Efficient Synthesis of Fully Substituted Pyrrolidine-Fused 3-Spirooxindoles via 1,3-Dipolar Cycloaddition of Aziridine and 3-Ylideneoxindole

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Abstract: Drug-like spirocyclic scaffolds have been prepared by fusing fully functionalized pyrrolidine with oxindoles in an approach based on 1,3-dipolar cycloaddition. Reaction between aziridine and 3-ylideneoxindole generated diverse spirooxindole-pyrrolidines in good yield (up to 95%) with high diastereoselectivity (up to >20:1). The reaction also proceeded smoothly with several other synthetically useful activated trisubstituted olefins. The mild reaction conditions, short reaction times, and high tolerance for various substitutions make this approach attractive for constructing pharmacologically interesting spiro-architectures.

Keywords: spirooxindole-pyrrolidine; 1,3-dipolar cycloaddition; aziridine; single-step reaction

1. Introduction

Since the first report of Steven rearrangement in 1928 [1], nitrogen ylides have attracted considerable attention from organic chemists because of their distinctive properties and usefulness in preparative organic syntheses [2–6]. As nitrogen-based 1,3-dipoles, they play important roles in organic synthesis, particularly in cycloadditions [7–10]. Nitrogen ylides have been used to achieve (3 + 2) annulation [11–15] and (3 + 3) annulation [16,17], providing a direct route to various nitrogen-containing heterocycles, including pyrrolidine [18–22], piperidine [23,24], and piperazine [25]. This strategy has proven powerful for synthesizing natural products as well as other biologically interesting compounds [26–29].

Spirooxindole-pyrrolidine, a privileged framework with crucial biological activities, is present in a large family of alkaloid and natural products (Figure 1) [30–33]. For example, spirotryprostatins A and B, both isolated from *Aspergillus fumigatus*, completely inhibit progression from G2 to M phase in mammalian tsFT210 cells [30]. The synthetic analogues of these natural products are often more efficacious and selective than the natural molecules [34–37]. For example, spirooxindole-pyrrolidine derivative MI-77301, an inhibitor of murine double minute 2 (MDM2), entered its second Phase I clinical trial in 2013 [37].
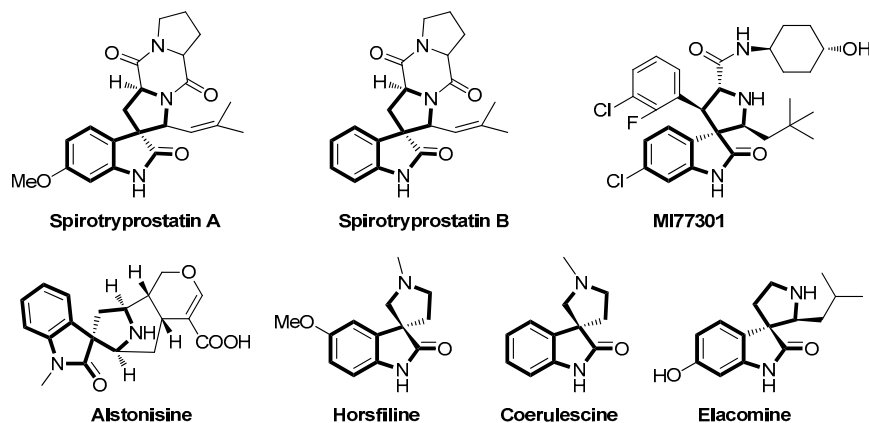
Figure 1. Examples of the spirooxindole-pyrrolidine framework in biologically active molecules.

Various elegant studies have generated molecules with spirooxindole-pyrrolidine skeletons [38–42] using diverse reactions, including 1,3-dipolar cycloaddition [43–52], ring-enlargement [53–55], intramolecular Mannich reaction [56], rearrangement [57] and alkylation [58]. Nitrogen ylides have been used to synthesize spirooxindole-pyrrolidines via 1,3-dipolar addition; this process shows high reactivity, high yield, and excellent stereoselectivity (Schemes 1a [43–47] and 1b [48–52]). In this approach, two steps are required to modify the nitrogen by alkylation, acylation, or, under harsh conditions, arylation. Developing a one-step strategy for constructing spirooxindoles containing a fully substituted pyrrolidine remains an important challenge.
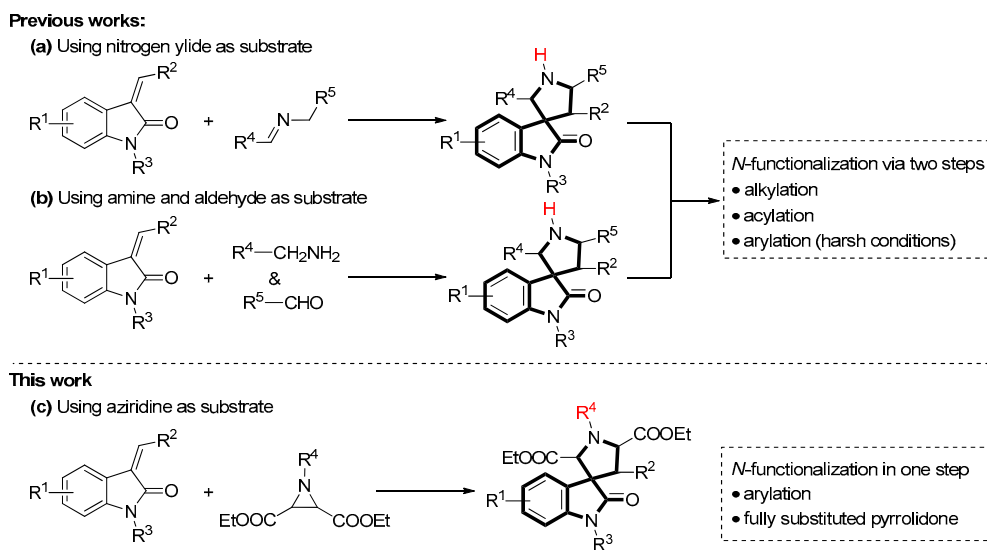
Scheme 1. 1,3-Dipolar cycloaddition-based synthesis of spirooxindole-pyrrolidines.

To construct functionalized spirooxindoles in a straightforward, single-step reaction, we envisioned 1,3-dipolar cycloaddition between 3-ylideneoxindole **1** and aziridine **2** (Scheme 1c). Aziridine could generate a 1,3-dipole through thermolysis, and then 1,3-dipolar cycloaddition of the 1,3-dipole with dipolarophile **1** would yield (3 + 2) cycloadduct **2** (Scheme 2). If successful, this approach would broaden the applications of aziridine and provide an alternative method for preparing pharmacologically interesting spirooxindole-pyrrolidines.
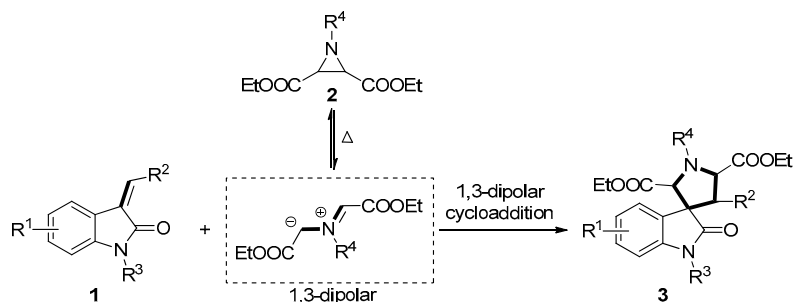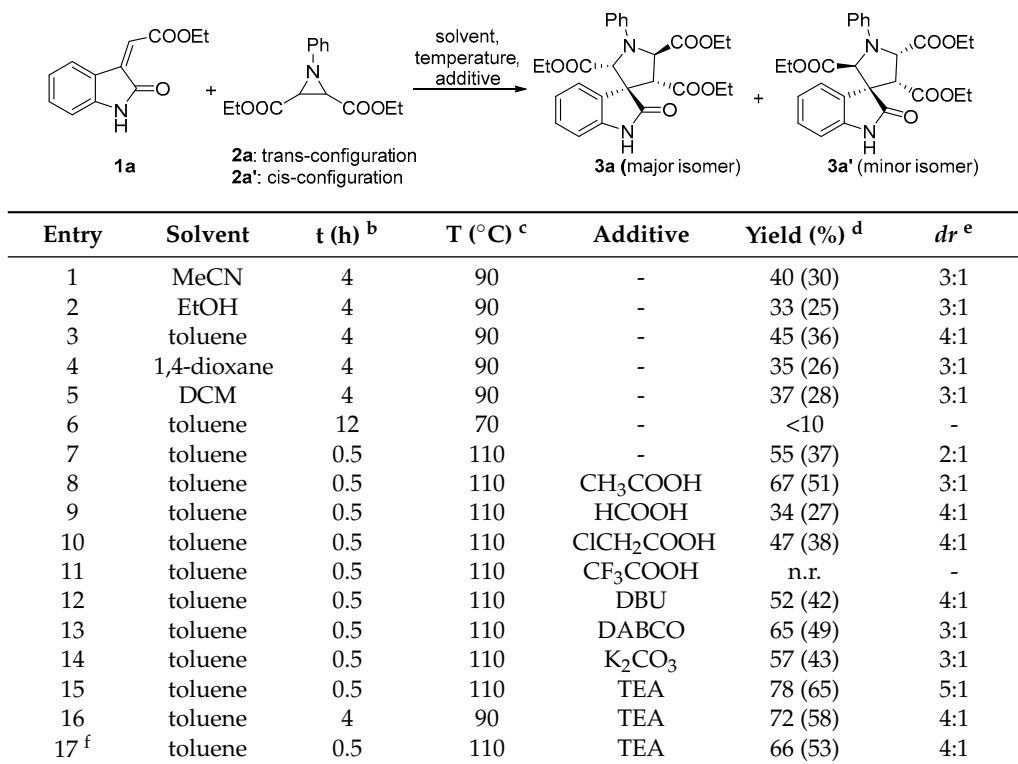
Scheme 2. Synthetic strategy.

2. Results and Discussion

Our investigation began with 3-ylideneoxindole **1a** and 1,3-dipolar aziridine **2a** in MeCN at 90 °C (Table 1, entry 1). The 1,3-dipolar cycloaddition proceeded rapidly, affording **3a** in 40% yield. Encouraged by this result, we optimized the reaction conditions, first by replacing MeCN with other solvents while keeping other conditions the same (Table 1, entries 2–5). Toluene led to the best yield (Table 1, entry 3), but it did not improve the *dr* value. Varying temperature did not increase yield, though it did accelerate the reaction (Table 1, entries 6, 7). Therefore, we examined whether acid or alkali additive might promote the conversion from aziridine to 1,3-dipole and thereby increase yield (Table 1, entries 8–15) [59,60]. Among the acid additives tested, acetic acid afforded the highest yield (Table 1, entry 8), whereas no reaction was observed with trifluoroacetic acid (Table 1, entry 11). Base additives increased yield more than acid additives, with triethylamine giving the best result (Table 1, entry 15). When we carried out this model reaction under 90 °C using TEA as base additive, a similar good result was also obtained, but the reaction did not proceed quickly enough. Obviously, thermodynamic factor played an important role in the 1,3-dipole generation (Table 1, entry 16). Finally, we found that a different configuration of aziridine also participated in the reaction, giving the product **3a** in moderate yield (Table 1, entry 17).

Using the optimized reaction conditions, we evaluated the substrate scope and limitations of 1,3-dipolar cycloaddition (Table 2). We first examined the reaction of 1,3-dipolar aziridine **2a** with **1**. The nature of the functional group at position R^1 on the oxindole core did not affect the reaction: both electron-deficient and electron-rich groups gave the corresponding products **3b–d** in high yield. Isopropoxyformoxyl, phenoxyformoxyl or dicyano groups at R^2 barely affected reaction efficiency, leading to satisfying yields and *dr* values for the corresponding products **3e–g**. Aryl or polycyclic aryl groups at R^2 afforded the products **3h–n** in moderate yield with high diastereoselectivity; yield was higher for electron-withdrawing substituents (Table 2, **3i–k**) than for electron-donating ones (Table 2, **3l–m**). A heteroaryl group at R^2 led to the corresponding products **3o** and **3p** in slightly lower yield. Various protecting groups, including benzyl and Boc groups, were well tolerated and enhanced the *dr* values obtained for products **3q** and **3r**. Finally, we made substitutions on the aziridine **2** that led to good yield of products **3s** and **3t**. The relative configuration of product **3a** was unambiguously determined by X-ray crystallographic analysis (Figure 2) [61].

To further probe the usefulness of this single-step reaction, we examined whether it was compatible with synthetically useful activated trisubstituted olefins. The reaction proceeded smoothly with several such substrates, including olefinic acenaphthene, indenedione, pyrazolone, and rhodanine, providing the corresponding pharmacologically important spirocyclic products (Scheme 3, **3u–x**) in good yields (up to 95%) with moderate to high diastereoselectivities (up to >20:1).

Table 1. Optimization of the reaction conditions [a].

Entry	Solvent	t (h) [b]	T (°C) [c]	Additive	Yield (%) [d]	dr [e]
1	MeCN	4	90	-	40 (30)	3:1
2	EtOH	4	90	-	33 (25)	3:1
3	toluene	4	90	-	45 (36)	4:1
4	1,4-dioxane	4	90	-	35 (26)	3:1
5	DCM	4	90	-	37 (28)	3:1
6	toluene	12	70	-	<10	-
7	toluene	0.5	110	-	55 (37)	2:1
8	toluene	0.5	110	CH_3COOH	67 (51)	3:1
9	toluene	0.5	110	HCOOH	34 (27)	4:1
10	toluene	0.5	110	$ClCH_2COOH$	47 (38)	4:1
11	toluene	0.5	110	CF_3COOH	n.r.	-
12	toluene	0.5	110	DBU	52 (42)	4:1
13	toluene	0.5	110	DABCO	65 (49)	3:1
14	toluene	0.5	110	K_2CO_3	57 (43)	3:1
15	toluene	0.5	110	TEA	78 (65)	5:1
16	toluene	4	90	TEA	72 (58)	4:1
17 [f]	toluene	0.5	110	TEA	66 (53)	4:1

[a] Reaction conditions: additive (0.5 mmol) was added to a solution of 3-ylideneoxindole **1a** (1.1 mmol) and aziridine **2a** (1.0 mmol) in solvent (2 mL) at the indicated temperature. [b] Time for one-step reaction. [c] Temperature of one-step reaction. [d] Total yield of the mixed two isomers; the yield of the isolated major isomer **3a** was shown in parentheses. [e] Based on crude ^{1}H-NMR analysis of the mixed two isomers. [f] **2a′** was used. MeCN = acetonitrile; DCM = dichloromethane; TEA = triethylamine.

3u, 76% (68%) yield, 8:1 *dr*

3v, 90% (72%) yield, 4:1 *dr*

3w, 93% (78%) yield, 5:1 *dr*

3x, 72% (69%) yield, >20:1 *dr*
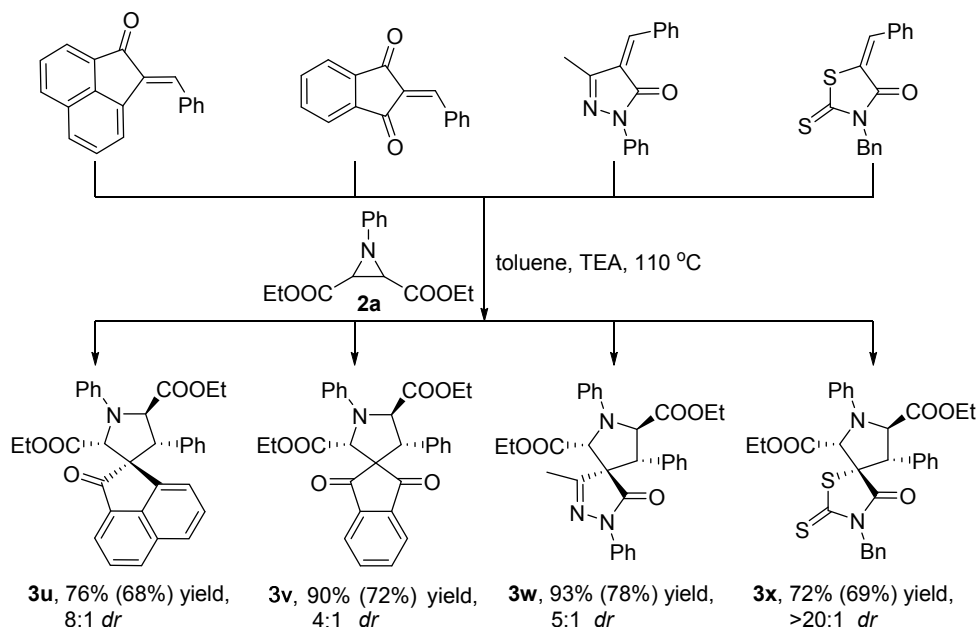
Scheme 3. Synthesis of pharmacologically important spiro-pyrrolidines.
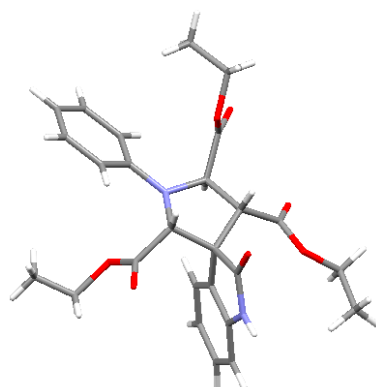
Figure 2. X-ray structure of **3a**.

Table 2. Evaluation of substrate scope under optimized reaction conditions [a].
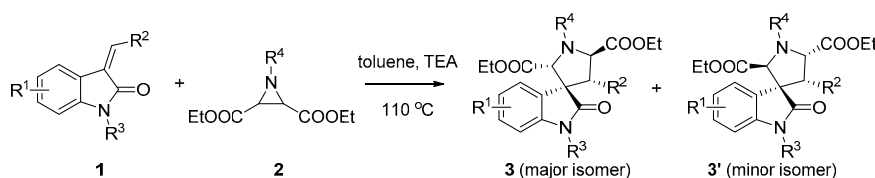
Entry	R^1	R^2	R^3	R^4	Product	Yield (%) [b]	*dr* [c]
1	H	COOEt	H	Ph	**3a**	78 (65)	5:1
2	4-Br	COOEt	H	Ph	**3b**	82 (59)	2.5:1
3	5-F	COOEt	H	Ph	**3c**	83 (67)	4:1
4	5-CH$_3$	COOEt	H	Ph	**3d**	81 (69)	6:1
5	H	COO*i*Pr	H	Ph	**3e**	81 (65)	4:1
6	H	COOPh	H	Ph	**3f**	87 (70)	4:1
7	H	(CN)$_2$	H	Ph	**3g**	86 (69)	4:1
8	H	Ph	H	Ph	**3h**	63 (61)	>20:1
9	H	4-Br-C$_6$H$_4$	H	Ph	**3i**	68 (58)	6:1
10	H	2-F-C$_6$H$_4$	H	Ph	**3j**	66 (63)	>20:1
11	H	4-NO$_2$-C$_6$H$_4$	H	Ph	**3k**	62 (52)	5:1
12	H	4-Me-C$_6$H$_4$	H	Ph	**3l**	58 (56)	>20:1
13	H	3,4-(MeO)$_2$-C$_6$H$_4$	H	Ph	**3m**	57 (46)	4:1
14	H	2-naphthyl	H	Ph	**3n**	55 (53)	>20:1
15	H	2-furyl	H	Ph	**3o**	46 (35)	3:1
16	H	2-thienyl	H	Ph	**3p**	52 (39)	3:1
17	H	COOEt	Bn	Ph	**3q**	88 (77)	7:1
18	H	COOEt	Boc	Ph	**3r**	82 (71)	6:1
19	H	COOEt	H	3-Me-C$_6$H$_4$	**3s**	70 (58)	5:1
20	H	COOEt	H	4-CF$_3$-C$_6$H$_4$	**3t**	67 (56)	5:1

[a] See entry 15 and footnote "a" in Table 1. [b] Total yield of the mixed two isomers; the yield of the isolated major isomer **3** was shown in parentheses. [c] Based on crude ^{1}H-NMR analysis of the mixed two isomers.

3. Materials and Methods

3.1. General Information

NMR data was obtained for ^{1}H at 400 MHz (Varian, Palo Alto, CA, USA) and for ^{13}C at 100 MHz. Chemical shifts were reported in ppm from tetramethylsilane using solvent resonance in CDCl$_3$ solution as the internal standard. ESI HRMS (Electrospray Ionization, High Resolution Mass Spectrum) was performed on a Waters SYNAPT G2 (Milford, MA, USA). Column chromatography was performed on silica gel (200–300 mesh) using an eluent of ethyl acetate and petroleum ether. TLC was performed on glass-backed silica plates; products were visualized using UV light and I$_2$. Melting points were determined on a Mel-Temp apparatus (Electrothermal, Staffordshire, UK) and were not corrected.

All chemicals were used from Adamas-beta (Adamas, Shanghai, China) without purification unless otherwise noted.

3.2. Synthesis

3.2.1. General Procedure for the Synthesis of Spirooxindole-Pyrrolidines **3a–t**

A mixture of 3-ylideneoxindole **1** (1.1 mmol), aziridine **2** (1.0 mmol) and additive TEA (0.5 mmol) in toluene (2 mL) was refluxed at 110 °C under an open atmosphere. The reaction mixture stirred for a specified reaction time until most of 3-ylideneoxindole **1** was consumed (monitored by TLC). Then, the reaction mixture was concentrated and the residue was purified by elaborative chromatography on silica gel to give the final products **3a–t** in good yield (up to 77%) with high diastereoselectivity (up to >20:1). The products were further identified by ^{1}H-NMR, ^{13}C-NMR and HRMS (See supplementary materials).

Triethyl-2-oxo-1′-phenylspiro(indoline-3,3′-pyrrolidine)-2′,4′,5′-tricarboxylate (**3a**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 78% yield (71.3 mg). The *dr* value was calculated to be 5:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3a** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 65% yield (59.4 mg). m.p. 130–132 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.04 (s, 1H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.25–7.18 (m, 3H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.85 (dd, *J* = 13.2, 7.6 Hz, 2H), 6.74 (d, *J* = 8.0 Hz, 2H), 5.42 (d, *J* = 8.4 Hz, 1H), 5.11 (s, 1H), 4.09–3.99 (m, 3H), 3.88–3.82 (m, 1H), 3.80–3.66 (m, 3H), 0.99 (t, *J* = 7.2 Hz, 3H), 0.79 (t, *J* = 7.2 Hz, 3H), 0.75 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 176.14, 171.80, 167.35, 167.32, 145.26, 141.23, 129.59, 128.73, 126.28, 125.67, 122.71, 120.26, 116.39, 109.40, 68.76, 64.88, 61.45, 61.41, 61.08, 58.06, 54.64, 13.85, 13.49, 13.42; HRMS: *m/z* calcd. for $C_{26}H_{28}N_2O_7$ + Na, 503.1794; found, 503.1790.

Triethyl-4-bromo-2-oxo-1′-phenylspiro(indoline-3,3′-pyrrolidine)-2′,4′,5′-tricarboxylate (**3b**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 82% yield (86.7 mg). The *dr* value was calculated to be 2.5:1 from crude ^{1}H-NMR analysis of the mixture. The pure major isomer **3b** could not be separated in pure form after elaborative chromatography; the yield of **3b** was calculated to be 59% based on the total yield and *dr* value. m.p. 128–130 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.74 (s, 1H), 7.24–7.14 (m, 4H), 6.87–6.82 (m, 2H), 6.72 (d, *J* = 8.0 Hz, 2H), 5.49 (s, 1H), 5.40 (d, *J* = 8.8 Hz, 1H), 4.81 (d, *J* = 8.8 Hz, 1H), 4.18–4.08 (m, 4H), 4.06–4.02 (m, 2H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 176.33, 172.46, 168.35, 168.22, 144.79, 144.09, 130.81, 128.81, 128.67, 127.02, 119.60, 118.46, 116.37, 115.42, 109.43, 64.93, 64.31, 61.69, 61.40, 58.94, 51.01, 14.01, 13.68, 13.62; HRMS: *m/z* calcd. for $C_{26}H_{27}BrN_2O_7$ + Na, 581.0899; found, 581.0901.

Triethyl-5-fluoro-2-oxo-1′-phenylspiro(indoline-3,3′-pyrrolidine)-2′,4′,5′-tricarboxylate (**3c**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 83% yield (78.2 mg). The *dr* value was calculated to be 4:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3c** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 67% yield (62.6 mg). m.p. 120–122 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.90 (s, 1H), 7.22 (t, *J* = 8.0 Hz, 2H), 7.13 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.99–6.92 (m, 1H), 6.89–6.84 (m, 2H), 6.76 (d, *J* = 8.0 Hz, 2H), 5.38 (d, *J* = 8.0 Hz, 1H), 5.11 (s, 1H), 4.09–4.01 (m, 3H), 3.94–3.72 (m, 4H), 1.01 (t, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H), 0.78 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 176.48, 171.68, 167.25, 167.13, 158.64 (d, J_{CF} = 243.4 Hz), 145.09, 137.56 (d, J_{CF} = 2.0 Hz), 128.78, 127.28 (d, J_{CF} = 8.1 Hz), 120.59, 116.60, 116.12 (d, J_{CF} = 23.2 Hz), 114.21 (d, J_{CF} = 25.3 Hz), 110.26 (d, J_{CF} = 8.1 Hz), 68.70, 64.70, 61.59, 61.54, 61.21, 58.60, 54.52, 13.86, 13.50, 13.48; HRMS: *m/z* calcd. for $C_{26}H_{27}FN_2O_7$ + Na, 521.1700; found, 521.1696.

Triethyl-5-methyl-2-oxo-1′-phenylspiro(indoline-3,3′-pyrrolidine)-2′,4′,5′-tricarboxylate (**3d**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 81% yield (75.7 mg). The *dr* value was calculated to be 6:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3d** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 69% yield (64.9 mg). m.p. 120–123 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.61 (s, 1H), 7.21 (dd, *J* = 8.4, 7.6 Hz, 2H), 7.15 (s, 1H), 7.02 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.84 (t, *J* = 7.2 Hz, 1H), 6.79–6.74 (m, 3H), 5.42 (d, *J* = 8.8 Hz, 1H), 5.11 (s, 1H), 4.10–4.01 (m, 3H), 3.90–3.82 (m, 1H), 3.78–3.74 (m, 1H), 3.72–3.69 (m, 2H), 2.27 (s, 3H), 1.00 (t, *J* = 7.2 Hz, 3H), 0.80 (t, *J* = 7.2 Hz, 3H), 0.75 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 176.60, 171.87, 167.38, 167.34, 145.31, 138.99, 132.18, 129.90, 128.74, 126.73, 125.68, 120.09, 116.19, 109.32, 68.71, 64.90, 61.44, 61.37, 61.02, 58.23, 54.68, 21.09, 13.86, 13.48, 13.40; HRMS: *m/z* calcd. for C$_{27}$H$_{30}$N$_2$O$_7$ + Na, 517.1951; found, 517.1954.

2′,5′-Diethyl-4′-isopropyl-2-oxo-1′-phenylspiro(indoline-3,3′-pyrrolidine)-2′,4′,5′-tricarboxylate (**3e**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 81% yield (76.3 mg). The *dr* value was calculated to be 4:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3e** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 65% yield (61.2 mg). m.p. 110–115 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.27 (d, *J* = 7.2 Hz, 1H), 7.92 (s, 1H), 7.25–7.20 (m, 3H), 7.05 (td, *J* = 7.6, 0.8 Hz, 1H), 6.89–6.83 (m, 2H), 6.67 (d, *J* = 8.0 Hz, 2H), 4.97 (d, *J* = 10.8 Hz, 1H), 4.70 (s, 1H), 4.66–4.58 (m, 1H), 4.50 (d, *J* = 10.8 Hz, 1H), 4.48–4.40 (m, 1H), 4.30–4.21 (m, 1H), 4.16–4.04 (m, 2H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.56 (d, *J* = 6.4 Hz, 3H). ^{13}C-NMR (101 MHz, CDCl$_3$) δ 175.43, 171.37, 169.77, 166.74, 145.38, 140.19, 130.54, 129.42, 129.03, 126.41, 123.49, 119.91, 114.74, 109.18, 71.32, 69.04, 62.16, 61.54, 61.42, 57.63, 52.95, 21.42, 20.56, 14.04, 13.99; HRMS: *m/z* calcd. for C$_{27}$H$_{30}$N$_2$O$_7$ + Na, 517.1951; found, 517.1948.

2′,5′-Diethyl-4′-phenyl-2-oxo-1′-phenylspiro(indoline-3,3′-pyrrolidine)-2′,4′,5′-tricarboxylate (**3f**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 87% yield (86.9 mg). The *dr* value was calculated to be 4:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3f** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 70% yield (69.5 mg). m.p. 135–137 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.68 (s, 1H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.30 (td, *J* = 7.6, 0.8 Hz, 1H), 7.23–7.14 (m, 4H), 7.13–7.05 (m, 2H), 6.91–6.84 (m, 2H), 6.78 (d, *J* = 8.0 Hz, 2H), 6.28–6.25 (m, 2H), 5.51 (d, *J* = 8.0 Hz, 1H), 5.19 (s, 1H), 4.30 (d, *J* = 8.0 Hz, 1H), 4.11–4.03 (m, 2H), 3.75–3.65 (m, 2H), 1.01 (t, *J* = 7.2 Hz, 3H), 0.74 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 176.29, 171.74, 167.25, 166.36, 149.72, 145.16, 141.62, 129.88, 129.33, 128.80, 126.46, 126.20, 125.62, 122.97, 120.96, 120.50, 116.59, 109.99, 68.88, 64.87, 61.60, 61.20, 58.22, 54.62, 13.88, 13.50; HRMS: *m/z* calcd. for C$_{30}$H$_{28}$N$_2$O$_7$ + Na, 551.1794; found, 551.1798.

Diethyl-4′,4′-dicyano-2-oxo-1′-phenylspiro(indoline-3,3′-pyrrolidine)-2′,5′-dicarboxylate (**3g**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 86% yield (75.3 mg). The *dr* value was calculated to be 4:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3g** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 69% yield (60.2 mg). m.p. 140–142 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.72 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.29–7.25 (m, 2H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.74 (t, *J* = 8.0 Hz, 2H), 5.44 (s, 1H), 5.23 (s, 1H), 4.36–4.24 (m, 2H), 3.83 (q, *J* = 7.2 Hz, 2H), 1.25–1.21(m, 3H), 0.78 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 172.46, 166.81, 165.21, 143.61, 141.50, 131.86, 129.18, 126.81, 123.48, 121.60, 121.55, 116.69, 111.71, 111.27, 109.85, 69.27, 66.25, 63.14, 61.89, 59.31, 45.06, 13.82, 13.46; HRMS: *m/z* calcd. for C$_{25}$H$_{22}$N$_4$O$_5$ + Na, 481.1488; found, 481.1489.

Diethyl-2-oxo-1′,4′-diphenylspiro(indoline-3,3′-pyrrolidine)-2′,5′-dicarboxylate (**3h**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 63% yield (57.6 mg).

The *dr* value was calculated to be >20:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3h** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 61% yield (55.8 mg). m.p. 130–132 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.34 (s, 1H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.21 (dd, *J* = 8.4, 7.6 Hz, 2H), 7.12–7.04 (m, 6H), 7.01–6.97 (m, 1H), 6.81 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 2H), 6.63 (d, *J* = 7.6 Hz, 1H), 5.39 (d, *J* = 10.4 Hz, 1H), 5.33 (s, 1H), 4.30 (d, *J* = 10.4 Hz, 1H), 4.00–3.89 (m, 2H), 3.80–3.65 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.68 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 176.48, 171.79, 167.85, 145.42, 140.58, 132.31, 129.10, 128.77, 128.34, 128.04, 128.01, 126.86, 125.52, 122.24, 119.40, 115.35, 109.64, 67.54, 67.20, 61.68, 61.26, 60.93, 57.21, 13.79, 13.46; HRMS: *m/z* calcd. for C$_{29}$H$_{28}$N$_2$O$_5$ + Na, 507.1896; found, 507.1900.

Diethyl-4′-(4-bromophenyl)-2-oxo-1′-phenylspiro(indoline-3,3′-pyrrolidine)-2′,5′-dicarboxylate (**3i**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 68% yield (73.2 mg). The *dr* value was calculated to be 6:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3i** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 58% yield (62.7 mg). m.p. 79–82 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.20 (s, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.24–7.20 (m, 4H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.02–6.94 (m, 3H), 6.83 (t, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 2H), 6.66 (d, *J* = 7.6 Hz, 1H), 5.33–5.31 (m, 2H), 4.24 (d, *J* = 10.4 Hz, 1H), 3.99–3.93 (m, 2H), 3.80–3.65 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.68 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 176.26, 171.62, 167.74, 145.25, 140.61, 131.41, 131.27, 130.02, 129.37, 128.81, 126.72, 125.12, 122.38, 122.24, 119.55, 115.34, 109.95, 67.49, 67.16, 61.46, 61.42, 61.02, 56.59, 13.82, 13.45; HRMS: *m/z* calcd. for C$_{29}$H$_{27}$BrN$_2$O$_5$ + Na, 585.1001; found, 585.1003.

Diethyl-4′-(2-fluorophenyl)-2-oxo-1′-phenylspiro(indoline-3,3′-pyrrolidine)-2′,5′-dicarboxylate (**3j**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 66% yield (63.1 mg). The *dr* value was calculated to be >20:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3j** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 63% yield (60.2 mg). m.p. 137–140 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.46 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 2H), 7.16–7.11 (m, 2H), 7.09–7.06 (m, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.88–6.80 (m, 3H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.41 (d, *J* = 9.6 Hz, 1H), 5.34 (s, 1H), 4.66 (d, *J* = 9.6 Hz, 1H), 4.04–3.92 (m, 2H), 3.79–3.66 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.68 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 176.82, 171.65, 167.92, 161.00 (d, J_{CF} = 249.5 Hz), 145.44, 141.01, 129.78 (d, J_{CF} = 3.0 Hz), 129.55 (d, J_{CF} = 9.1 Hz), 129.21, 128.81, 126.98, 125.44, 123.60 (d, J_{CF} = 3.0 Hz), 122.04, 120.17 (d, J_{CF} = 14.1 Hz), 119.51, 115.46, 115.39 (d, J_{CF} = 23.2 Hz), 109.71, 67.75, 67.11, 61.32, 60.98, 60.78, 49.67, 13.75, 13.43; HRMS: *m/z* calcd. for C$_{29}$H$_{27}$FN$_2$O$_5$ + Na; 525.1802; found, 525.1804.

Diethyl-4′-(4-nitrophenyl)-2-oxo-1′-phenylspiro(indoline-3,3′-pyrrolidine)-2′,5′-dicarboxylate (**3k**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 62% yield (62.8 mg). The *dr* value was calculated to be 5:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3k** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 52% yield (52.3 mg). m.p. 90–93 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.95 (d, *J* = 8.8 Hz, 2H), 7.94–7.89 (m, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 7.6 Hz, 1H), 5.41 (d, *J* = 10.0 Hz, 1H), 5.34 (s, 1H), 4.38 (d, *J* = 10.4 Hz, 1H), 4.02–3.92 (m, 2H), 3.82–3.67 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.69 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 175.72, 171.33, 167.55, 147.58, 145.05, 140.37, 140.00, 129.69, 129.31, 128.88, 126.70, 124.65, 123.26, 122.61, 119.84, 115.42, 109.97, 67.58, 66.90, 61.63, 61.41, 61.13, 56.49, 13.81, 13.46; HRMS: *m/z* calcd. for C$_{29}$H$_{27}$N$_3$O$_7$ + Na, 552.1747; found, 552.1744.

Diethyl-2-oxo-1′-phenyl-4′-(p-tolyl)spiro(indoline-3,3′-pyrrolidine)-2′,5′-dicarboxylate (**3l**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 58% yield

(55.3 mg). The *dr* value was calculated to be >20:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3l** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 56% yield (53.4 mg). m.p. 85–88 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.14 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.95–6.80 (m, 5H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.63 (d, *J* = 8.0 Hz, 1H), 5.35 (d, *J* = 10.4 Hz, 1H), 5.31 (s, 1H), 4.25 (d, *J* = 10.0 Hz, 1H), 4.00–3.89 (m, 2H), 3.80–3.65 (m, 2H), 2.13 (s, 3H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.68 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 176.55, 171.87, 167.89, 145.47, 140.63, 137.59, 132.16, 129.25, 129.06, 128.76, 127.83, 126.92, 125.33, 122.14, 119.38, 115.37, 109.69, 67.54, 67.44, 61.68, 61.23, 60.92, 57.20, 21.24, 13.79, 13.46; HRMS: *m/z* calcd. for C$_{30}$H$_{30}$N$_2$O$_5$ + Na, 521.2052; found, 521.2056.

Diethyl-4′-(3,4-dimethoxyphenyl)-2-oxo-1′-phenylspiro(indoline-3,3′-pyrrolidine)-2′,5′-dicarboxylate (**3m**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 57% yield (59.4 mg). The *dr* value was calculated to be 4:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3m** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 46% yield (47.5 mg). m.p. 100–103 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.52 (d, *J* = 7.2 Hz, 1H), 7.28 (s, 1H), 7.22 (dd, *J* = 8.0, 7.6 Hz, 2H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.82 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.66–6.63 (m, 2H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 5.30 (s, 1H), 5.24 (d, *J* = 10.4 Hz, 1H), 4.22 (d, *J* = 10.4 Hz, 1H), 4.02–3.91 (m, 2H), 3.83–3.79 (m, 1H), 3.75 (s, 3H), 3.71–3.67 (m, 1H), 3.61 (s, 3H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.69 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 175.17, 172.71, 168.64, 148.59, 148.03, 145.23, 141.06, 129.07, 128.81, 128.74, 124.30, 123.10, 122.96, 120.62, 118.92, 114.75, 111.36, 110.49, 109.64, 68.45, 65.15, 61.66, 61.29, 61.13, 58.39, 55.60, 55.49, 13.98, 13.64; HRMS: *m/z* calcd. for C$_{31}$H$_{32}$N$_2$O$_7$ + Na, 567.2107; found, 567.2110.

Diethyl-4′-(naphthalen-2-yl)-2-oxo-1′-phenylspiro(indoline-3,3′-pyrrolidine)-2′,5′-dicarboxylate (**3n**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 55% yield (55.7 mg). The *dr* value was calculated to be >20:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3n** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 53% yield (53.5 mg). m.p. 105–107 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.02 (s, 1H), 7.67–7.65 (m, 2H), 7.59–7.51 (m, 3H), 7.41–7.37 (m, 2H), 7.24–7.14 (m, 3H), 7.07–6.99 (m, 2H), 6.82 (t, *J* = 7.2 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.53 (d, *J* = 7.2 Hz, 1H), 5.50 (d, *J* = 10.4 Hz, 1H), 5.37 (s, 1H), 4.47 (d, *J* = 10.0 Hz, 1H), 3.96–3.88 (m, 2H), 3.81–3.62 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H), 0.66 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 176.39, 171.83, 167.84, 145.44, 140.61, 132.89, 132.87, 129.93, 129.18, 128.79, 128.14, 127.96, 127.62, 127.44, 126.91, 126.12, 126.02, 125.71, 125.47, 122.25, 119.46, 115.41, 109.78, 67.62, 67.48, 61.75, 61.31, 60.96, 57.42, 13.80, 13.46; HRMS: *m/z* calcd. for C$_{33}$H$_{30}$N$_2$O$_5$ + Na, 557.2052; found, 557.2049.

Diethyl-4′-(furan-2-yl)-2-oxo-1′-phenylspiro(indoline-3,3′-pyrrolidine)-2′,5′-dicarboxylate (**3o**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 46% yield (41.3 mg). The *dr* value was calculated to be 3:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3o** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 35% yield (31.1 mg). m.p. 140–143 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.41 (s, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.05 (s, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.85–6.77 (m, 2H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.07–6.01 (m, 2H), 5.27 (d, *J* = 10.0 Hz, 1H), 5.25 (s, 1H), 4.43 (d, *J* = 9.6 Hz, 1H), 4.11–3.94 (m, 2H), 3.79–3.66 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.71 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 176.58, 171.71, 167.64, 147.90, 145.28, 142.35, 140.79, 129.15, 128.80, 126.74, 125.63, 122.31, 119.66, 115.53, 110.03, 109.57, 107.99, 67.67, 66.83, 61.47, 61.02, 60.03, 50.42, 13.81, 13.48; HRMS: *m/z* calcd. for C$_{27}$H$_{26}$N$_2$O$_6$ + Na, 497.1689; found, 497.1687.

Diethyl-2-oxo-1′-phenyl-4′-(thiophen-2-yl)spiro(indoline-3,3′-pyrrolidine)-2′,5′-dicarboxylate (**3p**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 52% yield (48.1 mg). The *dr* value was calculated to be 3:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3p** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 39% yield (36.2 mg). m.p. 192–194 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.14 (s, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.23–7.18 (m, 3H), 7.06–7.01 (m, 2H), 6.84–6.70 (m, 6H), 5.29 (s, 1H), 5.17 (d, *J* = 10.4 Hz, 1H), 4.59 (d, *J* = 10.0 Hz, 1H), 4.05–3.93 (m, 2H), 3.82–3.67 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H), 0.70 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 176.14, 171.42, 167.67, 145.21, 141.10, 134.68, 129.51, 128.77, 127.24, 127.05, 126.19, 125.70, 125.39, 122.54, 119.60, 115.44, 109.82, 69.71, 67.23, 61.41, 61.21, 61.01, 53.06, 13.82, 13.47; HRMS: *m/z* calcd. for $C_{27}H_{26}N_2O_5S$ + Na, 513.1460; found, 513.1458.

Triethyl-1-benzyl-2-oxo-1′-phenylspiro(indoline-3,3′-pyrrolidine)-2′,4′,5′-tricarboxylate (**3q**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 88% yield (95.5 mg). The *dr* value was calculated to be 7:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3q** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 77% yield (83.6 mg). m.p. 170–172 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.48 (d, *J* = 8.0 Hz, 2H), 7.36–7.34 (m, 3H), 7.31–7.29 (m, 1H), 7.24–7.16 (m, 3H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.84 (t, *J* = 7.2 Hz, 1H), 6.76 (t, *J* = 8.4 Hz 3H), 5.44 (dd, *J* = 8.0, 1.0 Hz, 1H), 5.18 (s, 1H), 4.98 (d, *J* = 5.2 Hz, 2H), 4.10 (d, *J* = 8.4 Hz, 1H), 4.06–4.02 (m, 2H), 3.79–3.75 (m, 1H), 3.64–3.55 (m, 3H), 1.01–0.98 (m, 3H), 0.56–0.50 (m, 6H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 174.83, 171.78, 167.32, 167.28, 145.35, 143.43, 135.68, 129.38, 128.72, 128.68, 128.08, 127.92, 125.95, 125.38, 122.68, 120.20, 116.41, 108.67, 68.94, 65.08, 61.40, 60.99, 57.50, 54.78, 44.65, 22.66, 13.86, 13.30, 13.24; HRMS: *m/z* calcd. for $C_{33}H_{34}N_2O_7$ + Na, 593.2264; found, 593.2266.

1-(Tert-butyl)-2′,4′,5′-triethyl-2-oxo-1′-phenylspiro(indoline-3,3′-pyrrolidine)-1,2′,4′,5′-tetracarboxylate (**3r**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 82% yield (90.3 mg). The *dr* value was calculated to be 6:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3r** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 71% yield (77.4 mg). m.p. 150–153 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.86 (d, *J* = 8.4 Hz, 1H), 7.40 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.35–7.30 (m, 1H), 7.21 (dd, *J* = 8.0, 7.2 Hz, 2H), 7.12 (dd, *J* = 8.0, 7.6 Hz, 1H), 6.86 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 2H), 5.39 (d, *J* = 8.0 Hz, 1H), 5.14 (s, 1H), 4.08–3.96 (m, 3H), 3.78–3.65 (m, 4H), 1.68 (s, 9H), 0.97 (t, *J* = 6.8 Hz, 3H), 0.81–0.76 (m, 6H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 173.34, 171.55, 167.06, 166.75, 149.01, 145.13, 140.31, 129.80, 129.21, 128.73, 125.31, 124.64, 120.07, 116.70, 114.59, 84.73, 69.08, 64.90, 61.88, 61.49, 61.12, 58.18, 55.31, 42.99, 28.10, 14.15, 13.83, 13.38, 13.26; HRMS: *m/z* calcd. for $C_{31}H_{36}N_2O_9$ + Na, 603.2319; found, 603.2314.

Diethyl-2-oxo-4′-phenyl-1′-(m-tolyl)spiro(indoline-3,3′-pyrrolidine)-2′,5′-dicarboxylate (**3s**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 70% yield (62.3 mg). The dr value was calculated to be 5:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3s** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 58% yield (52.1 mg). m.p. 135–138 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.73 (s, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.61 (s, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 5.41 (d, *J* = 8.4 Hz, 1H), 5.11 (s, 1H), 4.09–4.02 (m, 3H), 3.88–3.84 (m, 1H), 3.77–3.68 (m, 3H), 2.27 (s, 3H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.81–0.74 (m, 6H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 176.66, 171.99, 167.45, 167.38, 145.19, 141.42, 138.41, 129.59, 128.56, 126.21, 125.70, 122.69, 121.19, 117.19, 113.43, 109.63, 68.72, 64.81, 61.42, 61.22, 61.07, 58.14, 54.64, 21.65, 13.90, 13.49, 13.40; HRMS: *m/z* calcd. for $C_{27}H_{30}N_2O_7$ + Na, 517.1951; found, 517.1954.

Diethyl-2-oxo-4′-phenyl-1′-(4-(trifluoromethyl)phenyl)spiro(indoline-3,3′-pyrrolidine)-2′,5′-dicarboxylate (**3t**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 67% yield (55.4 mg). The dr value was calculated to be 5:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3t** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 56% yield (46.2 mg). m.p. 145–147 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.62 (s, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.29–7.24 (m, 2H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 2H), 5.45 (d, *J* = 8.4 Hz, 1H), 5.14 (s, 1H), 4.16–4.07 (m, 2H), 4.03 (d, *J* = 8.4 Hz, 1H), 3.90–3.84 (m, 1H), 3.81–3.69 (m, 3H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.80 (t, *J* = 7.2 Hz, 3H), 0.76 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 176.21, 171.26, 166.92, 166.85, 147.99, 141.39, 129.90, 126.10, 126.09, 125.22, 124.54 (d, J_{CF} = 272.7 Hz), 122.82, 121.67 (d, J_{CF} = 33.3 Hz), 115.51, 109.75, 68.63, 64.62, 61.86, 61.61, 61.46, 58.06, 54.78, 13.90, 13.45, 13.40; HRMS: *m/z* calcd. for $C_{27}H_{27}F_3N_2O_7$ + Na, 571.1668; found, 571.1671.

3.2.2. Synthetic Transformations to Access Other Drug-Like Spirocyclic Scaffolds **3u–x**

A mixture of trisubstituted olefins (1.1 mmol), aziridine **2a** (1.0 mmol) and additive TEA (0.5 mmol) in toluene (2 mL) was refluxed at 110 °C under an open atmosphere. The reaction mixture would be cooled to room temperature until most of the 3-ylideneoxindole **1** was consumed (monitored by TLC). Then, the reaction mixture was concentrated and the residue was purified by elaborative chromatography on silica gel to give the final products **3u–x** in good yield (up to 78%) with moderate to high diastereoselectivity (up to >20:1). The products were further identified by ^{1}H-NMR, ^{13}C-NMR and HRMS.

Diethyl-2-oxo-1′,4′-diphenyl-2H-spiro(acenaphthylene-1,3′-pyrrolidine)-2′,5′-dicarboxylate (**3u**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 76% yield (75.4 mg). The *dr* value was calculated to be 8:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3u** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 68% yield (66.9 mg). m.p. 154–156 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.94–7.91 (m, 2H), 7.76–7.71 (m, 2H), 7.61–7.55 (m, 2H), 7.23 (t, *J* = 8.0 Hz, 2H), 7.00–6.97 (m, 2H), 6.87–6.81 (m, 4H), 6.76 (d, *J* = 8.0 Hz, 2H), 5.53 (d, *J* = 10.4 Hz, 1H), 5.44 (s, 1H), 4.48 (d, *J* = 10.0 Hz, 1H), 4.03–3.93 (m, 2H), 3.46–3.36 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.04 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 201.65, 171.97, 168.09, 145.61, 142.19, 134.83, 132.95, 132.84, 131.87, 130.23, 128.76, 128.22, 128.05, 127.81, 127.76, 127.62, 125.07, 123.99, 121.86, 119.30, 115.42, 68.07, 67.71, 66.11, 61.22, 60.41, 57.32, 13.82, 12.78; HRMS: *m/z* calcd. for $C_{33}H_{29}NO_5$ + Na, 542.1943; found, 542.1945.

Diethyl-1,3-dioxo-1′,4′-diphenyl-1,3-dihydrospiro(indene-2,3′-pyrrolidine)-2′,5′-dicarboxylate (**3v**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 90% yield (85.3 mg). The *dr* value was calculated to be 4:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3v** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 72% yield (68.2 mg). m.p. 133–135 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.94 (d, *J* = 7.6 Hz, 1H), 7.75–7.67 (m, 3H), 7.22–7.15 (m, 4H), 7.10–7.05 (m, 3H), 6.79 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 7.6 Hz, 2H), 5.57 (d, *J* = 10.0 Hz, 1H), 5.33 (s, 1H), 4.23 (d, *J* = 10.4 Hz, 1H), 4.01–3.92 (m, 2H), 3.84–3.72 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.64 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 198.08, 197.65, 171.57, 168.05, 145.09, 142.18, 142.05, 136.00, 135.74, 131.84, 128.71, 128.64, 128.46, 128.30, 123.27, 123.08, 119.11, 115.14, 66.58, 66.13, 65.76, 61.23, 61.18, 56.29, 13.82, 13.33; HRMS: *m/z* calcd. for $C_{30}H_{27}NO_6$ + Na, 520.1736; found, 520.1733.

Diethyl-1-methyl-4-oxo-3,7,9-triphenyl-2,3,7-triazaspiro(4.4)non-1-ene-6,8-dicarboxylate (**3w**). The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 93% yield (92.4 mg). The *dr* value was calculated to be 5:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3w** was obtained as a white solid after elaborative chromatography

(petroleum ether/ethyl acetate = 10:1) in 78% yield (76.8 mg). m.p. 165–167 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 6.8 Hz, 2H), 7.27 (s, 1H), 7.25–7.20 (m, 6H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.82 (t, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 2H), 5.62 (d, *J* = 9.6 Hz, 1H), 5.12 (s, 1H), 4.08–4.05 (m, 1H), 4.01 (d, *J* = 7.2 Hz, 1H), 3.98–3.90 (m, 3H), 2.47 (s, 3H), 0.94 (q, *J* = 6.8 Hz, 6H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 172.16, 169.60, 167.44, 157.03, 144.78, 137.18, 131.10, 128.86, 128.82, 128.64, 128.39, 125.23, 119.48, 118.97, 115.12, 65.83, 64.85, 64.69, 61.71, 61.43, 55.14, 13.88, 13.82, 13.74; HRMS: *m/z* calcd. for C$_{31}$H$_{31}$N$_3$O$_5$ + Na, 548.2161; found, 548.2159.

Diethyl-3-benzyl-4-oxo-7,9-diphenyl-2-thioxo-1-thia-3,7-diazaspiro(4.4)nonane-6,8-dicarboxylate (**3x**): The mixed two isomers were isolated by flash chromatography (petroleum ether/ethyl acetate = 5:1) in 72% yield (78.1 mg). The *dr* value was calculated to be >20:1 from crude ^{1}H-NMR analysis of the mixture. After which, the pure major isomer **3x** was obtained as a white solid after elaborative chromatography (petroleum ether/ethyl acetate = 10:1) in 69% yield (74.9 mg). m.p. 162–165 °C; ^{1}H-NMR (400 MHz, CDCl$_3$) δ 7.31–7.27 (m, 5H), 7.25–7.10 (m, 7H), 6.85 (t, *J* = 7.2 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 2H), 5.54 (s, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 4.69 (dd, *J* = 41.6, 14.0 Hz, 2H), 4.55 (d, *J* = 10.0 Hz, 1H), 4.07–4.03 (m, 1H), 3.94–3.85 (m, 3H), 0.94 (t, *J* = 7.2 Hz, 3H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR (101 MHz, CDCl$_3$) δ 172.68, 170.92, 169.02, 166.92, 144.85, 134.51, 131.38, 128.96, 128.88, 128.82, 128.78, 128.68, 128.66, 128.29, 120.49, 116.10, 69.76, 66.62, 61.87, 61.51, 57.08, 45.52, 43.00, 13.87, 13.74; HRMS: *m/z* calcd. for C$_{31}$H$_{30}$N$_2$O$_5$S$_2$ + Na, 597.1494; found, 597.1497.

4. Conclusions

In summary, we have developed an efficient single-step reaction between aziridines and 3-ylideneoxindoles to synthesize diverse spirooxindole-pyrrolidines. This is a straightforward technique for constructing fully substituted pyrrolidines bearing phenyl substituents on the nitrogen atom. The reaction also proceeded smoothly with several other synthetically useful activated trisubstituted olefins to afford some pyrrolidine-fused drug-like spirocyclic scaffolds. Further studies on the biological activities of the resulting spiro-architectures are underway in our laboratory.

Supplementary Materials: Supplementary Materials can be accessed at: http://www.mdpi.com/1420-3049/21/9/1113/s1.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DABCO	1,4-Diazabicyclo(2.2.2)octane
TEA	Triethylamine

References

1. Stevens, T.S.; Creighton, E.M.; Gordon, A.B.; MacNicol, M. Degradation of quaternary ammonium salts Part I. *J. Chem. Soc. (Resumed)* **1928**, 3193–3197. [CrossRef]
2. Pellissier, H. Asymmetric 1,3-dipolar cycloadditions. *Tetrahedron* **2007**, *63*, 3235–3285. [CrossRef]
3. Stanley, L.M.; Sibi, M.P. Enantioselective copper-catalyzed 1,3-dipolar cycloadditions. *Chem. Rev.* **2008**, *108*, 2887–2902. [CrossRef] [PubMed]
4. Kissane, M.; Maguire, A.R. Asymmetric 1,3-dipolar cycloadditions of acrylamides. *Chem. Soc. Rev.* **2010**, *39*, 845–883. [CrossRef] [PubMed]

5. Adrio, J.; Carretero, J.C. Recent advances in the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides. *Chem. Commun.* **2014**, *50*, 12434–12446. [CrossRef] [PubMed]

6. Singh, M.S.; Chowdhury, S.; Koley, S. Progress in 1,3-dipolar cycloadditions in the recent decade: an update to strategic development towards the arsenal of organic synthesis. *Tetrahedron* **2016**, *72*, 1603–1644. [CrossRef]

7. Nair, V.; Suja, T.D. Intramolecular 1,3-dipolar cycloaddition reactions in targeted syntheses. *Tetrahedron* **2007**, *63*, 12247–12275. [CrossRef]

8. Nájera, C.; Sansano, J.M. Coinage metal complexes as chiral catalysts for 1,3-dipolar cycloadditions. *J. Organomet. Chem.* **2014**, *771*, 78–92. [CrossRef]

9. Narayan, R.; Potowski, M.; Jia, Z.J.; Antonchick, A.P.; Waldmann, H. Catalytic Enantioselective 1,3-Dipolar Cycloadditions of Azomethine Ylides for Biology-Oriented Synthesis. *Acc. Chem. Res.* **2014**, *47*, 1296–1310. [CrossRef] [PubMed]

10. Hashimoto, T.; Maruoka, K. Recent Advances of Catalytic Asymmetric 1,3-Dipolar Cycloadditions. *Chem. Rev.* **2015**, *115*, 5366–5412. [CrossRef] [PubMed]

11. Zhu, W.; Cai, G.; Ma, D. A formal (3 + 2) cycloaddition process with nonactivated aziridines to polysubstituted indolizidines. *Org. Lett.* **2005**, *7*, 5545–5548. [CrossRef] [PubMed]

12. Zeng, W.; Zhou, Y.G. AgOAc catalyzed asymmetric (3 + 2) cycloaddition of azomethine ylides with chiral ferrocene derived P,S ligands. *Tetrahedron Lett.* **2007**, *48*, 4619–4622. [CrossRef]

13. Arai, T.; Mishiro, A.; Yokoyama, N.; Suzuki, K.; Sato, H. Chiral Bis(imidazolidine)pyridine-Cu-(OTf)₂: Catalytic Asymmetric Endo-Selective (3 + 2) Cycloaddition of Imino Esters with Nitroalkenes. *J. Am. Chem. Soc.* **2010**, *132*, 5338–5339. [CrossRef] [PubMed]

14. Arai, T.; Yokoyama, N.; Mishiro, A.; Sato, H. Catalytic Asymmetric *exo'*-Selective (3 + 2) Cycloaddition of Iminoesters with Nitroalkenes. *Angew. Chem. Int. Ed.* **2010**, *49*, 7895–7898. [CrossRef] [PubMed]

15. Li, Q.H.; Xue, Z.Y.; Tao, H.Y.; Wang, C.J. Cu(I)/DTBM-BIPHEP-catalyzed *exo*-selective 1,3-dipolar cycloaddition of azomethine ylides with *cis*-trifluorocrotonate for asymmetric construction of trifluoromethylated pyrrolidines. *Tetrahedron Lett.* **2012**, *53*, 3650–3653. [CrossRef]

16. Potowski, M.; Bauer, J.O.; Strohmann, C.; Antonchick, A.P.; Waldmann, H. Highly Enantioselective Catalytic (6 + 3) Cycloadditions of Azomethine Ylides. *Angew. Chem. Int. Ed.* **2012**, *51*, 9512–9516. [CrossRef] [PubMed]

17. Wu, Y.; Qiao, G.; Liu, H.; Zhang, L.; Sun, Z.; Xiao, Y.; Guo, H. Brønsted acid-promoted (3 + 3) cycloaddition of azomethine ylides with quinone monoimine: A practical method towards dihydrobenzoxazine derivatives. *RSC Adv.* **2015**, *5*, 84290–84294. [CrossRef]

18. Malatesti, N.; Boa, A.N.; Clark, S.; Westwood, R. 1,3-Dipolar cycloaddition reactions of benzo(*b*)thiophene 1,1-dioxide with azomethine ylides. *Tetrahedron Lett.* **2006**, *47*, 5139–5142. [CrossRef]

19. Ishii, K.; Kido, M.; Noji, M.; Sugiyama, S. Photoreactions of bicyclic aziridines with alkenes and alkynes: A novel synthetic methodology for 8-azabicyclo (3.2.1) octane derivatives. *Org. Biomol. Chem.* **2008**, *6*, 3186–3195. [CrossRef] [PubMed]

20. Liang, G.; Tong, M.C.; Wang, C.J. Silver Acetate/TF-BiphamPhos-Catalyzed *endo*-Selective Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Ylides with Vinyl Phenyl Sulfone. *Adv. Synth. Catal.* **2009**, *351*, 3101–3106. [CrossRef]

21. Ribeiro Laia, F.M.; Cardoso, A.L.; Beja, A.M.; Silva, M.R.; Pinho e Melo, T.M.V.D. Reactivity of allenoates towards aziridines: Synthesis of functionalized methylenepyrrolidines and pyrroles. *Tetrahedron* **2010**, *66*, 8815–8822. [CrossRef]

22. Yang, W.L.; Liu, Y.Z.; Luo, S.; Yu, X.; Fossey, J.S.; Deng, W.P. The copper-catalyzed asymmetric construction of a dispiropyrrolidine skeleton via 1,3-dipolar cycloaddition of azomethine ylides to α-alkylidene succinimides. *Chem. Commun.* **2015**, *51*, 9212–9215. [CrossRef] [PubMed]

23. Hong, B.C.; Gupta, A.K.; Wu, M.F.; Liao, J.H.; Lee, G.H. Hetero (6 + 3) cycloaddition of fulvenes with *N*-alkylidene glycine esters: A facile synthesis of the delavayine and incarvillateine framework. *Org. Lett.* **2003**, *5*, 1689–1692. [CrossRef] [PubMed]

24. Potowski, M.; Antonchick, A.P.; Waldmann, H. Catalytic asymmetric *exo*-selective (6 + 3) cycloaddition of iminoesters with fulvenes. *Chem. Commun.* **2013**, *49*, 7800–7802. [CrossRef] [PubMed]

25. Yuan, C.; Liu, H.; Gao, Z.; Zhou, L.; Feng, Y.; Xiao, Y.; Guo, H. Cu(I)-Catalyzed Highly Enantioselective (3 + 3) Cycloaddition between Two Different 1,3-Dipoles, Phthalazinium Dicyanomethanides and Iminoester-Derived Azomethine Ylides. *Org. Lett.* **2015**, *17*, 26–29. [CrossRef] [PubMed]

26. Wang, H.; Ganesan, A. A biomimetic total synthesis of (−)-spirotryprostatin B and related studies. *J. Org. Chem.* **2000**, *65*, 4685–4693. [CrossRef] [PubMed]

27. Sebahar, P.R.; Williams, R.M. The asymmetric total synthesis of (+)- and (−)-spirotryprostatin B. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667. [CrossRef]

28. Antonchick, A.P.; Schuster, H.; Bruss, H.; Schüermann, M.; Preut, H.; Rauh, D.; Waldmann, H. Enantioselective synthesis of the spirotryprostatin A scaffold. *Tetrahedron* **2011**, *67*, 10195–10202. [CrossRef]

29. Zhang, L.J.; Wang, Y.; Hu, X.Q.; Xu, P.F. Hydrogen-Bonding Network Promoted (3 + 2) Cycloaddition: Asymmetric Catalytic Construction of Spiro-pseudoindoxyl Derivatives. *Chem. Asian J.* **2016**, *11*, 834–838. [CrossRef] [PubMed]

30. Cui, C.B.; Kakeya, H.; Osada, H. Novel mammalian cell cycle inhibitors, spirotryprostatins A and B, produced by *Aspergillus fumigatus*, which inhibit mammalian cell cycle at G2/M phase. *Tetrahedron* **1996**, *52*, 12651–12666. [CrossRef]

31. Galliford, C.V.; Scheidt, K.A. Pyrrolidinyl-spirooxindole natural products as inspirations for the development of potential therapeutic agents. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748–8758. [CrossRef] [PubMed]

32. Senwar, K.R.; Sharma, P.; Reddy, T.S.; Jeengar, M.K.; Nayak, V.L.; Naidu, V.G.M.; Kamal, A.; Shankaraiah, N. Spirooxindole-derived morpholine-fused-1,2,3-triazoles: Design, synthesis, cytotoxicity and apoptosis inducing studies. *Eur. J. Med. Chem.* **2015**, *102*, 413–424. [CrossRef] [PubMed]

33. Yu, B.; Yu, D.Q.; Liu, H.M. Spirooxindoles: Promising scaffolds for anticancer agents. *Eur. J. Med. Chem.* **2015**, *97*, 673–698. [CrossRef] [PubMed]

34. Lo, M.M.C.; Neumann, C.S.; Nagayama, S.; Perlstein, E.O.; Schreiber, S.L. A library of spirooxindoles based on a stereoselective three-component coupling reaction. *J. Am. Chem. Soc.* **2004**, *126*, 16077–16086. [CrossRef] [PubMed]

35. Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; et al. Structure-based design of spiro-oxindoles as potent, specific small-molecule inhibitors of the MDM2-p53 interaction. *J. Med. Chem.* **2006**, *49*, 3432–3435. [CrossRef] [PubMed]

36. Shangary, S.; Qin, D.; McEachern, D.; Liu, M.; Miller, R.S.; Qiu, S.; Nikolovska-Coleska, Z.; Ding, K.; Wang, G.; Chen, J.; et al. Temporal activation of p53 by a specific MDM2 inhibitor is selectively toxic to tumors and leads to complete tumor growth inhibition. *Proc. Natl. Acad. Sci. USA.* **2008**, *105*, 3933–3938. [CrossRef] [PubMed]

37. Wang, S.; Sun, W.; Zhao, Y.; McEachern, D.; Meaux, I.; Barrière, C.; Stuckey, J.A.; Meagher, J.L.; Bai, L.; Liu, L.; et al. SAR405838: An Optimized Inhibitor of MDM2-p53 Interaction That Induces Complete and Durable Tumor Regression. *Cancer Res.* **2014**, *74*, 5855–5865. [CrossRef] [PubMed]

38. Zhou, F.; Liu, Y.L.; Zhou, J. Catalytic Asymmetric Synthesis of Oxindoles Bearing a Tetrasubstituted Stereocenter at the C-3 Position. *Adv. Synth. Catal.* **2010**, *352*, 1381–1407. [CrossRef]

39. Singh, G.S.; Desta, Z.Y. Isatins As Privileged Molecules in Design and Synthesis of Spiro-Fused Cyclic Frameworks. *Chem. Rev.* **2012**, *112*, 6104–6155. [CrossRef] [PubMed]

40. Franz, A.K.; Hanhan, N.V.; Ball-Jones, N.R. Asymmetric Catalysis for the Synthesis of Spirocyclic Compounds. *Acs Catal.* **2013**, *3*, 540–553. [CrossRef]

41. Hong, L.; Wang, R. Recent Advances in Asymmetric Organocatalytic Construction of 3,3′-Spirocyclic Oxindoles. *Adv. Synth. Catal.* **2013**, *355*, 1023–1052. [CrossRef]

42. Santos, M.M.M. Recent advances in the synthesis of biologically active spirooxindoles. *Tetrahedron* **2014**, *70*, 9735–9757. [CrossRef]

43. Antonchick, A.P.; Gerding-Reimers, C.; Catarinella, M.; Schüermann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. Highly enantioselective synthesis and cellular evaluation of spirooxindoles inspired by natural products. *Nat. Chem.* **2010**, *2*, 735–740. [CrossRef] [PubMed]

44. Liu, T.L.; Xue, Z.Y.; Tao, H.Y.; Wang, C.J. Catalytic asymmetric 1,3-dipolar cycloaddition of *N*-unprotected 2-oxoindolin-3-ylidene derivatives and azomethine ylides for the construction of spirooxindole-pyrrolidines. *Org. Biomol. Chem.* **2011**, *9*, 1980–1986. [CrossRef] [PubMed]

45. Awata, A.; Arai, T. Catalytic Asymmetric *exo′*-Selective (3 + 2) Cycloaddition for Constructing Stereochemically Diversified Spiro[pyrrolidin-3,3′-oxindole]s. *Chem. Eur. J.* **2012**, *18*, 8278–8282. [CrossRef] [PubMed]

46. Wang, L.; Shi, X.M.; Dong, W.P.; Zhu, L.P.; Wang, R. Efficient construction of highly functionalized spiro (γ-butyrolactone-pyrrolidin-3,3′-oxindole) tricyclic skeletons via an organocatalytic 1,3-dipolar cycloaddition. *Chem. Commun.* **2013**, *49*, 3458–3460. [CrossRef] [PubMed]

47. Arai, T.; Ogawa, H.; Awata, A.; Sato, M.; Watabe, M.; Yamanaka, M. PyBidine-Cu(OTf)$_2$-Catalyzed Asymmetric (3 + 2) Cycloaddition with Imino Esters: Harmony of Cu-Lewis Acid and Imidazolidine-NH Hydrogen Bonding in Concerto Catalysis. *Angew. Chem. Int. Ed.* **2015**, *54*, 1595–1599. [CrossRef] [PubMed]

48. Chen, X.H.; Wei, Q.; Luo, S.W.; Xiao, H.; Gong, L.Z. Organocatalytic Synthesis of Spiro(pyrrolidin-3,3′-oxindoles) with High Enantiopurity and Structural Diversity. *J. Am. Chem. Soc.* **2009**, *131*, 13819–13825. [CrossRef] [PubMed]

49. Ghandi, M.; Yari, A.; Rezaei, S.J.T.; Taheri, A. Synthesis of novel spiropyrrolidine/pyrrolizine-oxindole scaffolds through 1,3-dipolar cycloadditions. *Tetrahedron Lett.* **2009**, *50*, 4724–4726. [CrossRef]

50. Thangamani, A. Regiospecific synthesis and biological evaluation of spirooxindolopyrrolidines via (3 + 2) cycloaddition of azomethine ylide. *Eur. J. Med. Chem.* **2010**, *45*, 6120–6126. [CrossRef] [PubMed]

51. Sun, J.; Chen, L.; Gong, H.; Yan, C.G. Convenient synthesis of functionalized spiro (indoline-3,2′-pyrrolizines) or spiro(indoline-3,3′-pyrrolidines) via multicomponent reactions. *Org. Biomol. Chem.* **2015**, *13*, 5905–5917. [CrossRef] [PubMed]

52. Wang, Y.M.; Zhang, H.H.; Li, C.; Fan, T.; Shi, F. Catalytic asymmetric chemoselective 1,3-dipolar cycloadditions of an azomethine ylide with isatin-derived imines: diastereo- and enantioselective construction of a spiro(imidazolidine-2,3′-oxindole) framework. *Chem. Commun.* **2016**, *52*, 1804–1807. [CrossRef] [PubMed]

53. Overman, L.E.; Rosen, M.D. Total synthesis of (−)-spirotryprostatin B and three stereoisomers. *Angew. Chem. Int. Ed.* **2000**, *39*, 4596–4599. [CrossRef]

54. Lerchner, A.; Carreira, E.M. First total synthesis of (±)-strychnofoline via a highly selective ring-expansion reaction. *J. Am. Chem. Soc.* **2002**, *124*, 14826–14827. [CrossRef] [PubMed]

55. Meyers, C.; Carreira, E.M. Total synthesis of (−)-spirotryprostatin B. *Angew. Chem. Int. Ed.* **2003**, *42*, 694–696. [CrossRef] [PubMed]

56. Von Nussbaum, F.; Danishefsky, S.J. A rapid total synthesis of spirotryprostatin B: Proof of its relative and absolute stereochemistry. *Angew. Chem. Int. Ed.* **2000**, *39*, 2175–2178. [CrossRef]

57. Edmondson, S.; Danishefsky, S.J.; Sepp-Lorenzino, L.; Rosen, N. Total synthesis of spirotryprostatin A, leading to the discovery of some biologically promising analogues. *J. Am. Chem. Soc.* **1999**, *121*, 2147–2155. [CrossRef]

58. Genin, M.J.; Chidester, C.G.; Rohrer, D.C.; Romero, D.L. Design and synthesis of a conformationally constrained analog of the bis(heteroaryl)piperazine (BHAP) HIV-1 reverse transcriptase inhibitor atevirdine. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1875–1880. [CrossRef]

59. Ghorai, M.K.; Ghosh, K. Lewis acid mediated nucleophilic ring opening followed by cycloaddition of 2-aryl-*N*-tosylaziridines with carbonyl compounds: further support towards an S_N2-type mechanism. *Tetrahedron Lett.* **2007**, *48*, 3191–3195. [CrossRef]

60. Soeta, T.; Miyamoto, Y.; Fujinami, S.; Ukaji, Y. The Lewis acid-catalyzed (3 + 1 + 1) cycloaddition of azomethine ylides with isocyanides. *Tetrahedron* **2014**, *70*, 6623–6629. [CrossRef]

61. CCDC 1425280 Contains the Supplementary Crystallographic Data for this Paper. These Data Can be Obtained Free of Charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).