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Synthesis of planar chiral [2.2]paracyclophane-based amino thioureas and their application in asymmetric aldol reactions of ketones with isatins

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ABSTRACT

Several novel [2.2]paracyclophane-based amino thioureas have been designed and synthesized. The [2.2]paracyclophane-based amino thioureas were used as bifunctional catalysts for organocatalytic enantioselective aldol reactions between ketones and isatins, affording the desired adducts containing a chiral tertiary alcohol in high yields (up to 92% yield) and with good enantioselectivity (up to 88% ee). This is a successful example of employing planar chiral [2.2]paracyclophane-based amino thioureas in asymmetric aldol reactions.

1. Introduction

The asymmetric aldol reaction is one of the most powerful and efficient methods for the formation of chiral carbon–carbon bonds.[1] Since List and Barbas first reported the proline catalyzed cross-aldol reaction of ketones and aldehydes,[2] many amine derivatives have been applied to asymmetric cross-aldol reactions.[3] In particular, pyrrolidine-based secondary amines and primary amine catalysts often complement each other in their ability to activate different substrates,[4] and expand their application to a wide range of carbonyl compounds via enamine catalysis.[5] In 2005, Tomasini et al. reported the first asymmetric aldol reaction of isatin with acetone catalyzed by dipeptide-based organocatalysts.[1c] The asymmetric aldol condensation of ketones with various isatins has attracted more and more attention because 3-alkyl-3-hydroxyindolin-2-ones produced bearing a stereogenic quaternary center at C3 and make up the core of many natural products and pharmaceuticals, with a broad range of biological activities.[6,7] Thus, significant efforts have focused on developing efficient organocatalysts for asymmetric aldol reactions of isatins with ketones.[8]

Over the past few years, the utilization of chiral ureas/thioureas and amines has emerged as a viable strategy in the design of efficient organocatalysts for asymmetric organic transformations. Notable examples include Jacobsen's ureas/thioureas for a variety of reactions[9] and Takemoto's amine-thioureas for Michael addition and aza-Henry reactions.[10] A thiourea and an amine moiety could lead to a class of bifunctional organocatalysts. The double H-bond and amine center can activate both substrates simultaneously at defined positions in the transition states.[11]

Since planar chiral substituted [2.2]paracyclophanes were first reported as being used as ligands in asymmetric catalysis in 1997,[12] planar chiral molecules, such as ferrocene derivatives and substituted [2.2]paracyclophanes, have played an important role in asymmetric catalysis.[13] In recent years, a series of planar chiral ligands based on the [2.2]paracyclophane backbone have been prepared and their applications as rhodium or copper complexes in highly enantioselective transformations have also been demonstrated.[14] In spite of these efforts, examples of the synthesis and application of [2.2]paracyclophane-based organocatalysts are rare.[15] Herein we describe the synthesis of several new planar chiral amino thioureas and their application in organocatalytic enantioselective aldol reaction.

2. Results and discussion

Our synthetic route to catalysts **6**, **10a**, and **10b** is described in Schemes 1 and 2.

2.1. Synthesis of planar chiral amino thiourea derived from [2.2]paracyclophane

(R_P)-4-Bromo-12-formyl[2.2]paracyclophane **2** was synthesized from racemic 4,12-dibromo[2.2]paracyclophane by the reported procedure.[16,17] Aldehyde **2** was converted into the corresponding oxime by reaction with hydroxylamine hydrochloride and NaOAc in ethanol in quantitative yield. Methylation of the oxime with dimethyl sulfate followed by reduction of borane gave the desired (R_P)-4-aminomethyl-12-bromo[2.2]paracyclophane **3** in excellent

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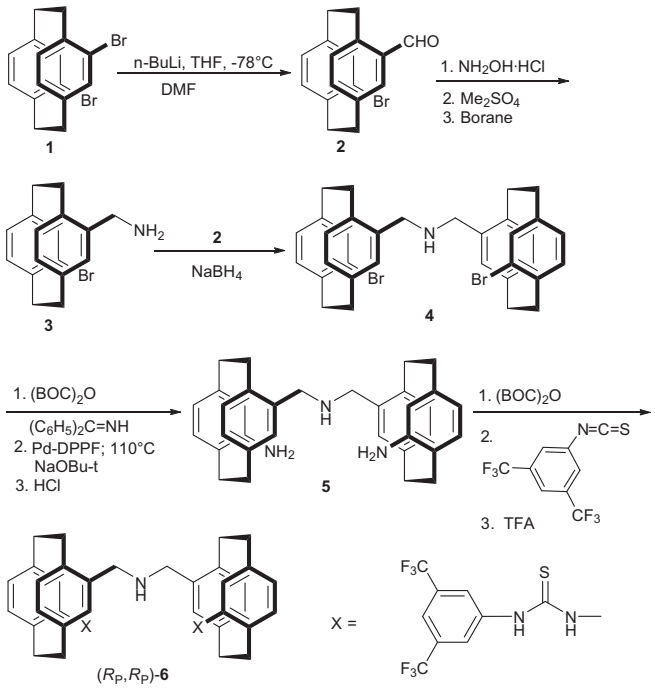
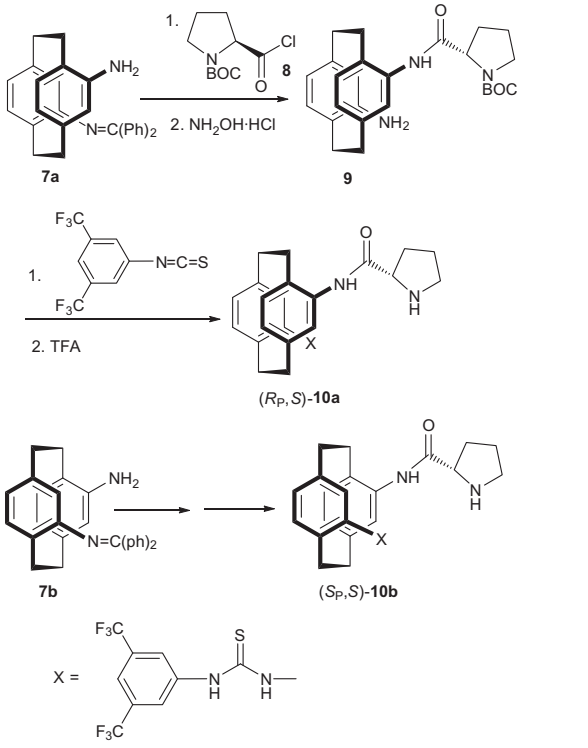


Scheme 1. Synthesis of planar chiral amino thiourea **6**.



Scheme 2. Synthesis of chiral amino thioureas **10a**, **10b**.

yield. A one-pot reductive amination of **2** with **3** using $NaBH_4$ as a reducing agent resulted in the chemoselective formation of the expected (R_P)-bis(12-bromo[2.2]paraclophane-4-methylene)amine **4** in good yield. Not as reported previously by us,[18] the Buchwald–Hartwig amination of **4** under standard conditions failed to give a satisfactory result. We therefore turned our attention to protect the amine function of **4** by means of a amine-protecting group, *tert*-butyloxycarbonyl. The Boc-protected compound **4** was subjected to a Pd-catalyzed amination with benzhydrylideneamine to afford, after hydrolysis by hydrochloric acid, triamino[2.2]paracyclophane **5** in satisfactory yield. For the synthesis of amino thiourea **6**, it is necessary to only protect the alkylamino group in **5**. Fortunately, the mono-Boc-protected compound **5** was easy to obtain directly due to the different reactivity of the two kinds of amino groups in **5**. The remaining amino groups reacted with 3,5-bis(trifluoromethyl)phenyl isothiocyanate to produce, after removal of the Boc-protecting group with trifluoroacetic acid, the final product (R_P,R_P)-**6** in good yield (Scheme 1).

2.2. Synthesis of planar and central chiral amino thioureas derived from proline and [2.2]paracyclophane 10a, 10b

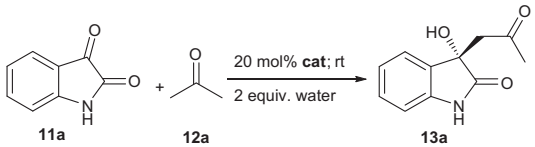
According to a previously described procedure,[19] starting from known compound (R_P)-4-amino-12-benzhydrylideneamino[2.2]paracyclophane **7a**,[18] the (*S*)-*N*-Boc-prolyl group was introduced via a classical coupling between **7a** and **8** to generate the corresponding amide. Deprotection of the benzhydrylideneamino group by hydroxylamine hydrochloride and NaOAc led to the isolation of the desired (R_P,*S*)-4-amino-12-(*N*-Boc-prolinamido)[2.2]paracyclophane **9a** with excellent chemoselectivity. Finally, the target product (R_P,*S*)-**10a** was obtained by a simple reaction between **9a** and 3,5-bis(trifluoromethyl)phenyl isothiocyanate followed by removal of the Boc-protecting group with TFA. The (S_P,*S*)-**10b** was prepared from (S_P)-4-amino-12-benzhydrylideneamino[2.2]paracyclophane **7b** and **8** following the representative procedure described above (Scheme 2).

2.3. Catalytic asymmetric aldol reactions

With these catalysts in hand, we next examined their efficiency in enantioselective aldol reactions with isatin **11a** and acetone **12a** as the model substrates. The results of the catalyst and solvent optimization are presented in Table 1.

It is well known that the addition of small quantities of water to the organocatalyzed aldol addition of acetone to isatin results in an increase in the enantioselectivity of the reaction.[8g,l] We therefore modified the reported procedure,[8g,l] with water as an additive, to evaluate the solvent effects. With CH_2Cl_2 as the solvent, the reaction was catalyzed by **10a** to afford the desired product **13a** in

Table 1
Catalyst and solvent optimization[a]



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**10a**	CH_2Cl_2	48	85	60
2	**10a**	Acetone	48	68	33
3	**10a**	Methanol	48	83	20
4	**10a**	Toluene	48	84	45
5	**10a**	Acetonitrile	48	79	15
6	**10a**	DME	48	83	43
7	**10a**	Dioxane	48	85	59
8	**10a**	Ether	48	86	67
9	**10a**	THF	48	89	76
10	**6**	THF	96	88	68
11	**10b**	THF	48	60	32

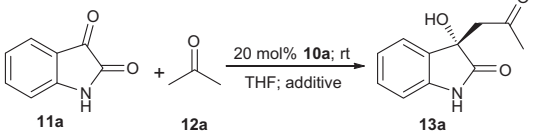
[a] The reaction was carried out with **11a** (0.136 mmol), 31 equiv **12a** (4.216 mmol), 20 mol % catalyst, (0.0272 mmol), and water (2 equiv) in 1.25 mL of the specified solvent at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC (Chiralpak IA column) analysis.

85% yield and 60% ee (Table 1, entry 1). However inferior yields and enantioselectivities were obtained when the reaction was conducted in acetone (Table 1, entry 2). Further solvent optimization (Table 1, entries 3–9) identified THF as the best solvent for this reaction, in which the ee value was improved to 76% (Table 1, entry 9). With THF as the optimal solvent, catalyst **6** showed a lower catalytic activity with a moderate enantioselectivity of 68% ee (Table 1, entry 10). However, compared with catalyst **10a**, a lower ee value was given by its diastereoisomer **10b** with a mismatched pair of chiralites (Table 1, entry 11). Screening of catalysts **10a** and **10b** revealed that the absolute configuration of product **13a** was determined by the central chirality of the catalysts.

In order to obtain better yields and enantioselectivities, we next investigated the impact of additives on the aldol reaction with **10a** as the catalyst and THF as the solvent (Table 2). These additives led to lower reaction yields and poor enantioselectivities in contrast to water (Table 2, entries 1–9). It should be noted that while the reaction time was obviously shortened from 48 to 4 h with $PhCO_2H$ as an additive, the ee value was poor at room temperature (Table 2, entry 1). Lowering the reaction temperature to −45 °C, led to only moderate enantioselectivity being obtained with an extension of the reaction time (Table 2, entry 10). Among the acids, phenols, amides, alcohols, and water screened, it appeared that water (2 equiv) was the most effective additive, achieving the highest enantioselectivity (Table 2, entry 13). Hence the water loading conditions were also studied, as reported by Tomasini,[8l] some negative effects on the enantioselectivity were observed when less or more water was added (Table 2, entries 11, 12, 14, and 15).

Having optimized the reaction conditions, we finally evaluated the substrate scope with various ketones and isatins. As shown in Table 3, with acetone as the substrate, various substituted isatins were applied to this reaction (Table 3, entries 1–8). The steric hindrance of the substituent on the nitrogen of isatin had an important influence on the enantioselectivity. The enantiomeric excess decreased from 76 to 25 to 4 as the size of substituent is increased from H to Me to trityl (Table 3, entries 1–3). On the other hand, the electronic properties of the substituent and its position on the isatin phenyl ring showed some influence on the enantioselectivities (Table 3, entries 4–8). For example, the ee value of 5-fluoroisatin **11h** (Table 3, entry 8) was much higher than that of 7-fluoroisatin **11e** (Table 3, entry 5). Acetone, acetophenone, and *p*-methoxyacetophenone were also examined in the reaction (Table 3, entries 9–12); the desired products were obtained in good yields (78–80%) with moderate enantioselectivities (58–72% ee).

Table 2
Additive effect on the reaction of isatin with acetone[a]

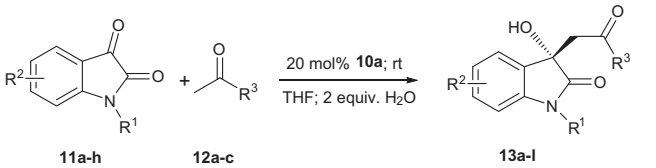


11a 12a 13a

Entry	Additive	Time (h)	Yield[b] (%)	ee (%)
1	$PhCO_2H$[c]	4	83	36
2	TFA[c]	48	79	50
3	4-Br-phenol[c]	48	74	34
4	4-NO_2-phenol[c]/H_2O[e]	48	73	40
5	4-NO_2-phenol[c]	48	80	54
6	4-NO_2-phenol[e]	48	78	64
7	*p*-Toluenesulfonamide[e]	48	81	24
8	Hexafluoroisopropanol[e]	48	75	36
9	Trifluoroethanol[e]	48	73	30
10	$PhCO_2H$[c,h]	96	91	58
11	None	48	85	40
12	H_2O[d]	48	75	48
13	H_2O[e]	48	89	76
14	H_2O[f]	48	77	35
15	H_2O[g]	48	70	32

[a] Unless otherwise noted, all reactions for the additive study were conducted using **11a** (0.136 mmol), **12a** (31 equiv 4.216 mmol), and 20 mol % catalyst loading of **10a**, in 1.25 mL of THF with additive at room temperature, ee was determined by chiral HPLC (Chiralpak IA colmun) analysis.
[b] Isolated yield.
[c] 20 mol % additive was used.
[d] 1 equiv. of H_2O was used.
[e] 2 equiv. of additive were used.
[f] 3 equiv. of H_2O were used.
[g] 10 equiv. of H_2O were used.
[h] The reaction was performed at −45 °C.

Table 3
Scope of substrates in the asymmeric aldol reaction[a]



11a-h 12a-c 13a-l

Entry	$R^1/R^2/R^3$	Time (h)	Yield[b] (%)	ee[c] (%)
1	H/H/Me	48	89 **13a**	76
2	Methyl/H/Me	48	87 **13b**	25
3	Trityl/H/Me	48	89 **13c**	4
4	H/7-Cl/Me	48	86 **13d**	66
5	H/7-F/Me	48	85 **13e**	60
6	H/5-Me/Me	48	88 **13f**	68
7	H/5-Cl/Me	48	83 **13g**	70
8	H/5-F/Me	48	92 **13h**	88
9	H/5-F/Ph	72	78 **13i**	64
10	H/5-F/4-$CH_3OC_6H_4$	96	79 **13j**	72
11	H/H/Ph	72	79 **13k**	58
12	H/H/4-$CH_3OC_6H_4$	96	80 **13l**	68

[a] Unless otherwise noted, reactions were carried out with **11** (0.136 mmol), **12** (31 equiv, 4.216 mmol) in THF (1.25 mL) with 20 mol % of catalyst **10a** and 2 equiv. of water at room temperature.
[b] Isolated yield.
[c] Enantiomeric excesses were determined by chiral HPLC analysis (Chiralpak IA-H column).

2.4. Transition state models for the asymmetric aldol reaction

The absolute configuration of the major enantiomers of **13a–b**, **13f–i**, and **13k–l** was determined to be (*S*) by comparison of the specific rotation with the literature data,[1b,4b,20] the absolute configuration of the major enantiomers of **13c–e** and **13j** was assigned as (*S*) by analogy, and through comparison of the specific rotation and chiral HPLC elution order, with configurationally defined examples. The observed absolute configuration of the products was in agreement with the proposed transition state model in which the isatin is activated by bifurcated H-bonding with the NH of prolinamide as well as the NH of the thiourea through hydrogen bond interactions,[21] while the R group of the enamine formed by reaction of the **10a** pyrrolidine moiety with ketone shields the *Si*-face of the carbonyl group of isatin, therefore, the nucleophilic addition of the enamine to the *Re*-face of the activated carbonyl group therefore leads to the major (*S*)-product (Fig. 1, model A).

Unlike the planar and central chiral prolinamido thiourea **10a**, when the planar chiral amino thiourea **6** was used as a bifunctional organocatalyst, a simple transition state model could account for the stereochemical outcome of the reaction (Fig. 1, model B). The carbonyl group of isatin was bonded by the NH of the thiourea and the resulting activated C=O bond is approached by the enamine β-C atom at its *Re*-face to avoid steric hindrance between the R group and the isatin aromatic ring, leading to an (*S*)-configuration at the newly formed stereogenic center.

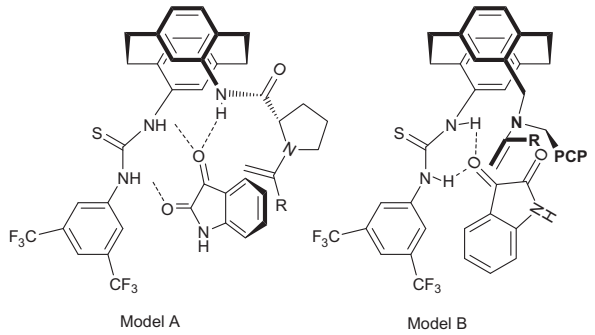


Figure 1. Proposed transition state models for the asymmetric aldol reactions.

3. Conclusion

In conclusion, several novel [2.2]paracyclophane-based amino thioureas have been synthesized and successfully applied to asymmetric aldol reaction of isatins with ketones. The corresponding aldol products were obtained in good enantioselectivities (up to 88% ee) and high yields (up to 92%). Further modification of [2.2]paracyclophane-based amino thioureas as well as investigations into other reaction variants are currently underway in our laboratory.

4. Experimental

4.1. General

Commercially available reagents were used without further purification unless otherwise noted. Ketones were obtained from commercial sources and were distilled or filtered through a plug of silica gel prior to use. Solvents were reagent grade and purified by standard techniques. Reactions were stirred magnetically under an argon atmosphere and monitored by thin layer chromatography (TLC). Purification of reaction products was carried out by column chromatography on silica gel. Melting points were recorded on a melting point apparatus and are uncorrected. Optical rotations were measured on a polarimeter and are reported in degrees (*c* g/100 mL, solvent). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE-300 at 298 K. Chemical shifts are reported in parts per million (ppm) downfield from tetra-methylsilane (TMS) with reference to the internal standard for ^{1}H NMR and ^{13}C NMR spectra. HRMS spectra were recorded on an Agilent 100 ABI-API4000 spectrometer. Enantiomeric excess was determined by HPLC on a Chiralpak IA chiral column using hexane/EtOH or hexane/*i*-PrOH as eluents with UV detection at 254 nm.

4.2. Synthesis of amino thiourea 6 derived from [2.2]paracyclophane

4.2.1. Preparation of (R_P)-4-aminomethyl-12-bromo[2.2]paracyclophane 3

(R_P)-4-Bromo-12-formyl[2.2]paracyclophane **2** (200 mg, 0.64 mmol) and NaOAc (262.4 mg, 3.20 mmol) were dissolved in EtOH (5.0 mL) at 78 °C. Hydroxylamine hydrochloride (177.9 mg, 2.56 mmol) was added to the stirred solution in portions. The mixture was stirred at 78 °C for 2 h. After completion (monitored by TLC), the solvent was removed under reduced pressure. Water (10 mL) was added to the residue, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 extract was washed with brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate = 5/1) to afford oxime as a white solid (210.0 mg) in essentially quantitative yield.

To a mixture of the oxime (100 mg, 0.304 mmol) and K_2CO_3 (252.1 mg, 1.82 mmol) in acetone (5.0 mL) was added dimethyl sulfate (0.12 mL, 1.22 mmol). After stirring for 24 h at room temperature, aq ammonia (1.0 mL) was added followed by water (15 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was washed twice with brine, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 10:1), to give the corresponding oxime ether (105.0 mg, 98% yield).

In an oven-dried Schlenk flask charged with the oxime ether (102.0 mg, 0.30 mmol) and anhydrous THF (1.0 mL), the resulting solution was stirred at 65 °C under argon and borane-methyl sulfide (0.75 mmol) was added dropwise via a syringe. The reaction mixture was stirred for 2 h at 65 °C, and then the solution was cooled to room temperature. Next MeOH (2.0 mL) was added, and the mixture was stirred for another 20 min. After the mixture was taken to dryness by a rotary evaporator, MeOH (5.0 mL) and 2 M hydrochloric acid (5.0 mL) were added to the residue and the solution was refluxed for 1 h. The mixture was cooled to 25 °C and then basified with NaOH pellets to pH 10. After evaporation under reduced pressure, the residue was extracted with CH_2Cl_2 (3 × 5.0 mL) and the combined organic phases were washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (CH_2Cl_2/ethanol = 15:1) to afford **3** as a white solid (75.6 mg, 80% yield). Mp: 156–158 °C. $[\alpha]_D^{20} = -165$ (*c* 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (br s, 2H), 2.76–2.93 (m, 3H), 3.02–3.20 (m, 3H), 3.33–3.46 (m, 2H), 3.59 (br s, 1H), 3.84 (br s, 1H), 6.44–6.54 (m, 4H), 6.65 (s, 1H), 7.00 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.8, 33.0, 33.5,35.5, 44.6, 126.6, 127.7, 131.3, 131.6, 133.2, 134.8, 135.3, 136.6, 138.9, 140.1, 141.4, 142.1; HRMS (ESI): calcd for $C_{17}H_{19}BrN$ $(M+H)^+$ 316.0701, found: 316.0690.

4.2.2. Preparation of (R_P,R_P)-bis(12-bromo[2.2]paraclophan-4-yl methylene)amine 4

An oven-dried Schlenk flask was charged with (R_P)-4-aminomethyl-12-bromo[2.2]paracyclophane **3** (589.2 mg, 1.87 mmol), (R_P)-4-formyl-12-bromo[2.2]paracyclophane **2** (587.2 mg, 1.87 mmol), THF (15 mL), and $NaBH_4$ (991.4 mg, 26.18 mmol). The mixture was stirred at room temperature for 3 days. Next, MeOH (15 mL) was added, and the mixture was stirred for another 1 h. After the mixture was evaporated to dryness under vacuum, MeOH (20 mL) and 12 M hydrochloric acid (10 mL) were added to the residue, and the resulting solution was refluxed for 1 h. The reaction mixture was cooled to 25 °C and added to satd aq NaOH (10 mL). Next, MeOH was removed under reduced pressure, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined extract was evaporated on a rotary evaporator, and the residue was purified by chromatography on silica gel (CH_2Cl_2/ethyl acetate = 15:1) to furnish **4** as a white solid (862.7 mg, 75% yield); Mp: 188–190 °C; $[\alpha]_D^{20} = -91$ (*c* 0.05, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (br s, 1H), 2.68–2.84 (m, 6H), 2.97–3.19 (m, 6H), 3.29–3.45 (m, 4H), 3.46 (d, J = 13.2 Hz, 2H), 3.65 (d, J = 13.2 Hz, 2H), 6.45 (dd, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 2H), 6.48–6.49 (m, 4H), 6.51 (d, J = 7.8 Hz, 2H), 6.56 (s, 2H), 7.03 (d, J = 1.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.8, 33.2, 33.6, 35.6, 51.8, 126.6, 129.5, 131.6, 133.3, 134.7, 135.3, 137.8, 138.9, 139.2, 139.6, 141.5; HRMS (ESI): calcd for $C_{34}H_{34}Br_2N$ $(M+H)^+$ 616.1038, found 616.1021.

4.2.3. Preparation of (R_P,R_P)-bis(12-amino[2.2]paracyclophan-4-yl methylene)amine 5

At first, (R_P,R_P)-bis(12-bromo[2.2]paraclophan-4-yl methylene)amine **4** (100 mg, 0.163 mmol) and di-*tert*-butyl pyrocarbonate (0.045 mL, 0.196 mmol) were dissolved in CH_2Cl_2 (3.0 mL) and stirred at ambient temperature until the starting material was

consumed. The mixture was concentrated to dryness under vacuum and directly purified by flash column chromatography (CH_2Cl_2) to yield 115.0 mg of *N*-Boc-protected amine (99% yield) as a white solid.

In a glovebox, an oven-dried Schlenk flask was charged with the *N*-Boc-protected amine (115.1 mg, 0.161 mmol), Pd-DPPF (5.8 mg, 0.5 mol %), benzhydrylideneamine (87.4 mg, 0.483 mmol), sodium *t*-butoxide (46.4 mg, 0.483 mmol), and toluene (2.0 mL). The mixture was stirred at 110 °C under nitrogen for 8 h. After the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (3.0 mL), HOAc was added until the mixture tested pH 6 by an indicator paper. Next, 3 M hydrochloric acid (1.0 mL) was added and stirred for 4 h at room temperature. After completion (monitored by TLC), the white precipitate formed was filtered. The filtered solid product was dispersed in ethanol (4.0 mL) and the pH of the suspension was adjusted to 9 by the addition of a 4 M NaOH aqueous solution slowly. The solvent was removed, and the residue was purified by chromatography on silica gel (CH_2Cl_2/ethanol 3:1) to furnish the desired product **5** (47.1 mg, 60% yield) as a white solid. Mp: 186–188 °C; $[\alpha]_D^{20} = -102$ (*c* 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57–2.71 (m, 4H), 2.73–2.81 (m, 3H), 2.89–2.99 (m, 3H), 3.02–3.09 (m, 7H), 3.24–3.29 (m, 2H), 3.40 (d, J = 13.2 Hz, 2H), 3.66 (d J = 13.2 Hz, 2H), 5.38 (d, J = 1.5 Hz, 2H), 6.07 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 2H), 6.27 (d, J = 7.8 Hz, 2H), 6.36 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 2H), 6.54 (d, J = 7.8 Hz, 2H), 7.05 (d, J = 1.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.0, 32.5, 33.1, 33.9, 51.4, 118.4, 122.7, 124.3, 128.0, 131.7, 134.3, 135.6, 137.4, 138.4, 139.5, 141.1, 145.0; HRMS (ESI): calcd for $C_{34}H_{38}N_3$ $(M+H)^+$ 488.3066, found 488.3074.

4.2.4. Preparation of (R_P,R_P)-bis(12-(3,5-bis(trifluoro-methyl)-phenyl thiocarboxamino)[2.2]paracyclophan-4-yl methylene)amine 6

To a solution of (R_P,R_P)-bis(12-amino[2.2]paracyclophan-4-yl methylene)amine **5** (93.1 mg, 0.191 mmol) in CH_2Cl_2 (1.5 mL) was added di-*tert*-butyl pyrocarbonate (0.05 mL, 0.21 mmol) at −5 °C. The mixture was stirred at −5 °C for 2 h. The crude product was rapidly purified by flash column chromatography (CH_2Cl_2/ethyl acetate 20:1) to afford 112 mg (quantitative yield) of the mono-Boc-protected **5** as a white solid.

To a stirred solution of mono-Boc-protected **5** (112.2 mg, 0.191 mmol) in anhydrous CH_2Cl_2 at 30 °C under argon, 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.10 mL, 0.573 mmol) was added dropwise via a syringe, and the reaction mixture was stirred overnight at 30 °C. After completion (monitored by TLC), the remaining 3,5-bis(trifluoromethyl)-phenyl isothiocyanate was removed rapidly by flash column chromatography (CH_2Cl_2/petroleum ether 2:1; CH_2Cl_2/ethyl acetate 50:1) to give the desired thiourea as a white solid (200.0 mg, 93% yield).

To a stirred solution of the thiourea (200.6 mg, 0.178 mmol) in CH_2Cl_2 (1.5 mL), TFA (1.0 mL) was added and the reaction mixture was stirred for 30 min at 0 °C. Saturated aqueous sodium carbonate solution was added until the mixture became basic (pH 8). The mixture was extracted by CH_2Cl_2 (3 × 10 mL) and the combined organic phases were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography ($CHCl_3$; $CHCl_3$/ethyl acetate 15:1) to give the desired product **6** (155.7 mg, 85% yield) as a white solid. Mp: 116–118 °C; $[\alpha]_D^{20} = -79$ (*c* 0.07, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.70–3.00 (m, 6H), 3.04–3.21 (m, 5H), 3.14–3.28 (m, 6H), 3.53–3.91 (m, 2H), 3.99–4.08 (m, 2H), 6.23 (s, 2H), 6.45–6.68 (m, 8H), 7.03 (s, 2H), 7.63 (s, 2H), 7.97 (s, 4H), 9.14 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.2, 32.5, 33.8, 34.1, 50.0, 119.0, 121.2 (J = 270.2 Hz), 124.4, 124.8, 127.5, 128.0, 128.4, 131.1, 131.6 (J = 33.8 Hz), 132.0, 132.2, 132.5, 133.3, 134.7, 135.2, 135.7, 136.4, 137.6, 139.9, 140.2, 142.5; HRMS (ESI): calcd for $C_{52}H_{44}F_{12}N_5S_2$ $(M+H)^+$ 1030.2847, found 1030.2861.

4.3. Synthesis of planar and central chiral amino thioureas derived from proline and [2.2]paracyclophane 10a, 10b

4.3.1. Preparation of (R_P,*S*)-4-amino-12-(*N*-Boc-prolinamido) [2.2]paracyclophane 9a

To a solution of (R_P)-4-amino-12-benzhydrylideneamino[2.2]paracyclophane **7a**[17] (97.3 mg, 0.242 mmol), and Et_3N (0.51 mL, 3.63 mmol) in anhydrous CH_2Cl_2 (2.0 mL) at 0 °C was added *N*-Boc-(*S*)-proline chloride **8**[18] (0.14 M in CH_2Cl_2, 3.46 mL, 0.484 mmol). The mixture was stirred at room temperature under nitrogen for 8 h. The reaction was quenched by the addition of 10% aq $NaHCO_3$ (2.0 mL). The organic layer was separated, washed with satd aq $NaHCO_3$ (2.0 mL), and dried over Na_2SO_4. After removal of the solvent in vacuum, the residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 10:1; petroleum ether/ethyl acetate = 4:1) to afford the desired amide as a yellow solid (111.7 mg, 77% yield).

The amide and NaOAc (61.3 mg, 0.745 mmol) were dissolved in EtOH (5.0 mL) at 45 °C, after which hydroxylamine hydrochloride (46.6 mg, 0.671 mmol) was added to the stirred solution in portions. The mixture was stirred at 45 °C for 6 h. After completion (monitored by TLC), the solvent was removed under reduced pressure. Water (10 mL) was then added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 extract was washed with brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The crude product was purified by flash column chromatography (CH_2Cl_2; CH_2Cl_2/ethyl acetate 5:1) to give the product **9a** as a white solid (77.0 mg, 95% yield). Mp: 180–181 °C; $[\alpha]_D^{20} = -248$ (*c* 0.09, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 9H), 1.89–2.05 (m, 2H), 2.51–2.60 (br s, 1H), 2.62–2.76 (m, 2H), 2.84–3.02 (m, 2H), 3.05–3.15 (m, 2H), 3.17–3.23 (m, 2H), 3.44 (br s, 2H), 3.85 (br s, 2H), 4.55 (s, 1H), 5.77 (s, 1H), 6.07 (d, J = 6.9 Hz, 1H), 6.28–6.33 (m, 2H), 6.52 (d, J = 7.8 Hz, 1H), 7.81 (s, 1H), 8.73 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 28.1, 28.5, 32.3, 32.5, 32.6, 33.4, 47.5, 61.2, 81.0, 119.0, 120.3, 122.5, 124.2, 129.2, 134.8, 135.5, 136.7, 140.7, 140.9, 146.4, 156.4, 170.1; HRMS (ESI): calcd for $C_{26}H_{34}N_3O_3$ $(M+H)^+$ 436.2600, found 436.2589.

4.3.2. Preparation of (R_P,*S*)-4-(3,5-bis(trifluoromethyl)-phenyl thiocarboxamino)-12-prolinamido[2.2]paracyclophane 10a

To a stirred solution of **9a** (300.1 mg, 0.689 mmol) in anhydrous CH_2Cl_2 at 30 °C under argon, 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.18 mL, 1.03 mmol) was added dropwise via syringe, and the reaction mixture was stirred overnight at 30 °C. After completion (monitored by TLC), the remaining 3,5-bis(trifluoromethyl) phenyl isothiocyanate was removed rapidly by flash column chromatography (CH_2Cl_2/ethyl acetate 25:1) to give the thiourea as a white solid (462.6 mg, 95% yield).

To a stirred solution of the thiourea (462.6 mg, 0.655 mmol) in CH_2Cl_2 (3.0 mL), TFA (3.0 mL) was added and the reaction mixture was stirred for 30 min at 0 °C. Next, satd aq $NaHCO_3$ solution was added until the stirred mixture tested basic (pH 8). The mixture was extracted by CH_2Cl_2 (3 × 15 mL), and the combined organic phases were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography ($CHCl_3$/ethanol 15:1) to give the desired product **10a** as a white solid (355.2 mg, 85% yield). Mp: 142–144 °C; $[\alpha]_D^{20} = -146$ (*c* 0.08, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.69–1.83 (m, 2H), 1.99–2.10 (m, 1H), 2.23–2.36 (m, 2H), 2.78–2.88 (m, 2H), 2.91–3.00 (m, 2H), 3.04–3.16 (m, 4H), 3.25–3.40 (m, 2H), 4.05 (dd, J_1 = 9.3 Hz, J_2 = 5.1 Hz, 1H), 6.22 (s, 1H), 6.40 (dd, J_1 = 7.8 Hz, J_2 = 1.5 Hz, 1H), 6.54 (d,

J = 8.1 Hz, 1H), 6.57 (dd, J_1 = 8.1 Hz, J_2 = 1.5 Hz, 1H), 6.66 (d, J = 7.8 Hz, 1H), 7.58 (s, 1H), 7.63(s, 1H), 7.81 (br s, 1H), 8.03 (s, 2H), 9.90 (s, 1H), 9.97 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 31.3, 32.0, 33.1, 33.2, 34.1, 47.5, 61.3, 118.7, 118.8, 121.2 (J = 277.5 Hz), 121.3, 124.2, 124.9, 127.3, 129.5, 129.8, 131.1, 131.6, 132.0 (J = 35.2 Hz), 132.5, 135.0, 136.2, 136.4, 136.5, 140.1, 141.3, 141.9, 174.1, 179.0; HRMS (ESI): calcd for $C_{30}H_{29}F_6N_4OS$ $(M+H)^+$ 607.1966, found 607.1940.

4.3.3. Preparation of (S_P,S)-4-(3,5-bis(trifluoromethyl)-phenyl thiocarboxamino)-12-prolinamido[2.2]paracyclo-phane 10b

Compound (S_P,S)-**10b** was prepared from (S_P)-4-benzhydrylidene amino-12-amino[2.2]paracyclophane **7b** following the representative procedure described as above. White solid, Mp: 142–144 °C; $[\alpha]_D^{20} = +86$ (c 0.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) 1.91–1.96 (m, 2H), 2.20–2.41 (m, 3H), 2.80–2.93 (m, 3H), 3.09–3.38 (m, 7H), 4.03 (dd, J_1 = 8.7 Hz, J_2 = 4.8 Hz, 1H), 6.14 (s, 1H), 6.41 (d, J = 7.8 Hz, 1H), 6.53–6.59 (m, 2H), 6.66 (d, J = 7.8 Hz, 1H), 7.56 (s, 1H), 7.64 (s, 1H), 7.82 (br s, 1H), 8.04 (s, 2H), 9.92 (s, 1H), 10.07 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.7, 31.0, 32.0, 33.3, 33.4, 34.1, 47.5, 61.0, 118.8, 121.3, 121.5 (J = 271.1 Hz), 124.32, 124.9, 127.4, 129.8, 129.9, 131.6, 132.0 (J = 33.8 Hz), 132.4, 132.5, 135.1, 136.3, 136.5, 140.2, 141.3, 141.7, 173.9, 179.1; HRMS (ESI): calcd for $C_{30}H_{29}F_6N_4OS$ $(M+H)^+$ 607.1966, found 607.1977.

4.4. General experimental procedure for the enantioselective aldol reaction

To a mixture of catalyst (0.0272 mmol, 20 mol %), isatin **11** (0.136 mmol), and the specified additive in THF (1.25 mL) was added carbonyl compound **12** (4.216 mmol) at room temperature. After stirring for 48 h at room temperature, the solvent was removed under reduced pressure to give a residue which was directly purified by column chromatography on silica gel to afford the aldol product. The enantiomeric excess was determined using HPLC on a Chiralpak IA chiral column, with UV detection at 254 nm.

Analytical characteristics for compounds **13a**–**b**, **13d**, **13f**–**13i**, and **13k**–**13l** were in agreement with previously reported spectra and properties.[1b,4b,8f,20]

4.4.1. (*S*)-3-Hydroxy-3-(2-oxopropyl)indolin-2-one 13a[1b]

White solid, 89% yield; Mp: 168–170 °C. $[\alpha]_D^{20} = -21.3$ (c 0.90, MeOH, 76% ee); enantiomeric excess of **13a** was measured by chiral stationary phase HPLC analysis using a Chiralpak IA column (4:1 hexane/*i*-PrOH at 0.5 mL/min, 20 °C), t_{major} = 21.1 min; t_{minor} = 28.0 min.

4.4.2. (*S*)-1-Methyl-3-hydroxy-3-(2-oxopropyl)indolin-2-one 13b[8f]

White solid, 87% yield; Mp: 153–155 °C; $[\alpha]_D^{20} = -4.4$ (c 0.65, MeOH, 25% ee); enantiomeric excess of **13b** was measured by chiral stationary phase HPLC analysis using a Chiralpak IA column (5:1 hexane/EtOH at 0.5 mL/min, 20 °C), t_{major} = 23.4 min, t_{minor} = 27.1 min.

4.4.3. (*S*)-1-Trityl-3-hydroxy-3-(2-oxopropyl)indolin-2-one 13c

White solid, 89% yield; Mp: 210–212 °C; $[\alpha]_D^{20} = -2.4$ (c 0.93, MeOH, 4% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.98 (d, J = 16.5 Hz, 1H), 3.14 (d, J = 16.5 Hz, 1H), 3.59 (br s, 1H), 6.28–6.31 (m, 1H), 6.90–6.95 (m, 2H), 7.17–7.28 (m, 10H), 7.48–7.50 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.4, 49.8, 73.8, 74.5, 116.4, 122.6, 123.0, 126.9, 127.7, 128.5, 129.4, 129.6, 141.9, 143.5, 177.8, 206.5. HRMS (ESI): calcd for $C_{30}H_{25}NO_3$ $(M+Na)^+$ 470.1732, found 470.1719. Enantiomeric excess of **13c** was measured by chiral stationary phase HPLC analysis using a Chiralpak IA column (5:1 hexane/*i*-PrOH at 0.5 mL/min, 20 °C), t_{major} = 21 min, t_{minor} = 27.9 min.

4.4.4. (*S*)-7-Chloro-3-hydroxy-3-(2-oxopropyl)indolin-2-one 13d[20c]

White solid, 86% yield; Mp: 175–177 °C. $[\alpha]_D^{20} = -14.5$ (c 0.75, MeOH, 66% ee); enantiomeric excess of **13d** was measured by chiral stationary phase HPLC analysis using a Chiralpak IA column (5:1 hexane/*i*-PrOH at 0.5 mL/min, 20 °C), t_{major} = 33.6 min, t_{minor} = 37.5 min.

4.4.5. (*S*)-7-Fluoro-3-hydroxy-3-(2-oxopropyl)indolin-2-one 13e

White solid, 85% yield; Mp: 185–187 °C. $[\alpha]_D^{20} = -13.1$ (c 0.67, MeOH, 60% ee). ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.00 (3H, s), 3.08 (d, J = 16.8 Hz, 1H), 3.35 (d, J = 17.1 Hz, 1H), 6.10 (s, 1H), 6.89–6.95 (m, 1H), 7.06–7.12 (m, 2H), 10.71 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6). δ 30.3, 50.2, 72.56, 72.6, 115.9, 116.1, 119.6, 122.0, 122.1, 129.4, 129.6, 134.6, 134.7, 144.7, 147.9, 177.9, 205.1. HRMS (ESI): calcd for $C_{11}H_{10}FNO_3$ $(M+Na)^+$ 246.0542, found 246.0561; $C_{11}H_{11}FNO_3$ $(M+H)^+$ 224.0723, found 224.0719. Enantiomeric excess of **13e** measured by chiral stationary phase HPLC analysis using a Chiralpak IA column (5:1 hexane/EtOH at 0.5 mL/min, 20 °C), t_{major} = 49.6 min, t_{minor} = 31.6 min.

4.4.6. (*S*)-5-Methyl-3-hydroxy-3-(2-oxopropyl)indolin-2-one 13f[8f]

White solid, 88% yield; Mp: 161–163 °C; $[\alpha]_D^{20} = -13.3$ (c 0.61 MeOH, 68% ee); enantiomeric excess of **13f** was measured by chiral stationary phase HPLC analysis using a Chiralpak IA column (5:1 hexane/EtOH at 0.5 mL/min, 20 °C), t_{major} = 23.4 min, t_{minor} = 27.1 min.

4.4.7. (*S*)-5-Chloro-3-hydroxy-3-(2-oxopropyl)indolin-2-one 13g[20a]

White solid, 83% yield; Mp: 158–160 °C. $[\alpha]_D^{20} = -15.1$ (c 0.47 MeOH, 70% ee); enantiomeric excess of **13g** was measured by chiral stationary phase HPLC analysis using a Chiralpak IA column (5:1 hexane/*i*-PrOH at 0.5 mL/min, 20 °C), t_{major} = 31.2 min, t_{minor} = 54.0 min.

4.4.8. (*S*)-5-Fluoro-3-hydroxy-3-(2-oxopropyl)indolin-2-one 13h[1b]

White solid, 92% yield; Mp: 183–185 °C; $[\alpha]_D^{20} = -40.1$ (c 0.71 MeOH, 88% ee); enantiomeric excess of **13h** was measured by chiral stationary phase HPLC analysis using a Chiralpak IA column (5:1 hexane/*i*-PrOH at 0.5 mL/min, 20 °C), t_{major} = 32.1 min, t_{minor} = 52.9 min.

4.4.9. (*S*)-5-Fluoro-3-hydroxy-3-(2-oxo-2-phenylethyl)-indolin-2-one 13i[1b]

White solid, 78% yield; Mp: 172–173 °C; $[\alpha]_D^{20} = -47.8$ (c 0.75 MeOH, 64% ee); enantiomeric excess of **13i** was measured by chiral stationary phase HPLC analysis using a Chiralpak IA column (5:1 hexane/EtOH at 0.5 mL/min, 20 °C), t_{major} = 62.0 min, t_{minor} = 110.6 min.

4.4.10. (*S*)-5-Fluoro-3-hydroxy-3-(2-(4-methoxyphenyl)-2-oxoethyl) indolin-2-one 13j

White solid, 79% yield; Mp: 170–172 °C; $[\alpha]_D^{20} = -52.6$ (c 0.82 MeOH, 72% ee). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.52–3.57 (d, J = 17.4 Hz, 1H), 3.83 (s, 3H), 4.03 (d, J = 17.7 Hz, 1H), 6.14 (s, 1H), 6.78 (q, 1H), 6.95–7.03 (m, 3H), 7.19 (dd, 1H) 7.87 (d, 2H), 10.25 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6); δ 45.8, 56.0, 73.8, 110.4, 110.5, 111.8, 112.2, 114.3, 115.1, 115.5, 129.6, 130.7, 134.1, 134.2, 139.6, 156.7, 159.8, 163.8, 178.9, 195.2; HRMS (ESI): calcd for $C_{17}H_{15}FNO_4$ $(M+H)^+$ 316.0985, found 316.0995; enantiomeric excess of the **13j** was measured by chiral stationary phase HPLC analysis using a Chiralpak IA column (1:1 hexane/EtOH at 0.5 mL/min, 20 °C), t_{major} = 22.6 min, t_{minor} = 45.3 min.

4.4.11. (*S*)-3-Hydroxy-3-(2-oxo-2-phenylethyl)indolin-2-one 13k[1b]

White solid, 79% yield; Mp: 173–175 °C; $[\alpha]_D^{20} = -45.7$ (*c* 0.47 MeOH, 58% ee); enantiomeric excess of **13k** was measured by chiral stationary phase HPLC analysis using a Chiralpak IA column (1:1 hexane/*i*-PrOH at 0.5 mL/min, 20 °C), $t_{major} = 17.2$ min, $t_{minor} = 27.4$ min.

4.4.12. (*S*)-3-Hydroxy-3-(2-(4-methoxyphenyl)-2-oxoethyl) indolin-2-one 13l[20b]

White solid, 80% yield; Mp: 181–183 °C; $[\alpha]_D^{20} = -83.5$ (*c* 0.86 MeOH, 68% ee); enantiomeric excess of the **13l** was measured by chiral stationary phase HPLC analysis using a Chiralpak IA column (1:1 hexane/*i*-PrOH at 0.5 mL/min, 20 °C), $t_{major} = 23.8$ min, $t_{minor} = 46.3$ min.

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