Advanced Synthesis & Catalysis

Accepted Article

Title: Asymmetric [3+2] Annulations to Construct 1,2-Bispirooxindoles Incorporating a Dihydropyrrolidine Motif

Authors: Qing He, Wei Du, and Ying-Chun Chen

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201700849

Link to VoR: http://dx.doi.org/10.1002/adsc.201700849

10.1002/adsc.201700849

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Asymmetric [3+2] Annulations to Construct 1,2-Bispirooxindoles Incorporating a Dihydropyrrolidine Motif

Qing He,[a] Wei Du,[a] and Ying-Chun Chen[a,b]*

[a] Department of Medicinal Chemistry, West China School of Pharmacy, Sichuan University, Chengdu 610041, People's Republic of China
Fax: (+86)-28-8550-2609; e-mail: ycchen@scu.edu.cn
[b] College of Pharmacy, Third Military Medical University, Chongqing 400038, People's Republic of China

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract: Constructing chiral bispirooxindoles is difficult to achieve but highly attractive owing to their many potential applications in medicinal chemistry. Here we present an asymmetric [3+2] annulation reaction of Morita–Baylis–Hillman carbonates from isatins and isatin-based *N*-Boc ketimines under the catalysis of the newly designed multifunctional 4-dimethylaminopyridine-type substance. The reaction shows high γ-regioselectivity, producing highly complex 1,2-bispirooxindoles incorporating a dihydropyrrolidine motif in excellent yields with moderate to outstanding stereoselectivity (*dr* >19:1, up to >99% *ee*). This protocol has been expanded to utilize trifluoromethyl-containing ketimines, delivering complicated architectures with fused and spirocyclic frameworks in modest enantioselectivity.

Keywords: bispirooxindoles; Morita–Baylis–Hillman carbonates; ketimines; [3+2] annulations; tetrasubstituted stereogenic center; Lewis base catalysis.

Introduction

Spirocyclic oxindoles incorporating a pyrrolidine motif are ubiquitous in natural products and synthetic bioactive substances.[1] Furthermore, the introduction of another spirocyclic framework into the pyrrolidine skeleton to construct more complex derivatives, especially in an adjacent pattern, draws particular interest, as significant medicinal potentials, such as anti-mycobacterium tuberculosis bacteria (MTB), anti-microbial and anti-tumor functions, were observed (Figure 1).[2] Such scaffolds could be synthesized by using various cycloaddition or annulation-based protocols,[3] while the methodologies of making such architectures asymmetrically are still limited,[4] which is partially due to the challenge imposed by constructing adjacent tetrasubstituted stereogenic centers.[5]

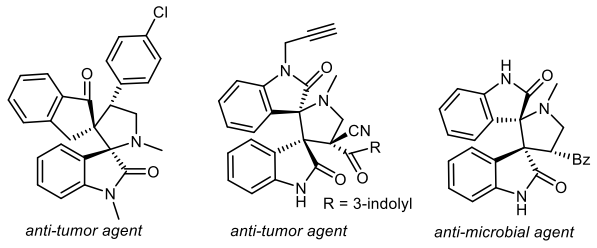
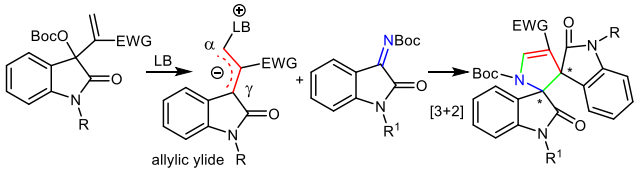


Figure 1. Representative bioactive 3,2′-pyrrolidinylspirooxindoles incorporating an adjacent spirocyclic motif.

Isatin-derived *N*-Boc ketimines are highly electrophilic reagents that have been widely applied to construct chiral 3-aminooxindoles[6] and to make 3,2′-pyrrolidinylspirooxindole derivatives through asymmetric [3+2] annulation reactions.[7] On the other hand, the Morita–Baylis–Hillman[8] (MBH) derivatives of isatins have been demonstrated to be ideal 3C synthons through the formation of zwitterionic allylic ylides with a Lewis base (LB) catalyst, efficiently producing a diversity of spirooxindoles in combination with differently structured electrophiles.[9] Hence it is predicted that the possible assembly of isatin-based ketimines and MBH carbonates of isatins would straightforwardly yield the desired 1,2-bispirooxindoles incorporating a dihydropyrrolidine framework, as illustrated in Scheme 1.

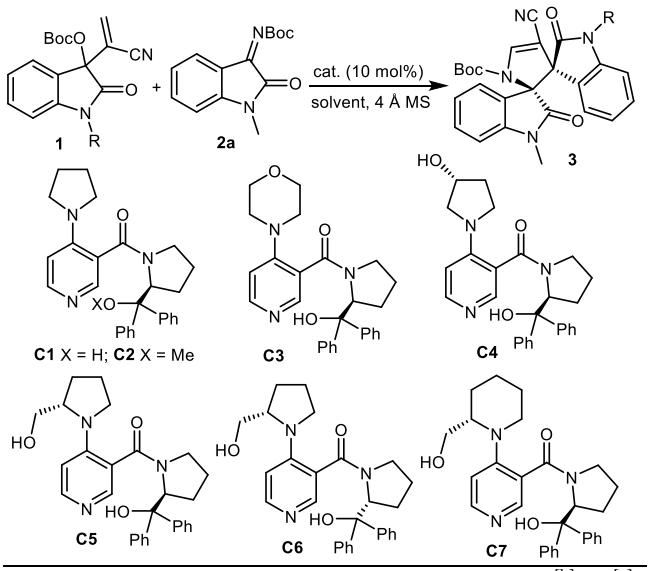


Scheme 1. [3+2] Annulation approach to access 1,2-bispirooxindoles incorporating a dihydropyrrolidine motif.

Results and Discussion

The initial investigation with MBH carbonate **1a** and isatin ketimine **2a** resulted in a complex mixture

Table 1. Screening conditions for the asymmetric [3+2] annulation reactions of **1** and **2a**.[a]

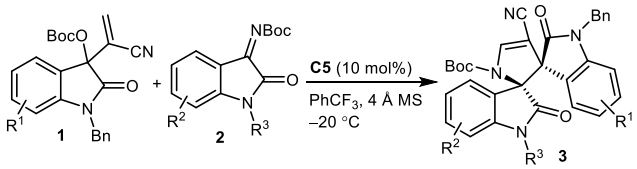


Entry	R	Cat	Solvent	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	Me/**1a**	DABCO	toluene	12	/	/
2	Me/**1a**	Ph_3P	toluene	12	/	/
3	Me/**1a**	DMAP	toluene	0.5	**3a**, 96	/
4	Me/**1a**	**C1**	toluene	0.5	**3a**, 98	39
5	Me/**1a**	**C2**	toluene	1	**3a**, 96	25
6	Me/**1a**	**C3**	toluene	4	**3a**, 98	35
7	Me/**1a**	**C4**	toluene	3	**3a**, 98	61
8	Me/**1a**	**C5**	toluene	3	**3a**, 98	76
9	Me/**1a**	**C6**	toluene	3	**3a**, 98	15
10	Me/**1a**	**C7**	toluene	4	**3a**, 98	65
11[d]	Me/**1a**	**C5**	toluene	24	**3a**, 98	78
12[d]	MOM/**1b**	**C5**	toluene	24	**3b**, 97	85
13[d]	Bn/**1c**	**C5**	toluene	24	**3c**, 98	86
14[d]	Boc/**1d**	**C5**	toluene	24	**3d**, 96	85
15[d]	Bn/**1c**	**C5**	DCE	7	**3c**, 95	91
16[d]	Bn/**1c**	**C5**	$CHCl_3$	20	**3c**, 98	93
17[d]	**Bn/1c**	**C5**	**$PhCF_3$**	**24**	**3c, 98**	**>99**

[a] Unless noted otherwise, reactions were performed using **1** (0.11 mmol), **2a** (0.1 mmol), catalyst (0.01 mmol) and 4 Å MS (50 mg) in solvent (2 mL) at rt.
[b] Yield of isolated product.
[c] Determined by HPLC analysis using a chiral stationary phase; ^{1}H NMR analysis indicated *dr* >19:1.
[d] At –20 °C.

under the catalysis of 1,4-diazabicyclo[2.2.2]octane (DABCO) in toluene at room temperature (Table 1, entry 1), while no apparent conversion was observed in the presence of Ph_3P (Table 1, entry 2), probably because of the bulky tetrahedral feature of the ylide intermediate, inhibiting the formation of the congested 1,2-bispirooxindole structure.[10] In contrast, planar 4-dimethylaminopyridine (DMAP) showed very high catalytic activity and the γ-regioselective [3+2] annulation product **3a** with the desired 1,2-bispirooxindole skeleton was isolated in an almost quantitative yield with exclusive diastereoselectivity (Table 1, entry 3). Subsequently, we explored the asymmetric version by employing some chiral DMAP-type catalysts.[11] As summarized in Table 1, chiral substance **C1** also exhibited excellent catalytic activity but low enantioselectivity (Table 1, entry 4). *O*-methyl ether **C2** showed poorer enantiocontrol (Table 1, entry 5). Subsequently, we further modified the structures of the catalysts. **C3** with a morpholine motif furnished inferior data (Table 1, entry 6). Interestingly, compound **C4** with a hydroxyl group at 3-position of pyrrolidine moiety enhanced the enantioselectivity significantly, indicating that the additional hydrogen-bonding interaction is probably beneficial for the enantiocontrol (Table 1, entry 7). Moreover, the enantioselectivity was further improved by using **C5** with a (*S*)-prolinol motif (Table 1, entry 8). Nevertheless, a very poor *ee* value was obtained for **C6** with mismatched (*S*,*R*)-chirality (Table 1, entry 9). In addition, catalyst **C7** with a piperidine-2-methanol motif delivered lower enantioselectivity (Table 1, entry 10). It was also found that the reaction took longer to complete at –20 °C while a better *ee* was obtained (Table 1, entry 11). The *N*-protection group of the MBH carbonate was further investigated (Table 1, entries 12–14), and high enantioselectivity was observed with an *N*-benzyl group (Table 1, entry 13). The solvent effects were tested as well (Table 1, entries 15–17), and the enantiomerically pure product **3c** was produced in 98% yield in $PhCF_3$ (Table 1, entry 17).

Table 2. Substrate scope of the asymmetric [3+2] annulations of MBH carbonates **1** and ketimines **2**.[a]



Entry	R^1	R^2	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	H	H	24	**3c**, 98	>99
2	5-Cl	H	12	**3e**, 96	95
3	5-Br	H	11	**3f**, 95	96
4	5-I	H	11	**3g**, 97	87
5[d]	5-NO_2	H	24	**3h**, 96	88
6[d]	6-Br	H	48	**3i**, 96	89
7[d]	7-Cl	H	48	**3j**, 97	88
8[e]	5-Me	H	48	**3k**, 96 (72)	79 (98)
9	5-MeO	H	48	**3l**, 96	75
10	5,7-Me_2	H	56	**3m**, 97	76
11	H	5-Me	30	**3n**, 98	95
12	H	5-MeO	30	**3o**, 96	94
13	H	5,7-Me_2	36	**3p**, 96	98
14[d]	5-Cl	5-Cl	72	**3q**, 98	79
15[d]	5-Cl	5-Br	55	**3r**, 95	87
16[d]	5-Cl	5-I	48	**3s**, 97	78
17[d]	5-Cl	6-Br	56	**3t**, 97	88
18[f]	H	H	40	**3u**, 97	97

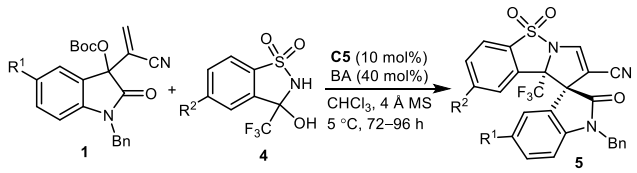
[a] Unless noted otherwise, reactions were performed using **1** (0.11 mmol), **2** (0.1 mmol, R^3 = Me), catalyst **C5** (0.01 mmol) and 4 Å MS (50 mg) in $PhCF_3$ (2 mL) at –20 °C.
[b] Yield of isolated product.
[c] Determined by HPLC analysis using a chiral stationary phase; ^{1}H NMR analysis indicated *dr* >19:1.

[d] In $CHCl_3$ at −40 °C.
[e] Data in parentheses were obtained after recrystallization.
[f] R^3 = Bn.

With the optimized catalytic conditions in hand, the scope and limitations of the new asymmetric reaction were further explored (Table 2). Excellent yields were obtained overall. An array of MBH carbonates **1** with different electron-withdrawing groups on the aryl ring resulted in high to outstanding enantioselectivity in the reactions with ketimine **2a** (Table 2, entries 2–7), while some reaction conditions were tuned accordingly (Table 2, entries 5–7). Nevertheless, the MBH carbonates **1** with electron-donating groups showed lower reactivity and only moderate enantiocontrol (Table 2, entries 8–10). In addition, the optical purity could be improved through recrystallization (Table 2, entry 8).

Substrates **2** with electron-donating substituents provided the corresponding [3+2] products **3n**–**p** in excellent enantioselectivity (Table 2, entries 11–13), while lower enantiocontrol was observed for the ketimines **2** bearing electron-withdrawing groups, even at lower temperature (Table 2, entries 14–17). In addition, ketimine **2** with a bigger *N*-benzyl group also underwent the annulation smoothly (Table 2, entry 18).

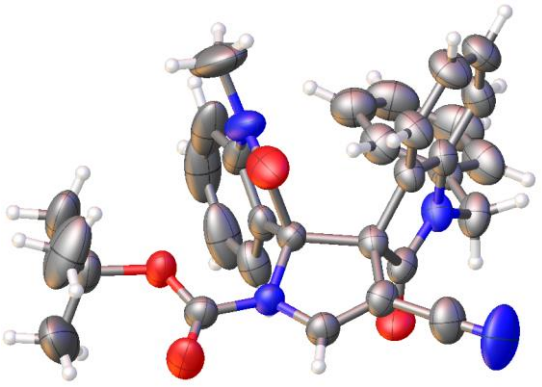
Table 3. Asymmetric [3+2] annulations of MBH carbonates **1** and CF_3-containing hemiaminals **4**.[a]



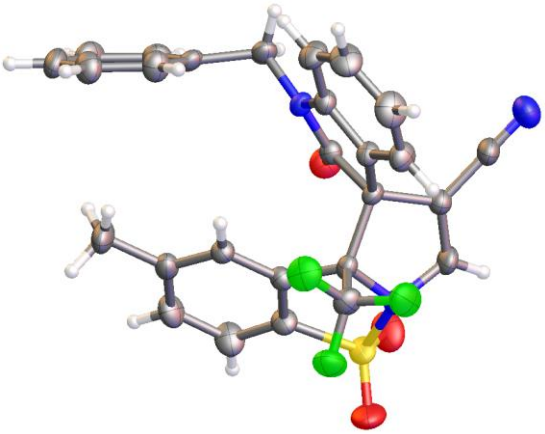
Entry	R^1	R^2	Yield[b] [%]	*ee*[c] [%]
1[d]	H	H	**5a**, 90 (70)	73 (96)
2	H	Me	**5b**, 92	76
3	Cl	Cl	**5c**, 94	60
4	Me	H	**5d**, 91	61
5[d]	Cl	H	**5e**, 92 (74)	74 (98)

[a] Reactions were performed using **1** (0.11 mmol), hemiaminal **4** (0.1 mmol), catalyst **C5** (0.01 mmol), benzoic acid (0.04 mmol) and 4 Å MS (50 mg) in $CHCl_3$ (1 mL) at 5 °C for 72–96 h.
[b] Yield of isolated product.
[c] Determined by HPLC analysis using a chiral stationary phase; ^{1}H NMR analysis indicated *dr* >19:1.
[d] Data in parentheses were obtained after recrystallization.

To further investigate the current chiral catalyst system, the [3+2] annulation reactions between isatin-based MBH carbonates **1** and trifluoromethyl (CF_3)-containing ketimines, generated *in situ* from the hemiaminal precursors **4**, were examined.[12,13] As summarized in Table 3, the annulations proceeded smoothly under the similar catalytic conditions using the catalytic amounts of benzoic acid as the imine formation promoter.[14] An array of products **5** incorporating spirocyclic frameworks were synthesized in excellent yields with moderate enantioselectivity (Table 3, entries 1–5) which can be greatly improved through recrystallization (Table 3, entries 1 and 5). It was noted that the chiral DABCO-based catalytic system appeared no to be compatible with the current asymmetric reactions.[13a]



bispirooxindole **3c**

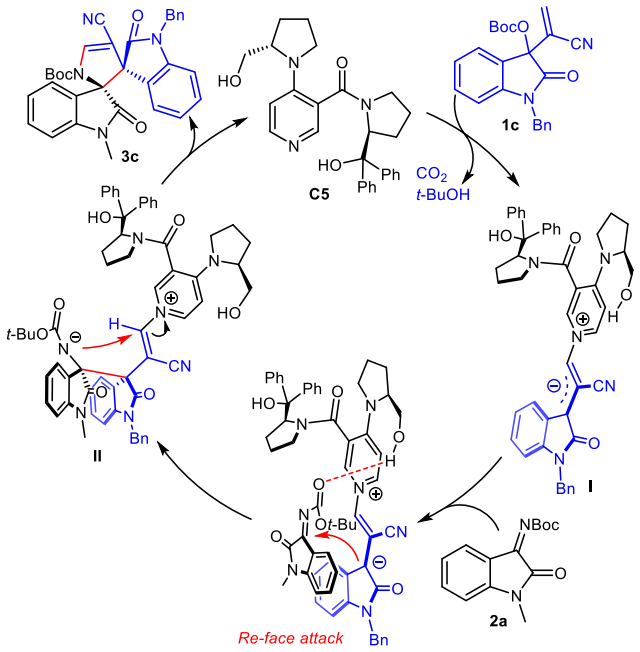


CF_3-containing spirooxindole **5b**

Figure 2. X-ray crystal structures of enantiopure **3c** and **5b**.

The absolute configuration of the chiral [3+2] annulation products **3c** and **5b** was unambiguously determined by X-ray crystallographic analysis, as outlined in Figure 2.[15] Thus, the other chiral products were assigned by analogy.

A plausible catalytic mechanism of the asymmetric annulation reaction is proposed in Scheme 2. Catalyst **C5** attacks MBH carbonate **1c** to form the zwitterionic allylic ylide **I**, which subsequently attacks ketimine **2a** from the *Re*-face with the possible assistance of a hydrogen-bonding interaction between the hydroxyl group of the pyrrolidine moiety and the *N*-Boc group, affording intermediate **II**. Finally, product **3c** is generated after cyclization and the release of the catalyst **C5**.



Scheme 2. Proposed catalytic mechanism of the asymmetric [3+2] annulation reaction.

After removal of the *N*-Boc group of product **3c**, the enamine moiety could be reduced diastereoselectively with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$, giving the more useful pyrrolidine derivative **6** in a moderate yield with slightly reduced enantiopurity (Scheme 3).[16]

Scheme 3. Transformations of [3+2] product **3c**.

Conclusion

We have investigated an asymmetric [3+2] annulation reaction of isatin-derived Morita–Baylis–Hillman carbonates and isatin-derived *N*-Boc ketimines. A newly developed catalysis of chiral 4-dimethylaminopyridine-type substance with additional hydrogen-bonding groups appears to be efficient in constructing a diversity of 1,2-bispirooxindoles with excellent yields, exclusive diastereoselectivity and moderate to remarkable enantioselectivity. The protocol was further expanded to an [3+2] annulation reaction between Morita–Baylis–Hillman carbonates and trifluoromethyl-substituted ketimines which generated *in situ* from the corresponding hemiaminals in the presence of acid additives, affording architectures with vicinal tetrasubstituted stereogenic centers with excellent diastereoselectivity and moderate enantioselectivity. Such substances may be potentially benefiting in medicinal chemistry.

Experimental Section

^1H NMR spectra were recorded at 400 MHz or 600 MHz (Varian) and ^{13}C NMR spectra were recorded at 100 MHz or 150 MHz (Varian). Chemical shifts are reported either in ppm downfield from $CDCl_3$ (δ = 7.26 ppm) for ^1H NMR, or relative to the central $CDCl_3$ resonance (δ = 77.0 ppm) for ^{13}C NMR. Coupling constants are given in Hz. Optical rotations were measured at 589 nm at 20 ºC. Enantiomeric excess was determined using HPLC analysis on Chiralpak ID, IE, IF, AD-H and Chiralcel OD-H columns. ESI-HR-MS was recorded on a Waters SYNAPT G2. TLC was performed on glass-backed silica plates. Column chromatography was performed using silica gel (200–300 mesh), eluting with ethyl acetate and petroleum ether. All other chemicals were used without purification as commercially available. Toluene, THF, ethyl acetate (EtOAc), petroleum ether, dichloromethane (DCM) and MeCN were freshly distilled before use.

General procedure for asymmetric [3+2] annulations

MBH carbonate **1** (0.11 mmol), ketimine **2** (0.1 mmol), catalyst **C5** (4.6 mg, 0.01 mmol) and 4 Å MS (50 mg) were stirred in trifluorotoluene (2.0 mL) at –20 °C (or in $CHCl_3$ at –40 °C). The reaction was monitored by TLC analysis. After the reaction was complete, the solution was concentrated and the residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:9 to 1:5) to afford the chiral product **3**.

The asymmetric [3+2] annulations of MBH carbonates **1** and CF_3-containing hemiaminals **4**: MBH carbonate **1** (0.11 mmol), hemiaminal **4** (0.1 mmol), catalyst **C5** (4.6 mg, 0.01 mmol), benzoic acid (4.9 mg, 0.04 mmol) and 4 Å MS (50 mg) were stirred in $CHCl_3$ (1.0 mL) at 5 °C. The reaction was monitored by TLC analysis. After the reaction was complete, the solution was concentrated and the residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether = 1:10 to 1:4) to afford the chiral product **5**.

***tert*-Butyl (3*R*,3′*R*)-1′′-benzyl-4′-cyano-1-methyl-2,2′′-dioxo-1′*H*-dispiro[indoline-3,2′-pyrrole-3′,3′′-indoline]-1′-carboxylate (3c):** yield: 52.2 mg (98%); white solid; $[\alpha]_D^{20}$ = –134.9 (*c* = 1.10 in $CHCl_3$); >99% *ee*, determined by HPLC analysis [Daicel chiralpak ID, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (minor) = 23.84 min, t (major) = 33.48 min]; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.12(s, 0.32H), 8.00 (s, 0.15H), 7.58–7.52 (m, 2H), 7.35–7.31 (m, 1H), 7.19–7.10 (m, 4H), 7.04–6.97 (m, 2H), 6.65 (d, *J* = 7.2 Hz, 1H), 6.55 (d, *J* = 6.8 Hz, 2H), 6.38 (d, *J* = 7.6 Hz, 1H), 5.08 (d, *J* = 16.0 Hz, 1H), 4.31 (d, *J* = 16.0 Hz, 1H), 2.90 (s, 3H), 1.46 (s, 3H), 1.01 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.3, 172.1, 149.5, 149.3, 149.1, 144.2, 143.5, 134.4, 130.6, 130.1, 128.6, 127.3, 126.9, 126.5, 126.3, 123.2, 123.1, 121.8, 113.7, 109.5, 108.4, 108.1, 90.7, 84.3, 83.5, 74.7, 65.4, 43.9, 27.9, 27.3, 25.9; ESI-HR-MS: *m/z* = 555.1998, calcd. for $(C_{32}H_{28}N_4O_4 + Na)^+$: 555.2003.

***tert*-Butyl (3*R*,3′*R*)-1′′-benzyl-5′′-chloro-4′-cyano-1-methyl-2,2′′-dioxo-1′*H*-dispiro[indoline-3,2′-pyrrole-3′,3′′-indoline]-1′-carboxylate (3e):** yield: 54.4 mg (96%); white solid; $[\alpha]_D^{20}$ = –38.6 (*c* = 1.05 in $CHCl_3$); 95% *ee*, determined by HPLC analysis [Daicel chiralpak ID, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (minor) = 19.96 min, t (major) = 33.15 min]; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.12 (s, 0.31H), 7.99 (s, 0.15H), 7.54 (s, 2H), 7.37–7.34 (m, 1H), 7.20–7.16 (m, 1H), 7.13–7.09 (m, 3H), 7.02–7.00 (m, 1H), 6.69–6.67 (m, 1H), 6.53–6.51 (m, 2H), 6.30 (d, *J* = 8.4 Hz, 1H), 5.07 (d, *J* =

16.0 Hz, 1H), 4.31 (d, *J* = 16.0 Hz, 1H), 2.96 (s, 3H), 1.46 (s, 3H), 1.01 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.0, 171.9, 149.9, 149.7, 149.0, 144.1, 142.1, 133.9, 130.6, 130.3, 128.8, 127.5, 127.2, 126.6, 126.4, 123.9, 123.5, 123.3, 122.8, 113.5, 110.5, 108.5, 108.3, 90.2, 84.6, 83.7, 74.7, 65.3, 44.1, 27.9, 27.3, 26.0; ESI-HR-MS: *m/z* = 589.1617, calcd. for $(C_{32}H_{27}ClN_4O_4 + Na)^+$: 589.1613.

***tert*-Butyl (3*R*,3′*R*)-1''-benzyl-5''-bromo-4'-cyano-1-methyl-2,2''-dioxo-1′*H*-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3f):** yield: 58.0 mg (95%); white solid; $[\alpha]_D^{20}$ = +41.8 (*c* = 1.00 in $CHCl_3$); 96% *ee*, determined by HPLC analysis [Daicel chiralpak ID, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (minor) = 21.01 min, t (major) = 35.97 min]; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.11 (s, 0.55H), 7.99 (s, 0.33H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.55–7.52 (m, 1H), 7.36–7.33 (m, 1H), 7.26–7.24 (m, 1H), 7.19–7.17 (m, 1H), 7.13–7.10 (m, 2H), 7.01–6.99 (m, 1H), 6.68–6.67 (m, 1H), 6.53–6.52 (m, 2H), 6.25 (d, *J* = 8.4 Hz, 1H), 5.05 (d, *J* = 15.6 Hz, 1H), 4.31 (d, *J* = 15.6 Hz, 1H), 2.96 (s, 3H), 1.46 (s, 3H), 1.02 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.9, 171.7, 149.9, 149.7, 149.0, 144.1, 142.5, 133.9, 133.5, 130.3, 129.9, 128.8, 127.5, 126.6, 126.4, 123.8, 123.3, 115.9, 113.5, 111.0, 108.5, 108.3, 90.2, 84.6, 83.7, 74.7, 65.2, 44.0, 28.0, 27.3, 26.0; ESI-HR-MS: *m/z* = 633.1108, calcd. for $(C_{32}H_{27}{}^{79}BrN_4O_4 + Na)^+$: 633.1112; *m/z* = 635.1093, calcd. for $(C_{32}H_{27}{}^{81}BrN_4O_4 + Na)^+$: 635.1097.

***tert*-Butyl (3*R*,3′*R*)-1''-benzyl-4'-cyano-5''-iodo-1-methyl-2,2''-dioxo-1′*H*-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3g):** yield: 64.0 mg (97%); white solid; $[\alpha]_D^{20}$ = +62.7 (*c* = 1.05 in $CHCl_3$); 87% *ee*, determined by HPLC analysis: [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 80/20, 1.0 mL min^{-1}, λ = 254 nm]: t (minor) = 18.86 min, t (major) = 21.97 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 0.28H), 7.99 (s, 0.15H), 7.84 (s, 1H), 7.54–7.52 (m, 1H), 7.45–7.43 (m, 1H), 7.36–7.32 (m, 1H), 7.20–7.16 (m, 1H), 7.13–7.09 (m, 2H), 7.01–7.00 (m, 1H), 6.68–6.67 (m, 1H), 6.52 (d, *J* = 6.8 Hz, 2H), 6.15 (d, *J* = 8.0 Hz, 1H), 5.04 (d, *J* = 16.0 Hz, 1H), 4.30 (d, *J* = 16.0 Hz, 1H), 2.96 (s, 3H), 1.46 (s, 3H), 1.01 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.9, 171.5, 149.9, 149.7, 149.0, 144.1, 143.2, 139.4, 135.4, 133.9, 130.3, 128.8, 127.5, 126.5, 126.3, 126.2, 124.0, 123.3, 113.5, 111.5, 108.5, 108.3, 90.1, 85.6, 84.6, 83.7, 74.8, 65.0, 44.0, 27.9, 27.3, 26.0; ESI-HR-MS: *m/z* = 681.0969, calcd. for $(C_{32}H_{27}IN_4O_4 + Na)^+$: 681.0971.

***tert*-Butyl (3*R*,3′*R*)-1''-benzyl-4'-cyano-1-methyl-5''-nitro-2,2''-dioxo-1′*H*-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3h):** yield: 55.5 mg (96%); white solid; $[\alpha]_D^{20}$ = +29.9 (*c* = 1.05 in $CHCl_3$); 88% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (minor) = 9.39 min, t (major) = 12.65 min]; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.47 (s, 1H), 8.16 (s, 0.47H), 8.10 (dd, *J* = 9.0 Hz, *J* = 2.4 Hz, 1H), 8.03 (s, 0.24H), 7.55–7.51 (m, 1H), 7.38–7.36 (m, 1H), 7.22–7.19 (m, 1H), 7.15–7.13 (m, 2H), 7.05–7.03 (m, 1H), 6.69–6.68 (m, 1H), 6.55–6.50 (m, 3H), 5.13 (d, *J* = 16.2 Hz, 1H), 4.40 (d, *J* = 16.2 Hz, 1H), 2.92 (s, 3H), 1.47 (s, 3H), 1.03 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.4, 171.5, 150.3, 150.0, 149.0, 148.8, 144.1, 143.8, 133.2, 130.6, 129.0, 127.9, 127.4, 126.7, 126.4, 123.6, 123.4, 123.0, 122.9, 113.2, 109.4, 108.8, 108.5, 89.4, 85.0, 84.1, 74.5, 64.9, 44.3, 27.9, 27.3, 26.2; ESI-HR-MS: *m/z* = 600.1854, calcd. for $(C_{32}H_{27}N_5O_6 + Na)^+$: 600.1861.

***tert*-Butyl (3*R*,3′*R*)-1''-benzyl-6''-bromo-4'-cyano-1-methyl-2,2''-dioxo-1′*H*-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3i)**: yield: 58.7 mg (96%); white solid; $[\alpha]_D^{20}$ = –98.2 (*c* = 1.10 in $CHCl_3$); 89% *ee*, determined by HPLC analysis [Daicel chiralpak ID, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (minor) = 17.30 min, t (major) = 23.99 min]; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.11 (s, 0.50H), 7.98 (s, 0.29H), 7.55–7.54 (m, 1H), 7.41–7.39 (m, 1H), 7.36–7.34 (m, 1H), 7.20–7.12 (m, 4H), 7.01–6.99 (m, 1H), 6.69–6.68 (m, 1H), 6.54–6.52 (m, 3H), 5.08 (d, *J* = 16.2 Hz, 1H), 4.26 (d, *J* = 16.2 Hz, 1H), 2.94 (s, 3H), 1.45 (s, 3H), 1.01 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.2, 172.0, 149.7, 149.5, 149.0, 144.9, 144.2, 133.8, 130.4, 128.8, 128.2, 127.5, 126.6, 126.3, 124.6, 124.0, 123.3, 120.9, 113.5, 112.9, 108.6, 108.4, 90.2, 84.6, 83.7, 74.5, 65.1, 44.0, 27.9, 27.3, 26.1; ESI-HR-MS: *m/z* = 633.1108, calcd. for $(C_{32}H_{27}{}^{79}BrN_4O_4 + Na)^+$: 633.1111; *m/z* = 635.1093, calcd. for $(C_{32}H_{27}{}^{81}BrN_4O_4 + Na)^+$: 635.1094.

***tert*-Butyl (3*R*,3′*R*)-1''-benzyl-7''-chloro-4'-cyano-1-methyl-2,2''-dioxo-1′*H*-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3j):** yield: 55.0 mg (97%); white solid; $[\alpha]_D^{20}$ = –180.7 (*c* = 1.10 in $CHCl_3$); 88% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (major) = 10.63 min, t (minor) = 12.11 min]; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.11(s, 0.55H), 7.98 (s, 0.27H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.45–7.41 (m, 1H), 7.33–7.30 (m, 1H), 7.17–7.10 (m, 4H), 6.99 (t, *J* = 7.8 Hz, 1H), 6.89–6.87 (m, 1H), 6.70–6.69 (m, 1H), 6.56–6.55 (m, 2H), 5.17 (d, *J* = 10.2 Hz, 1H), 5.03 (d, *J* = 10.2 Hz, 1H), 2.94 (s, 3H), 1.44 (s, 3H), 1.00 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.8, 172.0, 149.6, 149.4, 148.9, 144.0, 139.7, 136.4, 133.3, 130.4, 128.5, 126.7, 126.3, 125.7, 125.5, 124.8, 124.0, 123.7, 123.3, 115.4, 113.5, 108.5, 108.3, 90.5, 84.5, 83.7, 74.9, 64.9, 45.2, 27.9, 27.3, 26.1; ESI-HR-MS: *m/z* = 589.1613, calcd. for $(C_{32}H_{27}ClN_4O_4 + Na)^+$: 589.1619.

***tert*-Butyl (3*R*,3′*R*)-1''-benzyl-4'-cyano-1,5'',7''-trimethyl-2,2''-dioxo-1′*H*-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3k):** yield: 52.5 mg (96%); white solid; $[\alpha]_D^{20}$: –71.3 (*c* = 1.15 in $CHCl_3$); 79% *ee*, determined by HPLC analysis [Daicel chiralpak ID, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (minor) = 19.61 min, t (major) = 28.22 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 0.36H), 7.99 (s, 0.16H), 7.57–7.55 (m, 1H), 7.35–7.31 (m, 2H), 7.16–7.08 (m, 3H), 7.00–6.96 (m, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 6.54 (d, *J* = 6.8 Hz, 2H), 6.26 (d, *J* = 8.0 Hz, 1H), 5.05 (d, *J* = 16.0 Hz, 1H), 4.30 (d, *J* = 16.0 Hz, 1H), 2.91 (s, 3H), 2.27 (s, 3H), 1.46 (s, 3H), 1.01 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.1, 172.1, 149.4, 149.2, 149.1, 144.1, 141.0, 134.5, 132.7, 130.8, 130.1, 128.5, 128.5, 127.4, 127.2, 126.4, 126.3, 124.1, 123.0, 121.7, 113.8, 109.2, 108.1, 90.8, 84.2, 83.4, 74.8, 65.4, 43.8, 27.9, 27.3, 25.8, 20.9; ESI-HR-MS: *m/z* = 569.2159, calcd. for $(C_{33}H_{30}N_4O_4 + Na)^+$: 569.2158.

***tert*-Butyl (3*R*,3′*R*)-1''-benzyl-4'-cyano-5''-methoxy-1-methyl-2,2''-dioxo-1′*H*-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3l):** yield: 54.0 mg (96%); white solid; $[\alpha]_D^{20}$ = –40.8 (*c* = 1.40 in $CHCl_3$); 75% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (minor) = 10.00 min, t (major) = 11.87 min]; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.11 (s, 0.41H), 7.99 (s, 0.26H), 7.60–7.55 (m, 1H), 7.34–7.32 (m, 1H), 7.18–7.15 (m, 2H), 7.12–7.09 (m, 2H), 7.01–6.97 (m, 1H), 6.67–6.65 (m, 2H), 6.54–6.53 (m, 2H), 6.27 (d, *J* = 8.4 Hz, 1H), 5.13 (d, *J* = 16.2 Hz, 1H), 4.33 (d, *J* = 16.2 Hz, 1H), 3.75 (s, 3H), 2.94 (s, 3H), 1.46 (s, 3H), 1.01 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.2, 172.1, 156.1, 149.5, 149.3, 149.1, 144.2, 136.7, 134.5, 132.5, 130.2, 128.6, 127.3, 126.7, 126.4, 123.2, 122.9, 116.3, 113.7, 113.0, 112.8, 110.1, 108.4, 108.1, 90.8, 84.4, 83.5, 74.8, 65.8, 55.8, 44.0, 27.9, 27.3, 26.0; ESI-HR-MS: *m/z* = 585.2108, calcd. for $(C_{33}H_{30}N_4O_5 + Na)^+$: 585.2111.

***tert*-Butyl (3*R*,3′*R*)-1''-benzyl-4'-cyano-1,5'',7''-trimethyl-2,2''-dioxo-1′*H*-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3m):** yield: 54.4 mg (97%); white solid; $[\alpha]_D^{20}$ = –63.2 (*c* = 1.00 in $CHCl_3$); 76% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (major) = 6.55 min, t (minor) = 8.29 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 0.36H), 7.97 (s, 0.17H), 7.50–7.45 (m, 1H), 7.33–7.30 (m, 1H), 7.29–7.26 (m, 1H),

7.17–7.10 (m, 3H), 6.91–6.88 (m, 1H), 6.73–6.69 (m, 2H), 6.47–6.46 (m, 2H), 5.16 (d, *J* = 17.2 Hz, 1H), 4.24 (d, *J* = 17.2 Hz, 1H), 2.95 (s, 3H), 2.25 (s, 3H), 1.94 (s, 3H), 1.45 (s, 3H), 1.00 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 173.1, 172.4, 149.2, 144.0, 139.1, 136.7, 135.1, 132.6, 130.1, 128.7, 126.7, 125.5, 125.4, 125.0, 124.2, 123.1, 122.5, 119.4, 113.9, 108.3, 108.0, 91.4, 84.2, 83.3, 75.0, 64.9, 45.1, 27.9, 27.3, 25.9, 20.6, 18.3; ESI-HR-MS: *m/z* = 583.2316, calcd. for $(C_{34}H_{32}N_4O_4 + Na)^+$: 583.2319.

***tert*-Butyl (3*R*,3′*R*)-1′′-benzyl-4'-cyano-1,5-dimethyl-2,2′′-dioxo-1′*H*-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3n):** yield: 53.6 mg (98%); white solid; $[\alpha]_D^{20}$ = –53.3 (*c* = 1.15 in $CHCl_3$); 95% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (major) = 6.08 min, t (minor) = 11.55 min]; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.11 (s, 0.42H), 7.99 (s, 0.26H), 7.54–7.53 (m, 1H), 7.39–7.34 (m, 1H), 7.19–7.16 (m, 1H), 7.13–7.11 (m, 4H), 7.03–7.00 (m, 1H), 6.54 (m, 3H), 6.40–6.38 (m, 1H), 5.16 (d, *J* = 16.2 Hz, 1H), 4.28 (d, *J* = 16.2 Hz, 1H), 2.88 (s, 3H), 2.16 (s, 3H), 1.47 (s, 3H), 1.01 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.3, 172.0, 149.6, 149.1, 143.6, 141.7, 134.6, 132.9, 130.5, 130.3, 128.6, 127.2, 127.1, 126.8, 126.1, 124.1, 123.1, 121.8, 113.8, 109.4, 108.2, 108.0, 90.7, 84.3, 83.4, 74.8, 65.4, 43.8, 27.9, 27.3, 25.9, 20.9; ESI-HR-MS: *m/z* = 569.2159, calcd. for $(C_{33}H_{30}N_4O_4 + Na)^+$: 569.2155.

***tert*-Butyl (3*R*,3′*R*)-1′′-benzyl-4'-cyano-5-methoxy-1-methyl-2,2′′-dioxo-1′*H*-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3o):** yield: 54.0 mg (96%); white solid; $[\alpha]_D^{20}$ = –37.9 (*c* = 1.20 in $CHCl_3$); 94% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (major) = 9.45 min, t (minor) = 15.71 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (s, 0.31H), 7.99 (s, 0.16H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.21–7.12 (m, 5H), 7.04–7.00 (m, 1H), 6.86–6.84 (m, 1H), 6.60–6.54 (m, 3H), 6.43–6.41 (m, 1H), 5.13 (d, *J* = 16.0 Hz, 1H), 4.33 (d, *J* = 16.0 Hz, 1H), 3.60 (s, 3H), 2.89 (s, 3H), 1.47 (s, 3H), 1.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.4, 171.9, 156.2, 149.5, 149.2, 143.7, 137.4, 134.6, 130.6, 128.7, 127.3, 127.0, 126.2, 125.1, 123.2, 121.8, 116.0, 115.5, 113.7, 113.0, 112.8, 109.4, 108.7, 90.9, 84.4, 83.5, 75.1, 65.5, 55.9, 43.9, 28.0, 27.4, 26.0; ESI-HR-MS: *m/z* = 585.2108, calcd. for $(C_{33}H_{30}N_4O_5 + Na)^+$: 585.2112.

***tert*-Butyl (3*R*,3′*R*)-1′′-benzyl-4'-cyano-1,5,7-trimethyl-2,2′′-dioxo-1′*H*-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3p):** yield: 53.8 mg (96%); white solid; $[\alpha]_D^{20}$ = –91.1 (*c* = 1.30 in $CHCl_3$); 98% *ee*, determined by HPLC analysis [Daicel chiralpak IC, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (minor) = 11.23 min, t (major) = 15.53 min]; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.09 (s, 0.48H), 7.98 (s, 0.34H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.18–7.17 (m, 2H), 7.14–7.10 (m, 3H), 7.02–7.00 (m, 1H), 6.86–6.84 (m, 1H), 6.54–6.52 (m, 2H), 6.40–6.38 (m, 1H), 5.14 (d, *J* = 9.6 Hz, 1H), 4.24 (d, *J* = 9.6 Hz, 1H), 3.11 (s, 3H), 2.33 (s, 3H), 2.12 (s, 3H), 1.46 (s, 3H), 1.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 172.6, 172.4, 149.5, 149.2, 143.6, 139.3, 139.1, 134.7, 134.2, 132.6, 130.5, 128.5, 127.3, 127.0, 126.2, 125.1, 123.0, 122.0, 119.3, 113.9, 109.4, 90.6, 84.2, 83.3, 74.6, 65.6, 43.9, 29.3, 28.0, 27.3, 20.6, 18.6; ESI-HR-MS: *m/z* = 583.2316, calcd. for $(C_{34}H_{32}N_4O_4 + Na)^+$: 583.2315.

***tert*-Butyl (3*R*,3′*R*)-1′′-benzyl-5,5′′-dichloro-4'-cyano-1-methyl-2,2′′-dioxo-1′*H*-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3q):** yield: 58.9 mg (98%); white solid; $[\alpha]_D^{20}$ = +74.4 (*c* = 1.25 in $CHCl_3$); 79% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (major) = 6.54 min, t (minor) = 9.39 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 0.31H), 7.96 (s, 0.26H), 7.60–7.55 (m, 1H), 7.51 (s, 1H), 7.33–7.31 (m, 1H), 7.22–7.13 (m, 4H), 6.69 (d, *J* = 6.8 Hz, 2H), 6.60–6.58 (m, 1H), 6.42–6.40 (m, 1H), 5.10 (d, *J* = 16.0 Hz, 1H), 4.34 (d, *J* = 16.0 Hz, 1H), 2.95 (s, 3H), 1.48 (s, 4H), 1.06 (s, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.6, 171.4, 149.7, 149.4, 148.8, 142.6, 142.1, 134.0, 130.8, 130.3, 130.2, 128.8, 127.7, 127.1, 126.7, 126.5, 125.6, 124.5, 123.1, 113.3, 110.6, 109.5, 109.3, 90.5, 85.0, 84.1, 74.4, 64.2, 44.2, 28.0, 27.4, 26.2: ESI-HR-MS: *m/z* = 623.1223, calcd. for $(C_{32}H_{26}Cl_2N_4O_4 + Na)^+$: 623.1224.

***tert*-Butyl (3*R*,3′*R*)-1′′-benzyl-5-bromo-5′′-chloro-4'-cyano-1-methyl-2,2′′-dioxo-1′*H*-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3r):** yield: 61.3 mg (95%); white solid; $[\alpha]_D^{20}$ = +159.4 (*c* = 0.90 in $CHCl_3$); 87% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (major) = 6.46 min, t (minor) = 9.84 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 0.31H), 7.96 (s, 0.25H), 7.74–7.69 (m, 1H), 7.51–7.47 (m, 2H), 7.21–7.12 (m, 4H), 6.69 (d, *J* = 6.4 Hz, 2H), 6.54 (d, *J* = 7.6 Hz, 1H), 6.42–6.40 (m, 1H), 5.11 (d, *J* = 16.0 Hz, 1H), 4.33 (d, *J* = 16.0 Hz, 1H), 2.94 (s, 3H), 1.48 (s, 4H), 1.06 (s, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.6, 171.3, 149.7, 149.4, 143.0, 142.1, 134.0, 133.1, 130.8, 129.7, 129.3, 128.9, 127.7, 127.1, 126.5, 125.9, 124.8, 123.1, 115.9, 113.3, 110.6, 110.0, 109.8, 90.5, 85.0, 84.1, 74.2, 65.3, 44.2, 28.0, 27.4, 26.1; ESI-HR-MS: *m/z* = 667.0718, calcd. for $(C_{32}H_{26}{}^{79}BrClN_4O_4 + Na)^+$: 667.0719; *m/z* = 669.0698, calcd. for $(C_{32}H_{26}{}^{81}BrClN_4O_4 + Na)^+$: 669.0695.

***tert*-Butyl (3R,3'R)-1′′-benzyl-5′′-chloro-4'-cyano-5-iodo-1-methyl-2,2′′-dioxo-1'H-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3s):** yield: 67.2 mg (97%); white solid; $[\alpha]_D^{20}$ = +171.1 (*c* = 1.00 in $CHCl_3$); 78% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (major) = 6.20 min, t (minor) = 8.92 min]; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.09 (s, 0.43H), 7.96 (s, 0.33H), 7.89 (s, 0.5H), 7.84 (s, 0.4H), 7.69–7.65 (m, 1H), 7.51–7.50 (m, 1H), 7.23–7.19 (m, 3H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.68 (s, 2H), 6.45–6.43 (m, 1H), 6.41–6.37 (m, 1H), 5.12 (d, *J* = 15.6 Hz, 1H), 4.33 (d, *J* = 15.6 Hz, 1H), 2.96 (s, 3H), 1.48 (s, 4H), 1.06 (s, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.6, 171.1, 149.7, 149.5, 148.7, 143.7, 142.2, 139.1, 135.2, 134.7, 134.0, 130.8, 128.9, 128.9, 127.7, 127.1, 126.5, 126.1, 125.0, 123.1, 113.3, 110.6, 110.3, 90.4, 85.5, 85.0, 84.1, 74.1, 65.2, 44.2, 28.0, 27.4, 26.1; ESI-HR-MS: *m/z* = 715.0579, calcd. for $(C_{32}H_{26}ClIN_4O_4 + Na)^+$: 715.0581.

***tert*-Butyl (3*R*,3′*R*)-1′′-benzyl-6-bromo-5′′-chloro-4'-cyano-1-methyl-2,2′′-dioxo-1′*H*-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3t):** yield: 62.6 mg (97%); white solid; $[\alpha]_D^{20}$ = +49.1 (*c* = 1.05 in $CHCl_3$); 88% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (major) = 7.62 min, t (minor) = 11.46 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 0.28H), 7.96 (s, 0.25H), 7.50 (s, 1H), 7.40–7.34 (q, *J* = 8.0 Hz, 1H), 7.24 (s, 3H), 7.15–7.06 (m, 2H), 6.84 (s, 1H), 6.59–6.58 (m, 2H), 6.38 (d, *J* = 7.2 Hz, 1H), 5.11 (d, *J* = 16.0 Hz, 1H), 4.31 (d, *J* = 16.0 Hz, 1H), 2.95 (s, 3H), 1.46 (s, 4H), 1.05 (s, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.8, 171.7, 149.7, 149.4, 145.3, 142.1, 133.9, 130.9, 128.9, 127.9, 127.8, 127.5, 127.1, 126.4, 126.0, 124.5, 124.3, 123.2, 122.8, 113.3, 112.2, 111.8, 110.6, 90.3, 85.0, 84.1, 74.4, 65.2, 44.2, 28.0, 27.4, 26.2; ESI-HR-MS: *m/z* = 667.0718, calcd. for $(C_{32}H_{26}{}^{79}BrClN_4O_4 + Na)^+$: 667.0719; *m/z* = 669.0698, calcd. for $(C_{32}H_{26}{}^{81}BrClN_4O_4 + Na)^+$: 669.0696.

***tert*-Butyl (3*R*,3′*R*)-1,1′′-dibenzyl-4'-cyano-2,2′′-dioxo-1′*H*-dispiro[indoline-3,2'-pyrrole-3',3''-indoline]-1'-carboxylate (3u):** yield: 59.0 mg (97%); white solid; $[\alpha]_D^{20}$ = –20.7 (*c* = 0.56 in $CHCl_3$); 97% *ee*, determined by HPLC analysis [Daicel chiralpak ID, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (minor) = 22.11 min, t (major) = 37.61 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14(s, 0.54H), 8.01 (s, 0.26H), 7.59–7.55 (m, 2H), 7.17–7.13 (m, 2H), 7.11–7.08 (m, 2H), 6.98–6.92 (m, 6H), 6.53–6.41 (m, 6H), 5.16–5.09 (m, 1.57H), 4.98 (d, *J* = 16.4 Hz, 0.33H), 4.43 (d, *J* = 15.6 Hz, 0.28H), 4.29 (d, *J* = 16.0 Hz, 1H), 4.15 (d, *J* = 15.6 Hz, 0.58H), 1.48 (s, 3H), 1.00 (s,

6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 172.1, 149.3, 149.0, 143.8, 143.7, 134.2, 130.6, 130.2, 128.6, 127.7, 127.3, 127.2, 126.5, 126.2, 124.3, 123.7, 123.1, 122.3, 113.7, 109.7, 109.4, 90.6, 84.4, 83.7, 74.8, 65.8, 43.9, 43.8, 28.0, 27.3; ESI-HR-MS: *m/z* = 631.2316, calcd. for $(C_{38}H_{32}N_4O_4 + Na)^+$: 631.2311.

(1*R*,9b*S*)-1'-Benzyl-2'-oxo-9b-(trifluoromethyl)-9b*H*-spiro[benzo[*d*]pyrrolo[1,2-*b*]isothiazole-1,3'-indoline]-2-carbonitrile 5,5-dioxide (5a): yield: 45.7 mg (90%); white solid; $[\alpha]_D^{20}$ = –3.3 (*c* = 0.30 in $CHCl_3$); 73% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (minor) = 12.61 min, t (major) = 15.81 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.0 Hz, 1H), 7.69–7.63 (m, 2H), 7.57 (s, 1H), 7.47–7.43 (m, 1H), 7.31–7.22 (m, 5H), 7.15–7.14 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 4.64 (dd, *J* = 57.6 Hz, 15.6 Hz, 2H; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 171.0, 144.9 (d, *J* = 0.9 Hz), 143.9, 136.5, 134.4, 134.2, 132.3, 131.6, 128.9, 128.8, 128.2, 128.1, 128.1, 125.8–120.1 (q, *J* = 284.6 Hz), 124.1, 124.0, 122.5, 120.2, 111.4, 110.2, 101.8, 78.4–77.8 (q, *J* = 30.0 Hz), 63.2, 44.7(t, *J* = 5.1 Hz); ESI-HR-MS: *m/z* = 530.0757, calcd. for $(C_{26}H_{16}F_3N_3O_3S + Na)^+$: 530.0756.

(1*R*,9b*S*)-1'-Benzyl-8-methyl-2'-oxo-9b-(trifluoromethyl)-9b*H*-spiro[benzo[*d*]pyrrolo[1,2-*b*]isothiazole-1,3'-indoline]-2-carbonitrile 5,5-dioxide (5b): yield: 48.0 mg (92%); white solid; $[\alpha]_D^{20}$ = –3.8 (*c* = 0.21 in $CHCl_3$); 76% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 220 nm]: t (minor) = 11.03 min, t (major) = 14.66 min]; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.4 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.55 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.30–7.29 (m, 3H), 7.25–7.22 (m, 1H), 7.15 (d, *J* = 6.6 Hz, 2H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.84 (s, 1H), 4.68 (dd, *J* = 111.6 Hz, 15.6 Hz, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 146.0, 144.9 (d, *J* = 2.2 Hz), 143.9, 134.3, 134.0, 133.4, 131.5, 129.4, 129.0, 128.1, 128.1, 128.0, 128.0, 127.4, 127.3–118.7 (q, *J* = 284.3 Hz), 124.0, 122.2, 120.3, 111.5, 110.4, 101.8, 78.4–77.5 (q, *J* = 30.0 Hz), 63.2, 44.7(t, *J* = 3.8 Hz), 21.8; ESI-HR-MS: *m/z* = 544.0913, calcd. for $(C_{27}H_{18}F_3N_3O_3S + Na)^+$: 544.0922.

(1*R*,9b*S*)-1'-Benzyl-5',8-dichloro-2'-oxo-9b-(trifluoromethyl)-9b*H*-spiro[benzo[*d*]pyrrolo[1,2-*b*]isothiazole-1,3'-indoline]-2-carbonitrile 5,5-dioxide (5c): yield: 54.1 mg (94%); white solid; $[\alpha]_D^{20}$ = +30.3 (*c* = 0.60 in $CHCl_3$); 60% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 220 nm]: t (minor) = 6.94 min, t (major) = 10.22 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83–7.81 (m, 1H), 7.73–7.71 (m, 1H), 7.64 (s, 1H), 7.56 (s, 1H), 7.40–7.26 (m, 4H), 7.14–7.12 (m, 2H), 7.08 (s, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 4.71 (dd, *J* = 64.4 Hz, 15.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.7, 144.9 (d, *J* = 1.8 Hz), 142.3, 141.3, 135.1, 133.5, 133.3, 131.9, 130.9, 129.9, 129.4, 128.3, 127.1, 125.5–119.8 (q, *J* = 284.6 Hz), 124.1, 123.9, 121.5, 111.8, 110.9, 101.7, 78.2–77.6 (q, *J* = 31.4 Hz), 63.4, 45.0; ESI-HR-MS: *m/z* = 597.9977, calcd. for $(C_{26}H_{14}Cl_2F_3N_3O_3S + Na)^+$: 597.9980.

(1*R*,9b*S*)-1'-Benzyl-5'-methyl-2'-oxo-9b-(trifluoromethyl)-9b*H*-spiro[benzo[*d*]pyrrolo[1,2-*b*]isothiazole-1,3'-indoline]-2-carbonitrile 5,5-dioxide (5d): yield: 47.5 mg (91%); white solid; $[\alpha]_D^{20}$ = +5.5 (*c* = 0.22 in $CHCl_3$); 61% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 220 nm]: t (minor) = 14.02 min, t (major) = 16.64 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.6 Hz, 1H), 7. 63 (t, *J* = 7.6 Hz, 1H), 7.55 (s, 1H), 7.47 (s, 1H), 7.30–7.23 (m, 5H), 7.14–7.12 (m, 2H), 6.91 (t, *J* = 8.0 Hz, 2H), 4.61 (dd, *J* = 49.6 Hz, 15.2 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.9, 144.8, 141.4, 136.5, 134.5, 134.2, 133.7, 132.3, 131.9, 128.9, 128.8, 128.7, 128.1, 128.0, 125.8–120.1 (q, *J* = 284.4 Hz), 124.0, 122.4, 120.1, 111.5, 109.9, 101.9, 78.6–78.0 (q, *J* = 30.5 Hz), 63.3, 44.6, 21.2; ESI-HR-MS: *m/z* = 544.0913, calcd. for $(C_{27}H_{18}F_3N_3O_3S + Na)^+$: 544.0911.

(1*R*,9b*S*)-1'-Benzyl-5'-chloro-2'-oxo-9b-(trifluoromethyl)-9b*H*-spiro[benzo[*d*]pyrrolo[1,2-*b*]isothiazole-1,3'-indoline]-2-carbonitrile 5,5-dioxide (5e): yield: 49.8 mg (92%); white solid; $[\alpha]_D^{20}$ = +20.6 (*c* = 0.50 in $CHCl_3$); 74% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (minor) = 9.46 min, t (major) = 11.80 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.83 (m, 1H), 7.70–7.66 (m, 2H), 7.59 (s, 1H), 7.43 (dd, *J* = 8.4 Hz, *J* = 1.6 Hz, 1H), 7.33–7.27 (m, 4H), 7.13–7.11 (m, 2H), 6.96–6.92 (m, 2H), 4.64 (dd, *J* = 46.8 Hz, 15.2 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.6, 145.2 (d, *J* = 1.5 Hz), 142.4, 136.5, 134.3, 134.0, 132.5, 131.7, 129.6, 129.0, 128.6, 128.4, 128.0, 125.7–120.0 (q, *J* = 284.7 Hz), 123.9, 122.6, 121.9, 111.2, 111.2, 101.2, 78.6–78.0 (q, *J* = 30.9 Hz), 63.2, 44.8; ESI-HR-MS: *m/z* = 564.0367, calcd. for $(C_{26}H_{15}ClF_3N_3O_3S + Na)^+$: 564.0370.

Synthetic transformations

(3*S*,3'*S*,4'*S*)-1''-Benzyl-1-methyl-2,2''-dioxodispiro[indoline-3,2'-pyrrolidine-3',3''-indoline]-4'-carbonitrile (6): Product **3c** (53.2 mg, 0.1 mmol) was dissolved in DCM (1 mL), and TFA (0.15 mL) was added. Then the solution was stirred at ambient temperature for 5 h. The mixture was diluted with CH_2Cl_2 (10 mL) and neutralized with saturated $NaHCO_3$. The aqueous solution was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in DCM (1 mL), and Et_3SiH (0.64 mL, 4 mmol) and $BF_3{\cdot}Et_2O$ (0.52 mL, 4 mmol) were added in sequence at 0 °C. The mixture was stirred for additional 24 h. After completion, the solvent was evaporated under reduced pressure and the residue was subjected to column chromatography with petroleum ether/EtOAc (4:1) as the eluent to give product **6**: yield: 32.5 mg (75%); white solid; $[\alpha]_D^{20}$ = –185.6 (*c* = 0.23 in $CHCl_3$); >19:1 *dr*; 96% *ee*, determined by HPLC analysis [Daicel chiralpak AD-H, *n*-hexane/*i*-PrOH = 60/40, 1.0 mL min^{-1}, λ = 254 nm]: t (minor) = 17.41 min, t (major) = 22.68 min]; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (dd, *J* = 11.2, 8.0 Hz, 2H), 7.26–7.20 (m, 4H), 7.11–7.07 (m, 3H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 4.92 (dd, *J* = 27.2, 16.0 Hz, 2H), 4.66 (dd, *J* = 9.6, 8.0 Hz, 1H), 4.14–4.09 (m, 1H), 4.00 (dd, *J* = 11.2, 7.6 Hz, 1H), 3.68 (brs, 1H), 3.07 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 175.4, 174.3, 144.0, 143.5, 134.6, 130.4, 129.7, 128.7, 127.6, 127.1, 124.2, 123.8, 123.1, 123.1, 122.9, 122.2, 109.8, 108.5, 74.0, 61.9, 49.1, 43.8, 36.7, 25.7; ESI-HR-MS: *m/z* = 435.1816, calcd. for $(C_{27}H_{22}N_4O_2 + H)^+$: 435.1819.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (21572135 and 21125206).

References

[1] For selected reviews, see: a) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209; b) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902; *Angew. Chem. Int. Ed*. **2007**, *46*, 8748; c) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, 3003; d) G. S. Singh, Z. Y. Desta, *Chem. Rev.* **2012**, *112*, 6104; e) D. Cheng, Y. Ishihara, B. Tan, C. F. Barbas, III, *ACS Catal.* **2014**, *4*, 743; f) M. M. M. Santos, *Tetrahedron* **2014**, *70*, 9735;

g) V. Kumar, S. Patel, R. Jain, *Med. Res. Rev.* **2017**, DOI: 10.1002/med.21454.

[2] For selected examples, see: a) A. R. Suresh Babu, R. Raghunathan, *Tetrahedron* **2007**, *63*, 8010; b) R. R. Kumar, S. Perumal, P. Senthilkumar, P. Yogeeswari, D. Sriram, *J. Med. Chem.* **2008**, *51*, 5731; c) A. R. Suresh Babu, R. Raghunathan, N. Mathivanan, G. Omprabha, D. Velmurugan, R. Raghu, *Curr. Chem. Biol.* **2008**, *2*, 312; d) G. Periyasami, R. Raghunathan, G. Surendiran, N, Mathivanan, *Eur. J. Med. Chem.* **2009**, *44*, 959; e) A. S. Girgis, *Eur. J. Med. Chem.* **2009**, *44*, 91; f) A. Dandia, A. K. Jain, D. S. Bhati, *Tetrahedron Lett.* **2011**, *52*, 5333; g) Y. Arun, G. Bhaskar, C. Balachandran, S. Ignacimuthu, P. T. Perumal, *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1839; h) P. R. Mali, L. Chandrasekhara Rao, V. M. Bangade, P. K. Shirsat, S. A. George, N. Jagadeesh babu, H. M. Meshram, *New J. Chem.* **2016**, *40*, 2225; i) F. Rouatbi, M. Askri, F. Nana, G. Kirsch, D. Sriram, P. Yogeeswari, *Tetrahedron Lett.* **2016**, *57*, 163.

[3] For selected examples, see: a) Y.-Y. Han, W.-B. Chen, W.-Y. Han, Z.-J. Wu, X.-M. Zhang, W.-C. Yuan, *Org. Lett.* **2012**, *14*, 490; b) S. Wu, X. Zhu, W. He, R. Wang, X. Xie, D. Qin, L. Jing, Z. Chen, *Tetrahedron* **2013**, *69*, 11084; c) Q. Xu, D. Wang, Y. Wei, M. Shi, *ChemistryOpen* **2014**, *3*, 93; d) J. J. Badillo, C. J. A. Ribeiro, M. M. Olmstead, A. K. Franz. *Org. Lett.* **2014**, *16*, 6270; e) Q.-L. Wang, T. Cai, J. Zhou, F.Tian, X.-Y. Xu, L.-X. Wang, *Chem. Commun.* **2015**, *51*, 10726; f) J. Sun, L. Chen, H. Gong, C.-G. Yan, *Org. Biomol. Chem.* **2015**, *13*, 5905; g) G. Zhu, S. Liu, S. Wu, L. Peng, J. Qu, B. Wang, *J. Org. Chem.* **2017**, *82*, 4317.

[4] a) W. Dai, X.-L. Jiang, Q. Wu, F. Shi, S.-J. Tu, *J. Org. Chem.* **2015**, *80*, 5737; b) K. Zhao, Y. Zhi, X. Li, R. Puttreddy, K. Rissanen, D. Enders, *Chem. Commun.* **2016**, *52*, 2249; c) W.-J. Huang, Q. Chen, N. Lin, X.-W. Long, W.-G. Pan, Y.-S. Xiong, J. Weng, G. Lu, *Org. Chem. Front.* **2017**, *4*, 472.

[5] For selected examples, see: a) X. Guo, H. Huang, L. Yang, W. Hu, *Org. Lett.* **2007**, *9*, 4721; b) M. Li, W.-L. Yang, L.-R. Wen, F.-Q. Li, *Eur. J. Org. Chem.* **2008**, 2751; c) B. Dutta, N. Gilboa, I. Marek, *J. Am. Chem. Soc.* **2010**, *132*, 5588; d) F. Shi, Z.-L. Tao, S.-W. Luo, S.-J. Tu, L.-Z. Gong, *Chem. Eur. J.* 2012, *18*, 6885; e) J.-L. Li, B. Sahoo, C.-G. Daniliuc, F. Glorius, *Angew. Chem.* **2014**, *126*, 10683; *Angew. Chem. Int. Ed*. **2014**, *53*, 10515; f) Z. Zhang, X.-J. Tang, W. R. Dolbier, Jr, *Org. Lett.* **2016**, *18*, 1048; g) B.-X. Xiao, W. Du, Y.-C. Chen, *Adv. Synth. Catal.* **2017**, *359*, 1018; h) Y. Wang, Y. Chen, *Tetrahedron Lett.* **2017**, *58*, 1545.

[6] For selected examples, see: a) S. Nakamura, K. Hyodo, M. Nakamura, D. Nakane, H. Masuda, *Chem. Eur. J.* **2013**, *19*, 7304; b) J. Xu, C. Mou, T. Zhu, B.-A. Song, Y. R. Chi, *Org. Lett.* **2014**, *16*, 3272; c) Y. Yoshida, M. Sako, K. Kishi, H. Sasai, S. Hatakeyama, S. Takizawa, *Org. Biomol. Chem.* **2015**, *13*, 9022; d) K. S. Rao, P. Ramesh, L. Raju Chowhan, R. Trivedi, *RSC Adv.* **2016**, *6*, 84242; e) X. Zhang, J. Zhang, L. Lin, H. Zheng, W. Wu, X. Liu, X. Feng, *Adv. synth. Catal*. **2016**, *358*, 3021; f) C. S. Marques, A. J. Burke, *Eur. J. Org. Chem.* **2016**, 806; g) H.-Y. Wang, C.-W. Zheng, Z. Chai, J.-X. Zhang, G. Zhao, *Nat. Commun*. **2016**, *7*, 12720; h) L.-J. Zhou, Y.-C. Zhang, F. Jiang, G. He, J. Yan, H. Lu, S. Zhang, F. Shi, *Adv. Synth. Catal*. **2016**, *358*, 3069; i) C. Cheng, X. Lu, L. Ge, J. Chen, W. Cao, X. Wu, G. Zhao, *Org. Chem. Front.* **2017**, *4*, 101; j) for a review, see: B. Eftekhari-Sis, M. Zirak, *Chem. Rev.* **2017**, *117*, 8326.

[7] For selected examples, see: a) H. Lv, B. Tiwari, J. Mo, C. Xing, Y. R. Chi, *Org. Lett.* **2012**, *14*, 5412; b) M. Bai, B.-D. Cui, J. Zuo, J.-Q. Zhao, Y. You, Y.-Z. Chen, X.-Y. Xu, X.-M. Zhang, W.-C. Yuan, *Tetrahedron* **2015**, *71*, 949; c) H.-W. Zhao, B. Li, H.-L. Pang, T. Tian, X.-Q. Chen, X.-Q. Song, W. Meng, Z. Yang, Y.-D. Zhao, Y.-Y. Liu, *Org. Lett.* **2016**, *18*, 848; d) C. Wang, S. Zhu, G. Wang, Z. Li, X.-P. Hui, *Eur. J. Org. Chem.* **2016**, 5653; e) X. Han, W.-L. Chan, W. Yao, Y. Wang, Y. Lu, *Angew. Chem.* **2016**, *128*, 6602; *Angew. Chem. Int. Ed*. **2016**, *55*, 6492; f) M. G. Sankar, M. Garcia-Castro, C. Golz, C. Strohmann, K. Kumar, *Angew. Chem.* **2016**, *128*, 9861; *Angew. Chem. Int. Ed*. **2016**, *55*, 9709; g) P. Cheng, W. Guo, P. Chen, Y. Liu, X. Du, C. Li, *Chem. Commun.* **2016**, *52*, 3418; h) G. Zhu, Q. Wei, H. Chen, Y. Zhang, W. Shen, J. Qu, B. Wang, *Org. Lett.* **2017**, *19*, 1862; i) G. Zhu, S. Wu, X. Bao, L. Cui, Y. Zhang, J. Qu, H. Chen, B. Wang, *Chem. Commun.* **2017**, *53*, 4714.

[8]For selected reviews, see: a) D. Basavaiah, B. S. Reddy, S. S. Badsara, *Chem. Rev.* **2010**, *110*, 5447; b) T.-Y. Liu, M. Xie, Y.-C. Chen, *Chem. Soc. Rev.* **2012**, *41*, 4101; c) Y. Wei, M. Shi, *Chem. Rev.* **2013**, *113*, 6659; d) P. Xie, Y. Huang, *Org. Biomol. Chem*. **2015**, *13*, 8578.

[9] For selected examples, see: a) Y. Wang, L. Liu, T. Zhang, N.-J. Zhong, D. Wang, Y.-J. Chen, *J. Org. Chem.* **2012**, *77*, 4143; b) Y.-L. Liu, X. Wang, Y.-L. Zhao, F. Zhu, X.-P. Zeng, L. Chen, C.-H. Wang, X.-L. Zhao, J. Zhou, *Angew. Chem.* **2013**, *125*, 13980; *Angew. Chem. Int. Ed*. **2013**, *52*, 13735; c) J. Peng, G.-Y. Ran, W. Du, Y.-C. Chen, *Synthesis* **2015**, *47*, 2538; d) G. Zhan, M.-L. Shi, Q. He, W. Du, Y.-C. Chen, *Org. Lett.* **2015**, *17*, 4750; e) G.-Y. Ran, P. Wang, W. Du, Y.-C. Chen, *Org. Chem. Front.* **2016**, *3*, 861; f) K.-K. Wang, P. Wang, Q. Ouyang, W. Du, Y.-C. Chen, *Chem. Commun.* **2016**, *52*, 11104; g) J.-Y. Liu, H. Lu, C.-G. Li, Y.-M. Liang, P.-F. Xu, *Synlett* **2016**, *27*, 1287; h) K.-K. Wang, T. Jin, X. Huang, Q. Ouyang, W. Du, Y.-C. Chen, *Org. Lett.* **2016**, *18*, 872; i) Y.-Y. Zhao, S. Zhao, J.-K. Xie, X.-Q. Hu, P.-F. Xu, *J. Org. Chem.* **2016**, *81*, 10532; j) G. Zhan, M.-L. Shi, Q. He, W.-J. Lin, Q. Ouyang, W. Du, Y.-C. Chen, *Angew. Chem.* **2016**, *128*, 2187; *Angew. Chem. Int. Ed.* **2016**, *55*, 2147; k) X. Fan, H. Yang, M. Shi, *Adv. Synth. Catal.* **2017**, *359*, 49.

[10] a) J. Ammer, M. Baidya, S. Kobayashi, H. Mayr, *J. Phys. Org. Chem.* **2010**, *23*, 1029; b) J. L. Methot, W. R. Roush, *Adv. Synth. Catal.* **2004**, *346*, 1035.

[11] For selected examples, see: a) C. Ó. Dalaigh, S. J. Hynes, D. J. Maher, S. J. Connon, *Org. Biomol. Chem.* **2005**, *3*, 981; b) S. Yamada, T. Misono, Y. Iwai, A. Masumizu, Y. Akiyama, *J. Org. Chem.* **2006**, *71*, 6872; c) E. Larionov, M. Mahesh, A. C. Spivey, Y. Wei, H. Zipse, *J. Am. Chem. Soc.* **2012**, *134*, 9390; d) R.

Nishino, T. Furuta, K. Kan, M. Sato, M. Yamanaka, T. Sasamori, N. Tokitoh, T. Kawabata, *Angew. Chem.* **2013**, *125*, 6573; *Angew. Chem. Int. Ed.* **2013**, *52*, 6445; e) H. Mandai, K. Fujii, H. Yasuhara, K. Abe, K. Mitsudo, T. Korenaga, S. Suga, *Nat. Commun*. **2016**, *7*, 11297.

[12] a) S. Zhang, L. Li, Y. Hu, Y. Li, Y. Yang, Z. Zha, Z. Wang, *Org. Lett.* **2015**, *17*, 5036; b) S. Zhang, L. Cha, L. Li, Y. Hu, Y. Li, Z. Zha, Z. Wang, *J. Org. Chem.* **2016**, *81*, 3177.

[13] a) F. Wei, H.-Y. Huang, N.-J. Zhong, C.-L. Gu, D. Wang, L. Liu, *Org. Lett.* **2015**, *17*, 1688; b) J.-S. Yu, J. Zhou, *Org. Chem. Front.* **2016**, *3*, 298.

[14] For more screening details, see the Supporting Information.

[15] CCDC 1559688 (**3c**) and 1559689 (**5b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] P.-F. Zheng, Q. Ouyang, S.-L. Niu, L. Shuai, Y. Yuan, K. Jiang, T.-Y. Liu, Y.-C. Chen, *J. Am. Chem. Soc.* **2015**, *137*, 9390.

10.1002/adsc.201700849

FULL PAPER

Asymmetric [3+2] Annulations to Construct 1,2-Bispirooxindoles Incorporating a Dihydropyrrolidine Motif

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Qing He, Wei Du, and Ying-Chun Chen*