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Synthesis of Tridentate PNO Ligands with Planar Chirality and Application in Iridium-Catalyzed Asymmetric Hydrogenation of Simple Ketones

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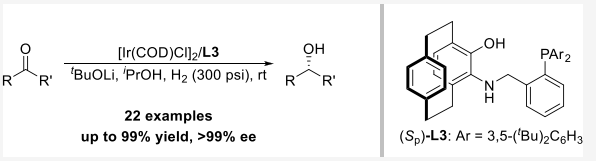
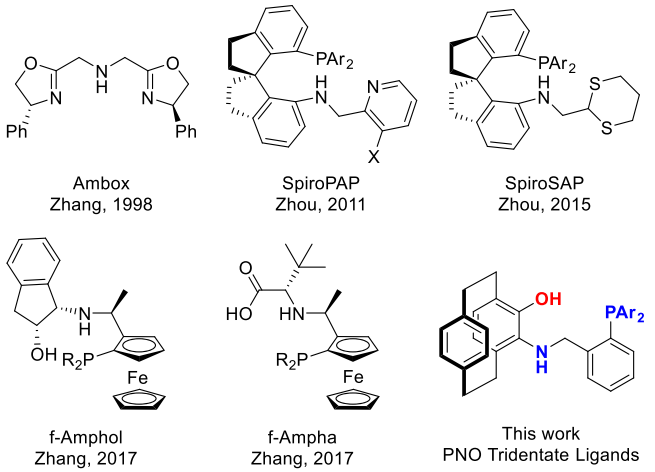
ABSTRACT: A series of [2,2]paracyclophane-based tridentate PNO ligands with planar chirality were designed and synthesized. The easily prepared chiral tridentate PNO ligands were successfully applied to the iridium-catalyzed asymmetric hydrogenation of simple ketones, giving chiral alcohols with high efficiency and excellent enantioselectivities (up to 99% yield and >99% ee). Control experiments revealed the indispensability of both N−H and O−H in the ligands.



Asymmetric hydrogenation of prochiral ketones is one of the most used and feasible reaction classes to achieve the corresponding valuable enantiopure alcohols due to its atom economy and high efficiency.[1] The milestone progress in this field was reported by Noyori's group in 1995,[2] which applied their [$RuCl_2$(diphosphine)-(diamine)] as catalyst to realize the asymmetric hydrogenation of ketones with excellent results. Encouraged by this landmark study, a myriad of tridentate ligands were developed for the asymmetric hydrogenation of prochiral ketones in the past few decades, and selected examples are displayed in Scheme 1.[3−8] For example, the NNN-type ligand Ambox was reported by Zhang's group and the PNS-type ligand was developed by Zhou's group. In 2011, Zhou's group reported a tridentate ligand based on a spiro amino phosphine skeleton.[6] By introducing an additional coordination group into the ligand, the formation of inactive dimerized complexes can be inhibited, and the hydrogenation of ketones was conducted with an iridium-SpiroPAP catalytic system to gain excellent results. Despite these fruitful outcomes, chiral PNO ligands were relatively less studied. Their applications to date mainly focused on ruthenium-catalyzed asymmetric hydrogenation or transfer hydrogenation,[7] and there still remains a noteworthy lacuna when it turns to iridium-catalyzed hydrogenation with the chiral PNO ligands. To the best of our knowledge, only Zhang's group developed chiral PNO tridentate ligands f-Amphol and f-Ampha with both planar chirality and central chirality for iridium-catalyzed asymmetric hydrogenation.[8] To widen the variety of tridentate PNO ligands and explore other possibilities in asymmetric catalysis, exploiting new tridentate PNO ligands with outstanding stability and deep chiral concave pockets was deemed necessary nonetheless.

[2.2]Paracyclophane as a chemically stable skeleton with distorted configuration and high steric bulkiness has received tremendous attention in recent years.[9] [2.2]Paracyclophanes have been utilized as an important toolbox in asymmetric catalysis. For instance, the commercially available phanephos has been employed in an extensive range of asymmetric reactions.[10] Furthermore, Guiry's group has recently reported new [2.2]paracyclophane-imidazoline N,O-ligands, and applied them in asymmetric Zn-catalyzed azomethine ylide cycloaddition.[11] Considering the ideal rigidity and stability of the [2,2]paracyclophane skeleton, we envisioned that [2,2]-

Scheme 1. Selected Examples of Tridentate Ligands in Asymmetric Hydrogenation of Ketones



Ambox Zhang, 1998 | SpiroPAP Zhou, 2011 | SpiroSAP Zhou, 2015

f-Amphol Zhang, 2017 | f-Ampha Zhang, 2017 | This work PNO Tridentate Ligands

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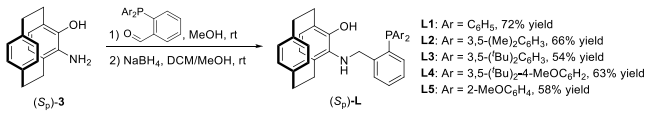
paracyclophane-based PNO tridentate ligands would be excellent candidates for iridium-catalyzed asymmetric hydrogenation. Herein, we report the synthesis of PNO tridentate ligands with planar chirality and their application in iridium-catalyzed asymmetric hydrogenation of simple ketones.

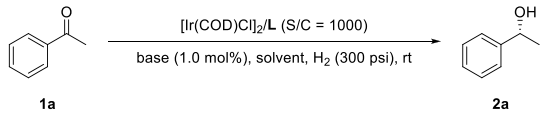
These planar-chiral tridentate PNO ligands were readily synthesized from the known (S_p)-**3**[12] by simple reductive amination with 2-diarylphosphanylbenzaldehydes in two steps with good or moderate yields (Scheme 2).

Scheme 2. Synthesis of Chiral Tridentate PNO Ligands



With the chiral tridentate PNO ligands in hand, we began our study by evaluating them in iridium-catalyzed hydrogenation of simple ketones. Acetophenone **1a** was selected as model substrate, and the solvent effect was investigated first with the catalyst generated *in situ* by mixing ligand **L1** with iridium precursor $[Ir(COD)Cl]_2$. Reactions were conducted under S/C = 1000. As shown in Table 1, the results

Table 1. Optimization of the Reaction Conditions



entry[a]	solvent	base	ligand	yield (%)[b]	ee (%)[c]
1	DCM	^{t}BuONa	**L1**	>95	72
2	THF	^{t}BuONa	**L1**	12	−6
3	toluene	^{t}BuONa	**L1**	>95	76
4	MeOH	^{t}BuONa	**L1**	8	29
5	EtOH	^{t}BuONa	**L1**	>95	79
6	^{i}PrOH	^{t}BuONa	**L1**	>95	81
7	^{i}PrOH	^{t}BuOLi	**L1**	>95	93
8	^{i}PrOH	^{t}BuOK	**L1**	93	71
9	^{i}PrOH	NaOH	**L1**	>95	79
10	^{i}PrOH	K_2CO_3	**L1**	trace	–
11	^{i}PrOH	Cs_2CO_3	**L1**	>95	44
12	^{i}PrOH	^{t}BuOLi	**L2**	96[d]	95
13	^{i}PrOH	^{t}BuOLi	**L3**	96[d]	97
14	^{i}PrOH	^{t}BuOLi	**L4**	94[d]	97
15	^{i}PrOH	^{t}BuOLi	**L5**	97[d]	95

[a]Reaction conditions: 2.0 mmol scale, S/C = 1000, 1.0 mol % base, 2.0 mL of solvent, rt. [b]Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c]Determined by HPLC. [d]Isolated yield.

demonstrated that the solvents played a crucial role in both reactivity and enantioselectivity (entries 1−6). The reaction proceeded smoothly in DCM, toluene, EtOH, and ^{i}PrOH with excellent reactivity and moderate enantioselectivity. However, when THF and MeOH were used, substrate **1a** barely converted to the corresponding **2a**. Through comparison, ^{i}PrOH was chosen as the best solvent. To further improve the enantioselectivity, several bases were screened (entries 6−11). Much to our delight, excellent yield and high enantioselectivity (>95% yield, 93% ee) could be achieved when ^{t}BuOLi was employed as base. Based on these encouraging results, the ligand effect of **L1**−**L5** was investigated at last (entries 12−15). A higher enantioselectivity and efficient conversion were obtained with **L3** and **L4** bearing hindered *tert*-butyl group. The introduction of a methyl or methoxy group led to minor influence of the reactivity and enantioselectivity.

With these established optimized conditions, we set out to explore the scope of prochiral ketones. A wide variety of alkyl aryl ketones were examined, and the results are summarized in Scheme 3. In most cases, the ketones were compatible with the mild reaction conditions, affording the corresponding chiral alcohols with high yields and excellent enantioselectivities, and no significant effect was observed, regardless of electronic properties, steric hindrance, or positions of substituents. To our delight, substrate acetylferrocene **1r** was hydrogenated smoothly, furnishing a pivotal ferrocene skeleton for the construction of chiral ligands. Hydrogenation of heteroaromatic ketone **1s** went successfully. However, only moderate enantioselectivity of 64% ee was observed, which might be ascribed to the coordination of oxygen atoms. In addition, a building block (**2t**) for a potent hNK-1 receptor antagonist could be obtained with 78% yield and 94% ee. Besides, hydrogenation of dialkyl and diaryl ketones were also considered. For ketone **1w**, which bears two alkyl groups, and **1x**, which bears two aryl groups, moderate enantioselectivity was afforded owing to the low differentiation of two alkyl or two aryl groups.

It is worth mentioning that a scale-up experiment with low catalyst loading was conducted as well. The same experimental results of substrate **1e** could be afforded when low catalyst loading (S/C = 10,000) was employed (98% yield, 98% ee, Scheme 4), and no erosion of enantioselectivity and yield was observed.

For a further understanding of the reaction mechanism, ligands **L6** and **L7** (Scheme 5) were synthesized to identify the indispensability of the O−H or N−H in our ligands. In accordance with expectations, the absence of either O−H or N−H resulted in trace amount of product **2a** (Scheme 5), which proved the integral role of both O−H and N−H in our PNO tridentate ligands.

Based on these control experiments and the putative mechanism of iridium-catalyzed asymmetric hydrogenation of simple ketones,[13] a plausible mechanism is proposed (Scheme 6). First, the PNO tridentate ligand reacted with iridium precursor, base, and hydrogen gas to form an iridium trihydride species. Then, Ir−H and N−H shifted to the C═O of the substrate through the transition state as shown in Scheme 6 to afford the chiral alcohol, and the iridium dihydride species was generated meanwhile. We reasoned that there remains a O−Li···O interaction between the catalyst and substrate.[13b] Subsequent hydrogenation of the iridium dihydride species under a hydrogen atmosphere should regenerate the reactive catalyst species.

Taken together, we have successfully developed a series of novel [2,2]paracyclophane-based tridentate PNO ligands with planar chirality, and applied them in iridium-catalyzed asymmetric hydrogenation of simple ketones with excellent results. Control experiments showed that N−H and O−H in the [2,2]paracyclophane-based tridentate PNO ligands are both necessary to proceed with iridium-catalyzed hydrogenation. Furthermore, the same results could be obtained when the catalyst loading decreased to S/C = 10,000. The outstanding performance of our ligands in asymmetric hydrogenation promoted us to investigate them in the

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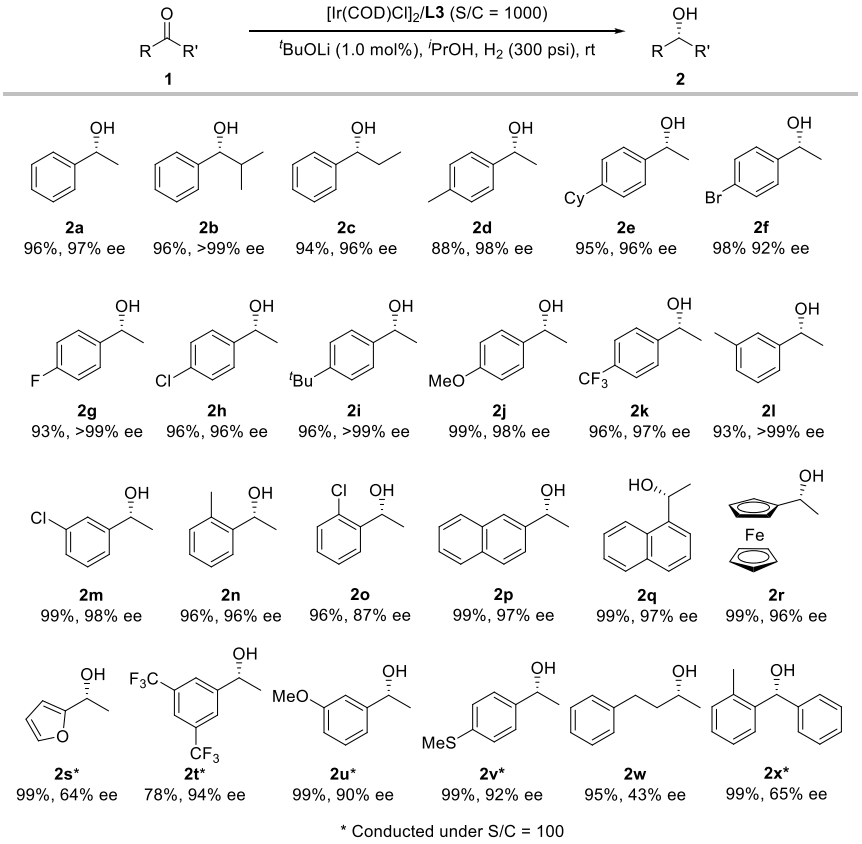
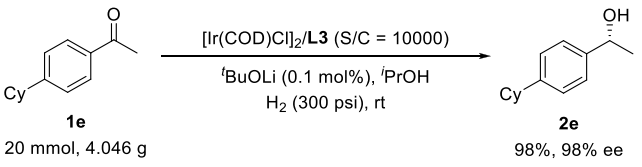
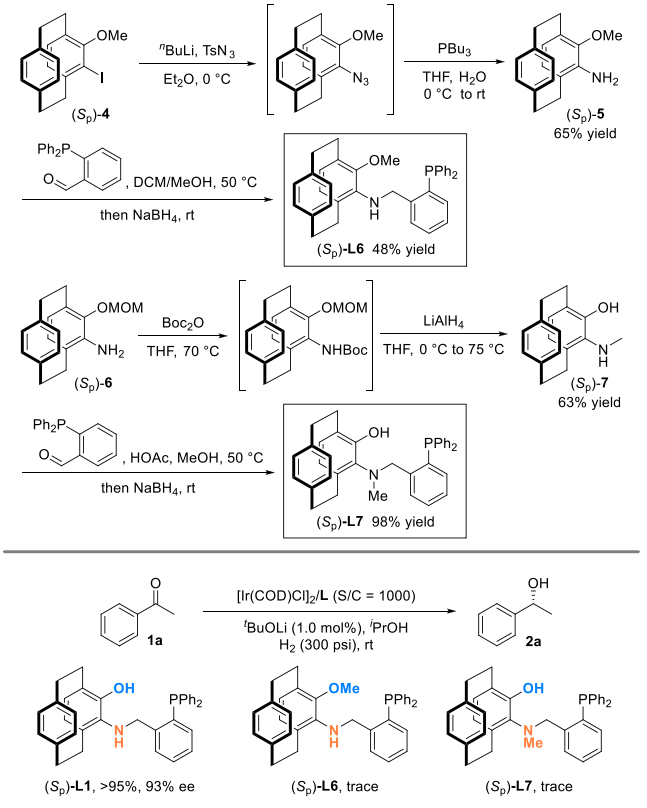
Scheme 3. Substrate Scope



Scheme 4. Scale-up Reaction under S/C = 10,000



Scheme 5. Synthesis of *N*- or *O*-Protected Chiral Ligands and Control Experiments



construction of other valuable chiral molecules in fine chemicals and pharmaceuticals.

EXPERIMENTAL SECTION

General Methods. 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{^{1}H} NMR, ^{19}F{^{1}H} NMR, and ^{31}P{^{1}H} NMR spectra were recorded at room temperature in $CDCl_3$ on 400 MHz instrument with TMS as internal standard. Enantiomeric excess was determined by HPLC analysis, using chiral column described below in detail. Optical rotations were measured by polarimeter. Flash column chromatography was performed on silica gel (200−300 mesh). The heat source for all heating reactions is the oil bath. High-resolution mass spectrometry (HRMS) was measured on an electrospray ionization (ESI) apparatus using the time-of-flight (TOF) mass spectrometry. All reactions were monitored by TLC analysis.

Materials. Aromatic ketones were purchased from commercial suppliers and purified by simple distillation or flash column chromatography prior to use. Other commercially available reagents and solvents were used throughout without further purification.

Procedures for Synthesis of Tridentate PNO Ligands with Planar Chirality. *Synthesis of Chiral Ligands (S_p)-L1−L5.* To a

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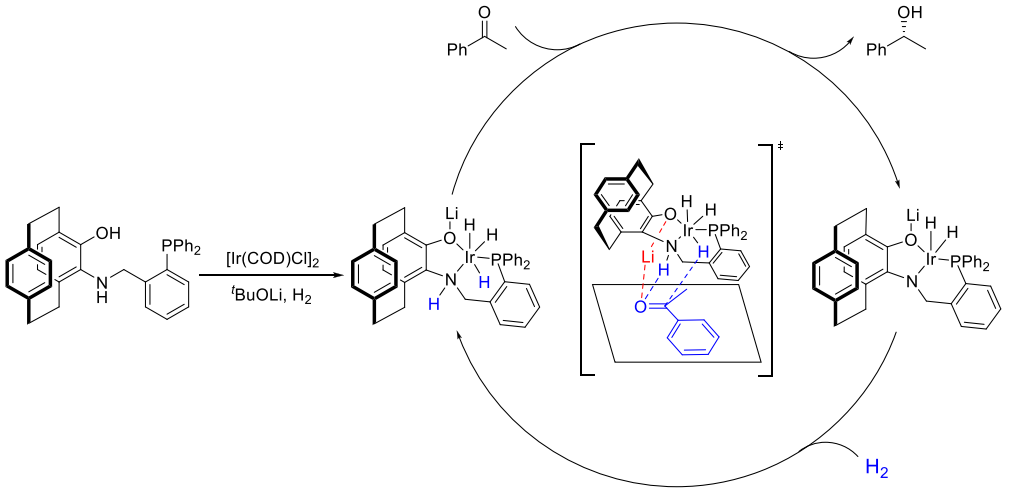
Scheme 6. Proposed Mechanism for Ir/PNO-Catalyzed Asymmetric Hydrogenation



solution of [2.2]paracyclophane-derived chiral amino-phenol (S_p)-**3** (0.421 g, 1.5 mmol) in methanol (15 mL, 0.10 M) was added 2-diarylphosphanylbenzaldehydes (1.5 mmol) at room temperature. The reaction mixture was stirred for 5 h. After the reaction was complete as monitored by TLC, the volatiles were removed under the reduced pressure. To a solution of the residue in dichloromethane (5.0 mL) and methanol (5.0 mL) was added sodium borohydride (0.340 g, 9.0 mmol) at room temperature and the mixture was stirred for 3 h. The reaction was quenched with water (5.0 mL) and extracted three times with dichloromethane (3 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtrated, and concentrated under the reduced pressure. The crude residue was purified by flash column chromatography using hexanes/ethyl acetate as eluent to afford the corresponding [2.2]-paracyclophane-derived chiral tridentate PNO ligands (S_p)-**L1**−**L5**.

(−)-(S_p)-5-Hydroxy-4-((2-diphenylphosphinophenyl)-benzylamino)-[2.2]paracyclophane ***(L1)***. 0.537 g, 72% yield, pale yellow oil, new compound, R_f = 0.55 (hexanes/ethyl acetate 10/1). $[\alpha]^{20}_D$ = −13.76 (*c* 0.85, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.24 (m, 13H), 7.18 (brs, 1H), 7.11−7.02 (m, 1H), 6.60−6.52 (m, 1H), 6.43−6.35 (m, 2H), 6.27 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.15 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.76−5.67 (m, 1H), 4.21−3.72 (m, 2H), 3.50−3.24 (m, 1H), 3.12−2.82 (m, 4H), 2.77−2.44 (m, 3H), 2.39 (brs, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.2, 144.4, 144.1, 139.6, 137.4, 137.23, 137.15, 137.0, 136.9, 136.0, 135.9, 135.28, 135.26, 134.1, 133.9, 133.7, 133.6, 133.4, 133.0, 132.1, 130.6, 130.2, 130.1, 129.7, 128.94, 128.91, 128.8, 128.74, 128.67, 128.4, 127.3, 126.9, 126.6, 125.0, 53.9, 53.7, 33.8, 33.7, 30.90, 30.88, 30.3. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ −17.19. HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{35}H_{32}NOPNa$ 536.2114, found 536.2111.

(−)-(S_p)-5-Hydroxy-4-((2-bis(3,5-dimethylphenyl)-phosphinophenyl)benzylamino)-[2.2]paracyclophane ***(L2)***. 0.134 g, 66% yield (0.36 mmol scale), pale yellow oil, new compound, R_f = 0.56 (hexanes/ethyl acetate 10/1). $[\alpha]^{20}_D$ = −25.38 (*c* 0.78, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.27 (m, 3H), 7.15−7.10 (m, 1H), 6.97 (t, *J* = 7.8 Hz, 6H), 6.56 (d, *J* = 7.8 Hz, 1H), 6.48−6.33 (m, 2H), 6.31−6.21 (m, 1H), 6.19−6.10 (m, 1H), 5.71 (d, *J* = 7.8 Hz, 1H), 4.07- 3.90 (m, 2H), 3.42−3.27 (m, 1H), 3.08−2.86 (m, 4H), 2.70−2.45 (m, 3H), 2.28 (d, *J* = 2.2 Hz, 12H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.2, 144.3, 144.1, 139.6, 138.1, 138.0, 137.5, 137.03, 136.96, 136.74, 136.69, 136.5, 136.3, 135.28, 135.26, 134.2, 134.1, 133.0, 132.1, 131.7, 131.5, 131.3, 131.1, 130.74, 130.68, 130.6, 130.12, 130.05, 129.5, 128.2, 127.3, 127.0, 126.5, 124.9, 53.9, 53.7, 33.8, 33.7, 30.9, 30.3, 21.7, 21.5, 21.4. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ −17.41. HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{39}H_{41}NOP$ 570.2920, found 570.2925.

(−)-(S_p)-5-Hydroxy-4-((2-bis(3,5-di-tert-butylphenyl)-phosphinophenyl)benzylamino)-[2.2]paracyclophane ***(L3)***. 0.167 g, 54% yield (0.42 mmol scale), pale yellow oil, new compound, R_f = 0.58 (hexanes/ethyl acetate 10/1). $[\alpha]^{20}_D$ = −19.60 (*c* 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.25 (m, 5H), 7.15−7.06 (m, 4H), 7.04- 6.98 (m, 1H), 6.55 (d, *J* = 7.8 Hz, 1H), 6.43−6.32 (m, 2H), 6.27 (d, *J* = 7.8 Hz, 1H), 6.13 (d, *J* = 7.9 Hz, 1H), 5.76 (d, *J* = 7.9 Hz, 1H), 4.12 (d, *J* = 12.4 Hz, 1H), 3.95 (d, *J* = 12.4 Hz, 1H), 3.41−3.23 (m, 1H), 3.13−2.77 (m, 4H), 2.65−2.44 (m, 3H), 1.24 (s, 36H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.3, 150.8, 150.74, 150.68, 144.2, 144.0, 139.5, 137.5, 137.2, 137.1, 136.2, 136.0, 134.9, 134.6, 134.1, 133.0, 132.1, 130.7, 130.1, 129.3, 128.1, 127.9, 127.8, 127.6, 127.3, 126.9, 126.3, 124.9, 122.7, 122.6, 53.8, 53.6, 34.9, 33.8, 33.7, 31.4, 31.0, 30.3, 29.8. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ −15.37. HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{51}H_{65}NOP$ 738.4798, found 738.4798.

(−)-(S_p)-5-Hydroxy-4-((2-bis(3,5-di-tert-butyl-4-methoxyphenyl)-phosphinophenyl)benzylamino)-[2.2]paracyclohane ***(L4)***. 0.181 g, 63% yield (0.36 mmol scale), pale yellow oil, new compound, R_f = 0.55 (hexanes/ethyl acetate 10/1). $[\alpha]^{20}_D$ = −22.86 (*c* 0.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.27 (m, 3H), 7.10 (d, *J* = 7.8 Hz, 4H), 7.04−6.93 (m, 1H), 6.58 (d, *J* = 7.8 Hz, 1H), 6.44−6.34 (m, 2H), 6.27 (d, *J* = 7.9 Hz, 1H), 6.14 (d, *J* = 7.9 Hz, 1H), 5.80−5.71 (m, 1H), 4.10 (d, *J* = 12.2 Hz, 1H), 3.94 (d, *J* = 12.2 Hz, 1H), 3.66 (s, 3H), 3.62 (s, 3H), 3.38−3.28 (m, 1H), 3.08−2.84 (m, 4H), 2.70−2.46 (m, 3H), 1.33 (s, 36H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.2, 160.1, 151.3, 143.8, 143.74, 143.71, 143.68, 139.5, 137.5, 137.4, 134.7, 134.5, 134.1, 133.0, 132.3, 132.14, 132.08, 132.0, 131.8, 130.7, 130.1, 129.3, 128.0, 127.4, 127.0, 126.4, 124.9, 64.4, 64.3, 53.8, 53.7, 35.90, 35.88, 33.9, 33.7, 32.0, 31.0, 30.3. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ −17.75. HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{53}H_{69}NO_3P$ 798.5010, found 798.5010.

(−)-(S_p)-5-Hydroxy-4-((2-bis(2-methoxyphenyl)-phosphinophenyl)benzylamino)-[2.2]paracyclophane ***(L5)***. 0.183 g, 58% yield (0.55 mmol scale), pale yellow oil, new compound, R_f = 0.35 (hexanes/ethyl acetate 10/1). $[\alpha]^{20}_D$ = −28.54 (*c* 1.10, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.26 (m, 4H), 7.25−7.20 (m, 1H), 7.05−6.98 (m 1H), 6.96−6.86 (m, 4H), 6.84−6.78 (m, 1H), 6.75−6.68 (m, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 6.42- 6.34 (m, 2H), 6.25 (d, *J* = 7.8 Hz, 1H), 6.13 (d, *J* = 7.7 Hz, 1H), 5.71 (d, *J* = 7.7 Hz, 1H), 4.14−3.89 (m, 2H), 3.83 (s, 3H), 3.72 (s, 3H), 3.40−3.28 (m, 1H), 3.13−2.83 (m, 4H), 2.66−2.48 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.5, 161.3, 161.2, 161.1, 151.3, 144.5, 144.3, 139.5, 137.7, 136.2, 136.1, 135.2, 134.4, 134.3, 133.9, 133.5, 132.9, 132.1, 130.5, 130.4, 130.3, 129.93, 129.86, 129.3, 128.1, 127.2, 127.0, 126.5, 125.14, 125.05, 124.9, 124.8, 124.7, 121.1, 120.9, 110.51, 110.49, 110.31, 110.29, 55.8, 55.6, 53.7, 53.6, 33.7, 31.0, 30.9, 30.4. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$) δ −37.99. HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{37}H_{37}NO_3P$ 574.2506, found 574.2517.

*Synthesis of Chiral Ligands (S_p)-**L6***. To a solution of [2.2]-paracyclophane-derived chiral iodoanisol (S_p)-**4** (0.136 g, 0.4 mmol)

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in ethyl ether (15 mL, 0.03 M) was added *n*-butyllithium (1.6 M in hexanes, 0.3 mL, 0.5 mmol) dropwise at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. Then, 4-toluenesulfonyl azide (0.110 g, 0.6 mmol) was added. After the reaction was complete as monitored by TLC, the reaction was quenched with water (5.0 mL) and extracted three times with dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate, filtrated, and concentrated under the reduced pressure. The residue was passed through a plug of silica gel to afford the azide.

To a solution of the intermediate azide (0.072 g, 0.3 mmol, 0.15 M) in tetrahydrofuran (2.0 mL) was added tributylphosphine (0.105 g, 0.5 mmol) and water (0.3 mL) at 0 °C. The reaction mixture was stirred at room temperature. After the reaction was complete as monitored by TLC, the reaction mixture was dried over anhydrous sodium sulfate, filtrated, and concentrated under the reduced pressure. The crude residue was further purified by flash column chromatography using hexanes/ethyl acetate as eluent to afford the chiral amine (S_p)-**5**. To a solution of chiral amine (S_p)-**5** (0.035 g, 0.14 mmol) in dichloromethane (1.0 mL) and methanol (3.0 mL) was added 2-diphenylphosphinobenzaldehyde (0.041 g, 0.14 mmol) at room temperature; the mixture was stirred at 50 °C. After the reaction was complete as monitored by TLC, sodium borohydride (0.227 g, 6.0 mmol) was added to the above mixture at room temperature. After the reaction was complete as monitored by TLC, the reaction was quenched with water (5.0 mL) and extracted three times with dichloromethane (3 × 5 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtrated, and concentrated under the reduced pressure. The residue was further purified by flash column chromatography using hexanes/ethyl acetate as eluent to afford the corresponding chiral tridentate PNO ligand (S_p)-**L6**.

(+)-(S_p)-5-Methoxy-4-amino-[2.2]paracyclophane ***(5)***. 0.035 g, 65% yield, white solid, mp 154−156 °C, new compound, R_f = 0.15 (hexanes/ethyl acetate 10/1). $[\alpha]^{20}_D$ = +12.45 (*c* 0.40, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (dd, *J* = 7.8, 1.9 Hz, 1H), 6.63 (dd, *J* = 7.7, 1.9 Hz, 1H), 6.52 (dd, *J* = 7.8, 2.0 Hz, 1H), 6.42 (dd, *J* = 7.8, 2.0 Hz, 1H), 6.18 (d, *J* = 7.8 Hz, 1H), 6.09 (d, *J* = 7.8 Hz, 1H), 3.61 (s, 3H), 3.55 (brs, 2H), 3.21−3.11 (m, 1H), 3.07−2.92 (m, 5H), 2.69−2.53 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 146.6, 139.00, 138.97, 138.0, 132.6, 132.2, 132.1, 130.1, 128.2, 126.6, 125.8, 124.0, 60.1, 34.2, 32.9, 31.1, 30.6. HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{20}NO$ 254.1539, found 254.1541.

(+)-(S_p)-5-Methoxy-4-((2-diphenylphosphinophenyl)-benzylamino)-[2.2]paracyclophane ***(L6)***. 0.036 g, 48% yield, pale yellow oil, new compound, R_f = 0.63 (hexanes/ethyl acetate 10/1). $[\alpha]^{20}_D$ = +27.80 (*c* 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.57−7.50 (m, 1H), 7.42−7.24 (m, 11H), 7.22−7.14 (m, 1H), 6.94−6.85 (m, 1H), 6.79−6.73 (m, 1H), 6.54−6.39 (m, 3H), 6.21 (d, *J* = 7.9 Hz, 1H), 6.14 (d, *J* = 7.9 Hz, 1H), 4.56−4.46 (m, 1H), 4.25−4.17 (m, 1H), 3.78 (brs, 1H), 3.34 (s, 3H), 3.26−3.15 (m, 1H), 3.14−2.86 (m, 5H), 2.61−2.48 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.6, 145.0, 144.7, 141.5, 139.0, 138.7, 136.8, 136.7, 136.5, 136.4, 135.5, 135.4, 134.1, 134.0, 133.9, 133.8, 133.6, 132.5, 132.3, 131.9, 131.8, 131.4, 129.2, 128.9, 128.8, 128.73, 128.66, 128.59, 128.55, 128.5, 128.2, 127.8, 127.5, 126.9, 60.90, 60.89, 51.7, 51.5, 34.1, 33.7, 30.7, 23.0. $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ −15.81. HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{36}H_{35}NOP$ 528.2451, found 528.2455.

Synthesis of Chiral Ligands (S_p)-L7. To a solution of chiral amine (S_p)-**6** (0.169 g, 0.6 mmol) in tetrahydrofuran (3.0 mL, 0.20 M) was added di-*tert*-butyl dicarbonate (0.169 g, 0.6 mmol) at room temperature. The reaction mixture was stirred at 75 °C. After the reaction was complete as monitored by TLC, the volatiles were removed under the reduced pressure. The residue was passed through a plug of silica gel to afford the intermediate.

To a solution of the intermediate amide (0.190 g, 0.5 mmol) in tetrahydrofuran (5.0 mL, 0.10 M) was added lithium aluminum hydride (0.076 g, 2.0 mmol) at 0 °C. The reaction mixture was then stirred at 75 °C. After the reaction was complete as monitored by TLC, the reaction was quenched with saturated aqueous solution of potassium sodium tartrate (10.0 mL) and extracted three times with ethyl acetate (3 × 5 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtrated, and concentrated under the reduced pressure. The residue was further purified by flash column chromatography using hexanes/ethyl acetate as eluent to afford (S_p)-**7**. To a solution of (S_p)-**7** (0.025 g, 0.1 mmol) in methanol (1.0 mL) was added acetic acid (3 drops) and 2-diphenylphosphinobenzaldehyde (0.029 g, 0.1 mmol) at room temperature. The reaction mixture was stirred at 50 °C for 6 h. Then, sodium borohydride (0.019 g, 0.5 mmol) was added to the reaction mixture at room temperature. After the reaction was complete as monitored by TLC, the reaction was quenched with water (5.0 mL) and extracted three times with dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate, filtrated, and concentrated under the reduced pressure. The residue was further purified by flash column chromatography using hexanes/ethyl acetate as eluent to afford the corresponding [2.2]paracyclophane-derived chiral tridentate PNO ligand (S_p)-**L7**.

(−)-(S_p)-5-Hydroxy-4-methylamino-[2.2]paracyclophane ***(7)***. 0.079 g, 63% yield (two steps), mp 169−170 °C, pale yellow solid, new compound, R_f = 0.35 (hexanes/ethyl acetate 5/1). $[\alpha]^{20}_D$ = −15.20 (*c* 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 6.86−6.75 (m, 1H), 6.60−6.41 (m, 3H), 6.28 (d, *J* = 7.9 Hz, 1H), 6.19 (d, *J* = 7.9 Hz, 1H), 3.33−3.23 (m, 1H), 3.11−2.96 (m, 4H), 2.89−2.80 (m, 1H), 2.77−2.67 (m, 1H), 2.63−2.58 (m, 1H), 2.55 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.1, 139.6, 137.7, 135.7, 133.9, 133.1, 132.3, 130.3, 127.1, 126.5, 126.1, 125.6, 36.3, 33.9, 33.7, 30.9, 30.2. HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{20}O$ 254.1539, found 254.1540.

(−)-(S_p)-5-Hydroxy-4-((2-diphenylphosphinophenyl)(benzyl-(methyl)amino))-[2.2]paracyclophane ***(L7)***. 0.052 g, 98% yield, colorless oil, new compound, R_f = 0.80 (hexanes/ethyl acetate 10/1). $[\alpha]^{20}_D$ = −110.39 (*c* 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.33−8.20 (m, 1H), 7.64−7.57 (m, 1H), 7.44−7.21 (m, 12H), 7.12−7.07 (m, 1H), 7.06−7.00 (m, 1H), 6.56−6.46 (m, 2H), 6.44−6.35 (m, 1H), 6.33−6.25 (m, 1H), 6.02−5.91 (m, 2H), 3.20−3.09 (m, 1H), 3.06−2.90 (m, 2H), 2.74- 2.65 (m, 1H), 2.62 (s, 3H), 2.60−2.46 (m, 2H), 2.32−2.22 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.0, 141.1, 140.9, 140.5, 139.3, 138.4, 138.2, 138.1, 137.5, 137.4, 136.8, 136.7, 134.7, 134.2, 134.1, 134.0, 133.9, 132.0, 131.8, 129.4, 129.3, 128.8, 128.60, 128.56, 128.53, 128.48, 128.43, 128.36, 128.2, 127.53, 127.47, 127.3, 126.7, 124.2, 120.9, 98.2, 98.0, 36.1, 34.2, 34.0, 31.7, 28.0. $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$) δ −17.58. HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{36}H_{35}NOP$ 528.2451, found 528.2450.

General Procedure for Iridium-Catalyzed Asymmetric Hydrogenation of Ketones. A mixture of $[Ir(COD)Cl]_2$ (0.7 mg, 0.05 mol %) and ligand (S_p)-**L3** (1.6 mg, 0.11 mol %) in isopropanol (1.0 mL) was stirred in a vial at room temperature for 1 h in a glovebox to give the catalyst solution. To another vial was added lithium *tert*-butoxide (1.6 mg, 0.02 mmol), **1** (2.0 mmol), isopropanol (1.0 mL), and the catalyst solution (1.0 mL). Then the mixture was transferred to an autoclave which was then charged with hydrogen gas (300 psi) and stirred at room temperature for 23 h. After careful release of the hydrogen gas, the autoclave was opened and the volatiles were removed under the reduced pressure. The crude residue was purified by silica gel column chromatography (hexanes/ethyl acetate 10/1) to give the reductive products **2**. The enantiomeric excesses were determined by chiral HPLC.

For substrates **2s**−**2v** and **2x**, the catalyst loading was 1 mol % (S/C = 100), and the amount of lithium *tert*-butoxide was 10 mol %. The reactions were conducted under 0.6, 0.3, 0.4, 0.4, and 0.2 mmol scale with isopropanol (2.0 mL), respectively.

Procedure of Asymmetric Hydrogenation of Substrate ***1e*** *under S/C = 10,000.* A mixture of $[Ir(COD)Cl]_2$ (0.7 mg, 0.005 mol %) and ligand (S_p)-**L3** (1.6 mg, 0.011 mol %) in isopropanol (1.0 mL) was stirred in a vial at room temperature for 1 h in a glovebox to give the catalyst solution. To another vial was added lithium *tert*-butoxide (1.6 mg, 0.02 mmol), **1e** (4.046 g, 20.0 mmol), isopropanol (11 mL) and the catalyst solution (1.0 mL). Then the mixture was transferred to an autoclave which was then charged with hydrogen gas (300 psi) and

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stirred at room temperature for 23 h. After careful release of the hydrogen gas, the autoclave was opened and the volatiles were removed under the reduced pressure. The crude residue was purified by silica gel column chromatography (hexanes/ethyl acetate 10/1) to give the reductive products **2e**. The enantiomeric excesses were determined by chiral HPLC.

(+)-(R)-1-Phenylethanol ***(2a)***. 0.234 g, 96% yield, colorless oil, R_f = 0.22 (hexanes/ethyl acetate 10/1), 97% ee, $[\alpha]^{20}_D$ = +58.19 (*c* 1.05, $CHCl_3$), [lit.:[8a] 99.7% ee, $[\alpha]^{20}_D$ = +53.1 (*c* = 1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 4H), 7.29−7.24 (m, 1H), 4.86 (q, *J* = 6.5 Hz, 1H), 2.13 (brs, 1H), 1.47 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.9, 128.5, 127.5, 125.4, 70.4, 25.2. HPLC (Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 10.3 min (major), 11.8 min (minor).

(+)-(R)-2-Methyl-1-phenylpropanol ***(2b)***. 0.289 g, 96% yield, colorless oil, R_f = 0.22 (hexanes/ethyl acetate 10/1), > 99% ee, $[\alpha]^{20}_D$ = +42.21 (*c* 1.04, $CHCl_3$), [lit.:[8a] >99% ee, $[\alpha]^{20}_D$ = +41.6 (*c* = 1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.25 (m, 5H), 4.36 (d, *J* = 6.8 Hz, 1H), 2.03−1.91 (m, 1H), 1.87 (brs, 1H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.7, 128.2, 127.4, 126.6, 80.1, 35.3, 19.0, 18.3. HPLC (Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 9.8 min (major).

(+)-(R)-1-Phenylpropanol ***(2c)***. 0.255 g, 94% yield, colorless oil, R_f = 0.22 (hexanes/ethyl acetate 10/1), 96% ee, $[\alpha]^{20}_D$ = +47.31 (*c* 1.08, $CHCl_3$), [lit.:[8a] >99% ee, $[\alpha]^{20}_D$ = +46.9 (*c* = 1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.31 (m, 4H), 7.30−7.25 (m, 1H), 4.58 (t, *J* = 6.6 Hz, 1H), 1.97 (brs, 1H), 1.89−1.66 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.6, 128.4, 127.5, 126.0, 76.0, 31.9, 10.2. HPLC (Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 98/2, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 13.5 min (major), 14.6 min (minor).

(+)-(R)-1-(4-Methylphenyl)ethanol ***(2d)***. 0.240 g, 88% yield, colorless oil, R_f = 0.22 (hexanes/ethyl acetate 10/1), 98% ee, $[\alpha]^{20}_D$ = +54.51 (*c* 1.02, $CHCl_3$), [lit.:[8a] >99% ee, $[\alpha]^{20}_D$ = +58.9 (*c* = 1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.9 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 4.84 (q, *J* = 6.5 Hz, 1H), 2.34 (s, 3H), 1.98 (brs, 1H), 1.46 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.9, 137.2, 129.2, 125.4, 70.3, 25.1, 21.1. HPLC (Chiralpak AD-H column, *n*-Hexane/*i*-PrOH = 98/2, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 13.6 min (major), 14.6 min (minor).

(+)-(R)-1-(4-Cyclohexylphenyl)ethanol ***(2e)***. 0.387 g, 95% yield, white solid, R_f = 0.25 (hexanes/ethyl acetate 10/1), 96% ee, $[\alpha]^{20}_D$ = +36.18 (*c* 1.10, $CHCl_3$), [lit.:[8b] >99% ee, $[\alpha]^{20}_D$ = +38.2 (*c* = 1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 4.84 (q, *J* = 6.5 Hz, 1H), 2.56−2.42 (m, 1H), 2.00−1.66 (m, 6H), 1.47 (d, *J* = 6.5 Hz, 3H), 1.44−1.14 (m, 5H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 147.5, 143.2, 127.0, 125.5, 70.3, 44.3, 34.5, 26.9, 26.2, 25.0. HPLC (Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 8.0 min (major), 8.6 min (minor).

(+)-(R)-1-(4-Bromophenyl)ethanol ***(2f)***. 0.394 g, 98% yield, colorless oil, R_f = 0.22 (hexanes/ethyl acetate 10/1), 92% ee, $[\alpha]^{20}_D$ = +38.25 (*c* 1.03, $CHCl_3$), [lit.:[8a] >99% ee, $[\alpha]^{20}_D$ = +39.4 (*c* = 1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 4.86 (q, *J* = 6.5 Hz, 1H), 1.95 (brs, 1H), 1.46 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.8, 131.6, 127.2, 121.2, 69.8, 25.3. HPLC (Chiralcel OD-H column, *n*-Hexane/ *i*-PrOH = 95/5, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 10.3 min (minor), 11.4 min (major).

(+)-(R)-1-(4-Fluorophenyl)ethanol ***(2g)***. 0.261 g, 93% yield, colorless oil, R_f = 0.22 (hexanes/ethyl acetate 10/1), > 99% ee, $[\alpha]^{20}_D$ = +49.27 (*c* 0.97, $CHCl_3$), [lit.:[8a] >99% ee, $[\alpha]^{20}_D$ = +49.7 (*c* = 1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 2H), 7.06−6.97 (m, 2H), 4.86 (q, *J* = 6.5 Hz, 1H), 2.12 (brs, 1H), 1.46 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.1 (d, $^1J_{C-F}$ = 245.2 Hz), 141.5 (d, $^4J_{C-F}$ = 3.2 Hz), 127.1 (d, $^3J_{C-F}$ = 8.0 Hz), 115.3 (d, $^2J_{C-F}$ = 21.2 Hz), 69.8, 25.3. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −115.34. HPLC (Chiralpak AS-H column, *n*-Hexane/*i*-PrOH = 98/2, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 13.4 min (major).

(+)-(R)-1-(4-Chlorophenyl)ethanol ***(2h)***. 0.301 g, 96% yield, colorless oil, R_f = 0.22 (hexanes/ethyl acetate 10/1), 96% ee, $[\alpha]^{20}_D$ = +46.11 (*c* 1.03, $CHCl_3$), [lit.:[8a] >99% ee, $[\alpha]^{20}_D$ = +51.3 (*c* = 1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.27 (m, 4H), 4.86 (q, *J* = 6.5 Hz, 1H), 2.06 (brs, 1H), 1.46 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.3, 133.1, 128.6, 126.8, 69.8, 25.3. HPLC (Chiralcel OJ-H column, *n*-Hexane/*i*-PrOH = 98/2, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 16.1 min (minor), 17.8 min (major).

(+)-(R)-1-(4-tert-Butylphenyl)ethanol ***(2i)***. 0.344 g, 96% yield, white solid, R_f = 0.30 (hexanes/ethyl acetate 10/1), > 99% ee, $[\alpha]^{20}_D$ = +44.60 (*c* 1.00, $CHCl_3$), [lit.:[8a] >99% ee, $[\alpha]^{20}_D$ = +47.8 (*c* = 1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.84 (q, *J* = 6.5 Hz, 1H), 1.48 (d, *J* = 6.5 Hz, 3H), 1.32 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.5, 142.8, 125.4, 125.2, 70.2, 34.5, 31.4, 25.0. HPLC (Chiralpak AD-H column, *n*-Hexane/*i*-PrOH = 98/2, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 10.5 min (major).

(+)-(R)-1-(4-Methoxyphenyl)ethanol ***(2j)***. 0.304 g, 99% yield, colorless oil, R_f = 0.16 (hexanes/ethyl acetate 10/1), 98% ee, $[\alpha]^{20}_D$ = +52.00 (*c* 1.00, $CHCl_3$), [lit.:[15] 94.4% ee, $[\alpha]^{20}_D$ = +52.4 (*c* = 1.18, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.83 (q, *J* = 6.5 Hz, 1H), 3.79 (s, 3H), 1.97 (brs, 1H), 1.46 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.0, 138.0, 126.7, 113.8, 70.0, 55.3, 25.1. HPLC (Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 13.7 min (major), 15.6 min (minor).

(+)-(R)-1-(4-Trifluoromethylphenyl)ethanol ***(2k)***. 0.380 g, 96% yield, colorless oil, R_f = 0.19 (hexanes/ethyl acetate 10/1), 97% ee, $[\alpha]^{20}_D$ = +34.34 (*c* 1.06, $CHCl_3$), [lit.:[8a] >99% ee, $[\alpha]^{20}_D$ = +35.2 (*c* = 1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 4.93 (q, *J* = 6.6 Hz, 1H), 2.45−2.19 (m, 1H), 1.48 (d, *J* = 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.7, 129.6 (q, $^2J_{C-F}$ = 32.3 Hz), 125.7, 125.4 (q, $^3J_{C-F}$ = 3.7 Hz), 124.2 (q, $^1J_{C-F}$ = 270.0 Hz), 69.8, 25.3. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −62.45. HPLC (Chiralcel OJ-H column, *n*-Hexane/*i*-PrOH = 98/2, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 14.0 min (minor), 15.4 min (major).

(+)-(R)-1-(3-Methylphenyl)ethanol ***(2l)***. 0.252 g, 93% yield, colorless oil, R_f = 0.23 (hexanes/ethyl acetate 10/1), > 99% ee, $[\alpha]^{20}_D$ = +51.44 (*c* 1.04, $CHCl_3$), [lit.:[8a] >99% ee, $[\alpha]^{20}_D$ = +51.3 (*c* = 1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.21 (m, 1H), 7.20−7.11 (m, 2H), 7.10−7.04 (m, 1H), 4.83 (q, *J* = 6.5 Hz, 1H), 2.35 (s, 3H), 2.03 (brs, 1H), 1.47 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.8, 138.2, 128.4, 128.2, 126.1, 122.5, 70.4, 25.2, 21.5. HPLC (Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 9.0 min (major).

(+)-(R)-1-(3-Chlorophenyl)ethanol ***(2m)***. 0.311 g, 99% yield, colorless oil, R_f = 0.21 (hexanes/ethyl acetate 10/1), 98% ee, $[\alpha]^{20}_D$ = +38.47 (*c* 1.05, $CHCl_3$), [lit.:[8a] >99% ee, $[\alpha]^{20}_D$ = +43.6 (*c* = 1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.34 (m, 1H), 7.29−7.19 (m, 3H), 4.85 (q, *J* = 6.5 Hz, 1H), 2.13 (brs, 1H), 1.46 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 147.9, 134.4, 129.8, 127.5, 125.6, 123.6, 69.8, 25.3. HPLC (Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 98/2, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 16.2 min (minor), 17.2 min (major).

(+)-(R)-1-(2-Methylphenyl)ethanol ***(2n)***. 0.261 g, 96% yield, colorless oil, R_f = 0.22 (hexanes/ethyl acetate 10/1), 96% ee, $[\alpha]^{20}_D$ = +73.14 (*c* 1.08, $CHCl_3$), [lit.:[8a] >99% ee, $[\alpha]^{20}_D$ = +77.0 (*c* = 1.0, $CHCl_3$)]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.45 (m, 1H), 7.26−7.09 (m, 3H), 5.10 (q, *J* = 6.4 Hz, 1H), 2.32 (s, 3H), 1.91 (s, 1H), 1.44 (d, *J* = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.9, 134.2, 130.4, 127.2, 126.4, 124.5, 66.8, 24.0, 19.0. HPLC (Chiralpak AD-H column, *n*-Hexane/*i*-PrOH = 98/2, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 14.0 min (major), 15.9 min (minor).

(+)-(R)-1-(2-Chlorophenyl)ethanol ***(2o)***. 0.301 g, 96% yield, colorless oil, R_f = 0.20 (hexanes/ethyl acetate 10/1), 87% ee, $[\alpha]^{20}_D$ = +59.26 (*c* 1.07, $CHCl_3$), [lit.:[8a] 99.2% ee, $[\alpha]^{20}_D$ = +58.6 (*c* =

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1.0, $CHCl_3$)]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62−7.53 (m, 1H), 7.37−7.24 (m, 2H), 7.23−7.15 (m, 1H), 5.27 (q, J = 6.4 Hz, 1H), 2.23 (s, 1H), 1.47 (d, J = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.1, 131.6, 129.4, 128.4, 127.2, 126.4, 67.0, 23.5. HPLC (Chiralcel OJ-H column, *n*-Hexane/*i*-PrOH = 98/2, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 14.9 min (minor), 15.7 min (major).

(+)-(R)-1-(2-Naphthyl)ethanol ***(2p)***. 0.342 g, 99% yield, white solid, R_f = 0.14 (hexanes/ethyl acetate 10/1), 97% ee, $[\alpha]^{20}_D$ = +50.28 (c 1.07, $CHCl_3$), [lit.:[8a] >99% ee, $[\alpha]^{20}_D$ = +50.2 (c = 1.0, $CHCl_3$)]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85−7.74 (m, 4H), 7.51−7.41 (m, 3H), 5.01 (q, J = 6.4 Hz, 1H), 2.11 (m, 1H), 1.55 (d, J = 6.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.2, 133.3, 132.9, 128.3, 128.0, 127.7, 126.2, 125.8, 123.9, 123.8, 70.5, 25.2. HPLC (Chiralcel OJ-H column, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 28.8 min (minor), 38.9 min (major).

(+)-(R)-1-(1-Naphthyl)ethanol ***(2q)***. 0.339 g, 99% yield, colorless oil, R_f = 0.21 (hexanes/ethyl acetate 10/1), 97% ee, $[\alpha]^{20}_D$ = +51.43 (c 0.99, $CHCl_3$), [lit.:[8a] >99% ee, $[\alpha]^{20}_D$ = +50.2 (c = 1.0, $CHCl_3$)]. ^1H NMR (400 MHz, $CDCl_3$) δ 8.11−8.01 (m, 1H), 7.89−7.81 (m, 1H), 7.79−7.71 (m, 1H), 7.67−7.59 (m, 1H), 7.55−7.37 (m, 3H), 5.62 (q, J = 6.5 Hz, 1H), 2.11 (brs, 1H), 1.63 (d, J = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.4, 133.8, 130.3, 128.9, 128.0, 127.9, 126.1, 125.6, 123.2, 122.0, 67.1, 24.4. HPLC (Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 85/15, flow = 0.8 mL/min, l = 254 nm, 30 °C) t_R = 8.7 min (minor), 12.8 min (major).

(−)-(R)-1-Ferrocenylethanol ***(2r)***. 0.456 g, 99% yield, yellow solid, R_f = 0.19 (hexanes/ethyl acetate 10/1), 96% ee, $[\alpha]^{20}_D$ = −29.72 (c 1.07, $CHCl_3$), [lit.:[8a] 98% ee, $[\alpha]^{20}_D$ = −29.6 (c = 1.0, $CHCl_3$)]. ^1H NMR (400 MHz, $CDCl_3$) δ 4.54 (q, J = 6.4 Hz, 1H), 4.26−4.11 (m, 9H), 1.90 (brs, 1H), 1.44 (d, J = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 94.8, 68.3, 68.0, 67.9, 66.2, 66.1, 65.6, 23.7. HPLC (Chiralcel OJ-H column, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 11.9 min (major), 13.0 min (minor).

(+)-(R)-1-(2-Furyl)ethanol ***(2s)***. 66.5 mg, 99% yield, colorless oil, R_f = 0.18 (hexanes/ethyl acetate 10/1), 64% ee, $[\alpha]^{20}_D$ = +10.95 (c 0.42, $CHCl_3$), [lit.:[8a] 96% ee, $[\alpha]^{20}_D$ = +16.6 (c = 1.0, $CHCl_3$)]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 1.8 Hz, 1H), 6.38−6.28 (m, 1H), 6.23 (d, J = 3.3 Hz, 1H), 4.88 (q, J = 6.6 Hz, 1H), 2.14 (brs, 1H), 1.54 (d, J = 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.6, 141.9, 110.1, 105.1, 63.6, 21.3. HPLC (Chiralcel OJ-H column, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 11.4 min (minor), 12.7 min (major).

(+)-(R)-1-(3,5-Bis(trifluoromethyl)phenyl)ethanol ***(2t)***. 60.4 mg, 78% yield, colorless oil, R_f = 0.26 (hexanes/ethyl acetate 10/1), 94% ee, $[\alpha]^{20}_D$ = +25.83 (c 1.02, $CHCl_3$), [lit.:[8a] 99.7% ee, $[\alpha]^{20}_D$ = +27.4 (c = 1.0, $CHCl_3$)]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 2H), 7.79 (s, 1H), 5.05 (q, J = 6.3 Hz, 1H), 2.01 (brs, 1H), 1.55 (dd, J = 6.5, 1.7 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 148.2, 131.7 (q, $^2J_{C-F}$ = 33.0 Hz), 125.6, 123.3 (q, $^1J_{C-F}$ = 270.8 Hz), 121.4−121.2 (m) 69.3, 25.5. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −62.83. HPLC (Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 98/2, flow = 0.8 mL/min, l = 220 nm, 30 °C,) t_R = 8.0 min (minor), 8.9 min (major).

(+)-(R)-1-(3-Methoxyphenyl)ethanol ***(2u)***. 60.7 mg, 99% yield, colorless oil, R_f = 0.16 (hexanes/ethyl acetate 10/1), 90% ee, $[\alpha]^{20}_D$ = +40.32 (c 0.94, $CHCl_3$), [lit.:[8a] 99.9% ee, $[\alpha]^{20}_D$ = +41.2 (c = 1.0, $CHCl_3$)]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.21 (m, 1H), 6.98−6.90 (m, 2H), 6.85−6.76 (m, 1H), 4.85 (q, J = 6.5 Hz, 1H), 3.80 (s, 3H), 2.05 (brs, 1H), 1.47 (d, J = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.8, 147.6, 129.6, 117.7, 112.9, 110.9, 70.3, 55.2, 25.2. HPLC (Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, l = 220 nm, 30 °C) t_R = 15.5 min (major), 17.5 min (minor).

(+)-(R)-1-(4-(Methylthio)phenyl)ethanol ***(2v)***. 67.3 mg, 99% yield, colorless oil, R_f = 0.16 (hexanes/ethyl acetate 10/1), 92% ee, $[\alpha]^{20}_D$ = +40.15 (c 1.05, $CHCl_3$), [lit.:[8a] >99% ee, $[\alpha]^{20}_D$ = +43.4 (c = 1.0, $CHCl_3$)]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 4.87 (q, J = 6.5 Hz, 1H), 2.48 (s, 3H), 1.83 (brs, 1H), 1.48 (d, J = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.8, 137.4, 126.8, 126.0, 70.0, 25.1, 16.0. HPLC (Chiralpak AS-H column, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, l = 254 nm, 30 °C) t_R = 20.7 min (major), 23.5 min (minor).

(−)-(R)-4-Phenylbutan-2-ol ***(2w)***. 0.285 g, 95% yield, colorless oil, R_f = 0.28 (hexanes/ethyl acetate 10/1), 43% ee, $[\alpha]^{20}_D$ = −7.60 (c 1.00, $CHCl_3$), [lit.:[14] 45% ee, $[\alpha]^{20}_D$ = −6.1 (c = 1.0, $CHCl_3$)]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.24 (m, 2H), 7.23−7.13 (m, 3H), 3.87−3.76 (m, 1H), 2.81−2.60 (m, 2H), 1.85−1.69 (m, 2H), 1.22 (d, J = 6.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.1, 128.4, 125.9, 67.5, 40.9, 32.2, 23.6. HPLC (Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 95/5, flow = 0.8 mL/min, l = 210 nm, 30 °C) t_R = 12.0 min (major), 17.3 min (minor).

(+)-(R)-Phenyl(o-tolyl)methanol ***(2x)***. 39.6 mg, 99% yield, white solid, R_f = 0.28 (hexanes/ethyl acetate 10/1), 65% ee, $[\alpha]^{20}_D$ = +4.61 (c 1.02, $CHCl_3$), [lit.:[16] 86% ee, $[\alpha]^{20}_D$ = +5.4 (c = 0.94, $CHCl_3$)]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, J = 7.4, 1.7 Hz, 1H), 7.37−7.28 (m, 4H), 7.28−7.16 (m, 3H), 7.14 (d, J = 1.7 Hz, 1H), 5.97 (s, 1H), 2.23 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.9, 141.5, 135.4, 130.6, 128.5, 127.61, 127.58, 127.2, 126.3, 126.2, 73.4, 19.4. HPLC (Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 98/2, flow = 1.2 mL/min, l = 230 nm, 30 °C) t_R = 22.5 min (minor), 24.0 min (major).

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c02358.

Copies of ^1H, $^{13}C\{^1H\}$, $^{19}F\{^1H\}$, and $^{31}P\{^1H\}$ spectra of all new compounds (PDF)

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Notes

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