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Asymmetric Synthesis of Spiro[isoxazolin-3,3′-oxindoles] via the Catalytic 1,3-Dipolar Cycloaddition Reaction of Nitrile Oxides

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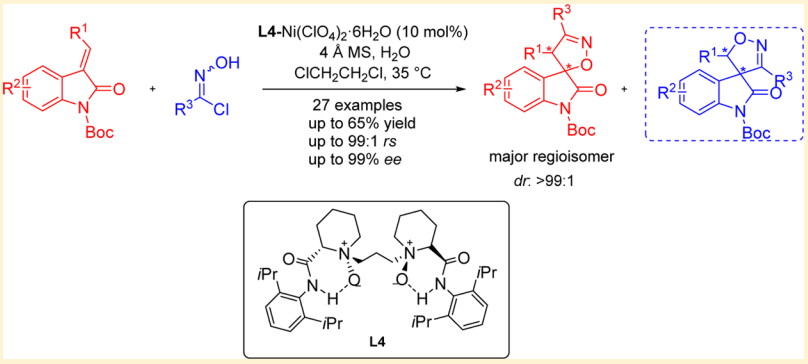
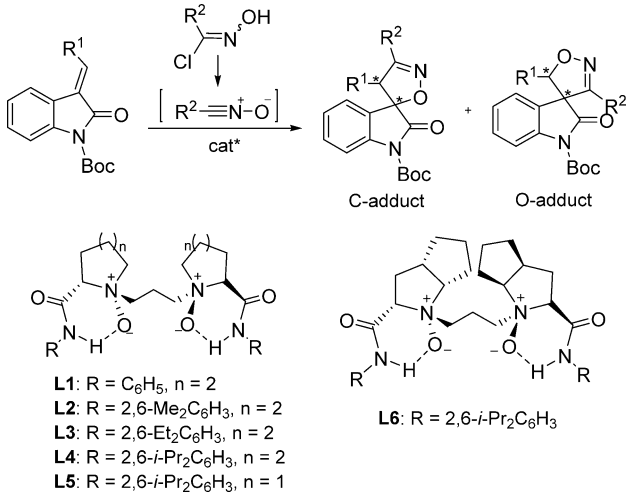
Supporting Information



ABSTRACT: A highly enantioselective 1,3-dipolar cycloaddition of nitrile oxides with 3-arylidene-oxindoles was realized by a chiral *N*,*N*′-dioxide−nickel(II) complex catalyst under mild reaction conditions. A series of spiro-isoxazoline-oxindole derivatives were obtained in moderate yields (up to 65%) with good regioselectivities (up to 99:1), excellent enantioselectivities (up to 99% *ee*), and exclusive diastereoselectivity as well.

Spirooxindoles are an important subset of oxindole-based molecules,[1] which represent an attractive synthetic target due to the biological activity and as the intermediates for generating further molecular complexity.[2] The asymmetric 1,3-dipolar cycloaddition reaction (1,3-DCR) provides a useful route to synthesize a variety of spirooxindoles when 3-arylidene-oxindole derivatives are employed as the dipolarophiles.[3] The extraordinary advancement in this area focused on the employment of the dipoles, such as nitrones,[4] azomethine imines,[5] azomethine ylides,[6] and nitrile imines.[7] From a synthetic point of view, the asymmetric 1,3-DCR between nitrile oxides and 3-arylidene-oxindoles can efficiently construct isoxazoline-based spirooxindoles with two stereocenters. Nevertheless, catalytic asymmetric 1,3-DCR of nitrile oxides is underdeveloped.[8] Owing to the instability of nitrile oxides, they are generally prepared in situ from the hydroximoyl chloride by treatment with a basic reagent. High electron-donor ability of an oxygen atom of the dipole,[9] as well as the propensity of the dipole to dimerize, enhances the complexity of achieving high efficiency in a Lewis acid mediated process.[10] Additionally, several challenges related to selectivity are also associated with the construction of such spirooxindole structures. The reaction potentially yields regioselectively either the favored C-adduct or the disfavored O-adduct (Scheme 1). Moreover, vicinal stereogenic centers bearing a unique spiro quaternary carbon and a tertiary carbon are created in the counter-competitive background reaction mediated by a base.

Scheme 1. 1,3-DCR between Nitrile Oxides and 3-Arylidene-Oxindoles and the Chiral Ligands Evaluated in the Reaction



Otherwise, the acid generated from hydroximoyl chloride may dull the chiral Lewis acids and deteriorate the enantioselectivity.

The pioneering work of chiral Lewis acids catalyzed 1,3-DCR of nitrile oxides was reported by Inomata and co-workers using

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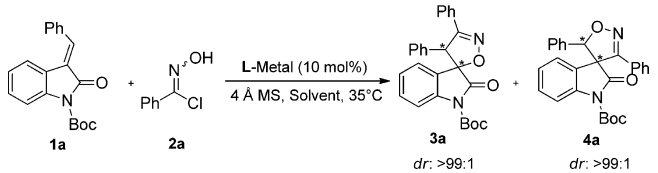
Table 1. Evaluation of the Reaction Conditions



entry[a]	ligand	metal salt	solvent	yield (%)[b]	3a:4a[c]	*ee* (%)[d]
1	**L1**	$Mg(ClO_4)_2$	CH_2Cl_2	50	94:6	5
2	**L1**	$Zn(OTf)_2$	CH_2Cl_2	54	97:3	trace
3	**L1**	$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	47	98:2	11
4	**L2**	$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	58	96:4	30
5	**L3**	$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	52	96:4	42
6	**L4**	$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	44	95:5	51
7	**L5**	$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	43	97:3	44
8	**L6**	$Ni(ClO_4)_2{\cdot}6H_2O$	CH_2Cl_2	35	99:1	33
9	**L4**	$Ni(ClO_4)_2{\cdot}6H_2O$	$CHCl_3$	33	93:7	87
10	**L4**	$Ni(ClO_4)_2{\cdot}6H_2O$	$ClCH_2CH_2Cl$	30	93:7	89
11[e]	**L4**	$Ni(ClO_4)_2{\cdot}6H_2O$	$ClCH_2CH_2Cl$	32	90:10	92
12[e,f]	**L4**	$Ni(ClO_4)_2{\cdot}6H_2O$	$ClCH_2CH_2Cl$	43	97:3	99
13[e,f,g]	**L4**	$Ni(ClO_4)_2{\cdot}6H_2O$	$ClCH_2CH_2Cl$	76	97:3	11

[a]Unless otherwise noted, the reactions were performed with **1a** (0.10 mmol), **2a** (0.10 mmol), **L** (0.01 mmol), metal (0.01 mmol), and 4 Å MS (40 mg) in 1.0 mL of the solvent at 35 °C for 24 h. [b]Isolated yield of the mixture of **3a** and **4a**. [c]Regioselectivity (**3a**:**4a**) determined by chiral HPLC analysis (Chiralpak IA). [d]Determined by chiral HPLC for the major regioisomer **3a**. [e]In 0.3 mL of $ClCH_2CH_2Cl$. [f]H_2O (3 μL) was added. [g]1.0 equiv of K_2CO_3 was added.

allylic alcohols as the dipolarophiles and a chiral diisopropyl tartrate−zinc complex as the catalyst.[11] Sibi and co-workers reported the successful reaction between the preformed nitrile oxides and oxazolidinone crotonates by a chiral bisoxazoline−magnesium catalyst.[8a,b] Afterward, Suga et al. demonstrated a chiral BINIM−Ni(II) complex catalyzed asymmetric cycloaddition of several nitrile oxides with good yields and enantioselectivities.[8c] However, the search for new dipolarophiles and chiral Lewis acid catalysts is still a promising strategy for the development of highly enantioselective 1,3-DCR of nitrile oxides. In the past several years, our research has been focused on developing chiral *N*,*N*′-dioxide−metal complexes catalysts. This undertaking has enabled efficient and selective catalysis of a range of asymmetric reactions.[12] We are inspired by the excellent performance and tolerance toward acids, bases, and moisture of these catalysts in asymmetric cyclization reactions[12] and expect these chiral Lewis acids also work in the construction of the new spirooxindole structures. Herein, we report a highly stereoselective cycloaddition between 3-arylidene-oxindoles and nitrile oxides using an *N*,*N*′-dioxide−nickel(II) complex as the catalyst (Scheme 1). Excellent enantioselectivities (85−99% *ee*'s) and good regioselectivities were achieved in the presence of 4 Å molecular sieves, albeit the yields were moderated.

Initially, 3-benzylidene-oxindole derivative **1a** was chosen as the model substrate to react with the nitrile oxide precursor **2a**. Various chiral Lewis acid catalysts that generated in situ from metal salts and the *N*,*N*′-dioxide **L1** (Scheme 1) were first evaluated. Four Å molecular sieves (4 Å MS) instead of a base were used to convert hydroximoyl chloride **2a** into the corresponding nitrile oxide.[8c] The representative results are summarized in Table 1. The C-adduct **3a** was obtained as the major product, and a trace amount of the regioisomer of the O-adduct **4a** was detected. Both the **L1**−$Mg(ClO_4)_2$ and **L1**−$Zn(OTf)_2$ complexes could promote the reaction in moderate yields, while the enantiomeric excess (*ee*) were poor (Table 1, entries 1, 2). The combination of $Ni(ClO_4)_2{\cdot}6H_2O$ with **L1** afforded the products in 47% yield, 98:2 *rs*, and 11% *ee* for **3a** (Table 1, entry 3). To our delight, increasing the steric hindrance of the amide subunits of the ligand benefited the enantioselectivity of the reaction, and the *N*,*N*′-dioxide **L2** bearing 2,6-dimethyl-substituted anilines raised the *ee* to 30%, though the yield did not change too much (Table 1, entry 4). When the ligands donated with more steric hindered amide moieties, such as when 2,6-diethyl or 2,6-diisopropyl anilines were used, the yields decreased slightly with maintained regioselectivities, while the *ee* improved to 42% and 51% for ligands **L3** and **L4**, respectively (Table 1, entries 5, 6). The *N*,*N*′-dioxide **L5** derived from *L*-proline and **L6** derived from *L*-ramipril exhibited inferior results in terms of yield and enantioselectivity (Table 1, entries 7 and 8 vs 6).

With the optimized catalyst in hand, we next tested the effect of the solvent on the reaction. The use of $CHCl_3$ led to the *ee* increased to 87% (Table 1, entry 9). When the reaction was performed in CH_2ClCH_2Cl, the yield was 30% and the *ee* increased to 89% (Table 1, entry 10). Decreasing the amount of CH_2ClCH_2Cl resulted in an improved enantioselectivity (92% *ee*), a decreased regioselectivity (90:10), and a yield of 32% (Table 1, entry 11). Fortunately we found that the addition of water had a positive effect on both the enantioselectivity and the yield (Table 1, entry 12). It may be for the reason that the water can absorb hydrochloride that was generated in the formation of nitrile oxide from the precursor **2a** in the presence of 4 Å molecular sieves, and then the adverse effect of acid to the chiral metal complex catalyst was minimized to a certain degree. It was also noteworthy that hydrochloride can remove the Boc group on the nitrogen of **1a**. Therefore, the low yield partly attributed to the deprotection of the *N*-Boc group by HCl, leading to the less effective N−H free 3-benzylideneindolinone which was detected in the reaction mixture. Although high yield could be obtained by the addition of K_2CO_3, the enantioselectivity dropped sharply as a result of the strong

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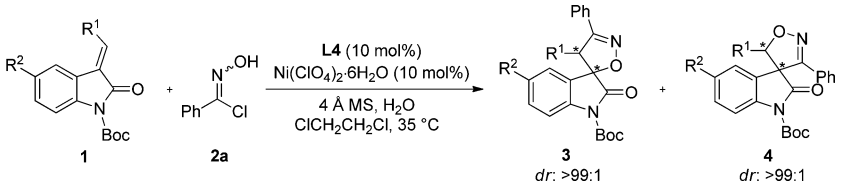
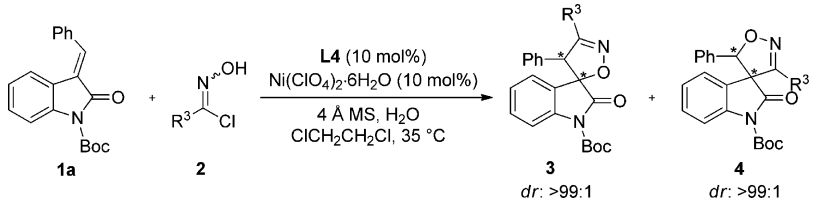
Table 2. Substrate Scope of 3-Arylidene-Oxindoles in the Asymmetric 1,3-Dipolar Cycloaddition Reaction



entry[a]	R^1, R^2 (**1**)	**3**	yield (%)[b]	**3**:**4**[c]	*ee* (%)[d]
1	Ph, H (**1a**)	**3a**	43	97:3	>99
2	3-FC_6H_4, H (**1b**)	**3b**	30	98:2	>99
3	4-FC_6H_4, H (**1c**)	**3c**	45	98:2	>99
4	2-ClC_6H_4, H (**1d**)	**3d**	48	>99:1	96
5	3-ClC_6H_4, H (**1e**)	**3e**	44	96:4	99
6	4-ClC_6H_4, H (**1f**)	**3f**	31	94:6	99
7	2,6-$Cl_2C_6H_3$, H (**1g**)	**3g**	53	>99:1	99
8	2-BrC_6H_4, H (**1h**)	**3h**	48	>99:1	97
9	3-BrC_6H_4, H (**1i**)	**3i**	65	68:32	99
10	4-BrC_6H_4, H (**1j**)	**3j**	42	92:8	>99
11	3-MeC_6H_4, H (**1k**)	**3k**	40	98:2	>99
12	4-MeC_6H_4, H (**1l**)	**3l**	35	>99:1	97
13	4-$F_3CC_6H_4$, H (**1m**)	**3m**	32	99:1	>99
14	3-$MeOC_6H_4$, H (**1n**)	**3n**	40	90:10	>99
15	3-$PhOC_6H_4$, H (**1o**)	**3o**	41	>99:1	97
16	2-naphthyl, H (**1p**)	**3p**	40	71:29	93
17	Ph, 5-F (**1q**)	**3q**	35	98:2	>99
18	Ph, 5-Br (**1r**)	**3r**	44	96:4	96
19	Ph, 5-MeO (**1s**)	**3s**	38	94:6	97

[a]Unless otherwise noted, the reactions were performed with **L4** (0.01 mmol), $Ni(ClO_4)_2·6H_2O$ (0.01 mmol), **1** (0.10 mmol), **2a** (0.10 mmol), H_2O (3 μL), and 4 Å MS (40 mg) in 0.3 mL of $ClCH_2CH_2Cl$ at 35 °C for 24 h. [b]Isolated yield of the mixture of **3** and **4**. [c]Regioselectivity (**3**:**4**) determined by chiral HPLC analysis (Chiralpak IA or ID). [d]Determined by chiral HPLC for the major regioisomer.

Table 3. Substrate Scope of the Nitrile Oxide Precursors



entry[a]	R^3 (**2**)	**3**	yield (%)[b]	**3**:**4**[c]	*ee* (%)[d]
1	4-FC_6H_5 (**2t**)	**3t**	60	96:4	97
2	3-ClC_6H_5 (**2u**)	**3u**	44	>99:1	87
3	4-ClC_6H_5 (**2v**)	**3v**	52	>99:1	92
4	3-BrC_6H_5 (**2w**)	**3w**	46	95:5	99
5	4-BrC_6H_5 (**2x**)	**3x**	49	>99:1	93
6	4-MeC_6H_5 (**2y**)	**3y**	40	96:4	99
7	4-$F_3CC_6H_5$ (**2z**)	**3z**	53	99:1	92
8	4-$MeOC_6H_5$ (**2aa**)	**3aa**	43	90:10	95

[a]Unless otherwise noted, the reactions were performed with **L4** (0.01 mmol), $Ni(ClO_4)_2·6H_2O$ (0.01 mmol), **1a** (0.10 mmol), **2** (0.10 mmol), H_2O (3 μL), and 4 Å MS (40 mg) in 0.3 mL of $ClCH_2CH_2Cl$ at 35 °C for 24 h. [b]Isolated yield of the mixture of **3** and **4**. [c]Regioselectivity (**3**:**4**) determined by chiral HPLC analysis (Chiralpak IA). [d]Determined by chiral HPLC for the major regioisomer.

background reaction (Table 1, entry 13). Therefore, the optimal reaction conditions were 10 mol % of **L4**–$Ni(ClO_4)_2·6H_2O$ (1:1) with 4 Å molecular sieves and a small amount of H_2O in CH_2ClCH_2Cl at 35 °C for 24 h, which afforded the product with 43% yield, 97:3 regioselectivity, and 99% *ee*. The C-adduct and O-adduct regioisomers could not be isolated by column chromatography.

Under the optimized conditions, the scope of 3-arylidene-oxindoles was examined, and the results are summarized in Table 2. The enantiocontrol of the reaction was sensitive to neither the electronic property nor the steric hindrance of substituents on the phenyl ring. 3-Arylidene-oxindoles with either electron-withdrawing or electron-donating substituents on the aromatic ring provided the corresponding products in excellent enantioselectivities (96–99% *ee*'s; Table 2, entries 1–15). High regioselectivities were achieved in most cases. Especially, *ortho*-halo-substituted dipolarophiles, such as **1d**, **1g**, and **1h**, afforded the spirooxindoles **3** in up to 99:1

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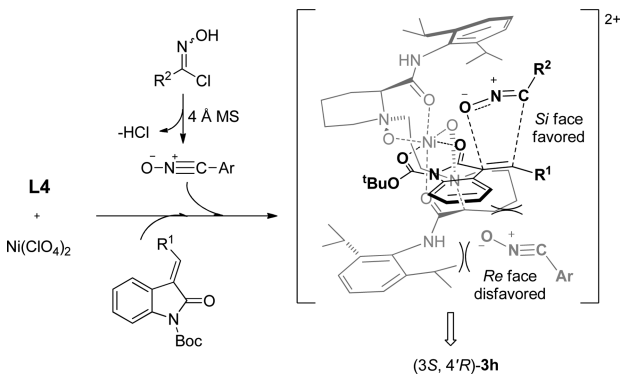
regioselectivity (Table 2, entries 4, 7, 8). One exception was 3-bromo-substituted substrate **1i**, which performed the asymmetric 1,3-DCR with moderate *rs*, generating 5-substituted adduct **3i** and 4-substituted adduct **4i** in a 68:32 ratio and 65% yield (Table 2, entry 9). As well, the fused-ring substrate **1p** was also tolerable to afford the desired product with 71:29 regioselectivity and 93% *ee* (Table 2, entry 16). The reduced regioselectivity might mainly be influenced by steric factors due to important differences in terminal nitriloxide atoms involved in bond formation. Moreover, the 5-substituted oxindole derivatives could also afford the corresponding products in good results (Table 2, entries 17−19). Unfortunately, alkylideneoxindoles do not react under the optimized conditions. The absolute configuration of the product **3h** was determined to be (3*S*,4′*R*) by X-ray crystallography analysis (see details in the Supporting Information).[14]

Next, the performance of other nitrile oxide precursors **2** was investigated. As shown in Table 3, cycloaddition of aryl-substituted nitrile oxides gave the corresponding products in good to excellent regioselectivities and enantioselectivities depending on the position and electronic nature of the substituents. The enantioselectivities were lower with 3-chloro-substituted hydroximoyl chloride (Table 3, entry 2). Electron-donating substituted dipoles yielded relatively lower regioselectivity in comparison with most of the electron-withdrawing ones (Table 3, entries 6 and 8). The 4-methoxyl-substituted nitrile oxide produced the product with 90:10 *rs*, and good *ee* (Table 3, entry 8).

To demonstrate the practicality of the present approach, the reaction was scaled up to a gram scale. Under the optimized reaction conditions, upon treatment of 3 mmol of the starting materials, the corresponding product **3g** was produced without any loss of the reactivity and enantioselectivity (48% yield, 99:1 *rs*, and 98% *ee*). It was noted that there was no self-disproportionation of enantiomers observed in the purification process via achiral chromatography.[15]

An asymmetric catalytic model was proposed as a hexa-coordinated octahedral structure on the basis of the X-ray structural analysis of the *N*,*N*′-dioxide−Ni(II) complex as reported in the previous reports.[13d,g] As shown in Scheme 2, nitrile oxide was generated from *N*-hydroximoyl chloride **2** assisted with 4 Å molecular sieves. The *Re* face of oxindole derivative **1** is effectively shielded by the amide moiety and piperidine ring underneath of the ligand. In contrast, the *Si* face is located in a relatively open space. The highly selective approach of the nitrile oxide toward the *Si* face of bidentate-coordinated 3-arylidene-oxindole gives the (3*S*,4′*R*)-adduct **3**, which is consistent with the observed absolute configuration of the cyclic product.

Scheme 2. Proposed Catalytic Model for the Asymmetric 1,3-DCR



In summary, we have developed a highly enantioselective *N*,*N*′-dioxide−nickel(II) complex catalytic system for the asymmetric 1,3-dipolar cycloaddition of nitrile oxides with 3-arylidene-oxindoles. The corresponding spiro-isoxazoline-oxindole derivatives were afforded in moderate yields and high regio-, diastereo-, and enantioselectivities under mild reaction conditions.

EXPERIMENTAL SECTION

General Remarks. Reactions were carried out using commercially available reagents in a dry apparatus. $ClCH_2CH_2Cl$ was directly distilled before use. Enantiomeric excesses (*ee*'s) were determined by HPLC analysis using the corresponding commercial chiral column as stated in the experimental procedures at 23 °C with a UV detector at 254 nm. Optical rotations were reported as follows: $[\alpha]_D^{25}$ (*c* g/100 mL, solvent). ^1H NMR spectra were recorded on commercial instruments (400 MHz). ^{13}C NMR spectra was collected on commercial instruments (100 MHz) with complete proton decoupling.

General Procedure for the Catalytic Asymmetric 1,3-Dipolar Cycloaddition Reaction. To a dry reaction tube were added **L4** (0.01 mmol, 6.5 mg), $Ni(ClO_4)_2{\cdot}6H_2O$ (0.01 mmol, 3.7 mg), 4 Å MS (40 mg), and $ClCH_2CH_2Cl$ (0.3 mL). After stirring at 35 °C for 1 h, **1** (0.1 mmol), **2** (0.1 mmol), and H_2O (3 μL) were added. The reaction mixture continued stirring at 35 °C for 24 h. The crude mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 10/1 to 5/1) to afford the desired product as a white solid. The enantiomeric excess (*ee*) was determined by high-performance liquid chromatography (HPLC), and the regioselectivity was determined by ^1H NMR.

*tert-Butyl-2-oxo-3′,4′-diphenyl-4′H-spiro[indoline-3,5′-isoxazole]-1-carboxylate (**3a**).* Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 18.9 mg, 43% yield, 97:3 *rs*, and 99% *ee*, mp 168−170 °C; $[\alpha]_D^{18}$ = −218.8 (*c* = 0.35 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 4.94 min (minor), 5.92 min (minor regioisomer), 6.22 min (major), 7.43 min (minor regioisomer). ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 6.8 Hz, 2H), 7.32- 7.26 (m, 3H), 7.23 (m, 4H), 7.06 (d, *J* = 3.2 Hz, 2H), 6.75 (t, *J* = 7.6 Hz, 1H), 6.27 (d, *J* = 7.6 Hz, 1H), 5.08 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.3, 157.9, 148.0, 139.8, 132.2, 129.8, 129.4, 128.0, 127.7, 127.6, 127.3, 126.8, 125.7, 123.2, 120.2, 113.9, 87.2, 83.9, 59.8, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{25}N_2O_4$ ([M + H$^+$]) = 441.1814, Found 441.1819.

*tert-Butyl-4′-(3-fluorophenyl)-2-oxo-3′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3b**).* Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 13.7 mg, 30% yield, 98:2 *rs*, and 99% *ee*, mp 165−166 °C; $[\alpha]_D^{17}$ = −283.6 (*c* = 0.28 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 5.24 min (minor), 5.91 min (minor regioisomer), 6.85 min (major), 8.85 min (minor regioisomer).^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.38−7.30 (m, 3H), 7.26−7.23 (m, 2H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.80−6.77 (m, 2H), 6.35 (d, *J* = 7.6 Hz, 1H), 5.06 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.0, 157.6, 147.9, 139.8, 134.7, 130.0, 129.7, 129.7, 129.6, 127.8, 127.0, 126.7, 125.5, 123.8, 123.3, 119.9, 115.2, 115.0, 114.8, 114.6, 114.1, 87.1, 84.0, 59.3, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{24}FN_2O_4$ ([M + H$^+$]) = 459.1720, Found 459.1713.

*tert-Butyl-4′-(4-fluorophenyl)-2-oxo-3′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3c**).* Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 20.7 mg, 45% yield, 98:2 *rs*, and 99% *ee*, mp 161−162 °C; $[\alpha]_D^{16}$ = −240.1 (*c* = 0.33 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 5.47 min

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(minor), 6.29 min (minor regioisomer), 7.54 min (minor regioisomer), 8.39 min (major).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.2 Hz, 2H), 7.39−7.27 (m, 4H), 7.06−6.99 (m, 2H), 6.96 (t, J = 8.4 Hz, 2H), 6.81 (t, J = 7.6 Hz, 1H), 6.30 (d, J = 7.6 Hz, 1H), 5.07 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.1, 157.8, 147.9, 139.8, 129.9, 129.8, 129.7, 129.5, 127.7, 127.0, 126.7, 125.6, 123.3, 120.1, 115.3, 115.0, 114.0, 84.0, 59.0, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{24}FN_2O_4$ ([M + H^+]) = 459.1720, Found 459.1712.

tert-Butyl-4′-(2-chlorophenyl)-2-oxo-3′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3d**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 22.7 mg, 48% yield, >99:1 *rs*, and 96% *ee*, mp 149−150 °C; $[\alpha]_D^{18}$ = −196.5 (c = 0.41 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 5.21 min (minor), 7.92 min (major).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 7.2 Hz, 2H), 7.38−7.27 (m, 4H), 7.22 (s, 4H), 6.75 (t, J = 7.6 Hz, 1H), 6.19 (d, J = 7.2 Hz, 1H), 5.61 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.1, 157.2, 148.0, 140.3, 133.6, 130.5, 129.9, 129.6, 129.4, 128.9, 128.8, 127.8, 127.0, 126.7, 126.2, 124.9, 123.0, 120.3, 114.0, 86.9, 83.8, 56.2, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{24}{}^{34.9689}ClN_2O_4$ ([M + H^+]) = 475.1425, Found 475.1425; HRMS (ESI-TOF) calcd for $C_{27}H_{24}{}^{36.9659}ClN_2O_4$ ([M + H^+]) = 477.1395, Found 477.1422.

tert-Butyl-4′-(3-chlorophenyl)-2-oxo-3′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3e**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 21.0 mg, 44% yield, 96:4 *rs*, and 99% *ee*, mp 162−164 °C; $[\alpha]_D^{11}$ = −279.4 (c = 0.25 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 9.15 min (minor), 10.20 min (minor regioisomer), 10.92 min (major), 13.14 min (minor regioisomer).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.2 Hz, 1H), 7.59−7.54 (m, 2H), 7.31−7.21 (m, 4H), 7.19 (s, 1H), 7.14 (t, J = 7.7 Hz, 1H), 6.98 (s, 1H), 6.90 (d, J = 7.6 Hz, 1H), 6.75 (t, J = 7.6 Hz, 1H), 6.25 (d, J = 7.6 Hz, 1H), 4.96 (s, 1H), 1.57 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.0, 157.6, 147.9, 139.8, 134.2, 134.1, 130.1, 129.6, 129.3, 128.1, 127.9, 127.8, 126.8, 126.7, 126.2, 125.6, 123.3, 119.7, 114.1, 87.1, 84.1, 59.2, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{23}{}^{34.9689}ClN_2NaO_4$ ([M + Na^+]) = 497.1244, Found 497.1243; HRMS (ESI-TOF) calcd for $C_{27}H_{23}{}^{36.9659}ClN_2NaO_4$ ([M + Na^+]) = 499.1214, Found 499.1130.

tert-Butyl-4′-(4-chlorophenyl)-2-oxo-3′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3f**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 15.0 mg, 31% yield, 94:6 *rs*, and 99% *ee*, mp 164−165 °C; $[\alpha]_D^{18}$ = −256.2 (c = 0.29 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 5.44 min (minor), 6.45 min (minor regioisomer), 7.40 min (minor regioisomer), 8.62 min (major).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 7.6 Hz, 2H), 7.40−7.27 (m, 4H), 7.25 (d, J = 10.8 Hz, 3H), 6.99 (d, J = 8.0 Hz, 2H), 6.83 (t, J = 7.6 Hz, 1H), 6.33 (d, J = 7.6 Hz, 1H), 5.05 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.0, 157.7, 147.9, 139.8, 133.6, 130.8, 130.0, 129.6, 129.4, 128.3, 127.8, 127.0, 126.7, 125.6, 123.4, 120.0, 114.1, 87.01, 84.0, 59.1, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{24}{}^{34.9689}ClN_2O_4$ ([M + H^+]) = 475.1425, Found 475.1417; HRMS (ESI-TOF) calcd for $C_{27}H_{24}{}^{36.9659}ClN_2O_4$ ([M + H^+]) = 477.1395, Found 477.1453.

tert-Butyl-4′-(2,6-dichlorophenyl)-2-oxo-3′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3g**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 27.1 mg, 53% yield, >99:1 *rs*, and 99% *ee*, mp 178−180 °C; $[\alpha]_D^{18}$ = −386.6 (c = 0.37 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 7.55 min (minor), 9.49 min (major).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.38 (d, J = 7.2 Hz, 1H), 7.36−7.19 (m, 5H), 7.17 (d, J = 8.0 Hz, 2H), 7.11−7.04 (m, 1H), 6.91 (t, J = 7.6 Hz, 1H), 5.95 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.6, 156.6, 147.9, 140.0, 135.4, 135.3, 130.1, 129.7, 129.5, 129.1, 129.1, 128.0, 127.7, 127.5, 125.8, 125.2, 123.5, 121.0, 114.2, 87.4, 83.8, 57.0, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{23}{}^{34.9689}Cl_2N_2O_4$ ([M + H^+]) = 509.1035, Found 509.1032; HRMS (ESI-TOF) calcd for $C_{27}H_{23}{}^{36.9659}Cl_2N_2O_4$ ([M + H^+]) = 513.0975, Found 513.0982.

tert-Butyl-4′-(2-bromophenyl)-2-oxo-3′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3h**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 25.0 mg, 48% yield, >99:1 *rs*, and 97% *ee*, mp 166−167 °C; $[\alpha]_D^{16}$ = −178.3 (c = 0.55 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 6.91 min (minor) 13.33 min (major).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 6.8 Hz, 2H), 7.42 (d, J = 8.0 Hz, 1H), 7.37−7.30 (m, 3H), 7.30−7.25 (m, 2H), 7.22 (d, J = 6.4 Hz, 1H), 7.14 (t, J = 7.2 Hz, 1H), 6.75 (t, J = 7.6 Hz, 1H), 6.18 (d, J = 7.6 Hz, 1H), 5.61 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.0, 157.3, 148.0, 140.4, 132.2, 132.2, 129.9, 129.6, 129.6, 129.0, 127.8, 126.9, 126.8, 126.7, 125.0, 124.6, 123.0, 120.3, 114.0, 86.9, 83.8, 58.7, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{24}{}^{78.9183}BrN_2O_4$ ([M + H^+]) = 519.0919, Found 519.0913; HRMS (ESI-TOF) calcd for $C_{27}H_{24}{}^{80.9163}BrN_2O_4$ ([M + H^+]) = 521.0899, Found 521.0898.

tert-Butyl-4′-(3-bromophenyl)-2-oxo-3′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3i**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 33.7 mg, 65% yield, 68:32 *rs*, and 99% *ee*, mp 148−150 °C. HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 4.93 min (minor), 6.01 min (minor regioisomer), 6.57 min (major), 8.40 min (minor regioisomer).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.2 Hz, 1H), 7.63 (d, J = 7.2 Hz, 2H), 7.59−7.47 (m, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.6 Hz, 2H), 7.15−7.12 (m, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.82 (t, J = 7.6 Hz, 1H), 6.32 (d, J = 7.6 Hz, 1H), 5.01 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.9, 157.6, 147.9, 139.8, 134.5, 130.9, 130.8, 130.1, 129.6, 129.6, 127.8, 127.0, 126.7, 126.5, 125.6, 123.3, 122.2, 119.8, 114.1, 87.1, 84.1, 59.2, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{24}{}^{78.9183}BrN_2O_4$ ([M + H^+]) = 519.0919, Found 519.0912; HRMS (ESI-TOF) calcd for $C_{27}H_{24}{}^{80.9163}BrN_2O_4$ ([M + H^+]) = 521.0899, Found 521.0914.

tert-Butyl-4′-(4-bromophenyl)-2-oxo-3′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3j**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 21.8 mg, 42% yield, 92:8 *rs*, and >99% *ee*, mp 166−168 °C; $[\alpha]_D^{17}$ = −270.6 (c = 0.33 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 5.66 min (minor), 6.79 min (minor regioisomer), 7.68 min (minor regioisomer), 8.94 min (major).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.37−7.28 (m, 4H), 6.93 (d, J = 8.0 Hz, 2H), 6.84 (t, J = 7.6 Hz, 1H), 6.33 (d, J = 7.6 Hz, 1H), 5.04 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.0, 157.6, 147.9, 139.8, 131.3, 130.0, 129.7, 129.6, 127.8, 126.9, 126.7, 125.6, 123.4, 121.7, 119.9, 114.1, 87.0, 84.0, 59.1, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{24}{}^{78.9183}BrN_2O_4$ ([M + H^+]) = 519.0919, Found 519.0926; HRMS (ESI-TOF) calcd for $C_{27}H_{24}{}^{80.9163}BrN_2O_4$ ([M + H^+]) = 521.0899, Found 521.0923.

tert-Butyl-2-oxo-3′-phenyl-4′-(m-tolyl)-4′H-spiro[indoline-3,5′-isoxazole]-1-carboxylate (**3k**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 17.7 mg, 40% yield, 98:2 *rs*, and >99% *ee*, mp 148−150 °C; $[\alpha]_D^{17}$ = −249.5 (c = 0.39 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 4.65 min (minor), 5.24 min (minor regioisomer), 5.48 min (minor regioisomer), 5.10 min (major).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.4 Hz, 1H), 7.70−7.61 (m, 2H), 7.35−7.23 (m, 4H), 7.14 (t, J = 7.8 Hz, 1H), 7.07 (d, J = 7.2 Hz, 1H), 6.86 (s, 2H), 6.76 (t, J = 7.6 Hz, 1H), 6.28 (d, J = 7.6 Hz, 1H), 5.01 (s, 1H), 2.24 (s, 3H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.3, 158.2, 148.0, 139.8, 137.8, 132.0, 129.8, 129.3, 128.6, 128.3, 127.9, 127.6, 127.4, 126.8, 125.8, 125.2, 123.1, 120.2, 113.8, 87.2, 83.9, 59.7, 27.0, 20.3. HRMS (ESI-TOF) calcd for $C_{28}H_{27}N_2O_4$ ([M + H^+]) = 455.1971, Found 455.1970.

tert-Butyl-2-oxo-3′-phenyl-4′-(p-tolyl)-4′H-spiro[indoline-3,5′-isoxazole]-1-carboxylate (**3l**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 15.7 mg, 35% yield, >99:1 *rs*, and 97% *ee*, mp 180−181 °C; $[\alpha]_D^{18}$ = −288.8 (c =

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0.24 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm) retention time: 6.10 min (minor), 9.29 min (major),.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 6.8 Hz, 2H), 7.26−7.30 (m, 3H), 7.23−7.26 (m, 2H), 7.06 (d, J = 7.6 Hz, 2H), 6.92 (d, J = 7.6 Hz, 2H), 6.77 (t, J = 7.6 Hz, 1H), 6.33 (d, J = 7.6 Hz, 1H), 5.04 (s, 1H), 2.29 (s, 3H), 1.63 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.3, 158.1, 148.0, 139.8, 137.4, 129.7, 129.3, 129.0, 128.7, 128.0, 127.6, 127.4, 126.8, 125.9, 123.2, 120.3, 113.8, 87.1, 83.9, 59.5, 27.0, 20.1. HRMS (ESI-TOF) calcd for $C_{28}H_{27}N_2O_4$ ([M + H$^+$]) = 455.1971, Found 455.1965.

tert-Butyl-2-oxo-3′-phenyl-4′-(4-(trifluoromethyl)phenyl)-4′H-spiro[indoline-3,5′-isoxazole]-1-carboxylate (**3m**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 16.2 mg, 32% yield, 99:1 *rs*, and >99% *ee*, mp 175−176 °C; $[\alpha]_D^{17}$ = −269.9 (c = 0.31 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 4.87 min (minor), 5.54 min (minor regioisomer), 7.06 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 7.4 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.39−7.29 (m, 3H), 7.27 (d, J = 6.8 Hz, 1H), 7.18 (d, J = 7.8 Hz, 2H), 6.78 (t, J = 7.6 Hz, 1H), 6.24 (d, J = 7.6 Hz, 1H), 5.14 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.9, 157.4, 147.9, 139.8, 136.4, 130.1, 129.7, 128.5, 127.8, 126.8, 126.7, 125.4, 125.0, 125.0, 123.3, 119.7, 114.1, 87.2, 84.1, 59.3, 27.0. HRMS (ESI-TOF) calcd for $C_{28}H_{24}F_3N_2O_4$ ([M + H$^+$]) = 509.1688, Found 509.1681.

tert-Butyl-4′-(3-methoxyphenyl)-2-oxo-3′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3n**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 18.5 mg, 40% yield, 90:10 *rs*, and >99% *ee*, mp 146−148 °C; $[\alpha]_D^{17}$ = −259.4 (c = 0.39 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 5.54 min (minor), 6.25 min (minor regioisomer), 6.98 min (major), 8.58 min (minor regioisomer).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (t, J = 10.0 Hz, 1H), 7.65 (d, J = 7.2 Hz, 2H), 7.36−7.28 (m, 3H), 7.25 (d, J = 7.2 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 6.79 (t, J = 7.4 Hz, 2H), 6.66 (d, J = 7.4 Hz, 1H), 6.57 (s, 1H), 6.39 (d, J = 7.6 Hz, 1H), 5.03 (s, 1H), 3.68 (s, 3H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.3, 159.0, 157.9, 148.0, 139.8, 133.6, 129.8, 129.4, 129.1, 127.7, 127.3, 126.7, 125.7, 123.3, 120.4, 120.2, 113.9, 113.7, 112.9, 87.1, 83.9, 59.7, 54.3, 27.0. HRMS (ESI-TOF) calcd for $C_{28}H_{27}N_2O_5$ ([M + H$^+$]) = 471.1920, Found 471.1924.

tert-Butyl-2-oxo-4′-(3-phenoxyphenyl)-3′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3o**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 21.6 mg, 41% yield, >99:1 *rs*, and 97% *ee*, mp 165−167 °C; $[\alpha]_D^{17}$ = −307.0 (c = 0.36 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 5.48 min (minor), 5.94 min (major).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.2 Hz, 1H), 7.64 (d, J = 7.2 Hz, 2H), 7.41−7.30 (m, 4H), 7.25 (d, J = 3.6 Hz, 1H), 7.23−7.18 (m, 2H), 7.05 (t, J = 7.3 Hz, 1H), 6.99−6.87 (m, 2H), 6.87−6.82 (m, 1H), 6.67 (d, J = 7.9 Hz, 2H), 6.62 (s, 1H), 6.45 (d, J = 7.5 Hz, 1H), 5.05 (s, 1H), 1.63 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.2, 157.4, 156.5, 155.7, 147.9, 139.8, 134.1, 129.9, 129.5, 129.4, 128.7, 127.7, 127.1, 126.8, 125.7, 123.2, 122.8, 122.3, 120.4, 118.6, 118.3, 117.4, 114.0, 87.2, 84.0, 59.7, 27.0. HRMS (ESI-TOF) calcd for $C_{33}H_{29}N_2O_5$ ([M + H$^+$]) = 533.2076, Found 533.2079.

tert-Butyl-4′-(naphthalen-2-yl)-2-oxo-3′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3p**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 19.5 mg, 40% yield, 71:29 *rs*, and 93% *ee*, mp 165−166 °C. HPLC (Chiralpak ID, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 11.73 min (minor), 13.13 min (major), 15.77 min (minor regioisomer), 20.11 min (minor regioisomer). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 1H), 7.73−7.71 (m, 1H), 7.67−7.64 (m, 2H), 7.62−7.59 (m, 2H), 7.55−7.51 (m, 2H), 7.42−7.39 (m, 2H), 7.25−7.23 (m, 2H), 7.13−7.10 (m, 1H), 7.07−7.02 (m, 1H), 6.52 (t, J = 7.6 Hz, 1H), 6.19 (d, J = 7.6 Hz, 1H), 5.15 (s, 1H), 1.58 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.3, 159.2, 149.1, 140.9, 133.2, 133.0, 130.8, 130.4, 129.0, 128.7, 127.8, 126.7, 121.1, 114.9, 88.2, 85.0, 61.0, 28.1. HRMS (ESI-TOF) calcd for $C_{31}H_{27}N_2O_4$ ([M + H$^+$]) = 491.1971, Found 491.1975.

tert-Butyl-5-fluoro-2-oxo-3′,4′-diphenyl-4′H-spiro[indoline-3,5′-isoxazole]-1-carboxylate (**3q**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 11.2 mg, 35% yield, 98:2 *rs*, and >99% *ee*, mp 164−165 °C; $[\alpha]_D^{16}$ = −286.2 (c = 0.21 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 4.67 min (minor), 5.55 min (minor regioisomer), 6.17 min (major).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 9.0, 4.5 Hz, 1H), 7.58 (d, J = 7.2 Hz, 2H), 7.28 (dd, J = 8.8, 4.3 Hz, 2H), 7.24−7.22 (m, 3H), 7.19 (s, 1H), 7.03−6.95 (m, 2H), 6.88 (td, J = 8.8, 2.7 Hz, 1H), 5.91 (dd, J = 8.2, 2.7 Hz, 1H), 5.03 (s, 1H), 1.56 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.9, 159.5, 157.9, 147.9, 131.7, 129.5, 128.3, 127.9, 127.7, 127.0, 126.8, 122.1, 116.5, 116.3, 115.3, 115.2, 113.2, 113.0, 86.8, 84.1, 60.0, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{24}FN_2O_4$ ([M + H$^+$]) = 459.1720, Found 459.1715.

tert-Butyl-5-bromo-2-oxo-3′,4′-diphenyl-4′H-spiro[indoline-3,5′-isoxazole]-1-carboxylate (**3r**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 15.5 mg, 44% yield, 96:4 *rs*, and 96% *ee*, mp 164−166 °C; $[\alpha]_D^{16}$ = −118.7 (c = 0.29 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 4.89 min (minor), 5.52 min (minor regioisomer), 5.88 min (minor regioisomer), 6.69 min (major).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 7.4 Hz, 2H), 7.39−7.34 (m, 2H), 7.32 (d, J = 2.7 Hz, 4H), 7.26 (s, 1H), 7.04 (d, J = 4.1 Hz, 2H), 6.32 (s, 1H), 5.08 (s, 1H), 1.63 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.5, 157.8, 147.8, 138.7, 132.6, 131.7, 129.5, 128.9, 128.3, 127.9, 127.7, 127.0, 126.8, 122.3, 116.2, 115.5, 86.8, 84.3, 60.0, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{24}{}^{78.9183}BrN_2O_4$ ([M + H$^+$]) = 519.0919, Found 519.0922; HRMS (ESI-TOF) calcd for $C_{27}H_{24}{}^{80.9163}BrN_2O_4$ ([M + H$^+$]) = 521.0899, Found 521.0956.

tert-Butyl-5-methoxy-2-oxo-3′,4′-diphenyl-4′H-spiro[indoline-3,5′-isoxazole]-1-carboxylate (**3s**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 18.0 mg, 38% yield, 94:6 *rs*, and 97% *ee*, mp 168−170 °C; $[\alpha]_D^{16}$ = −199.2 (c = 0.37 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 5.60 min (minor), 7.33 min (minor regioisomer), 8.39 min (major).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 7.2 Hz, 2H), 7.35 (dd, J = 12.8, 6.0 Hz, 2H), 7.30 (d, J = 7.0 Hz, 4H), 7.08 (s, 2H), 6.79 (dd, J = 9.0, 2.6 Hz, 1H), 5.79 (d, J = 2.4 Hz, 1H), 5.08 (s, 1H), 3.34 (s, 3H), 1.63 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.3, 158.0, 155.2, 148.1, 133.1, 132.3, 129.4, 128.2, 128.1, 127.7, 127.6, 127.2, 126.8, 121.0, 116.7, 115.0, 110.0, 87.1, 83.7, 59.7, 54.3, 27.0. HRMS (ESI-TOF) calcd for $C_{28}H_{27}N_2O_5$ ([M + H$^+$]) = 471.1920, Found 471.1920.

tert-Butyl-3′-(4-fluorophenyl)-2-oxo-4′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3t**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 27.4 mg, 60% yield, 96:4 *rs*, and 97% *ee*, mp 94−95 °C; $[\alpha]_D^{11}$ = −209.8 (c = 0.54 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 5.61 min (minor), 6.69 min (minor regioisomer), 7.01 min (major), 7.91 min (minor regioisomer).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.2 Hz, 1H), 7.64 (dd, J = 8.6, 5.3 Hz, 2H), 7.26 (dd, J = 10.0, 6.8 Hz, 4H), 7.15−7.01 (m, 3H), 6.99 (d, J = 8.6 Hz, 2H), 6.75 (t, J = 7.4 Hz, 1H), 6.27 (d, J = 7.6 Hz, 1H), 5.04 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.3, 157.0, 147.9, 139.8, 131.9, 129.9, 128.8, 128.7, 128.1, 128.0, 127.7, 125.7, 123.2, 120.0, 115.0, 114.8, 113.9, 87.2, 84.0, 59.7, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{23}FKN_2O_4$ ([M + K$^+$]) = 497.1279, Found 497.1273.

tert-Butyl-3′-(3-chlorophenyl)-2-oxo-4′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3u**). Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 20.8 mg, 44% yield, >99:1 *rs*, and 87% *ee*, mp 136−138 °C; $[\alpha]_D^{11}$ = −243.8 (c = 0.40 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 4.86 min (minor), 6.07 min (major).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 1H), 7.72 (t, J = 1.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.38−

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7.30 (m, 2H), 7.30−7.28 (m, 2H), 7.26−7.19 (m, 2H), 7.08−7.00 (m, 2H), 6.76 (t, J = 7.6 Hz, 1H), 6.26 (d, J = 7.6 Hz, 1H), 5.03 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.1, 157.0, 147.9, 139.8, 133.7, 131.6, 129.9, 129.4, 129.0, 128.9, 128.2, 128.0, 127.8, 126.6, 125.7, 124.9, 123.2, 119.8, 113.9, 87.4, 84.0, 59.4, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{23}{}^{34.9689}ClN_2NaO_4$ ([M + Na^+]) = 497.1244, Found 497.1239; HRMS (ESI-TOF) calcd for $C_{27}H_{23}{}^{36.9659}ClN_2NaO_4$ ([M + Na^+]) = 499.1214, Found 499.1093.

*tert-Butyl-3′-(4-chlorophenyl)-2-oxo-4′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3v**).* Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 24.5 mg, 52% yield, >99:1 *rs*, and 92% *ee*, mp 89−90 °C; $[\alpha]_D^{16}$ = −217.2 (c = 0.41 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 5.48 min (minor), 7.32 min (major).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.33−7.24 (m, 7H), 7.03 (d, J = 3.6 Hz, 2H), 6.76 (t, J = 7.6 Hz, 1H), 6.28 (d, J = 7.6 Hz, 1H), 5.04 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.2, 157.0, 147.9, 139.8, 135.4, 131.8, 129.9, 128.2, 128.0, 128.0, 128.0, 127.7, 125.8, 125.7, 123.2, 120.0, 113.9, 87.4, 84.0, 59.6, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{23}{}^{34.9689}ClN_2NaO_4$ ([M + Na^+]) = 497.1244, Found 497.1244; HRMS (ESI-TOF) calcd for $C_{27}H23^{36.9659}ClN_2NaO_4$ ([M + Na^+]) = 499.1214, Found 499.1126.

*tert-Butyl-3′-(3-bromophenyl)-2-oxo-4′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3w**).* Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 23.7 mg, 46% yield, 95:5 *rs*, and 99% *ee*, mp 170−172 °C; $[\alpha]_D^{14}$ = −180.6 (c = 0.32 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 95:5, flow rate 1.0 mL/min, λ = 254 nm) retention time: 7.97 min (minor), 10.56 min (minor regioisomer), 11.62 min (major).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (t, J = 1.6 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.48 (dd, J = 8.0, 1.5 Hz, 2H), 7.28 (m, 4H), 7.17 (t, J = 8.0 Hz, 1H), 7.09−6.97 (m, 2H), 6.81−6.71 (m, 1H), 6.33−6.21 (m, 1H), 5.02 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.1, 156.91, 147.9, 139.8, 132.3, 131.6, 129.9, 129.5, 129.3, 129.2, 128.2, 128.0, 127.8, 125.7, 125.3, 123.2, 121.8, 119.8, 113.9, 87.4, 84.0, 59.4, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{23}{}^{78.9183}BrN_2NaO_4$ ([M + Na^+]) = 541.0739, Found 541.0742; HRMS (ESI-TOF) calcd for $C_{27}H_{23}{}^{80.9163}BrN_2NaO_4$ ([M + Na^+]) = 543.0719, Found 543.0709.

*tert-Butyl-3′-(4-bromophenyl)-2-oxo-4′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3x**).* Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 25.3 mg, 49% yield, >99:1 *rs*, and 93% *ee*, mp 140−142 °C; $[\alpha]_D^{16}$ = −201.6 (c = 0.43 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 5.73 min (minor), 7.81 min (major).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.27−7.26 (m, 2H), 7.24 (m, 2H), 7.03−7.02 (m, 2H), 6.75 (t, J = 7.6 Hz, 1H), 6.27 (d, J = 7.6 Hz, 1H), 5.04 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.2, 157.1, 147.9, 139.8, 131.8, 130.9, 129.9, 128.2, 128.1, 128.0, 127.7, 126.2, 125.7, 123.8, 123.2, 120.0, 113.9, 87.4, 84.0, 59.5, 27.0. HRMS (ESI-TOF) calcd for $C_{27}H_{23}{}^{78.9183}BrN_2NaO_4$ ([M + Na^+]) = 541.0739, Found 541.0743; HRMS (ESI-TOF) calcd for $C_{27}H_{23}{}^{80.9163}BrN_2NaO_4$ ([M + Na^+]) = 543.0719, Found 543.0611.

*tert-Butyl-2-oxo-4′-phenyl-3′-(p-tolyl)-4′H-spiro[indoline-3,5′-isoxazole]-1-carboxylate (**3y**).* Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 18.2 mg, 40% yield, 96:4 *rs*, and 99% *ee*, mp 143−145 °C; $[\alpha]_D^{12}$ = −260.3 (c = 0.35 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 5.49 min (minor), 6.63 min (major), 8.33 min (minor regioisomer), 8.703 min (minor regioisomer).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.25 (m, 4H), 7.11 (d, J = 7.6 Hz, 2H), 7.05 (d, J = 3.2 Hz, 2H), 6.75 (t, J = 7.6 Hz, 1H), 6.27 (d, J = 7.6 Hz, 1H), 5.07 (s, 1H), 2.32 (s, 3H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.3, 157.9, 148.0, 139.8, 139.7, 132.3, 129.7, 128.4, 128.1, 128.0, 127.5, 126.7, 125.7, 124.4, 123.1, 120.3, 113.8, 87.0, 83.9, 59.9, 27.0, 20.4. HRMS (ESI-TOF) calcd for $C_{28}H_{26}N_2NaO_4$ ([M + Na^+]) = 477.1790, Found 477.1789.

*tert-Butyl-2-oxo-4′-phenyl-3′-(4-(trifluoromethyl)phenyl)-4′H-spiro[indoline-3,5′-isoxazole]-1-carboxylate (**3z**).* Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 26.0 mg, 53% yield, 99:1 *rs*, and 92% *ee*, mp 108−110 °C; $[\alpha]_D^{16}$ = −197.2 (c = 0.46 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 5.45 min (minor), 6.57 min (major), 7.27 min (minor regioisomer), 8.12 min (minor regioisomer).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.29−7.28 (m, 2H), 7.27−7.25 (m, 2H), 7.08−7.00 (m, 2H), 6.77 (t, J = 7.6 Hz, 1H), 6.29 (d, J = 7.6 Hz, 1H), 5.08 (s, 1H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.1, 156.9, 147.9, 139.9, 131.6, 130.0, 128.2, 128.0, 127.9, 126.9, 125.7, 124.7, 124.6, 123.3, 119.8, 114.0, 87.6, 84.1, 59.4, 27.0. HRMS (ESI-TOF) calcd for $C_{28}H_{23}F_3KN_2O_4$ ([M + K^+]) = 547.1242, Found 547.1233.

*tert-Butyl-3′-(4-methoxyphenyl)-2-oxo-4′-phenyl-4′H-spiro-[indoline-3,5′-isoxazole]-1-carboxylate (**3aa**).* Purified by flash chromatography (petroleum ether:EtOAc = 10:1) to afford a white solid, 20.4 mg, 43% yield, 90:10 *rs*, and 95% *ee*, mp 131−132 °C; $[\alpha]_D^{13}$ = −238.1 (c = 0.40 in CH_2Cl_2). HPLC (Chiralpak IA, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL/min, λ = 254 nm) retention time: 6.406 min (minor), 7.64 min (minor regioisomer), 8.77 min (major), 9.942 min (minor regioisomer).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.2 Hz, 1H), 7.63−7.55 (m, 2H), 7.27−7.24 (m, 4H), 7.05 (m, 2H), 6.85−6.79 (m, 2H), 6.75 (m, 1H), 6.27 (dd, J = 7.6, 0.8 Hz, 1H), 5.05 (s, 1H), 3.78 (s, 3H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.4, 160.2, 157.5, 148.0, 139.8, 132.3, 129.7, 128.4, 128.1, 128.0, 127.5, 125.7, 123.1, 120.4, 119.7, 113.8, 113.1, 86.9, 83.9, 60.0, 54.3, 27.0. HRMS (ESI-TOF) calcd for $C_{28}H_{26}N_2NaO_5$ ([M + Na^+]) = 493.1739, Found 493.1740.

■ ASSOCIATED CONTENT

Supporting Information

Full optimization details, ^{1}H and ^{13}C NMR spectra, HPLC analyses for all the products, and X-ray crystal data of compound **3h** (CIF) are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. (b) Shangary, S.; Wang, S. *Annu. Rev. Pharmacol. Toxicol.* **2009**, *49*, 223. (c) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem.* **2006**, *49*, 3432. (d) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.

(2) (a) Komakine, N.; Takaishi, Y.; Honda, G.; Ito, M.; Takeda, Y.; Kodzhimatov, O. K.; Ashurmetov, O. *Nat. Med. (Tokyo, Jpn.)* **2005**, *59*, 45. (b) Khuzhaev, V. U.; Zhalolov, I.; Turgunov, K. K.; Tashkhodzhaev, B.; Levkovich, M. G.; Aripova, S. F.; Shashkov, A. S. *Chem. Nat. Compd.* **2004**, *40*, 269. (c) Kamano, Y.; Zhang, H.-p.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Pettit, G. R. *Tetrahedron Lett.* **1995**, *36*, 2783. (d) Zhang, H.-P.; Kamano, Y.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Itokawa, H.; Pettit, G. R. *Tetrahedron* **1995**, *51*, 5523. (e) Tang, Y.-Q.; Sattler, I.; Thiericke, R.; Grabley, S. *Eur. J. Org. Chem.* **2001**, 261. (f) Kitajima, M.; Mori, I.; Arai, K.; Kogure, N.; Takayama,

H. *Tetrahedron Lett.* **2006**, *47*, 3199. (g) Koguchi, Y.; Kohno, J.; Nishio, M.; Takahashi, K.; Okuda, T.; Ohnuki, T.; Komatsubara, S. *J. Antibiot (Tokyo)* **2000**, *53*, 105. (h) Suarez-Castillo, O. R.; Sanchez-Zavala, M.; Melendez-Rodriguez, M.; Aquino-Torres, E.; Morales-Rios, M. S.; Joseph-Nathan, P. *Heterocycles* **2007**, *71*, 1539. (i) Kohno, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Kuroda, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. *J. Org. Chem.* **2000**, *65*, 990. (j) Kobayashi, J.; Suzuki, H.; Shimbo, K.; Takeya, K.; Morita, H. *J. Org. Chem.* **2001**, *66*, 6626. (k) Rasmussen, H. B.; MacLeod, J. K. *J. Nat. Prod.* **1997**, *60*, 1152. (l) Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20. (m) Kagata, T.; Saito, S.; Shigemori, H.; Ohsaki, A.; Ishiyama, H.; Kubota, T.; Kobayashi, J. *J. Nat. Prod.* **2006**, *69*, 1517. (n) Anthoni, U.; Christophersen, C.; Nielsen, P. H. *Alkaloids: Chem. Biol. Perspect.* **1999**, *13*, 163.

(3) (a) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247−7290. (b) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104. (c) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, *41*, 3003. (d) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165. (e) Trost, B. M.; Cramer, N.; Silverman, S. M. *J. Am. Chem. Soc.* **2007**, *129*, 12396. (f) Tan, B.; Candeias, N. R.; Barbas, C. F. *J. Am. Chem. Soc.* **2011**, *133*, 4672.

(4) (a) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (b) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235. (c) Gothelf, K. V.; Thomsen, I.; Jorgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59. (d) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840. (e) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355. (f) Simonsen, K. B.; Bayon, P.; Hazell, R. G.; Gothelf, K. V.; Jorgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845. (g) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *64*, 5017. (h) Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431. (i) Shirahase, M.; Kanemasa, S.; Oderaotoshi, Y. *Org. Lett.* **2004**, *6*, 675. (j) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718. (k) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodriguez, R.; Oro, L. A.; Balana, A. I.; Lahoz, F. J.; Tejero, T.; Merino, P.; Franco, S.; Montesa, I. *J. Am. Chem. Soc.* **2004**, *126*, 2716. (l) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926. (m) San, S. C.; Marta, N.; Catherine, A. E.; Charles, W. J. *Tetrahedron Lett.* **2007**, *48*, 277. (n) Jen, W. S.; Wiener, J. M.; MacMillan, W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (o) Aleman, J.; Fraile, A.; Marzo, L.; Ruano, J. L. G.; Izquierdo, C.; Diaz-Tendero, S. *Adv. Synth. Catal.* **2012**, *354*, 1665. (p) Sakakura, A.; Hori, M.; Fushimi, M.; Ishihara, K. *J. Am. Chem. Soc.* **2010**, *132*, 15550.

(5) (a) Suga, H.; Funyu, A.; Kakehi, A. *Org. Lett.* **2007**, *9*, 97. (b) Sibi, M. P.; Rane, D.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2008**, *10*, 2971. (c) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132* (12), 4076.

(6) (a) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (b) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schuermann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2010**, *2*, 735. (c) Liu, T.-L.; Xue, Z.-Y.; Tao, H.-Y.; Wang, C.-J. *Org. Biomol. Chem.* **2011**, *9*, 1980.

(7) Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8276.

(8) (a) Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366. (b) Sibi, M. P.; Ma, Z.; Itoh, K.; Prabagaran, N.; Jasperse, C. P. *Org. Lett.* **2005**, *7*, 2349. (c) Suga, H.; Adachi, Y.; Fujimoto, K.; Furihata, Y.; Tsuchida, T.; Kakehi, A.; Baba, T. *J. Org. Chem.* **2009**, *74*, 1099. (d) Brinkmann, Y.; Madhushaw, R. J.; Jazzar, R.; Bernardinelli, G.; Kuendig, E. P. *Tetrahedron* **2007**, *63*, 8413. (e) Yamamoto, H.; Hayashi, S.; Kubo, M.; Harada, M.; Hasegawa, M.; Noguchi, M.; Sumimoto, M.; Hori, K. *Eur. J. Org. Chem.* **2007**, 2859. (f) Risitano, F.; Grassi, G.; Foti, F.; Bruno, G.; Rotondo, A. *Heterocycles* **2003**, *60*, 857. (g) Savage, G. P. *Curr. Org. Chem.* **2010**, *14*, 1478. (h) Dadiboyena, S. *Curr. Org. Synth.* **2013**, *10*, 661. (i) Xu, J. P.; Wang, J.; Ellis, E. D.; Hamme, A. T. *Synthesis* **2006**, *22*, 3815. (j) Maheswari, S. U.; Perumal, S. *Tetrahedron Lett.* **2012**, *53*, 6885. (k) Occhiato, E. G.; Guarna, A.; Brandi, A.; Goti, A.; De Sarlo, F. *J. Org. Chem.* **1992**, *57*, 4206. (l) Broggini, G.; Bruche, L.; Zecchi, G.; Pilati, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 533. (m) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Masciocchi, N.; Sottocornola, S. *Org. Lett.* **2006**, *8*, 4521. (n) Ribeiro, C. J. A.; Kumar, S. P.; Moreira, R.; Santos, M. M. M. *Tetrahedron Lett.* **2012**, *53*, 281.

(9) (a) Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. *J. Am. Chem. Soc.* **1994**, *116*, 2324. (b) Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron* **2001**, *57*, 8313. (c) Rasmussen, B. S.; Elezcano, U.; Skrydstrup, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1723.

(10) (a) Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: Weinheim, 1988. (b) Padwa, A., Pearson, W. H., Eds. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Wiley: Chichester, U.K., 2002.

(11) (a) Ukaji, Y.; Sada, K.; Inomata, K. *Chem. Lett.* **1993**, *22*, 1847. (b) Shimizu, M.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **1996**, *25*, 455. (c) Yoshida, Y.; Ukaji, Y.; Fujinami, S.; Inomata, K. *Chem. Lett.* **1998**, *27*, 1023. (d) Tsuji, M.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2002**, 1112. (e) Toker, J. D.; Wentworth, P., Jr.; Hu, Y.; Houk, K. N.; Janda, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 3244.

(12) For reviews of chiral *N*,*N*′-dioxide−metal complexes in asymmetric catalysis, see: (a) Liu, X. H.; Lin, L. L.; Feng, X. M. *Acc. Chem. Res.* **2011**, *44*, 574. (b) Huang, S. X.; Ding, K. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 7734. (c) Shen, K.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Chem. Sci.* **2012**, *3*, 327. (d) Liu, X. H.; Lin, L. L.; Feng, X. M. *Org. Chem. Front.* **2014**, *1*, 298.

(13) For selected asymmetric reactions catalyzed by chiral *N*,*N*′-dioxide−metal complexes, see: (a) Li, W.; Liu, X. H.; Hao, X. Y.; Hu, X. L.; Chu, Y. Y.; Cao, W. D.; Qin, S.; Hu, C. W.; Lin, L. L.; Feng, X. M. *J. Am. Chem. Soc.* **2011**, *133*, 15268. (b) Zhou, L.; Liu, X. H.; Ji, J.; Zhang, Y. H.; Hu, X. L.; Lin, L. L.; Feng, X. M. *J. Am. Chem. Soc.* **2012**, *134*, 17023. (c) Wang, G.; Liu, X. H.; Huang, T. Y.; Kuang, Y. L.; Lin, L. L.; Feng, X. M. *Org. Lett.* **2013**, *15*, 76. (d) Li, J. T.; Lian, X. J.; Liu, X. H.; Lin, L. L.; Feng, X. M. *Chem.—Eur. J.* **2013**, *19*, 5134. (e) Zheng, K.; Lin, L. L.; Feng, X. M. *Acta Chim. Sin.* **2012**, *70*, 1785. (f) Zhao, J. N.; Liu, X. H.; Luo, W. W.; Xie, M. S.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 3473. (g) Zhao, J. N.; Liu, X. H.; Luo, W. W.; Xie, M. S.; Lin, L. L.; Feng, X. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 3473. (h) Xie, M. S.; Wu, X. X.; Wang, G.; Lin, L. L.; Feng, X. M. *Acta Chim. Sin.* **2014**, *72*, 856.

(14) CCDC 994333 (**3h**) contains 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.

(15) Soloshonok, V. A.; Roussel, C.; Kitagawa, O.; Sorochinsky, A. E. *Chem. Soc. Rev.* **2012**, *41*, 4180.

(16) (a) Houk, K. N.; Gonzalez, J.; Li, Y. *Acc. Chem. Res.* **1995**, *28*, 81−90. (b) Morao, I.; Cossio, F. P. *J. Org. Chem.* **1999**, *64*, 1868.