7.50$ Hz), 7.13 (*t*, 1H, $J = 7.80$ Hz), 7.02 (*d*, 1H, $J = 7.80$ Hz), 6.54 (*d*, 1H, $J = 7.50$ Hz), 4.86 (*d*, 1H, $J = 11.40$ Hz), 4.24–4.17 (*m*, 1H), 3.88 (*t*, 1H, $J = 10.50$ Hz), 2.73–2.59 (*m*, 2H), 2.05–1.97 (*m*, 2H), 1.92–1.66 (*m*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 196.75, 180.91, 140.51, 138.15, 136.71, 132.80, 132.52, 129.29, 128.65, 127.93, 127.64, 127.23, 124.75, 122.12, 110.02, 73.47, 71.70, 64.37, 52.17, 48.04, 30.46, 27.05; ESI Mass: *m*/*z* [M^+]: 444.18.

2′-(3-Bromobenzoyl)-1′-(4-chlorophenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro [indoline-3,3′-pyrrolizin]-2-one (8j) White solid (99% yield). m.p. 108–110 °C; 87% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, $\lambda = 254$ nm, *t* (major) = 2.92 min, *t* (minor) = 8.99 min]. $[\alpha]_D^{25} = -140.2°$ ($c = 1.35$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.66 (s, 1H), 7.44 (*d*, 2H, $J = 8.43$ Hz), 7.32 (*t*, 4H, $J = 6.66$ Hz), 7.27 (*d*, 2H, $J = 2.7$ Hz), 7.24–7.19 (*m*, 1H), 7.01 (*t*, 1H, $J = 7.12$ Hz), 4.80 (*d*, 1H, $J = 11.40$ Hz), 4.23–4.16 (*m*, 1H), 3.85 (*t*, 1H, $J = 10.63$ Hz), 2.71–2.57 (*m*, 2H), 2.05–1.90 (*m*, 2H), 1.88–1.67 (*m*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 196.13, 180.97, 147.94, 147.54, 141.03, 135.86, 131.91, 130.18, 129.70, 129.42, 128.77, 127.77, 125.01, 124.35, 122.87, 110.71, 73.74, 72.10, 65.23, 53.17, 48.50, 30.81, 27.49; ESI Mass: *m*/*z* [$M + H^+$]: 523.11.

2′-Benzoyl-1′-(4-nitrophenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (8k) Pale orange solid (96% yield). m.p. 108–110 °C; 86% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, $\lambda = 254$ nm, *t* (major) = 18.22 min, *t* (minor) = 20.57 min]. $[\alpha]_D^{25} = -120.1°$ ($c = 1.30$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.18 (*d*, 2H, $J = 8.58$ Hz), 8.09 (*s*, 1H), 7.69 (*d*, 2H, $J = 8.61$ Hz), 7.36 (*d*, 2H, $J = 7.83$ Hz), 7.26–7.12 (*m*, 4H), 7.00 (*t*, 1H, $J = 7.17$ Hz), 6.56 (*d*, 1H, $J = 7.68$ Hz), 4.90 (*d*, 1H, $J = 11.34$ Hz), 4.30–4.23 (*m*, 1H), 4.02 (*t*, 1H, $J = 10.53$ Hz), 2.76–2.58 (*m*, 2H), 2.06–1.94 (*m*, 2H), 1.91–1.69 (*m*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 196.55, 180.58, 147.62, 146.91, 140.59, 136.57, 132.88, 129.44, 129.13, 128.87, 127.98, 127.62, 127.19, 124.59, 123.72, 122.18, 110.01, 73.25, 71.51, 64.63, 52.62, 47.92, 30.24, 26.89; ESI Mass: *m*/*z* [$M + H^+$]: 455.20.

2′-(3-Bromobenzoyl)-1′-(4-nitrophenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro [indoline-3,3′-pyrrolizin]-2-one (8l) Pale orange solid (95% yield). m.p. 120–122 °C; 88% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, $\lambda = 254$ nm, *t* (major) = 16.31 min, *t* (minor) = 22.44 min]. $[\alpha]_D^{25} = -73.5°$ ($c = 1.05$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.19 (*d*, 2H, $J = 8.61$ Hz), 7.95 (*s*,

1H), 7.69 (*d*, 2H, *J* = 8.55 Hz), 7.33 (*d*, 3H, *J* = 8.49 Hz), 7.25 (*d*, 3H, *J* = 8.94 Hz), 7.15 (*d*, 1H, *J* = 8.16 Hz), 7.14 (*d*, 1H, *J* = 7.53 Hz), 7.02 (*t*, 1H, *J* = 7.50 Hz), 4.84 (*d*, 1H, *J* = 11.31 Hz), 4.30–4.23 (*m*, 1H), 4.00 (*t*, 1H, *J* = 10.54 Hz), 2.75–2.59 (*m*, 2H), 2.07–1.90 (*m*, 2H), 1.77–1.66 (*m*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 196.13, 180.97, 147.94, 147.54, 141.03, 135.86, 131.91, 130.18, 129.70, 129.42, 128.77, 127.77, 125.01, 124.35, 122.87, 110.71, 73.74, 72.10, 65.23, 53.17, 48.50, 30.81, 27.49; ESI Mass: *m*/*z* [M + H$^+$]: 534.08.

2′-Benzoyl-1′-(2,4-difluorophenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (8m) White solid (98% yield). m.p. 125–127 °C; 72% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, λ = 254 nm, *t* (major) = 3.49 min, *t* (minor) = 16.97 min]. $[\alpha]_D^{25} = -100.1°$ (*c* = 1.29, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.66 (s, 1H), 7.54–7.46 (*m*, 2H), 7.41–7.33 (*m*, 4H), 7.24–7.12 (*m*, 3H), 7.10 (*d*, 1H, *J* = 7.14 Hz), 7.02 (*t*, 1H, *J* = 7.42 Hz), 6.88–6.77 (*m*, 2H), 6.53 (*d*, 1H, *J* = 7.56 Hz), 5.04 (*d*, 1H, *J* = 11.34 Hz), 4.22–4.16 (*m*, 2H), 2.68–2.57 (*m*, 2H), 2.05–1.97 (*m*, 2H), 1.93–1.74 (*m*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 196.65, 180.95, 140.60, 136.68, 132.81, 129.62, 129.36, 127.92, 127.64, 127.10, 124.69, 122.19, 111.51, 111.23, 110.15, 104.00, 103.66, 73.42, 70.81, 62.58, 47.98, 45.53, 30.49, 27.07; ESI Mass: *m*/*z* [M + H$^+$]: 446.19.

2′-(3-Bromobenzoyl)-1′-(2,4-difluorophenyl)-1′,2′,5′,6′,7′,7a′-hexahydro spiro[indoline-3,3′-pyrrolizin]-2-one (8n) White solid (99% yield). m.p. 135–137 °C; 75% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, λ = 254 nm, *t* (major) = 3.39 min, *t* (minor) = 12.42 min]. $[\alpha]_D^{25} = -51.7°$ (*c* = 1.31, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.44 (s, 1H), 7.46 (*t*, 2H, *J* = 6.54 Hz), 7.32–7.21 (*m* 5H), 7.13 (*t*, 2H, *J* = 7.57 Hz), 7.00 (*t*, 3H, *J* = 8.34 Hz), 6.62 (*d*, 1H, *J* = 7.68 Hz), 4.80 (*d*, 1H, *J* = 11.40 Hz), 4.23–4.16 (*m*, 1H), 3.87 (*t*, 1H, *J* = 10.59 Hz), 2.68–2.61 (*m*, 2H), 2.04–1.87 (*m*, 2H), 1.76–1.65 (*m*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 196.04, 181.32, 163.50, 160.26, 140.81, 135.61, 131.45, 129.65, 129.50, 129.39, 128.26, 127.42, 122.38, 115.74, 115.46, 110.54, 73.74, 71.95, 64.49, 52.25, 48.29, 30.63, 27.25; ESI Mass: *m*/*z* [M$^+$]: 524.09.

2′-Benzoyl-1′-(2-methoxyphenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (8o) White solid (94% yield). m.p. 120–122 °C; 96% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, λ = 254 nm, *t* (major) = 20.07 min, *t* (minor) = 28.28 min]. $[\alpha]_D^{25} = -73.5°$ (*c* = 1.21, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.11 (*s*, 1H), 7.47–7.39 (*m*, 4H), 7.32 (*t*, 2H, *J* = 2.86 Hz), 7.16 (*d*, 2H, *J* = 7.14 Hz), 7.09–7.00 (*m* 2H), 6.93–6.86 (*m*, 2H), 6.56 (*d*, 1H, *J* = 7.53 Hz), 5.33 (*d*, 1H, *J* = 10.50 Hz), 4.29 (*t*, 2H, *J* = 10.14 Hz), 3.93 (*s*, 3H), 2.67–2.61 (*m*, 2H), 1.99–1.85 (*m*, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 197.25, 181.25, 157.85, 140.62, 137.14, 132.52, 129.08, 128.63, 127.83, 127.65, 127.44, 127.31, 125.24, 122.02, 120.64, 110.97, 109.98, 73.70, 70.62, 61.62, 55.50, 48.01, 47.39, 30.81, 27.22; ESI Mass: *m*/*z* [M + H$^+$]: 440.23.

2′-(3-Bromobenzoyl)-1′-(2-chlorophenyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro [indoline-3,3′-pyrrolizin]-2-one (8p) White solid (95% yield). m.p. 226–228 °C; 94% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, $\lambda = 254$ nm, *t* (major) = 3.08 min, *t* (minor) = 5.88 min]. $[\alpha]_D^{25} = -63.7°$ ($c = 1.32$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.61 (s, 1H), 7.62 (*d*, 1H, $J = 7.74$ Hz), 7.40 (*d*, 2H, $J = 7.98$ Hz), 7.31 (*d*, 4H, $J = 8.85$ Hz), 7.24 (*d*, 1H, $J = 7.56$ Hz), 7.18–7.11 (*m*, 2H), 7.05 (*t*, 1H, $J = 7.48$ Hz), 5.03 (*d*, 1H, $J = 11.58$ Hz), 4.62 (*t*, 1H, $J = 10.71$ Hz), 4.15–4.10 (*m*, 1H), 2.65 (*d*, 2H, $J = 5.46$ Hz), 1.97–1.88 (*m*, 4H).^{13}C NMR (75 MHz, $CDCl_3$) δ_C 196.18, 181.32 140.96, 137.39, 136.05, 135.23, 131.82, 130.44, 129.79, 128.53, 128.49, 128.35, 127.82, 127.66, 125.22, 123.02, 110.74, 74.04, 72.92, 64.22, 48.67, 48.45, 30.69, 27.62; ESI Mass: *m*/*z* [M^+]: 522.10.

2′-(3-Bromobenzoyl)-1′-(2,4-dichlorophenyl)-1′,2′,5′,6′,7′,7a′-hexahydro spiro[indoline-3,3′-pyrrolizin]-2-one (8q) White solid (97% yield). m.p. 125–127 °C; 76% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, $\lambda = 254$ nm, *t* (major) = 7.26 min, *t* (minor) = 15.35 min]. $[\alpha]_D^{25} = -63.7°$ ($c = 1.05$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.23 (*s*, 1H), 7.56 (*d*, 1H, $J = 8.55$ Hz), 7.41 (*d*, 1H, $J = 1.89$ Hz), 7.32 (*d*, 3H, $J = 8.55$ Hz), 7.26 (*d*, 3H, $J = 7.74$ Hz), 7.14 (*t*, 1H, $J = 7.54$ Hz), 7.03 (*t*, 1H, $J = 7.51$ Hz), 6.62 (*d*, 1H, $J = 7.65$ Hz), 4.94 (*d*, 1H, $J = 11.52$ Hz), 4.55 (*t*, 1H, $J = 10.65$ Hz), 4.11–4.06 (*m*, 1H), 2.68–2.61 (*m*, 2H), 1.99–1.84 (*m*, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 195.72, 181.05, 140.75, 135.73, 135.51, 135.46, 133.00, 132.00, 131.47, 129.76, 129.37, 129.06, 128.29, 127.65, 127.33, 124.68, 122.65, 127.33, 124.68, 122.65, 110.51, 73.62, 72.35, 63.79, 48.28, 47.72, 30.19, 27.14; ESI Mass: *m*/*z* [$M + H^+$]: 556.11.

2′-(3-Bromobenzoyl)-1′-(3,4-dimethoxyphenyl)-1′,2′,5′,6′,7′,7a′-hexahydro spiro[indoline-3,3′-pyrrolizin]-2-one (8r) White solid (98% yield). m.p. 124–126 °C; 94% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, $\lambda = 254$ nm, *t* (major) = 20.07 min, *t* (minor) = 28.28 min]. $[\alpha]_D^{25} = -100.15°$ ($c = 1.65$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.22 (s, 1H), 7.33–7.24 (*m*, 6H), 7.14 (*t*, 2H, $J = 7.47$ Hz), 7.04 (*d*, 2H, $J = 9.00$ Hz), 6.81 (*d*, 1H, $J = 8.16$ Hz), 6.62 (*d*, 1H, $J = 7.53$ Hz), 4.82 (*d*, 1H, $J = 11.40$ Hz), 4.28–4.20 (*m*, 1H), 3.90 (*s*, 3H), 3.82 (*s*, 3H), 2.67–2.62 (*m*, 2H), 2.07–1.99 (*m*, 2H), 1.935–1.676 (*m*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 196.14, 181.26, 148.96, 147.98, 140.76, 135.73, 132.06, 131.42, 129.55, 129.43, 128.18, 127.47, 124.93, 122.31, 119.98, 111.36, 111.25, 110.48, 73.93, 71.91, 64.46, 55.94, 55.82, 52.66, 48.24, 30.88, 27.37; ESI Mass: *m*/*z* [$M + H^+$]: 549.16.

2′-Benzoyl-1′-(*o*-tolyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (8s) White solid (97% yield). m.p. 130–132 °C; 93% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, $\lambda = 254$ nm, *t* (major) = 6.54 min, *t* (minor) = 8.22 min]. $[\alpha]_D^{25} = -120.1°$ ($c = 1.29$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.24 (s, 1H), 7.39 (*d*, 3H, $J = 7.86$ Hz), 7.32–7.23 (*m*,

5H), 7.12 (*d*, 3H, *J* = 7.62 Hz), 7.02 (*t*, 1H, *J* = 7.47 Hz), 6.61 (*d*, 1H, *J* = 7.62 Hz), 4.85 (*d*, 1H, *J* = 11.43 Hz), 4.25–4.17 (*m*, 1H), 3.85 (*t*, 1H, *J* = 10.65 Hz), 2.67–2.61 (*m*, 2H), 2.29 (*s*, 3H), 2.04–1.96 (*m*, 2H), 1.91–1.69 (*m*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 196.07, 181.39, 140.75, 136.66, 136.48, 135.76, 131.40, 129.44, 128.15, 127.93, 127.49, 125.00, 122.34, 110.47, 73.83, 72.09, 64.30, 52.68, 48.32, 30.72, 27.31, 21.06; ESI Mass: *m*/*z* [M + H$^+$]: 424.21.

2′-(3-Bromobenzoyl)-1′-(*o*-tolyl)-1′,2′,5′,6′,7′,7a′-hexahydrospiro[indoline-3,3′-pyrrolizin]-2-one (8t) White solid (98% yield). m.p. 187–189 °C; 94% ee's, determined by HPLC [Chiralcel OD-H, *n*-hexane/*i*-propanol = 80/20, 1 ml/min, λ = 254 nm, *t* (major) = 7.67 min, *t* (minor) = 10.69 min]. $[\alpha]_D^{25} = -132.2°$ (*c* = 1.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.01 (s, 1H), 7.39 (*t*, 4H, *J* = 7.15 Hz), 7.31 (*d*, 1H, *J* = 7.23 Hz), 7.25 (*d*, 2H, *J* = 4.53 Hz), 7.18–7.09 (*m*, 3H), 7.02 (*d*, 1H, *J* = 7.53 Hz), 6.55 (*d*, 1H, *J* = 7.62 Hz), 4.91 (*d*, 1H, *J* = 11.49 Hz), 4.25–4.18 (*m*, 1H), 3.87 (*t*, 1H, *J* = 10.69 Hz), 2.69–2.60 (*m*, 2H), 2.29 (*s*, 3H), 2.05–1.97 (*m*, 2H), 1.91–1.75 (*m*, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 197.09, 181.49, 145.07, 140.87, 137.05, 136.73, 136.53, 132.89, 129.74, 129.39, 128.62, 128.54, 128.05, 127.98, 127.87, 127.46, 125.14, 122.22, 121.07, 110.33, 73.91, 72.13, 64.39, 52.63, 48.31, 30.78, 27.31, 21.58, 21.05; ESI Mass: *m*/*z* [M$^+$]: 502.13.

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