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Article

Copper-Catalyzed Enantioselective Synthesis of Spirohydroindoles by Ethoxyformylmethylene Oxindole and Iminoester 1,3-Dipole Cycloaddition: An Examination of Associated Biological Activities

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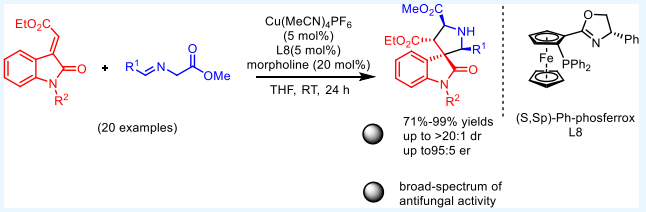
ABSTRACT: A highly enantioselective 1,3-dipolar cycloaddition of ethoxyformylmethylene oxindole with iminoesters has been achieved using the Cu(I)-(*S*,*Sp*)-Ph Phosferrox catalytic system, generating a series of chiral spiro[pyrrolidin-3,3′-oxindole] compounds with four consecutive stereocenters, including a spirocycle quaternary center (71%−99% yield, up to >20:1 dr and 95:5 er). The compounds exhibited good inhibitory activity against *Valsa mali* (*V.m.*), *Fusarium oxysporium* (*F.o.*), and *Alternaria brassicae* (*A.b.*).



INTRODUCTION

Spirocyclic skeletal structures involving intricate formations and well-defined stereoconformations are abundant in natural products and synthetic drugs.[1] The spiro[pyrrolidin-3,3′-oxindole] is a prime example of a chiral spirocyclic fragment,[2] with an associated stereoisomerism and chemical reactivity that has been the subject of significant research in medicinal chemistry. Spirotryprostatins A, pteropodine, cyanogramide, MI-219, rhynchophylline, and strychnofoline (Figure 1) have exhibited excellent antitumor, antibacterial, and other biological activities.[3] However, few studies have addressed the fungicidal activity of compounds with a spiro[pyrrolidine-3,3′-oxindole]-like core structure against phytopathogenic fungus.

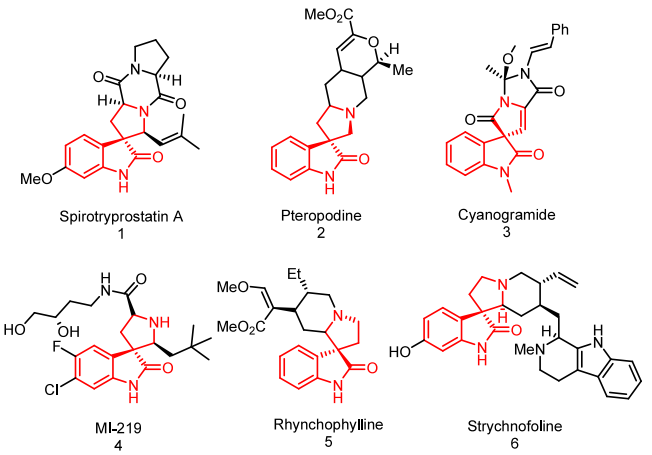


Figure 1. Representative examples of biologically active compounds containing spiro[pyrrolidine-3,3'-oxindole].

These fungi attack plant organs, including roots, leaves, flower spikes, and fruits, causing disease that impairs growth and reduces crop yields. A comprehensive analysis of the fungicidal impact of spiro[pyrrolidine-3,3′-oxindole]-like substances can facilitate the discovery of potent compounds to prevent the growth of plant pathogenic fungus.[4]

Various methods have been developed to generate chiral 3,3′-pyrrolidinone-based spiroindole compounds. The most effective, uncomplicated, and economical of these approaches involves the asymmetric 1,3-dipole cycloaddition of methylene indole ketone derivatives and iminoesters.[5] In 2009, Gong et al. synthesized spiro[pyrrolidine-3,3′-oxindole] for the first time by asymmetric catalytic 1,3-dipolar cycloaddition using a Brønsted acid and chiral phosphate complexes. In 2010, Waldmann reported the Cu(I)/N, P-ferrocenyl complex catalyzed asymmetric synthesis of spiro[pyrrolidine-3,3′-oxindole]. Wang employed the Ag(I)/TF-BiphamPhos catalyst to produce functionalized compound derivatives with moderate enantioselectivity. In 2012, Arai and co-workers developed the bis(imidazolidine)pyridine (PyBidine)-Cu(OTf)$_2$ complex, which promoted an exoselective 1,3-dipolar cycloaddition with high enantioselectivity. In 2020, Wei et al. synthesized chiral phosphine catalysts that delivered outstanding performance in asymmetric 1,3-dipolar cycloaddition reactions.[6]

Ester groups commonly occur as functional moieties in natural products and pharmaceuticals and have an appreciable

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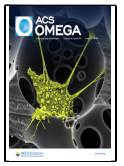


impact on biological activity and pharmacological effects.[7] The addition of an ester group at the 4-position of the spiro[pyrrolidine-3,3′-oxindole] scaffold via ester-substituted 3-methylene-2-oxindoles can serve as a basis for probing possible antimicrobial potential and postsynthetic modifications. In this study, a Cu(I)-(*S*,*S*p)-Ph-Phosferrox catalyst was used to generate a series of ester substituted chiral spiro-[pyrrolidine-3,3′-oxyindole] compounds with a single stereoconfiguration. We examined the resultant antifungal activity against plant pathogenic fungi.

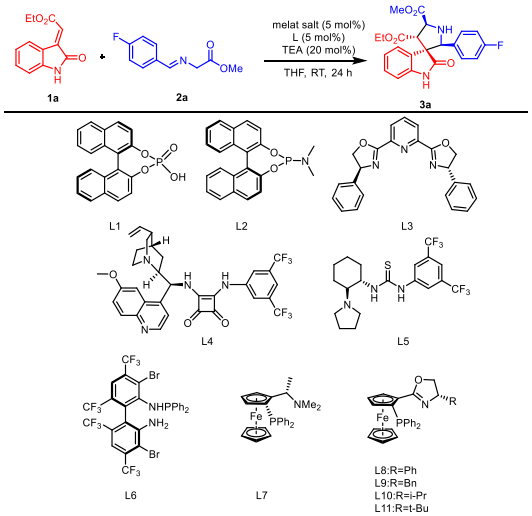
RESULTS AND DISCUSSION

The use of ethyl (*E*)-2-(2-oxoindolin-3-ylidene)acetate **1a** and *N*-[(4-fluorophenyl)methylene]glycine methyl ester **2a** as model substrates generated racemic spirooxindole compound **3a** (Table 1, entry 2). In order to obtain a single configuration of compound **3a**, various commercial chiral ligands and catalysts were screened. Entry 8 in Table 1 shows a 95% yield of product **3a** obtained with an 83:17 dr and 80:20 er using (*S*)-TF-BiphamPhos (L6). However, the high cost and general diastereoselectivity and enantioselectivity of the L6 ligand represent definite drawbacks. A series of commercially available ferrocene chiral ligands were tested with the goal of reducing the cost and improving the enantioselectivity (Table 1, entries 9−13). The (*S*,*S*p)-Ph-Phosferrox ligand (L8) has emerged as a promising lower cost option that delivered an enantioselectivity (er) as high as 92:8 (Table 1, entry 9). Consequently, (*S*,*S*p)-Ph-Phosferrox L8 was selected as the chiral ligand for further investigation. Several metal salts were assessed, where the use of copper salts (Table 1, entry 16) resulted in better diastereoselectivities (>20:1 dr) and enantioselectivities (90:10 er).

Solvent dependency was investigated (Table 2, entries 1−6), and THF was identified as the optimal solvent. In order to optimize reaction conditions, different bases were screened (Table 2, entries 6−10), where use of the organic base morpholine (Table 2, entry 10), resulted in a 98% yield, high diastereomeric selectivity (>20:1 dr), and high enantiomer selectivity (95:5). The temperature or amount of catalyst had little effect on the reaction (Table 2, entries 11−14).

Applying the optimized conditions, the reactions of aryl and aliphatic-substituted methylene ylides have been investigated (Table 3). The cycloaddition reaction produced spirocycles **3a**−**3m** in moderate to high yields with excellent diastereoselectivity regardless of the electronic effect of the aryl substituent (R), where both electron-withdrawing and -donating groups were readily tolerated. *para*-Substituted aryl groups generated better enantioselectivity compared with

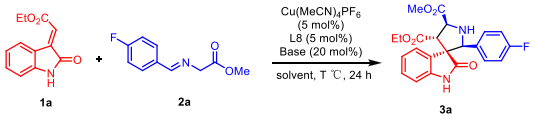
Table 1. Screening of the Ligand and Metal Salt[a]



entry	metal salt	ligand	yield (%)[b]	dr[c]	er[d]
1			17	56:44	50:50
2	AgOAc		30	60:40	51:49
3	AgOAc	L1	74	74:26	49:51
4	AgOAc	L2	81	64:46	60:40
5	AgOAc	L3	70	83:17	52:48
6		L4	67	88:12	50:50
7		L5	92	94:6	40:60
8	AgOAc	L6	95	83:17	80:20
9	AgOAc	L7	77	66:34	36:64
10	AgOAc	L8	61	80:20	92:8
11	AgOAc	L9	72	90:10	87:13
12	AgOAc	L10	74	89:11	84:16
13	AgOAc	L11	69	81:19	83:17
14	Ag_2CO_3	L8	85	83:17	90:10
15	Ag_2O	L8	78	81:19	90:10
16	$Cu(MeCN)_4PF_6$	L8	65	>20:1	90:10

[a]Unless otherwise stated, reactions were carried out with 0.1 mmol of **1a** and 0.2 mmol of **2a** in 1 mL of THF at RT. [b]The yield was determined by ^{1}H NMR analysis of the crude reaction mixture. [c]The dr was determined by ^{1}H NMR analysis of the crude reaction mixture. [d]The enantiomeric ratio (er) was determined by HPLC analysis using a chiral stationary phase.

Table 2. Reaction Optimizations[a]



entry	base	solvent	T(°C)	yield (%)[b]	dr[c]	er[d]
1	TEA	DCM	RT	60	92:8	86:14
2	TEA	MB	RT	48	>20:1	74:26
3	TEA	MTBE	RT	57	>20:1	76:24
4	TEA	Et_2O	RT	43	>20:1	81:19
5	TEA	IPA	RT	48	83:17	77:23
6	TEA	THF	RT	65	>20:1	90:10
7	DBU	THF	RT	90	78:22	70:30
8	K_2CO_3	THF	RT	95	>20:1	70:30
9	Cs_2CO_3	THF	RT	90	89:11	84:16
10	morpholine	THF	RT	98	>20:1	95:5
11	morpholine	THF	0	95	>20:1	86:14
12	morpholine	THF	−20	92	>20:1	84:16
13[e]	morpholine	THF	RT	93	>20:1	90:10
14[f]	morpholine	THF	RT	98	>20:1	96:4

[a]Reactions were carried out with 0.1 mmol of **1a** and 0.2 mmol of **2a**, $Cu(MeCN)_4PF_6$ (0.005 mmol), L8 (0.005 mmol), and base (0.02 mmol) in 1 mL of solvent at RT. [b]The yield was determined by ^{1}H NMR analysis of the crude reaction mixture. [c]The dr was determined by ^{1}H NMR analysis of the crude reaction mixture. [d]The enantiomeric ratio (er) was determined by HPLC analysis using a chiral stationary phase. [e]Reactions were carried out with 0.1 mmol of **1a** and 0.2 mmol of **2a**, $Cu(MeCN)_4PF_6$ (0.003 mmol), L8 (0.003 mmol), and morpholine (0.02 mmol) in 1 mL of THF at RT. [f]Reactions were carried out with 0.1 mmol of **1a** and 0.2 mmol of **2a**, $Cu(MeCN)_4PF_6$ (0.01 mmol), L8 (0.01 mmol), and morpholine (0.02 mmol) in 1 mL of THF at RT.

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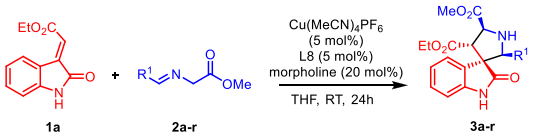
Table 3. Scope of Substrates[a]



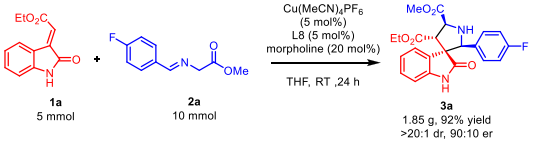
entry	R^1	3	yield (%)[b]	dr[c]	er[d]
1	4-FPh	**3a**	98	>20:1	95:5
2	Ph	**3b**	90	>20:1	92:8
3	4-NO_2Ph	**3c**	99	>20:1	74:26
4	4-MePh	**3d**	74	84:16	73:27
5	4-OMePh	**3e**	81	91:9	95:5
6	3-FPh	**3f**	97	95:5	81:19
7	3-NO_2Ph	**3g**	98	>20:1	60:40
8	3-MePh	**3h**	98	90:10	72:28
9	3-OMePh	**3i**	93	>20:1	80:20
10	2-FPh	**3j**	92	>20:1	87:13
11	2-NO_2Ph	**3k**	98	>20:1	14:86
12	2-MePh	**3l**	71	90:10	79:21
13	2-OMePh	**3m**	70	89:11	96:4
14	2-thienyl	**3n**	92	>20:1	87:13
15	3-thienyl	**3o**	88	>20:1	84:16
16	1-naphthyl	**3p**	83	>20:1	97:3
17	2-naphthyl	**3q**	86	>20:1	85:15
18	cyclohexyl	**3r**	97	>20:1	94:6

[a]Reactions were carried out with 0.1 mmol of **1a** and 0.2 mmol of **2a**, $Cu(MeCN)_4PF_6$ (0.005 mmol), L8 (0.005 mmol), and base (0.02 mmol) in 1 mL of solvent at RT. [b]Isolated yield. [c]The dr was determined by ^1H NMR analysis of the crude reaction mixture. [d]The enantiomeric ratio (er) was determined by HPLC analysis using a chiral stationary phase.

ortho- and *meta*-substituents. The heteroaromatic thienyl- and naphthyl-substituted imine esters were obtained with good yields of compounds **3n**−**3q**, and high diastereoselectivity (>20:1 dr) with moderate enantioselectivity (84:16−98:2 er). In addition, aliphatic cyclohexyl-substituted imide esters, showing high yields and good stereoselectivity, generated target product **3r**.

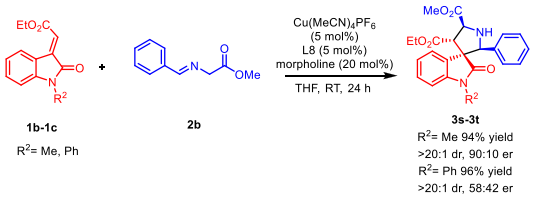
The applicability of this reaction was assessed in a large-scale asymmetric cycloaddition (Scheme 1) using **1a** and **2a** under optimized conditions. The reaction generated 1.85 g 3a in 90% yield with high associated diastereoselectivity and enantioselectivity (>20:1 dr, 90:10 er).

Scheme 1. Scale-up Synthesis of 3a



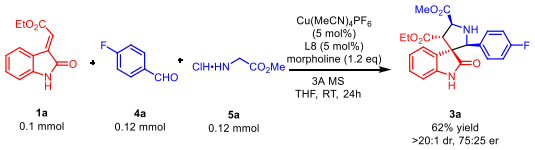
Methylene indolones were studied to assess the shielding of active N−H bonds by methyl and phenyl groups (Scheme 2). The results reveal high yields and diastereoselectivities when using methyl and phenyl as shielding groups. However, the associated enantioselectivity was significantly lower for **3t** phenyl (58:42 er) relative to **3s** methyl (90:10 er) substitution. These findings suggest that the reactivity of the N−H bond is important only where a shielding group exhibiting larger site resistance is used.

Scheme 2. 1,3-Dipolar Cycloaddition Reaction of 1b and 1c



Moreover, the reaction was conducted using a one-pot method (Scheme 3), resulting in a lower yield of compound **3a**

Scheme 3. One-Pot Synthesis of 3a



and enantiomeric ratio when compared to standard conditions. Issues associated with incomplete and insufficient reaction are currently under investigation as part of a program of process optimization.

The absolute configuration of compound **3b** was identified by X-ray analysis, as illustrated in Figure 2.[8] We have

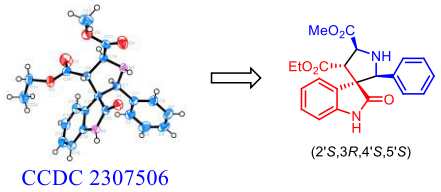


Figure 2. ORTEP diagram of **3b**, ellipsoids show 50% probability levels.

endeavored to elucidate the elevated stereoselectivity of the cycloaddition product utilizing transition states (Figure 3).[9]

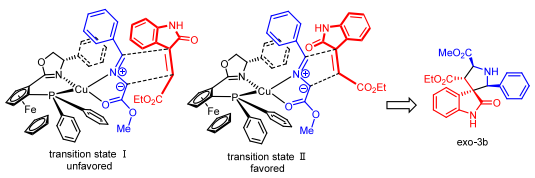


Figure 3. Proposed transition states.

The chiral ligand (*S*,Sp)-Ph-Phosferrox has a greater tendency to form a chiral complex with Cu(I), involving coordination of Cu(I)-Phosferro and methyliminoylidene through oxygen of the carbonyl group and the imide nitrogen. This results in the formation of a tetrahedral complex, where the azomethylidene is oriented perpendicular to the Cu(I)-Phosferro complex and within the pincer "embrace" of the complex. The bulky phenyl group on the oxazoline ring of the Phosferro ligand shields the "bottom" side of the azomethine ylide with the result that the pro-dipole reagent presents a less hindered "top" side. As the double bond in the dipole assumes an E configuration, there are two possible modes of attack: endoaddition and exoaddition. The ester group of the dipole acts as a repulsive force with respect to the two large phenyl groups associated

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with the P of the Phosferro ligand. The instability of the endoaddition transition state I and the small yet stable exoaddition transition state II results in the formation of the highly stereoselective exo-(2′*S*,3*R*,4′*S*,5′*S*) product, while the remaining products may be similar in structure.[10]

In order to assess the antifungal properties of spiro-[pyrrolidine-3,3′-hydroxyindole] analogues on phytopathogenic fungi, the minimum inhibitory concentration (MIC) method was implemented to evaluate effectiveness with respect to eight species: *Valsa mali (V.m.)*, *Fusarium oxysporium (F.o.)*, *Fusarium graminearum (F.g.)*, *Alternaria solani (A.s.)*, *Alternaria brassicae (A.b.)*, *Alternaria alternate (A.a.)*, *Curvularia lunata (C.l.)*, and *Mycosphaerella melonis (M.e.)*.[11]

Table 4 illustrates that compounds **3a**, **3b**, **3d**, **3g**, **3e**, **3n**, **3p**, and **3r** exhibited a significant inhibitory effect on all eight plant pathogens tested. Most of these compounds displayed excellent inhibitory activity against *V.m.*, *F.o.*, and *A.b.* In particular, compounds **3a** and **3r** demonstrated superior inhibitory effects against *V.m.*, **3b**, **3n**, and **3r** against *F.o.*, and **3r** against *A.b.*, compared to the positive control ketoconazole. Compounds **3a**, **3b**, **3d**, **3g**, **3e**, **3n**, **3p**, and **3r** exhibited broad-spectrum inhibitory effects against *A.s.*, *A.a.*, *C.l.*, and *M.e.* Some compounds were able to achieve the level of positive control, with **3d**, **3n**, and **3r** achieving a minimum inhibitory concentration of 64 μg mL^{-1} against *A.s.*, **3a** achieving a minimum inhibitory concentration of 32 μg mL^{-1}, and **3b**, **3g**, and **3r** achieving a minimum inhibitory concentration of 64 μg mL^{-1} against *C.l.*. Both **3g** and **3e** exhibited a minimum inhibitory concentration of 64 μg mL^{-1} for *M.e.*, indicating that substituents, whether electron-donating or electron-absorbing, have a significant impact on the antimicrobial activity of *A.s.*, *A.a.*, and *A.b.*. Furthermore, aliphatic groups have a wider range of antimicrobial activity compared with aromatic groups. For *F.g.*, compounds **3a**−**3r** revealed good inhibitory activity with most exhibiting values of 128 μg mL^{-1}, which dropped to 64 μg mL^{-1} upon substituent modifications of −4F and −Cy.

Table 4. Minimum Inhibitory Concentrations (MICs) of Target Compounds

	MIC/(μg•mL^{-1})							
compound	*V.m.*	*F.o.*	*F.g.*	*A.s.*	*A.b.*	*A.a.*	*C.l.*	*M.e.*
3a	64	64	64	64	32	32	128	128
3b	128	32	128	64	64	64	64	128
3d	128	64	128	64	64	128	128	128
3g	128	64	128	128	32	64	64	64
3e	128	64	128	128	32	128	128	64
3n	128	32	128	64	32	128	128	128
3p	128	64	128	64	64	64	128	128
3r	64	32	64	64	16	128	64	128
PC[a]	128	64	32	64	32	32	64	64

[a]The positive control was ketoconazole.

CONCLUSIONS

In summary, we have established a highly stereoselective 1,3-dipole cycloaddition using a Cu(I)-(*S*,Sp)-Ph-Phosferrox catalytic strategy. The indigo red-derived ester-substituted methylene indolones underwent a cycloaddition with glycine-derived imine esters under mild conditions, resulting in the formation of a series of spiro[pyrrolidine-3,3′-oxindole] compounds with high yields and good stereoselectivity. The minimum inhibitory concentration (MIC) method was employed to determine the antifungal activities of these compounds against eight plant pathogens. The results indicate that most of the compounds exhibited excellent inhibitory activities against *V.m.*, *F.o.*, and *A.b.* Compound **3r** showed a MIC against *A.b.* as low as 16 μg mL^{-1}, surpassing that of the positive ketoconazole control, making it a valuable potential antipathogenic drug in combating plant pathogens.

EXPERIMENTAL SECTION

General Information. Solvent was removed by a rotary evaporator. All experimental chemicals were weighed using a BS2202S analytical balance. The ^{1}H NMR spectra were determined using TMS as the internal reference on a JEOL ECP500 FT NMR spectrometer operating at 400 MHz. The ^{13}C NMR spectra were determined using TMS as the internal reference with a JEOL ECP500 FT NMR spectrometer operating at 101 MHz. All organic solvents used in this study were dried over suitable drying agents and distilled prior to use. Enantiomeric ratio (er) was determined using an HPLC instrument equipped with a Daicel Chiralpak AD-H column and a D1100 UV−vis Detector (λ fixed at 254 nm). Mass spectra were obtained utilizing a Bruker Impact HD Q-TOF high-resolution mass spectrometer. XY280B Pressure Steam Sterilizer, SW-CJ-ID Ultraclean and Sterile Workbench, C204 Biological Microscope, 96-well Culture Plate and Hematocrit Plate are scientific equipment used for measurement, sterilizing, laboratory work, and cell culture. Ag(I) and Cu(I) salts, base, and chiral ligands were purchased from commercial sources and used as received without further purification. Methylene indolones **1a**−**1c** were prepared according to the previously reported method. *N*-Benzylideneiminoglycinates **2a**−**2r** were prepared according to the reported procedure.[12]

General Procedure A for the Preparation of rac-Spiro-[pyrrolidin-3,3′-oxindoles] Derivatives ***3a***−***3t***. Cu-(MeCN)$_4$PF$_6$ (1.9 mg, 0.005 mmol) and morpholine (1.74 mg, 0.02 mmol) were added to a dry 10 mL Schlenk flask together with 0.5 mL of freshly distilled THF under nitrogen. The reaction mixture was stirred for 1 h at room temperature. A solution of *N*-benzylideneiminoglycinates **2** (0.2 mmol, 2equiv) in THF (0.25 mL) was slowly added to the reaction mixture,followed by a solution of methyleneindolinone **1** (0.1 mmol, 1equiv) in THF (0.25 mL), and the reaction was stirred at room temperature for 24 h. When the starting material was consumed (monitored by TLC), the reaction mixture was washed through a diatomaceous earth pad with 25 mL of DCM, the solvent was removed under reduced pressure, and the residue was subjected to direct silica gel column chromatography (PE:EA = 4:1) to give the corresponding products *rac*-**3a**−**3t**.

General Procedure B for the Preparation of Chiral Spiro[pyrrolidin-3,3′-oxindoles] Derivatives ***3a***−***3t***. Cu-(MeCN)$_4$PF$_6$ (1.9 mg, 0.005 mmol), morpholine (1.74 mg, 0.02 mmol), and L8 (26 mg, 0.005 mmol) were added to a dry 10 mL Schlenk flask under nitrogen together with 0.5 mL of freshly distilled THF. The reaction mixture was stirred for 1 h at room temperature. A solution of *N*-benzylideneiminoglycinates **2** (0.2 mmol, 2equiv) in THF (0.25 mL) was slowly added to the reaction mixture followed by a solution of methyleneindolinone **1** (0.1 mmol, 1equiv) in THF (0.25 mL), and the reaction was stirred at room temperature for 24 h. When the starting material was consumed (monitored by

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TLC), the reaction mixture was washed through a diatomaceous earth pad with 25 mL of DCM, the solvent was removed under reduced pressure, and the residue was directly subjected to silica gel column chromatography (PE:EA = 4:1) to give the corresponding chiral products **3a**−**3t**.

*Scale-Up Procedure for the Catalytic Asymmetric 1,3-Dipolar Cycloaddition of ethyl (E)-2-(2-Oxoindolin-3-ylidene)acetate **1a** with N-[(4-Fluorophenyl)methylene]-glycine Methyl Ester **2a**.* $Cu(MeCN)_4PF_6$ (93.18 mg, 0.25 mmol), morpholine (87.12 mg, 1 mmol), and L8 (128.85 mg, 0.25 mmol) were added to a dry 50 mL Schlenk flask under nitrogen together with 10 mL of freshly distilled THF. The reaction mixture was stirred for 1 h at room temperature. A solution of *N*-benzylideneiminoglycinates **2a** (10 mmol, 2equiv) in THF (5 mL) was slowly added to the reaction mixture followed by a solution of methyleneindolinone **1a** (5 mmol, 1equiv) in THF (5 mL), and the reaction was stirred at room temperature for 24 h. When the starting material was consumed (monitored by TLC), the reaction mixture was washed through a diatomaceous earth pad with 100 mL of DCM, the solvent was removed under reduced pressure and the residue was directly subjected to silica gel column chromatography (PE:EA = 4:1) to obtain 1.85 g of **3a** compound

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2′-(4-fluorophenyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3a**).* Yield: 40.4 mg (98%); white solid. mp 154−156 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.45 (s, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 7.7 Hz, 0H), 7.08 (t, J = 7.6 Hz, 1H), 6.94−6.86 (m, 2H), 6.80 (t, J = 8.7 Hz, 2H), 6.73 (d, J = 7.8 Hz, 1H), 4.74 (d, J = 8.2 Hz, 1H), 4.56 (s, 1H), 3.98−3.87 (m, 2H), 3.85 (s, 3H), 3.68 (d, J = 8.2 Hz, 1H), 0.83 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ: 178.89, 171.29, 170.48, 163.26, 161.62, 141.16, 130.50, 128.98, 127.93, 127.67, 124.04, 122.76, 114.98, 114.84, 109.82, 72.47, 63.02, 61.56, 61.15, 56.55, 52.64, 13.69. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 19.633 min, τ_{minor} = 12.065 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{21}FN_2O_5$, 413.1513; found, 413.1502.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2-oxo-2′-phenylspiro-[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3b**).* Yield: 35.4 mg (90%); white solid. mp 146−148 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.22 (s, 1H), 7.29 (d, *J* = 7.4 Hz, 1H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 3.1 Hz, 1H), 7.06 (d, *J* = 7.0 Hz, 2kkH), 6.87 (d, *J* = 7.2 Hz, 2H), 6.73 (d, *J* = 7.8 Hz, 1H), 4.74 (d, *J* = 8.2 Hz, 1H), 4.57 (s, 1H), 3.91 (qd, *J* = 7.2, 2.6 Hz, 2H), 3.83 (s, 3H), 3.66 (d, *J* = 8.3 Hz, 1H), 0.84 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ: 179.31, 171.43, 170.62, 141.41, 134.65, 128.91, 128.06, 128.01 (2C), 127.85, 126.16 (2C), 124.02, 122.67, 109.97, 73.04, 63.13, 61.75, 61.18, 56.77, 52.70, 13.76. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 16.718 min, τ_{minor} = 11.547 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{22}N_2O_5$, 395.1607; found, 395.1595.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2′-(4-nitrophenyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3c**).* Yield: 43.4 mg (99%); white solid. mp 169−170 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.98 (d, *J* = 7.2 Hz, 2H), 7.74 (s, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.28 (d, *J* = 6.8 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 7.8 Hz, 1H), 4.75 (d, *J* = 8.3 Hz, 1H), 4.68 (s, 1H), 3.92 (dtdd, *J* = 8.5, 7.0, 4.8, 2.4 Hz, 2H), 3.86 (s, 3H), 3.70 (d, *J* = 8.3 Hz, 1H), 0.84 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ: 178.17, 171.07, 170.19, 147.70, 142.57, 141.00, 129.52, 127.29 (2C), 127.24, 124.19, 123.25 (2C), 123.16, 110.09, 71.86, 62.93, 61.38, 61.30, 56.35, 52.86, 13.73. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 22.110 min, τ_{minor} = 20.211 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{22}N_3O_7$, 440.1458; found, 440.1462.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2-oxo-2′-(p-tolyl)spiro-[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3d**).* Yield: 30.2 mg (74%); white solid. mp 145−146 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32 (d, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 7.7 Hz, 2H), 6.81 (d, *J* = 7.8 Hz, 2H), 6.75 (d, *J* = 7.8 Hz, 1H), 4.80 (d, *J* = 7.9 Hz, 1H), 4.62 (s, 1H), 3.96 (ddt, *J* = 10.4, 8.2, 3.5 Hz, 2H), 3.88 (s, 3H), 3.72 (d, *J* = 8.0 Hz, 1H), 2.25 (s, 3H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ: 179.16, 171.46, 170.62, 141.28, 137.68, 131.66, 128.83, 128.75 (2C), 128.01, 126.05 (2C), 124.07, 122.68, 109.82, 72.98, 63.14, 61.74, 61.15, 56.94, 52.69, 21.11, 13.75. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 16.914 min, τ_{minor} = 13.568 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{24}N_2O_5$, 409.1763; found, 409.1756.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2′-(4-methoxyphenyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3e**).* Yield: 34.3 mg (81%); white solid. mp 153−154 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.86 (s, 1H), 7.28 (d, *J* = 5.5 Hz, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 2H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 2H), 4.74 (d, *J* = 8.3 Hz, 1H), 4.54 (s, 1H), 3.91 (qt, *J* = 7.1, 3.7 Hz, 2H), 3.84 (s, 3H), 3.69 (s, 1H), 3.66 (s, 3H), 0.83 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ: 179.05, 171.45, 170.63, 159.26, 141.22, 128.79, 128.04, 127.42 (2C), 126.74, 124.08, 122.65, 113.39 (2C), 109.72, 72.94, 63.15, 61.75, 61.11, 56.86, 55.08, 52.64, 13.74. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 12.340 min, τ_{minor} = 10.835 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{24}N_2O_6$, 425.1713; found, 425.1696.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2′-(3-fluorophenyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3f**).* Yield: 40.0 mg (97%); white solid. mp 137−139 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.31−7.22 (m, 2H), 7.10 (d, *J* = 7.6 Hz, 1H), 7.09−6.99 (m, 1H), 6.83 (t, *J* = 9.6 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 6.69−6.59 (m, 2H), 4.73 (d, *J* = 8.3 Hz, 1H), 4.57 (s, 1H), 3.90 (dddd, *J* = 8.6, 7.0, 5.2, 2.1 Hz, 2H), 3.84 (s, 3H), 3.67 (d, *J* = 9.7 Hz, 1H), 0.83 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ: 179.01, 171.25, 170.43, 141.30, 137.47, 129.55, 129.19 (2C), 127.60, 124.00, 122.88, 121.83, 115.12, 113.53, 110.10, 72.18, 62.93, 61.40, 61.25, 56.59, 52.75, 13.73. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 12.702 min, τ_{minor} = 10.642 min. HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{21}FN_2O_5$, 413.1513; found, 413.1503.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2′-(3-nitrophenyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3g**).* Yield: 43.0 mg (98%); white solid. mp 170−172 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.06−7.97 (m, 2H), 7.77 (s, 1H), 7.32 (dd, *J* = 7.8, 3.8 Hz, 2H), 7.29 (d, *J* = 3.1 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 4.76 (d, *J* = 8.3 Hz,

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1H), 4.68 (s, 1H), 3.92 (qd, J = 7.2, 1.8 Hz, 2H), 3.86 (s, 3H), 3.71 (d, J = 8.3 Hz, 1H), 0.84 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-d) δ: 178.47, 171.07, 170.21, 147.85, 140.98, 137.48, 132.44, 129.59, 129.09 (2C), 127.22, 124.11, 123.18, 121.45, 110.23, 71.73, 62.91, 61.37, 61.21, 56.29, 52.85, 13.73. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 23.596 min, τ_{minor} = 13.615 min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{22}N_3O_7$, 440.1458; found, 440.1457.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2-oxo-2′-(m-tolyl)spiro-[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3h**).* Yield: 40.0 mg (98%); white solid. mp 167−168 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.96 (s, 1H), 7.34−7.29 (m, 1H), 7.26 (t, J = 7.7 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 4.7 Hz, 2H), 6.76 (d, J = 7.6 Hz, 2H), 6.63 (t, J = 4.5 Hz, 1H), 4.77 (d, J = 8.3 Hz, 1H), 4.58 (s, 1H), 3.95 (qt, J = 7.1, 3.5 Hz, 2H), 3.87 (s, 3H), 3.69 (d, J = 8.3 Hz, 1H), 2.17 (s, 3H), 0.87 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-d) δ: 179.15, 171.45, 170.64, 141.36, 137.58, 134.52, 128.86, 128.77, 127.96, 127.85, 126.82, 124.08, 123.15, 122.69, 109.81, 73.05, 63.16, 61.72, 61.17, 56.88, 52.69, 21.37, 13.76. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 15.379 min, τ_{minor} = 9.965 min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{24}N_2O_5$, 409.1763; found, 409.1752.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2′-(3-methoxyphenyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3i**).* Yield: 39.4 mg (93%); white solid. mp 185−186 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.63 (s, 1H), 7.33−7.27 (m, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.54 (d, J = 7.7 Hz, 1H), 6.34 (s, 1H), 4.75 (d, J = 8.2 Hz, 1H), 4.57 (s, 1H), 3.92 (dddd, J = 11.0, 8.6, 6.1, 3.7 Hz, 2H), 3.85 (s, 3H), 3.67 (d, J = 8.2 Hz, 1H), 3.53 (s, 3H), 0.84 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-d) δ: 178.80, 171.28, 170.59, 159.05, 141.32, 136.06, 129.12, 128.95, 127.87, 124.13, 122.76, 118.27, 114.31, 111.14, 109.82, 72.91, 63.12, 61.57, 61.21, 56.76, 54.98, 52.74, 13.77. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 20.832 min, τ_{minor} = 11.704 min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{24}N_2O_6$, 425.1713; found, 425.1700.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2′-(2-fluorophenyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3j**).* Yield: 38.0 mg (92%); white solid. mp 151−153 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 8.20 (s, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.13 (q, J = 7.6 Hz, 1H), 7.03 (dt, J = 15.6, 7.7 Hz, 2H), 6.79−6.69 (m, 2H), 4.94 (s, 1H), 4.75 (d, J = 10.5 Hz, 1H), 3.92−3.86 (m, 2H), 3.84 (d, J = 2.0 Hz, 3H), 3.74 (d, J = 8.6 Hz, 1H), 0.81 (t, J = 7.2 Hz,3H). ^{13}C NMR (101 MHz, chloroform-d) δ: 178.92, 171.48, 170.15, 140.90, 129.58, 129.50, 128.81, 128.48, 127.70, 124.40, 123.93, 122.61, 115.15, 114.92, 109.65, 65.82, 62.82, 61.33, 61.17, 56.35, 52.74, 13.69. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 22.248 min, τ_{minor} = 13.210 min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{21}FN_2O_5$, 413.1513; found, 413.1504.

*4′-Ethyl-5′-methyl-(2′R,3S,4′R,5′R)-2′-(2-nitrophenyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3k**).* Yield: 43.0 mg (98%); white solid. mp 149−150 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 8.17 (d, J = 9.5 Hz, 0H), 7.89 (s, 1H), 7.84−7.77 (m, 1H), 7.69 (t, J = 8.4 Hz, 1H), 7.45−7.37 (m, 1H), 7.29 (d, J = 7.3 Hz, 1H), 7.08 (t, J = 8.1 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 5.29 (s, 1H), 4.84 (d, J = 10.1 Hz, 1H), 3.94 (d, J = 10.1 Hz, 1H), 3.87 (s, 3H), 3.87−3.72 (m, 2H), 0.79 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-d) δ: 176.45, 172.33, 168.65, 147.80, 140.77, 135.24, 133.33, 130.83, 129.54, 129.20, 128.59, 124.28, 123.78, 122.97, 109.82, 66.02, 61.20, 61.16, 60.75, 54.31, 52.84, 13.59. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 19.660 min, τ_{minor} = 24.719 min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{22}N_3O_7$, 440.1458; found, 440.1453.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2-oxo-2′-(o-tolyl)spiro-[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3l**).* Yield: 29.0 mg (71%); white solid. mp 166−168 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.65 (d, J = 7.8 Hz, 1H), 7.41−7.32 (m, 2H), 7.30 (s, 1H), 7.20 (dt, J = 14.7, 7.6 Hz, 2H), 7.11 (t, J = 7.2 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 6.72 (d, J = 7.7 Hz, 1H), 4.95 (s, 1H), 4.75 (d, J = 9.1 Hz, 1H), 3.95−3.88 (m, 2H), 3.89 (d, J = 2.7 Hz, 3H), 3.87 (s, 1H), 1.68 (s, 3H), 0.81 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-d) δ: 179.21, 171.48, 170.20, 141.15, 136.20, 133.67, 130.24, 128.86 (2C), 127.80, 127.46, 125.71, 124.41, 122.46, 109.84, 69.11, 62.71, 61.50, 61.01, 56.47, 52.70, 19.40, 13.66. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 13.735 min, τ_{minor} = 10.943 min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{24}N_2O_5$, 409.1763; found, 409.1755.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2′-(2-methoxyphenyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3m**).* Yield: 29.7 mg (70%); white solid. mp 134−135 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.81 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.05−6.94 (m, 2H), 6.80 (t, J = 7.6 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 6.58 (dd, J = 8.0, 4.3 Hz, 2H), 5.14 (s, 1H), 4.80 (d, J = 6.6 Hz, 1H), 4.07 (d, J = 6.6 Hz, 1H), 3.87 (d, J = 2.1 Hz, 1H), 3.83 (s, 3H), 3.62 (s, 3H), 0.62 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-d) δ 179.05, 171.45, 170.63, 159.26, 141.22, 128.79, 128.04, 127.42 (2C), 126.74, 124.08, 122.65, 113.39 (2C), 109.72, 72.94, 63.15, 61.75, 61.11, 56.86, 55.08, 52.64, 13.74. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 13.639 min, τ_{minor} = 10.786 min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{24}N_2O_6$, 425.1713; found, 425.1710.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2-oxo-2′-(thiophen-2-yl)spiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3n**).* Yield: 37.0 mg (92%); white solid. mp 148−149 °C; ^{1}H NMR (400 MHz, chloroform-d) δ 7.75 (s, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 7.5 Hz, 1H), 7.07 (dd, J = 15.6, 8.0 Hz, 1H), 7.04 (s, 0H), 6.83−6.77 (m, 2H), 6.67 (d, J = 3.6 Hz, 1H), 4.83 (s, 1H), 4.77 (d, J = 7.6 Hz, 1H), 3.99−3.88 (m, 2H), 3.84 (s, 3H), 3.69 (d, J = 7.6 Hz, 1H), 0.87 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-d) δ: 178.73, 170.88, 170.51, 141.53 (2C), 129.21, 126.65 (2C), 124.73, 124.55, 124.09, 122.85, 109.96, 68.86, 63.09, 61.30, 61.13, 56.75, 52.74, 13.73. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 22.788 min, τ_{minor} = 11.467 min. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{20}H_{20}N_2O_5S$, 401.1171; found, 401.1163.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2-oxo-2′-(thiophen-3-yl)spiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3o**).*

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Yield: 35.2 mg (88%); white solid. mp 154−155 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.99 (s, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.11 (t, J = 8.3 Hz, 1H), 7.06−6.99 (m, 2H), 6.97 (t, J = 8.1 Hz, 1H), 6.73 (dd, J = 4.9, 1.5 Hz, 1H), 6.70 (d, J = 7.7 Hz, 1H), 4.69 (s, 1H), 4.43 (d, J = 10.3 Hz, 1H), 4.25 (d, J = 10.2 Hz, 1H), 3.90 (s, 3H), 3.80−3.59 (m, 2H), 0.64 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ: 179.47, 171.28, 170.64, 141.50 (2C), 135.76, 128.99, 127.48, 125.41, 123.91, 122.71, 121.62, 109.98, 69.63, 63.39, 61.28, 61.20, 57.02, 52.64, 13.74. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 20.417 min, τ_{minor} = 11.674 min. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{20}H_{20}N_2O_5S$, 401.1171; found, 401.1167.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2′-(naphthalen-1-yl)-2-oxospiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3p**).* Yield: 37.0 mg (83%); white solid. mp 166−168 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.77−7.67 (m, 2H), 7.57 (d, J = 8.5 Hz, 1H), 7.52 (s, 1H), 7.48−7.42 (m, 2H), 7.42−7.37 (m, 1H), 7.27 (d, J = 7.7 Hz, 1H), 7.20−7.11 (m,2 H), 6.89 (d, J = 8.5 Hz, 1H), 6.67 (d, J = 7.7 Hz, 1H), 4.85 (d, J = 8.3 Hz, 1H), 4.80 (s, 1H), 3.97 (qt, J = 7.1, 3.8 Hz, 2H), 3.91 (s, 3H), 3.78 (d, J = 8.3 Hz, 1H), 0.88 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ: 178.68, 171.41, 170.57, 141.19, 133.03, 132.91, 132.41, 128.94, 128.20, 128.02, 127.57, 127.48, 126.04 (2C), 125.37, 124.17, 124.11, 122.75, 109.75, 73.20, 63.21, 61.69, 61.16, 56.90, 52.70, 13.74. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 14.899 min, τ_{minor} = 8.093 min. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{26}H_{24}N_2O_5$, 445.1763; found, 445.1756.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2′-(naphthalen-2-yl)-2-oxospiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3q**).* Yield: 38.0 mg (86%); white solid. mp 161−163 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.65 (ddd, J = 9.6, 6.3, 3.2 Hz, 2H), 7.58 (s, 1H), 7.46 (d, J = 12.1 Hz, 2H), 7.39−7.35 (m, 2H), 7.35−7.32 (m,1H), 7.20 (t, J = 7.7 Hz, 1H), 7.10 (t, J = 7.7 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 6.58 (d, J = 7.7 Hz, 1H), 4.78 (d, J = 8.4 Hz, 1H), 4.72 (s, 1H), 3.96−3.84 (m, 2H), 3.84 (s, 3H), 3.72 (d, J = 8.4 Hz, 1H), 0.82 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ: 178.72, 171.38, 170.51, 141.21, 132.99, 132.88, 132.44, 128.88, 128.14, 128.02, 127.51, 127.44, 125.98 (2C), 125.35, 124.11, 124.07, 122.67, 109.73, 73.14, 63.16, 61.65, 61.09, 56.87, 52.61, 13.69. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 19.448 min, τ_{minor} = 14.029 min. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{26}H_{24}N_2O_5$, 445.1763; found, 445.1748.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2′-cyclohexyl-2-oxospiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3r**).* Yield: 39.0 mg (97%); white solid. mp 158−159 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.25 (s, 1H), 7.21 (t, J = 7.8 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.99 (td, J = 7.6, 1.0 Hz, 1H), 6.87 (d, J = 7.7 Hz, 1H), 4.49 (d, J = 9.0 Hz, 1H), 3.78 (s, 3H), 3.76−3.64 (m, 2H), 3.51 (d, J = 9.1 Hz, 1H), 3.27 (d, J = 9.6 Hz, 1H), 1.76 (dtt, J = 14.3, 11.1, 3.4 Hz, 1H), 1.69−1.64 (m, 1H), 1.53−1.48 (m, 1H), 1.37 (d, J = 9.8 Hz, 1H), 1.30−1.23 (m, 1H), 1.21−1.14 (m, 1H), 0.99 (dddd, J = 29.5, 14.4, 9.0, 3.2 Hz, 5H), 0.73 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 180.34, 171.41, 169.88, 140.64, 128.53, 124.22, 122.57, 109.66, 74.97, 62.67, 60.86, 59.80, 59.51, 52.54, 39.06, 31.77, 29.96 (2C), 26.02, 25.70 (2C), 13.54. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 11.139 min, τ_{minor} = 9.983 min. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{22}H_{28}N_2O_5$, 401.2076; found, 401.2064.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-1-methyl-2-oxo-2′-phenylspiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3s**).* Yield: 38.3 mg (94%); white solid. mp 130−132 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.34−7.24 (m, 2H), 7.13 (d, J = 7.1 Hz, 1H), 7.10 (s, 1H), 7.07 (s, 1H), 6.81 (d, J = 7.0 Hz, 2H), 6.64 (d, J = 7.7 Hz, 1H), 4.76 (d, J = 7.9 Hz, 1H), 4.56 (s, 1H), 3.95 (dddd, J = 17.9, 10.8, 7.1, 3.6 Hz, 2H), 3.86 (s, 3H), 3.65 (d, J = 7.9 Hz, 1H), 2.78 (s, 3H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ: 176.92, 171.43, 170.98, 144.20, 134.43, 128.86, 127.99, 127.82 (2C), 127.15, 126.05 (2C), 123.68, 122.68, 108.05, 73.37, 63.55, 61.75, 61.12, 56.56, 52.64, 25.82, 13.81. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 34.273 min, τ_{minor} = 15.052 min. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{23}H_{24}N_2O_5$, 409.1763; found, 409.1750.

*4′-Ethyl-5′-methyl-(2′S,3R,4′S,5′S)-2-oxo-1,2′-diphenylspiro[indoline-3,3′-pyrrolidine]-4′,5′-dicarboxylate (**3t**).* Yield: 45.1 mg (96%); white solid. mp 139−141 °C; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.39 (d, J = 7.4 Hz, 1H), 7.36−7.32 (m, 2H), 7.30 (d, J = 7.4 Hz, 1H), 7.21 (dd, J = 14.2, 7.6 Hz, 2H), 7.15 (d, J = 7.8 Hz, 2H), 7.13 (s, 1H), 6.87 (d, J = 7.5 Hz, 2H), 6.69 (d, J = 7.3 Hz, 2H), 6.59−6.54 (m, 2H), 4.81 (d, J = 8.0 Hz, 1H), 4.64 (s, 1H), 4.01 (dd, J = 17.3, 7.2 Hz, 2H), 3.85 (s, 3H), 3.78 (d, J = 8.0 Hz, 1H), 0.94 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ: 176.42, 171.25, 170.90, 144.30, 134.32, 133.73, 129.43 (2C), 128.75, 128.15 (2C), 127.99 (2C), 127.01, 126.47 (2C), 126.20 (2C), 123.90, 123.12, 109.28, 74.10, 63.65, 61.94, 61.15, 56.72, 52.61, 13.83. The er was determined by HPLC using a Daicel Chiralpak AD-H [hexane/i-PrOH (50:50)]; flow rate 0.5 mL/min; τ_{major} = 23.421 min, τ_{minor} = 13.861 min. HRMS (ESI) m/z: [M + H]$^+$ calcd for $C_{28}H_{26}N_2O_5$, 471.1920; found, 471.1913.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c00051.

Crystallographic data, NMR, and HPLC spectra (PDF)

Accession Codes

CCDC 2307506 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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