Dearomative Spirocyclization of Tryptamine-Derived Isocyanides via Iron-Catalyzed Carbene Transfer

Thomas R. Roose, Finn McSorley, Bryan Groenhuijzen, Jordy M. Saya, Bert U. W. Maes,* Romano V. A. Orrù, and Eelco Ruijter*

ABSTRACT: Tryptamine-derived isocyanides are valuable building blocks in the construction of spirocyclic indolenines and indolines via dearomatization of the indole moiety. We report the Bu₄N[Fe-(CO)₃NO]-catalyzed carbene transfer of α-diazo esters to 3-(2-isocyanoethyl)indoles, leading to ketenimine intermediates that undergo spontaneous dearomative spirocyclization. The utility of this iron-catalyzed carbene transfer/spirocyclization cascade was demonstrated by its use as a key step in the formal total synthesis of monoterpenoid indole alkaloids (±)-aspidofractinine, (±)-limaspermidine, (±)-aspidospermidine, and (±)-17-demethoxy-N-acetylcylindrocarine.

INTRODUCTION

Functionalized isocyanides have proven valuable building blocks in organic chemistry. Tethering the isocyanide moiety to other reactive functionalities provides great opportunities for the development of novel cascade and multicomponent processes.¹ For example, 3-(2-isocyanoethyl)indoles (1, Scheme 1a) have recently attracted considerable interest, as they allow for facile construction of polycyclic spiroindolenines/indolines through dearomatization of the indole moiety.³⁻⁵ These spiroindolenines/indolines (2) are of considerable relevance as these motifs occur in, e.g., medicinally relevant compounds,⁶ such as Sky kinase inhibitor ⁵ ²⁻⁵ and monoterpenoid indole alkaloids of the Aspidosperma and Strychnos types (Scheme 1b).⁸ Notably, strategies toward construction of these natural products often involve dearomatization of the indole moiety.² Several strategies for the dearomative spirocyclization of 3-(2-isocyanoethyl)indoles ¹ have been reported,³⁻⁵ which differ in the transformation of the isocyano moiety providing different functionalities allowing spirocyclization (Scheme 2a). The first strategy (I) relies on trapping the isocyano moiety by an electrophile, resulting in nitritium ion ⁷. Subsequently, this intermediate is trapped in an intramolecular fashion by the indole C₃ position. Multiple electrophiles have been applied in the formation of spirocyclic indolenines and indolines.³ Moreover, our group has demonstrated that using NIS as electrophile, 3-(2-isocyanoethyl)indoles ¹ could be applied in the formal total synthesis of (±)-aspidofractinine.⁶ A less explored strategy (II) involves transition-metal-catalyzed imidoylative cross-coupling,¹⁰ which proceeds via imidoylpalladium intermediate ⁸ (Scheme 2a).⁵ The third strategy (III) proceeds via heteroallene ⁹, which can be accessed via selective transition-metal-catalyzed carbene (Y = CR⁶) or nitrene transfer (Y = N) to the isocyanide moiety,¹¹ followed by nucleophilic addition of the C₃-position of the indole to the heteroallene (Scheme 2a).⁴ Although one base-metal-catalyzed example is reported for the nitrene transfer to isocyanide ¹,⁴ no base-metal-
catalyzed carbene transfers to 3-(2-isocyanoethyl)indoles (1) have been reported.

In 2020, Chen and co-workers reported the dearomative spirocyclization of isocyanides 1 using strategy III, proceeding via ketenimine intermediate 9 (Y = CR₆, Scheme 2a). They described the Pd-catalyzed carbene transfer to isocyanide 1 in the construction of spiroindolenine 15 and polycyclic spiroindolines 16 (Scheme 2b). Although this method displays a broad scope, a high loading of the precious palladium catalyst (10−15%) is required. In addition, despite obtaining pentacyclic scaffold 17 (resembling the core of monoterpenoid indole alkaloids), the authors could not obtain the correct relative stereochemistry at the C−E ring junction, which should be cis-fused as in, e.g., aspidospermidine (3, Scheme 1b).

Shifting from Pd-catalyzed processes to base metals, such as iron, is highly desired, due to their high abundance on Earth and low cost. Recently, our group developed an iron-catalyzed carbene transfer reaction to isocyanides for the construction of multiple heterocycles. The ferrate complex, Bu₄N[Fe(CO)₃NO] (also known as the Hieber anion), was demonstrated to effectively catalyze the transfer of carbenes to isocyanides to give a ketenimine intermediate. In this work, we demonstrate for the first time that the Hieber anion can be employed to catalyze a dearomative spirocyclization of 3-(2-isocyanoethyl)indoles (1). The process proceeds via carbene transfer to the isocyanide moiety (Scheme 3b) to afford spiroindolenines 19 as potential synthetic intermediates in the total synthesis of indole alkaloids.

**Results and Discussion**

We started our investigation using isocyanide 1a and ethyl diazoacetate (22) as model reactants for optimization (Table 1). Various iron-based catalysts (entries 1−6) were found to be inferior to the Bu₄N[Fe(CO)₃NO] as a catalyst of the reaction (entry 7). The addition of phosphine ligands negatively affected the reaction (entries 8 and 9).

Furthermore, performing the reaction at lower temperature afforded the product in low yield with slow conversion (entry 10). In addition, the reaction was found to proceed in several solvents (entries 12−16), albeit not as efficiently as in DCE. Thus, we opted to continue with the conditions in entry 7, affording spiroindolenine 23a in 96% isolated yield.
The Journal of Organic Chemistry

Table 1. Optimization of the Fe-Catalyzed Carbene Transfer to 3-(2-Isocyanatoethyl)indole 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Fe]-cat.</th>
<th>Additive (mol %)</th>
<th>Solvent</th>
<th>Yield of 23a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fe(CO)_4</td>
<td></td>
<td>DCE</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>Fe(P)</td>
<td></td>
<td>DCE</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>Fe(TPP)/Cl</td>
<td></td>
<td>DCE</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>Fe(TPP)/Cl</td>
<td>Zn (50)</td>
<td>DCE</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>Fe(ClO_4)_2</td>
<td>TMEDA (6)</td>
<td>DCE</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>Fe(ClO_4)_2</td>
<td>DPPE (6)</td>
<td>NaBarF (6)</td>
<td>trace</td>
</tr>
<tr>
<td>7</td>
<td>Bu_N[Fe(CO)_3]NO</td>
<td></td>
<td>DCE</td>
<td>98 (96+)</td>
</tr>
<tr>
<td>8</td>
<td>Bu_N[Fe(CO)_3]NO</td>
<td>PPh_3 (6)</td>
<td>DCE</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
<td>Bu_N[Fe(CO)_3]NO</td>
<td>P(2-Fur)_3 (6)</td>
<td>DCE</td>
<td>86</td>
</tr>
<tr>
<td>10</td>
<td>Bu_N[Fe(CO)_3]NO</td>
<td></td>
<td>DCE</td>
<td>22</td>
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<td>0</td>
</tr>
<tr>
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<td></td>
<td>DMF</td>
<td>85</td>
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<tr>
<td>16</td>
<td>Bu_N[Fe(CO)_3]NO</td>
<td></td>
<td>i-PrOH</td>
<td>56</td>
</tr>
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</table>

*Reactions performed on a 0.5 mmol scale of 1a and 0.6 mmol of 22. Yields are determined by 'H NMR analysis using 2,5-dimethylfuran as internal standard. *Isolated yield. *Full conversion of ethyl diazoacetate (22) prior to full conversion of isocyanide 1a. *No full conversion of isocyanide 1a observed by TLC analysis after 22–24 h at 80 °C. *Reaction performed at 60 °C.

With the optimal conditions in hand, we started to investigate the scope of the Fe-catalyzed carbene transfer/spirocyclization cascade with regard to C2-substituted indole isocyanides 1b–p (Scheme 3). Aliphatic substituents were generally well tolerated, affording indolenine 23b (R² = Me) in good yield. A slower conversion and lower yields were observed with increasing bulk of the aliphatic substituent (23c, R² = t-Bu, Scheme 3). Decoration of the indole benzene ring with several substituents at different positions afforded spiroindolenines 23d–i in good to excellent yield. In addition, the reaction allowed the presence of aromatic indole substituents (R³) including a 2-naphthyl group, and the corresponding indolenines (23j–n) were obtained in good yield. To our delight, even the use of a 2-bromoindole isocyanide 1o (R² = Br) afforded 23o in good yield, providing an imidoyl halide as a functional handle at the C2-position. In addition, the tautomerized bis-β-enamino ester 23p was obtained in moderate yield starting from 2-(2-methoxy-2-oxoethyl)indole isocyanide 1p (R² = CH_3CO.Me).

After investigation of the isocyanide scope, the scope of diazo compounds was briefly explored (Scheme 3). We started with the use of diazo precursors for donor–acceptor carbenes (18a, R³ = Ph, R⁴ = Me), which afforded the products 23aa and 23ba in only trace amounts. In contrast, in the analogous Pd-catalyzed reaction, these carbenes were converted to indolenines 23aa and 23ba in good to excellent yield. A similar limitation in scope of α-diazo esters was observed in the recently reported iron-catalyzed intermolecular carbene transfer to isocyanides, where we used amidines to trap the ketenimine intermediate. Next, we employed diethyl 2-diazo glutarate (18b) of the acceptor-type carbene class, which was reacted with isocyanides 1a and 1b to give the corresponding spiroindolenines 23ab and 23bb in moderate yield. Extending the carbon chain to diethyl 2-diazo glutarate (18c) afforded only a trace amount of product 23bc as judged by 'H NMR analysis of the crude product. In addition, the use of α-diazo ester 18e (R¹ = COMe, R⁴ = Me) from the acceptor–acceptor class did afford spiroindolenine 23be, albeit in low yield. Finally, we employed α-diazo ester 18d (R¹ = E-CH = CHCO.Me, R⁴ = Me) in combination with isocyanide 1a, which allowed for a carbene transfer/spirocyclization/Mannich cascade affording tetracyclic spiroindoline 24 as described by Chen et al. (Scheme 1b). Unfortunately, with [Fe(CO)_3]NO Bu_N as catalyst this cascade did not occur.

In addition to the isocyanide scope bearing a C2 indole substituent, we explored the scope of the C2-unsubstituted isocyanides, where R² = H (Scheme 4). Based on previous work, we envisioned that the corresponding spiroindolines, containing an imine functionality, are relatively less stable compared to their corresponding C2-substituted counterparts. Fortunately, the obtained spiroindoline 25a with the benchmark substrate (1a) is relatively stable upon isolation and column chromatography. However, the stability of the spiroindoline derived from isocyanides 1q–x differs significantly depending on the substitution pattern on the indole moiety (R¹). For example, the spiroindoline derived from isocyanide 1q (R¹ = 5-OMe) could not be isolated and fully degraded upon isolation. Therefore, we decided to in situ transform all C2-unsubstituted spiroindolines 23 to the more stable spiroindolines 25q–x via a one-pot spirocyclization/reduction sequence (Scheme 4). After a brief optimization (Table S3) we were able to isolate benchmark...
spiroindoline 25a in 77% yield using NaBH₄ as the reducing agent (method A). Various C5-substituted indole isocyanides (1q–v) were converted to the corresponding spiroindolines 25q–v in moderate to good yield (Scheme 4). Next, we investigated tryptamine-derived isocyanides bearing a substituent on the ethylene linker (1w, 1x). Initially, low yields were observed for spiroindolines 25w and 25x employing NaBH₄ deuteride (method A). Gratifyingly, changing to slightly different conditions (method B) using NaBH₄CN as the hydride source, spiroindolenines 25w and 25x could be isolated in reasonable yield.

Conversion of 1w to 25w proceeded with moderate diastereoselectivity (2.2:1 dr). A slightly higher stereoinduction (3:1 dr) was observed for 25x. Advantageously, when C2-methyl-substituted isocyanide 1b was employed in the one-pot sequence, spiroindoline 25b was obtained as a single diastereomer. Based on literature precedent,10 the relative stereochemistry was assumed to proceed with the hydride approaching from the least hindered face.

In order to show the utility of the Fe-catalyzed carbene transfer/spirocyclization cascade methodology, we investigated the conversion of a suitably functionalized isocyanide to the core scaffold of monoterpene indole alkaloids (Scheme 5). To our delight, isocyanide 1y could be subjected to the one-pot spirocyclization/reduction sequence as the free alcohol, affording spiroindoline 25y in 66% yield as a single diastereomer on a 6.3 mmol scale. Next, the alcohol in 25y was converted to the corresponding iodoide, which under the reactions conditions immediately cyclized to afford tetracycle 25z in excellent yield. Subsequent Boc-protection results in the desired scaffold 20, which can be transformed into pentacyclic 19-oxaoaspidospermidine (27) as demonstrated by Saya et al.13 Further, Dufour et al. demonstrated that scaffold 27 can be transformed into (±)-aspidofractine,13 while more recently, Martin et al. also reported the conversion of indole 27 to (±)-limaspermide, (±)-aspidospermidine, and (±)-17-demethoxy-N-acetyllycllinocarione.18

In conclusion, we report the use of Bu₄N[Fe(CO)₃]NO as catalyst in the carbene transfer/dearomative spirocyclization cascade toward spiroindolines. In addition, the corresponding spiroindolines could be obtained via a one-pot reduction sequence. In general, the reaction displays a high functional group tolerance for the isocyanide 1. However, the Bu₄N[Fe(CO)₃]NO-catalyzed reaction is less tolerant of α-diazo ester input compared to the Pd-catalyzed reaction developed by Chen and co-workers.65 Nonetheless, using a carefully chosen C2-prefunctionalized 3-(2-isocyanoethyl)indole, we were able to apply the Bu₄N[Fe(CO)₃]NO-catalyzed carbene transfer/dearomative spirocyclization/reduction sequence in the formal total synthesis of the monoterpene indole alkaloids (±)-aspidofractine, (±)-limaspermide, (±)-aspidospermidine, and (±)-17-demethoxy-N-acetyllycllinocarione.

**Experimental Section**

**General Information.** Unless stated otherwise, all solvents and commercially available reagents were used as purchased. Anhydrous dichloromethane, THF, DMF, and toluene were obtained via the PureSolv MD 5 Solvent Purification System. All other solvents were used as purchased from the corresponding supplier. Diazocompounds used in this work were either obtained commercially or synthesized according to the corresponding literature procedures. **Caution!** It should be noted that diazo compounds can be potentially explosive. Correct safety measures, such as the scale of the reaction, and careful handling are required. Use of appropriate safety gear, including a blast shield, is strongly recommended. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 600 MHz (150 MHz for 13C), Bruker Avance 500 MHz (126 MHz for 1H), and (470 MHz for 31P) or Bruker Avance 300 MHz (75.4 MHz for 13C) using the residual solvent as internal standard (δH: 7.26 ppm, 13C(1H): δ 77.16 ppm for CDCl₃, 13C(1H): δ 39.52 ppm for DMSO-d₆). Chemical shifts (δ) are given in ppm, and coupling constants (J) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sex (sexet), sep (septet), br (broad singlet), and m (multiplet) or combinations thereof. Electro spray ionization (ESI) high-resolution mass spectrometry was carried out using a Bruker QTOF impact II instrument in positive-ion mode (capillary potential of 4500 V). Flash chromatography was performed on Silicycle Silia-P flash silica gel (particle size 40–63 μm, pore diameter 60 Å) using the indicated eluent. Thin-layer chromatography (TLC) was performed using TLC plates from Merck using the corresponding literature procedures. Compounds were visualized by UV detection (254 nm) and KMnO₄ stain. SFC-MS analysis was conducted using a Shimadzu Nexera SFC-MS equipped with a Nexera X2 SIL-30AC autosampler, Nexera UC LC-30AD SF CO₂ pump, Nexera X2 LC-30AD liquid chromatograph, Nexera UC SFC-30A back pressure regulator, prominence SPD-M20A diode array detector, prominence CTO-20AC column oven, and CRM-20A system controller. A gradient of supercritical CO₂ (A) and methanol (B) was used: Method: 2% B/98% A → 100% B/0% A over the course of 7 min. The flow was maintained at 2.0 mL/min, and the sample injection volume was 5 μL. Mass spectrometry analyses were performed using a Shimadzu LCMS-2020 mass spectrometer. The data were acquired in full-scan APCl mode (MS) from m/z 100 to 800 in positive ionization mode. Data was processed using Shimadzu LabSolution 5.82.

**General Procedure A: Synthesis of Spiroindolines 23.** To a flame-dried Schlenk flask under N₂ atmosphere, charged with a stirring bar, was added Bu₄N[Fe(CO)₃]NO (10.3 mg, 0.025 mmol, 0.05 equiv). Subsequently, 1,2-DCE was added (2 mL), and the mixture was stirred until the catalyst was dissolved. This was followed by the addition of tryptamine-derived isocyanide (0.5 mmol, 1.0 equiv) and ethyl diazoacetate (22) (0.6 mmol, 1.2 equiv). The solution was placed in a preheated oil bath and stirred at 80°C until full conversion of the isocyanide was observed on TLC. Subsequently, the reaction mixture cooled to room temperature and directly...
subjected to purification by flash column chromatography, using a mixture of EtOAc:Hx as eluent.

**General Procedure B: Synthesis of Spiroindolines 25.** To a flame-dried Schlenk flask under N₂ atmosphere, charged with a stirring beam, was added Bu₃N[Fe(CO)₃]NO₂ (0.05 equiv). Subsequently, 1,2-DCE was added (0.25 M), and the mixture was stirred until the catalyst was dissolved. This was followed by the addition of tryptamine-derived isocyanide (0.5 mmol, 1.0 equiv) and ethyl diazoacetate (22) (0.6 mmol, 1.2 equiv). The solution was placed in a preheated oil bath and stirred at 80 °C until full conversion of the isocyanide was observed on TLC. Subsequently, the reaction mixture was cooled to 0 °C and diluted with MeOH to a concentration of 0.125 M, after which NaBH₄ (1.05 equiv) was added. The reaction was stirred at 0 °C until full conversion of indolenine intermediate 23 was observed on TLC. Afterward, the reaction mixture was quenched with saturated aqueous NH₄Cl solution and stirred vigorously for 15 min. The aqueous layer was extracted with CH₂Cl₂ (3×), and the organic layers were collected, washed with brine, dried over Na₂SO₄, and filtered. The filtrate was concentrated in vacuo. Subsequently, the crude product was subjected to flash column chromatography, using a mixture of EtOAc:Hex as eluent, to prepare the pure title compound.

**General Procedure C: Synthesis of Spiroindolines 23 for Diazo Scope.** To a flame-dried Schlenk flask under N₂ atmosphere, charged with a stirring beam, was added Bu₃N[Fe(CO)₃]NO₂ (20.6 mg, 0.025 mmol, 0.05 equiv). Subsequently, 1,2-DCE was added (2 mL), and the mixture was stirred until the catalyst was dissolved. This was followed by the addition of tryptamine-derived isocyanide (0.5 mmol, 1.0 equiv) and diazoacetate (18) (0.6 mmol, 1.2 equiv). The solution was placed in a preheated oil bath and stirred at 80 °C for 2–24 h. Subsequently, the reaction mixture was cooled to room temperature and directly purified via flash column chromatography using a mixture of EtOAc:Hx as eluent to prepare the title compound.

**Ethyl (Z)-2-[2-(Indole-3,3′-pyrroli-dine-2′-ylidene)acetate (23d).** Ethyl (Z)-2-(2,(2-(4-(4H-

-ylidene)acetaate was prepared according to general procedure A starting from 2-(2-isocyanato)-2-methyl-1H-indole (107.3 mg, 0.50 mmol, 1.0 equiv). The title compound was isolated as a yellow waxy solid (136 mg, 0.45 mmol, 90%). R<sub>f</sub> = 0.19 (cyclohexane:EtOAc 2:1); H NMR (500 MHz, CDCl₃): δ = 8.12 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 6.83 (dd, J = 8.4, 2.5 Hz, 1H), 6.79 (d, J = 2.5 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.93–3.80 (m, 2H), 3.91 (s, 1H), 3.79 (s, 1H), 2.41–2.25 (m, 2H), 2.24 (s, 3H), 1.17 (s, J = 7.1 Hz, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 179.7 (Cₘ), 170.9 (Cₙ), 164.3 (C₡), 158.6 (Cₖ), 148.5 (Cₙₙ), 143.6 (Cₙₙₙ), 120.5 (CHₓ), 111.3 (CH₃), 108.9 (CH₃), 77.3 (CH₃), 68.0 (Cₖₙ), 59.0 (CH₅), 55.8 (CH₃), 46.0 (CH₃), 31.8 (CH₃), 16.3 (CH₃), 14.6 (CH₃) ppm. HRMS (ESI): m/z calculated for C₂₂H₂₂N₂O₂ [M+H⁺] = 313.1911, found = 313.1914.

**Ethyl (Z)-2-(5-Methoxy-2-methylsphiro[isohe-3′,3′-pyrroli-dine-2′-ylidene)acetate (23d).** Ethyl (Z)-2-(5-methoxy-2-methylsphiro[isohe-3′,3′-pyrroli-dine-2′-ylidene)acetate was prepared according to general procedure A starting from 3-(2-isocyanato)-5-methoxy-2-methyl-1H-indole (107.3 mg, 0.50 mmol, 1.0 equiv). The title compound was isolated as a yellow waxy solid (136 mg, 0.45 mmol, 90%). R<sub>f</sub> = 0.19 (cyclohexane:EtOAc 2:1); H NMR (500 MHz, CDCl₃): δ = 8.12 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 6.83 (dd, J = 8.4, 2.5 Hz, 1H), 6.79 (d, J = 2.5 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 3.93–3.80 (m, 2H), 3.91 (s, 1H), 3.79 (s, 1H), 2.41–2.25 (m, 2H), 2.24 (s, 3H), 1.17 (s, J = 7.1 Hz, 3H) ppm; ¹³C NMR (126 MHz, CDCl₃): δ = 179.7 (Cₙ), 170.9 (C₈), 164.3 (Cₙₙₙ), 158.6 (Cₙₙₙₙ), 148.5 (Cₙₙₙₙₙ), 143.6 (Cₙₙₙₙₙₙ), 120.5 (CHₙₙₙₙₙₙ), 111.3 (CHₙₙₙₙₙₙₙ), 108.9 (CHₙₙₙₙₙₙₙ), 77.3 (CHₙₙₙₙₙₙₙ), 68.0 (Cₙₙₙₙₙₙₙ), 59.0 (CHₙₙₙₙₙₙₙ), 55.8 (CHₙₙₙₙₙₙₙ), 46.0 (CHₙₙₙₙₙₙₙ), 31.8 (CHₙₙₙₙₙₙₙ), 16.3 (CHₙₙₙₙₙₙₙ), 14.6 (CHₙₙₙₙₙₙₙ) ppm. HRMS (ESI): m/z calculated for C₂₂H₂₂N₂O₂ [M+H⁺] = 313.1911, found = 313.1914.
The Journal of Organic Chemistry

9.7, 7.5 Hz, 1H), 2.23 (s, 3H), 2.12 (ddd, J = 13.8, 8.4, 3.4 Hz, 1H), 1.15 (t, J = 7.1 Hz, 3H) ppm. \(^{13}\) C\(^{1}\)H NMR (126 MHz, CDCl\(_3\)): \(\delta\) 183.3 (C\(_3\)), 170.8 (C\(_2\)), 157.4 (C\(_{16}\)), 140.1 (C\(_{18}\)), 130.5 (CH), 129.8 (CH), 119.3 (CH), 118.0 (C\(_6\)), 76.6 (CH), 69.8 (C\(_9\)), 59.0 (CH), 46.4 (CH), 26.7 (CH\(_2\)), 16.2 (CH\(_3\)) ppm. HRMS (ESI): \(m/z\) calculated for C\(_{33}\)H\(_{48}\)BrN\(_2\)O\(_2\) [M+H\(^{+}\)] = 439.0546, found = 439.0555.

**Ethyl (Z)-2-[(5-Bromo-2-methylsiloxy)indole-3,3′-pyrroline]-2′-yldiene)acetate (23h)**. Ethyl (Z)-2-[(5-bromo-2-methylsiloxy)indole-3,3′-pyrroline]-2′-yldiene)acetate was prepared according to general procedure A starting from 5-bromo-2-(2-isocyanatovinyl)acetate-1H-indole (123.0 mg, 0.5 mmol, 1.0 equiv). The title compound was isolated as a yellow solid (124 mg, 0.35 mmol, 72%). \(R\_f = 0.23\) (cyclohexane:EtOAc 2:1);

**Ethyl (Z)-2-[(5-Bromo-2-methylsiloxy)indole-3,3′-pyrroline]-2′-yldiene)acetate (23i)**. Ethyl (Z)-2-[(5-bromo-2-methylsiloxy)indole-3,3′-pyrroline]-2′-yldiene)acetate was prepared according to general procedure A starting from 7-bromo-3-(2-isocyanoethyl)-2-methyl-H-indole (130.2 mg, 0.5 mmol, 1.0 equiv). The title compound was isolated as a brown solid (110 mg, 0.31 mmol, 63%). \(R\_f = 0.23\) (cyclohexane:EtOAc 2:1);

**Ethyl (Z)-2-[(2-Phenylspiro[indole-3,3′-pyrroline]-2′-yldiene)acetate (23j)**. Ethyl (Z)-2-[(2-phenylspiro[indole-3,3′-pyrroline]-2′-yldiene)acetate was prepared according to general procedure A starting from 3-(2-isocyanoethyl)-2-phenyl-H-indole (140.3 mg, 0.5 mmol, 1.0 equiv). The title compound was isolated as a white solid (115 mg, 0.30 mmol, 60%). \(R\_f = 0.30\) (1% Et\(_3\)N in EtOAc:Hex = 1:4);

**Ethyl (Z)-2-[(2-Naphthyl-2-yl)spiro[indole-3,3′-pyrroline]-2′-yldiene)acetate (23m)**. Ethyl (Z)-2-[(2-naphthyl-2-yl)spiro[indole-3,3′-pyrroline]-2′-yldiene)acetate was prepared according to general procedure A starting from 3-(2-isocyanatoethyl)-2-(2-naphthyl)-1H-indole (148.1 mg, 0.5 mmol, 1.0 equiv). The product was purified by flash column chromatography using EtOAc:Hex = 1:4 as eluent to obtain the product as a white solid (115 mg, 0.30 mmol, 60%).
Ethyl (Z)-2-(5-methylspiro[indoline-3,3′-pyrrolidin]-2′-ylidene)acetate was prepared according to general procedure B starting from 3-(2-isocyanoethyl)-5-methyl-1H-indole (92.2 mg, 0.5 mmol, 1.0 equiv), ethyl diazoacetate (0.6 mmol, 1.2 equiv), Bu$_3$N[Fe(CO)$_3$NO] (103 mg, 0.25 mmol, 0.5 equiv) and NaBH$_4$ (20 mg, 0.53 mmol). Extra portions of NaBH$_4$ were added over time until full conversion of the indolene intermediate was observed. The title compound was isolated as a white yellow solid (99 mg, 0.38 mmol, 77%).

Ethyl (Z)-2-(6-(methylthio)spiro[indoline-3,3′-pyrrolidin]-2′-ylidene)acetate (25z). Ethyl (Z)-2-(6-(methylthio)spiro[indoline-3,3′-pyrrolidin]-2′-ylidene)acetate was prepared according to general procedure B starting from 3-(2-isocyanoethyl)-6-methyl-1H-indole (100.1 mg, 0.5 mmol, 1.0 equiv), ethyl diazoacetate (0.6 mmol, 1.2 equiv), Bu$_3$N[Fe(CO)$_3$NO] (103 mg, 0.25 mmol, 0.5 equiv) and NaBH$_4$ (20 mg, 0.53 mmol). Extra portions of NaBH$_4$ were added over time until full conversion of the indolene intermediate was observed. The title compound was isolated as a white-yellow solid (97 mg, 0.34 mmol, 67%).

Ethyl (Z)-2-(5-(methylthio)spiro[indoline-3,3′-pyrrolidin]-2′-ylidene)acetate (25x). Ethyl (Z)-2-(5-(methylthio)spiro[indoline-3,3′-pyrrolidin]-2′-ylidene)acetate was prepared according to general procedure B starting from 3-(2-isocyanoethyl)-5-methyl-1H-indole (92.2 mg, 0.5 mmol, 1.0 equiv), ethyl diazoacetate (0.6 mmol, 1.2 equiv), Bu$_3$N[Fe(CO)$_3$NO] (103 mg, 0.25 mmol, 0.5 equiv) and NaBH$_4$ (20 mg, 0.53 mmol). Extra portions of NaBH$_4$ were added over time until full conversion of the indolene intermediate was observed. The title compound was isolated as a white-yellow solid (97 mg, 0.34 mmol, 67%).

Ethyl (Z)-2-(5-(methylthio)spiro[indoline-3,3′-pyrrolidin]-2′-ylidene)acetate (25y). Ethyl (Z)-2-(5-(methylthio)spiro[indoline-3,3′-pyrrolidin]-2′-ylidene)acetate was prepared according to general procedure B starting from 3-(2-isocyanoethyl)-5-methyl-1H-indole (92.2 mg, 0.5 mmol, 1.0 equiv), ethyl diazoacetate (0.6 mmol, 1.2 equiv), Bu$_3$N[Fe(CO)$_3$NO] (103 mg, 0.25 mmol, 0.5 equiv) and NaBH$_4$ (20 mg, 0.53 mmol). Extra portions of NaBH$_4$ were added over time until full conversion of the indolene intermediate was observed. The title compound was isolated as a white-yellow solid (97 mg, 0.34 mmol, 67%).
Ethyl (Z)-2-(5-chlorospiro[indoline-3,3'-pyrrolidin]-2'-yldiene)acetate (25e). Ethyl (Z)-2-(5-chlorospiro[indoline-3,3'-pyrrolidin]-2'-yldiene)acetate was prepared according to general procedure B starting from 5-chloro-3-(2-isocyanoethyl)-1H-indole (124.4 mg, 0.5 mmol, 1.0 equiv) and NaBH₄ (2.0 mg, 0.05 mmol, 1.0 equiv). The title compound was isolated as a white solid (96 mg, 0.33 mmol, 66%), Rf = 0.48 (Hex:EtOAc = 1:1).

1H NMR (500 MHz, CDCl₃): δ 7.94 (s, 1H), 7.15 (dd, J = 8.3, 2.0 Hz, 1H), 7.08 (d, J = 2.1 Hz, 1H), 6.54 (d, J = 8.3 Hz, 1H), 4.42 (s, 1H), 4.08 (q, J = 7.1 Hz, 2H), 3.80 (br, 1H), 3.68–3.50 (m, 4H), 2.42 (ddd, J = 12.8, 7.1, 4.1 Hz, 1H), 2.14 (dt, J = 12.7, 7.7 Hz, 1H), 1.23 (t, J = 7.1 Hz, 3H) ppm; 13C{¹H} NMR (126 MHz, CDCl₃): δ 171.2 (C'), 169.9 (C'), 149.8 (C'), 134.3 (C'), 128.5 (CH), 124.0 (CH), 123.9 (C'), 110.8 (CH), 77.8 (CH), 59.7 (CH), 58.9 (CH), 57.3 (C'), 45.0 (CH), 37.2 (CH), 14.7 (CH₃) ppm. HRMS (ESI): m/z calculated for C₂₁H₂₂CINO₂[M + H⁺]⁺ = 337.1056, found = 337.1055.

Methyl (3Z,3′)-2′-(Ethyloxy-2-oxoethylidene)spiro[indoline-3,3′-pyrrolidin]-5′-carboxylate (25w). To a flame-dried Schlenk flask under N₂ atmosphere, charged with a stirring bar, was added Bu₄N[Fe(CO)₅] (10.3 mg, 0.025 mmol, 0.05 equiv) and ethyl diazooacetate (0.66 mmol, 1.2 equiv) and NaBH₄ (20.0 mg, 0.53 mmol). The title compound was isolated as a light-brown solid (102 mg, 0.30 mmol, 61%).

1H NMR (500 MHz, CDCl₃): δ 8.09 (s, 1H), 7.20–7.13 (m, 2H), 7.10 (t, J = 7.7, 1.2 Hz, 1H), 6.84–6.75 (m, 2H), 6.66 (d, J = 7.6 Hz, 1H), 6.60 (d, J = 7.8 Hz, 1H), 6.51 (t, J = 1.8 Hz, 1H), 4.53 (s, 1H), 4.09 (q, J = 6.9 Hz, 2H), 4.00 (dd, J = 10.0, 7.3 Hz, 1H), 3.83 (dd, J = 10.3, 6.7 Hz, 1H), 3.65 (s, 3H), 3.57 (t, J = 6.9 Hz, 1H), 3.46–3.32 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H) ppm; 13C{¹H} NMR (126 MHz, CDCl₃): δ 171.4 (C'), 159.6 (C'), 151.4 (C'), 140.4 (C'), 132.3 (C'), 129.6 (CH), 128.9 (CH), 123.7 (CH), 119.9 (CH), 119.6 (CH), 113.6 (CH), 112.9 (CH), 110.4 (CH), 78.1 (CH), 61.5 (CH), 58.8 (CH), 55.1 (CH), 53.9 (CH), 52.6 (CH), 49.8 (CH), 44.7 (CH) ppm. HRMS (ESI): m/z calculated for C₁₇H₁₇NO₂[M + H⁺]⁺ = 265.1680, found = 265.1682.
(td, J = 7.6, 1.3 Hz, 1H), 7.31 (d, J = 7.4 Hz, 1H), 7.27 (td, J = 7.4, 1.1 Hz, 1H), 3.84 (dd, J = 10.1, 7.2, 6.1, 0.9 Hz, 1H), 3.77 (dd, J = 10.1, 7.7, 5.8, 1.0 Hz, 1H), 3.60 (s, 3H), 3.43 (s, 3H), 2.47 (dd, J = 12.8, 7.6, 6.1 Hz, 1H), 2.36−2.16 (m, 2H), 2.14 (dd, J = 13.0, 7.5, 5.8 Hz, 1H) ppm; 13C{1H} NMR (150 MHz, CDCl3); δ 173.0 (C6), 172.7 (CH), 170.5 (C5), 160.3 (C4), 154.6 (C3), 140.3 (C2), 129.1 (CH), 127.3 (CH), 122.5 (CH), 122.1 (CH), 85.4 (C4), 67.2 (C2), 51.6 (CH2), 51.1 (CH3), 45.4 (CH2), 32.7 (CH3) ppm. HRMS (ESI): m/z calculated for \( \text{C11H13NO2} \ [\text{M+H}]^+ = 195.1339 \), found = 195.1335.

**Dimethyl (R,Z)-2-(2-Methylspiro[indole-3,3′-pyrroli]-2'-ylidene)acetate (23bb)**

Dimethyl (R,Z)-2-(2-methylspiro[indole-3,3′-pyrroli]-2'-ylidene)acetate was prepared according to general procedure C starting from 2-(methyl)-3-(3-isocyanoaryl)-1H-indole (92.1 mg, 0.5 mmol, 1.0 equiv). The title compound was isolated as a white solid (84 mg, 0.26 mmol, 51%). Rf = 0.68 (EtOAc);

\( \delta \text{H} \) NMR (600 MHz, CDCl3): 8.85 (s, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.34 (td, J = 7.6, 1.3 Hz, 1H), 7.24 (d, J = 7.4 Hz, 1H), 7.18 (td, J = 7.5, 1.0 Hz, 1H), 3.86−3.75 (m, 2H), 3.60 (s, 3H), 3.7 (s, 3H), 2.31 (3H), 2.30−2.19 (m, 4H), δ ppm; 13C{1H} NMR (150 MHz, CDCl3); δ 173.0 (C6), 172.3 (C5), 170.7 (C4), 161.9 (C3), 154.6 (C2), 128.9 (CH), 126.3 (CH), 122.5 (CH), 120.8 (CH), 85.3 (C4), 67.9 (C2), 51.4 (CH2), 51.0 (CH3), 45.2 (CH2), 34.3 (CH3), 30.4 (CH2), 16.8 (CH3) ppm. HRMS (ESI): m/z calculated for \( \text{C11H13NO2} \ [\text{M+H}]^+ = 195.1349 \), found = 194.3989.

**Benzyl (R,Z)-2-(2-Methylspiro[indole-3,3′-pyrroli]-2'-ylidene)-3-oxobutanoate (23be)**

Benzyl (R,Z)-2-(2-methylspiro[indole-3,3′-pyrroli]-2'-ylidene)-3-oxobutanoate was prepared according to general procedure C starting from 2-(methyl)-3-(3-isocyanoaryl)-1H-indole (92.1 mg, 0.5 mmol, 1.0 equiv). The title compound was isolated as a white solid (17 mg, 0.05 mmol, 9%). Rf = 0.16 (Hex:EtOAc = 3:7);

\( \delta \text{H} \) NMR (500 MHz, CDCl3); δ 8.02 (s, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.34 (td, J = 7.6, 2.1 Hz, 1H), 7.25−7.16 (m, 5H), 7.08−7.01 (m, 2H), 4.45 (s, 2H), 3.97−3.80 (m, 2H), 2.37 (dd, J = 13.1, 7.6, 5.9 Hz, 1H), 2.31 (3H), 2.26−2.16 (m, 4H) ppm; 13C{1H} NMR (126 MHz, CDCl3); δ 196.7 (C6), 181.5 (C5), 168.6 (C7), 167.0 (C6), 155.0 (C5), 141.7 (C4), 136.3 (C3), 128.8 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 126.0 (CH), 121.2 (CH), 120.5 (CH), 100.7 (C7), 69.5 (C5), 64.8 (CH3), 45.6 (CH2), 35.6 (CH2), 29.5 (CH2), 17.0 (CH3) ppm. HRMS (ESI): m/z calculated for \( \text{C11H13NO2} \ [\text{M+H}]^+ = 195.13703 \), found = 195.13702.

**Ethyl (Z)-2-(2-(2-Hydroxyethyl)spiro[indole-3,3′-pyrroli]-2'-ylidene)acetate (25s)**

2-(3-(3-Isocyanoaryl)-1H-indol-2-yl)ethanol-1-ol (1.33 g, 6.33 mmol, 1.0 equiv) was added to a solution of BaO(FeCO3)NO3 (260 mg, 0.63 mmol, 0.10 equiv) in anhydrous 1,2-DCE (25 mL). Ethyl 2-diazooacetate (0.94 mL, 7.60 mmol, 1.2 equiv) was added and the mixture was heated to 80 °C for 1.5 h and then allowed to cool to room temperature. The reaction was placed in an ice bath, and MeOH (10 mL) and NaBH4 (251 mg, 6.65 mmol, 1.05 equiv) were added. After complete conversion of the spiroindolenine was observed on TLC, the reaction was quenched with a saturated NH4Cl solution and extracted with CH2Cl2 (3x). The combined organic layers were dried over Na2SO4, filtered, and concentrated in vacuo. FCC (gradient: 20% → 80% EtOAc in cyclohexane) yielded the product as a light-brown solid as a single diastereomer (1.12 g, 3.70 mmol, 59%). Rf = 0.28 (EtOAc/ cyclohexane 4:1);

\( \delta \text{H} \) NMR (500 MHz, CDCl3); δ 7.97−7.84 (m, 1H), 7.18 (s, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.90 (td, J = 7.5, 1.1 Hz, 1H), 4.46 (m, 1H), 4.11 (qd, J = 7.1, 1.3 Hz, 1H), 3.74 (td, J = 10.3, 6.3 Hz, 1H), 3.61 (t, J = 9.5 Hz, 1H), 2.48−2.38 (m, 1H), 2.26 (dd, J = 12.1, 6.1 Hz, 1H), 2.22−2.05 (m, 2H), 1.73−1.52 (m, 12H), 1.24 (t, J = 7.1 Hz, 3H) ppm; 13C{1H} NMR (150 MHz, CDCl3); δ 169.3 (C2), 162.2 (C3), 152.0 (C4), 142.3 (C5), 134.4 (C6), 128.7 (CH), 123.0 (CH), 112.7 (CH), 114.7 (CH), 89.9 (C8), 81.1 (C9), 66.2 (CH2), 59.1 (CH3), 53.8 (C4), 44.0 (CH3), 39.3 (CH), 31.4 (CH2), 28.6 (CH3), 18.4 (CH2), 14.8 (CH3) ppm. HRMS (ESI): m/z calculated for \( \text{C11H13NO2} \ [\text{M+H}]^+ = 185.2212 \), found = 185.2217.

**ASSOCIATED CONTENT**

**Data Availability Statement**

The data underlying this study are available in the published article and its Supporting Information.

**Supporting Information**

Experimental procedures, characterization data, and 1H and 13C NMR spectra for new compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds 1g, 1h, 1i, 1k−1n, 1p, 1x, 1y, 20, 23a, 23ab, 23b, 23ab, 23bb, 23bc, 23c−23g, 23i, 23j−23o, 25a,
25b, 25q, 25r—25w, 25w_D1, 25w_D2, 25x_D1, 25x_D2, 25y, and 26 (ZIP)

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Notes
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