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PAPER

Catalytic asymmetric 1,3-dipolar cycloaddition of *N*-unprotected 2-oxoindolin-3-ylidene derivatives and azomethine ylides for the construction of spirooxindole-pyrrolidines†‡

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Asymmetric 1,3-dipolar cycloaddition of *N*-unprotected 2-oxoindolin-3-ylidene with azomethine ylides for the construction of spirooxindole-pyrrolidines bearing four contiguous stereogenic centers has been achieved with AgOAc/TF-BiphamPhos complexes for the first time. This catalytic system performance well over a broad scope of substrates, providing the synthetically useful adducts in high yields and excellent diastereoselectivities and moderate enantioselectivities.

Introduction

The spirocyclic oxindole-pyrrolidine moiety with up to four contiguous stereogenic centers is the core structure of natural alkaloids and bioactive molecules.[1] Typical examples are the spirotryprostatins A and B,[2] isolated from the fermentation broth of *Aspergillus fumigatus*, salacin,[3] and the synthetic spirooxindole-pyrrolidine analogues (Fig. 1).[4] These optically active spirooxindole-pyrrolidines exhibit a broad array of important biological and potentially valuable pharmaceutical properties, which have inspired organic chemists to pursue efficient synthetic methods for those challenging compounds in the past years.[1b,1c] Distinguished achievements have been reported by Williams employing chiral-auxiliary-induced 1,3-dipolar cycloaddition reaction,[5] Overman using Pd-catalyzed intramolecular Heck reaction[6] and Trost using Pd-catalyzed alkylation reaction.[7] Most recently, Gong reported an elegant organocatalyzed asymmetric 1,3-dipolar cycloaddition reaction between *N*-Boc 2-oxoindolin-3-ylidene derivatives and *in situ* formed azomethine ylides leading to the first asymmetric synthesis of spirooxindole-pyrrolidine derivatives.[8] For *N*-unprotected 2-oxoindolin-3-ylidene derivatives as dipolarophiles in 1,3-dipolar cycloaddition, however, only limited racemic versions were scattered in the literatures.[9]

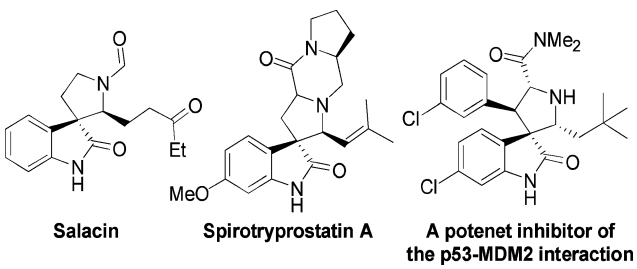

Fig. 1 Representatives of biologically active spriooxindole-containing compounds.

Recently, we reported that Cu(I) or Ag(I)/TF-BiphamPhos complexes exhibited excellent results in asymmetric 1,3-dipolar cycloaddition of azomethine ylides and electron-deficient alkenes.[10] Encouraged by these achievements and stimulated by the biological significance of the spirooxindole-pyrrolidine derivatives[1–4] and the challenging synthetic difficulties associated with regioselectivity, enantioselectivity and diastereoselectivity control,[9] we wondered if our catalytic system could provide straightforward access to such compounds. Interestingly, despite the importance the spirooxindole-pyrrolidine derivatives in the pharmaceutical chemistry, to our knowledge, only one recent report of Waldmann and co-workers presenting the 1,3-dipolar cycloaddition of *N*-unprotected 2-oxoindolin-3-ylidenes and azomethine ylides, which has been published concurrently with the preparation of the present manuscript, in an asymmetric fashion.[11] Herein, we reported Ag(I)/TF-Bipham-Phos catalyzed asymmetric synthesis of spirooxindole-pyrrolidine derivatives containing a unique spiro quaternary stereogenic centers[12] *via* 1,3-dipolar cycloaddition of *N*-unprotected 2-oxoindolin-3-ylidenes and azomethine ylides.

Results and discussion

Our initial studies began with the reaction of 2-oxoindolin-3-benzylidene **4a** with *N*-(4-chlorobenzylidene)-glycine methyl ester **5a** in the presence of $AgOAc/PPh_3$ (5 mol%) and Et_3N (15 mol%).

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‡ Crystal data for (2′*R*,3′*S*,4′*R*,5′*R*)-**6aa**: $C_{25}H_{21}ClN_2O_3$, $M_r = 432.89$, $T = 293$ K, Orthorhombic, space group $P2_12_12_1$, $\alpha = 10.270(3)$, $b = 11.202(3)$, $c = 18.897(6)$ Å, $V = 2174.0(11)$ Å^3, $Z = 4$, 12338 reflections masured, 4250 unique ($R_{int} = 0.0160$) which were used in all caclculations. The final wR_2 = 0.0822 (all data), Flack $\chi = 0.03(6)$. CCDC 775772.

Although this 1,3-dipolar cycloaddition occurred with full conversion, the spirocyclic oxindole-pyrrolidine **6aa** was obtained as the major product contaminated with some unidentified impurities. Switching the ligand from PPh_3 into (±)-TF-BiphamPhos **1a**, we were pleased to find that much cleaner reaction was achieved and the corresponding adduct **6aa** was observed as the sole product (>98:<2 regioselectivity and diastereoselectivity). Encouraged by the result, this cycloaddition reaction was subsequently examined with different metal salts and chiral ligands to establish optimal reaction conditions, and the representative results were summarized in Table 1. Combined with chiral TF-BiphamPhos **1a**, both Ag(I) and Cu(I/II) salts afforded the desired adduct with excellent diastereoselectivity (Table 1, entries 1–4). In general, silver salts gave better enantioselectivity than copper salts, and the adduct **6aa** was achieved with moderate enantioselectivity (60% ee) when using AgOAc/TF-BiphamPhos **1a** as the catalyst (Table 1, entry 1). Due to the fact that almost the same selectivity was achieved with AgOAc and $AgSbF_6$ (Table 1, entries 1 and 2), the easily handled and cost-efficient AgOAc was chose as the metal precursor for the further reaction optimization. Subsequent ligand screening could not improve the enantioselectivity, and ligand **1b–1d** containing the bulky substituents on the phosphorous atom and **1e** bearing two bromine at the 3,3′-position of TF-Bipham backbone showed a litter lower ee values, although the corresponding regio- and diastereoselectivity remained at the same level (Table 1, entries 5–8). Other commercially available chiral ligands were also tested in this transformation: when BINAP/$Cu(CH_3CN)_4BF_4$ and BINAP/AgOAc complexes were employed as the catalyst, 13% ee and 17% ee were observed for the desired adduct **6aa**, respectively; while only 20% ee was achieved when AgOAc or $Cu(CH_3CN)_4BF_4$ was chosen as the metal precursor and (*S*)-Monophos was using as the chiral ligand (Table 1, entries 9–12). The solvent effect was also studied, and CH_2Cl_2 and $CHCl_3$ were revealed to be the two best solvents (Table 1, entries 13–17). Further examination of the base revealed that no significant improvement upon yield and enantioselectivity could be realized with other organic or inorganic base (Table 1, entries 18–20). Reducing the temperature from room temperature to 0 °C did not improve the enantioselectivity (Table 1, entries 21 and 22). Thus, the optimized reaction conditions were established as 5 mol% of AgOAc/**1a** and 15 mol% Et_3N in CH_2Cl_2 or $CHCl_3$ at room temperature.

With the optimal reaction conditions in hand, a series of representative imino esters and 2-oxoindolin-3-ylidenes were next explored to test the substrate scope. As shown in Table 2, a wide array of imino esters derived from various aromatic aldehydes reacted smoothly with 2-oxoindolin-3-benzylidene **4a** to afford the adducts **6aa–6ag** in high yields, excellent diastereoselectivities (>98:<2) and moderate enantioselectivities (50–71% *ee*)[13] (Table 1, entries 1–7). It appears that the position and the electronic property of the substituents on the aromatic rings have very limited effect on the enantioselectivities. Fortunately, enantioenriched compound **6aa** can be easily obtained by direct recrystallization of the crude product in EtOAc (Table 2, entry 1). Prompted by the results of imino esters from aromatic aldehydes, we then investigated the more challenging imino ester **5h** from aliphatic cyclohexanecarbaldehyde, for which no 1,3-dipolar cycloaddition occurred in the literature.[11] To our delight, imino ester **5h** was also compatible with our catalytic system giving the desired adduct **6ah** with 92% yield and 50% ee (Table 2, entry 8). For dipolarophile partners, various 2-oxoindolin-3-ylidenes bearing electron-rich and electron-deficient group on the phenyl ring with different substitution patterns proved to be viable substrates for this reaction, providing high diastereoselectivities and moderate enantioselectivities (Table 2, entries 9–13). 2-Oxoindolin-3-propylidene with alkyl substitution **4g** was also tolerated in this transformation affording the corresponding adduct with good yield and 60% ee (Table 2, entry 14). Methyl oxoindolylidene acetate **4h** directly obtained from istain and Wittig reagent[9,14] worked well in this reaction producing the adduct **6ha** with high region-/diastereoselectivity and moderate enantioselectivity.

The relative and absolute configuration of **6aa** achieved by AgOAc/(*S*)-TF-BiphamPhos **1a** was unequivocally determined as (2′*R*,3*S*,4′*R*,5′*R*) by X-ray diffraction analysis (Fig. 2). Those of other adducts were deduced on the basis of these results. This asymmetric 1,3-dipolar cycloaddition reaction can be explained through the proposed transition state as illustrated in Fig. 3. The *in situ*-formed azomethine ylide is coordinated to the metallic center and oriented in such way to form favored tetracoordinated transition state,[15] followed by cycloaddition with 2-oxoindolin-3-ylidene from *Si* face (C═N) of the azomethine ylide to give the adduct in (2′*R*,3*S*,4′*R*,5′*R*)-configuration, which is compatible with the experimental results. Nevertheless, the real catalytic mechanism still needs further investigation.

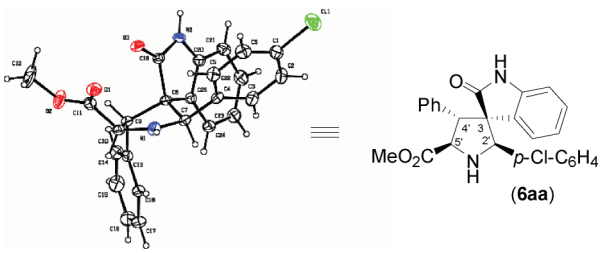


Fig. 2 X-ray structure of **6aa**.

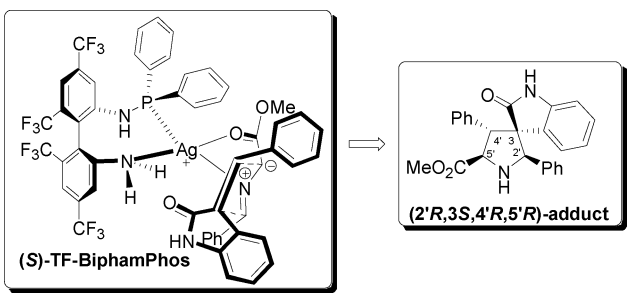


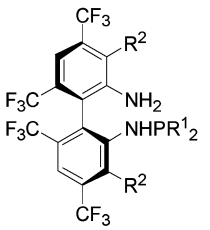
Fig. 3 Proposed transition state using *N*-unprotected 2-oxoindolin-3-benzylidene as dipolarophile.

Conclusion

In summary, we have presented the first example of catalytic asymmetric 1,3-dipolar cycloaddition using *N*-unprotected 2-oxoindolin-3-ylidenes as the dipolarophiles. Although the achieved enantioselectivities were not very high, this study provided a rather simply and high efficient method for the synthesis of multiple functionalized spirooxindole-pyrrolidine derivatives

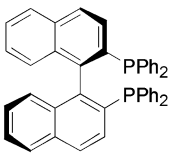
Table 1 Asymmetric 1,3-dipolar cycloaddition of 2-oxoindolin-3-benzylidene **4a** with azomethine ylide **5a**[a]

4a **5a** **6aa**

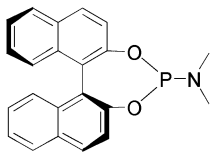


1a: R^1 = Ph, R^2 = H;
1b: R^1 = 3,5-bis(methyl)phenyl, R^2 = H;
1c: R^1 = 3,5-bis(trifluoromethyl)phenyl, R^2 = H;
1d: R^1 = Cy, R^2 = H;
1e: R^1 = Ph, R^2 = Br;

(*S*)-TF-BiphamPhos



(*R*)-BINAP **2**



(*S*)-Monophos **3**

Entry	L	[M][b]	Base	Solvent	*T*/°C	Time (h)	Yield[c] (%)	Ee[d] (%)
1	**1a**	AgOAc	TEA	DCM	rt	3	95	60
2	**1a**	$AgSbF_6$	TEA	DCM	rt	3	80	59
3	**1a**	$CuBF_4$	TEA	DCM	rt	3	93	35
4	**1a**	$Cu(OTf)_2$	TEA	DCM	rt	2	90	40
5	**1b**	AgOAc	TEA	DCM	rt	3	87	35
6	**1c**	AgOAc	TEA	DCM	rt	3	83	53
7	**1d**	AgOAc	TEA	DCM	rt	3	80	57
8	**1e**	AgOAc	TEA	DCM	rt	3	73	53
9	**2**	AgOAc	TEA	DCM	rt	8	35	13
10	**2**	$CuBF_4$	TEA	DCM	rt	8	47	17
11	**3**	AgOAc	TEA	DCM	rt	5	81	20
12	**3**	$CuBF_4$	TEA	DCM	rt	5	58	20
13	**1a**	AgOAc	TEA	PhMe	rt	3	70	20
14	**1a**	AgOAc	TEA	THF	rt	5	71	27
15	**1a**	AgOAc	TEA	$CHCl_3$	rt	5	91	59
16	**1a**	AgOAc	TEA	EtOH	rt	5	76	11
17	**1a**	AgOAc	TEA	Et_2O	rt	5	80	7
18	**1a**	AgOAc	DIPEA	DCM	rt	3	83	59
19	**1a**	AgOAc	NBu_3	DCM	rt	5	85	60
20	**1a**	AgOAc	K_2CO_3	DCM	rt	3	74	60
21	**1a**	AgOAc	TEA	DCM	0	3	91	50
22	**1a**	AgOAc	TEA	DCM	−20	6	75	47

[a] The reactions were carried out with 0.20 mmol of **4a** and 0.40 mmol of **5a** in 2 mL CH_2Cl_2. [b] $CuBF_4$ = $Cu(CH_3CN)_4BF_4$. [c] Isolated yield, and >98:<2 regio-/diastereomeric ratio was determined by the crude ^1H NMR. [d] Enantioselectivity was determined by chiral HPLC analysis.

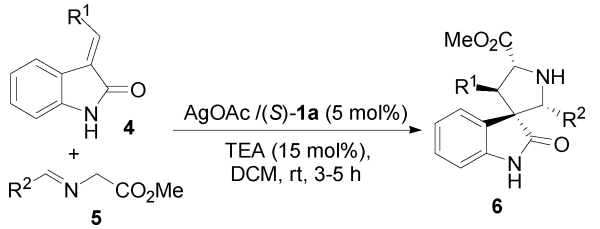
bearing four vicinal stereogenic centers. Efforts are currently underway to elucidate the mechanistic details and the scope and limitations of this reaction, and the results will be reported in due course.

Experimental

General

All reactions were carried out using standard Schlenk techniques unless specified other otherwise. The degassed dry solvents are used throughout each experiment. ^1H NMR spectra were recorded on a VARIAN Mercury 300 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data are reported as (s = single, d = double, t = triple, q = quartet, m = multiple or unresolved, brs = broad single, coupling constant(s) in Hz, integration). ^{13}C NMR spectra were recorded on a VARIAN Mercury 75 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in ppm with the internal chloroform signal at 77.0 ppm as a standard. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with

Table 2 Asymmetric 1,3-dipolar cycloaddition of 2-oxoindolin-3-ylidene **4** with azomethine ylide **5** catalyzed by AgOAc/**1a**[a]



Entry	4	R^1	5	R^2	6	Yield (%)[b]	Ee (%)[c]
1	**4a**	C_6H_5	**5a**	*p*-Cl–C_6H_4	**6aa**	95	60 (99)[d]
4	**4a**	C_6H_5	**5d**	*p*-Br–C_6H_4	**6ad**	80	50
5	**4a**	C_6H_5	**5e**	*o*-Br–C_6H_4	**6ae**	81	59
6	**4a**	C_6H_5	**5f**	*p*-F–C_6H_4	**6af**	84	65
7	**4a**	C_6H_5	**5g**	*p*-Me-C_6H_4	**6ag**	63	71
8	**4a**	C6H5	**5h**	Cy	**6ah**	92	50
9	**4b**	*p*-Cl–C_6H_4	**5a**	*p*-Cl–C_6H_4	**6ba**	91	59
10	**4c**	p-Br-C6H4	**5a**	p-Cl-C6H4	**6ca**	75	50
11	**4d**	*p*-Me-C_6H_4	**5a**	*p*-Cl–C_6H_4	**6da**	89	59
12	**4e**	*p*-MeO-C_6H_4	**5a**	*p*-Cl–C_6H_4	**6ea**	73	61
13	**4f**	*o*-MeO-C_6H_4	**5a**	*p*-Cl–C_6H_4	**6fa**	80	50
14	**4g**	Et	**5a**	*p*-Cl–C_6H_4	**6ga**	85	60
15	**4h**	COOMe	**5a**	p-Cl-C6H4	**6ha**	86	53

[a] All of the reaction was carried out with 0.20 mmol of **4** and 0.40 mmol of **5** in 2 mL of solvent. [b] Isolated yield. [c] Enantiomeric excesses were determined by chiral HPLC analysis. [d] The date in parenthesis was achieved through simply recrystallization in EtOAc.

silica gel-coated plates. Diastereomeric ratios were determined from crude ^{1}H NMR or HPLC analysis. Enantiomeric ratios were determined by HPLC, using a chiralcel AD-H column, a chiralpak AS-H column with hexane and *i*-PrOH as solvents. Ligands **1a–f** were prepared according to the literature procedure reported by us.[10a] 2-Oxoindolin-3-ylidene derivatives were prepared according to the literature procedure.[16] The racemic adducts were attained by using AgOAc/(±)-TF-BiphamPhos as the catalyst. The absolute (2′*R*,3*S*,4′*R*,5′*R*)-**6aa** achieved by AgOAc/(*S*)-TF-BiphamPhos was determined unequivocally according to the X-ray diffraction analysis, and those of other adducts were deduced on the basis of these results.

Synthetic details

General procedure for racemic 1,3-dipolar cycloaddition of azomethine ylides with 2-oxoindolin-3-ylidene catalyzed by AgOAc/(±)-TF-BiphamPhos complex. Under argon atmosphere, (±)-TF-BiphamPhos **1a** (7.8 mg, 0.012 mmol) and AgOAc (1.7 mg, 0.010 mmol) were dissolved in 2 mL DCM, and stirred at room temperature for about 1 h. Then, imine substrate (0.4 mmol), Et_3N (0.03 mmol) and 2-oxoindolin-3-ylidene (0.2 mmol) were added sequentially. Once starting material was consumed (monitored by TLC), the organic solvent was removed and the residue was purified by column chromatography to give the cycloaddition product (63-95% yield), which was used as the racemic sample for the chiral HPLC analysis.

General procedure for asymmetric 1,3-dipolar cycloaddition of azomethine ylides with 2-oxoindolin-3-ylidene catalyzed by AgOAc/(*S*)-TF-BiphamPhos complex. Under argon atmosphere (*S*)-TF-BiphamPhos **1a** (7.8 mg, 0.012 mmol) and AgOAc (1.7 mg, 0.010 mmol) were dissolved in 2 mL DCM, and stirred at room temperature for about 1 h. Then, imine substrate (0.4 mmol), Et_3N (0.03 mmol) and 2-oxoindolin-3-ylidene (0.2 mmol) were added sequentially. Once starting material was consumed (monitored by TLC), the mixture was filtered through celite and the filtrate was concentrated to dryness. The product purified by column chromatography to give the corresponding cycloaddition product, which was then directly analyzed by chiral HPLC to determine the enantiomeric excess.

(2′*R*,3*S*,4′*R*,5′*R*)-methyl 2′-(4-chlorophenyl)-2-oxo-4′-phenylspiro[indoline-3,3′- pyrrolidine]-5′-carboxylate (6aa). The title compound was prepared according to the general procedure as described above in 95% yield. m.p. 178–180 °C; $[\alpha]_D^{25}$ = +88.2 (*c* 0.82, $CHCl_3$);^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 8.42 (s, 1H), 7.22–7.14 (m, 5H), 6.97–6.81 (m, 5H), 6.64 (t, *J* = 7.5 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 6.02 (d, *J* = 7.2 Hz, 1H), 4.64 (s, 1H), 4.53 (d, *J* = 4.2 Hz, 1H), 4.07 (d, *J* = 4.2 Hz, 1H), 3.74 (s, 3H), 3.47 (brs, 1H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 52.76, 57.06, 64.19, 66.05, 71.76, 109.77, 122.18, 125.23, 127.59, 127.80, 128.03, 128.37, 128.74, 129.03, 133.90, 134.61, 138.81, 141.17, 173.25, 179.78; IR (KBr) ν 3684, 3621, 3437, 3019, 2976, 2400, 1738 cm^{-1}. HRMS calcd. for $C_{25}H_{21}ClN_2O_3$+H$^+$: 433.1313, found 433.1305. The product was analyzed by HPLC to determine the enantiomeric excess: 60% ee (Chiralcel AS-H, i-propanol/hexane = 30/70, flow rate 1.0 mL min^{-1}, λ = 254 nm); t_r = 6.00 and 9.72 min.

(2′*R*,3*S*,4′*R*,5′*R*)-methyl 2-oxo-2′,4′-diphenylspiro[indoline-3,3′-pyrrolidine]-5′-carboxylate (6ab). The title compound was prepared according to the general procedure as described above in 70% yield. m.p. 108-110 °C; $[\alpha]_D^{25}$ = +60.4 (*c* 0.90, $CHCl_3$);^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 8.53 (brs, 1H), 7.31–7.21 (m, 4H), 7.13–6.98 (m, 5H), 6.92 (d, *J* = 7.2 Hz, 2H), 6.67 (t, *J* = 7.5 Hz, 1H), 6.55 (d, *J* = 7.8 Hz, 1H), 6.04 (d, *J* = 7.2 Hz, 1H), 4.72 (s, 1H), 4.60 (d, *J* = 5.1 Hz, 1H), 4.14 (d, *J* = 4.8 Hz, 1H), 3.79 (s, 3H);^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 52.81, 57.33, 64.28, 66.25, 72.47, 109.69, 122.02, 125.34, 126.61, 127.67, 127.81, 128.25, 128.81, 129.18; 135.56, 139.31, 141.45, 173.32, 180.29; IR (KBr) ν 3683, 3621, 3438, 3019, 2976, 2400, 1736, 1712 cm^{-1}. HRMS calcd. for $C_{25}H_{22}N_2O_3$+H$^+$: 399.1703, found 399.1696. The product was analyzed by HPLC to determine the enantiomeric excess: 58% ee (Chiralcel AD-H, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm); t_r = 10.59 and 12.28 min.

(2′*R*,3′*S*,4′*R*,5′*R*)-methyl 2′-(2-chlorophenyl)-2-oxo-4′-phenylspiro[indoline-3,3′-pyrrolidine]-5′-carboxylate (6ac). The title compound was prepared according to the general procedure as described above in 84% yield. m.p. 167–168 °C; $[\alpha]_D^{25}$ = –3.0 (*c* 0.98, $CHCl_3$);^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 8.09 (s, 1H), 8.06 (d, *J* = 4.5 Hz, 1H), 7.30 (m, 1H), 7.15–7.03 (m, 9H), 6.94 (m, 1H), 6.56 (d, *J* = 7.5 Hz, 1H), 5.27 (s 1H), 4.73 (d, *J* = 8.1 Hz, 1H), 4.09 (d, *J* = 9.0 Hz, 1H), 3.72 (s, 3H);^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 52.73, 56.65, 63.90, 64.15, 66.47, 109.83, 122.22, 125.22, 127.13, 127.76, 128.30, 128.45, 128.90, 129.12, 129.49, 129.66, 133.80, 135.38, 136.91, 140.67, 173.71, 178.22; IR (KBr) ν 3683, 3620, 3439, 3019, 2976, 2400, 1731 cm^{-1}. HRMS calcd. for $C_{25}H_{21}ClN_2O_3$+H$^+$: 433.1313, found 433.1310. The product was analyzed by HPLC to determine the enantiomeric excess:

65% ee (Chiralcel AD-H, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm); t_r = 9.77 and 13.32 min.

(2′*R*,3′*S*,4′*R*,5′*R*)-methyl 2′-(4-bromophenyl)-2-oxo-4′-phenylspiro[indoline-3,3′-pyrrolidine]-5′-carboxylate (6ad). The title compound was prepared according to the general procedure as described above in 86% yield. m.p. 152–153 °C; $[\alpha]_D^{25}$ = +71.4 (*c* 1.20, $CHCl_3$);^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.97 (s, 1H), 7.34–7.20 (m, 7H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.69 (t, *J* = 7.8 Hz, 1H), 6.10 (d, *J* = 7.5 Hz, 1H), 6.01 (d, *J* = 7.5 Hz, 1H), 4.72 (s, 1H), 4.64 (d, *J* = 4.8 Hz, 1H), 4.16 (d, *J* = 4.5 Hz, 1H), 3.82 (s, 3H);^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 52.83, 57.01, 64.16, 66.10, 71.76, 109.87, 122.18, 122.21, 125.25, 127.47, 127.89, 128.43, 128.49, 128.82, 129.12, 131.32, 135.13, 138.97, 141.34, 173.42, 180.05; IR (KBr) ν 3684, 3621, 3436, 3019, 2976, 2400, 1713 cm^{-1}. HRMS calcd. for $C_{25}H_{21}BrN_2O_3$+H$^+$: 477.0808 found 477.0800. The product was analyzed by HPLC to determine the enantiomeric excess: 59% ee (Chiralcel AD-H, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm); t_r = 12.76 and 17.87 min.

(2′*R*,3′*S*,4′*R*,5′*R*)-methyl 2′-(2-bromophenyl)-2-oxo-4′-phenyl spiro[indoline-3,3′-pyrrolidine]-5′-carboxylate (6ae). The title compound was prepared according to the general procedure as described above in 63% yield. m.p. 160–162 °C; $[\alpha]_D^{25}$ = −12.6 (*c* 0.86, $CHCl_3$);^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 8.04 (d, *J* = 7.8 Hz, 1H), 7.76 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 2H), 7.16–6.93 (m, 8H), 6.58 (d, *J* = 7.8 Hz, 1H), 5.38 (s 1H), 4.85 (d, *J* = 8.1 Hz, 1H), 4.01 (d, *J* = 8.7 Hz, 1H), 3.75 (s, 3H);^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 52.77, 56.54, 63.87, 63.94, 68.73, 109.82, 122.29, 124.46, 125.19, 127.76, 127.80, 128.27, 128.53, 128.91, 129.28, 129.83, 129.99, 132.43, 134.91, 138.73, 140.60, 173.67, 177.83; IR (KBr) ν 3618, 3019, 2976, 2399, 1733, 1216 cm^{-1}. HRMS calcd. for $C_{25}H_{21}BrN_2O_3$+H$^+$: 477.0808 found 477.0810,. The product was analyzed by HPLC to determine the enantiomeric excess: 71% ee (Chiralcel AD-H, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm); t_r = 10.80 and 13.67 min.

(2′*R*,3′*S*,4′*R*,5′*R*)-methyl 2′-(4-fluorophenyl)-2-oxo-4′-phenylspiro[indoline-3,3′-pyrrolidine]-5′-carboxylate (6af). The title compound was prepared according to the general procedure as described above in 80% yield. m.p. 89–90 °C; $[\alpha]_D^{25}$ = +67.9 (*c* 1.12, $CHCl_3$);^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 8.53 (s, 1H), 7.24–7.13 (m, 5H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.86–6.82 (m, 2H), 6.65–6.58 (m, 3H), 6.52 (d, *J* = 7.5 Hz, 1H), 5.95 (d, *J* = 7.2 Hz, 1H), 4.62 (s, 1H), 4.52 (d, *J* = 4.8 Hz, 1H), 4.06 (d, *J* = 4.5 Hz, 1H), 3.72 (s, 3H);^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 52.30, 56.72, 63.80, 65.71, 71.43, 76.41, 109.22, 114.53, 114.81, 121.70, 124.85, 127.10, 127.37, 127.81, 127.91, 128.35, 128.65, 131.08, 138.68, 140.90, 160.49, 163.76, 172.86, 179.68; IR (KBr) ν 3683, 3621, 3437, 3019, 2975, 2400, 1734, 1713 cm^{-1}. HRMS calcd. for $C_{25}H_{21}FN_2O_3$+H$^+$:,417.1609 found 417.1603. The product was analyzed by HPLC to determine the enantiomeric excess: 50% ee (Chiralcel AD-H, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm); t_r = 10.33 and 12.67 min.

(2′*R*,3′*S*,4′*R*,5′*R*)-methyl 2-oxo-4′-phenyl-2′-p-tolylspiro-[indoline-3,3′-pyrroli-dine]-5′-carboxylate (6ag). The title compound was prepared according to the general procedure as described above in 81% yield. m.p. 143–144 °C; $[\alpha]_D^{25}$ = +72.8 (*c* 1.20, $CHCl_3$);^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 8.45 (s, 1H), 7.33–7.23 (m, 5H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.86 (m, 4H), 6.69 (t, *J* = 7.8 Hz, 1H), 6.56 (d, *J* = 7.5 Hz, 1H), 6.07 (d, *J* = 7.5 Hz, 1H), 4.72 (s 1H), 4.63 (d, *J* = 4.8 Hz, 1H), 4.16 (d, *J* = 4.5 Hz, 1H), 3.82 (s, 3H), 2.19 (s, 3H),; ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 21.34, 52.81, 57.44, 64.27, 66.21, 72.33, 109.68, 122.00, 125.32, 126.54, 127.80, 128.17, 128.79, 129.00, 129.20, 132.60, 137.80, 139.34, 141.42, 173.27, 180.32; IR (KBr) ν 3683, 3619, 3437, 3019, 2976, 2400, 1738 cm^{-1}. HRMS calcd. for $C_{26}H_{24}N_2O_3$+H$^+$: 413.1860 found 413.1857. The product was analyzed by HPLC to determine the enantiomeric excess: 59% ee (Chiralcel AD-H, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm); t_r = 11.41 and 17.69 min.

(2′*R*,3′*S*,4′*R*,5′*R*)-methyl 2′-cyclohexyl-2-oxo-4′-phenylspiro-[indoline-3,3′-pyrro-lidine]-5′-carboxylate (6ah). The title compound was prepared according to the general procedure as described above in 92% yield. m.p. 178–179 °C; $[\alpha]_D^{25}$ = −5.4 (*c* 0.32, $CHCl_3$);^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.10–6.93 (m, 6H), 6.68–6.60 (m, 2H), 6.22 (d, *J* = 5.7 Hz, 1H), 4.39 (d, *J* = 5.1 Hz, 1H), 3.87 (d, *J* = 7.5 Hz, 1H), 3.65 (s, 3H), 3.40 (d, *J* = 8.1 Hz, 1H), 2.07–0.78 (m, 11H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 25.92, 26.25, 30.22, 32.01, 39.73, 52.60, 61.16, 62.09, 64.90, 73.74, 109.55, 121.94, 125.27, 127.44, 127.81, 128.31, 128.74, 130.40, 137.90, 172.70, 181.53; HRMS calcd. for $C_{25}H_{28}N_2O_3$+H$^+$: 405.2172 found 405.2171. The product was analyzed by HPLC to determine the enantiomeric excess: 50% ee (Chiralcel AD-H, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm); t_r = 6.01 and 13.27 min.

(2′*R*,3′*S*,4′*R*,5′*R*)-methyl 2′,4′-bis(4-chlorophenyl)-2-oxospiro [indoline-3,3′-pyrrolidine]-5′-carboxylate (6ba). The title compound was prepared according to the general procedure as described above in 91% yield. m.p. 152–154 °C; $[\alpha]_D^{25}$ = +81.3 (*c* 0.88, $CHCl_3$);^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.84 (s, 1H), 7.30–7.06 (m, 7H), 6.67 (t, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 6.18 (d, *J* = 7.8 Hz, 1H), 4.66 (s 1H), 4.54 (d, *J* = 5.1 Hz, 1H), 4.10 (d, *J* = 6.0 Hz, 1H), 3.80 (s, 3H);^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 51.60, 55.19, 62.83, 64.63, 70.43, 109.77, 121.18, 123.89, 126.14, 126.75, 127.14, 127.41, 127.66, 129.13, 132.35, 132.68, 133.30, 135.94, 140.05, 171.81, 178.61; IR (KBr) ν 3684, 3620, 3436, 3019, 2976, 2400, 1734, 1716 cm^{-1}. HRMS calcd. for $C_{25}H_{20}Cl_2N_2O_3$+H$^+$: 467.0924 found 467.0914. The product was analyzed by HPLC to determine the enantiomeric excess: 59% ee (Chiralcel AD-H, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm); t_r = 11.04 and 13.84 min.

(2′*R*,3′*S*,4′*R*,5′*R*)-methyl 4′-(4-bromophenyl)-2′-(4-chlorophenyl)-2-oxospiro[indoline-3,3′-pyrrolidine]-5′-carboxylate (6ca). The title compound was prepared according to the general procedure as described above in 75% yield. m.p. 159–160 °C; $[\alpha]_D^{25}$ = +183.2 (*c* 0.78, $CHCl_3$);^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 8.04 (s, 1H), 7.42 (d, *J* = 7.5 Hz, 2H), 7.10–7.05 (m, 5H), 6.98 (d, *J* = 7.2 Hz, 2H), 6.78 (t, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 6.21 (d, *J* = 7.2 Hz, 1H), 4.68 (s, 1H), 4.55 (d, *J* = 5.7 Hz, 1H), 4.10 (d, *J* = 5.1 Hz, 1H), 3.81 (s, 3H);^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 51.59, 55.27, 62.78, 64.55, 70.43, 108.79, 120.50, 123.88, 126.16, 126.75, 127.13, 127.41, 129.48, 130.59, 132.66, 133.34, 136.44, 140.06, 171.82, 178.61; IR (KBr) ν 3683, 3620, 3437, 3018, 2976, 2400, 1733, 1716 cm^{-1}. HRMS calcd. for $C_{25}H_{20}BrClN_2O_3$+H$^+$: 511.0419 found 511.0415. The product

was analyzed by HPLC to determine the enantiomeric excess: 50% ee (Chiralcel AD-H, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm); t_r = 11.57 and 14.26 min.

(2′*R*,3′*S*,4′*R*,5′*R*)-methyl 2′-(4-chlorophenyl)-2-oxo-4′-p-tolyl-spiro[indoline-3,3′-pyrrolidine]-5′-carboxylate (6da). The title compound was prepared according to the general procedure as described above in 89% yield. $[\alpha]_D^{25}$ = +94.2 (*c* 0.94, $CHCl_3$);^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 8.17 (s, 1H), 7.03–6.96 (m, 7H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.64 (t, *J* = 7.5 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 6.02 (d, *J* = 7.8 Hz, 1H), 4.63 (s, 1H), 4.52 (d, *J* = 5.1 Hz, 1H), 4.04 (d, *J* = 4.8 Hz, 1H), 3.73 (s, 3H), 2.27 (s, 3H);^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 21.37, 52.96, 56.46, 63.96, 66.12, 71.49, 109.70, 122.35, 125.48, 127.05, 128.08, 128.52, 128.97, 129.56, 134.18, 135.73, 137.66, 141.02, 172.90, 179.48; IR (KBr) ν 3684, 3621, 3019, 2976, 2400, 1716 cm^{-1}. HRMS calcd. for $C_{26}H_{23}ClN_2O_3$+H^+: 447.1470 found 447.1470. The product was analyzed by HPLC to determine the enantiomeric excess: 50% ee (Chiralcel AD-H, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm); t_r = 9.29 and 14.22 min.

(2′*R*,3′*S*,4′*R*,5′*R*)-methyl 2′-(4-chlorophenyl)-4′-(4-methoxy-phenyl)-2-oxospiro-[indoline-3,3′-pyrrolidine]-5′-carboxylate (6ea). The title compound was prepared according to the general procedure as described above in 73% yield. m.p. 148–150 °C; $[\alpha]_D^{25}$ = +239.2 (*c* 1.24, $CHCl_3$);^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 8.39 (s, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.07–7.00 (m, 3H), 6.88–6.80 (m, 4H), 6.72 (t, *J* = 7.8 Hz, 1H), 6.57 (d, *J* = 7.8 Hz, 1H), 6.13 (d, *J* = 7.5 Hz, 1H), 4.67 (s, 1H), 4.53 (d, *J* = 4.8 Hz, 1H), 4.08 (d, *J* = 4.8 Hz, 1H), 3.78 (s, 6H);^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 52.83, 55.54, 56.40, 64.31, 66.39, 71.73, 109.80, 114.12, 122.32, 125.43, 127.61, 128.07, 128.42, 130.17, 131.02, 133.93, 134.55, 141.27, 159.13, 173.38, 179.92; IR (KBr) ν 3684, 3621, 3437, 3019, 2976, 2400, 1734, 1713 cm^{-1}. HRMS calcd. for $C_{26}H_{23}ClN_2O_4$+H^+: 463.1419 found 463.1406. The product was analyzed by HPLC to determine the enantiomeric excess: 65% ee (Chiralcel AD-H, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm); t_r = 12.03 and 18.27 min.

(2′*R*,3′*S*,4′*R*,5′*R*)-methyl 2′-(4-chlorophenyl)-4′-(2-methoxy-phenyl)-2-oxospiro-[indoline-3,3′-pyrrolidine]-5′-carboxylate (6fa). The title compound was prepared according to the general procedure as described above in 80% yield. m.p. 184–186 °C; $[\alpha]_D^{25}$ = +47.6 (*c* 1.14, $CHCl_3$);^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 8.04 (s, 1H), 7.60 (d, *J* = 7.2 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.01–7.00 (m, 4H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.64 (t, *J* = 8.1 Hz, 2H), 6.53 (d, *J* = 8.1 Hz, 1H), 6.15 (d, *J* = 7.8 Hz, 1H), 4.73 (d, *J* = 8.1 Hz, 1H), 4.48 (s, 1H), 4.39 (d, *J* = 8.1 Hz, 1H), 3.81 (s, 3H), 3.16 (s, 3H);^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 52.43, 52.77, 54.26, 63.17, 64.04, 72.10, 109.44, 110.00, 120.32, 121.70, 124.07, 126.76, 126.93, 127.87, 128.22, 128.49, 129.02, 133.66, 134.31, 141.78, 157.26, 172.73, 181.61; IR (KBr) ν 3684, 3620, 3436, 3019, 2976, 2400, 1734, 1716 cm^{-1}. HRMS calcd. for $C_{26}H_{23}ClN_2O_4$+H^+: 463.1419 found 463.1413. The product was analyzed by HPLC to determine the enantiomeric excess: 60% ee (Chiralcel AD-H, i-propanol/hexane = 30/70, flow rate 1.0 mL min^{-1}, λ = 254 nm); t_r = 8.46 and 32.28 min.

(2′*R*,3′*S*,4′*R*,5′*R*)-methyl 2′-(4-chlorophenyl)-4′-ethyl-2-oxo-spiro[indoline-3,3′-pyrrolidine]-5′-carboxylate (6ga). The title compound was prepared according to the general procedure as described above in 85% yield. m.p. 94–96 °C; $[\alpha]_D^{25}$ = +59.1 (*c* 1.20, $CHCl_3$);^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 8.18 (br s, 1H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.09–6.98 (m, 3H), 6.78 (d, *J* = 8.1 Hz, 2H), 6.69 (t, *J* = 8.1 Hz, 1H), 4.41 (s, 1H), 3.81 (s, 1H), 3.79 (s, 3H), 3.17 (br s, 1H), 2.61 (q, *J* = 7.8 Hz, 1H), 1.69–1.53 (m, 2H), 0.55 (t, *J* = 7.2 Hz, 3H);^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 12.35, 24.18, 31.21, 52.80, 54.93, 62.80, 66.97, 72.19, 110.30, 122.66, 125.19, 127.84, 128.34, 128.72, 129.02, 133.81, 134.49, 172.73, 180.62; IR (KBr) ν 3684, 3620, 3436, 3019, 2976, 2400, 1734, 1716 cm^{-1}. HRMS calcd. for $C_{21}H_{21}ClN_2O_3$+H^+: 385.1314 found 385.1311. The product was analyzed by HPLC to determine the enantiomeric excess: 49% ee (Chiralcel AD-H, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm); t_r = 13.80 and 21.99 min.

(2′*R*,3′*S*,4′*R*,5′*R*)-dimethyl 2′-(4-chlorophenyl)-2-oxospiro-[indoline-3,3′-pyrro-lidine]-4′,5′-dicarboxylate (6ha). The title compound was prepared according to the general procedure as described above in 80% yield. m.p. 132–134 °C; $[\alpha]_D^{25}$ = +64.4 (*c* 0.82, $CHCl_3$);^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 8.16 (br s, 1H), 7.19 (d, *J* = 7.2 Hz, 1H), 7.04–6.99 (m, 3H), 6.75 (d, *J* = 8.1 Hz, 2H), 6.68 (t, *J* = 7.8 Hz, 1H), 4.70 (d, *J* = 7.5 Hz, 1H), 4.50 (s, 1H), 3.77 (s, 3H), 3.61 (d, *J* = 7.5 Hz, 1H), 3.38 (s, 3H);^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 52.00, 52.54, 55.92, 61.17, 62.65, 71.70, 110.06, 122.60, 123.44, 126.75, 127.40, 127.98, 128.98, 132.62, 133.74, 141.04, 170.87, 178.66; IR (KBr) ν 3684, 3620, 3436, 3019, 2976, 2400, 1734, 1716 cm^{-1}. HRMS calcd. for $C_{21}H_{20}ClN_2O_5$+H^+: 415.1055 found 415.1050. The product was analyzed by HPLC to determine the enantiomeric excess: 60% ee (Chiralcel AD-H, i-propanol/hexane = 20/80, flow rate 1.0 mL min^{-1}, λ = 254 nm); t_r = 23.24 and 35.05 min.

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