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Note

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Chiral Phosphoric Acid-Catalyzed Synthesis of Fluorinated 5,6-Dihydroindolo[1,2-c]quinazolines with Quaternary Stereocenters

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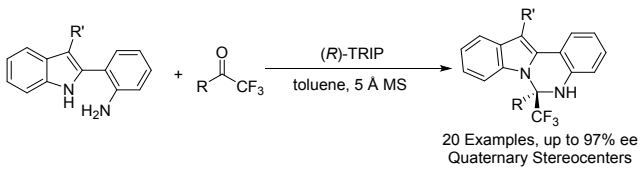
ABSTRACT



A chiral phosphoric acid-catalyzed enantioselective synthesis of fluorinated 5,6-dihydroindolo[1,2-c]quinazolines has been developed by condensation/amine addition cascade from 2-(1*H*-indolyl)anilines and fluorinated ketones, giving the fluorinated aminals with quaternary stereogenic centers with excellent yields and up to 97% ee. A series of the fluorinated aromatic, aliphatic ketones and ethyl trifluoropyruvate are suitable.

Chiral aminal moieties are common structural unit in myriad natural products, synthetic pharmaceutical molecules and chiral catalysts.[1] Among them, the optically active 5,6-dihydroindolo[1,2-c]quinazolines could be also found in natural products and pharmaceutical molecules.[2] For instance, (-)-goniomitine is a natural occurring alkaloid,[2a] and compound **A** is an original semi-synthetic cytotoxic bisindole alkaloid[2b] (Figure 1).

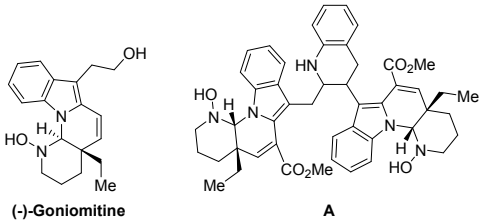


Figure 1. The selected bioactive 5,6-dihydroindolo[1,2-c]quinazolines .

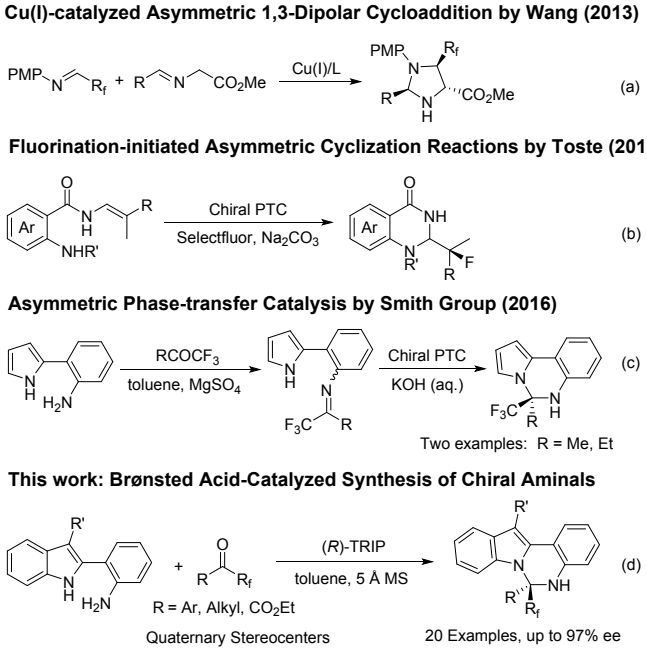
Owing to the importance of chiral aminals, continuous efforts have been devoted to synthesize these compounds. In 2003, Ramsden's group reported the first enantioselective synthesis of the chiral aminal by asymmetric hydrogenation of dihydropyrrolobenzothiadiazine dioxide using a diphosphine ruthenium diamine catalyst with 87% ee.[3] Since then, some efficient methods have been successfully developed for synthesis of chiral aminals. Enantioselective amidations of imines catalyzed by VAPOL-derived phosphoric acid were developed by Antilla's group.[4] Asymmetric cyclization of aldehydes or aldimines with 2-aminobenzamides, 2-amino-benzenesulfona-mides, *N*-(2,6-diisopropylbenzyl)ethane-1,2-diamine and 2-(1*H*-pyrrol-2-yl)aniline could be catalyzed by Brønsted acids,[5] Lewis acids[6] and organocatalysts,[7] respectively. Diastereo- and enantioselective [3+2],[8] [3+3],[9] and [4+2][10] cycloadditions were also established. Antilla's, You's and Ma's groups demonstrated asymmetric cascade dearomatization procedures for formation of pyrroloindolines.[11] Chiral phosphoric acid catalyzed asymmetric tandem 1,5-hydride transfer/ring closing to give cyclic aminals was disclosed by Gong's group.[12] Li and co-workers described a novel approach to aminals *via* palladium-catalyzed C−N coupling with chiral bisphosphine monooxides.[13] Enantioselective *N*–H functionalizations of indoles catalyzed by chiral phosphoric acids or dinuclear zinc-ProPhenol were realized.[14]

Compared to chiral aminals containing tertiary stereocenters, asymmetric synthesis of chiral aminals bearing quaternary stereocenters have been relatively less studied owing to low activity of ketones and ketimines. Consequently, the reactions of highly reactive cyclic isatins were investigated by List,[5a] Shi[9,15] and Wang[16] to give spirocyclic aminals using chiral phosphoric acids as catalysts. Another approach to chiral aminals containing quaternary stereocenters is enantioselective hydrazination of α-aminocarbonyl compounds by organocatalysis.[17] Recently, Zhong and co-workers demonstrated a chiral SPINOL-derived phosphoric acid-catalyzed asymmetric *N*-alkylation reaction of indoles and 3-aryl 3-hydroxyisoin-dolinones with excellent enantioselectivities.[14d]

The chemistry of organofluorine compounds has been of great importance, since the incorporation of fluorine into organic molecules can modify their physical, chemical, and biological properties.[18] However,

asymmetric synthesis of fluorinated aminals has been rarely explored. Wang group developed Cu(I)-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with fluorinated imines for synthesis of fluorinated imidazolidines (Scheme 1a).[8b] Toste and co-workers demonstrated enantioselective synthesis of fluoro−dihydroquinazolones by fluorination-initiated asymmetric cyclization (Scheme 1b).[19] Cation-directed highly enantioselective *N*-functionalization of pyrroles was developed by Smith group, which was the only enantioselective synthesis of chiral aminals with quaternary stereogenic centers from linear aliphatic ketones (Scheme 1c).[7a] The method acquired pre-preparation of ketimines by condensation of 2-(1*H*-pyrrol-2-yl)aniline and excess trifluoromethyl ketones with moderate yields. Due to relatively lower reactivity of linear aromatic ketones, to the best of our knowledge, the use of linear aromatic ketones for enantioselective synthesis of aminals has not been documented. Herein, we reported a chiral phosphoric acid-catalyzed direct enantioselective synthesis of fluorinated 5,6-dihydroindolo[1,2-c]quinazolines with quaternary stereocenters from linear fluorinated ketones and 2-(1*H*-indolyl)anilines with excellent yields and up to 97% ee (Scheme 1d).

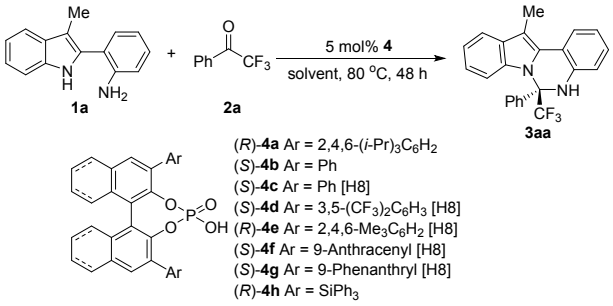
Scheme 1. Synthesis of chiral fluorinated aminals



Initially, we chose 5 mol% of chiral phosphoric acid (*R*)-**4a** as catalyst to test the reaction of 2-(1*H*-indolyl)aniline **1a** and simple trifluoromethyl phenyl ketone **2a** in toluene at room temperature, but no reaction was observed. To our delight, the desired product **3aa** could be obtained in 61% yield and 92% ee when the reaction was performed at 80 °C for 48 h (Table 1, entry 1). Subsequently, different solvents including 1,2-dichloroethane, acetonitrile and 1,4-dioxane were examined (Table 1, entries 2-4). The results revealed that solvents effect played a crucial role; toluene is the best in term of yield and enantioselectivity.

Further screening of aromatic solvents, toluene was more suitable than the others (Table 1, entries 5-7). Subsequently, some commercially available chiral phosphoric acids were evaluated using toluene as solvent (Table 1, entries 8-14). It should be noteworthy that steric hindrance of the substituted groups at the 3,3′-positions of chiral phosphoric acids displayed a profound influence on enantioselectivity and reactivity. The sterically congested catalysts furnished the reaction in higher yields (Table 1, entries 10-13 vs 8-9). However, catalyst (*R*)-**4h** bearing a triphenylsilyl group at 3,3'-positions of the binaphthyl unit was not effective (Table 1, entry 14). In the presence of 50 mg 5 Å MS as dehydrating agent, the reaction proceeded smoothly, giving **3aa** in 71% yield without influence of enantisoselectivity (Table 1, entry 15). Increasing the ratio of **2a** to 1.5 equiv., the yield can improved to 95% with slightly lower ee (Table 1, entry 16). When reaction temperature was decreased to 70 °C, 94% ee could be obtained (Table 1, entry 17) albeit with low reactivity. Raising the temperature to 90 °C, the ee value dropped to 85% (Table 1, entry 18). Additionally, the reaction concentrations had remarkable influences on reactivity (Table 1, entries 19 and 20). Prolong reaction time to 72 h using 1.0 mL toluene, 94% yield and 92% ee could be gained (Table 1, entry 21). Finally, the optimized reaction condition was established: 5 mol% (*R*)-**4a** as catalyst, 1.5 equiv. of **2a** to **1a** in the presence of 50 mg 5 Å MS in toluene (0.1 M) for 72 h.

Table 1. Optimization of the reaction conditions [a]



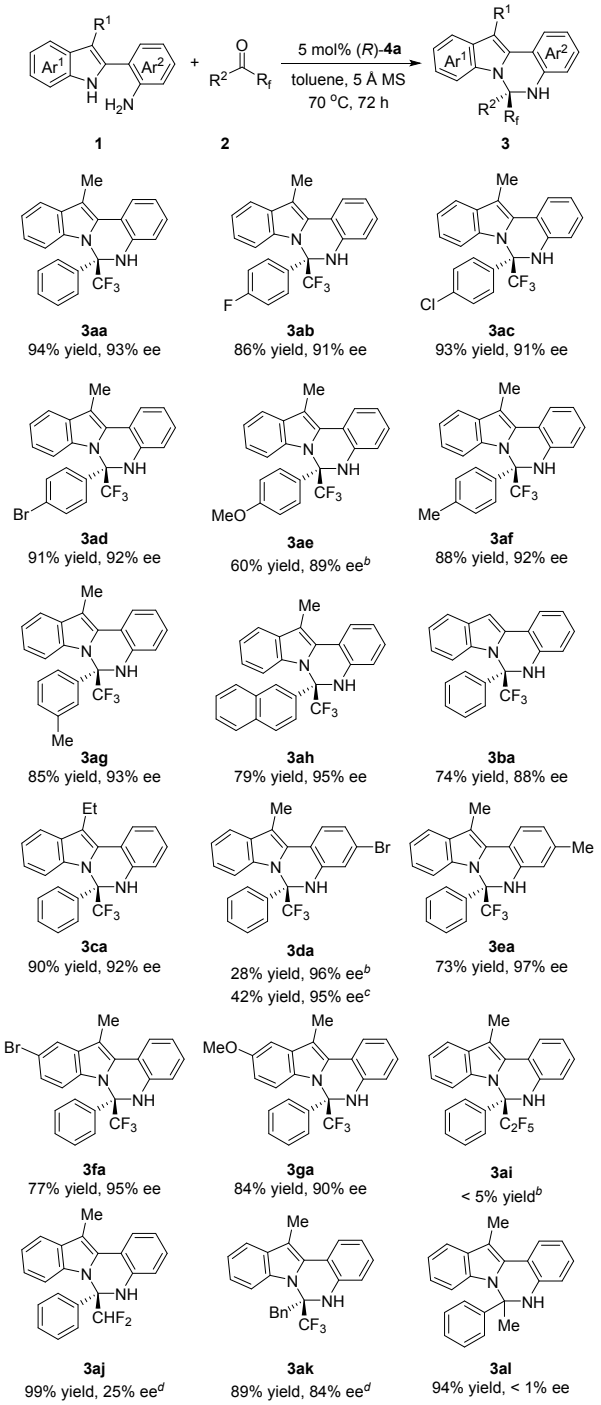
Entry	CPA	Solvent	*T* (°C)	Yield (%)[b]	ee (%)[c]
1	(*R*)-**4a**	toluene	80	61	92 (*R*)
2	(*R*)-**4a**	DCE	80	80	87 (*R*)
3	(*R*)-**4a**	MeCN	80	13	89 (*R*)
4	(*R*)-**4a**	1,4-dioxane	80	< 5	-
5	(*R*)-**4a**	benzene	80	35	93 (*R*)
6	(*R*)-**4a**	*o*-xylene	80	50	92 (*R*)
7	(*R*)-**4a**	PhCl	80	79	87 (*R*)
8	(*S*)-**4b**	toluene	80	36	15 (*S*)
9	(*S*)-**4c**	toluene	80	31	10 (*S*)
10	(*S*)-**4d**	toluene	80	70	50 (*S*)
11	(*R*)-**4e**	toluene	80	59	40 (*R*)
12	(*S*)-**4f**	toluene	80	92	75 (*S*)
13	(*S*)-**4g**	toluene	80	91	73 (*S*)
14	(*R*)-**4h**	toluene	80	< 5	-
15[d]	(*R*)-**4a**	toluene	80	71	92 (*R*)
16[e]	(*R*)-**4a**	toluene	80	95	90 (*R*)

17[e]	(*R*)-**4a**	toluene	70	81	94 (*R*)
18[e]	(*R*)-**4a**	toluene	90	97	85 (*R*)
19[e,f]	(*R*)-**4a**	toluene	70	97	90 (*R*)
20[e,g]	(*R*)-**4a**	toluene	70	45	94 (*R*)
21[e,j]	(*R*)-**4a**	toluene	70	94	92 (*R*)

[a] Conditions: **1a** (0.10 mmol) and **2a** (0.10 mmol) in toluene (1.0 mL) using 5 mol% **4** as catalyst at 80 °C for 48 h. [b] Determined by ^{1}H NMR. [c] Determined by HPLC. [d] 50 mg 5 Å MS was used. [e] 50 mg 5 Å MS and **2a** (0.15 mmol) were used. [f] 0.5 mL toluene was used. [g] 2.0 mL toluene was used. [j] 72 h.

Under the optimal condition, a series of substrates were explored to determine the generality of this method, and the results are summarized in Scheme **2**. Most of substrates performed well under the standard reaction conditions. Aromatic trifluoromethyl ketones bearing electron-withdrawing groups and weak electron-donating groups delivered the corresponding products in high yields with excellent enantioselectivities (Scheme 2, **3aa-3ad**, **3af-3ag**). The 4-methoxyl substituted ketone **2e** afforded expected **3ae** with moderate 60% yield and 89% ee after prolonged time. In addition, 2-naphthyl trifluoromethyl ketone **2h** gave 95% ee. Next, the reaction of various 2-(1*H*-indolyl)anilines and ketone **2a** were investigated (Scheme 2, **3ba-3ga**). No substituent at 3-position of indole, the *N*-functionalization of **1b** was predominant in 74% yield with 88% ee and C3-alkylation side-product was isolated (see Experimental Section). 3-Ethylindole **1c** underwent smoothly and gave **3ca** in 90% yield and 92% ee (Scheme 2, **3ca**). The substituted groups at *meta*-position of aniline moiety increased enantioselectivities (Scheme 2, **3da** and **3ea**). With an electron-withdrawing group, aniline **1d** gave product **3da** with 28% yield and 96% ee (Scheme 2, **3da**). When reaction temperature was raised to 90 °C for 120 h, a limited influence of yield and stereoselectivity was observed. The best enantioselectivity was given with *m*-methyl substituted anline **1e** (Scheme 2, **3ea**). The 5-bromo substituted indole **1f** gave product with relatively higher ee than 5-methoxyl substituted indole **1g** (Scheme 2, **3fa** vs **3ga**). The pentafluoroethyl ketone **2i** gave poor reactivity (Scheme 2, **3ai**), the reason is not clear. The difluoromethyl ketone **2j** afforded **3aj** in quantitative yield but poor 25% ee. Furthermore, alphatic trifluoromethyl ketone **2k** furnished the reaction with good yield and enantioselectivity (Scheme 2, **3ak**). The absolute configuration of product **3aa** was assigned as *R* based on the X-ray diffraction analysis after recrystallization from mixed solvents methanol/ethyl acetate/hexanes to upgrade ee to > 99%.

Scheme 2. Substrate scope [a]



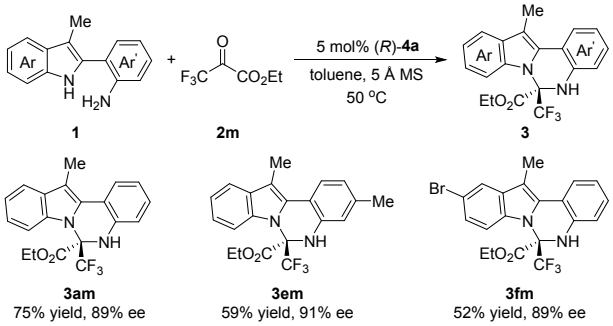
[a] Conditions: **1** (0.20 mmol) and **2** (0.3 mmol) in toluene (2.0 mL) using 5 mol% (*R*)-**4a** as catalyst in the presence of 100 mg 5 Å MS at 70 °C for 72 h. [b] 70 °C for 120 h. [c] 90 °C for 120 h. [d] 70 °C for 12 h.

Acetophenone was also tested under the above standard condition. To our surprise, the corresponding aminal could be isolated with 94% yield but poor enantioselectivity (Scheme 2, **3al**). Changing reaction conditions could not obviously improve the enantioselectivity. The above experimental results show the trifluoromethyl group plays a vital role in enantiocontrol. The experimental results show the trifluoromethyl group plays a vital role in enantiocontrol. In recent years, fluorine effect was observed in asymmetric

organocatalysis by many groups.[20] For example, Lin Group observed a remarkable fluorine effect in chiral phosphoric acid-catalyzed asymmetric synthesis of bihydrobenzoxazinones, mechanistic studies through combination theory calculations with the experimental suggested the CF_3 moiety serving as an attractive hydrogen-bond acceptor.[20c] Based on the previous reports, we speculated the reactivity trends may also owe to fluorine effect or possible H···F hydrogen bond between fluorine and N-H of indole or chiral phosphoric acid.

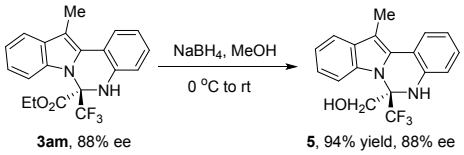
α-Diamino acids and derivatives were valuable and unusual substructures with important biological and pharmacological properties, such as anticonvulsant activity.[21] To the best of our knowledge, catalytic enantioselective synthesis of chiral α-diamino acids have not been reported. Then, we expanded the reaction of ethyl trifluoropyruvate **2m**. 2-(1*H*-indolyl)aniline **1a** reacted with **2m** to afford the desired **3am** with 75% yield and 89% ee after lowering temperature to 50 °C for 42 h (Scheme 3, **3am**). Other two anilines (**1e** & **1f**) were used, moderate yields, 91% and 89% ee were observed (Scheme 3, **3em** and **3fm**).

Scheme 3. Substrate scope: ethyl trifluoropyruvate



The product transformation was conducted (Scheme 4). The α-diamino ester **3am** could be converted to the corresponding α-diaminoalcohol **5** with sodium borohydride in methanol without loss of optical purity.

Scheme 4. Product transformation



In conclusion, we have developed a chiral phosphoric acid-catalyzed condensation/amine addition cascade for synthesis of chiral fluorinated aminals with quaternary stereocenters, giving the chiral dihydroindolo[1,2-c]quinazolines with good yields and up to 97% ee. The substrate scope could be extended to aromatic, aliphatic trifluoromethyl ketones and ethyl trifluoropyruvate. Detailed mechanistic studies and further

expanding the scope of this chemistry are currently ongoing in our laboratory.

EXPERIMENTAL SECTION

Commercially All reactions were carried out under an atmosphere of nitrogen using the standard Schlenk techniques, unless otherwise noted. Commercially available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. ^{1}H NMR, ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz with the Brucker spectrometer. ^{19}F was recorded at 376 MHz with Brucker spectrometer. Chemical shifts are reported in ppm using tetramethylsilane as internal standard when using $CDCl_3$, CD_2Cl_2 and CD_3OD as solvent for ^{1}H NMR spectra. The following abbreviations were used to symbolize the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Flash column chromatography was performed on silica gel (200-300 mesh). All reactions were monitored by TLC analysis. Optical rotations were measured by the polarimeter. Enantiomeric excess was determined by HPLC analysis using chiral column described below in detail. High-resolution mass spectrometry (HRMS) was measured on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry.

Procedures for Synthesis of 2-(1*H*-Indolyl)anilines 1. 2-(1*H*-Indolyl)aniline derivatives **1a** and **1c-1g** could be conveniently synthesized from the indoles and 2-nitrobromobenzenes in two steps according to the known literature procedures with minor modification.[22-23] **1b** was prepared by Fisher indole synthesis according to a reported method.[24] Among them, compound **1b** is the known compound.[24]

General Procedure A for Synthesis of 2-(1*H*-Indolyl)anilines 1a, 1c, 1e and 1g. 2-(2-Nitrophenyl)-1*H*-indoles were prepared from indoles and 1-bromo-2-nitrobenzenes in the presence of cesium carbonate under reflux with acetonitrile as solvent. The corresponding 2-(1*H*-indolyl)anilines could be obtained after reduction of above nitro-compounds using Pd/C as catalyst under hydrogen gas.

In a dried round bottomed flask was added indoles (0.20 mol), 1-bromo-2-nitrobenzenes (0.10 mol), cesium carbonate (0.20 mol, 65.16 g) and anhydrous acetonitrile (500 mL). The resulting suspension was stirred for 24 h under inert atmosphere under reflux. The solvent was evaporated under vacuum and water was added. The mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water and brine, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give the crude product.

The above crude product (28.1 mmol) was dissolved in ethanol (250 mL) and dichloromethane (5 mL), Pd/C (1.200 g, 10 wt. %) was added, and the mixture was stirred under hydrogen gas (balloon pressure) overnight. The mixture was filtered through celite, the solvent was evaporated under the reduced pressure.

The residue was purified by column chromatography on silica gel using hexanes and ethyl acetate as eluent to give the desired compouds **1**.

General Procedure B for Synthesis of 2-(1*H*-Indolyl)anilines 1d and 1f. 2-(2-Nitrophenyl)-1*H*-indoles could be synthesized from indoles and 1-bromo-2-nitrobenzenes. Reduction of them by employing iron powder and concentrated hydrochloric acid gave 2-(1*H*-indolyl)anilines **1d** and **1f**.

In a dried round bottomed flask was added indoles (0.20 mol), 1-bromo-2-nitrobenzenes (0.10 mol), cesium carbonate (0.20 mol, 65.16 g) and anhydrous acetonitrile (500 mL). The resulting suspension was stirred for 24 h under inert atmosphere under reflux. The solvent was evaporated under vacuum and water was added. The mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water and brine, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give the crude product.

To a solution of 2-(2-nitrophenyl)-1*H*-indoles (5.62 mmol) in ethanol (24 mL) was added iron powder (33.72 mmol, 1.888 g) and concentrated hydrogen chloride (6.0 mL) under nitrogen. The mixture was stirred under reflux for 4 h. After cooled to room temperature, excess sodium hydroxide solution was added. The mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate. After concentrated under the reduced pressure, the residue was purified by flash column chromatography to afford the pure products **1**.

2-(3-Methyl-1H-indol-2-yl)aniline (1a). 5.340 g, 24% yield in 2 steps, yellow solid, m.p. = 105-107 °C, new compound, R_f = 0.35 (hexanes/ethyl acetate 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (brs, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.26–7.11 (m, 4H), 6.90–6.70 (m, 2H), 3.82 (brs, 2H), 2.28 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.0, 136.0, 131.8, 131.2, 129.5, 129.4, 122.1, 119.4, 118.8, 118.39, 118.36, 115.7, 110.7, 109.8, 9.4. HRMS (ESI-TOF) *m/z* Calculated for $C_{15}H_{15}N_2$ $[M+H]^+$ 223.1230, found 223.1235.

2-(3-Ethyl-1H-indol-2-yl)aniline (1c). 0.831 g, 18% yield in 2 steps, yellow oil, new compound, R_f = 0.30 (hexanes/ethyl acetate 10:1); ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.22–7.14 (m, 2H), 7.13–7.07 (m, 1H), 7.06–7.00 (m, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 6.81–6.74 (m, 1H), 2.72 (q, *J* = 7.5 Hz, 2H), 1.21 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 145.8, 136.7, 131.7, 130.8, 128.8, 128.1, 120.9, 118.9, 118.19, 118.18 117.3, 115.3, 114.8, 110.6, 17.5, 14.5. HRMS (ESI-TOF) *m/z* Calculated for $C_{16}H_{17}N_2$ $[M+H]^+$ 237.1386, found 237.1390.

5-Bromo-2-(3-methyl-1H-indol-2-yl)aniline (1d). 1.072 g, 18% yield in 2 steps, yellow solid, m.p. = 163-164 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate 10:1); ^{1}H NMR (400 MHz, CD_3OD) δ 7.41 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.04–6.98 (m, 1H), 6.97–6.88 (m, 3H), 6.75 (dd, *J* = 8.1, 2.0 Hz,

1H), 2.12 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD) δ 147.5, 136.6, 132.1, 131.1, 129.1, 122.3, 121.2, 119.5, 118.4, 117.9, 117.3, 110.5, 108.2, 8.1. HRMS (ESI-TOF) *m/z* Calculated for $C_{15}H_{14}BrN_2$ $[M+H]^+$ 301.0335, found 301.0331.

5-Methyl-2-(3-methyl-1H-indol-2-yl)aniline (1e). 1.034 g, 22% yield in 2 steps, yellow oil, new compound, R_f = 0.35 (hexanes/ethyl acetate 10:1); ^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.13–7.06 (m, 2H), 7.06–7.01 (m, 1H), 6.69 (s, 1H), 6.62 (d, *J* = 7.7 Hz, 1H), 2.30 (s, 3H), 2.22 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD) δ 145.3, 138.7, 136.5, 132.4, 130.6, 129.2, 120.9, 118.5, 118.2, 117.8, 116.2, 116.0, 110.4, 107.7, 20.1, 8.1. HRMS (ESI-TOF) *m/z* Calculated for $C_{16}H_{17}N_2$ $[M+H]^+$ 237.1386, found 237.1402.

2-(5-Bromo-3-methyl-1H-indol-2-yl)aniline (1f). 1.059 g, 23% yield in 2 steps, yellow oil, new compound, R_f = 0.20 (hexanes/ethyl acetate 10:1); ^{1}H NMR (400 MHz, CD_3OD) δ 7.54 (d, *J* = 1.6 Hz, 1H), 7.18–7.03 (m, 1H), 7.11–7.04 (m, 3H), 6.79–6.73 (m, 1H), 6.70–6.64 (m, 1H), 2.09 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD) δ 145.7, 135.1, 134.0, 131.0, 130.6, 129.0, 123.5, 120.4, 118.0, 117.3, 115.4, 112.0, 111.4, 107.6, 7.9. HRMS (ESI-TOF) *m/z* Calculated for $C_{15}H_{14}BrN_2$ $[M+H]^+$ 301.0335, found 301.0334.

Procedures for Enantioselective Synthesis of Chiral 5,6-Dihydroindolo[1,2-c]quinazolines. To a 25 ml sealed tube charged with 2-(1*H*-indolyl)anilines **1** (0.20 mmol), chiral phosphoric acid TRIP (*R*)-**4a** (7.5 mg, 0.01 mmol), dry toluene (2.0 mL) and 5 Å MS (100 mg) was added ketones **2** (0.3 mmol) under nitrogen. The mixture was kept stirring at 70 °C for 72 h. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on a silica gel using hexanes/ethyl acetate as the eluent to give the desirable products **3**.

(*R*)-(+)-12-Methyl-6-phenyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline (3aa). 71 mg, 94% yield, white solid, m.p. = 96-97 °C, new compound, R_f = 0.65 (hexanes/ethyl acetate 10:1), 93% ee, $[\alpha]^{20}_D$ = +61.54 (*c* 1.42, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.58–7.43 (m, 3H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.14–7.00 (m, 2H), 6.86 (t, *J* = 7.7 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.25 (d, *J* = 8.4 Hz, 1H), 4.67 (brs, 1H), 2.74 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 138.1, 136.4, 134.7, 130.7, 130.1, 129.6, 128.9, 128.4, 127.8, 125.6 (q, *J* = 296.0 Hz), 125.1, 122.1, 120.3, 120.0, 118.4, 117.1, 113.7, 112.8, 108.5, 75.4 (q, *J* = 30 Hz), 11.1; $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -72.0. Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 98/2, detector: 254 nm, flow rate: 1.0 mL/min, 30 °C), retention time 7.2 min (major) and 9.5 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{23}H_{18}F_3N_2$ $[M+H]^+$ 379.1417, found 379.1421.

(+)-6-(4-Fluorophenyl)-12-methyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline (3ab). 68 mg, 86% yield, colorless oil, new compound, R_f = 0.70 (hexanes/ethyl acetate 10:1), 91% ee, $[\alpha]^{20}_D$ = +48.23

(*c* 1.36, EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (d, *J* = 7.8 Hz, 1H), 7.66–7.52 (m, 2H), 7.42 (d, *J* = 7.9 Hz, 1H), 7.14–6.97 (m, 3H), 6.87 (t, *J* = 7.5 Hz, 1H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.10 (d, *J* = 8.4 Hz, 1H) 2.52 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 163.2 (d, *J* = 247.0 Hz), 139.4, 134.5, 133.0 (d, *J* = 3.0 Hz), 130.7, 130.6 (dq, *J* = 8.0 Hz, *J* = 1.0 Hz), 129.8, 127.6, 125.8 (q, *J* = 296.0 Hz), 124.4, 121.4, 119.6, 118.9, 117.8, 116.2, 115.1 (d, *J* = 22.0 Hz), 113.3, 112.3, 107.2, 75.0 (q, *J* = 30.0 Hz), 9.7; ^{19}F{^{1}H} NMR (376 MHz, CD_3OD) δ -73.3 (s, 3F), -113.3 (s, 1F). Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 95/5, detector: 254 nm, flow rate: 1.0 mL/min, 30 °C), retention time 5.9 min (major) and 6.9 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{23}H_{17}F_4N_2$ $[M+H]^+$ 397.1322, found 397.1350.

(+)-6-(4-Chlorophenyl)-12-methyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline (3ac). 77 mg, 93% yield, colorless oil, new compound, R_f = 0.80 (hexanes/ethyl acetate 10:1), 91% ee, $[\alpha]^{20}_D$ = +64.67 (*c* 1.54, EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.01–6.94 (m, , 1H), 6.87–6.80 (m, 1H), 6.80–6.69 (m, 2H), 6.67–6.59 (m, 1H), 6.09 (d, *J* = 8.4 Hz, 1H), 2.47 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 139.3, 135.6, 135.4, 134.4, 130.7, 129.9, 129.7, 128.4, 127.6, 125.7 (q, *J* = 295.0 Hz), 124.4 121.4, 119.7, 118.9, 117.9, 116.2, 113.3, 112.3, 107.3, 75.0 (q, *J* = 30.0 Hz), 9.7; ^{19}F{^{1}H} NMR (376 MHz, CD_3OD) δ -73.2. Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 95/5, detector: 254 nm, flow rate: 1.0 mL/min, 30 °C), retention time 6.0 min (major) and 7.4 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{23}H_{17}ClF_3N_2$ $[M+H]^+$ 413.1027, found 413.1041.

(+)-6-(4-Bromophenyl)-12-methyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline (3ad). 84 mg, 91% yield, colorless oil, new compound, R_f = 0.70 (hexanes/ethyl acetate 10:1), 92% ee, $[\alpha]^{20}_D$ = +58.26 (*c* 1.67, EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (d, *J* = 7.7 Hz, 1H), 7.55–7.37 (m, 5H), 7.06–6.96 (m, 1H), 6.88 (t, *J* = 7.3 Hz, 1H), 6.80 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 6.71–6.62 (m, 1H), 6.12 (d, *J* = 8.4 Hz, 1H), 2.52 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 139.2, 136.1, 134.4, 131.5, 130.7, 130.1, 129.7, 127.6, 125.7 (q, *J* = 295.0 Hz), 124.4, 123.6, 121.5, 119.7, 119.0, 117.9, 116.2, 113.4, 112.3, 107.4, 75.1 (q, *J* = 30.0 Hz), 9.8; ^{19}F{^{1}H} NMR (376 MHz, CD_3OD) δ -73.3 (s, 3F). Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 95/5, detector: 254 nm, flow rate: 1.0 mL/min, 30 °C), retention time 6.5 min (major) and 7.9 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{23}H_{17}BrF_3N_2$ $[M+H]^+$ 457.0522, found 457.0517.

(+)-6-(4-Methoxyphenyl)-12-methyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline (3ae). 49 mg, 60% yield, colorless oil, new compound, R_f = 0.25 (hexanes/ethyl acetate 20:1), 89% ee, $[\alpha]^{20}_D$ = +45.30 (*c* 0.98, EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H),

7.40 (d, *J* = 8.0 Hz, 1H), 7.00 (t, *J* = 7.7 Hz, 1H), 6.89–6.81 (m, 3H), 6.81–6.75 (m, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.66–6.59 (m, 1H), 6.13 (d, *J* = 8.5 Hz, 1H), 3.68 (s, 3H), 2.51 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD) δ 160.6, 139.6, 134.7, 130.6, 129.8, 129.6, 128.6, 127.5, 126.0 (q, *J* = 295.0 Hz), 124.3, 121.2, 119.4, 118.7, 117.6, 116.3, 113.5, 113.3, 112.6, 107.0, 75.1 (q, *J* = 30.0 Hz), 54.4, 9.7; $^{19}F\{^{1}H\}$ NMR (376 MHz, CD_3OD) δ -73.4. Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 95/5, detector: 254 nm, flow rate: 1.0 mL/min, 30 °C), retention time 8.6 min (major) and 10.7 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{24}H_{20}F_3N_2O$ $[M+H]^+$ 409.1522, found 409.1533.

(+)-12-Methyl-6-(*p*-tolyl)-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline (3af). 69 mg, 88% yield, colorless oil, new compound, R_f = 0.30 (hexanes/ethyl acetate 50:1), 92% ee, $[\alpha]^{20}_D$ = +54.85 (*c* 1.38, EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.72 (d, *J* = 7.8, 1H), 6.47–6.33 (m, 3H), 7.10 (d, *J* = 8.1 Hz, 2H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.57 (t, *J* = 7.6 Hz, 1H) 6.09 (d, *J* = 8.4 Hz, 1H), 2.49 (s, 3H), 2.23 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD) δ 139.7, 139.5, 134.6, 133.9, 130.6, 129.8, 128.8, 128.1, 127.5, 126.0 (q, *J* = 295.0 Hz), 124.3, 121.2, 119.4, 118.7, 117.6, 116.2, 113.3, 112.6, 107.0, 75.2 (q, *J* = 30.0 Hz), 19.8, 9.8; $^{19}F\{^{1}H\}$ NMR (376 MHz, CD_3OD) δ -73.2. Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 98/2, detector: 254 nm, flow rate: 1.0 mL/min, 30 °C), retention time 7.2 min (major) and 11.0 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{24}H_{20}F_3N_2$ $[M+H]^+$ 393.1573, found 393.1608.

(+)-12-Methyl-6-(*m*-tolyl)-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline (3ag). 67 mg, 85% yield, white solid, m.p. = 150-151 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate 50:1), 93% ee, $[\alpha]^{20}_D$ = +60.67 (*c* 1.34, EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (d, *J* = 7.8, 1H), 7.44–7.31 (m, 3H), 7.23–7.11 (m, 2H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.75 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.58 (t, *J* = 7.7 Hz, 1H), 6.09 (d, *J* = 8.4 Hz, 1H), 2.49 (s, 3H), 2.15 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, CH_3OD) δ 139.5, 138.3, 136.8, 134.6, 130.6, 130.1, 129.8, 128.9, 128.0, 127.5, 126.0 (q, *J* = 295.0 Hz), 125.0, 124.4, 121.2, 119.5, 118.7, 117.7, 116.2, 113.3, 112.6, 107.0, 75.3 (q, *J* = 29.0 Hz), 20.2, 9.8; $^{19}F\{^{1}H\}$ NMR (376 MHz, CH_3OD) δ -73.1. Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 95/5, detector: 254 nm, flow rate: 1.0 mL/min, 30 °C), retention time 4.8 min (major) and 6.2 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{24}H_{20}F_3N_2$ $[M+H]^+$ 393.1573, found 393.1608.

(+)-12-Methyl-6-(naphthalen-2-yl)-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline (3ah). 68 mg, 79% yield, white solid, m.p. = 214-215 °C, new compound, R_f = 0.30 (hexanes /ethyl acetate 100:1), 95% ee, $[\alpha]^{20}_D$ = +20.85 (*c* 1.18, EtOAc); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.28 (s, 1H), 7.94–7.85 (m, 2H), 7.84–7.73 (m, 2H), 7.59–7.41 (m, 4H), 7.13–7.05 (m, 1H), 6.70–6.88 (m, 2H), 6.72–6.57 (m, 2H), 6.18 (d, *J* = 8.5 Hz, 1H), 4.71 (brs, 1H), 2.63 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_2Cl_2) δ 138.1, 134.7, 133.6, 133.4, 132.4,

130.7, 129.5, 129.1, 129.0, 127.9, 127.8, 127.6, 127.0, 126.9 (q, J = 3.0 Hz), 125.77, 125.76 (q, J = 295.0 Hz), 125.0, 122.1, 120.2, 120.1, 118.4, 116.8, 113.8, 112.6, 108.6, 75.6 (q, J = 30.0 Hz), 10.8; $^{19}F\{^{1}H\}$ NMR (376 MHz, CD_2Cl_2) δ -72.1. Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 95/5, detector: 254 nm, flow rate: 1.0 mL/min, 30 °C), retention time 7.3 min (major) and 10.5 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{27}H_{20}F_3N_2$ $[M+H]^+$ 429.1573, found 429.1571.

(+)-6-Phenyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline (3ba). 54 mg, 74% yield, colorless oil, new compound, R_f = 0.60 (hexanes/ethyl acetate 20:1), 88% ee, $[\alpha]^{20}_D$ = +97.40 (*c* 1.08, EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.61 (d, J = 7.7 Hz, 3H), 7.44–7.28 (m, 4H), 7.05–6.96 (m, 1H), 6.90–6.79 (m, 2H), 6.78–6.66 (m, 2H), 6.63–6.54 (m, 1H), 6.10 (d, J = 8.5 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD) δ 138.7, 136.6, 135.7, 135.1, 129.9, 129.5, 128.43, 128.38, 128.1 (q, J = 2.0 Hz), 125.9 (q, J = 295.0 Hz), 123.2, 120.9, 120.1, 119.8, 118.8, 114.4, 113.3, 112.7, 96.3, 75.7 (q, J = 30.0 Hz); $^{19}F\{^{1}H\}$ NMR (376 MHz, CD_3OD) δ -73.5. Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 90/10, detector: 254 nm, flow rate: 1.0 mL/min, 30 °C), retention time 6.7 min (major) and 10.2 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{22}H_{16}F_3N_2$ $[M+H]^+$ 365.1260, found 365.1258.

(+)-6-Phenyl-6-(trifluoromethyl)-6,11-dihydro-5H-indolo[3,2-c]quinoline (3ba'). 4 mg, 5% yield, pale yellow oil, new compound, R_f = 0.35 (hexanes/ethyl acetate 20:1), 35% ee, $[\alpha]^{20}_D$ = +2.50 (*c* 0.08, EtOAc); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.48 (brs, 1H), 7.73–7.59 (m, 2H), 7.34–7.21 (m, 5H), 7.07–6.95 (m, 2H), 6.81–6.67 (m, 3H), 6.56 (d, J = 8.0 Hz, 1H), 4.56 (brs, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_2Cl_2) δ 141.2, 140.3, 137.1, 132.7, 129.3, 128.31, 128.28, 127.9 (q, J = 2.0 Hz), 126.7 (q, J = 289.0 Hz), 125.8, 122.5, 120.50, 119.6 (q, J = 2.0 Hz), 118.3, 113.1, 112.3, 111.1, 104.5, 66.0 (q, J = 29.0 Hz); $^{19}F\{^{1}H\}$ NMR (376 MHz, CD_2Cl_2) δ -74.9. Enantiomeric excess was determined by HPLC (IB column, elute: *n*-Hexane/*i*-PrOH = 90/10, detector: 254 nm, flow rate: 0.8 mL/min, 30 °C), retention time 11.1 min (major) and 12.6 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{22}H_{16}F_3N_2$ $[M+H]^+$ 365.1260, found 365.1264.

(+)-12-Ethyl-6-phenyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline (3ca). 71 mg, 90% yield, colorless oil, new compound, R_f = 0.50 (hexanes/ethyl acetate 20:1), 92% ee, $[\alpha]^{20}_D$ = +38.73 (*c* 1.42, EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.71 (dd, J = 7.9, 0.8 Hz, 1H), 7.56 (d, J = 7.6 Hz, 2H), 7.41 (d, J = 7.9 Hz, 1H), 7.37–7.26 (m, 3H), 6.99 (d, J = 6.8 Hz, 1H), 6.89–6.69 (m, 3H), 6.64–6.53 (m, 1H), 6.07 (d, J = 8.5 Hz, 1H), 3.12–2.95 (m, 2H), 1.27 (t, J = 7.5 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD) δ 139.5, 136.9, 134.7, 129.8, 129.4, 129.2, 128.3, 128.2, 127.6, 125.9 (q, J = 295.0 Hz), 124.1, 121.3, 119.5, 118.9, 117.6, 115.9, 114.1, 113.5, 112.6, 75.3 (q, J = 30.0 Hz), 17.8, 13.5; $^{19}F\{^{1}H\}$ NMR (376 MHz, CD_3OD) δ -73.0. Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 95/5, detector: 254

nm, flow rate: 1.0 mL/min, 30 °C), retention time 5.1 min (major) and 6.5 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{24}H_{20}F_3N_2$ $[M+H]^+$ 393.1573, found 393.1592.

(+)-3-Bromo-12-methyl-6-phenyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline (3da). 26 mg, 28% yield, colorless oil, new compound, R_f = 0.70 (hexanes/ethyl acetate 10:1), 96% ee, $[\alpha]^{20}_D$ = +8.65 (*c* 0.52, EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.68–7.53 (m, 3H), 7.46–7.31 (m, 4H), 6.96–6.90 (m, 2H), 6.96–6.84 (m, 1H), 6.67–6.58 (m, 1H), 6.07 (d, *J* = 8.5 Hz, 1H), 2.50 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 140.7, 136.4, 134.6, 130.5, 129.6, 128.9, 128.4, 128.1, 125.8 (q, *J* = 295.0 Hz), 125.7, 121.6, 121.5, 120.7, 119.7, 117.9, 115.8, 115.3, 112.5, 107.8, 75.2 (q, *J* = 30.0 Hz), 9.7; $^{19}F\{^1H\}$ NMR (376 MHz, CD_3OD) δ -73.4. Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 95/5, detector: 254 nm, flow rate: 1.0 mL/min, 30 °C), retention time 6.1 min (major) and 7.2 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{23}H_{17}BrF_3N_2$ $[M+H]^+$ 457.0522, found 457.0532.

(+)-3,12-Dimethyl-6-phenyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline (3ea). 57 mg, 73% yield, pink solid, m.p. = 190-191 °C, new compound, R_f = 0.55 (hexanes/ethyl acetate 20:1), 97% ee, $[\alpha]^{20}_D$ = +39.38 (*c* 1.14, EtOAc); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.70 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.48–7.30 (m, 4H), 6.95–6.86 (m, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.69–6.61 (m, 1H), 6.46 (s, 1H), 6.07 (d, *J* = 8.5 Hz, 1H), 4.59 (brs, 1H), 2.55 (s, 3H), 2.21 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_2Cl_2) δ 138.3, 138.1, 136.5, 134.6, 130.8, 130.1, 129.8, 128.8, 128.2 (q, *J* = 2.0 Hz), 125.7 (q, *J* = 295.0 Hz), 124.9, 121.7, 121.2, 120.0, 118.2, 114.2, 112.5, 107.6, 75.4 (q, *J* = 30.0 Hz), 21.1, 10.7; $^{19}F\{^1H\}$ NMR (376 MHz, CD_2Cl_2) δ -72.3. Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 95/5, detector: 254 nm, flow rate: 1.0 mL/min, 30 °C), retention time 5.6 min (major) and 8.1 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{24}H_{20}F_3N_2$ $[M+H]^+$ 393.1573, found 393.1581.

(+)-10-Bromo-12-methyl-6-phenyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline (3fa). 70 mg, 77% yield, colorless oil, new compound, R_f = 0.55 (hexanes/ethyl acetate 10:1), 95% ee, $[\alpha]^{20}_D$ = +66.28 (*c* 1.40, EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.59–7.51 (m, 3H), 7.39–7.26 (m, 3H), 7.06–6.99 (m, 1H), 6.82–6.72 (m, 2H), 6.67 (dd, *J* = 8.9, 2.0 Hz, 1H), 5.95 (d, *J* = 8.9 Hz, 1H), 2.45 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, CD_3OD) δ 139.6, 136.4, 133.2, 132.5, 131.3, 129.6, 128.4, 128.12, 128.08, 125.9 (q, *J* = 295.0 Hz), 124.6, 123.8, 120.3, 118.9, 115.7, 114.0, 113.5, 112.9, 106.5, 75.4 (q, *J* = 30.0 Hz), 9.7; $^{19}F\{^1H\}$ NMR (376 MHz, CD_3OD) δ -73.2. Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 95/5, detector: 254 nm, flow rate: 1.0 mL/min, 30 °C), retention time 6.1 min (major) and 7.7 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{23}H_{17}BrF_3N_2$ $[M+H]^+$ 457.0522, found 457.0546.

(+)-10-Methoxy-12-methyl-6-phenyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline (3ga). 69 mg, 84% yield, pink oil, new compound, R_f = 0.65 (hexanes/ethyl acetate 10:1), 90% ee, $[\alpha]^{20}_D$ = +48.37 (*c* 0.86, EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.74 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.62–7.54 (m, 2H), 7.41–7.29 (m, 3H), 7.02–6.97 (m, 1H) 6.89 (d, *J* = 2.5 Hz, 1H), 6.82–6.76 (m, 1H), 6.73 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.26 (dd, *J* = 9.1, 2.5 Hz, 1H), 5.94 (d, *J* = 9.1 Hz, 1H), 3.66 (s, 3H), 2.50 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 154.2, 139.4, 136.9, 131.2, 130.5, 129.7, 129.4, 128.3, 128.2, 127.4, 125.9 (q, *J* = 296.0 Hz), 124.2, 118.7, 116.2, 113.3, 113.2, 111.0, 106.8, 99.6, 75.3 (q, *J* = 30.0 Hz), 54.7, 9.8; ^{19}F{^{1}H} NMR (376 MHz, CD_3OD) δ -73.2. Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/ *i*-PrOH = 95/5, detector: 254 nm, flow rate: 1.0 mL/min, 30 °C), retention time 7.0 min (major) and 8.2 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{24}H_{20}F_3N_2O$ $[M+H]^+$ 409.1522, found 409.1530.

(+)-6-(Difluoromethyl)-12-methyl-6-phenyl-5,6-dihydroindolo[1,2-c]quinazoline (3aj). 72 mg, 99% yield, colorless oil, new compound, R_f = 0.55 (hexanes/ethyl acetate 10:1), 25% ee, $[\alpha]^{20}_D$ = +15.94 (*c* 1.38, EtOAc); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.79 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 7.5 Hz, 2H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.43–7.32 (m, 3H), 7.08–7.00 (m, 1H), 6.94–6.84 (m, 2H), 6.70–6.62 (m, 2H), 6.24 (t, *J* = 54.5 Hz, 1H), 6.04 (d, *J* = 8.5 Hz, 1H), 4.63 (brs, 1H), 2.56 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2) δ 138.6, 137.0, 134.9, 130.7, 129.9, 129.3, 128.8, 128.6 (t, *J* = 2.0 Hz), 128.0, 125.1, 121.9, 120.1, 119.8, 118.4, 117.0, 115.1 (t, *J* = 254.0 Hz), 114.3, 112.2, 108.3, 74.1 (t, *J* = 23. 0 Hz), 10.8; ^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2) δ -123.6 (d, *J* = 276.8 Hz, 1F), -128.4 (d, *J* = 276.8 Hz, 1F). Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 95/5, detector: 254 nm, flow rate: 1.0 mL/min, 30 °C), retention time 6.7 min (major) and 8.1 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{23}H_{19}F_2N_2$ $[M+H]^+$ 361.1511, found 361.1543.

(+)-6-Benzyl-12-methyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline (3ak). 70 mg, 89% yield, white solid, m.p. = 145-146 °C, new compound, R_f = 0.75 (hexanes/ethyl acetate 10:1), 84% ee, $[\alpha]^{20}_D$ = +94.28 (*c* 1.40, EtOAc); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.68 (d, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.15–6.95 (m, 8H), 6.81 (t, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 7.9 Hz, 1H), 4.32–4.19 (m, 2H), 3.60 (d, *J* = 15.4 Hz, 1H), 2.48 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2) δ 137.6, 134.7, 132.6, 131.1, 130.4, 129.2, 128.4, 128.0, 125.7 (q, *J* = 295.0 Hz), 127.6, 125.0, 122.6, 120.27, 120.26, 118.9, 116.6, 114.1, 113.2 (q, *J* = 2.0 Hz), 108.9, 73.8 (q, *J* = 29.0 Hz), 38.5, 10.9; ^{19}F{^{1}H} NMR (376 MHz, CD_2Cl_2) δ -78.2. Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 95/5, detector: 254 nm, flow rate: 1.0 mL/min, 30 °C), retention time 6.3 min (major) and 7.1 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{24}H_{20}F_3N_2$ $[M+H]^+$ 393.1573, found 393.1573.

6,12-Dimethyl-6-phenyl-5,6-dihydroindolo[1,2-c]quinazoline (3al). 61 mg, 94% yield, white solid, known compound,[25] R_f = 0.50 (hexanes/ethyl acetate 10:1), < 1% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.66–7.59 (m, 2H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.42–7.34 (m, 3H), 7.14–7.06 (m, 1H), 7.05–6.98 (m, 1H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.85–6.76 (m, 1H), 6.68 (dd, *J* = 7.9, 0.7 Hz, 1H), 6.22 (d, *J* = 8.4 Hz, 1H), 4.24 (brs, 1H), 2.66 (, 3H), 2.02 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.4, 140.0, 134.1, 130.5, 129.9, 129.0, 128.7, 127.6, 127.5, 125.2, 121.5, 119.8, 119.1, 118.4, 117.9, 115.2, 111.7, 107.3, 73.5, 24.9, 11.1. Enantiomeric excess was determined by HPLC (IB column, elute: *n*-Hexane/*i*-PrOH = 70/30, detector: 254 nm, flow rate: 0.7 mL/min, 30 °C), retention time 7.1 min and 7.6 min (major).

(+)-Ethyl 12-methyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline-6-carboxylate (3am). 56 mg, 75% yield, pale yellow solid, m.p. = 156-158 °C, new compound, R_f = 0.40 (hexanes/ ethyl acetate 10:1), 89% ee, $[\alpha]^{20}_D$ = +69.10 (*c* 1.12, EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.70 (d, *J* = 7.9 Hz, 1H), 7.53–7.43 (m, 1H), 7.10–6.98 (m, 4H), 6.86–6.73 (m, 2H), 4.31–4.14 (m, 2H), 2.49 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 164.9, 137.8, 134.0, 130.5, 127.8, 124.4, 124.2 (q, *J* = 294.0 Hz), 122.0, 120.2, 119.2, 118.2, 115.5, 113.6, 110.1 (q, *J* = 3.0 Hz), 107.4, 73.7 (q, *J* = 30.0 Hz), 63.1, 12.7, 9.5; ^{19}F{^{1}H} NMR (376 MHz, CD_3OD) δ -77.3. Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 80/20, detector: 254 nm, flow rate: 0.8 mL/min, 30 °C), retention time 5.4 min and 5.9 min (major). HRMS (ESI-TOF) *m/z* Calculated for $C_{20}H_{18}F_3N_2O_2$ $[M+H]^+$ 375.1315, found 375.1319.

(+)-Ethyl 3,12-dimethyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline-6-carboxylate (3em). 46 mg, 59% yield, pink solid, m.p. = 137-138 °C, new compound, R_f = 0.40 (hexanes /ethyl acetate 10:1), 91% ee, $[\alpha]^{20}_D$ = +58.80 (*c* 0.92, EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (d, *J* = 8.5 Hz, 1H), 7.50–7.44 (m, 1H), 7.05–6.98 (m, 3H), 6.67–6.59 (m, 2H), 4.30–4.16 (m, 2H), 2.46 (s, 3H), 2.20 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 165.0, 138.1, 137.8, 133.9, 130.6, 128.1, 124.4, 124.3 (q, *J* = 294.0 Hz), 121.7, 120.2, 120.1, 118.0, 114.0, 112.9, 110.1 (q, *J* = 2.0 Hz), 106.6, 73.7 (q, *J* = 30.0 Hz), 63.0, 20.1, 12.7, 9.4; ^{19}F{^{1}H} NMR (376 MHz, CD_3OD) δ -77.2. Enantiomeric excess was determined by HPLC (OD-H column, elute: *n*-Hexane/*i*-PrOH = 70/30, detector: 254 nm, flow rate: 0.7 mL/min, 30 °C), retention time 5.5 min and 5.9 min (major). HRMS (ESI-TOF) *m/z* Calculated for $C_{21}H_{20}F_3N_2O_2$ $[M+H]^+$ 389.1471, found 389.1475.

(+)-Ethyl 10-bromo-12-methyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazoline-6-carboxylate (3fm). 47 mg, 52% yield, pale yellow solid, m.p. = 203-204 °C, new compound, R_f = 0.45 (hexanes/ethyl acetate 10:1), 89% ee, $[\alpha]^{20}_D$ = +50.95 (*c* 0.94, EtOAc); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.75 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 1.9 Hz, 1H), 7.18 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.15–7.08 (m, 1H), 6.99–6.88 (m, 2H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.94 (brs, 1H), 4.38–4.19 (m, 2H), 2.50 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H);

$^{13}C\{^{1}H\}$ NMR (100 MHz, CD_2Cl_2) δ 164.3, 136.3, 132.8, 132.5, 128.8, 128.7, 125.4, 125.2, 123.7 (q, *J* = 293 Hz), 121.5, 121.3, 116.0, 114.8, 114.0, 112.3 (q, *J* = 2.0 Hz), 108.5, 73.9 (q, *J* = 30.0 Hz), 64.2, 13.6, 10.6; $^{19}F\{^{1}H\}$ NMR (376 MHz, CD_2Cl_2) δ -75.8. Enantiomeric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 70/30, detector: 254 nm, flow rate: 0.7 mL/min, 30 °C), retention time 5.5 min (major) and 6.7 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{20}H_{17}BrF_3N_2O_2$ $[M+H]^+$ 453.0420, found 453.0420.

General Procedure for the Scale-up Reaction. To a 25 ml sealed tube charged with 2-(1*H*-indolyl)aniline **1a** (222 mg, 1.0 mmol), chiral phosphoric acid TRIP (*R*)-**4a** (37.6 mg, 0.05 mmol), dry toluene (10.0 mL) and 5 Å MS (500 mg) was added ketone **2a** (211 μL, 1.5 mmol) under nitrogen. The mixture was kept stirring at 70 °C for 72 h. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on a silica gel using hexanes/ethyl acetate (30:1) as the eluent to give the desirable product **3aa** (363 mg, 96% yield, 94% ee) as white solid.

Determination of the Absolute Configuration. The absolute configuration of 12-methyl-6-phenyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c] quinazoline (+)-(**3aa**) was assigned as (*R*) based on the X-ray diffraction analysis after recrystallization from mixture solvents methanol/ethyl acetate/hexanes to upgrade ee to > 99%. The absolute configurations of the other chiral products are assigned by analogy. The CCDC number is 1873205. These details can be obtained free of charge via www.ccdc.com.ac.uk/data_request/cif from the Cambridge Crystallographic Data Centre.

Product Elaboration. To a solution of (*R*)-(+)-**3am** (56 mg, 0.15 mmol, 88% ee) in anhydrous methanol (3 mL) was added sodium borohydride (114 mg, 3.0 mmol) at 0 °C under nitrogen. After stirring for 30 min, the suspension was warmed to room temperature and stirred overnight. TLC showed 3am was not consumed completely; sodium borohydride (114 mg, 3.0 mmol) was added in portions until disappearance by TLC. The solvent was evaporated in vacuo and the residue was dissolved by saturated ammonium solvent and ethyl acetate. The mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate. After concentrated under the reduced pressure, the residue was purified by flash column chromatography using hexanes/ethyl acetate (4:1) as the eluent to afford the pure product (*R*)-(-)-**5** (47 mg, 94%) as white solid.

(-)-(*R*)-(12-Methyl-6-(trifluoromethyl)-5,6-dihydroindolo[1,2-c]quinazolin-6-yl)methanol (5). 47 mg, 94% yield, white solid, m.p. = 165-167 °C, new compound, R_f = 0.30 (hexanes/ethyl acetate 2:1), 88% ee, $[\alpha]^{20}_D$ = -10.53 (*c* 0.94, EtOAc); ^{1}H NMR (400 MHz, CD_3OD) δ 7.68 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 2H), 7.11–6.95 (m, 3H), 6.88–6.74 (m, 2H), 4.67 (d, *J* = 12.2 Hz, 1H), 4.40 (d, *J* = 12.2 Hz, 1H), 2.48 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, CD_3OD) δ 139.2, 134.5, 130.8, 129.3, 127.6, 125.6 (q, *J* = 296 Hz), 124.4,

122.1, 119.6, 118.9, 118.0, 116.5, 113.8, 112.2 (q, J = 1.0 Hz), 107.3, 74.1 (q, J = 28.0 Hz), 61.3, 9.7. $^{19}F\{^1H\}$ NMR (376 MHz, CD_3OD) δ -78.7. Enantio- meric excess was determined by HPLC (IA column, elute: *n*-Hexane/*i*-PrOH = 70/30, detector: 254 nm, flow rate: 0.7 mL/min, 30 °C), retention time 6.2 min (major) and 6.8 min. HRMS (ESI-TOF) *m/z* Calculated for $C_{18}H_{16}F_3N_2O$ $[M+H]^+$ 333.1209, found 333.1221.

ASSOCIATED CONTENT

Supporting information

NMR spectra of products, and HPLC for racemic and chiral products of all compounds. This material is available free of charge via the internet at http://pubs.acs.org.

Copies of ^1H, $^{13}C\{^1H\}$ and $^{19}F\{^1H\}$ spectra of all new compounds (PDF)

X-ray crystallography data and CIF file for **3aa** (CCDC 1873205)

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Notes

The authors declare no competing financial interest.

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