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

Tang-Lin Liu,^a Zhi-Yong Xue,^a Hai-Yan Tao^a and Chun-Jiang Wang^{*a,b}

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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



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

tiguous stereogenic centers has been 2. This catalytic system performance eful adducts in high yields and reported by Williams employing chiral-auxiliary-induced 1,3dipolar cycloaddition reaction,⁵ Overman using Pd-catalyzed intramolecular Heck reaction⁶ 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 2oxoindolin-3-ylidene derivatives as dipolarophiles in 1,3-dipolar cycloaddition, however, only limited racemic versions were scattered in the literatures.⁹

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 derivatives1-4 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 Nunprotected 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 centers¹² 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-3benzylidene **4a** with N-(4-chlorobenzylidene)-glycine methyl ester **5a** in the presence of AgOAc/PPh₃ (5 mol%) and Et₃N (15 mol%).

^aCollege of Chemistry and Molecular Sciences, Wuhan University, Wuhan, 430072, China. E-mail: cjwang@whu.edu.cn; Fax: +86-27-68754067

^bState Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin, 300071, China

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[‡] Crystal data for (2'*R*,3'*S*,4'*R*,5'*R*)-6aa: C₂₅H₂₁ClN₂O₃, M_r = 432.89, *T* = 293 K, Orthorhombic, space group *P*₂₁2₁2₁, α = 10.270(3), *b* = 11.202(3), *c* = 18.897(6) Å, *V* = 2174.0(11) Å³, *Z* = 4, 12338 reflections masured, 4250 unique (*R*_{int} = 0.0160) which were used in all caclculations. The final w*R*₂ = 0.0822 (all data), Flack χ = 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 PPh₃ into (\pm) -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 AgSbF₆ (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(CH₃CN)₄BF₄ 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(CH₃CN)₄BF₄ 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 CH₂Cl₂ and CHCl₃ 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% Et₃N in CH₂Cl₂ or CHCl₃ 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,3S,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,3S,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-oxoin-dolin-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 1Asymmetric 1,3-dipolar cycloaddition of 2-oxoindolin-3-benzylidene 4a with azomethine ylide $5a^{a}$



^{*a*} The reactions were carried out with 0.20 mmol of **4a** and 0.40 mmol of **5a** in 2 mL CH₂Cl₂. ^{*b*} CuBF₄ = Cu(CH₃CN)₄BF₄. ^{*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 CDCl₃. 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). ¹³C NMR spectra were recorded on a VARIAN Mercury 75 MHz spectrometer in CDCl₃. 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

R ²			DAc TE/ DC	(S)-1a (5 mol%), (15 mol%), M, rt, 3-5 h			
Entry	4	R ¹	5	\mathbb{R}^2	6	Yield (%) ^b	Ee (%) ^c
1	4a	C ₆ H ₅	5a	p-Cl-C ₆ H ₄	6aa	95	60 (99) ^d
4	4a	C_6H_5	5d	p-Br-C ₆ H ₄	6ad	80	50
5	4a	C_6H_5	5e	o-Br-C ₆ H 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 ₆ H ₄	6ag	63	71
8	4a	C6H5	5h	Cy	6ah	92	50
9	4b	p-Cl–C ₆ H 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 ₆ H ₄	5a	p-Cl–C ₆ H ₄	6da	89	59
12	4e	p-MeO-C ₆ H ₄	5a	p-Cl–C ₆ H ₄	6ea	73	61
13	4f	o-MeO-C ₆ H ₄	5a	p-Cl–C ₆ H ₄	6fa	80	50
14	4g	Et	5a	p-Cl–C ₆ H ₄	6ga	85	60
15	4h	COOMe	5a	p-Cl-C6H4	6ha	86	53

Table 2Asymmetric 1,3-dipolar cycloaddition of 2-oxoindolin-3-ylidene4 with azomethine ylide 5 catalyzed by $AgOAc/1a^{\alpha}$

^{*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 ¹H 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/(\pm)-TF-BiphamPhos complex. Under argon atmosphere, (\pm)-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), Et₃N (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), Et₃N (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,3S,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, CHCl₃);¹H NMR (CDCl₃, 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 (CDCl₃, 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) v 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,3S,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 (CDCl₃, 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);¹³C NMR (CDCl₃, 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) v 3683, 3621, 3438, 3019, 2976, 2400, 1736, 1712 cm⁻¹. HRMS calcd. for C₂₅H₂₂N₂O₃+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, $\lambda = 254$ 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, CHCl₃);¹H NMR (CDCl₃, 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);¹³C NMR (CDCl₃, 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) v 3683, 3620, 3439, 3019, 2976, 2400, 1731 cm⁻¹. HRMS calcd. for C₂₃H₂₁ClN₂O₃+H⁺: 433.1313, found 433.1310. The product was analyzed by HPLC to determine the enantiomeric excess: Downloaded by UNIVERSITY OF ALABAMA AT BIRMINGHAM on 06 January 2013 Published on 08 December 2010 on http://pubs.rsc.org | doi:10.1039/C0OB00943A 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, CHCl₃);¹H NMR (CDCl₃, 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);¹³C NMR (CDCl₃, 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) v 3684, 3621, 3436, 3019, 2976, 2400, 1713 cm⁻¹. HRMS calcd. for C₂₅H₂₁BrN₂O₃+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, CHCl₃);¹H NMR (CDCl₃, 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);¹³C NMR (CDCl₃, 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) v 3618, 3019, 2976, 2399, 1733, 1216 cm⁻¹. HRMS calcd. for C₂₅H₂₁BrN₂O₃+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, $\lambda = 254$ 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, CHCl₃);¹H NMR (CDCl₃, 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);¹³C NMR (CDCl₃, 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) v 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, $\lambda = 254$ 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, CHCl₃);¹H NMR (CDCl₃, 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),; ¹³C NMR (CDCl₃, 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) v 3683, 3619, 3437, 3019, 2976, 2400, 1738 cm⁻¹. HRMS calcd. for C₂₆H₂₄N₂O₃+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, $\lambda = 254$ 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, CHCl₃);¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₂₅H₂₈N₂O₃+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, $\lambda = 254$ 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, CHCl₃);¹H NMR (CDCl₃, 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);¹³C NMR (CDCl₃, 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) v 3684, 3620, 3436, 3019, 2976, 2400, 1734, 1716 cm⁻¹. HRMS calcd. for C₂₅H₂₀Cl₂N₂O₃+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, $\lambda = 254$ 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; $[\alpha]_D^{25} = +183.2 (c \ 0.78, CHCl_3);^1H NMR (CDCl_3, TMS, 300 MHz) <math>\delta$ 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);¹³C 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) v 3683, 3620, 3437, 3018, 2976, 2400, 1733, 1716 cm⁻¹. HRMS calcd. for C₂₅H₂₀BrClN₂O₃+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, $\lambda = 254$ 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-tolylspiro[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 (CDCl₃, 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);¹³C NMR (CDCl₃, 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) v 3684, 3621, 3019, 2976, 2400, 1716 cm⁻¹. HRMS calcd. for C₂₆H₂₃ClN₂O₃+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, $\lambda = 254$ nm); t_r = 9.29 and 14.22 min.

(2'R, 3'S, 4'R, 5'R)-methyl 2'-(4-chlorophenyl)-4'-(4-methoxyphenyl)-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);¹³C NMR (CDCl₃, 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) v 3684, 3621, 3437, 3019, 2976, 2400, 1734, 1713 cm⁻¹. HRMS calcd. for $C_{26}H_{23}CIN_2O_4+H^+$: 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, $\lambda = 254$ nm); t_r = 12.03 and 18.27 min.

(2'R, 3'S, 4'R, 5'R)-methyl 2'-(4-chlorophenyl)-4'-(2-methoxyphenyl)-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);¹³C NMR (CDCl₃, 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) v 3684, 3620, 3436, 3019, 2976, 2400, 1734, 1716 cm⁻¹. HRMS calcd. for $C_{26}H_{23}CIN_2O_4+H^+$: 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, $\lambda = 254$ nm); t_r = 8.46 and 32.28 min.

(2'*R*,3'*S*,4'*R*,5'*R*)-methyl 2'-(4-chlorophenyl)-4'-ethyl-2-oxospiro[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, CHCl₃);¹H NMR (CDCl₃, 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);¹³C NMR (CDCl₃, 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) v 3684, 3620, 3436, 3019, 2976, 2400, 1734, 1716 cm⁻¹. HRMS calcd. for C₂₁H₂₁ClN₂O₃+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, CHCl₃);¹H NMR (CDCl₃, 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);¹³C NMR (CDCl₃, 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) v 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, $\lambda = 254$ nm); t_r = 23.24 and 35.05 min.

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