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Stereoselective Synthesis of Chiral IBR2 Analogues

Xiao-Long Qiu,*,† Jiewen Zhu,† Guikai Wu,† Wen-Hwa Lee,*,† and A. Richard Chamberlin‡,§

Department of Biological Chemistry, School of Medicine, Department of Chemistry, and Department of Pharmaceutical Sciences, University of California, Irvine, Irvine, California 92697

qiux@uci.edu; whlee@uci.edu

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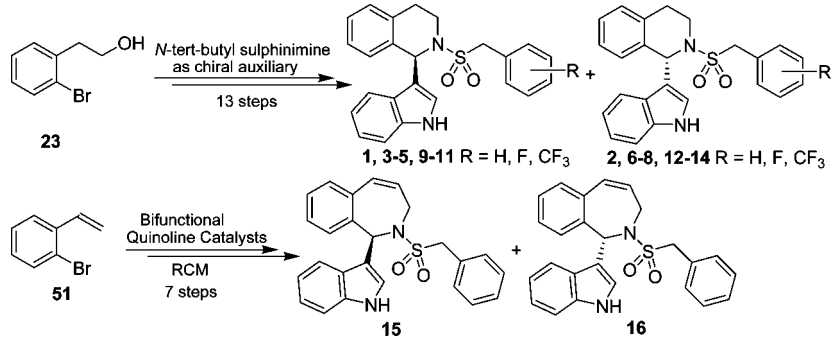

Two stereoselective routes were developed to synthesize optically pure IBR2 analogues **1**−**16**. The first features addition of *N*-Boc-3-bromoindole **26** to the sulfinamide **25**, providing a 1:1 ratio of the separable diasteroisomers **27** and **28** in good yield. In a straightforward fashion, the sulfinamides **27** and **28** were conveniently converted into the key amines **39** and **47** over 8 steps, respectively, from which a series of 3,4-dihydroisoquinolinyl IBR2 analogues **1**−**14** containing fluorinated and trifluoromethylated benzyl groups were prepared. Another route highlights the highly enantioselective addition of indole to the sulfonyl amide **50** with bifunctional aminothioureas **57** and **58** as catalysts. After the reaction conditions were optimized, the desired sulfonyl amides (*R*)-**55** and (*S*)-**55** were obtained in 99% ee and 98% ee, respectively. Acylation of (*R*)-**55** and (*S*)-**55** separately and subsequent allylation gave compounds **60** and **63**, respectively, which were further subjected to RCM to furnish compounds **61** and **64** and, after removal of the Boc groups, the desired IBR2 analogues **15** and **16**.

It is well-known that Rad51 plays an essential role in DNA damage repair and cell proliferation. For example, it has been demonstrated that inactivation of mouse *Rad51* gene would result in embryonic lethality[1] and depletion of Rad51 in DT40 chicken B lymphocytes clearly leads to cell cycle arrest and subsequent cell death.[2] Expression of Rad51 protein and the rate of Rad51-mediated homologous recombination (HR) are both elevated in various types of rapidly proliferating cancer cells, including breast cancer, pancreatic cancer, nonsmall-cell lung carcinoma, glioblastoma, acute myelogenous leukemia (AML), and chronic myelogenous leukemia (CML), compared to normal cells.[3−6] It is also well-known that Rad51 overexpression may contribute to tumor progression[7] and is positively correlated with the resistance to DNA damage inducing radio- or chemotherapies,[8] whereas its depletion with siRNA or antisense increases radiosensitivity.[9,10] Moreover, Rad51 inter-

* To whom correspondence should be addressed.
† Department of Biological Chemistry, School of Medicine.
‡ Department of Chemistry.
§ Department of Pharmaceutical Sciences.

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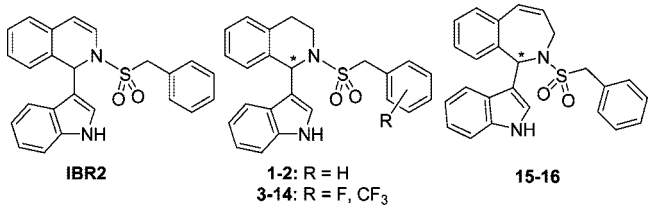

FIGURE 1. Structure of IBR2 and rationale of the designed chiral IBR2 analogues.

acts with the tumor suppressor BRCA2 via direct binding to its six conserved BRC repeats.[11,12] In the presence of excess BRC peptide derived from BRCA2, DNA binding and nucleoprotein filament formation of Rad51 were disrupted in vitro.[13] In cancer cells, an excess of BRC repeats inhibits IR-induced Rad51 foci formation.[14,15] These results suggest that the binding of exogenous BRC repeats inhibits the Rad51 functions both in vitro and in vivo. Consistent with this observation, the crystal structure of teh Rad51−BRC peptide complex[16] shows that the BRC repeat mimics the Rad51 oligomerization motif. Thus, small molecules mimicking elements of the BRC repeat structure show some promise in treating cancer by potentially preventing the deleterious effects of Rad51 overexpression.

Very recently, our group successfully validated a small molecular inhibitor of Rad51, designated as IBR2 (Figure 1), by a reverse yeast two-hybrid screening.[17] Rad51 was rapidly degraded in IBR2-treated cancer cells, and the homologous recombination repair was impaired, subsequently leading to cell death. In spite of the efficacy of IBR2 in our original studies, some problems were apparent. First of all, IBR2 is not stable and was found to decompose to the extent of approximately 50% (0.1 M in CH_2Cl_2) after 2 months, producing indole (40% yield) along with other unidentified compounds. Additionally, the corresponding biological results will be integrated into a complete SAR analysis project. Additionally, the bioactivity of IBR2 was not high and IC_{50} values were in the range of 10−20 μM for most cancer cell lines. Thus, we sought to develop an efficient synthetic route by which more stable and highly bioactive IBR2 analogues might be produced. Since one possible source of instability in IBR2—as well as a logical candidate for structure variation in analogues—is the enamide-containing heterocycle ring of the dihydroisoquiniline ring, we further envisioned testing a convergent strategy for preparing analogues that would bring together the requisite structural components, isoquinoline, indole, and benzylsulfonyl, and allow for the eventual preparation of a wide variety of IBR2 variants.

With these considerations in mind, two types of chiral IBR2 analogues, **1**−**2** and **15**−**16**, were designed, synthesized (Figure 1). Another rationale for designing these compounds was that IBR compounds, from molecular docking study, may bind with Rad51 by extending its phenyl sulfonyl moiety into a binding site for Phe1524 of BRC4 of BRCA2. Nevertheless, the binding model needs to be refined and consolidated, because it is not completely clear at the moment how the orientation of isoquinoline and indole ring systems may affect the activity. One of the interesting questions is how the dihedral angle of indole−C1−N−sulfonyl (and hence the orientation of the indole moiety) may affect activity. Thus, the 3,4-dihydro 6-membered ring and the 7-membered ring analogues **1**−**2**, **15**−**16** may be beneficial for assessment of this specific question. Chiral analogues **1**−**2** featured the transformation of the double bond of enamine moiety in IBR2 to a single bond. Additionally, in view of the fact that introduction of fluorine atom(s) into many biologically active molecules could bring about remarkable and profound changes in their physical, chemical, and biological properties, including a profound effect on drug disposition, in terms of distribution, drug clearance, route(s), extent of drug metabolism, and metabolic stability,[18] a series of monofluorinated and trifluoromethylated IBR2 analogues **3**−**14** were also synthesized, in addition to **15**−**16** containing an enlarged isoquinoline ring.

Results and Discussion

Stereoselective Synthesis of IBR2 Analogues 1−14. Although there are some reports on the synthesis of racemic tetrahydroisoquinolines and their derivatives,[19] introducing a chiral center at the 1-position on the isoquinoline scaffold efficiently has been proven difficult. Takamura et al. have tried to stereoselectively synthesize 1-substituted isoquinoline (as well as quinoline) using bifunctional Lewis acid−base catalysts.[20] Although working efficiently in quinoline substrates, the bifunctional catalysts gave only poor diastereoselectivity (∼3% ee) in isoquinoline substrates (R = H). Their modeling studies suggested that there seems to be no significant preference between the two transition states involving either the *s*-cis or *s*-trans acyl isoquinolium intermediates, at least sterically. Establishing C1 chirality of tetrahydroisoquinoline via a ring-closure substrate-induction was accomplished in the Bringmann group utilizing a chiral center at the 3-position.[21] However, our system does not have a preexisting chiral center on the substrate. Thus, it would be more reasonable and supposedly effective to use 1,2-induction, if substrate-induction would be the only option. Hence we considered to alternatively use a chiral auxiliary group on the N to facilitate this. The retrosynthetic analysis of chiral IBR2 analogues **1**−**14** (Figure 2) was based

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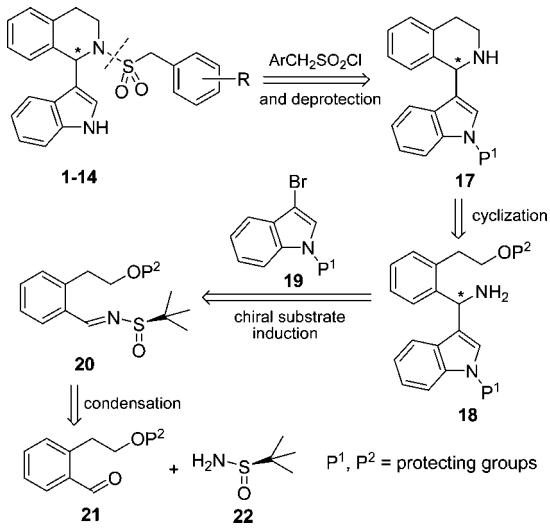
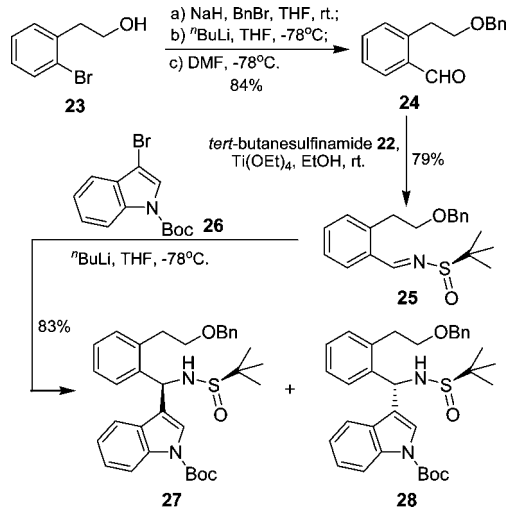


FIGURE 2. Retrosynthetic analysis of target molecules **1**−**14**.

SCHEME 1



on the asymmetric induction provided by Ellman's *N*-*tert*-butyl sulfinimine as the chiral auxiliary[22] for selectively introducing the single stereogenic center in the targets. Our chiral target molecules would be delivered via benzylsulfonylation of the intermediate **17** and subsequent deprotection, and cyclization of intermediate **18** would pave the way to the amine **17**. The amine **18** in turn might be provided by means of addition of protected 3-bromoindole **19** to the *N*-*tert*-butyl sulfinimine derivative **20**, which could be obtained by condensation between the aldehyde **21** and the chiral Ellman reagent **22**.

The synthesis embarked with the conversion of the commercially available bromide **23** into the aldehyde **24** in two steps, including benzylation followed by treatment with *n*-BuLi/THF/DMF at −78 °C (Scheme 1). Next, condensation of the aldehyde **24** with (*R*)-Ellman sulfinamide **22** gave the sulfinimine derivative **25** in 79% yield. Addition proceeded well by treatment of compound **25** with a solution of 1-Boc-3-lithioindole (prepared in situ via reaction of 1-Boc-3-bromoindole **26** with *n*-BuLi) at −78 °C, and the desired sulfinimides were isolated in 83% yield. Unfortunately, the two diastereoisomers **27** and **28** were produced in a 1:1 ratio,[23] showing somewhat disappointingly that the chiral sulfinimine auxiliary had no influence on the facial selectivity of attack by the lithiated indole nucleophile under these conditions. Although excellent selectivity was achieved in a somewhat different system (see below), in this particular case the diastereoisomers **27** and **28** could be readily separated by silica gel column chromatography. The Ellman auxiliary thus serves in this case as a very convenient resolving agent, allowing the preparation of both enantiomers of IBR2 analogues.

Thus, starting with the optically pure sulfinimide **27**, HCl-mediated removal of the *tert*-butanesulfinyl group cleanly provided the amine product **29** in 95% yield (Scheme 2). Subjecting the amine **29** to hydrogenation provided the amino alcohol **30** in 95% yield, which was further protected with TBDMSCl to afford compound **31** in 70% overall yield. Exposure of the amine **31** to CbzCl/DMAP/CH_2Cl_2 delivered compound **32** in 96% yield and subsequent removal of the silyl group in **32** with TBAF yielded the alcohol **33** in 92% yield. Additionally, treatment of **30** with CbzCl/DMAP could alternatively afford **33** in 52% yield along with the bis-Cbz compound **34** in 20% yield. Alcohol **33** was further mesylated to give compound **35** in 88% yield. Once hydrogenation of the mesylate **35** was carried out with Pd/C as catalyst in EtOH,[24] the desired cyclic amine **36** was isolated in 97% yield, which led directly to the desired sulfonamide **37** in 78% yield via benzylsulfonylation. Unfortunately, TFA-mediated removal of the Boc group in **37** only gave the IBR2 analogue **38** in low yield and furthermore was determined to have racemized by chiral HPLC analysis. To solve this problem, we slightly reordered the synthetic route, removing the Boc group prior to benzylsulfonylation. Thus, exposure of amine **36** to NaOMe/MeOH/THF for 2 days furnished the indole derivative **39** in 86% yield,[25] which was then subjected to benzylsulfonylation to afford the desired chiral IBR2 analogue **1**. Chiral HPLC analysis confirmed that enantiomeric purity of **1** was very high (98% ee favorite *R*), and its absolute configuration was further confirmed by X-ray diffraction. In addition, a series of chiral monofluorinated and trifluoromethylated IBR2 analogues, **3**−**5** and **9**−**11**, were also accessed via sulfonylation of the key intermediate **39** with different fluorinated arylsulfonyl chlorides.

Utilizing similar reaction procedures, the *S* configuration IBR2 analogues **2**, **6**−**8**, and **12**−**14** were also prepared starting from sulfinimide **28** in a straightforward fashion (Scheme 3).

Highly Enantioselective Synthesis of IBR2 Analogues 15 and 16. Although the first route proved to be satisfactory in many ways, we opted to explore additional avenues that might be more concise in general and more enantioselective in the key bond-forming step. Thus, an alternative retrosynthetic analysis of chiral IBR2 analogues **15** and **16** inspired an improved route in which the ring closure to form the nitrogen-containing ring of the isoquinoline moiety be carried out via ring closure metathesis (RCM) of an intermediate such as **48**,[26] and that the absolute stereochemistry would be controlled by an asymmetric Friedel−Crafts (F−C) reaction of an achiral

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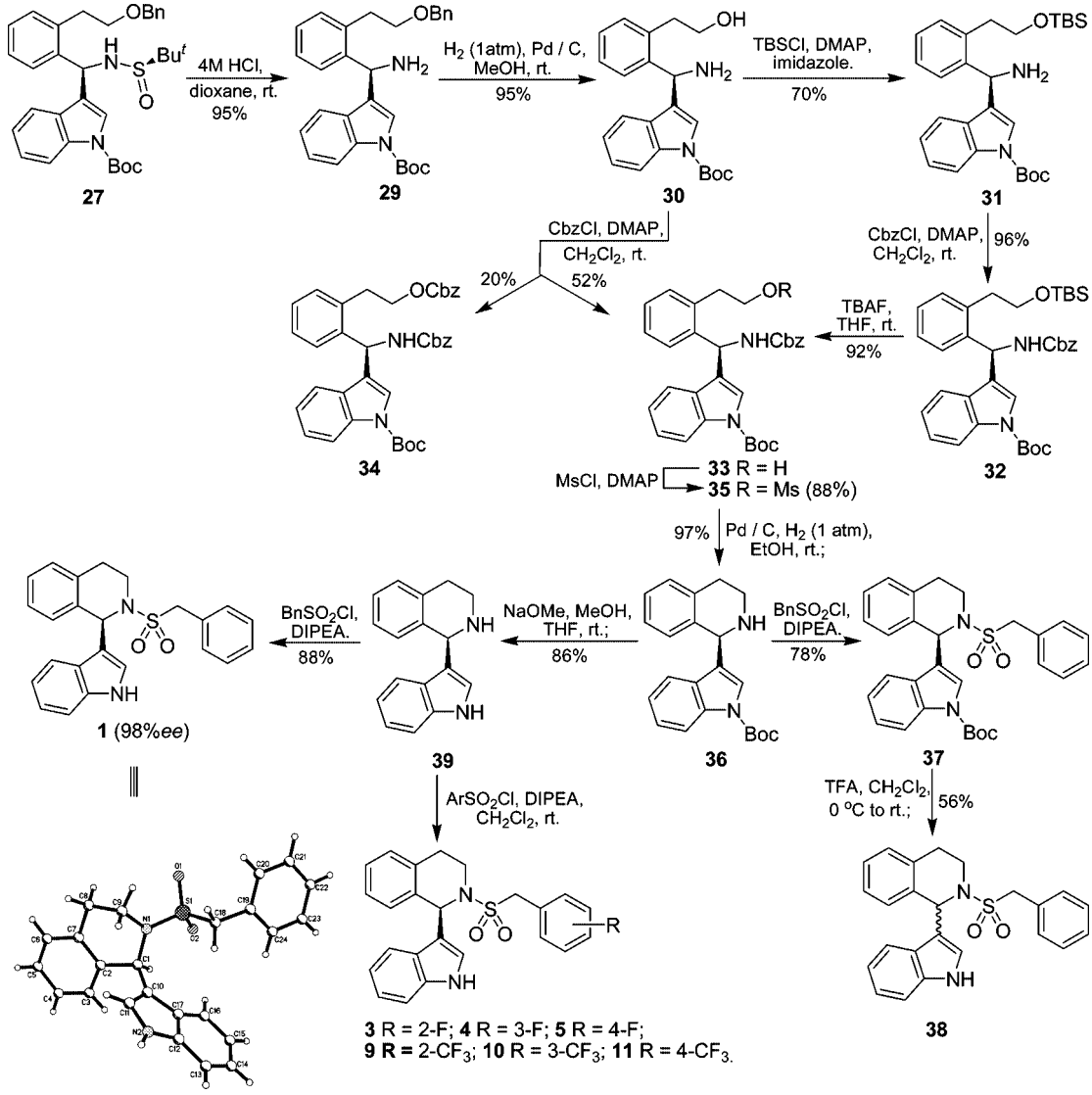
SCHEME 2



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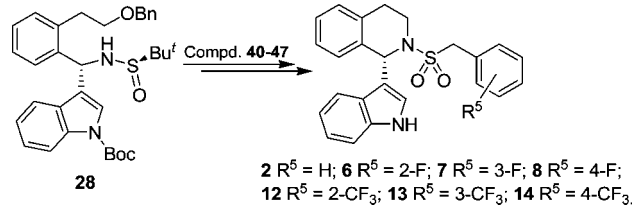

sulfonimine (**50**) with indole with use of thiourea alkaloids or bisoxazoline Cu(II) complex as catalysts (Figure 3).[27,28]

Because the original Zhou and Deng reports of the asymmetric F−C reactions[26−28] included only examples of aryl sulfoamides, we decided to test benzyl sulfonamides in the same process. Thus, the requisite starting benzyl imine **50** (Scheme 4, R = Bn) was readily prepared from 2-bromostyrene, **51**, by treatment of the corresponding bromide **51** with *n*-BuLi at −78 °C followed by anhydrous DMF to give the aldehyde **52** (73%), which then provided the imine **50** by condensation with benzylsulfonamide. The "conventional" *N*-tosyl imine **53** was also prepared by a similar sequence (Scheme 4, R = Ts).

With the imines **50** and **53** in hand, asymmetric F−C reactions with indole (unprotected) were investigated (Table 1). First, the applicability of different catalysts was investigated with *N*-tosyl imine **53** as substrate (entries 1 and 2). Bisoxazoline Cu(II) complex **56** (generated in situ through reaction of (*S*)-

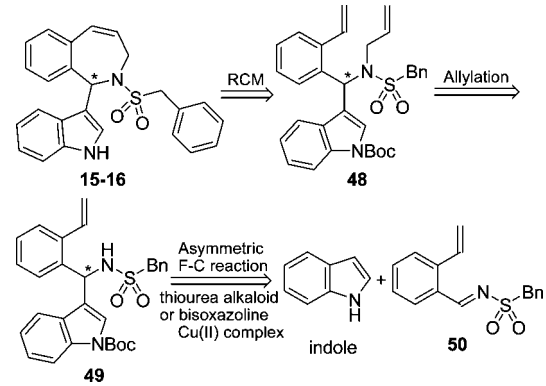

FIGURE 3. Retrosynthetic analysis of target molecules **15**−**16.**

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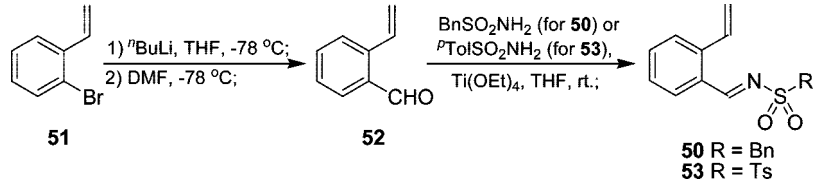
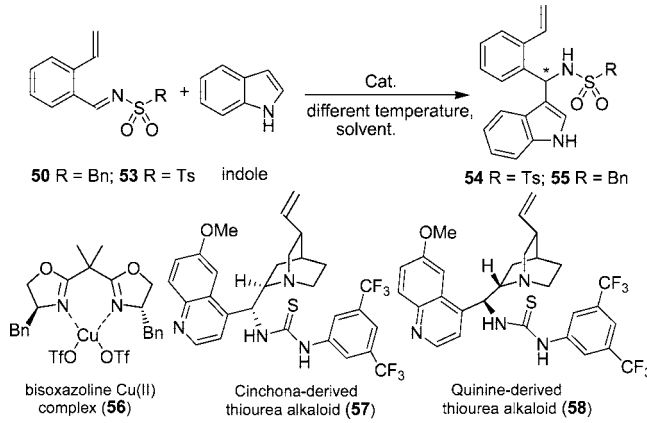


TABLE 1. Asymmetric Friedel−Crafts Reactions of Imines 50 and 53 with Indole



entry	imine	conc of imine (M)	indole (equiv)	cat. (10 mol %)	solvent	*T* (°C)	time (day)	product yield(%)	product ee (%)
1	**53**	0.08	5.0	**56**	CH_2Cl_2	rt	3	**54**: 22	90 (*R*)
2	**53**	2.00	2.0	**57**	EtOAc	50	2	**54**: 80	95 (*R*)
3	**50**	1.26	2.0	**57**	EtOAc	50	2	**55**: 48	92 (*R*)
4	**50**	2.0	2.0	**57**	EtOAc	rt	4	**55**: 40	95 (*R*)
5	**50**	1.0	2.0	**57**	EtOAc	rt	7	**55**: 23	96 (*R*)
6	**50**	0.5	2.0	**57**	EtOAc	rt	7	**55**: 13	96 (*R*)
7	**50**	2.0	2.0	**57**	EtOAc	0	7	**55**: 40	96 (*R*)
8	**50**	2.0	2.0	**57**	EtOAc	0	12	**55**: 55	99 (*R*)
9	**50**	2.0	2.0	**58**	EtOAc	rt	7	**55**: 42	98 (*S*)

Bn-bisoxazoline and $Cu(OTf)_2$) catalyzed the F−C reaction of imine **53** with indole in low yield (22%) and in good enantioselectivity (90% ee) (entry 1). To our delight, substitution of cinchona-derivated thiourea alkaloid **57** for catalyst **56** dramatically improves this asymmetric F−C reaction, and the desired sulfonamide **54** was obtained in 80% yield and in 95% ee (entry 2). We were also pleased to find that F−C reaction of **50** with indole catalyzed by alkaloid **57** at 50 °C delivered the desired sulfonamide **55** in 48% yield and in 92% ee (entry 3). Although the yield was slightly decreased, the enantioselectivity could be further improved to 95% ee when reaction was performed at room temperature for 4 days (entry 4). The same enantioselectivities were observed when the concentration of indole was reduced, although the yields of **55** were significantly decreased (entries 4−6). By prolonging the reaction time from 4 days to 7 days, the asymmetric reaction also proceeded well even at 0 °C, and under those conditions **55** was produced in 40% yield and in 96% ee (entry 4 vs entry 7). After further optimization, we established that, at 0 °C for 12 days in EtOAc with thiourea alkaloid **57** as catalyst, the F−C reaction of **50** with indole gave the amide **55** in 55% yield and in 99% ee (entry 8). Utilizing the quinine-derived thiourea alkaloid **58** as catalyst, the F−C reaction progressed very well and the *S* configuration product **55** was afforded in 42% yield and 98% ee when the reaction was performed at room temperature for 7 days (entry 9).

With these procedures providing ample quantities of enantioenriched chiral precursors, we proceeded to test the proposed RCM. Thus, protection of the chiral amide (*R*)-**55** with Boc_2O gave compound **59** in 96% yield, which was further subjected to allylation to afford the diene **60** in almost quantitative yield (Scheme 5). RCM of compound **60** catalyzed by Grubbs first generation catalyst smoothly provided the cyclic precursor **61** in good yield.[29] Finally, removal of the Boc group with Verkade's base delivered the desired IBR2 analogue **15** in 65% yield.[30] The absolute configuration of compound **15** was confirmed by X-ray diffraction. Using similar reaction conditions, the corresponding *S*-enantiomer, **16**, was also conveniently prepared starting from the optically pure (*S*)-**55** (Scheme 6).

In summary, we have developed two routes to synthesize enantiomerically pure IBR2 analogues **1**−**16**. One route features the addition of *N*-Boc-3-bromoindole **26** to the sulfinamide **25**, providing good yield of the readily separable diasteroisomers **27** and **28** in a 1:1 ratio, and allowing for the preparation of useful amounts of either enantiomer in this series of analogues. The other route highlights the highly enantioselective addition of unprotected indole to the sulfonyl amide **50**, mediated by bifunctional amino-thioureas **57** and **58** as catalysts. Screening the biological activity of the IBR2 analogues **1**−**16**, and others prepared by this methodology, in a series of cancer cell lines is in progress and will be reported elsewhere.

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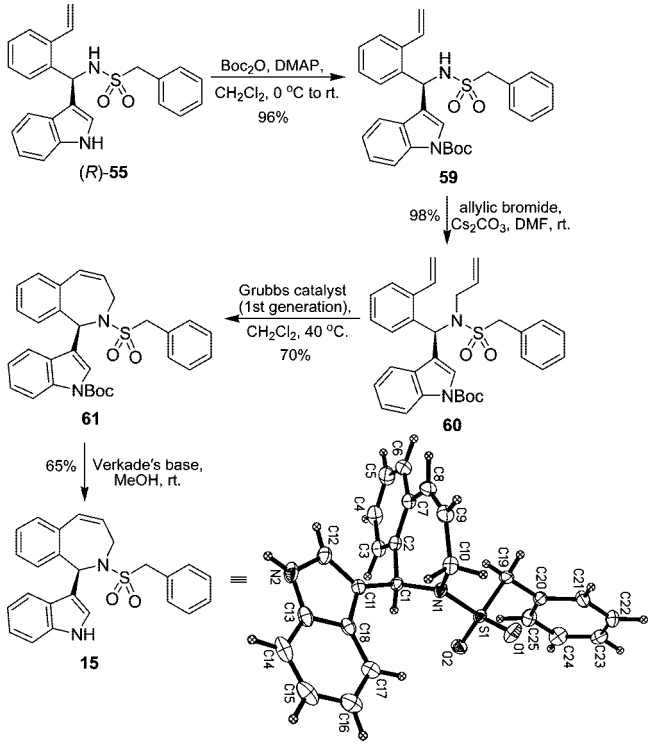
SCHEME 5



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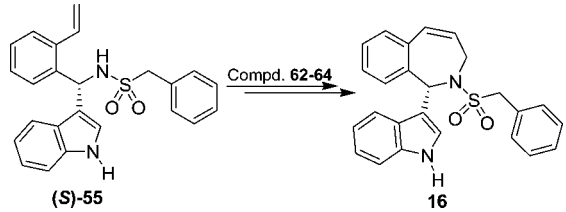

Experiment Section

2-(2-Benzyloxyethyl)benzaldehyde (24). A mixture of TBAI (30 mg, 0.08 mmol) and NaH (255 mg, 60% in oil, 6.37 mmol) in THF (15 mL) was cooled to 0 °C. Then, compound **23** (1.07 g, 5.33 mmol) in THF (15 mL) was added dropwise. The resulting mixture was heated to 45 °C for 20 min. After that, the mixture was cooled to 0 °C again and BnBr (1.37 g, 7.99 mmol) was added dropwise. The mixture was stirred overnight at room temperature. H_2O (50 mL) was added to quench the reaction and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over anhydrous Na_2SO_4. After removal of all the solvent, the residue was purified by silica gel chromatography (hexane/EtOAc = 100:1) to afford an oil (1.54 g). This oil (1.54 g) was dissolved in THF (20 mL) and the resulting solution was cooled to −78 °C. *n*-BuLi (3.20 mL, 2.46 M in hexane, 7.94 mmol) was added dropwise. After the mixture was stirred at −78 °C for 30 min, anhydrous DMF (1.36 mL, 17.56 mmol) was added dropwise. The mixture was stirred for another 30 min before H_2O (5 mL) was added to quench the reaction. After the mixture was warmed to room temperature, H_2O (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After removal of all the solvent, the residue was purified by silica gel chromatography (hexane/EtOAc = 100:1 to 15:1) to afford **24** as an oil (1.09 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.76 (dd, J = 7.6, 1.2 Hz, 1H), 7.43 (td, J = 7.5, 1.2 Hz, 1H), 7.31 (td, J = 7.4, 0.8 Hz, 1H), 7.28−7.20 (m, 6H), 4.44 (s, 2H), 3.66 (t, J = 6.4 Hz, 2H), 3.30 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 192.4, 141.5, 138.3, 134.2, 133.5, 131.9, 131.7, 128.3, 127.4, 127.4, 126.8, 72.8, 70.6, 32.9; MS (ESI) m/z 241 (M + H^+), 263 (M + Na^+); ESI-HRMS calcd for $C_{16}H_{17}O_2$ (M + H^+) 241.1228, found 241.1231.

(*R*)-2-Methylpropane-2-sulfinic Acid 1-[2-(2-Benzyloxyethyl)-phenyl]meth-(*E*)-ylideneamide (25). To a solution of aldehyde **24** (490 mg, 2.04 mmol) and (*R*)-*tert*-butanesulfinamide **22** (280 mg, 2.31 mmol) in THF (20 mL) was added $Ti(OEt)_4$ (20% in EtOH, 2.3 mL). The resulting mixture was stirred at room temperature overnight. Then, H_2O (30 mL) was added to quench the reaction and CH_2Cl_2 (20 mL) was added. After filtration, the filtrate was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by silica gel chromatography (hexane/EtOAc = 10:1) to give compound **25** (556 mg, 79%) as a light yellow oil. $[\alpha]^{20}_D$ −95.7 (*c* 0.93 CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.86 (s, 1H), 7.95 (dd, J = 8.3, 1.3 Hz, 1H), 7.45 (ddd, J = 7.8, 7.3, 1.3 Hz, 1H), 7.37−7.24 (m, 7H), 4.50−4.45 (m, 2H), 3.73−3.65 (m, 2H), 3.28 (t, J = 6.8 Hz, 2H), 1.23 (s, 9H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 162.2, 141.2, 139.1, 133.0, 132.4, 131.9, 130.2, 128.8, 128.0, 127.9, 127.4, 73.4, 71.4, 57.9, 33.9, 22.8; MS (ESI) m/z 344 (M + H^+), 366 (M + Na^+); ESI-HRMS calcd for $C_{20}H_{25}NO_2SNa$ (M + Na^+), 366.1504, found 366.1497.

3-[(*R*)-[2-(2-Benzyloxyethyl)phenyl]-((*R*)-2-methylpropane-2-sulfinylamino)methyl]indole-1 Carboxylic Acid *tert*-Butyl Ester (27) and 3-[(*S*)-[2-(2-Benzyloxyethylphenyl]-((*R*)-2-methylpropane-2-sulfinylamino)methyl]indole-1-carboxylic Acid *tert*-Butyl Ester (28). Under the protection of N_2, a solution of 3-bormo-1-*N*-*tert*-butyloxycarbonylindole **26** (600 mg, 2.00 mmol) in THF (10 mL) was cooled to −78 °C. *n*-BuLi (0.7 mL, 2.86 M in hexane, 2.00 mmol) was added dropwise. The resulting mixture was stirred at −78 °C for 30 min. Then, a solution of compound **25** (535 mg, 1.56 mmol) in THF (6 mL) was added dropwise. After the mixture was stirred at −78 °C for 20 min, H_2O (3 mL) was dropwise added to quench the reaction. The mixture was warmed to room temperature and H_2O (50 mL) was added. The resulting aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, and then dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1 to 4:1) to afford **27** (less polar, 415 mg, 47.5%) as a white foam and **28** (more polar, 430 mg, 49%) as a white foam. **27**: $[\alpha]^{20}_D$ −25.9 (*c* 0.75 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 7.0 Hz, 1H), 7.35−7.15 (m, 11H), 6.21 (d, J = 2.5 Hz, 1H), 4.46−4.40 (m, 2H), 3.79 (s, 1H), 3.70−3.65 (m, 1H), 3.62−3.57 (m, 1H), 3.03−2.93 (m, 2H), 1.62 (s, 9H), 1.21 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 138.7, 138.5, 137.1, 135.9, 130.5, 128.7, 128.5, 128.3, 128.0, 127.8, 127.7, 126.8, 125.7, 125.1, 123.4, 122.4, 119.8, 115.6, 84.3, 73.1, 70.8, 56.1, 50.6, 33.1, 28.4, 22.9; MS (ESI) m/z 561 (M + H^+); ESI-HRMS calcd for $C_{33}H_{40}N_2O_4SNa$ (M + Na^+) 583.2606, found 583.2628. **28**: $[\alpha]^{20}_D$ +2.6 (*c* 1.15 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.60 (s, 1H), 7.36 (d, J = 7.5 Hz, 2H), 7.28−7.06 (m, 10H), 6.18 (d, J = 3.0 Hz, 1H), 4.52−4.46 (m, 2H), 3.90 (d, J = 3.0 Hz, 1H), 3.77−3.72 (m, 2H), 3.24−3.14 (m, 2H), 1.66 (s, 9H), 1.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 139.0, 138.3, 137.4, 135.9, 130.5, 129.1, 128.4, 128.3, 128.2, 127.6, 127.5, 126.8, 125.4, 124.6, 122.6, 121.6, 120.4, 115.3, 83.4, 73.0, 70.8, 56.0, 51.8, 32.2, 28.3, 22.9; MS (ESI) m/z 583 (M + Na^+); ESI-HRMS calcd for $C_{33}H_{40}N_2O_4SNa$ (M + Na^+) 583.2606, found 583.2597.

3-{(*R*)-Amino[2-(2-benzyloxyethyl)phenyl]methyl}indole-1-carboxylic Acid *tert*-Butyl Ester (29). To a solution of **27** (376 mg, 0.67 mmol) in MeOH (7 mL) was added 4 M HCl solution (in dioxane, 7 mL). After the mixture was stirred at room temperature for 30 min, the mixture was carefully poured into an aqueous $NaHCO_3$ solution (3.00 g of $NaHCO_3$ in H_2O (50 mL)). Then, the resulting aqueous solution was extracted with CH_2Cl_2 (3 × 60 mL).

The combined organic layers were washed with brine and then dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 30:1) to afford **29** (290 mg, 95%) as a clear oil. $[\alpha]^{20}_D$ −66.4 (*c* 1.10 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (br, 1H), 7.52 (d, *J* = 1.0 Hz, 1H), 7.32−7.13 (m, 11H), 7.08−7.05 (m, 1H), 5.65 (s, 1H), 4.48 (s, 2H), 3.77−3.68 (m, 2H), 3.22−3.16 (m, 1H), 3.09−3.03 (m, 1H), 1.86 (br, 2H), 1.66 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0, 142.9, 138.3, 136.6, 136.1, 130.2, 129.4, 128.5, 127.8, 127.8, 127.4, 127.2, 127.1, 125.5, 124.5, 123.4, 122.6, 120.0, 115.4, 83.7, 73.2, 71.4, 48.9, 33.0, 28.4; MS (ESI) *m*/*z* 457 (M + H^+), 913 (2 M + Na^+); ESI-HRMS calcd for $C_{29}H_{33}N_2O_3$ (M + H^+) 457.2491, found 457.2482.

3-{(*R*)-Amino[2-(2-hydroxyethyl)phenyl]methyl}indole-1-carboxylic Acid *tert*-Butyl Ester (30). To a stirred solution of **29** (290 mg, 0.64 mmol) in MeOH (10 mL) was added 1 M HCl in dioxane (1 mL), followed by Pd/C (200 mg, 10% Pd). The mixture was hydrogenated at room temperature under 1 atm for 1 h. Then, the mixture was filtrated and the filtrate was neutralized with a $NaHCO_3$ aqueous solution (500 mg $NaHCO_3$ in 100 mL of H_2O). The resulting mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with brine, and then dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 30:1) to deliver compound **30** as a white foam (220 mg, 95%). $[\alpha]^{20}_D$ −59.9 (*c* 1.10 $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.12 (d, *J* = 8.4 Hz, 1H), 7.67 (s, 1H), 7.32−7.22 (m, 3H), 7.10−7.03 (m, 4H), 5.61 (s, 1H), 4.02−3.97 (m, 1H), 3.76 (ddd, *J* = 10.0, 9.8, 3.6 Hz, 1H), 3.25 (ddd, *J* = 14.4, 9.6, 4.4 Hz, 1H), 3.06−2.98 (m, 4H), 1.70 (s, 9H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 150.2, 141.8, 139.8, 136.6, 131.0, 129.4, 128.5, 127.6, 127.1, 125.7, 125.0, 123.6, 122.9, 120.3, 115.8, 84.4, 64.3, 49.4, 36.3, 28.5; MS (ESI) *m*/*z* 733 (2 M + H^+); ESI-HRMS calcd for $C_{22}H_{26}N_2O_3Na$ (M + Na^+) 389.1841, found 389.1851.

3-((*R*)-Amino{2-[2-(*tert*-butyldimethylsilanyloxy)ethyl]phenyl}-methyl)indole-1-carboxylic Acid *tert*-Butyl Ester (31). The white foam **30** (220 mg, 0.81 mmol) was dissolved in CH_2Cl_2 (15 mL). After the solution was cooled to 0 °C, imidazole (78 mg, 1.15 mmol) and DMAP (5 mg, 0.04 mmol) were added. Five minutes later, a solution of TBDMSCl (150 mg, 1.00 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 1.5 h. After that, all the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 40:1) to afford **31** (271 mg, 70%) as a light yellow oil. $[\alpha]^{20}_D$ −60.8 (*c* 1.00 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (br, 1H), 7.56 (d, *J* = 1.0 Hz, 1H), 7.40 (d, *J* = 7.0 Hz, 1H), 7.35−7.26 (m, 4H), 7.24−7.16 (m, 2H), 5.72 (s, 1H), 3.97−3.89 (m, 2H), 3.17−3.12 (m, 1H), 3.07−3.02 (m, 1H), 2.02 (br, 2H), 1.73 (s, 9H), 0.91 (s, 9H), 0.05, 0.04 (2s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8, 142.4, 136.3, 130.4, 129.1, 127.2, 126.8, 126.8, 125.2, 124.3, 123.3, 122.4, 119.8, 115.2, 83.6, 64.6, 48.6, 35.7, 28.2, 25.9, 18.4, −5.4; MS (ESI) *m*/*z* 503 (M + Na^+), 961 (2 M + H^+); ESI-HRMS calcd for $C_{28}H_{40}N_2O_3SiNa$ (M + Na^+) 503.2706, found 503.2704.

3-((*R*)-Benzyloxycarbonylamino{2-[2-(*tert*-butyldimethylsilanyloxy)ethyl]phenyl}methyl)indole-1-carboxylic Acid *tert*-Butyl Ester (32). To a 0 °C solution of **31** (271 mg, 0.56 mmol) in CH_2Cl_2 (15 mL) was added DMAP (5 mg, 0.04 mmol) and DIPEA (150 μL, 0.84 mmol). After the mixture was stirred at 0 °C for 10 min, CbzCl (115 μL, 0.82 mmol) was added dropwise. The mixture was stirred at room temperature for 20 min. Then, all the solvent was removed in vacuo and the residue was purified by silica gel column chromatography (hexane/EtOAc = 12:1) to afford **32** (331 mg, 96%) as a white foam. $[\alpha]^{20}_D$ +7.6 (*c* 0.98 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 6.5 Hz, 1H), 7.43−7.22 (m, 13H), 6.48 (d, *J* = 8.5 Hz, 1H), 5.65 (d, *J* = 10.0 Hz, 1H), 5.22 (dd, *J* = 12.5, 12.5 Hz, 2H), 3.99−3.95 (m, 1H), 3.88−3.84 (m, 1H), 3.09−3.04 (m, 1H), 2.98−2.93 (m, 1H), 1.72 (s, 9H), 0.88 (s, 9H), 0.01, −0.01 (2s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 149.9, 138.6, 137.2, 136.6, 136.0, 131.2, 129.0, 128.7, 128.3, 127.9, 127.1, 126.9, 124.9, 124.6, 122.9, 122.3, 120.0, 115.5, 84.1, 67.1, 64.1, 49.2, 36.1, 28.3, 26.1, 18.5, −5.3; MS (ESI) *m*/*z* 632 (M + NH_4^+), 1246 (2 M + NH_4^+), 1251 (2 M + Na^+); ESI-HRMS calcd for $C_{36}H_{46}N_2O_5SiNa$ (M + Na^+) 637.3074, found 637.3060.

3-{(*R*)-Benzyloxycarbonylamino[2-(2-hydroxyethyl)phenyl]methyl}indole-1-carboxylic Acid *tert*-Butyl Ester (33). To a solution of compound **32** (331 mg, 0.53 mmol) in THF (20 mL) was added TBAF (1 M in THF, 0.59 mL) dropwise at 0 °C. Then, the mixture was stirred at room temperature for 30 min. After that, all the solvent was removed and the residue was purified by silica gel chromatography (hexane/EtOAc = 2:1) to give compound **33** (249 mg, 92%) as a white foam. $[\alpha]^{20}_D$ +18.9 (*c* 1.10 CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.09 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.37−7.24 (m, 10H), 7.20−7.14 (m, 2H), 6.47 (d, *J* = 7.0 Hz, 1H), 5.70 (d, *J* = 7.5 Hz, 1H), 5.16−5.08 (m, 2H), 3.88−3.84 (m, 2H), 2.98−2.87 (m, 2H), 2.21 (br, 1H), 1.62 (s, 9H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 156.2, 150.1, 139.8, 137.8, 137.2, 136.5, 131.1, 129.2, 129.0, 128.6, 128.5, 128.4, 127.4, 127.3, 125.3, 125.2, 123.2, 121.9, 120.1, 115.9, 84.6, 67.4, 64.2, 49.4, 36.3, 28.4; MS (ESI) *m*/*z* 523 (M + Na^+), 1023 (2 M + Na^+); ESI-HRMS calcd for $C_{30}H_{32}N_2O_5Na$ (M + Na^+) 523.2209, found 523.2206.

3-{(*R*)-Benzyloxycarbonylamino[2-(2-benzyloxycarbonyloxyethyl)phenyl]methyl}indole-1-carboxylic Acid *tert*-Butyl Ester (34). To a 0 °C solution of **30** (206 mg, 0.56 mmol) in CH_2Cl_2 (12 mL) was added DIPEA (111 μL, 0.62 mmol) followed by CbzCl (84 μL, 0.56 mmol) dropwise. The mixture was stirred at room temperature for 10 min. Then, all the solvent was removed in vacuo and the residue was purified by silica gel chromatography (hexane/EtOAc = 2:1) to give the compound **33** (165 mg, 52%) as an oil and **34** (80 mg, 20%) as an oil. Compound **34**: $[\alpha]^{20}_D$ +5.8 (*c* 1.10 CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.12 (d, *J* = 8.0 Hz, 1H), 7.44−7.26 (m, 16H), 7.20−7.15 (m, 2H), 6.45 (d, *J* = 7.6 Hz, 1H), 5.62 (d, *J* = 7.8 Hz, 1H), 5.19−5.10 (m, 4H), 4.50−4.44 (m, 1H), 4.36−4.30 (m, 1H), 3.16−3.05 (m, 2H), 1.64 (s, 9H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 155.9, 155.5, 150.1, 139.7, 137.3, 136.5, 136.1, 135.7, 131.1, 129.3, 129.0, 129.0, 128.9, 128.8, 128.6, 128.5, 128.4, 127.8, 127.6, 125.2, 123.2, 121.9, 120.2, 115.8, 84.5, 70.0, 68.4, 67.4, 49.2, 32.2, 28.4; MS (ESI) *m*/*z* 635 (M + H^+), 652 (M + NH_4^+), 657 (M + Na^+); ESI-HRMS calcd for $C_{38}H_{38}N_2O_7Na$ (M + Na^+) 657.2577, found 657.2578.

3-{(*R*)-Benzyloxycarbonylamino[2-(2-methanesulfonyloxyethyl)-phenyl]methyl}indole-1-carboxylic Acid *tert*-Butyl Ester (35). Compound **34** (249 mg, 0.5 mmol) was dissolved in CH_2Cl_2 (20 mL) and the resulting solution was cooled to 0 °C. After DMAP (5 mg, 0.04 mmol) and DIPEA (104 μL, 0.58 mmol) were added sequentially, MsCl (60 μL, 0.77 mmol) was added dropwise. The mixture was stirred at room temperature for 30 min. After that, the solvent was removed in vacuo and the residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1 to 3:1) to afford **35** (255 mg, 88%) as a white foam. $[\alpha]^{20}_D$ +28.4 (*c* 1.05 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.47−7.21 (m, 12H), 7.12 (s, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 5.52 (d, *J* = 8.0 Hz, 1H), 5.15 (dd, *J* = 12.4, 12.4 Hz, 2H), 4.54−4.49 (m, 1H), 4.45−4.39 (m, 1H), 3.21−3.11 (m, 2H), 2.80 (s, 3H), 1.65 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 149.8, 139.2, 136.5, 136.0, 134.0, 131.1, 128.7, 128.4, 128.3, 128.2, 128.0, 127.0, 125.2, 123.2, 121.4, 119.8, 115.6, 84.5, 69.9, 67.3, 48.6, 37.1, 32.4, 28.3; MS (ESI) *m*/*z* 601 (M + Na^+), 1179 (2 M + Na^+); ESI-HRMS calcd for $C_{31}H_{34}N_2O_7SNa$ (M + Na^+) 601.1984, found 601.1981.

(*R*)-3-(1,2,3,4-Tetrahydroisoquinolin-1-yl)indole-1-carboxylic Acid *tert*-Butyl Ester (36). To a solution of **35** (255 mg, 0.44 mmol) in EtOH (15 mL) was added Pd/C (120 mg, 10% Pd). The mixture was hydrogenated at room temperature under 1 atm for 1.5 h. Then, the solvent was removed in vacuo and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 40:1 to 10:1) to afford **36** (149 mg, 97%) as a white foam. $[\alpha]^{20}_D$ +17.0 (*c* 0.40 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 6.5 Hz,

1H), 7.55 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.26−7.21 (m, 3H), 7.14−7.11 (m, 1H), 7.03 (d, J = 8.0 Hz, 1H), 5.57 (s, 1H), 4.63 (br, 1H), 3.39 (dt, J = 12.5, 6.0 Hz, 1H), 3.25−3.13 (m, 2H), 3.00 (dt, J = 15.5, 5.5 Hz, 1H), 1.73 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 136.0, 135.9, 134.6, 129.3, 129.2, 127.8, 127.0, 126.2, 126.0, 124.7, 122.8, 122.2, 120.3, 115.5, 84.1, 53.5, 41.8, 28.9, 28.4; MS (ESI) m/z 349 (M + H^+), 697 (2 M + H^+); ESI-HRMS calcd for $C_{22}H_{25}N_2O_2$ (M + H^+) 349.1916, found 349.1912.

3-((*R*)-2-Phenylmethanesulfonyl-1,2,3,4-tetrahydroisoquinolin-1-yl)indole-1-carboxylic Acid *tert*-Butyl Ester (37). To a 0 °C solution of compound **36** (8 mg, 0.023 mmol) in CH_2Cl_2 (2 mL) was added $BnSO_2Cl$ (21 mg, 0.11 mmol). Then, DMAP (5 mg, 0.04 mmol) was added and the resulting mixture was stirred at room temperature for 30 min. After that, all the solvent was removed and the residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1 to 5:1) to afford **37** (9 mg, 78%) as a white foam. $[\alpha]^{20}_D$ +56.0 (c 1.06 $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 7.5 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.41 (ddd, J = 9.3, 1.5, 1.0 Hz, 1H), 7.35−7.28 (m, 3H), 7.23−7.18 (m, 5H), 7.06 (d, J = 7.5 Hz, 1H), 7.02 (d, J = 7.5 Hz, 2H), 6.41 (s, 1H), 4.04 (dd, J = 13.5, 13.5 Hz, 2H), 3.67 (dd, J = 6.5, 6.5 Hz, 1H), 3.30 (ddd, J = 16.5, 4.5, 2.0 Hz, 1H), 3.05 (ddd, J = 17.5, 7.0, 4.5 Hz, 1H), 2.81 (dd, J = 3.5, 4.4 Hz, 1H), 1.72 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7, 135.3, 134.4, 133.4, 130.6, 129.2, 129.1, 128.6, 128.4, 128.3, 128.0, 127.3, 126.5, 126.4, 124.9, 123.1, 121.7, 120.5, 115.2, 84.3, 77.4, 59.3, 51.9, 39.5, 28.2; MS (ESI) m/z 520 (M + NH_4^+), 525 (M + Na^+); ESI-HRMS calcd for $C_{29}H_{34}N_3O_4S$ (M + NH_4^+) 520.2270, found 520.2278.

1-(1*H*-Indol-3-yl)-2-phenylmethanesulfonyl-1,2,3,4-tetrahydroisoquinoline (38). To a 0 °C solution of **37** (148 mg, 0.295 mmol) in CH_2Cl_2 (8 mL) was added a solution of TFA (1 mL) in CH_2Cl_2 (2 mL) dropwise. Then, the resulting mixture was stirred at room temperature for 3 h. A solution of $NaHCO_3$ (1.3 g, 15.47 mmol) in H_2O (50 mL) was carefully added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine, and then dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1 to 3:1) to deliver the racemic compound **38** (66 mg, 56%) as a white foam.

(*R*)-1-(1*H*-Indol-3-yl)-1,2,3,4-tetrahydroisoquinoline (39). To a 0 °C solution of **36** (139 mg, 0.40 mmol) in THF (9 mL) was added a solution of NaOMe (108 mg, 1.997 mmol) in MeOH (9 mL) in one portion. The resulting mixture was stirred at room temperature for 2 days. Then, all the solvent was removed in vacuuo and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH = 15:1 to 5:1) to afford **39** (85 mg, 86%) as a white foam. $[\alpha]^{20}_D$ +7.6 (c 1.00 CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.63 (s, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.19−7.12 (m, 3H), 7.03−6.98 (m, 2H), 6.94−6.92 (m, 2H), 5.45 (s, 1H), 3.29−3.23 (m, 1H), 3.12−3.00 (m, 2H), 2.92−2.84 (m, 1H), 2.70 (br, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 139.2, 137.2, 135.9, 129.5, 128.1, 126.9, 126.6, 126.0, 124.6, 122.4, 120.2, 119.9, 119.8, 111.8, 54.7, 42.6, 30.3; MS (ESI) m/z 249 (M + H^+); ESI-HRMS calcd for $C_{17}H_{17}N_2$ (M + H^+) 249.1392, found 249.1391.

(*R*)-1-(1*H*-Indol-3-yl)-2-phenylmethanesulfonyl-1,2,3,4-tetrahydroisoquinoline (1). To a 0 °C solution of **39** (66 mg, 0.27 mmol) in CH_2Cl_2 (6 mL) was added DMAP (3 mg, 0.025 mmol) and DIPEA (57 μL, 0.32 mmol). Then, a solution of $BnSO_2Cl$ (61 mg, 0.32 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The resulting mixture was stirred at room temperature for 15 min. After that, all the solvent was removed in vacuo and the residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1 to 3:1) to afford **1** (94 mg, 88%) as a white foam. $[\alpha]^{20}_D$ +90.4 (c 1.04 CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.36 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.27−7.11 (m, 8H), 7.03 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 7.2 Hz, 2H), 6.85 (d, J = 2.4 Hz, 1H), 6.42 (s, 1H), 3.95−3.86 (m, 2H), 3.56 (dd, J = 6.4, 6.4 Hz, 1H), 3.24 (ddd, J = 13.6, 4.4, 4.4 Hz, 1H), 3.01 (ddd, J = 17.2, 6.0, 4.4 Hz, 1H), 2.77 (dd, J = 4.0, 2.8 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 136.9, 136.3, 134.1, 131.2, 129.6, 129.6, 128.8, 128.8, 128.7, 127.4, 126.9, 126.6, 125.9, 123.1, 120.8, 120.4, 117.7, 111.9, 59.3, 53.1, 40.0, 29.1; MS (ESI) m/z 403 (M + H^+), 420 (M + NH_4^+), 425 (M + Na^+); ESI-HRMS calcd for $C_{24}H_{23}N_2O_2S$ (M + H^+) 403.1480, found 403.1476.

(*R*)-2-(2-Fluorophenylmethanesulfonyl)-1-(1*H*-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline (3). Compound **3** (45 mg, 75%) was prepared as a white foam with the same conditions as described for compound **1**. $[\alpha]^{20}_D$ +110.0 (c 0.60 CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.31 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.39 (dt, J = 8.0, 0.8 Hz, 1H), 7.29−7.23 (m, 3H), 7.19 (ddd, J = 8.2, 0.8, 1.2 Hz, 1H), 7.15−7.07 (m, 3H), 7.05−7.01 (m, 2H), 6.95 (ddd, J = 9.6, 1.2, 1.2 Hz, 1H), 6.82 (d, J = 2.4 Hz, 1H), 6.41 (s, 1H), 3.98 (s, 2H), 3.77 (ddt, J = 6.4, 6.8, 1.6 Hz, 1H), 3.44 (ddd, J = 16.6, 4.8, 2.0 Hz, 1H), 3.14 (ddd, J = 18.0, 6.8, 5.6 Hz, 1H), 2.86 (ddd, J = 16.8, 1.2, 0.8 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 162.7, 160.7, 136.9, 136.2, 134.0, 133.0, 133.0, 131.0, 130.9, 129.7, 128.6, 127.5, 126.8, 126.7, 126.1, 124.6, 124.6, 123.0, 120.7, 120.4, 117.5, 117.3, 117.2, 116.0, 115.8, 111.8, 53.3, 52.0 (d, J = 2.1 Hz), 39.9, 28.8; ^{19}F NMR (376 MHz, CD_2Cl_2) δ −117.5 (s, 1F); MS (ESI) m/z 421 (M + H^+), 438 (M + NH_4^+), 443 (M + Na^+); ESI-HRMS calcd for $C_{24}H_{22}FN_2O_2S$ (M + H^+) 421.1386, found 421.1371.

(*R*)-2-(3-Fluorophenylmethanesulfonyl)-1-(1*H*-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline (4). Compound **4** (35 mg, 73%) was prepared as a white foam with the same conditions as described for the compound **1**. $[\alpha]^{20}_D$ +72.7 (c 0.60 CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.36 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.25−7.19 (m, 3H), 7.16−7.10 (m, 3H), 7.02 (d, J = 7.6 Hz, 1H), 6.95 (td, J = 8.4, 2.0 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.70 (d, J = 7.6 Hz, 1H), 6.60 (d, J = 9.6 Hz, 1H), 6.42 (s, 1H), 3.92 (d, J = 13.6 Hz, 1H), 3.86 (d, J = 13.6 Hz, 1H), 3.58 (dd, J = 6.4, 6.4 Hz, 1H), 3.24 (ddd, J = 13.6, 4.4, 4.4 Hz, 1H), 3.02 (ddd, J = 17.6, 6.8, 4.8 Hz, 1H), 2.79 (dd, J = 16.8, 3.2 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 163.9, 161.9, 136.8, 136.2, 134.0, 132.0, 131.9, 130.4, 130.3, 129.6, 128.6, 127.5, 127.0, 127.0, 126.9, 126.7, 125.9, 123.2, 120.8, 120.3, 118.1, 117.9, 117.7, 115.8, 115.6, 111.9, 58.8, 53.1, 40.1, 29.2; ^{19}F NMR (376 MHz, CD_2Cl_2) δ −113.8 (s, 1F); MS (ESI) m/z 421 (M + H^+), 438 (M + NH_4^+), 443 (M + Na^+); ESI-HRMS calcd for $C_{24}H_{22}FN_2O_2S$ (M + H^+) 421.1386, found 421.1385.

(*R*)-2-(4-Fluorophenylmethanesulfonyl)-1-(1*H*-indol-3-yl)-1,2,3,4-tetrahydroisoquinoline (5). Compound **5** (50 mg, 83%) was prepared as a white foam with the same conditions as described for the compound **1**. $[\alpha]^{20}_D$ +80.6 (c 0.42 CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.33 (s, 1H), 7.73 (d, J = 6.0 Hz, 1H), 7.42 (d, J = 6.4 Hz, 1H), 7.24−7.19 (m, 3H), 7.14−7.10 (m, 2H), 7.09 (d, J = 6.0 Hz, 1H), 6.88−6.82 (m, 5H), 6.39 (s, 1H), 3.93 (d, J = 10.8 Hz, 1H), 3.85 (d, J = 11.2 Hz, 1H), 3.55 (ddt, J = 10.8, 5.2, 5.2 Hz, 1H), 3.23 (ddd, J = 13.2, 3.2, 1.2 Hz, 1H), 3.01 (ddd, J = 14.2, 5.6, 4.0 Hz, 1H), 2.78 (ddd, J = 13.4, 1.2, 0.8 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 136.9, 136.3, 134.1, 133.0, 132.9, 129.7, 128.7, 127.5, 126.9, 126.7, 125.9, 125.6, 125.6, 123.2, 120.8, 120.4, 115.8, 111.9, 58.5, 53.1, 40.1, 29.2; ^{19}F NMR (376 MHz, CD_2Cl_2) δ −114.6 (s, 1F); MS (ESI) m/z 443 (M + Na^+); ESI-HRMS calcd for $C_{24}H_{21}FN_2O_2SNa$ (M + Na^+) 443.1205, found 443.1197.

(*R*)-1-(1*H*-Indol-3-yl)-2-(2-trifluoromethylphenylmethanesulfonyl)-1,2,3,4-tetrahydroisoquinoline (9). Compound **9** (30 mg, 85%) was prepared as a white foam with the same conditions as described for compound **1**. $[\alpha]^{20}_D$ +115.8 (c 0.43 CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.30 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.56−7.48 (m, 2H), 7.43 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.27−7.24 (m, 2H), 7.21−7.15 (m, 2H), 7.12−7.08 (m, 2H), 6.80 (d, J = 2.0 Hz, 1H), 6.48 (s, 1H), 4.10 (d, J = 14.0 Hz, 1H), 4.03 (d, J = 14.4 Hz, 1H), 3.87 (ddd, J = 13.8, 7.0, 1.2 Hz, 1H), 3.51 (ddd, J = 13.4, 4.4, 4.8 Hz, 1H), 3.20

(ddd, J = 18.4, 7.2, 5.6 Hz, 1H), 2.92 (dd, J = 4.0, 4.8 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 137.0. 136.0, 133.9, 133.6, 132.4, 129.8, 129.8, 129.0, 128.8, 128.2 (q, J = 1.9 Hz), 127.7, 127.0 (q, J = 4.7 Hz), 126.8, 126.7, 126.0, 126.0, 123.5, 123.0, 120.7, 120.6, 120.4, 120.4, 117.4, 111.8, 55.0, 53.5, 39.7, 28.4; ^{19}F NMR (376 MHz, CD_2Cl_2) δ −58.7 (s, 3F); MS (ESI) m/z 471 (M + H$^+$), 488 (M + NH$_4^+$), 493 (M + Na$^+$); ESI-HRMS calcd for $C_{25}H_{25}F_3N_3O_2S$ (M + NH$_4^+$) 488.1620, found 488.1633.

(*R*)-1-(1*H*-Indol-3-yl)-2-(3-trifluoromethylphenylmethanesulfonyl)-1,2,3,4-tetrahydroisoquinoline (10). Compound **10** (41 mg, 88%) was prepared as a white foam with the same conditions as described for compound **1**. $[\alpha]^{20}_D$ +63.2 (*c* 0.89 CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.38 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 7.5 Hz, 1H), 7.44 (dt, J = 8.0, 1.0 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.26−7.15 (m, 5H), 7.12 (td, J = 8.0, 1.5 Hz, 1H), 7.03 (s, 1H), 7.02 (d, J = 8.5 Hz, 1H), 6.83 (d, J = 2.5 Hz, 1H), 6.47 (s, 1H), 3.98 (d, J = 13.5 Hz, 1H), 3.93 (d, J = 13.5 Hz, 1H), 3.50 (ddt, J = 14.5, 6.0, 1.3 Hz, 1H), 3.20 (ddd, J = 13.3, 4.0, 4.5 Hz, 1H), 3.02 (ddd, J = 17.5, 6.0, 5.0 Hz, 1H), 2.78 (dd, J = 3.0, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 136.8, 136.2, 134.7, 133.9, 131.1, 130.9, 130.8, 130.6, 130.1, 129.6, 129.5, 128.7, 127.8 (q, J = 3.1 Hz), 127.5, 126.9, 126.8, 125.9, 125.6 (q, J = 3.8 Hz), 123.4, 123.3, 121.0, 120.0, 117.7, 112.0, 58.8, 53.0, 40.2, 29.3; ^{19}F NMR (376 MHz, CD_2Cl_2) δ −63.2 (s, 3F); MS (ESI) m/z 471 (M + H$^+$), 488 (M + NH$_4^+$), 493 (M + Na$^+$); ESI-HRMS calcd for $C_{25}H_{25}F_3N_3O_2S$ (M + NH$_4^+$) 488.1620, found 488.1621.

(*R*)-1-(1*H*-Indol-3-yl)-2-(4-trifluoromethylphenylmethanesulfonyl)-1,2,3,4-tetrahydroisoquinoline (11). Compound **11** (36 mg, 85%) was prepared as a white foam with the same conditions as described for compound **1**. $[\alpha]^{20}_D$ +71.7 (*c* 0.48 CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.34 (s, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.44−7.40 (m, 3H), 7.25−7.19 (m, 3H), 7.15−7.09 (m, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.0 Hz, 1H), 6.83 (d, J = 2.8 Hz, 1H), 6.38 (s, 1H), 4.01 (d, J = 13.6 Hz, 1H), 3.93 (d, J = 13.6 Hz, 1H), 3.60 (ddt, J = 13.8, 6.4, 1.4 Hz, 1H), 3.26 (ddd, J = 13.6, 4.0, 4.4 Hz, 1H), 3.03 (ddd, J = 17.4, 6.0, 4.4 Hz, 1H), 2.81 (dd, J = 2.8, 3.6 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 136.9, 136.2, 133.9, 133.8, 131.6, 130.5, 129.6, 128.6, 127.5, 126.8, 126.8, 126.0, 125.7 (q, J = 3.8 Hz), 123.5, 123.2, 120.8, 120.4, 117.6, 112.0, 58.9, 53.2, 40.1, 29.1; ^{19}F NMR (376 MHz, CD_2Cl_2) δ −63.3 (s, 3F); MS (ESI) m/z 471 (M + H$^+$), 488 (M + NH$_4^+$), 493 (M + Na$^+$); ESI-HRMS calcd for $C_{25}H_{22}F_3N_2O_2S$ (M + H$^+$) 471.1354, found 471.1351.

2-Vinylbenzaldehyde (52). To a solution of compound **51** (5.00 g, 25.91 mmol) in THF (80 mL) was added *n*-BuLi (1.6 M in hexane, 20 mL, 32.00 mmol) at − 78 °C dropwise. After the mixture was stirred at −78 °C for 30 min, anhydrous DMF (4.0 mL, 51.66 mmol) was added dropwise. Then, the mixture was stirred at −78 °C for another 30 min. H_2O (5 mL) was added to quench the reaction. The mixture was warmed to room temperature. H_2O (100 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic phases were dried with anhydrous Na_2SO_4. After removal of all the solvent, the residue was purified by silica gel chromatography (hexane/EtOAc = 40:1) to give compound **52** (2.50 g, 73%) as an oil. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 10.28 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.61−7.54 (m, 3H), 7.46−7.43 (m, 1H), 5.73 (dd, J = 17.3, 1.3 Hz, 1H), 5.51 (dd, J = 11.3, 1.3 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 192.7, 140.8, 134.2, 133.9, 133.4, 131.7, 128.5, 127.8, 119.5; MS (ESI) m/z 133 (M + H$^+$), 155 (M + Na$^+$); ESI-HRMS calcd for C_9H_8ONa (M + Na$^+$) 155.0473, found 155.0470.

4-Methyl-*N*-[1-(2-vinylphenyl)meth-(*E*)-ylidene]benzenesulfonamide (53). To a solution of compound **52** (556 mg, 4.21 mmol) in THF (15 mL) was added toluenesulfonyl amide (936 mg, 5.48 mmol). Then, Ti(OEt)$_4$ (20% in EtOH, 5 mL) was added dropwise. After that, the resulting mixture was stirred overnight at room temperature. H_2O (30 mL) was added to quench the reaction and the mixture was filtered. The filtrate was extracted with CH_2Cl_2 (3 × 30 mL). The organic phases were dried over anhydrous Na_2SO_4. After removal of all the solvent, the residue was recrystallized from hexane/EtOAc (2:1) to afford compound **53** (518 mg, 43%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.63−7.57 (m, 2H), 7.40 (d, J = 8.0 Hz, 3H), 7.34−7.29 (m, 1H), 5.65 (dd, J = 34.3, 14.3 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 144.8, 142.5, 135.4, 134.7, 132.9, 130.0, 129.9, 129.3, 128.2, 128.2, 127.8, 121.1, 21.8; MS (ESI) m/z 286 (M + H$^+$), 437 (M + Na$^+$), 593 (2 M + Na$^+$); ESI-HRMS calcd for $C_{16}H_{16}NO_2S$ (M + H$^+$) 286.0896, found 286.0901.

Preparation of Amide (*R*)-54 with Bisoxazoline Cu(II) Complex As Catalyst. $Cu(OTf)_2$ (98%, 15.0 mg, 0.04 mmol), and (*S*)-Bn-bisoxazoline (22 mg, 0.06 mmol) were dissolved in CH_2Cl_2 (5 mL) under N_2 atmosphere. The solution was stirred at room temperature for 2 h, then 4 Å molecular sieves (100 mg) was added and the mixture was stirred for another 10 min. Subsequently, compound **53** (114 mg, 0.4 mmol) and indole (234 mg, 2.0 mmol) were added, and the reaction mixture was stirred at room temperature. The mixture was stirred for 3 days. After that, the solvent was removed under vacuum and the residue was purified by flash column chromatography on silica gel eluted with hexane/EtOAc (3:1) to afford compound (*R*)-**54** (36 mg, 22%, 90% ee) as a white foam.

Preparation of Amide (*R*)-54 with Cinchona-Derivated Thiourea Alkaloid 57 As Catalyst. To a mixture of compound **53** (85 mg, 0.3 mmol) and catalyst **57** (18 mg, 0.03 mmol) in EtOAc (150 μL) was added indole (70 mg, 0.6 mmol) in one portion. Then, the mixture was heated to 50 °C and reaction was stirred at 50 °C for 48 h. After that, all the solvent was removed and the residue was purified by silica gel chromatography (hexane/EtOAc = 3:1) to give (*R*)-**54** (96 mg, 80%, 95% ee) as a white foam.

***N*-[(*R*)-(1*H*-Indol-3-yl)(2-vinylphenyl)methyl]-4-methylbenzenesulfonamide, (*R*)-54.** $[\alpha]^{20}_D$ +54.0 (*c* 1.0 CH_2Cl_2, 95% ee); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.16 (s, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.40−7.32 (m, 3H), 7.24−7.15 (m, 6H), 7.00 (t, J = 8.0 Hz, 1H), 6.83 (dd, J = 17.2, 10.8 HZ, 1H), 6.58 (d, J = 2.4 Hz, 1H), 6.09 (d, J = 6.8 Hz, 1H), 5.52 (dd, J = 17.6, 0.8 Hz, 1H), 5.20 (d, J = 10.8, 1.0 Hz, 1H), 5.13 (d, J = 6.4 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 144.0, 137.8, 137.8, 137.1, 136.7, 134.4, 129.9, 128.2, 128.0, 127.7, 127.6, 126.9, 126.0, 124.9, 123.1, 120.4, 119.4, 117.4, 116.3, 111.8, 52.2, 21.7; MS (ESI) m/z 420 (M + NH$_4^+$), 425 (M + Na$^+$), 822 (2 M + Na$^+$); ESI-HRMS calcd for $C_{24}H_{22}N_2O_2SNa$ (M + Na$^+$) 425.1300, found 425.1293.

***N*-[(*R*)-(1*H*-Indol-3-yl)(2-vinylphenyl)methyl]-*C*-phenylmethanesulfonamide, (*R*)-55.** Compound (*R*)-**55** was prepared, under different temperature and substrate concentration, using a similar reaction condition as described for (*R*)-**54** with thiourea alkaloid **57** as catalyst. $[\alpha]^{20}_D$ +80.2 (*c* 0.51 CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.23 (s, 1H), 7.64 (dd, J = 7.6, 1.2 Hz, 1H), 7.59−7.53 (m, 1H), 7.52−7.49 (m, 1H), 7.42−7.37 (n, 3H), 7.32−7.18 (m, 4H), 7.12−7.06 (m, 3H), 7.03 (d, J = 10.8 Hz, 1H), 6.80 (dd, J = 2.6, 1.2 Hz, 1H), 6.34 (d, J = 7.6 Hz, 1H), 5.63 (dd, J = 17.0, 1.4 Hz, 1H), 5.32 (dd, J = 15.6, 1.6 Hz, 1H), 4.96 (d, J = 7.6 Hz, 1H), 4.05 (d, J = 14.0 Hz, 1H), 4.00 (d, J = 13.6 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 138.6, 137.2, 136.9, 134.4, 131.2, 129.5, 128.9, 128.7, 128.7, 127.9, 127.4, 126.0, 124.5, 123.1, 120.6, 120.0, 118.0, 116.7, 111.9, 60.6, 52.6; MS (ESI) m/z 420 (M + NH$_4^+$), 425 (M + Na$^+$), 822 (2 M + NH$_4^+$); ESI-HRMS calcd for $C_{24}H_{26}N_3O_2S$ (M + NH$_4^+$) 420.1746, found 420.1746.

***N*-[(*S*)-(1*H*-Indol-3-yl)(2-vinylphenyl)methyl]-*C*-phenylmethanesulfonamide (*S*)-55.** Compound (*S*)-**55** was prepared at room temperature with a similar reaction condition as described for (*R*)-**54** with thiourea alkaloid **58** as catalyst. $[\alpha]^{20}_D$ −63.0 (*c* 0.75 CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.22 (s, 1H), 7.62 (d, J = 6.8 Hz, 1H), 7.56−7.54 (m, 1H), 7.49−7.47 (m, 1H), 7.39−7.35 (n, 3H), 7.29−7.17 (m, 4H), 7.09−7.01 (m, 4H), 6.76 (d, J = 1.6 Hz, 1H), 6.33 (d, J = 6.4 Hz, 1H), 5.62 (dd, J = 13.8, 1.0 Hz, 1H), 5.32 (dd, J = 10.4, 1.2 Hz, 1H), 5.04 (d, J = 6.0 Hz, 1H), 4.01 (d, J = 10.4 Hz, 1H), 3.97 (d, J = 11.2 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 138.7, 137.4, 137.1, 134.6, 131.3, 129.7,

129.1, 129.0, 128.8, 128.8, 128.1, 127.4, 126.1, 124.6, 123.2, 120.7, 120.0, 118.1, 116.9, 112.0, 60.8, 52.6; MS (ESI) *m*/*z* 425 (M + Na^+), 827 (2 M + Na^+); ESI-HRMS calcd for $C_{24}H_{22}N_2O_2SNa$ (M + Na^+) 425.1300, found 425.1295.

3-[(*R*)-Phenylmethanesulfonylamino(2-vinylphenyl)methyl]indole-1-carboxylic Acid *tert*-Butyl Ester (59). To a 0 °C solution of (*R*)-**55** (77 mg, 0.19 mmol) and DMAP (3 mg, 0.02 mmol) in THF (2 mL) was added a solution of Boc_2O (42 mg, 0.19 mmol) in THF (2 mL) dropwise. Then, the resulting mixture was stirred at room temperature for 1 h. After that, all the solvent was removed in vacuo and the residue was purified by silica gel column (hexane/EtOAC = 7:1) to give compound **59** (93 mg, 96%) as a white foam. $[\alpha]^{20}_D$ +12.2 (*c* 1.03 CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.0 Hz, 1H), 7.59−7.55 (m, 2H), 7.42−7.36 (m, 3H), 7.34−7.32 (m, 1H), 7.31−7.30 (m, 1H), 7.29−7.26 (m, 1H), 7.24−7.18 (m, 3H), 7.12 (dd, *J* = 10.8, 11.2 Hz, 1H), 7.02−7.00 (m, 2H), 6.31 (dd, *J* = 1.2, 1.2 Hz, 1H), 5.66 (dd, *J* = 1.2, 1.2 Hz, 1H), 5.39 (dd, *J* = 1.6, 1.6 Hz, 1H), 4.99 (d, *J* = 8.0 Hz, 1H), 4.07 (d, *J* = 14.0 Hz, 1H), 3.95 (d, *J* = 14.0 Hz, 1H), 1.65 (s, 9H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 149.7, 137.1, 136.7, 133.8, 130.7, 128.7, 128.6, 128.6, 128.5, 128.4, 127.8, 127.3, 124.9, 124.9, 123.0, 121.0, 120.1, 118.5, 115.3, 84.2, 60.3, 51.8, 28.2; MS (ESI) *m*/*z* 520 (M + NH_4^+), 525 (M + Na^+), 1022 (2 M + NH_4^+); ESI-HRMS calcd for $C_{29}H_{30}N_2O_4SNa$ (M + Na^+) 525.1824, found 525.1827.

3-[(*R*)-(Allylphenylmethanesulfonylamino)(2-vinylphenyl)methyl]indole-1-carboxylic Acid *tert*-Butyl Ester (60). To a mixture of **59** (92.7 mg, 0.18 mmol) and Cs_2CO_3 (72 mg, 0.22 mmol) in DMF (1 mL) was added allylic bromide (0.05 mL, 0.57 mmol) dropwise. Then, the mixture was stirred at room temperature until all the starting material was consumed. The mixture was directly subjected to purification by silica gel chromatography (hexane/EtOAc = 10:1 to 7:1) to afford compound **60** (98 mg, 98%) as a white foam. $[\alpha]^{20}_D$ −7.2 (*c* 1.36 CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 1.2 Hz, 1H), 7.38−7.25 (m, 11H), 7.20−7.11 (m, 2H), 6.83 (s, 1H), 5.68 (dd, *J* = 17.4, 1.4 Hz, 1H), 5.40−5.31 (m, 2H), 4.88 (ddd, *J* = 22.0, 17.2, 1.2 Hz, 1H), 4.11−3.94 (m, 4H), 1.68 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 137.8, 135.6, 134.9, 134.3, 131.1, 129.3, 129.0, 128.8, 128.8, 128.7, 128.1, 127.2, 126.4, 125.1, 123.2, 120.3, 119.8, 118.0, 115.4, 84.4, 60.7, 55.4, 49.2, 28.4; MS (ESI) *m*/*z* 560 (M + NH_4^+), 565 (M + Na^+); ESI-HRMS calcd for $C_{32}H_{34}N_2O_4SNa$ (M + Na^+) 565.2137, found 565.2119.

3-((*R*)-2-Phenylmethanesulfonyl-2,3-dihydro-1*H*-benzo[*c*]azepin-1-yl)indole-1-carboxylic Acid *tert*-Butyl Ester (61). To a solution of **60** (98 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) was added Grubbs' first catalyst (7.5 mg, 0.009 mmol). Then, the mixture was heated to reflux for 4 h. After the mixture was cooled to room temperature and all the solvent was removed in vacuo, the residue was purified by silica gel chromatography (hexane/EtOAc = 15:1) to provide compound **61** (65 mg, 70%) as a white foam. In addition, starting material (14 mg) was recovered. $[\alpha]^{20}_D$ +36.2 (*c* 0.8 CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.5 Hz, 1H), 7.94 (d, *J* = 7.0 Hz, 1H), 7.42−7.23 (m, 9H), 7.15−7.13 (m, 2H), 6.90 (s, 1H), 6.57 (s, 1H), 6.46 (d, *J* = 12.5 Hz, 1H), 5.57 (ddd, *J* = 12.3, 4.5, 2.0 Hz, 1H), 4.37 (dd, *J* = 20.5, 5.0 Hz, 1H), 3.92 (d, *J* = 13.5 Hz, 1H), 3.68 (d, *J* = 13.5 Hz, 1H), 3.62 (dt, *J* = 20.5, 2.5 Hz, 1H), 1.63 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 138.4, 135.6, 134.9, 133.1, 130.9, 130.3, 130.1, 129.6, 128.8, 128.7, 128.6, 128.6, 128.5, 128.2, 127.0, 125.2, 123.6, 120.0, 116.7, 115.4, 84.4, 59.5, 59.1, 46.6, 28.3; MS (ESI) *m*/*z* 532 (M + NH_4^+), 537 (M + Na^+); ESI-HRMS calcd for $C_{30}H_{30}N_2O_4SNa$ (M + Na^+) 537.1824, found 537.1813.

(*R*)-1-(1*H*-Indol-3-yl)-2-phenylmethanesulfonyl-2,3-dihydro-1*H*-benzo[*c*]azepine (15). To a stirred solution of **61** (40 mg, 0.077 mmol) in MeOH was added a solution of Verkade's base (8 mg) in MeOH (20 μL). Then, the resulting solution was stirred at room temperature for 2 days. After that, the solvent was removed in vacuo and the residue was purified by silica gel chromatography (hexane/EtOAc = 3:1) to furnish compound **15** (21 mg, 65%) as a white foam. In addition, starting material (5 mg) was recovered. $[\alpha]^{20}_D$ +90.3 (*c* 0.4 CH_2Cl_2); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.19 (s, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.40−7.36 (m, 4H), 7.32−7.22 (m, 5H), 7.19−7.14 (m, 3H), 6.62 (s, 1H), 6.50 (s, 1H), 6.48 (d, *J* = 15.0 Hz, 1H), 5.58 (ddd, *J* = 10.0, 4.8, 2.0 Hz, 1H), 4.31 (dd, *J* = 21.0, 5.0 Hz, 1H), 3.95 (d, *J* = 13.5 Hz, 1H), 3.65 (d, *J* = 13.5 Hz, 1H), 3.54 (dt, *J* = 20.5, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 140.0, 137.1, 135.3, 133.4, 131.2, 130.8, 130.5, 129.9, 129.7, 129.3, 128.9, 128.7, 128.7, 128.3, 126.1, 123.2, 120.9, 119.6, 112.5, 111.8, 59.9, 59.6, 46.5; MS (ESI) *m*/*z* 437 (M + Na^+); ESI-HRMS calcd for $C_{25}H_{22}N_2O_2SNa$ (M + Na^+) 437.1300, found 437.1297.

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Supporting Information Available: Copies of ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra of compounds **1**−**16**, **24**, **25**, **27**−**37**, **39**−**47**, **52**, **53**−**55**, and **59**−**64**, experimental procedures for compounds **2**, **6**−**8**, **12**−**14**, **16**, **57**, **58**, and **62**−**64**, chiral HPLC analysis of compounds **1**−**16** and **54**−**55**, crystallographic data (CIF) and ORTEP drawing for compounds **1** and **15**, and a mechanism explanation about poor diastereoselectivity. This material is available free of charge via the Internet at http://pubs.acs.org.

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