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Approach to Chiral 1-Substituted Isoquinolone and 3-Substituted

Isoindolin-1-one by Addition-Cyclization Process

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Abstract



An approach to access 1-substituted-isoquinolones has been developed through the addition-cyclization of imines with Grignard reagents in the presence of 2,2'-dipyridyl. A number of substituted aromatic magnesium reagents were amenable to this process, and the desired products were obtained with excellent yields and outstanding diastereoselectivities (dr>99:1). The utility of this convenient approach is demonstrated by the formal synthesis of (*S*)-cryptostyline II. Moreover, *N*-methylmorpholine (NMM) was found to be an effective additive for the formation of 3-substitutedisoindolin-1-ones using one-pot addition-cyclization-deprotection of imine with Grignard reagents.

Introduction

The enantioselective construction of a stereogenic center at the a-position of nitrogen-containing heterocycles (*N*-heterocycles) is one of the top research topics in synthetic heterocyclic chemistry. Many chiral pharmaceutical agents contain these skeletons¹. Among them, chiral 1-substituted-isoquinolone **1** and 3-substitutedisoindolin-1-one **2** are widely served as key intermediates in the synthesis of isoquinoline and indole alkaloids². For instance, (*S*)-cryptostyline I, II, III (**3-5**), isolated from *Cryptostylis fulva* and *Cryptostylis erythroglosa*^{3a}, are used as

probes for dopamine receptor D_1^{3b} . Canadine (6), a protoberberine alkaloid isolated from *Corydalis yanhusuo*, can act as a calcium channel blocker⁴. PD-172938 (7)⁵ shows good affinity for dopamine D₄ receptor, and lennoxamine (8)⁶ is an alkaloid isolated from barberries species (Figure 1).



Figure 1. Structures of several natural products.

From the synthetic point of view, 1-substituted-isoquinolone **1** could be conveniently converted to 1-substituted-tetrahydroisoquinoline although the latter was readily accessible through catalytic enantioselective processes such as asymmetric hydrogenation of amines or imines⁷, the copper-catalyzed allylation⁸, asymmetric alkynylation/lactamization cascade process^{9,10} and palladium-catalyzed intramolecular allylic amination¹¹, as well as other diastereoselective processes¹². Asymmetric approaches to isoquinolone **1** include an intramolecular Heck cyclization¹³, 1,3-membered ring-closure of chiral hydrazones¹⁴ and reactions of chiral acyliminium ions¹⁵, as well as a chiral-appendage-mediated carbanion method¹⁶. In spite of these robust processes, a straightforward and high diastereoselective approach to isoquinolone **1** is still in demand. As for 3-substituted isoindolin-1-one **2**, recent efforts led to a number of powerful approaches including reduction of N-imide ion¹⁷, nucleophilic addition¹⁸, coupling of aryl boric acid with imide¹⁹ and multi component

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Mannich reaction²⁰. Due to the potential racemization of 3-subsituted isoindolin-1-ones under acidic, basic or reductive conditions^{17a}, the straightforward and efficient approach to chiral 3-aryl isoindolin-1-ones is still quite limited. Therefore, an efficient method to chiral 3-aryl isoindolin-1-ones under mild racemization-free conditions is still needed.

Nowadays, diastereoselective addition controlled by Davis and Ellman's chiral auxiliaries (e.g. *p*-toluenesulfinamide and 2-methylpropane-2-sulfinamide) is one of the most versatile and practical methods to chiral amines²¹. In recent years, we explored the chemistry in this field^{22,23}, and successfully developed a one-pot intramolecular tandem protocol to access *trans*-5-hydroxy-6-substituted-2-piperidinones or

trans-4-hydroxy-5-substituted-2-pyrrolidinones through the nucleophilic addition of α -chiral aldimines with Grignard reagents²². Encouraged by our previous results (Fig. 2, eq. 1), we envisioned that 1-substituted-isoquinolone (1)/3-substitutedisoindolin-1-one (2) should be accessible *via* the addition-cyclization process of the imine 9/10/13/15 with Grignard reagents (Fig. 2, eq. 2). In continuation of our efforts to develop effective synthetic approaches to *a*-chiral substituted nitrogen-containing heterocycles, herein we describe our exploration in this aspect to provide 1-substituted-isoquinolone scaffold (1), 3-substituted isoindolin-1-one (2) and its application in total synthesis of (*S*)-(+)-cryptostyline II (4).

Our previous work²²



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Figure 2. Our strategy to access 11/12/14/16.

Results and discussions

Our investigation started with the addition of imine 9 with phenyl magnesium bromide. As shown in Table 1, neither desired addition nor addition-cyclization product **11a** was isolated under multiple conditions. The attempt to use Lewis acids, such as AlMe₃ and $ZnCl_2^{24a}$, turned out to be fruitless (Table 1, entries 1-4). We suspected that the high reactivity of Grignard reagent caused the messy reactions. The complexation of Grignard reagent with a simple organic ligand (such as TMEDA, BDMAEE, etc.)^{24b-d} is one of the most effective means to lower its reactivity. Several additives were examined and the results are summarized (Table 1, entries 5-12). First, bis(2-dimethylaminoethyl) ether (BDMAEE) was examined based on literature, unfortunately no conversion of imine 9 was observed (Table 1, entry 5). Considering the additional complexation of oxygen in BDMAEE, tetramethylethylenediamine (TMEDA) was then investigated. To our delight, the desired **11a** was generated in 45% yield with high diastereoselectivity (dr > 99:1) (Table 1, entries 6-7). The reason of low yield was probably that the complexation ability of BDMAEE or TMEDA is too strong regarding the nucleophilic attack to imine double bond. To verify this hypothesis, other additives with weak complexing ability like N-methylmorpholine $(NMM)^{24e}$, PPh₃ and triethylamine (TEA) were examined (Table 1, entries 8-10). When TEA was used, the desired addition-cyclization product **11a** was produced in 65% yield with high diastereoselectivity (dr > 99:1) (Table 1, entry 10). Notably, 2,2'-dipyridyl could afford the desired **11a** in 77% yield with high diastereoselectivity (dr > 99:1) (Table 1, entry 11). When o-Phenanthroline was used, the desired product 11a was given in 41% yield (dr>99:1) (Table 1, entry 12), suggesting that o-phenanthroline may complex with PhMgBr more tightly than 2,2'-dipyridyl.

Table 1. Optimization of the addition-cyclization.

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| | | Additive PhMgBr | | | ^t Bu |
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| Prop | osed coordinatio | on mode: | | 11a | |
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| Entry ^a | additive | Solvent | T/ºC | Y‰ ^b | <i>dr</i> ^c |
| 1 | / | THF | -15 | complex | - |
| 2 | AlMe ₃ | THF | -78 | NR | - |
| 3 | $ZnCl_2$ | THF | -78 | NR | - |
| 4 | / | THF/DCM | -78 | complex | - |
| 5 | BDMAEE | THF | -15 | NR | - |
| 6 | TMEDA | THF | -15 | 32 | 99:1 |
| 7 | TMEDA | THF/DCM | -15 | 45 | 99:1 |
| 8 | NMM | THF/DCM | -15 | 53 | 99:1 |
| 9 | PPh ₃ | THF/DCM | -15 | 40 | 99:1 |
| 10 | TEA | THF/DCM | -15 | 65 | 99:1 |
| 11 | 2,2'-Dipyridyl | THF/DCM | -15 | 77 | 99:1 |
| 12 | o-Phenanthroline | THF/DCM | -15 | 41 | 99:1 |

^{*a*} The reactions were performed with aldimine **9** (1.00 mmol), additive (6.00 mmol) (for bidentate additives, BDMAEE, TMEDA, 2,2'-dipyridyl and *o*-phenanthroline, 3.00 mmol was used), PhMgBr (3.0 mL, 1.0 M in THF) in dry solvent (6 mL) for 1 h. ^{*b*} Isolated yield. ^{*c*} *dr* was determined by ¹H NMR.

Next, we turned our attention to investigate the scope and limitation of this addition-cyclization process for substituted imines 9/13 and various Grignard reagents. Different substituted aryl Grignard reagents were surveyed under the above optimal conditions, as summarized in Scheme 1. *Ortho-*, *para-* and *meta-*substituted aryl Grignard reagents all proved to be suitable substrates, giving the desired products with high diastereoselectivities and in good yields (11b-l and 14b-e). Moreover, α - and β -naphthyl Grignard reagents could give the desired products 11m-n and 14f in moderate yields and with excellent diastereoselectivities (*dr*>99:1). On the other hand,

the reactions with alkyl Grignard reagents were generally poor, affording the desired products **110-p** in moderate yields and with low diastereoselectivities. We also explored the cyclic or hindered chain Grignard reagents (cyclopentyl, isopropyl, *tert*-butyl, ect.) none of them could generate the desired product.

Scheme 1. Reactions with different Grignard reagents.

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RMgBr (3.0 mL, 1.0 M in THF) in dry DCM (6 mL) at -15 °C for 1 h to give 11. ^b The reactions were performed with aldimine 13 (1.00 mmol), 2,2'-dipyridyl (3.00 mmol), RMgBr (3.0 mL, 1.0 M in THF) in dry DCM (6 mL) at -50 °C for 1 h to give 14. ^c Isolated

yield. $^{d} dr$ was determined by ¹H NMR.

[1,3]Dioxolo[4,5-g]isoquinolines widely exist in nature. We explored the reaction of substrate **15** with Grignard reagents, as summarized in Scheme 2. Phenyl, 3-fluorophenyl, 3-trifluoromethylphenyl, 4-phenylphenyl and β -naphthyl Grignard reagents all led to the desired products with high diastereoselectivities (*dr*>99:1) and in good yields (**16a-e**).

Scheme 2. The addition-cyclization of other substrates.



^{*a*} The reactions were performed with aldimine **15** (1.00 mmol), 2,2'-dipyridyl (3.00 mmol), RMgBr (3.0 mL, 1.0 M in THF) in dry DCM (6 mL) at -15 °C for 1 h. ^{*b*} Isolated yield. ^{*c*} dr was determined by ¹H NMR.

The relative stereochemistry of the products **11a-p**, **14a-f** and **16a-e** were unambiguously assigned as *trans*-form by X-ray crystallographical analysis of

compounds 11g and 16d (see the Supporting Information).

The removal of chiral auxiliary was straightforward and with high yield. For example, the treatment of chiral 1-substituted isoquinolone **14e** with HCl/MeOH generated in situ from oxalyl chloride $[(COCl)_2]$ and methanol produced the known lactam **17** in 91% yield, which could be readily converted to (S)-(+)-cryptostyline II (**4**)^{13a}(Scheme 3).

Scheme 3. The application in formal synthesis of (S)-(+)-cryptostyline II.



Next, we turned our attention to investigate the tandem process of α -chiral aldimine 10 with Grignard reagents. Due to the easy racemization of the 3-carbon-subsituted isoindolin-1-ones 12 under acidic, basic or reductive conditions, straightforward and efficient approach is still quite limited^{17b}. Very preparation of chiral recently, an interesting 3-carbon-subsituted isoindolin-1-ones motivated us to expand our chemistry to the imine substrate reagents^{18h}. with Grignard Although the desired addition-cyclization-deprotection product 12a was generated in 92% yield when the imine **10** was treated with 4-methoxyphenyl magnesium bromide, the enantioselectivity was relatively low compared with the results for substrates 9/13/15. Moreover, almost none of the results are repeatable for this process (Table

2, entry 1). The addition of other simple organic ligands (such as TMEDA, BDMAEE et al.) failed to improve the enantioselectivity of **12a** (Table 2, entries 2-4). When NMM was used, the enantioselectivity could reach to 88% (Table 2, entries 5-6).

 Table 2. Optimization of the addition-deprotection-cyclization.



^{*a*} The reactions were performed with aldimine **10** (0.75 mmol), additive (2,2'-dipyridyl, TMEDA and BDMAEE for 2.25 mmol; NMM for 4.50 mmol), 4-methoxyphenyl magnesium bromide (2.3 mL, 1.0 M in THF) in dry solvent (3 mL) for 2.5 h. ^{*b*} Isolated yield. ^{*c*} *ee* was determined by HPLC. ^{*d*} When the **12a** was recrystallized in EA/PE, the enantioselectivity of new crystal could reach to 97.5% *ee*.

With NMM as the organic base ligand, various Grignard reagents were also examined and the results are summarized in Scheme 4. In general, most substituted aromatic Grignard reagents could react smoothly to afford 3-aryl isoindolin-1-ones in excellent yields and with moderate to good enantioselectivities (**12a-g** and **12i-k**), while several *ortho-* or *meta*-substituted aromatic Grignard reagents led to slightly lower enantioselectivities for the desired products (**12h** and **12l**). A few bicyclic aromatic reagents, including α - and β -naphthyl Grignard reagents, also afforded the desired tandem products (**12m-n**) in excellent yields and with good enantioselectivities.

Scheme 4. The addition-cyclization-deprotection of substrate 10.



12I, 92%, 62% *ee* **12m**, 90%, 88% *ee*

^{*a*} The reactions were performed with aldimine **10** (0.75 mmol), NMM (4.50 mmol), Grignard reagents (2.3 mL, 1.0 M in THF) in dry THF (3 mL) at -15 °C for 2.5 h. ^{*b*} Isolated yield. ^{*c*} *ee* was determined by HPLC.

Conclusion

In summary, we established a convenient and one-pot method for highly diastereoselective synthesis of 1-substituted isoquinolones **11a-n**, **14a-g** and **16a-e** through the reactions of 9/13/15 with Grignard reagents. It is worth mentioning that 2,2'-dipyridyl was found as an effective additive to improve the diastereoselectivity (dr>99:1) of **11a-n**, **14a-g** and **16a-e**. This convenient approach was utilized to formally synthesize the (S)-cryptostyline II (4). Moreover, for the formation of 3-substituted isoindolin-1-ones **12a-n** by one-pot addition-cyclization-deprotection of imine **10** with Grignard reagents, 4-methylmorpholine (NMM) was found to be an effective additive. Interestingly, the chiral auxiliary was simultaneously removed

under the reaction conditions, and the desired 3-substituted isoindolin-1-ones **12a-n** were obtained in high yields and with good enantioselectivities.

Experimental Section

General Considerations THF was distilled from sodium/benzophenone. Reactions were monitored by thin layer chromatography (TLC) on glass plates coated with silica gel with fluorescent indicator. Flash chromatography was performed on silica gel (300–400) with PE/EA as eluent. Optical rotations were measured on a polarimeter with a sodium lamp. HRMS were measured on LTQ-Orbit. IR spectra were recorded using film on a Fourier Transform Infrared Spectrometer. NMR spectra were recorded at 400 MHz, and chemical shifts are reported in δ (ppm) referenced to an internal TMS standard for ¹H NMR and CDCl₃ (77.16 ppm) for ¹³C NMR.

Methyl (R,E)-2-(2-(((tert-butylsulfinyl)imino)methyl)phenyl)acetate 9

To a solution of o-Tolylacetic acid (20.00 g, 133.17 mmol), CH₃I (24.9 mL, 399.52 mmol), NaHCO₃ (22.37 g, 266.35 mmol) were stirred in DMF (200 mL) at room temperature for 12h. Then the mixture was quenched with water as well as extracted with EA for four times. The combined organic layers were washed with water and brine. Dried, filtrated and concentrated, the residue was dissolved in CH₃CN (200 mL) and treated with NBS (26.07 g, 146.49 mmol) at 80°C for 2h. Then the mixture was concentrated and purified by flash chromatography on silica gel (PE/EA=20/1) to give brominated compound (30.43 g, 94%). The brominated compound (30.43 g, 125.17 mmol) was dissolved in CHCl₃ (200 mL) and treated with Bis(tetrabutylammonium) dichromate (TBADC) (105.29 g, 150.21 mmol) at 70°C for 1h. Then the mixture was concentrated. The residue was quenched with a saturated aqueous solution of NaHCO₃ and extracted with EtOAc (200 mL \times 3). The combined organic layers were washed with brine. Dried, filtrated and concentrated, the residue was purified by flash chromatography on silica gel (PE/EA=9/1) to give aldehyde (17.40 g, 78%), which was dissolved in DCM (120 mL). Then (R)-2- methyl-2-propanesulfinamide (11.82 g, 97.65 mmol), cupric sulphate anhydrous (31.17 g, 195.30 mmol) and PPTS (2.46 g, 9.77 mmol) were added in one portion and the mixture was stirred for 24 h. The

resulting mixture was filtrated and the filtrate was concentrated to give the crude product, which was purified by flash chromatography on silica gel (PE/EA=4/1) to give compound **9** (24.73 g, 90%) as a colorless oil. $[\alpha]_D^{23}$ = -95.5 (*c* 1.00, CHCl₃); IR (film) v_{max} 2954, 1739, 1605, 1569, 1435, 1364, 1341, 1314, 1164, 1083, 919, 761 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.72 (s, 1H), 7.88-7.82 (m, 1H), 7.50-7.40 (m, 2H), 7.33-7.29 (m, 1H), 4.12-4.00 (m, 2H), 3.66 (s, 3H), 1.26 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.4, 162.8, 135.0, 132.5, 132.5, 132.2, 132.1, 128.0, 57.5, 52.2, 39.5, 22.5 ppm; HRMS (ESI-Orbitrap) *m*/*z*: [M+H]⁺ calcd for C₁₄H₂₀NO₃S: 282.1158, found: 282.1159.

Methyl (*R*,*E*)-2-(((*tert*-butylsulfinyl)imino)methyl)benzoate **10**

To a solution of 2-formylbenzoic acid (10.00 g, 66.61 mmol), CH₃I (12.4 mL, 199.83 mmol), NaHCO₃ (11.19 g, 133.22 mmol) were stirred in DMF (100 mL) at room temperature for 12h. Then the mixture was quenched with water as well as extracted with EA for four times. The combined organic layers were washed with water and brine. Dried, filtrated and concentrated, the residue was dissolved in DCM (260 mL). Then (R)-2- methyl-2-propanesulfinamide (8.07 g, 66.61 mmol), cupric sulphate anhydrous (21.26 g, 133.22 mmol) and PPTS (837 mg, 3.33 mmol) were added in one portion and the mixture was stirred for 24 h. The resulting mixture was filtrated and the filtrate was concentrated to give the crude product, which was purified by flash chromatography on silica gel (PE/EA=4/1) to give compound 10 (16.91 g, 95%) as a colorless oil. $[\alpha]_D^{22}$ = -197.9 (c 1.00, CHCl₃); IR (film) v_{max} 2980, 2954, 2924, 2863, 1721, 1606, 1566, 1434, 1364, 1288, 1265, 1132, 1084, 825, 764 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.22 (s, 1H), 8.04-8.01 (m, 1H), 7.97-7.94 (m, 1H), 7.64-7.59 (m, 1H), 7.58-7.53 (m, 1H), 3.95 (s, 3H), 1.29 (s, 9H) ppm; 13 C NMR (100 MHz, CDCl₃) δ 167.1, 162.7, 134.6, 132.2, 131.4, 131.4, 130.6, 129.0, 58.0, 52.7, 22.8 ppm; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for C₁₃H₁₈NO₃S: 268.1002, found: 268.0996. (*R*,*E*)-2-(2-(((*tert*-butylsulfinyl)imino)methyl)-4,5-dimethoxyphenyl)acetate Methyl

To a solution of 3,4-dimethoxyphenylacetic acid (25.00 g, 127.42 mmol) was stirred in AcOH (65 mL) at 80°C. Then concentrated hydrochloric acid (20 mL), HCHO (20

mL) were added and the mixture was stirred for 2 h. The mixture was concentrated and diluted with DCM. The organic layer was washed with a saturated aqueous solution of NaHCO₃ and brine. Dried, filtrated and concentrated, the residue was dissolved in toluene (200 mL). Then KOH (28.01 g, 509.68 mmol), BnBr (37.8 mL, 318.55 mmol) were added in one portion and the mixture was stirred at 120 °C for 24 h. The resulting mixture was allowed to room temperature, diluted with water and extracted with EtOAc (200 mL \times 3). The combined organic layers were washed with brine. Dried, filtrated and concentrated, the residue was dissolved in DMF (200 mL). Then CH₃I (23.8 mL, 382.26 mmol), NaHCO₃ (21.41 g, 254.84 mmol) were added in one portion and the mixture was stirred at room temperature for 12 h. The mixture was quenched with water as well as extracted with EtOAc (200 mL \times 4). The combined organic layers were washed with water and brine. Dried, filtrated and concentrated, the residue was purified by flash chromatography on silica gel (PE/EA=5/1) to give ester (32.41 g, 3 steps for 77%) as a yellow oil. IR (film) v_{max} 2949, 2847, 2831, 1737, 1609, 1520, 1454, 1281, 1218, 1160, 1108, 936, 919, 752 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.34 (m, 4H), 7.32-7.28 (m, 1H), 6.87 (s, 1H), 6.77 (s, 1H), 4.52 (s, 4H), 3.88 (s, 3H), 3.87 (s, 3H), 3.65 (s, 2H), 3.61 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 172.3, 148.7, 148.0, 138.2, 128.9, 128.5, 128.1, 127.8, 125.7, 114.1, 113.1, 72.3, 70.4, 56.1, 56.1, 52.1, 37.8 ppm; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for C₁₉H₂₃O₅: 331.1540, found: 331.1540. The ester (20.00 g, 60.54 mmol), 10% Pd/C (2.00 g) and 20% Pd(OH)₂/C (2.00 g) were stirred in MeOH (300 mL) under a H₂ atmosphere for 8 h. The mixture was filtered and concentrated. The residue was dissolved in DCM (300 mL). Then DMP (30.81 g, 72.65 mmol) was added and the mixture was stirred at room temperature for 30 min. Then the mixture was quenched with a solution of $NaHCO_3$ and $Na_2S_2O_3$ as well as extracted with DCM (200 mL \times 3). The combined organic layers were washed with brine and dried over MgSO4. The resulting mixture was filtrated and concentrated to give crude aldehyde, which was dissolved in DCM (300 mL). Then (R)-2methyl-2-propanesulfinamide (7.33 g, 60.54 mmol), cupric sulphate anhydrous (19.32 g, 121.08 mmol) and PPTS (0.76 g, 3.03 mmol) were added in one portion and the

mixture was stirred for 24 h. The resulting mixture was filtrated and the filtrate was concentrated to give the crude product, which was purified by flash chromatography on silica gel (PE/EA=2/1) to give **13** (16.74 g, 81%) as a yellow oil. $[\alpha]_D^{23}$ = -31.2 (*c* 1.00, CHCl₃); IR (film) v_{max} 2957, 2924, 2867, 1738, 1586, 1564, 1517, 1463, 1320, 1270, 1165, 1126, 1078, 1011, 810, 763 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.65 (s, 1H), 7.42 (s, 1H), 6.78 (s, 1H), 4.01-3.97 (m, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 3.67 (s, 3H), 1.25 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.6, 161.2, 152.1, 148.4, 129.3, 125.3, 114.3, 113.5, 57.5, 56.2, 52.2, 38.6, 24.3, 22.5 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₁₆H₂₄NO₅S: 342.1370, found: 342.1370.

To a solution of 2-(benzo[d][1,3]dioxol-5-yl)acetic acid (20.00 g, 111.01 mmol) was stirred in AcOH (64 mL) at 80°C. Then concentrated hydrochloric acid (20 mL), HCHO (20 mL) were added and the mixture was stirred for 2 h. The mixture was concentrated and diluted with DCM. The organic layer was washed with a saturated aqueous solution of NaHCO₃ and brine. Dried, filtrated and concentrated, the residue was dissolved in HBr/CH₃OH (50 mL/200 mL). The mixture was stirred at 90°C for 2 h and concentrated. The residue was dissolved in CHCl₃ (200 mL) and treated with TBADC (77.81 g, 111.01 mmol) at 70°C for 1h. Then the mixture was concentrated and quenched with a saturated aqueous solution of NaHCO₃ as well as extracted with EtOAc (200 mL \times 3). The combined organic layers were washed with brine. Dried, filtrated and concentrated, the residue was purified by flash chromatography on silica gel (PE/EA=4/1) to give aldehyde (18.50 g, 75%), which was dissolved in DCM (120 mL). Then (R)-2-methyl-2-propanesulfinamide (10.08 g, 83.26 mmol), cupric sulphate anhydrous (26.58 g, 166.52 mmol) and PPTS (2.09 g, 8.33 mmol) were added in one portion and the mixture was stirred for 24 h. The resulting mixture was filtrated and the filtrate was concentrated to give the crude product, which was purified by flash chromatography on silica gel (PE/EA=2/1) to give compound 15 (25.47 g, 94%) as a yellow oil. $[\alpha]_D^{23} = -58.4$ (c 1.00, CHCl₃); IR (film) v_{max} 2980, 2953, 2923, 2865, 1739, 1621, 1579, 1507, 1484, 1434, 1384, 1338, 1268, 1197, 1158, 1081, 1036, 920, 804, 771, 745 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.63 (s, 1H), 7.41 (s, 1H), 6.77 (s, 1H), 6.05-6.03 (m, 2H), 3.93 (s, 2H), 3.67 (s, 3H), 1.24 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.3, 160.5, 151.0, 147.7, 131.2, 127.0, 111.6, 109.7, 102.1, 57.6, 52.3, 38.6, 22.6 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₁₅H₂₀NO₅S: 326.1057, found: 326.1060.

General procedure for synthesis of 11, 14 and 16: To a compound 9, 13 or 15 (1.0 mmol) in anhydrous DCM (6 mL) was treated with a solution of Grignard reagents (3.0 mL, 1 M in THF) and 2,2'-dipyridyl (469 mg, 3.0 mmol) at -15 °C for 1h (-50 °C for 13). The mixture was quenched with a saturated NH₄Cl aqueous solution and extracted with EtOAc (30 mL \times 3) and the combined organic layers were washed with brine. Dried, filtered and concentrated, the residue was purified by flash chromatography on silica gel to give 11 (PE/EA=4/1), 14 (PE/EA=2/1) or 16 (PE/EA=4/1).

(S)-2-((R)-tert-Butylsulfinyl)-1-phenyl-1,4-dihydroisoquinolin-3(2H)-one (11a)

White solid (252 mg, 77%), m.p. 166-167 °C. $[\alpha]_D^{25}$ = +132.1 (*c* 1.00, CHCl₃); IR (film) v_{max} 3029, 2965, 2925, 2849, 1677, 1493, 1457, 1382, 1249, 1179, 1106, 1084, 909, 830, 750 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.53-7.49 (m, 1H), 7.40-7.36 (m, 2H), 7.34-7.28 (m, 2H), 7.27-7.18 (m, 3H), 7.12-7.08 (m, 1H), 6.19 (s, 1H), 3.90 (d, *J* = 18.8 Hz, 1H), 3.68 (d, *J* = 18.8 Hz, 1H), 1.15 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 140.3, 137.7, 130.5, 129.0, 127.9, 127.8, 127.6, 126.4, 126.1, 60.4, 53.5, 39.7, 22.8 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₁₉H₂₂NO₂S: 328.1366, found: 328.1367.

(*S*)-2-((*R*)-*tert*-Butylsulfinyl)-1-(*p*-tolyl)-1,4-dihydroisoquinolin-3(2H)-one (**11b**) White solid (253 mg, 74%), m.p. 148-150 °C. $[\alpha]_D^{25}$ = +116.5 (*c* 1.00, CHCl₃); IR (film) ν_{max} 3008, 2967, 2925, 2861, 1676, 1512, 1458, 1381, 1250, 1179, 1109, 1084, 840, 746 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.52-7.47 (m, 1H), 7.28-7.23 (m, 3H), 7.22-7.17 (m, 1H), 7.14-7.08 (m, 3H), 6.15 (s, 1H), 3.90 (d, *J* = 18.4 Hz, 1H), 3.67 (d, *J* = 18.8 Hz, 1H), 2.29 (s, 3H) 1.15 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 138.0, 137.4, 137.3, 130.4, 129.7, 127.8, 127.8, 127.6, 126.3, 126.0, 60.4, 53.3, 39.7,

22.9, 21.1 ppm; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ calcd for C₂₀H₂₄NO₂S: 342.1522, found: 342.1520.

(*S*)-2-((*R*)-*tert*-Butylsulfinyl)-1-(4-methoxyphenyl)-1,4-dihydroisoquinolin-3(2H)-one (**11c**)

Colorless oil (250 mg, 70%). $[\alpha]_D^{25}$ = +116.7 (*c* 1.00, CHCl₃); IR (film) v_{max} 2961, 2924, 2853, 1676, 1609, 1511, 1458, 1382, 1303, 1250, 1177, 1109, 1083, 1032, 842, 772, 745 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.49-7.44 (m, 1H), 7.31-7.17 (m, 4H), 7.12-7.08 (m, 1H), 6.87-6.81 (m, 2H), 6.14 (s, 1H), 3.90 (d, *J* = 18.8 Hz, 1H), 3.75 (s, 3H), 3.67 (d, *J* = 18.4 Hz, 1H), 1.16 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.2, 158.9, 137.9, 132.4, 130.2, 127.7, 127.7, 127.5, 125.9, 114.3, 60.3, 55.3, 53.0, 39.6, 22.8 ppm; HRMS (ESI-Orbitrap) *m*/*z*: [M+H]⁺ calcd for C₂₀H₂₄NO₃S: 358.1471, found: 358.1472.

(*S*)-1-([1,1'-Biphenyl]-4-yl)-2-((*R*)-*tert*-butylsulfinyl)-1,4-dihydroisoquinolin-3(2H)-o ne (**11d**)

White solid (327 mg, 81%), m.p. 151-153 °C. $[\alpha]_D^{26}$ = +143.1 (*c* 1.00, CHCl₃); IR (film) v_{max} 2982, 2965, 2924, 1676, 1486, 1384, 1249, 1108, 1084, 912, 847, 756 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.57-7.51 (m, 5H), 7.46-7.39 (m, 4H), 7.36-7.26 (m, 2H), 7.25-7.20 (m, 1H), 7.14-7.10 (m, 1H), 6.24 (s, 1H), 3.94 (d, *J* = 18.8 Hz, 1H), 3.70 (d, *J* = 18.4 Hz, 1H), 1.18 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.5, 140.5, 140.2, 139.1, 137.7, 130.5, 129.0, 128.0, 127.9, 127.7, 127.6, 127.1, 126.8, 126.1, 60.4, 53.3, 39.8, 22.9 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₅H₂₆NO₂S: 404.1679, found: 404.1677.

(*S*)-1-(4-butylphenyl)-2-((*R*)-*tert*-Butylsulfinyl)-1,4-dihydroisoquinolin-3(2H)-one (**11e**)

Colorless oil (318 mg, 83%). $[\alpha]_D^{25}$ = +55.1 (*c* 1.00, CHCl₃); IR (film) v_{max} 2959, 2929, 2873, 2859, 1731, 1680, 1459, 1381, 1272, 1116, 1086, 843, 746 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.51-7.47 (m, 1H), 7.28-7.23 (m, 3H), 7.22-7.17 (m, 1H), 7.13-7.07 (m, 3H), 6.16 (s, 1H), 3.90 (d, *J* = 18.4 Hz, 1H), 3.66 (d, *J* = 18.8 Hz, 1H), 2.57-2.51 (m, 2H), 1.58-1.49 (m, 2H), 1.36-1.27 (m, 2H), 1.15 (s, 9H), 0.92-0.86 (m, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 142.3, 137.9, 137.4, 130.5, 128.9, 127.8, 127.8,

127.5, 126.2, 126.1, 60.4, 53.4, 39.7, 35.2, 33.5, 22.8, 22.4, 14.0 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₃H₃₀NO₂S: 384.1992, found: 384.1993. (*S*)-2-((*R*)-*tert*-Butylsulfinyl)-1-(4-fluorophenyl)-1,4-dihydroisoquinolin-3(2H)-one (**11f**)

Colorless oil (266 mg, 77%). $[\alpha]_D^{25}$ = +119.0 (*c* 1.00, CHCl₃); IR (film) v_{max} 2961, 2926, 2865, 1678, 1508, 1380, 1228, 1160, 1099, 1083, 846, 747 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.49-7.45 (m, 1H), 7.38-7.32 (m, 2H), 7.30-7.20 (m, 2H), 7.14-7.10 (m, 1H), 7.05-6.97 (m, 2H), 6.17 (s, 1H), 3.87 (d, *J* = 18.8 Hz, 1H), 3.69 (d, *J* = 18.4 Hz, 1H), 1.15 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.1, 162.0 (d, *J* = 245.7 Hz), 137.4, 136.3 (d, *J* = 2.8 Hz), 130.3, 128.1, 128.0, 127.9, 127.7, 126.1, 115.9 (d, *J* = 21.5 Hz), 60.4, 52.9, 39.6, 22.9 ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ -114.5 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₁₉H₂₁FNO₂S: 346.1272, found: 346.1270.

(*S*)-2-((*R*)-*tert*-Butylsulfinyl)-1-(3-fluorophenyl)-1,4-dihydroisoquinolin-3(2H)-one (**11g**)

Colorless oil (290 mg, 84%). $[\alpha]_D^{25}$ = +119.5 (*c* 0.20, CHCl₃); IR (film) v_{max} 2959, 2921, 2851, 1680, 1590, 1488, 1380, 1249, 1116, 1085, 852, 771, 746 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.52-7.46 (m, 1H), 7.33-7.21 (m, 3H), 7.20-7.16 (m, 1H), 7.14-7.10 (m, 1H), 7.10-7.05 (m, 1H), 6.96-6.89 (m, 1H), 6.17 (s, 1H), 3.87 (d, *J* = 18.8 Hz, 1H), 3.68 (d, *J* = 18.8 Hz, 1H), 1.16 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.2, 163.0 (d, *J* = 246.3 Hz), 143.0 (d, *J* = 6.3 Hz), 137.1, 130.7 (d, *J* = 8.2 Hz), 130.5, 128.2, 127.9, 127.7, 126.2, 122.0 (d, *J* = 1.9 Hz), 114.7 (d, *J* = 21.0 Hz), 113.7 (d, *J* = 22.4 Hz), 60.5, 53.1, 39.6, 22.8 ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ -111.1 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₁₉H₂₁FNO₂S: 346.1272, found: 346.1270.

(*S*)-2-((*R*)-*tert*-Butylsulfinyl)-1-(3-methoxyphenyl)-1,4-dihydroisoquinolin-3(2H)-one (**11h**)

White solid (232 mg, 65%), m.p. 100-102 °C. $[\alpha]_D^{25}$ = +117.1 (*c* 1.00, CHCl₃); IR (film) v_{max} 2961, 2925, 2855, 1678, 1604, 1490, 1458, 1380, 1305, 1255, 1152, 1084, 850, 743 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.52-7.47 (m, 1H), 7.29-7.18 (m, 3H),

7.12-7.07 (m, 1H), 6.98-6.94 (m, 1H), 6.92-6.89 (m, 1H), 6.78-6.72 (m, 1H), 6.14 (s, 1H), 3.92 (d, J = 18.4 Hz, 1H), 3.76 (s, 3H), 3.66 (d, J = 18.8 Hz, 1H), 1.17 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.3, 160.0, 141.9, 137.6, 130.0, 127.9, 127.8, 127.6, 126.2, 118.6, 112.8, 112.4, 60.4, 55.3, 53.4, 39.7, 22.8 ppm; HRMS (ESI-Orbitrap) m/z: [M+H]⁺ calcd for C₂₀H₂₄NO₃S: 358.1471, found: 358.1475.

(S)-2-((R)-*tert*-Butylsulfinyl)-1-(3-(trifluoromethyl)phenyl)-1,4-dihydroisoquinolin-3(2H)-one (11i)

Colorless oil (285 mg, 72%). $[\alpha]_D^{26}$ = +95.8 (*c* 1.00, CHCl₃); IR (film) v_{max} 2969, 2928, 1677, 1492, 1458, 1382, 1330, 1264, 1167, 1124, 1075, 890, 846, 748 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.65-7.62 (m, 1H), 7.60-7.56 (m, 1H), 7.53-7.44 (m, 3H), 7.33-7.23 (m, 2H), 7.16-7.13 (m, 1H), 6.24 (s, 1H), 3.84 (d, *J* = 18.4 Hz, 1H), 3.73 (d, *J* = 18.8 Hz, 1H), 1.15 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.3, 141.4, 136.8, 131.4 (d, *J* = 32.4 Hz), 130.3, 129.9, 129.7, 128.4, 128.1, 127.9, 126.2, 124.6 (d, *J* = 3.6 Hz), 123.8 (d, *J* = 271.0 Hz), 123.1 (d, *J* = 3.7 Hz), 60.7, 53.2, 39.6, 22.8 ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ -62.8 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₀H₂₁F₃NO₂S: 396.1240, found: 396.1238.

(*S*)-2-((*R*)-*tert*-Butylsulfinyl)-1-(m-tolyl)-1,4-dihydroisoquinolin-3(2H)-one (**11j**) White solid (236 mg, 69%), m.p. 164-165 °C. $[\alpha]_D^{25}$ = +143.8 (*c* 1.00, CHCl₃); IR (film) v_{max} 2961, 2925, 2853, 1678, 1604, 1492, 1380, 1255, 1116, 1104, 1084, 850, 743 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.54-7.48 (m, 1H), 7.29-7.24 (m, 1H), 7.23-7.14 (m, 4H), 7.12-7.08 (m, 1H), 7.05-7.00 (m, 1H), 6.15 (s, 1H), 3.92 (d, *J* = 18.8 Hz, 1H), 3.67 (d, *J* = 18.8 Hz, 1H), 2.31 (s, 3H) 1.15 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.5, 140.2, 138.8, 137.8, 130.5, 128.8, 128.4, 127.9, 127.8, 127.6, 127.2, 126.2, 123.3, 60.4, 53.5, 39.8, 22.8, 21.7 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₀H₂₄NO₂S: 342.1522, found: 342.1521.

(*S*)-2-((*R*)-*tert*-Butylsulfinyl)-1-(o-tolyl)-1,4-dihydroisoquinolin-3(2H)-one (**11k**) White solid (270 mg, 79%), m.p. 113-115 °C. $[\alpha]_D^{25}$ = +206.3 (*c* 1.00, CHCl₃); IR (film) v_{max} 2963, 2926, 2855, 1670, 1494,1393, 1378, 1304, 1269, 1174, 1100, 1081, 859, 745 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.45-7.39 (m, 1H), 7.29-7.25 (m, 1H), 7.22-7.10 (m, 6H), 6.46 (s, 1H), 4.35 (d, *J* = 20.0 Hz, 1H), 3.79 (d, *J* = 20.0 Hz, 1H), 2.71 (s, 3H) 1.00 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 173.2, 141.0, 136.7, 135.4, 131.7, 129.6, 128.2, 127.9, 127.7, 127.3, 126.7, 126.7, 126.3, 61.0, 49.9, 39.4, 22.8, 20.8 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₀H₂₄NO₂S: 342.1522, found: 342.1520.

(*S*)-2-((*R*)-*tert*-Butylsulfinyl)-1-(2-methoxyphenyl)-1,4-dihydroisoquinolin-3(2H)-one (111)

White solid (236 mg, 66%), m.p. 52-54 °C. $[\alpha]_D^{26}$ = +152.6 (*c* 0.50, CHCl₃); IR (film) v_{max} 2963, 2924, 1674, 1489, 1463, 1386, 1243, 1105, 1083, 1026, 915, 753 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.67-7.61 (m, 1H), 7.33-7.29 (m, 1H), 7.25-7.16 (m, 3H), 7.12-7.07 (m, 1H), 6.95-6.85 (m, 2H), 6.57 (s, 1H), 4.10 (d, *J* = 19.2 Hz, 1H), 3.90 (s, 3H), 3.75 (d, *J* = 19.6 Hz, 1H), 1.06 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 175.0, 156.5, 136.3, 129.3, 127.6, 127.4, 127.1, 127.0, 120.6, 111.5, 60.5, 55.5, 48.7, 39.6, 22.8 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₀H₂₄NO₃S: 358.1471, found: 358.1475.

(*S*)-2-((*R*)-*tert*-Butylsulfinyl)-1-(naphthalen-1-yl)-1,4-dihydroisoquinolin-3(2H)-one (**11m**)

White solid (264 mg, 70%), m.p. 151-153 °C. $[\alpha]_D^{26}$ = +337.3 (*c* 1.00, CHCl₃); IR (film) v_{max} 2961, 2922, 2857, 1672, 1510, 1393, 1366, 1349, 1266, 1164, 1120, 1106, 1079, 914, 863, 788, 772, 756, 739 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.75-8.70 (m, 1H), 7.88-7.84 (m, 1H), 7.78-7.68 (m, 2H), 7.61-7.50 (m, 3H), 7.44-7.39 (m, 1H), 7.18-7.08 (m, 4H), 4.35 (d, *J* = 20.0 Hz, 1H), 3.90 (d, *J* = 19.6 Hz, 1H), 0.95 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.2, 138.5, 136.4, 134.4, 130.3, 129.5, 129.3, 128.9, 128.2, 127.8, 127.4, 127.1, 126.3, 126.0, 125.3, 123.6, 60.8, 48.4, 39.5, 22.8 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₃H₂₄NO₂S: 378.1522, found: 378.1523.

(*S*)-2-((*R*)-*tert*-Butylsulfinyl)-1-(naphthalen-2-yl)-1,4-dihydroisoquinolin-3(2H)-one (**11n**)

White solid (272 mg, 72%), m.p. 95-97 °C. $[\alpha]_D^{25}$ = +120.5 (*c* 1.00, CHCl₃); IR (film) v_{max} 2963, 2926, 2855, 1750, 1677, 1244, 1107, 1083, 856, 741 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.83-7.76 (m, 4H), 7.62-7.57 (m, 1H), 7.52-7.44 (m, 3H), 7.30-7.24

(m, 1H), 7.23-7.17 (m, 1H), 7.12-7.07 (m, 1H), 6.35 (s, 1H), 3.98 (d, J = 18.4 Hz, 1H), 3.72 (d, J = 18.4 Hz, 1H), 1.16 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.5, 137.4, 133.0, 132.5, 130.6, 129.2, 128.0, 128.0, 127.8, 127.7, 127.6, 126.8, 126.5, 126.2, 124.7, 124.5, 60.4, 53.6, 39.7, 22.8 ppm; HRMS (ESI-Orbitrap) m/z: [M+H]⁺ calcd for C₂₃H₂₄NO₂S: 378.1522, found: 378.1526.

(*S*)-2-((*R*)-*tert*-Butylsulfinyl)-6,7-dimethoxy-1-phenyl-1,4-dihydroisoquinolin-3(2H)one (**14a**)

White solid (201 mg, 52%), m.p. 153-155 °C. $[\alpha]_D^{25}$ = +41.1 (*c* 1.00, CHCl₃); IR (film) v_{max} 3012, 2963, 2931, 2865, 2833, 1676, 1515, 1379, 1300, 1251, 1123, 1104, 753 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.30 (m, 4H), 7.25-7.20 (m, 1H), 6.98 (s, 1H), 6.59 (s, 1H), 6.09 (s, 1H), 3.93-3.85 (m, 4H), 3.81 (s, 3H), 3.61 (d, *J* = 18.8 Hz, 1H), 1.13 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 148.7, 148.3, 140.8, 129.8, 129.0, 127.5, 126.2, 122.3, 110.6, 109.4, 60.3, 56.2, 56.1, 53.3, 39.1, 22.8 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₁H₂₆NO₄S: 388.1577, found: 388.1579.

(*S*)-1-([1,1'-Biphenyl]-4-yl)-2-((*R*)-*tert*-butylsulfinyl)-6,7-dimethoxy-1,4-dihydroisoq uinolin-3(2H)-one (**14b**)

Colorless oil (352 mg, 76%). $[\alpha]_D^{25}$ = +44.0 (*c* 1.00, CHCl₃); IR (film) v_{max} 2959, 2930, 2861, 2830, 1676, 1516, 1376, 1250, 1103, 1080, 839, 757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.58-7.52 (m, 4H), 7.45-7.39 (m, 4H), 7.36-7.30 (m, 1H), 7.02 (s, 1H), 6.61 (s, 1H), 6.14 (s, 1H), 3.95-3.88 (m, 4H), 3.83 (s, 3H), 3.63 (d, *J* = 18.8 Hz, 1H), 1.17 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 148.8, 148.4, 140.4, 140.1, 139.6, 129.8, 128.9, 127.6, 127.0, 126.7, 122.4, 110.7, 109.3, 60.4, 56.3, 56.1, 53.1, 39.2, 22.9 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₇H₃₀NO₄S: 464.1890, found: 464.1892.

(*S*)-2-((*R*)-*tert*-Butylsulfinyl)-1-(3-fluorophenyl)-6,7-dimethoxy-1,4-dihydroisoquinol in-3(2H)-one (**14c**)

Colorless oil (328 mg, 81%). $[\alpha]_D^{25}$ = +34.8 (*c* 1.00, CHCl₃); IR (film) v_{max} 2961, 2928, 2853, 1677, 1515, 1464, 1376, 1250, 1224, 1123, 1104, 757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.27 (m, 1H), 7.17-7.13 (m, 1H), 7.08-7.03 (m, 1H), 6.96-6.90

(m, 2H), 6.60 (s, 1H), 6.06 (s, 1H), 3.91 (s, 3H), 3.88-3.80 (m, 4H), 3.62 (d, J = 18.8 Hz, 1H), 1.14 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.3, 163.1 (d, J = 246.6 Hz), 149.0, 148.5, 143.6 (d, J = 6.2 Hz), 130.7 (d, J = 8.2 Hz), 129.2, 122.4, 121.9 (d, J = 2.8 Hz), 114.7 (d, J = 20.9 Hz), 113.6 (d, J = 22.3 Hz), 110.7, 109.4, 60.5, 56.4, 56.2, 52.9 (d, J = 1.4 Hz), 39.1, 22.9 ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ -111.1 ppm; HRMS (ESI-Orbitrap) m/z: [M+H]⁺ calcd for C₂₁H₂₅FNO₄S: 406.1483, found: 406.1486.

(*S*)-2-((*R*)-*tert*-Butylsulfinyl)-6,7-dimethoxy-1-(3-(trifluoromethyl)phenyl)-1,4-dihydr oisoquinolin-3(2H)-one (**14d**)

Colorless oil (296 mg, 65%). $[\alpha]_D^{25}$ = +30.9 (*c* 1.00, CHCl₃); IR (film) v_{max} 2963, 2933, 2863, 2837, 1678, 1516, 1465, 1330, 1251, 1167, 1125, 1105, 1076, 757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.64-7.60 (m, 1H), 7.58-7.44 (m, 3H), 6.97 (s, 1H), 6.62 (s, 1H), 6.14 (s, 1H), 3.91 (s, 3H), 3.85-3.77 (m, 4H), 3.63 (d, *J* = 18.8 Hz, 1H), 1.12 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.1, 149.1, 148.6, 142.1, 131.4 (d, *J* = 32.3 Hz), 129.8, 129.7, 128.9, 124.5 (d, *J* = 3.7 Hz), 123.8 (d, *J* = 270.9 Hz), 123.0 (d, *J* = 3.6 Hz), 122.4, 110.8, 109.4, 60.6, 56.4, 56.2, 52.9, 39.1, 22.8 ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ -62.8 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₂H₂₅F₃NO₄S: 456.1451, found: 456.1450.

(*S*)-2-((*R*)-*tert*-Butylsulfinyl)-1-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1,4-dihydroiso quinolin-3(2H)-one (**14e**)

Colorless oil (282 mg, 63%). $[\alpha]_D^{25}$ = +34.4 (*c* 1.00, CHCl₃); IR (film) v_{max} 3002, 2957, 2933, 2836, 1673, 1515, 1463, 1258, 1104, 1026, 757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.97-6.92 (m, 1H), 6.91-6.88 (m, 1H), 6.86-6.83 (m, 1H), 6.82-6.78 (m, 1H), 6.60 (s, 1H), 6.01 (s, 1H), 3.93-3.88 (m, 4H), 3.86-3.82 (m, 9H), 3.62 (d, *J* = 18.8 Hz, 1H), 1.15 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.2, 149.3, 148.7, 148.4, 148.4, 133.6, 130.0, 122.1, 118.4, 111.3, 110.7, 109.8, 109.3, 60.5, 56.3, 56.2, 56.0, 56.0, 53.1, 39.1, 22.9 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₃H₃₀NO₆S: 448.1788, found: 448.1787.

(*S*)-2-((*R*)-*tert*-Butylsulfinyl)-6,7-dimethoxy-1-(naphthalen-2-yl)-1,4-dihydroisoquino lin-3(2H)-one (**14f**)

Colorless oil (289 mg, 66%). $[\alpha]_D^{25}$ = +33.1 (*c* 1.00, CHCl₃); IR (film) v_{max} 3010, 2961, 2932, 1676, 1516, 1464, 1351, 1301, 1250, 1122, 1102, 1079, 757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.84-7.76 (m, 4H), 7.53-7.44 (m, 3H), 7.06 (s, 1H), 6.59 (s, 1H), 6.25 (s, 1H), 3.96 (d, *J* = 18.8 Hz, 1H), 3.93 (s, 3H), 3.80 (s, 3H), 3.65 (d, *J* = 18.8 Hz, 1H), 1.14 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.6, 148.8, 148.4, 137.9, 132.5, 129.5, 129.2, 128.0, 127.7, 126.8, 126.5, 124.7, 124.4, 122.5, 110.7, 109.5, 60.4, 56.3, 56.1, 53.5, 39.2, 22.9 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₅H₂₈NO₄S: 438.1734, found: 438.1733.

(S)-6-((R)-*tert*-Butylsulfinyl)-5-phenyl-5,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-7(6H)-one (16a)

Colorless oil (256 mg, 69%). $[\alpha]_D^{25}$ = +35.4 (*c* 1.00, CHCl₃); IR (film) v_{max} 3010, 2965, 2924, 2853, 1676, 1502, 1485, 1380, 1270, 1236, 1119, 1086, 1038, 755 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.29 (m, 4H), 7.25-7.20 (m, 1H), 6.96 (s, 1H), 6.54 (s, 1H), 6.04 (s, 1H), 5.93 (d, *J* = 1.2 Hz, 1H), 5.90 (d, *J* = 1.2 Hz, 1H), 3.81 (d, *J* = 18.4 Hz, 1H), 3.55 (d, *J* = 18.8 Hz, 1H), 1.13 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.3, 147.4, 147.1, 140.4, 131.1, 129.0, 127.6, 126.3, 123.7, 108.0, 106.8, 101.5, 60.3, 53.3, 39.5, 22.8 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₀H₂₂NO₄S: 372.1264, found: 372.1263.

(*S*)-6-((*R*)-*tert*-Butylsulfinyl)-5-(3-fluorophenyl)-5,8-dihydro-[1,3]dioxolo[4,5-g]isoq uinolin-7(6H)-one (**16b**)

Colorless oil (230 mg, 59%). $[\alpha]_D^{25}$ = +33.4 (*c* 1.00, CHCl₃); IR (film) v_{max} 2965, 2922, 2849, 1680, 1485, 1378, 1236, 1087, 1038, 762 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.27 (m, 1H), 7.16-7.11 (m, 1H), 7.06-7.01 (m, 1H), 6.97-6.91 (m, 2H), 6.56 (s, 1H), 6.02 (s, 1H), 5.95 (d, *J* = 1.2 Hz, 1H), 5.92 (d, *J* = 1.2 Hz, 1H), 3.78 (d, *J* = 18.4 Hz, 1H), 3.57 (d, *J* = 18.8 Hz, 1H), 1.14 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.2, 163.1 (d, *J* = 246.3 Hz), 147.5 (d, *J* = 40.1 Hz), 143.1 (d, *J* = 6.1 Hz), 130.7 (d, *J* = 8.1 Hz), 130.5, 123.8, 121.9 (d, *J* = 2.8 Hz), 114.7 (d, *J* = 20.9 Hz), 113.6 (d, *J* = 22.5 Hz), 108.1, 106.8, 101.6, 60.5, 52.8, 39.4, 22.8 ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ -111.1 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₀H₂₁FNO₄S: 390.1170, found: 390.1169.

(*S*)-6-((*R*)-*tert*-Butylsulfinyl)-5-(3-(trifluoromethyl)phenyl)-5,8-dihydro-[1,3]dioxolo[4,5-g]isoquinolin-7(6H)-one (**16c**)

Colorless oil (277 mg, 63%). $[\alpha]_D^{25}$ = +31.3 (*c* 1.02, CHCl₃); IR (film) v_{max} 2965, 2927, 1683, 1504, 1486, 1330, 1167, 1125, 1086, 1039, 759 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.61-7.58 (m, 1H), 7.56-7.44 (m, 3H), 6.96 (s, 1H), 6.58 (s, 1H), 6.09 (s, 1H), 5.96 (d, *J* = 1.2 Hz, 1H), 5.93 (d, *J* = 1.2 Hz, 1H), 3.73 (d, *J* = 18.8 Hz, 1H), 3.58 (d, *J* = 18.8 Hz, 1H), 1.12 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.1, 147.8, 147.4, 141.6, 131.4 (d, *J* = 32.2 Hz), 130.2, 129.8, 129.7, 124.6 (d, *J* = 3.7 Hz), 123.8 (d, *J* = 270.8 Hz), 123.9, 122.9 (d, *J* = 3.7 Hz), 108.2, 106.8, 101.6, 60.5, 52.8, 39.5, 22.8 ppm; ¹⁹F NMR (376 MHz, CDCl₃) δ -62.8 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₁H₂₁F₃NO₄S: 440.1138, found: 440.1139.

(*S*)-5-([1,1'-biphenyl]-4-yl)-6-((*R*)-*tert*-Butylsulfinyl)-5,8-dihydro-[1,3]dioxolo[4,5-g] isoquinolin-7(6H)-one (**16d**)

White solid (412 mg, 92%), m.p. 108-110 °C. $[\alpha]_D^{25}$ = +40.1 (*c* 1.00, CHCl₃); IR (film) v_{max} 2961, 2925, 2894, 1678, 1502, 1484, 1378, 1235, 1086, 1039, 757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.57-7.51 (m, 4H), 7.44-7.38 (m, 4H), 7.35-7.30 (m, 1H), 6.99 (s, 1H), 6.55 (s, 1H), 6.09 (s, 1H), 5.92 (d, *J* = 1.6 Hz, 1H), 5.89 (d, *J* = 1.6 Hz, 1H), 3.84 (d, *J* = 18.8 Hz, 1H), 3.57 (d, *J* = 18.8 Hz, 1H), 1.16 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.3, 147.4, 147.1, 140.4, 140.1, 139.2, 131.0, 128.9, 127.7, 127.6, 127.0, 126.7, 123.8, 108.0, 106.7, 101.4, 60.3, 53.0, 39.5, 22.8 ppm; HRMS (ESI-Orbitrap) *m/z*: [M+H]⁺ calcd for C₂₆H₂₆NO₄S: 448.1577, found: 448.1579.

(*S*)-6-((*R*)-*tert*-Butylsulfinyl)-5-(naphthalen-2-yl)-5,8-dihydro-[1,3]dioxolo[4,5-g]isoq uinolin-7(6H)-one (**16e**)

Colorless oil (303 mg, 72%). $[\alpha]_D^{25}$ = +21.6 (*c* 1.00, CHCl₃); IR (film) v_{max} 3008, 2969, 2925, 1675, 1502, 1483, 1367, 1270, 1236, 1113, 1086, 1038, 757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.82-7.76 (m, 4H), 7.51-7.42 (m, 3H), 7.04 (s, 1H), 6.51 (s, 1H), 6.20 (s, 1H), 5.90 (d, *J* = 1.2 Hz, 1H), 5.86 (d, *J* = 1.2 Hz, 1H), 3.87 (d, *J* = 18.4 Hz, 1H), 3.72 (d, *J* = 18.8 Hz, 1H), 1.14 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 147.4, 147.0, 137.4, 133.0, 132.5, 130.7, 129.1, 128.0, 127.7, 126.8, 126.4, 124.6, 124.3, 123.9, 107.9, 106.8, 101.4, 60.3, 53.4, 39.5, 22.8 ppm; HRMS

(ESI-Orbitrap) m/z: $[M+H]^+$ calcd for C₂₄H₂₄NO₄S: 422.1421, found: 422.1424.

(*S*)-1-(3,4-Dimethoxyphenyl)-6,7-dimethoxy-1,4-dihydroisoquinolin-3(2H)-one (**17**) A solution of compound **14e** (500 mg, 1.12 mmol) in dry MeOH (10 mL) was treated with (COCl)₂ (0.95 mL, 11.20 mmol). After being stirred overnight, the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel to give **17** as a yellow oil (349 mg, 91%). $[\alpha]_D^{26}$ = +1.2 (*c* 0.50, CHCl₃); IR (film) v_{max} 2959, 2920, 2847, 1639, 1516, 1464, 1310, 1250, 1206, 1140, 1024, 840, 757 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.30 (brs, 1H), 6.88-6.83 (m, 1H), 6.82-6.78 (m, 1H), 6.71 (s, 1H), 6.66 (s, 1H), 6.38 (s, 1H), 5.57 (s, 1H), 3.89 (s, 6H), 3.83 (s, 3H), 3.71 (s, 3H), 3.69 (brs, 2H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 169.3, 149.8, 149.4, 149.1, 148.3, 133.5, 125.8, 122.4, 120.2, 111.3, 110.4, 110.2, 109.7, 60.1, 56.2, 56.1, 56.1, 56.1, 35.3 ppm; HRMS (ESI-Orbitrap) *m*/*z*: [M+H]⁺ calcd for C₁₉H₂₂NO₅: 344.1492, found: 344.1493.

General procedure for synthesis of 12: To a compound 10 (200 mg, 0.75 mmol) in anhydrous THF (3 mL) was treated with a solution of Grignard reagents (2.3 mL, 1 M in THF) and NMM (0.50 mL, 4.50 mmol) at -15 °C for 2.5h. The mixture was quenched with a saturated NH₄Cl aqueous solution and extracted with EtOAc (30 mL \times 3) and the combined organic layers were washed with brine. Dried, filtered and concentrated, the residue was purified by flash chromatography on silica gel (PE/EA=2/1) to give 12.

(S)-3-(4-methoxyphenyl)isoindolin-1-one (12a)

White solid (156 mg, 87%). Enantiomer ratio: 88%. $[\alpha]_D^{23}$ = +76.6 (*c* 0.5, MeOH); IR (film) ν_{max} 3424, 2982, 2841, 1647, 1514, 1469, 1453, 1269, 1108, 1051, 1031, 1016, 698 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, *J* = 7.2 Hz, 1H), 7.53-7.44 (m, 2H), 7.23-7.16 (m, 3H), 6.90-6.83 (m, 3H), 5.59 (s, 1H), 3.79 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.1, 159.9, 148.4, 132.4, 131.0, 130.4, 128.4, 128.2, 123.8, 123.4, 114.5, 60.5, 55.5 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]⁺ Calcd for C₁₅H₁₄NO₂: 240.1019, found: 240.1020.

(S)-3-(p-tolyl)isoindolin-1-one (12b)

White solid (152 mg, 91%). Enantiomer ratio: 78%. $[\alpha]_D^{24}$ = +84.0 (*c* 0.50, MeOH);

IR (film) v_{max} 3442, 3243, 2922, 1682, 1649, 1636, 1463, 1206, 1139, 1014, 735 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, J = 7.6 Hz, 1H), 7.51-7.43 (m, 2H), 7.22 (d, J= 7.6 Hz, 1H), 7.16-7.14 (m, 4H), 7.00 (brs, 1H), 5.59 (s, 1H), 2.33 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.2, 148.3, 138.5, 135.5, 132.4, 131.0, 129.9, 128.4, 126.9, 123.9, 123.4, 60.7, 21.3 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]⁺ Calcd for C₁₅H₁₄NO: 224.1070, found: 224.1068.

(*S*)-3-(4-fluorophenyl)isoindolin-1-one (**12c**)

White solid (155 mg, 91%). Enantiomer ratio: 89%, $[\alpha]_D^{25}$ = +106.4 (*c* 0.50, MeOH); IR (film) v_{max} 3214, 3078, 1717, 1508, 1469, 1223, 1137, 856, 737, 692 cm⁻¹; ¹⁹F NMR (376 MHz, CD₃OD) δ -116.1 ppm; ¹H NMR (400 MHz, CD₃OD) δ 7.82 (d, *J* = 7.6 Hz, 1H), 7.60-7.49 (m, 2H), 7.31-7.26 (m, 2H), 7.12-7.06 (m, 2H), 5.73 (s, 1H) ppm; ¹³C NMR (100 MHz, CD₃OD) δ 173.2, 164.1 (d, *J* = 243.8 Hz), 149.8, 136.1 (d, *J* = 3.2 Hz), 133.6, 132.2, 129.9 (d, *J* = 8.4 Hz), 129.5, 124.6, 124.3, 116.8, 116.6, 61.5 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]⁺ Calcd for C₁₄H₁₁FNO: 228.0819, found: 228.0818.

(S)-3-([1,1'-biphenyl]-4-yl)isoindolin-1-one (12d)

White solid (212 mg, 99%). Enantiomer ratio: 97%, $[\alpha]_D^{21} = +217.0$ (*c* 0.10, MeOH); IR (film) v_{max} 3415, 2950, 2843, 1700, 1648, 1454, 1110, 1054, 1033, 1015, 722 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.95-7.88 (m, 1H), 7.60-7.55 (m, 4H), 7.55-7.48 (m, 2H), 7.48-7.42 (m, 2H), 7.39-7.33 (m, 3H), 7.31-7.28 (m, 1H), 6.72 (brs, 1H), 5.70-5.67 (m, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.0, 148.0, 141.8, 140.5, 137.5, 132.5, 130.9, 129.0, 128.6, 128.0, 127.7, 127.4, 127.2, 124.0, 123.5, 60.6 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]⁺ Calcd for C₂₀H₁₆NO: 286.1226, found: 286.1222.

(*S*)-3-(4-butylphenyl)isoindolin-1-one (**12e**)

White solid (157 mg, 79%). Enantiomer ratio: 80%, $[\alpha]_D^{27}$ = +70.6 (*c* 0.50, MeOH); IR (film) ν_{max} 3225, 2955, 2927, 1694, 1656, 1467, 1424, 1315, 1209, 1139, 781, 736 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.92-7.84 (m, 1H), 7.53-7.43 (m, 2H), 7.29-7.22 (m, 1H), 7.20-7.12 (m, 5H), 5.64-5.59 (m, 1H), 2.63-2.55 (m, 2H), 1.64-1.53 (m, 2H), 1.38-1.28 (m, 2H), 0.97-0.89 (m, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.3,

| 148.3, 143.5, 135.6, 132.3, 131.0, 129.2, 128.4, 126.8, 123.8, 123.4, 60.8, 35.4, 33.7, |
|---|
| 22.5, 14.0 ppm; HRMS (ESI-Orbitrap) m/z : $[M + H]^+$ Calcd for C ₁₈ H ₂₀ NO: 266.1539, |
| found: 266.1541. |
| (S)-3-phenylisoindolin-1-one (12f) |
| White solid (155 mg, 99%). Enantiomer ratio: 77%, $[\alpha]_D^{26}$ = +124.0 (<i>c</i> 0.25, MeOH); |
| IR (film) v_{max} 3445, 2841, 1634, 1449, 1194, 1053, 1033, 1014, 739, 700 cm ⁻¹ ; ¹ H |
| NMR (400 MHz, CD ₃ OD) δ 7.85-7.80 (m, 1H), 7.58-7.48 (m, 2H), 7.38-7.26 (m, 6H), |
| 5.74-5.71 (m, 1H); ¹³ C NMR (150 MHz, CD ₃ OD) δ 173.3, 150.0, 140.0, 133.5, 130.0, |
| 129.4, 127.9, 124.6, 124.3, 62.3 ppm; HRMS (ESI-Orbitrap) <i>m/z</i> : [M + H] ⁺ Calcd for |
| C ₁₄ H ₁₂ NO: 210.0913, found: 210.0912. |
| (S)-3-(<i>m</i> -tolyl)isoindolin-1-one (12g) |
| White solid (142 mg, 85%). Enantiomer ratio: 88%, $[\alpha]_D^{24}$ = +122.4 (<i>c</i> 0.50, MeOH); |
| IR (film) v_{max} 3448, 2978, 2843, 1655, 1637, 1469, 1054, 1033, 1015, 727, 643 cm ⁻¹ ; |
| ¹ H NMR (400 MHz, CDCl ₃) δ 7.88 (d, J = 7.6 Hz, 1H), 7.53-7.43 (m, 2H), 7.26-7.22 |
| (m, 2H), 7.14-7.02 (m, 4H), 5.59 (s, 1H), 2.32 (s, 3H) ppm; ¹³ C NMR (100 MHz, |
| CDCl ₃) δ 171.4, 148.2, 139.0, 138.5, 132.3, 131.0, 129.4, 129.0, 128.4, 127.4, 124.1, |
| 123.8, 123.4, 61.0, 21.5 ppm; HRMS (ESI-Orbitrap) m/z : $[M + H]^+$ Calcd for |
| C ₁₅ H ₁₄ NO: 224.1070, found: 224.1070. |
| (S)-3-(3-methoxyphenyl)isoindolin-1-one (12h) |
| White solid (162 mg, 90%). Enantiomer ratio: 68%, $[\alpha]_D^{27}$ = +94.4 (<i>c</i> 0.50, MeOH); |
| IR (film) v_{max} 3444, 2963, 2918, 1688, 1659, 1635, 1469, 1045, 1035, 731, 700 cm ⁻¹ ; |
| ¹ H NMR (400 MHz, CDCl ₃) δ 7.88 (d, J = 7.2 Hz, 1 H), 7.54-7.43 (m, 2H), 7.31-7.25 |
| (m, 2H), 7.12 (brs, 1H), 6.92-6.83 (m, 2H), 6.80-6.77 (m, 1H), 5.61 (s, 1H), 3.77-3.75 |
| (m, 3H) ppm; 13 C NMR (100 MHz, CDCl ₃) δ 171.3, 160.3, 147.9, 140.1, 132.4, 130.9, |
| 130.3, 128.5, 123.9, 123.4, 119.2, 114.0, 112.3, 60.9, 55.4 ppm; HRMS (ESI-Orbitrap) |
| m/z : $[M + H]^+$ Calcd for C ₁₅ H ₁₄ NO ₂ : 240.1019, found: 240.1016. |
| (S)-3-(3-fluorophenyl)isoindolin-1-one (12i) |
| White solid (147 mg, 86%). Enantiomer ratio: 88%, $[\alpha]_D^{23}$ = +115.2 (<i>c</i> 0.50, MeOH); |
| IR (film) v_{max} 3445, 2920, 1684, 1634, 1447, 1265, 1055, 1031, 1012, 733, 694 cm ⁻¹ ; |
| 19 F NMR (376 MHz, CD ₃ OD) δ -114.4 ppm: ¹ H NMR (400 MHz, CD ₃ OD) δ 7.82 (d. |

J = 7.6 Hz, 1H), 7.60-7.49 (m, 2H), 7.41-7.31 (m, 2H), 7.13 (d, J = 7.6 Hz, 1H), 7.07-6.99 (m, 2H), 5.75 (s, 1H) ppm; ¹³C NMR (100 MHz, CD₃OD) δ 173.3, 164.5 (d, J = 244.1 Hz), 149.4, 143.0 (d, J = 6.8 Hz), 133.7, 132.1, 131.9 (d, J = 8.1 Hz), 129.6, 124.6, 124.4, 123.7 (d, J = 2.9 Hz), 116.1 (d, J = 21.3 Hz), 114.5 (d, J = 22.4 Hz), 61.6 ppm; HRMS (ESI-Orbitrap) m/z: [M + H]⁺ Calcd for C₁₄H₁₁FNO: 228.0819, found: 228.0817.

(S)-3-(3-(trifluoromethyl)phenyl)isoindolin-1-one (12j)

White solid (198 mg, 95%). Enantiomer ratio: 84%, $[\alpha]_D^{25}$ = +84.8 (*c* 0.50, MeOH); IR (film) v_{max} 3445, 2920, 1722, 1645, 1634, 1340, 1304, 1110, 1014, 739, 708cm⁻¹; ¹⁹F NMR (376 MHz, CDCl₃) δ -62.6 ppm; ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, *J* = 7.6 Hz, 1H), 7.68 (brs, 1H), 7.61-7.46 (m, 6H), 7.23 (d, *J* = 7.2 Hz, 1H), 5.71 (s, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.5, 147.3, 139.8, 132.7, 131.6 (d, *J* = 32.2 Hz), 130.8, 130.3, 129.8, 128.9, 125.6 (d, *J* = 4.4 Hz), 124.1, 123.9 (d, *J* = 270.8Hz), 123.8 (d, *J* = 4.2 Hz), 123.4, 60.5 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]⁺ Calcd for C₁₅H₁₁F₃NO: 278.0787, found: 278.0789.

(S)-3-(o-tolyl)isoindolin-1-one (12k)

White solid (144 mg, 86%). Enantiomer ratio: 82%, $[\alpha]_D^{25}$ = +93.6 (*c* 0.50, MeOH); IR (film) v_{max} 3443, 2918, 1690, 1638, 1469, 1314, 1135, 1012, 737, 622 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.90-7.87 (m, 1H), 7.52-7.44 (m, 2H), 7.23-7.19 (m, 3H), 7.15-7.09 (m, 1H), 7.04-7.02 (m, 1H), 5.92 (s, 1H), 2.44 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.3, 148.0, 136.2, 136.1, 132.4, 131.5, 131.4, 128.4, 127.3, 124.0, 123.3, 58.1, 19.5 ppm; HRMS (ESI-Orbitrap) *m*/*z*: [M + H]⁺ Calcd for C₁₅H₁₄NO: 224.1070, found: 224.1068.

(S)-3-(2-methoxyphenyl)isoindolin-1-one (12l)

Yellow solid (165 mg, 92%). Enantiomer ratio: 62%, $[\alpha]_D^{26}$ = +139.4 (*c* 0.50, MeOH); IR (film) v_{max} 3447, 2920, 2849, 1693, 1633, 1490, 1461, 1245, 1049, 1022, 739, 622 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.86 (d, *J* = 7.2 Hz, 1H), 7.53-7.41 (m, 3H), 7.31-7.26 (m, 1H), 7.22 (brs, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.97 (d, *J* = 4.0 Hz, 1H), 6.90-6.83 (m, 1H), 6.15 (s, 1H), 3.95 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.3, 157.3, 147.7, 132.0, 131.6, 129.4, 128.2, 126.7, 126.6, 123.9, 123.8, 121.0,

 110.9, 55.6, 54.9 ppm; HRMS (ESI-Orbitrap) m/z: $[M + H]^+$ Calcd for C₁₅H₁₄NO₂: 240.1019, found: 240.1022.

(S)-3-(naphthalen-1-yl)isoindolin-1-one (12m)

White solid (175 mg, 90%). Enantiomer ratio: 88%, $[\alpha]_D^{20}$ = +376.0 (c 0.10, MeOH); IR (film) v_{max} 3194, 2918, 2843, 1696, 1655, 1508, 1422, 1307, 1139, 909, 748, 723 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.19 (brs, 1H), 7.95-7.90 (m, 2H), 7.85-7.80 (m, 1H), 7.65-7.53 (m, 2H), 7.50-7.43 (m, 2H), 7.42-7.38 (m, 2H), 7.31-7.28 (m, 1H), 7.25-7.21 (m, 1H), 6.50 (s, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.3, 147.9, 134.3, 132.3, 131.3, 131.2, 129.4, 129.2, 128.6, 127.0, 126.2, 125.8, 124.2, 123.3, 122.7 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]⁺ Calcd for C₁₈H₁₄NO: 260.1070, found: 260.1072.

(S)-3-(naphthalen-2-yl)isoindolin-1-one (12n)

White solid (169 mg, 87%). Enantiomer ratio: 86%, $[\alpha]_D^{26} = +167.2$ (*c* 0.25, MeOH); IR (film) ν_{max} 3193, 3051, 2843, 1695, 1656, 1469, 1346, 1199, 909, 822, 723 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 7.92 (brs, 1H), 7.89-7.80 (m, 4H), 7.61-7.45 (m, 5H), 7.32 (d, J = 7.2 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 5.92-5.87 (m, 1H) ppm; ¹³C NMR (150 MHz, CD₃OD) δ 173.4, 150.0, 137.3, 134.9, 134.8, 133.6, 132.4, 129.9, 129.5, 128.9, 128.8, 127.5, 127.5, 127.4, 124.9, 124.8, 124.3, 62.4 ppm; HRMS (ESI-Orbitrap) *m/z*: [M + H]⁺ Calcd for C₁₈H₁₄NO: 260.1070, found: 260.1072.

Supporting Information: Copies of ¹H, ¹⁹F and ¹³C NMR spectra, HPLC (**12a-n**) and X-ray structural data (CIF) (**11g**; **16d**). The Supporting Information is available free of charge on the ACS Publications website at <u>http://pubs.acs.org</u>.

Accession Codes

CCDC 1839098 and 1839101 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Notes

The authors declare no competing financial interest.

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References

1. (a) Shamma, M.; Moniot, J. L. The Isoquinoline Alkaloids, Chemistry and Pharmacology, Academic Press, New York and London, 1972. (b) Larock, R. C. Comprehensive Organic Transformations; VCH: New York, 1989; 819. (c) Scott, J. D.; Williams, R. M. Chemistry and biology of the tetrahydroisoquinoline antitumor. *Chem. Rev.* **2002**, *102*, 1669-1730. (d) Bentley, K. W. β-Phenylethylamines and the isoquinoline alkaloids. *Nat. Prod. Rep.*, **2004**, *21*, 395-424. (e) Singh, I. P.; Shah, P. Tetrahydroisoquinolines in therapeutics: a patent review (2010-2015). *Expert. Opin. Ther. Pat.* **2017**, *27*, 17-36.

2. (a) Sovic, I.; Karminski-Zamola, G. Derivatives of isoindoline, synthesis and biological activity. II. Biological activity of isoindoline derivatives. *Kem. Ind.* **2014**, *63*, 183-191. (b) Liu, W.; Liu, S.; Jin, R.; Guo, H.; Zhao, J. Novel strategies for catalytic asymmetric synthesis of C1-chiral 1,2,3,4-tetrahydroisoquinolines and 3,4-dihydrotetrahydroisoquinolines. *Org. Chem. Front.* **2015**, *2*, 288-299. (c) Chrzanowska, M.; Grajewska, A.; Rozwadowska, M. D. Asymmetric Synthesis of Isoquinoline Alkaloids: 2004-2015. *Chem. Rev.* **2016**, *116*, 12369-12465.

3. (a) Brossi, A.; Teitel, S. Synthesis and absolute configuration of cryptostylines I, II, and III. *Helv. Chim. Acta* **1971**, *54*, 1564-1571. (b) Minor, D. L.; Wyrick, S. D.; Charifson, P. S.; Watts, V. J.; Nichols, D. E.; Mailman, R. B. Synthesis and Molecular Modeling of 1-Phenyl-1,2,3,4-tetrahydroisoquinolines and Related 5,6,8,9-Tetrahydro-13bH-dibenzo[a,h]quinolizines as D1 Dopamine Antagonists. *J. Med. Chem.* **1994**, *37*, 4317-4328.

4. Bracca, A. B. J.; Kaufman, T. S. Synthetic approaches to carnegine, a simple tetrahydroisoquinoline alkaloid. *Tetrahedron* **2004**, *60*, 10575-10610.

5. Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. Isoindolinone enantiomers having affinity for the dopamine D4 receptor. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499-1502.

6. Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. A new approach to isoindolobenzazepines. A simple synthesis of lennoxamine. *Tetrahedron* **2000**, *56*, 1491-1499.

7. For selected recent representative results, see: (a) Li, C.; Xiao, J. Asymmetric Hydrogenation of Cyclic Imines with an Ionic Cp*Rh(III) Catalyst. J. Am. Chem. Soc. 2008, 130, 13208-13209. (b) Chang, M.; Li, W.; Zhang, X. A highly efficient and enantioselective tetrahydroisoquinoline alkaloids: asymmetric access to hydrogenation with an iridium catalyst. Angew. Chem. Int. Ed. 2011, 50, 10679-10681. (c) Berhal, F.; Wu, Z.; Zhang, Z.; Ayad, T.; Ratovelomanana-Vidal, V. Enantioselective Synthesis of 1-Aryl-tetrahydroisoquinolines through Iridium Catalyzed Asymmetric Hydrogenation. Org. Lett. 2012, 14, 3308-3311. (d) Wu, Z.; Perez, M.; Scalone, M.; Ayad, T.; Ratovelomanana-Vidal, V. Ruthenium-Catalyzed Asymmetric Transfer Hydrogenation of 1-Aryl-Substituted Dihydroisoquinolines: Access to Valuable Chiral 1-Aryl-Tetrahydroisoquinoline Scaffolds. Angew. Chem., Int. Ed. 2013, 52, 4925-4928. (e) Zhu, J.; Tan, H.; Yang, L.; Dai, Z.; Zhu, L.; Ma, H.; Deng, Z.; Tian, Z.; Qu, X. Enantioselective Synthesis of 1-Aryl-Substituted Tetrahydroisoquinolines Employing Imine Reductase. ACS Catal. 2017, 7, 7003-7007. (f) Li, H.; Tian, P.; Xu, J.-H.; Zheng, G.-W. Identification of an imine reductase for

asymmetric reduction of bulky dihydroisoquinolines. *Org. Lett.* **2017**, *19*, 3151-3154. (g) Zhou, H.; Liu, Y.; Yang, S.; Zhou, L.; Chang, M. One-Pot N-Deprotection and Catalytic Intramolecular Asymmetric Reductive Amination for the Synthesis of Tetrahydroisoquinolines. *Angew. Chem., Int. Ed.* **2017**, *56*, 2725-2729.

8. Itoh, T.; Miyazaki, M.; Fukuoka, H.; Nagata, K.; Ohsawa, A. Formal Total Synthesis of (-)-Emetine Using Catalytic Asymmetric Allylation of Cyclic Imines as a Key Step. *Org. Lett.* **2006**, *8*, 1295-1297.

9. For selected recent results, see: (a) Li, Z.; Li, C.-J. Catalytic Enantioselective Alkynylation of Prochiral sp3 C-H Bonds Adjacent to a Nitrogen Atom. Org. Lett. 2004. 6, 4997-4999. (b) Taylor, A. M.; Schreiber, S. L. Enantioselective Addition of Terminal Alkynes to Isolated Isoquinoline Iminiums. Org. Lett. 2006, 8, 143-146. (c) Li, Z.; MacLeod, P. D.; Li, C.-J. Studies on Cu-catalyzed asymmetric alkynylation of tetrahydroisoquinoline derivatives. Tetrahedron: Asymmetry 2006, 17, 590-597. (d) Wang, S.; Onaran, M. B.; Seto, C. T. Enantioselective Synthesis of 1-Aryltetrahydroisoquinolines. Org. Lett. 2010, 12, 2690-2693. (e) Hashimoto, T.; Omote, M.; Maruoka, K. Catalytic Asymmetric Alkynylation of C1-Substituted C.N-Cyclic Azomethine Imines by Cul/Chiral Bronsted Acid Co-Catalyst. Angew. Chem., Int. Ed. 2011, 50, 8952-8955. (f) Perepichka, I.; Kundu, S.; Hearne, Z.; Li, C.-J. Efficient merging of copper and photoredox catalysis for the asymmetric cross-dehydrogenative-coupling of alkynes and tetrahydroisoquinolines. Org. Biomol. Chem. 2015, 13, 447-451. (g) Huang, T.; Liu, X.; Lang, J.; Xu, J.; Lin, L.; Feng, X. Asymmetric Aerobic Oxidative Cross-Coupling of Tetrahydroisoquinolines with Alkynes. ACS Catal. 2017, 7, 5654-5660.

10. For selected recent results, see: (a) Takasu, K.; Maiti, S.; Ihara, M. Asymmetric intramolecular aza-Michael reaction using environmentally friendly organocatalysis. *Heterocycles* **2003**, *59*, 51-55. (b) Fustero, S.; Moscardo, J.; Jimenez, D.; Peerez-Carrion, M. D.; Sanchez-Rosesllo, M.; del Pozo, C. Organocatalytic approach to benzofused nitrogen-containing heterocycles: enantioselective total synthesis of (+)-Angustureine. *Chem.-Eur. J.* **2008**, *14*, 9868-9872. (c) Enders, D.; Liebich, J. X.; Raabe, G. Organocatalytic Asymmetric Synthesis of trans-1,3-Disubstituted

Tetrahydroisoquinolines via a Reductive Amination/Aza-Michael Sequence. *Chem.-Eur. J.* **2010**, *16*, 9763-9766. (d) Neel, A. J.; Hehn, J. P.; Tripet, P. F.; Toste, F. D. Asymmetric Cross-Dehydrogenative Coupling Enabled by the Design and Application of Chiral Triazole-Containing Phosphoric Acids. *J. Am. Chem. Soc.* **2013**, *135*, 14044-14047. (e) Jiang, J.; Ma, X.; Ji, C.; Guo, Z.; Shi, T.; Liu, S.; Hu, W. Ruthenium(II)/Chiral Bronsted Acid Co-Catalyzed Enantioselective Four-Component Reaction/Cascade Aza-Michael Addition for Efficient Construction of 1,3,4-Tetrasubstituted Tetrahydroisoquinolines. *Chem.-Eur. J.* **2014**, *20*, 1505-1509.

11. (a) Ito, K.; Akashi, S.; Saito, B.; Katsuki, T. Asymmetric intramolecular allylic amination: Straightforward approach to chiral C1-substituted tetrahydroisoquinolines. *Synlett* **2003**, 1809-1812. (b) Sasamoto, N.; Dubs, C.; Hamashima, Y.; Sodeoka, M. Pd(II)-Catalyzed Asymmetric Addition of Malonates to Dihydroisoquinolines. *J. Am. Chem. Soc.* **2006**, *128*, 14010-14011. (c) Shi, C.; Ojima, I. Asymmetric synthesis of 1-vinyltetrahydroisoquinoline through Pd-catalyzed intramolecular allylic amination. *Tetrahedron* **2007**, *63*, 8563-8570.

12. For selected recent results, see: (a) Frisch, K.; Landa, A.; Saaby, S.; Joergensen, K. A. Organocatalytic diastereo- and enantioselective annulation reactions-construction of optically active 1,2-dihydroisoquinoline and 1,2-dihydrophthalazine derivatives. *Angew. Chem., Int. Ed.* **2005**, *44*, 6058-6063. (b) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. Catalytic Enantioselective 1,3-Dipolar Cycloaddition of C,N-Cyclic Azomethine Imines with α ,β-Unsaturated Aldehydes. *J. Am. Chem. Soc.* **2010**, *132*, 4076-4077. (c) De, C. K.; Mittal, N.; Seidel, D. A Dual-Catalysis Approach to the Asymmetric Steglich Rearrangement and Catalytic Enantioselective Addition of O-Acylated Azlactones to Isoquinolines. *J. Am. Chem. Soc.* **2011**, *133*, 16802-16805. (d) Zhang, G; Zhang, Y.; Wang, R. Catalytic Asymmetric Activation of a Csp3-H Bond Adjacent to a Nitrogen Atom: A Versatile Approach to Optically Active α-Alkyl α-Amino Acids and C1-Alkylated Tetrahydroisoquinoline Derivatives. *Angew. Chem., Int. Ed.* **2011**, *50*, 10429-10432. (e) Zhang, J.; Tiwari, B.; Xing, C.; Chen, X.; Chi, Y. R. Enantioselective Oxidative Cross-Dehydrogenative Coupling of Tertiary Amines to Aldehydes. *Angew. Chem., Int. Ed.* **2012**, *51*, 3649-3652. (f) Zhang,

G.; Ma, Y.; Wang, S.; Kong, W.; Wang, R. Chiral organic contact ion pairs in metal-free catalytic enantioselective oxidative cross-dehydrogenative coupling of tertiary amines to ketones. *Chem. Sci.* **2013**, *4*, 2645-2651. (g) Mengozzi, L.; Gualandi, A.; Cozzi, P. G. A highly enantioselective acyl-Mannich reaction of isoquinolines with aldehydes promoted by proline derivatives: an approach to 13-alkyl-tetrahydroprotoberberine alkaloids. *Chem. Sci.* **2014**, *5*, 3915-3921.

13. (a) Kurihara, K.; Yamamoto, Y.; Miyaura, N. An N-linked bidentate phosphoramidite ligand (N-Me-BIPAM) for rhodium-catalyzed asymmetric addition of arylboronic acids to N-sulfonylarylaldimines. *Adv. Synth. Catal.* **2009**, *351*, 260-270. (b) Shuler, S. A.; Yin, G.; Krause, S. B.; Vesper, C. M.; Watson, D. A. Synthesis of Secondary Unsaturated Lactams via an Aza-Heck Reaction. *J. Am. Chem. Soc.* **2016**, *138*, 13830-13833.

14. Enders, D.; Braig, V.; Raabe, G. Asymmetric synthesis of 3-aryl-substituted 2,3-dihydro-1H-isoindol-1-ones. *Can. J. Chem.* **2001**, *79*, 1528-1535.

15. Gonzalez-Temprano, I.; Sotomayor, N.; Lete, E. Highly Diastereoselective Intramolecular α -Amidoalkylation Reactions of Hydroxylactams Derived from N-Phenethylimides. Enantioselective Synthesis of Dihydropyrrolo[2,1-a] isoquinolones. *Synlett* **2002**, 593-597.

16. (a) Camarero, C.; Gonzalez-Temprano, I.; Gomez-SanJuan, A.; Arrasate, S.; Lete,
E.; Sotomayor, N. Stereocontrolled conjugate additions to dihydroindolizinone systems. Synthesis of enantiopure polysubstituted tetrahydropyrrolo[2,1-a]isoquinolones. *Tetrahedron* 2009, *65*, 5787-5798. (b) Amat,
M.; Elias, V.; Llor, N.; Subrizi, F.; Molins, E.; Bosch, J. A General Methodology for the Enantioselective Synthesis of 1-Substituted Tetrahydroisoquinoline Alkaloids. *Eur. J. Org. Chem.* 2010, *2010*, 4017-4026.

17. (a) Chen, M.-D.; He, M.-Z.; Zhou, X.; Huang, L.-Q.; Ruan, Y.-P.; Huang, P.-Q.
Studies on the diastereoselective reductive alkylation of (*R*)-phenylglycinol derived phthalimide: observation of stereoelectronic effects. *Tetrahedron* 2005, *61*, 1335-1344.
(b) Deniau, E.; Couture, A.; Grandclaudon, P. A conceptually new approach to the asymmetric synthesis of 3-aryl and alkyl poly-substituted isoindolinones. *Tetrahedron:*

Asymmetry 2008, 19, 2735-2740. (c) Jiang, L.-J.; Teng, B.; Zheng, J.-F.; Ye, J.-L.; Huang, P.-Q. Bis-Lewis acids-catalyzed highly diastereoselective one-pot reductive dehydroxylation of chiral N,O-acetals. Tetrahedron 2010, 66, 172-175. (d) Zhang, Y.; He. L.: Shi. L. Asymmetric hydrogenolysis of racemic 3-substituted-3-hydroxy-isoindolin-1-ones employing SPINOL-derived chiral phosphoric acid. Tetrahedron Lett. 2018, 59, 1592-1595.

18. (a) Enders, D.; Braig, V.; Raabe, G. Asymmetric synthesis of 3-aryl-substituted 2,3-dihydro-1H-isoindol-1-ones. Can. J. Chem. 2001, 79, 1528-1535. (b) Perard-Viret, J.; Prange, T.; Tomas, A.; Royer, J. A simple and efficient asymmetric synthesis of 3-alkyl-isoindolin-1-ones. Tetrahedron 2002, 58, 5103-5108. (c) Comins, D. L.; Schilling, S.; Zhang, Y. Asymmetric Synthesis of 3-Substituted Isoindolinones: Application to the Total Synthesis of (+)-Lennoxamine. Org. Lett. 2005, 7, 95-98. (d) Sun, X.-W.; Liu, M.; Xu, M.-H.; Lin, G.-Q. Remarkable Salt Effect on In-Mediated Allylation of N-tert-Butanesulfinyl Imines in Aqueous Media: Highly Practical Asymmetric Synthesis of Chiral Homoallylic Amines and Isoindolinones. Org. Lett. 2008, 10, 1259-1262. (e) Reddy, N. S. S.; Reddy, B. J. M.; Reddy, B. V. S. A synthesis convergent and stereoselective total of (-)-crispine A. (-)-benzo[a]quinolizidine and (-)-salsolidine. *Tetrahedron Lett.* 2013, 54, 4228-4231. (f) Meng, J.-L.; Jiao, T.-Q.; Chen, Y.-H.; Fu, R.; Zhang, S.-S.; Zhao, Q.; Feng, C.-G.; Lin. G.-O. Synthesis of chiral isoindolinones via asymmetric propargylation/lactamization cascade. Tetrahedron Lett. 2018, 59, 1564-1567. (g) Brahmchari, D.; Verma, A. K.; Mehta, S. Regio- and Stereoselective Synthesis of Isoindolin-1-ones through BuLi-Mediated Iodoaminocyclization of 2-(1-Alkynyl)benzamides. J. Org. Chem. 2018, 83, 3339-3347. (h) Kawecki, R.; Stanczyk, W.; Jaglinska, A. Stereoselective synthesis of isoindolinones and *tert*-butyl sulfoxides. Tetrahedron 2018, 74, 578-584.

19. Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. Design of *C*₂-symmetric tetrahydropentalenes as new chiral diene ligands for highly enantioselective Rh-catalyzed arylation of *N*-tosylarylimines with arylboronic acids. *J. Am. Chem. Soc.* **2007**, *129*, 5336-5337.

20. (a) Bisai, V.; Suneja, A.; Singh, V. K. Asymmetric Alkynylation/Lactamization Cascade: An Expeditious Entry to Enantiomerically Enriched Isoindolinones. Angew. Chem., Int. Ed. 2014, 53, 10737-10741. (b) Karmakar, R.; Suneja, A.; Bisai, V.; Singh, V. K. Ni(II)-Catalyzed Highly Stereo- and Regioselective Syntheses of Isoindolinones and Isoquinolinones from in Situ Prepared Aldimines Triggered by Homoallylation/Lactamization Cascade. Org. Lett. 2015, 17, 5650-5653. (c) Di Mola, A.; Tiffner, M.; Scorzelli, F.; Palombi, L.; Filosa, R.; De Caprariis, P.; Waser, M.; Massa, A. Bifunctional phase-transfer catalysis in the asymmetric synthesis of biologically active isoindolinones. Beilstein J. Org. Chem. 2015, 11, 2591-2599. (d) Bisai, V.; Unhale, R. A.; Suneja, A.; Dhanasekaran, S.; Singh, V. K. An Efficient Entry to syn- and anti-Selective Isoindolinones via an Organocatalytic Direct Mannich/Lactamization Sequence. Org. Lett. 2015, 17, 2102-2105. (e) Suneja, A.; Bisai, V.; Singh, V. K. Asymmetric Syntheses of Medicinally Important Isoindolinones (S)-PD 172938, (R)-JM 1232, and Related Structures. J. Org. Chem. , *81*, 4779-4788.

21. (a) Zhou, P.; Chen, B.-C.; Davis, F. A. Recent advances in asymmetric reactions using sulfinimines (*N*-sulfinyl imines). *Tetrahedron* 2004, *60*, 8003-8030. (b) Robak, M. T.; Herbage, M. A.; Ellman, J. A. Synthesis and Applications of *tert*-Butanesulfinamide. *Chem. Rev.* 2010, *110*, 3600-3740.

22. (a) Si, C.-M.; Huang, W.; Du, Z.-T.; Wei, B.-G.; Lin, G.-Q. Diastereoconvergent Synthesis of *trans*-5-Hydroxy-6-Substituted-2-Piperidinones by Addition-Cyclization-Deprotection Process. *Org. Lett.* **2014**, *16*, 4328-4331; (b) Si, C.-M.; Mao, Z.-Y.; Dong, H.-Q.; Du, Z.-T.; Wei, B.-G.; Lin, G.-Q. Divergent Method to *trans*-5-Hydroxy-6-alkynyl/alkenyl-2-piperidinones: Syntheses of (-)-Epiquinamide and (+)-Swainsonine. *J. Org. Chem.* **2015**, *80*, 5824-5833; (c) Si, C.-M.; Mao, Z.-Y.; Liu, Y.-W.; Du, Z.-T.; Wei, B.-G.; Lin, G-Q. Stereoselective formation of chiral *trans*-4-hydroxy-5-substituted 2-pyrrolidinones: syntheses of streptopyrrolidine and 3-*epi*-epohelmin A. *Org. Chem. Front.* **2015**, *2*, 1485-1499.

23. For selected recent papers; see: (a) Liu, Y.-W.; Han, P.; Zhou, W.; Mao, Z.-Y.; Si, C.-M.; Wei, B.-G. Asymmetric syntheses of epohelmins A and B by In-mediated

allylation. Org. Biomol. Chem. 2016, 14, 10714-10722. (b) Si, C.-M.; Shao, L.-P.; Mao. Z. -Y.: Zhou. W.; Wei, B.-G. An efficient approach to trans-4-hydroxy-5-substituted 2-pyrrolidinones through a stereoselective tandem Barbier process: divergent syntheses of (3R,4S)-statines, (+)-preussin and (-)-hapalosin. Org. Biomol. Chem. 2017, 15, 649-661. (c) Han, P.; Zhou, Z.; Si, C.-M.; Sha, X.-Y.; Gu, Z.-Y.; Wei, B.-G.; Lin, G.-Q. Asymmetric Synthesis of Rupestonic Acid and Pechueloic Acid. Org. Lett. 2017, 19, 6732-6735. (d) Mao, Z.-Y.; Liu, Y.-W.; Han, P.; Dong, H.-Q.; Si, C.-M.; Wei, B.-G.; Lin, G.-Q. Regio- and Stereoselective Cascades via Aldol Condensation and 1,3-Dipolar Cycloaddition for Construction of Functional Pyrrolizidine Derivatives. Org. Lett. 2018, 20, 1090-1093.

24. (a) Fu, Y.; Zhao, X.-L.; Hugel, H.; Hou, B.; Huang, D.; Du, Z. The Influence of Main Group Metallic Lewis Acids on the Formation and Reactivity of Grignard Reagents. *Curr. Org. Chem.* **2015**, *19*, 2324-2343. (b) Wang, X. J.; Zhang, L.; Sun, X.; Xu, Y.; Krishnamurthy, D.; Senanayake, C. H. Addition of grignard reagents to aryl acid chlorides: an efficient synthesis of aryl ketones. *Org. Lett.* **2005**, *7*, 5593-5595. (c) Fan, X.-Y.; Yang, Y.-X.; Zhuo, F.-F.; Yu, S.-L.; Li, X.; Guo, Q.-P.; Du, Z.-X.; Da, C.-S. AlCl₃ and BDMAEE: A Pair of Potent Reactive Regulators of Aryl Grignard Reagents and Highly Catalytic Asymmetric Arylation of Aldehydes. *Chem. - Eur. J.* **2010**, *16*, 7988-7991. (d) Yang, Y.-X.; Liu, Y.; Zhang, L.; Jia, Y.-E.; Wang, P.; Zhuo, F.-F.; An, X.-T.; Da, C.-S. Aryl Bromides as Inexpensive Starting Materials in the Catalytic Enantioselective Arylation of Aryl Aldehydes: The Additive TMEDA Enhances the Enantioselectivity. *J. Org. Chem.* **2014**, *79*, 10696-10702. (e) Wang, P.; Liu, Y.; Zhang, Y.-L.; Da, C.-S. The inexpensive additive *N*-methylmorpholine effectively decreases the equivalents of nucleophiles in the catalytic highly enantioselective arylation of aryl aldehydes. *Chirality* **2017**, *29*, 443-450.