Protecting-group directed stereospecific organocatalytic [3+2] cycloadditions: a facile access to chiral spirocyclic oxindoles

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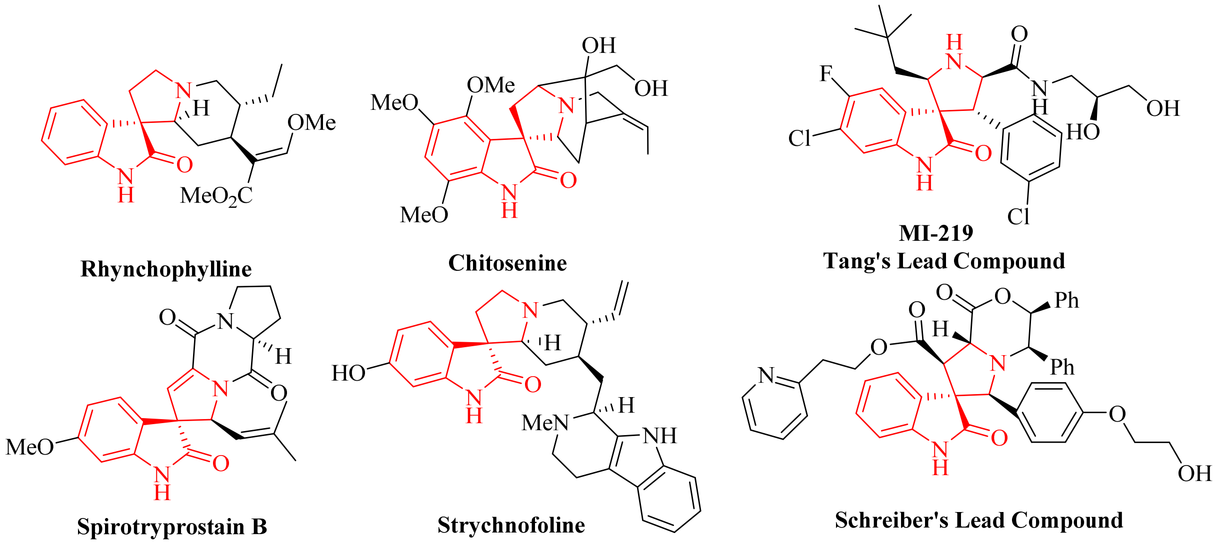
Dedicated to Professor Pierre Vogel on the occasion of his 70th birthday

Abstract
An efficient organocatalytic [3+2] cycloaddition between isocyanides and methyleneindolinones, with simultaneous formation of two quaternary stereocenters, for the rapid construction of dihydrospiro[pyrrolidin-3,3′-oxindole] derivatives with high enantiopurity and structural diversity was developed. Furthermore, different protecting group on the nitrogen atom of methyleneindolenones gave rise to a different major diastereoisomer, suggesting a new avenue of great importance to medicinal chemistry and diversity-oriented synthesis.

Keywords: Asymmetric catalysis, oxindoles, spirocyclic, organocatalysis, protecting group

Introduction

The spiro[pyrrolidin-3,3′-oxindole] skeleton is commonly presented in a large number of natural products[1-3] as well as medicinally relevant compounds[4-6] (Figure 1) and associated with significant biological activities. For instance, the Spirotryprostain B, isolated from the fermentation broth of Aspergillus fumigatus, has been proved to render complete inhibition of the G2/M progression in mammalian tsFT210 cells.[7] In light of promising bioactivities, the therapeutic potential of this attractive heterocyclic spiro motifs has led to a demand for efficient construction of spiro[pyrrolidin-3,3′-oxindole] ring system with high enantioselectivity.



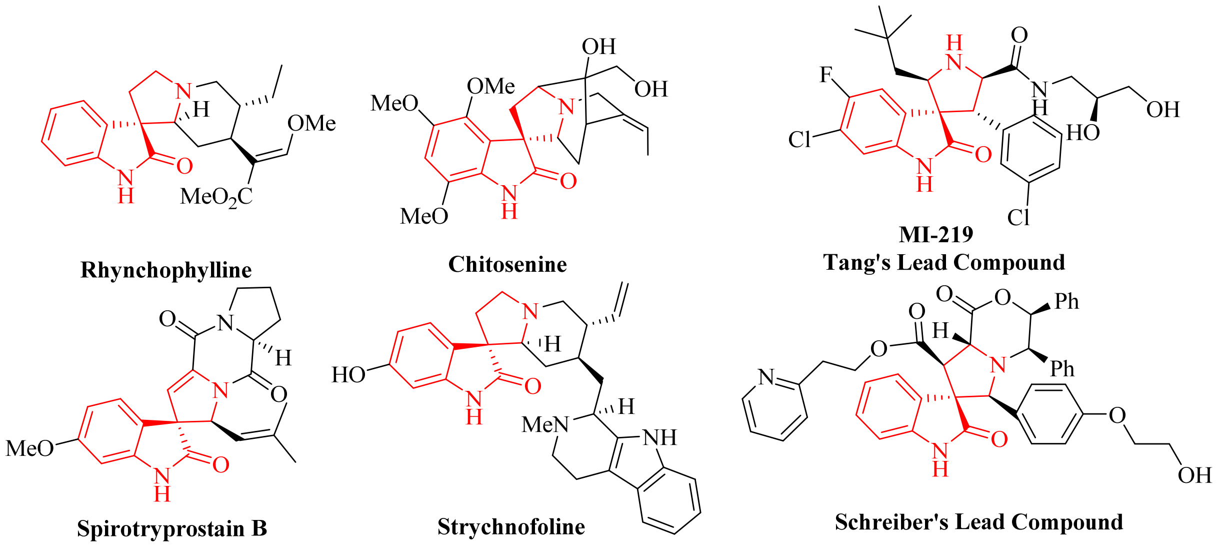


Figure 1. Some examples of natural occurring and biologically active spirocyclic oxindoles.

Over the past several years, intensive effort has been put into the asymmetric construction of this type of spirocyclic oxindole skeletons. However, resulting from the spiro structure, only a few transformations have achieved the goal.[8-21] The challenges associated with the stereocontrolled construction of spirocyclic oxindole core arise from introducing quaternary carbon stereocenter at C-3 of oxindole,[22,23] which is highly sterically congested. As a result, the direct catalytic enantioselective synthesis of the spirocyclic oxindole structure with two quaternary carbon chiral centers[24,25] remains a daunting challenge.

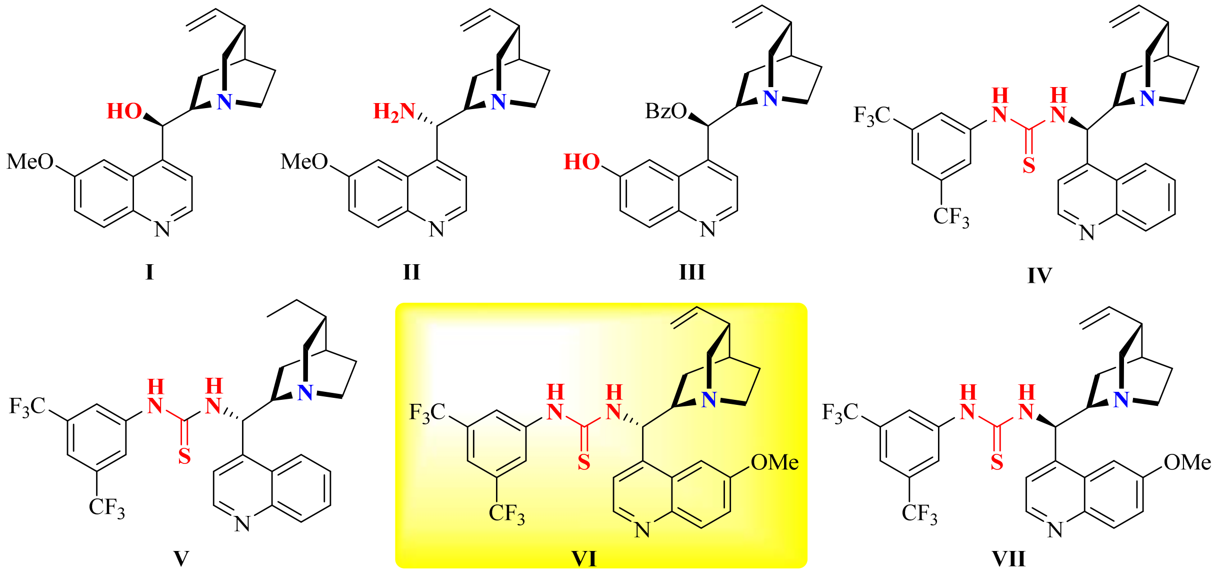
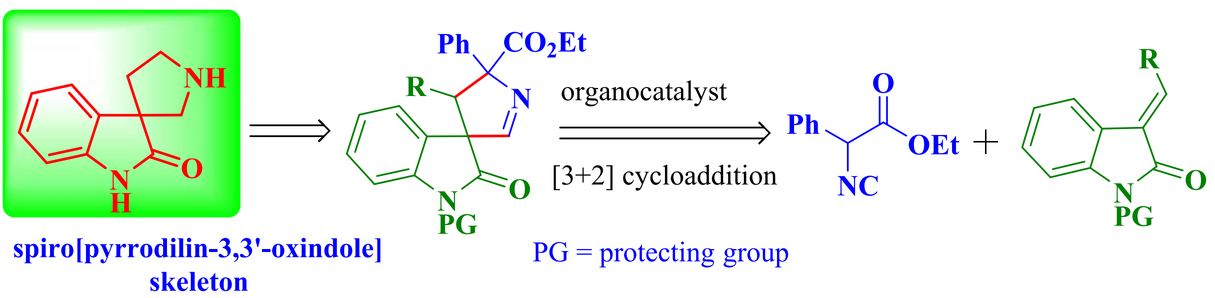


Figure 2. Structures of cinchona alkaloid derived organocatalysts.

Cinchona alkaloids[26-37] and their derivatives (Figure 2) have proven to be powerful organocatalysts for various organocatalytic[38-42] asymmetric C-C bond formations. Recently, isocyanide has been reported as an efficient nucleophile,[43-46] as the α-hydrogen atom is sufficiently acidic to be deprotonated by cinchona alkaloids. Inspired by this discovery, it is envisioned that the [3+2] cycloaddition of isocyanide and methyleneindolinone may be promoted by bifunctional cinchona alkaloid catalysts, leading to a direct stereoselective access to dihydrospirocyclic oxindoles, which may be easily transformed into the spiro[pyrrolidin-3,3′-oxindole] derivatives (Scheme 1).



Scheme 1. Proposed strategy for construction of spiro[pyrrolidin-3,3′-oxindole] skeletons by [3+2] cycloaddition between isocyanides and methyleneindolinones.

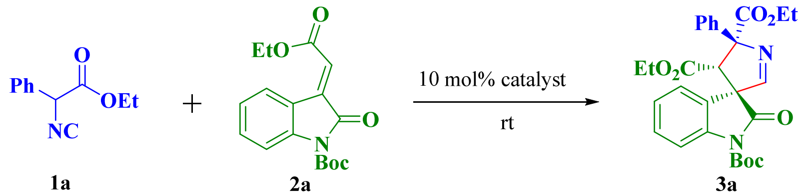
In this communication, the discovery of the first asymmetric organocatalytic [3+2] cycloaddition between isocyanide and methyleneindolinone with simultaneously formation of two quaternary and one tertiary stereocenters is reported for the rapid construction of dihydrospiro[pyrrolidin-3,3′-oxindole] derivatives with high enantiopurity and structural diversity. Furthermore, different protecting group gave rise to different major diastereoisomer, which suggested a new avenue of great importance to medicinal chemistry and diversity-oriented synthesis.

Results and Discussion

The initial optimization began with the addition of isocyanide **1a** (1.5 equiv) to methyleneindolinone **2a** in CH_2Cl_2 in the presence of commercially available quinine (catalyst **I**, 10 mol%) at room temperature. Although the reaction proceeded smoothly, the major product was separated from a 1.1 to 1 mixture of diastereoisomers in 43% yield with a poor enantioselectivity (32% ee, Table 1, entry 1). Several other cinchona alkaloids were tested (catalysts **II** and **III**) under the same condition, however, the yield and selectivity were generally not good (Table 1, entries 2 and 3). Notably, a significant improvement in both diastereo- and enantioselectivity was observed when cinchona alkaloids containing thiourea scaffolds were screened (Table 1, entries 4-7). The reactions fully completed within 2 hours and the highest ee was achieved using catalyst **VI**, accomplished with good yield (76%) and catalyst **VII** produced the opposite enantiomer with comparable ee value. A subsequent solvent screening revealed that nonpolar solvents are beneficial to this type of reaction, as slight increase in enantioselectivity and yield was observed in toluene (Table 1, entry 8). There was somewhat drop in ee when only 1.0 equiv of isocyanide **1a** was used (Table 1, entry 10). Decreasing the reaction temperature prolonged the reaction time with no improvement in either enantioselectivity or yield (Table 1, entry 11). Finally, 5 mol% catalyst loading was found to be better for obtaining high yield and excellent enantioselectivity (Table 1, entries 12 and 13).

With the optimized condition in hand, the scope of Boc-protected methyleneindolinones was investigated (Table 2). The presence of both electron withdrawing group and donating group at the indolinone moiety was all tolerated to afford more than 99% ee (Table 2, entries 1-5). Methyleneindolinone derivatives bearing various substituents at the C-C double bond also participated in the direct [3+2] cycloaddition reactions. Excellent enantioselectivity in up to >99% ee was generally obtained with ester substituents on the C-C double bond (Table 2, entries 6 and 7). It was noteworthy that a slight drop in ee (only 98%) with prolonged reaction time was observed as the ester substituents were replaced by ketones (Table 2, entries 8-10). The absolute configuration of Boc-protected product **3c** was determined by X-ray crystallography (Figure 3).

Table 1. Catalyst screening and optimization of cycloaddition reaction conditions[a]



Entry	Catalyst	Solvent	Time (h)	Yield (%) [b]	dr [c]	ee (%) [d]
1	**I**	DCM	6	43	1.1:1	32
2	**II**	DCM	5	45	1.2:1	49
3	**III**	DCM	5	61	2.0:1	89
4	**IV**	DCM	2	67	3.2:1	95
5	**V**	DCM	2	76	4.1:1	96
6	**VI**	DCM	2	76	4.2:1	97
7	**VII**	DCM	2	74	4.0:1	97
8	**VI**	toluene	2	78	4.5:1	>99
9	**VI**	Et_2O	4	63	3.8:1	98
10 [e]	**VI**	toluene	4	71	5.0:1	97
11 [f]	**VI**	toluene	5	78	5.6:1	32
12 [g]	**VI**	toluene	2	80	5.5:1	>99
13 [h]	**VI**	toluene	4	75	5.2:1	89

[a]All reactions were carried out by using isocyanide **1a** (0.15 mmol, 1.5 equiv) and methyleneindolinone **2a** (0.1 mmol, 1.0 equiv) with 10 mol% of catalyst at 23 °C. [b]Isolated yield (major isomer). [c]dr determined by crude ^{1}H-NMR; the relative configuration of the minor diastereoisomer corresponds to that of compound **5a** (see Table 3). [d]ee was determined by chiral HPLC. [e]Only 1.0 equivalent **1a** was used. [f]The reaction was conducted at 0 °C. [g]5 mol% catalyst was used. [h] Catalyst loading was 2 mol%.

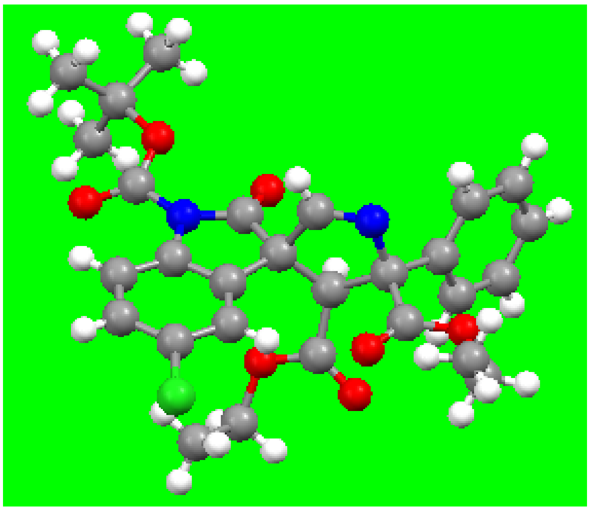


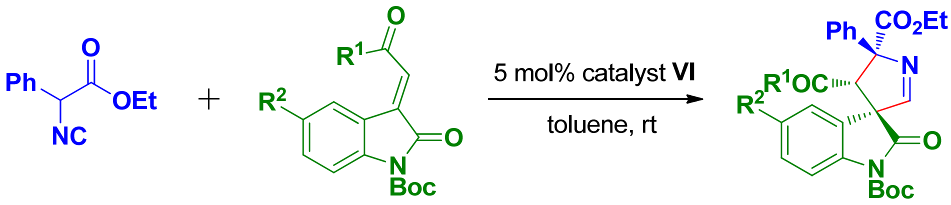
Figure 3. X-ray crystallography of Boc-protected product **3c**.

In the course of cycloaddition between isocyanide and Boc-protected methyleneindolinones, besides the isolated major isomer, some minor compound was also observed in small amount. Since the spiro[indoline-3,3′-pyrrolidine] core is of promising biological properties, there is a high possibility that the minor stereoisomers process unique bioactivities. Therefore, it is a very great importance for "diversity-oriented synthesis",[47] if the minor isomers could be formed as major products.

Based on the previous reports[48] and our comprehension of this cycloaddition reaction, we anticipated that changing the electronic and steric properties of the methyleneindolinones by modification of the protecting group on nitrogen atom might be a promising approach to affect the diastereoselectivity. Remarkably, a new diastereoisomer[49] was obtained as major product by simply replacing the protecting Boc-group with benzyl group. Several methyleneindolinones were selected for investigation of the generality of this approach (Table 3). Good yields and excellent enantioselectivities were obtained with methyleneindolinones bearing various substituents on the indolinone moiety and C-C double bond. Compared with the Boc-protected substrates, the reaction with the Bn-protecting group is generally slower and needs double catalyst loading (10 mol%).

Although the electronic and steric properties of the substrates pay a crucial role to the stereoselectivity of cycloaddition reaction, from the results of this specific reaction, the steric hindrance of protecting group is the determinant factor for high diastereoselectivity. For further understanding the inherent insight, we obtained the structure of a Bn-protected substrate by X-ray crystallography (see the Supporting material). As one face may be blocked by the presence of protecting group, leaving one site open for the cycloaddition. Thus, a catalytic activation mode of the cycloaddtion reactions was proposed (Figure 4).

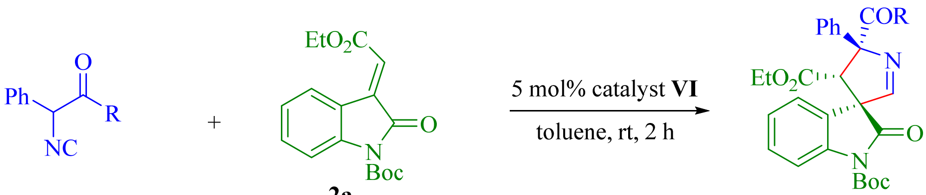
Table 2. Boc-protected substrates scope of the cycloaddition reactions[a]



Entry	R^1	R^2	3	Time (h)	Yield (%) [b]	dr [c]	ee (%) [d]
1	OEt	H	**3a**	2	80	5.5:1	>99
2	OEt	F	**3b**	2	75	5.0:1	>99
3	OEt	Cl	**3c**	2	71	5.2:1	>99
4	OEt	Br	**3d**	2	63	4.8:1	>99
5	OEt	Me	**3e**	2	72	5.0:1	>99
6	OMe	H	**3f**	2	76	5.6:1	>99
7	OBn	H	**3g**	2	68	4.7:1	>99
8	Me	H	**3h**	3	64	4.0:1	>99
9	Ph	H	**3i**	3	42	2.6:1	97
10	*p*-Br-C_6H_4	H	**3J**	3	61	4.0:1	98

[a] All reactions were carried out by using isocyanide **1a** (0.15 mmol, 1.5 equiv) and methyleneindolinone **2a-2J** (0.1 mmol, 1 equiv) with 5 mol% of catalyst **VI** at 23 °C. [b] Isolated yield (major isomer). [c] dr determined by crude ^{1}H-NMR. [d] ee was determined by chiral HPLC.

Further exploration of substrate scope was focused on the variation of isocyanides. Two more the methyl and benzyl isocyano-esters (**1b** and **1c**) were tested as typical examples (Scheme 2). Gratifyingly, both reactions proceeded smoothly in high yield and enantioselectivity, further illustrating the validity and generality of this direct asymmetric cycloaddition.



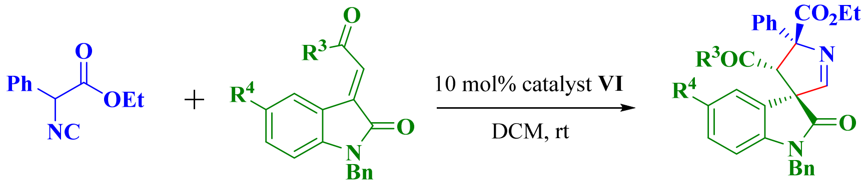
1b: R = OMe,
1c: R = OBn,

2a

3k: R = OMe, 71% yield, 5.0:1 dr, >99% ee
3l: R= OBn, 73% yield, 5.5:1 dr, >99% ee

Scheme 2. Reactions with various isocyanides.

Table 3. Scope of the [3+2] cycloaddition with Bn-protected substrates[a]



Entry	R^3	R^4	**5**	Time (h) [b]	Yield (%) [b]	ee (%) [c]
1	OEt	H	**5a**	2	81	98
2	OEt	F	**5b**	2	67	99
3	OEt	Cl	**5c**	2	73	97
4	OEt	Br	**5d**	2	75	98
5	Ph	Cl	**5e**	3	63	>99

[a]All reactions were carried out by using isocyanide **1a** (0.15 mmol, 1.5 equiv) and methyleneindolinone **4a-4e** (0.1 mmol, 1 equiv) with 10 mol% of catalyst **VI** at 23 °C. [b]Isolated yield. (Crude ^{1}H-NMR displayed only one major isomer. However, the product is not very stable, which decreased the isolated yield.) [c]ee was determined by chiral HPLC.

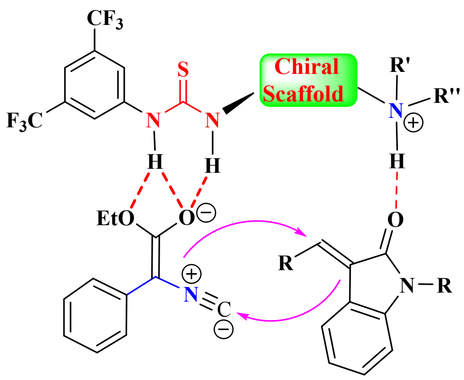


Figure 4. Proposed activation mode of the catalyst and substrates.

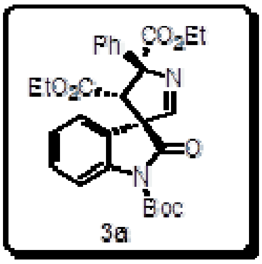
Conclusions

An asymmetric organocatalytic [3+2] cycloaddition of isocyanide and methyleneindolinone has been developed in good yield and excellent enantioselectivity, tolerating a broad range of substrates. The approach was associated with the formation of two quaternary and one tertiary carbon stereogenic centers, providing a highly stereoselective solution to the complex spiro[pyrrolilin-3,3′-oxindole] ring skeleton. Remarkably, two different major diastereoisomers can be selectively achieved by choosing different protecting groups on the nitrogen atom of methyleneindolinones. The success of this strategy opens up new perspectives in the construction of complex spiro[pyrrolidin-3,3′-oxindole] structure for a rapid access to biologically and pharmaceutically active candidates.

Experimental Section

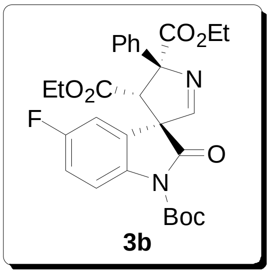
General. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F at 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate. Flash chromatography was performed using Merck silica gel 60 with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use.
Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on Bruker AMX 400 spectrophotometer ($CDCl_3$ as solvent). Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 7.26, singlet). Multiplicities were given as: s (singlet), d (doublet), t (triplet), dd (double of doublet) or m (multiplets). The number of protons (n) for a given resonance is indicated by nH. Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-d (δ 77.0, triplet).
Enantioselectivities were determined by High performance liquid chromatography (HPLC) analysis employing a Daicel Chiralpak AD-H or OD-H. Optical rotations were measured in CH_2Cl_2 on a Schmidt + Haensdch polarimeter (Polartronic MH8) with a 1.0 mL cell (c given in g/100 mL). Absolute configuration of the products was determined by X-ray.
High resolution mass spectrometry (HRMS) was recorded on Finnigan MAT 95×P spectrometer.

General experimental procedure for the construction of spirocyclic oxindoles with organocatalytic [3+2] cycloaddition reactions (3a-3J). To a solution of methyleneindolinone (0.1 mmol, 1 equiv), and isocyanide (0.15 mmol, 1.5 equiv) in toluene (0.2 mL) was added catalyst **VI** (0.005 mmol, 0.05 equiv). The resulting mixture was stirred at room temperature (23 °C). After the reaction completed, the mixture was quenched with water (5 mL) and extracted with ethyl acetate (2 x 5 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was then removed under reduced pressure. The product was afforded by silica gel flash chromatography using gradient elution (EtOAc/Hexane = 1:10 to 1:6).



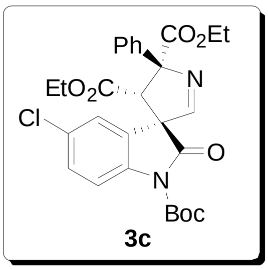
Chemical Formula: $C_{28}H_{30}N_2O_7$
Exact Mass: 506.2053

1-*tert*-Butyl 4′,5′-diethyl (3*R*,4′*S*,5′*R*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro[indoline-3,3′-pyrrole]-1,4′,5′-tricarboxylate (3a). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* 8.0 Hz, 1H), 7.78 (d, *J* 8.0 Hz, 1H), 7.57 (d, *J* 7.2 Hz, 1H), 7.41-7.26 (m, 5H), 7.20 (t, *J* 7.6 Hz, 1H), 4.35-4.22 (m, 2H), 4.18 (s, 1H), 3.88-3.77 (m, 2H), 1.62 (s, 9H), 1.26 (t, *J* 6.8 Hz, 3H), 0.75 (t, *J* 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.21, 170.73, 168.06, 161.85, 148.79, 141.91, 139.87, 129.71, 128.12, 127.68, 126.83, 126.58, 125.00, 123.97, 114.90, 87.89, 85.08, 70.27, 62.69, 62.50, 61.15, 28.02, 13.90, 13.36. HPLC: Chiralpak AD-H (hexane/i-PrOH = 92/8, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 6.7 min, t_R (minor) = 9.8 min; >99% ee. $[\alpha]_D^{21}$ = -9.7 (c = 1.0, CH_2Cl_2). HRMS (ESI) calcd for $C_{28}H_{31}N_2O_7$ $(M+H)^+$, m/z 507.2131, found 507.2135.



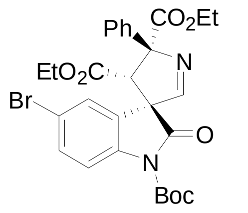
Chemical Formula: $C_{28}H_{29}FN_2O_7$
Exact Mass: 524.1959

1-*tert*-Butyl 4′,5′-diethyl 5-fluoro (3*R*,4′*S*,5′*R*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro [indoline- 3,3′-pyrrole]-1,4′,5′-tricarboxylate (3b). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* 4.4, 9.2 Hz, 1H), 7.67 (dd, *J* 2.8, 8.4 Hz, 1H), 7.58 (d, *J* 7.2 Hz, 2H), 7.35 (m, 4H), 7.12 (m, 1H), 4.38-4.27 (m, 2H), 4.19 (s, 1H), 3.98-3.84 (m, 2H), 1.63 (s, 9H), 1.30 (t, *J* 7.2 Hz, 3H), 0.84 (t, *J* 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.86, 170.58, 167.83, 161.41, 161.28, 158.85, 148.73, 141.62, 135.86, 128.16, 127.77, 126.80, 125.90, 125.81, 116.32, 116.19, 116.09, 114.46, 114.20, 88.07, 85.30, 70.22, 62.70, 62.65, 61.31, 28.00, 13.90, 13.44. HPLC: Chiralpak OD-H (hexane/i-PrOH = 97/3, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 7.4 min, t_R (major) = 9.1 min; >99% ee. $[\alpha]_D^{21}$ = -16.4 (c = 1.0, CH_2Cl_2). HRMS (ESI) calcd for $C_{28}H_{30}FN_2O_7$ $(M+H)^+$, m/z 525.2037, found 525.2034.



Chemical Formula: $C_{28}H_{29}ClN_2O_7$
Exact Mass: 540.1663

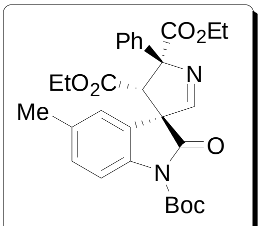
1-*tert*-Butyl 4′,5′-diethyl 5-chloro (3*R*,4′*S*,5′*R*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro [indoline- 3,3′-pyrrole]-1,4′,5′-tricarboxylate (3c). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* 8.8 Hz, 1H), 7.84 (d, *J* 2.0 Hz, 1H), 7.59 (d, *J* 7.2 Hz, 2H), 7.41-7.28 (m, 5H), 4.39-4.29 (m, 2H), 4.18 (s, 1H), 4.01-3.96 (m, 1H), 3.88-3.84 (m, 1H), 1.63 (s, 9H), 1.32 (t, *J* 7.2 Hz, 3H), 0.85 (t, *J* 7.1 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.57, 170.32, 167.75, 161.30, 148.60, 141.66, 138.38, 130.53, 129.68, 128.17, 127.79, 126.78, 126.74, 125.80, 116.15, 88.10, 85.48, 69.98, 62.69, 62.68, 61.35, 27.99, 13.96, 13.46. HPLC: Chiralpak AD-H (hexane/i-PrOH = 95/5, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 9.1 min, t_R (major) = 11.6 min; >99% ee. $[\alpha]_D^{21}$ = 39.0 (c = 1.0, CH_2Cl_2). HRMS (ESI) calcd for $C_{28}H_{30}ClN_2O_7$ $(M+H)^+$, m/z 541.1742, found 541.1745.



3d

Chemical Formula: $C_{28}H_{29}BrN_2O_7$
Exact Mass: 584.1158

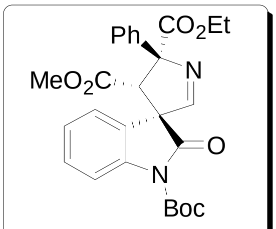
1-*tert*-Butyl 4′,5′-diethyl 5-bromo (3*R*,4′*S*,5′*R*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro[indoline -3,3′-pyrrole]-1,4′,5′-tricarboxylate (3d). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.88 (d, *J* 8.8 Hz, 1H), 7.59-7.54 (m, 3H), 7.39-7.28 (m, 4H), 4.41-4.28 (m, 2H), 4.17 (s, 1H), 4.03-3.95 (m, 1H), 3.90-3.82 (m, 1H), 1.63 (s, 9H), 1.33 (t, J 7.2 Hz, 3H), 0.85 (t, *J* 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.44, 170.24, 167.73, 161.29, 148.58, 141.66, 138.89, 132.62, 129.51, 128.18, 127.80, 126.78, 126.12, 117.99, 116.55, 88.11, 85.52, 69.88, 62.70, 62.69, 61.37, 27.99, 14.01, 13.48. HPLC: Chiralpak AD-H (hexane/i-PrOH = 97/3, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 15.0 min, t_R (major) = 21.0 min; >99% ee. $[\alpha]_D^{21}$ = 39.2 (c = 1.0, CH_2Cl_2). HRMS (ESI) calcd for $C_{28}H_{30}BrN_2O_7$ $(M+H)^+$, m/z 585.1236, found 585.1234.



3e

Chemical Formula: $C_{29}H_{32}N_2O_7$
Exact Mass: 520.2210

1-*tert*-Butyl 4′,5′-diethyl 5-methyl (3*R*,4′*S*,5′*R*)-2-oxo-5′-phenyl-4′,5′-dihydro-spiro[indoline-3,3′-pyrrole]-1,4′,5′-tricarboxylate (3e). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* 8.4 Hz, 1H), 7.59-7.55 (m, 3H), 7.40-7.31 (m, 4H), 7.20 (d, *J* 8.3 Hz, 1H), 4.37-4.28 (m, 2H), 4.19 (s, 1H), 3.95-3.78 (m, 2H), 2.37 (s, 3H), 1.63 (s, 9H), 1.31 (t, *J* 7.2 Hz, 3H), 0.78 (t, *J* 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.27, 170.54, 168.08, 162.05, 148.83, 142.01, 137.50, 134.61, 130.15, 128.11, 127.66, 126.97, 126.82, 123.85, 114.70, 87.83, 84.90, 70.32, 62.61, 62.39, 61.10, 28.03, 21.18, 13.97, 13.38. HPLC: Chiralpak AD-H (hexane/i-PrOH = 95/5, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 8.6 min, t_R (major) = 11.5 min; >99% ee. $[\alpha]_D^{21}$ = 15.1 (c = 1.0, CH_2Cl_2). HRMS (ESI) calcd for $C_{29}H_{33}N_2O_7$ $(M+H)^+$, m/z 521.2288, found 521.2289.

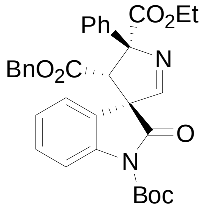


3f

Chemical Formula: $C_{27}H_{28}N_2O_7$
Exact Mass: 492.1897

1-*tert*-Butyl 5′-ethyl 4′-methyl (3*R*,4′*S*,5′*R*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro[indoline- 3,3′-pyrrole]-1,4′,5′-tricarboxylate (3f). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* 8.0 Hz, 1H), 7.71 (d, *J* 7.6 Hz, 1H), 7.59 (d, *J* 1.2 Hz, 2H), 7.57-7.33 (m, 5H), 7.23 (t, *J* 7.6 Hz, 1H), 4.37-4.26 (m, 2H), 4.22 (s, 1H), 3.38 (s, 3H), 1.64 (s, 9H), 1.29 (t, *J* 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.94, 170.76, 168.65, 161.89, 148.79, 141.71, 139.63, 129.75, 128.17, 127.76, 126.80, 126.37, 124.92, 123.72, 114.97, 88.24, 85.14, 70.25, 62.53, 62.31, 52.05, 28.03, 13.92. HPLC: Chiralpak AD-H (hexane/i-PrOH = 95/5, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 11.7 min, t_R (minor) = 14.4 min; >99% ee. $[\alpha]_D^{21}$ = -7.5 (c = 1.0, CH_2Cl_2). HRMS (ESI) calcd for $C_{27}H_{29}N_2O_7$ $(M+H)^+$, m/z 493.1975, found 493.1969.

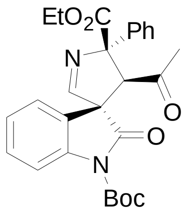
4′-Benzyl 1-*tert*-butyl 5′-ethyl (3*R*,4′*S*,5′*R*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro [indoline-3,3′-pyrrole]-1,4′,5′-tricarboxylate (3g). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* 8.0 Hz, 1H), 7.78 (d, *J* 7.6 Hz, 1H), 7.57 (d, *J* 1.4 Hz, 2H), 7.56-7.18 (m, 9H), 6.91 (d, *J* 6.4 Hz, 2H), 4.87 (d, *J* 12 Hz, 1H), 4.69 (d, *J* 12.0 Hz, 1H), 4.37-4.25 (m, 3H), 1.60 (s, 9H), 1.27 (t, *J* 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.02, 170.68, 167.95, 161.98, 148.62, 141.76, 139.76, 134.39, 129.77, 128.41, 128.37, 128.30, 128.14, 127.72, 126.85, 126.47, 125.05, 123.68, 115.09, 88.01, 84.95, 70.24, 67.35, 62.54, 62.52, 27.99, 13.90. HPLC: Chiralpak AD-H (hexane/i-PrOH = 90/10, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 10.8 min, t_R (minor) = 13.2 min; >99% ee. $[\alpha]_D^{21}$ = -9.7 (c = 1.0, CH_2Cl_2). HRMS (ESI) calcd for $C_{33}H_{33}N_2O_7$ $(M+H)^+$, m/z 569.2288, found 569.2290.



3g

Chemical Formula: $C_{33}H_{32}N_2O_7$
Exact Mass: 568.2210

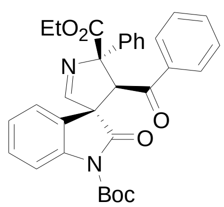
1-*tert*-Butyl 5′-ethyl 4′-acetyl (3*R*,4′*S*,5′*S*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro[indoline-3,3′-pyrrole]-1,5′-dicarboxylate (3h). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* 8.0 Hz, 1H), 7.66 (d, *J* 7.6 Hz, 1H), 7.50-7.34 (m, 6H), 7.24-7.21 (m, 2H), 4.42-4.28 (m, 2H), 4.23 (s, 1H), 1.73 (s, 3H), 1.65 (s, 9H), 1.33 (t, *J* 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 201.64, 173.05, 171.16, 161.31, 148.60, 141.67, 139.48, 130.08, 128.28, 127.80, 126.74, 126.59, 125.45, 123.18, 115.29, 87.98, 85.45, 71.13, 69.56, 62.52, 30.20, 28.03, 13.91. HPLC: Chiralpak OD-H (hexane/i-PrOH = 97/3, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 17.9 min, t_R (minor) = 21.6 min; >99% ee. $[\alpha]_D^{21}$ = 35.2 (c = 1.0, CH_2Cl_2). HRMS (ESI) calcd for $C_{27}H_{29}N_2O_6$ $(M+H)^+$, m/z 477.2026, found 477.2028.



3h

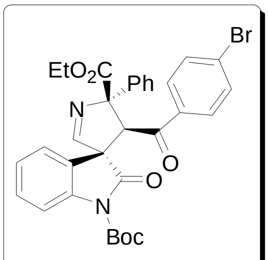
Chemical Formula: $C_{27}H_{28}N_2O_6$
Exact Mass: 476.1947

1-*tert*-Butyl 5′-ethyl 4′-benzoyl (3*R*,4′*S*,5′*S*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro[indoline-3,3′-pyrrole]-1,5′-dicarboxylate (3i). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* 7.6 Hz, 1H), 7.56 (d, *J* 7.2 Hz, 2H), 7.49 (d, J 8.0 Hz, 1H), 7.42-7.28 (m, 7H), 7.21-7.12 (m, 4H), 5.05 (s, 1H), 4.48-4.30 (m, 2H), 1.61 (s, 9H), 1.32 (t, *J* 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 196.40, 173.54, 171.15, 160.73, 148.23, 142.43, 139.16, 137.37, 133.00, 129.79, 128.33, 128.19, 127.59, 127.28, 127.22, 126.93, 125.07, 122.31, 114.39, 87.91, 84.96, 70.66, 66.77, 62.48, 28.01, 13.88. HPLC: Chiralpak IC (hexane/i-PrOH = 90/10, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 13.8 min, t_R (minor) = 29.5 min; 97% ee. $[\alpha]_D^{21}$ = -7.7 (c = 1.0, CH_2Cl_2). HRMS (ESI) calcd for $C_{32}H_{31}N_2O_6$ $(M+H)^+$, m/z 539.2182, found 539.2183.



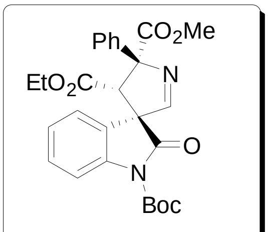
3i

Chemical Formula: $C_{32}H_{30}N_2O_6$
Exact Mass: 538.2104



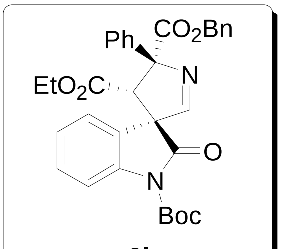
Chemical Formula: $C_{32}H_{29}BrN_2O_6$
Exact Mass: 616.1209

1-*tert*-Butyl 5′-ethyl 4′-(4-bromobenzoyl) (3*R*,4′*S*,5′*S*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro- [indoline-3,3′-pyrrole]-1,5′-dicarboxylate (3J). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* 7.6 Hz, 1H), 7.53 (d, *J* 8.0 Hz, 3H), 7.39-7.33 (m, 6H), 7.26-7.23 (m, 1H), 7.19-7.13 (m, 3H), 4.99 (s, 1H), 4.44-4.31 (m, 2H), 1.63 (s, 9H), 1.31 (t, *J* 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 195.40, 173.45, 170.98, 160.61, 148.05, 142.22, 139.11, 136.10, 131.63, 129.99, 128.80, 128.26, 128.19, 127.70, 127.78, 126.87, 125.14, 122.15, 114.47, 87.95, 85.26, 70.58, 66.65, 62.53, 28.02, 13.87. HPLC: Chiralpak AD-H (hexane/i-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 16.9 min, t_R (minor) = 26.5 min; 98% ee. $[\alpha]_D^{21}$ = -15.9 (c = 1.0, CH_2Cl_2). HRMS (ESI) calcd for $C_{32}H_{30}BrN_2O_6$ $(M+H)^+$, m/z 617.1287, found 617.1284.



Chemical Formula: $C_{27}H_{28}N_2O_7$
Exact Mass: 492.1897

1-*tert*-Butyl 4′-ethyl 5′-methyl (3*R*,4′*S*,5′*S*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro [indoline-3,3′- pyrrole]-1,4′,5′-tricarboxylate (3k). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J 8.0 Hz, 1H), 7.77 (d, *J* 7.6 Hz, 1H), 7.57 (d, *J* 7.2 Hz, 2H), 7.41-7.30 (m, 5H), 7.21 (t, *J* 7.6 Hz, 1H), 4.20 (s, 1H), 3.87-3.76 (m, 5H) (-CH3 and –CH2 overlap), 1.62 (s, 9H), 0.73 (t, *J* 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.15, 171.33, 168.13, 161.88, 148.77, 141.75, 139.91, 129.78, 128.22, 127.80, 126.84, 126.53, 125.10, 123.82, 114.91, 87.70, 85.11, 70.38, 62.78, 61.25, 53.34, 28.02, 13.35. HPLC: Chiralpak AD-H (hexane/i-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 6.7 min, t_R (minor) = 8.4 min; >99% ee. $[\alpha]_D^{21}$ = -12.8 (c = 1.2, CH_2Cl_2). HRMS (ESI) calcd for $C_{27}H_{29}N_2O_7$ $(M+H)^+$, m/z 493.1975, found 493.1972.

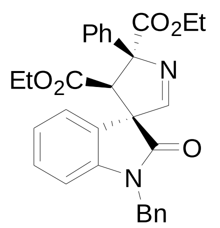


Chemical Formula: $C_{33}H_{32}N_2O_7$
Exact Mass: 568.2210

-5′-Benzyl 1-*tert*-butyl 4′-ethyl (3*R*,4′*S*,5′*S*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro [indoline-3,3′- pyrrole]-1,4′,5′-tricarboxylate (3l). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* 8.0 Hz, 1H), 7.58-7.54 (m, 3H), 7.38-7.29 (m, 7H), 7.26-7.22 (m, 3H), 7.02 (t, *J* 7.6 Hz, 1H), 5.27 (dd, *J* 12.6, 24.5 Hz, 2H), 4.22 (s, 1H), 3.84-3.72 (m, 2H), 1.61 (s, 9H), 0.70 (t, J 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.14, 170.43, 168.01, 162.00, 148.77, 141.78, 139.82, 135.25, 129.68, 128.42, 128.17, 128.11, 127.94, 127.79, 126.88, 126.52, 124.97, 123.74, 114.88, 87.82, 85.10, 70.32, 67.94, 62.63, 61.22, 28.02, 13.32. HPLC: Chiralpak AD-H (hexane/i-PrOH = 90/10, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 14.3 min, t_R (major) = 19.4 min; >99% ee. $[\alpha]_D^{21}$ = -13.4 (c = 0.8, CH_2Cl_2). HRMS (ESI) calcd for $C_{33}H_{33}N_2O_7$ $(M+H)^+$, m/z 569.2288, found 569.2290.

General procedure for the construction of spirocyclic oxindoles with organocatalytic [3+2]cycloaddition reactions (5a-3f): To a solution of methyleneindolinone (0.1 mmol, 1 equiv) and isocyanide **1a** (0.15 mmol, 1.5 equiv) in DCM (0.2 mL) was added catalyst **VI** (0.01

mmol, 0.1 equiv). The resulting mixture was stirred at room temperature (23 °C). After the reaction completed, the mixture was quenched with water (5 mL) and extracted with DCM (2 x 5 mL). The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was then removed under reduced pressure. The product was afforded by silica gel flash chromatography using gradient elution (EtOAc/Hexane = 1:10 to 1:6).

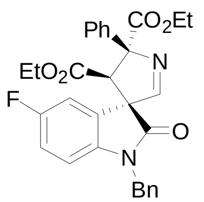


5a

Chemical Formula: $C_{30}H_{28}N_2O_5$
Exact Mass: 496.1998

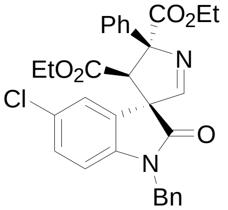
Diethyl 1-benzyl (3*R*,4′*S*,5′*S*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro[indoline-3,3′-pyrrole]-4′,5′- dicarboxylate (5a). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* 1.2 Hz, 2H), 7.71 (s, 1H), 7.56-7.32 (m, 8H), 7.26 (t, *J* 7.6 Hz, 1H), 7.17 (d, J 7.6 Hz, 1H), 6.98 (t, 7.6 Hz, 1H), 6.80 (d, J 8.0 Hz, 1H), 5.03 (d, *J* 15.6, Hz, 1H), 4.96 (d, J 15.6, Hz, 1H),4.86 (s, 1H), 4.36 (q, *J* 7.1 Hz, 2H), 3.67-3.63 (m, 2H), 1.32 (t, *J* 7.2 Hz, 3H), 0.78 (t, *J* 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.41, 171.56, 167.83, 163.22, 143.64, 138.95, 135.18, 129.88, 128.96, 128.19, 128.09, 127.93, 127.34, 126.81, 126.64, 123.80, 122.98, 109.59, 89.39, 68.51, 62.50, 60.66, 59.18, 44.38, 14.02, 13.49. HPLC: Chiralpak IB (hexane/i-PrOH = 85/15, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 10.9 min, t_R (major) = 12.6 min; 98% ee. $[\alpha]_D^{21}$ = 58.7 (c = 1.0, CH_2Cl_2). HRMS (ESI) calcd for $C_{30}H_{29}N_2O_5$ $(M+H)^+$, m/z 497.2076, found 497.2079.

Diethyl 1-benzyl 5-fluoro (3*R*,4′*R*,5′*R*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro[indoline-3,3′-pyrrole]-4′,5′- dicarboxylate (5b). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* 7.6 Hz, 2H), 7.51 (s, 1H), 7.42-7.30 (m, 8H), 6.93 (t, *J* 8.4 Hz, 2H), 6.67 (q, *J* 4.0 Hz, 1H), 4.94 (d, *J* 3.6 Hz, 2H), 4.82 (s, 1H), 4,32 (q, *J* 7.2 Hz, 2H), 3.67-3.61 (m, 2H), 1.28 (t, J 7.2 Hz, 3H), 0.81 (t, *J* 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 173.05, 171.31, 167.73, 162.53, 160.24, 139.57, 138.72, 134.82, 129.00, 128.23, 128.20, 128.03, 127.25, 126.53, 125.27, 125.18, 116.33, 116.10, 115.27, 115.01, 110.08, 110.01, 89.51, 68.54, 62.52, 59.34, 44.50, 13.97, 13.48. HPLC: Chiralpak OD-H (hexane/i-PrOH = 95/5, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 29.6 min, t_R (major) = 40.7 min; 99% ee. $[\alpha]_D^{21}$ = -81.9 (c = 1.1, CH_2Cl_2). HRMS (ESI) calcd for $C_{30}H_{28}FN_2O_5$ $(M+H)^+$, m/z 515.1982, found 515.1979.



5b

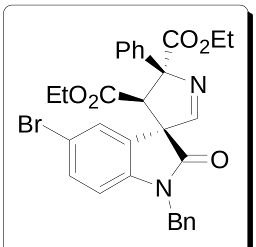
Chemical Formula: $C_{30}H_{27}FN_2O_5$
Exact Mass: 514.1904



5c

Chemical Formula: $C_{30}H_{27}ClN_2O_5$
Exact Mass: 530.1608

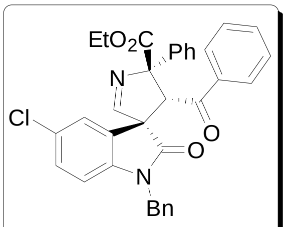
Diethyl 1-benzyl 5-chloro (3*R*,4′*R*,5′*R*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro [indoline-3,3′-pyrr ole]-4′,5′-dicarboxylate (5c). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* 7.2 Hz, 2H), 7.51 (s, 1H), 7.42-7.27 (m, 10H), 7.63 (d, *J* 8.4 Hz, 1H), 4.93 (s, 2H), 4.80 (s, 1H), 4.35-4.27 (m, 2H), 3.70-3.58 (m, 2H), 1.28 (t, *J* 7.2 Hz, 3H), 0.81 (t, *J* 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.77, 171.28, 167.71, 162.36, 142.66, 138.81, 134.63, 132.68, 130.02, 129.04, 128.25, 128.19, 128.08, 127.22, 126.47, 125.68, 115.67, 110.98, 89.48, 68.17, 62.53, 60.96, 59.65, 44.42, 13.98, 13.51. HPLC: Chiralpak OD-H (hexane/i-PrOH = 90/10, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 19.4 min, t_R (major) = 25.1 min; 97% ee. $[\alpha]_D^{21}$ = -17.5 (c = 1.1, CH_2Cl_2). HRMS (ESI) calcd for $C_{30}H_{28}ClN_2O_5$ $(M+H)^+$, m/z 531.1687, found 531.1683.



5d

Chemical Formula: $C_{30}H_{27}BrN_2O_5$
Exact Mass: 574.1103

Diethyl 1-benzyl 5-bromo (3*R*,4′*R*,5′*R*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro[indoline-3,3′-pyrrole]-4′,5′-dicarboxylate (5d). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* 7.2 Hz, 2H), 7.51 (s, 1H), 7.42-7.27 (m, 8H), 7.21-7.18 (m, 2H), 6.67 (d, *J* 8.4 Hz, 1H), 4.93 (s, 2H), 4.80 (s, 1H), 4.34-4.29 (m, 2H), 3.68-3.60 (m, 2H), 1.28 (t, *J* 7.2 Hz, 3H), 0.81 (t, J 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 172.88, 171.29, 167.71, 162.38, 142.16, 138.77, 134.66, 129.77, 129.03, 128.46, 128.25, 128.19, 128.07, 127.34, 127.22, 126.48, 125.33, 110.46, 89.50, 68.26, 62.53, 59.56, 44.46, 13.98, 13.48. HPLC: Chiralpak OD-H (hexane/i-PrOH = 90/10, flow rate 1 mL/min, λ = 210 nm), t_R (minor) = 19.5 min, t_R (major) = 26.6 min; 98% ee. $[\alpha]_D^{21}$ = -25.5 (c = 1.0, CH_2Cl_2). HRMS (ESI) calcd for $C_{30}H_{28}BrN_2O$ $(M+H)^+$, m/z 575.1182, found 575.1180.



5e

Chemical Formula: $C_{34}H_{27}ClN_2O_4$
Exact Mass: 562.1659

Ethyl 4′-benzoyl-1-benzyl 5-chloro (3*R*,4′*R*,5′*S*)-2-oxo-5′-phenyl-4′,5′-dihydrospiro[indoline -3,3′-pyrrole]-5′-carboxylate (5e). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.71-7.85 (m, 2H), 7.51-7.47 (m, 4H), 7.36-7.27 (m, 8H), 7.16-7.06 (m, 4H), 6.53 (d, J 8.4 Hz, 1H), 5.97 (s, 1H), 5.02 (d, *J* 15.6 Hz, 1H), 4.82 (d, *J* 15.6 Hz, 1H), 4.38-4.31 (m, 2H), 1.28 (t, *J* 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 195.52, 173.45, 172.23, 162.32, 141.55, 138.30, 138.14, 134.64, 133.47, 129.57, 128.98, 128.69, 128.65, 128.32, 128.24, 128.05, 128.00, 127.01, 126.51, 124.69, 110.25, 91.07, 69.53, 62.69, 57.79, 50.84, 44.33, 13.95. HPLC: Chiralpak AD-H (hexane/i-PrOH = 80/20, flow rate 1 mL/min, λ = 210 nm), t_R (major) = 22.5 min, t_R (minor) = 43.5 min; >99% ee. $[\alpha]_D^{21}$ = -44.7 (c = 1.2, CH_2Cl_2). HRMS (ESI) calcd for $C_{34}H_{28}ClN_2O_4$ $(M+H)^+$, *m/z* 563.1738, found 563.1735.

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