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Enantioselective Hydroformylation of Aniline Derivatives

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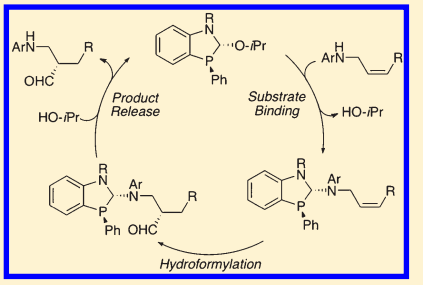
Supporting Information

ABSTRACT: We have developed a ligand that reversibly binds to aniline substrates, allowing for the control of regioselectivity and enantioselectivity in hydroformylation. In this paper we address how the electronics of the aniline ring affect both the binding of the substrate to the ligand and the enantioselectivity in this reaction.



Asymmetric hydroformylation (AHF) is an efficient and practical means of producing chiral aldehyde products. The challenges in AHF are controlling both the enantioselectivity and the regioselectivity of the reaction.[1] Hydroformylation of terminal olefins generally has the tendency to form the achiral linear isomers, whereas 1,2-disubstituted olefins show poor regiocontrol. Therefore, the majority of AHF has been performed on symmetrical substrates or olefins with an electronic preference to form the branched isomers (such as styrene). These classes of substrates have been found to be receptive to AHF, and a variety of ligands have been developed that promote the reaction with high enantioselectivity.[2−14] Most recently, Zhang[15] and Landis[16] have also demonstrated success in the AHF of substrates that contain an internal directing group. Our research group has tried to diversify the substrate scope of AHF by expanding to substrates that are not electronically activated and do not have a directing group as part of the molecule. This is achieved by having a phosphorus-based ligand that reversibly and covalently binds to common organic functionalities.[17−29] Upon binding the substrate, the phosphine ligand serves as the directing group controlling the regioselectivity. Importantly, the reversibility of the bonding between the substrate and ligand allows the ligand to be employed catalytically.[30−34] We recently applied this concept to the AHF of *p*-methoxyphenyl (PMP)-protected amines toward the synthesis of β-amino alcohols.[35] Although the PMP group is a useful protecting group, aniline derivatives are an important class of molecules found broadly in biologically active compounds. In this paper we explore how the electronics of the nitrogen affects both binding of the substrate to the ligand and the enantioselectivity of the hydroformylation reaction.

We initiated our investigation by studying the exchange reaction of a variety of electronically modified anilines with ligand **1**.[36] The electronics of the aniline affect the affinity of the substrate for the ligand but do not prevent binding in any of the tested substrates. Electron-poor anilines have a lower binding affinity than electron-rich rings, with all of the K_{eq} values being within 1 order of magnitude of each other (Table 1). To gain further insight into the factors that affect binding, the equilibrium data were plotted versus both σ_p and σ_+ Hammett parameters. The data correlate slightly better to the σ_+ values than the σ_p values, consistent with there being a minor resonance component to the binding affinity (Figure 1). The ρ value is small and negative (−0.47), suggesting only a modest favorability for binding of electron-rich rings. One interpretation of these data is that the nitrogen lone pair is conjugated to the aromatic ring in

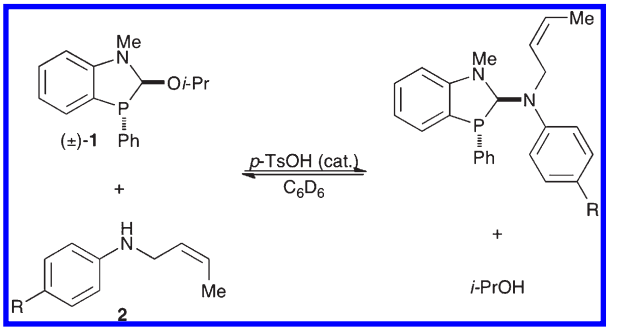


Table 1. Electronic Effects on Binding to (±)-1

entry	R	K_{eq}[a]
1	OMe (**2a**)	2.9 ± 0.7
2	Me (**2b**)	1.3 ± 0.5
3	H (**2c**)	1.2 ± 0.3
4	Cl (**2d**)	1.2 ± 0.2
5	CN (**2e**)	0.64 ± 0.03
6	NO_2 (**2f**)	0.43 ± 0.07

[a] K_{eq} values were determined by ^{1}H NMR in triplicate.

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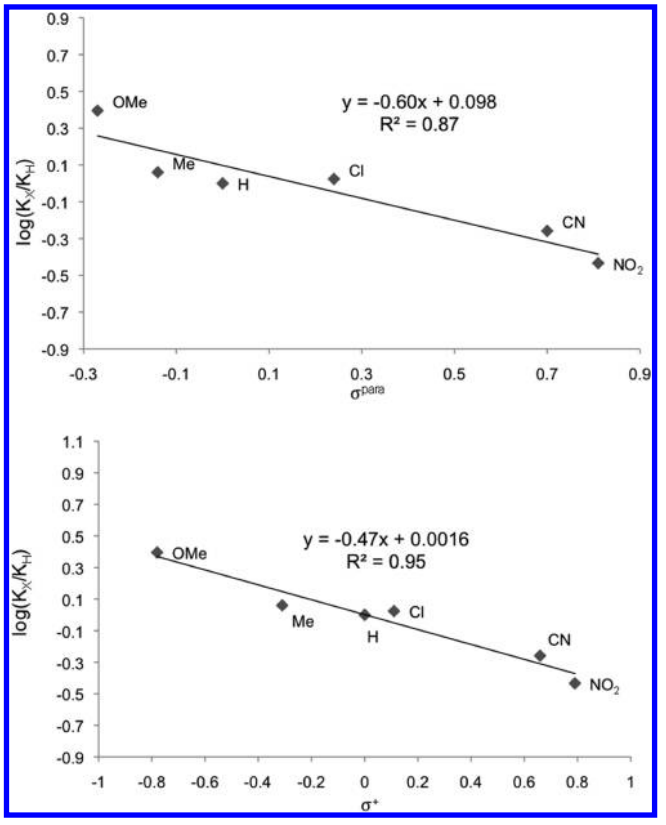


Figure 1. Hammett plots.

the secondary anilines, but upon binding to the ligand the steric repulsion between the aromatic ring and ligand rotates the lone pair out of conjugation. Since resonance-stabilizing electron-withdrawing groups are in direct conjugation with the nitrogen lone pair, the equilibrium shifts toward the starting materials as compared to donating groups. Alternatively, when the aniline is bound to the ligand, the aniline nitrogen lone pair can participate in donation into σ^* of either the C−N or C−P bonds of the heterocyclic ring.[37,38] In this case donating groups would enhance this interaction while withdrawing groups would mitigate it.

Having investigated the effects of electronics on binding affinity to the ligand, we probed the consequences on hydroformylation. For the hydroformylation studies the benzyl ethers were used as substrates, because these compounds are readily accessible in large quantities as geometrically pure compounds from commercially available *cis*-1,4-butenediol (note that hydroformylation of (*Z*)-*N*-(but-2-en-1-yl)aniline (**2c**) afforded the desired product in 74% ^{1}H NMR yield and 90% ee). As previously reported using ligand **3**, *p*-methoxyphenyl (PMP) substrates give the product in high enantioselectivity (92% ee) and good yield (70%; Table 2, entry 1).[39] Unsubstituted and electronically neutral aromatics form the product in comparable levels of enantioselectivity and slightly elevated isolated yields (Table 2, entries 2−4). When an electron-withdrawing substituent is in the para position of the aromatic ring, both the yield and enantioselectivities decrease (Table 2, entries 5 and 6). On the basis of gas uptake curves, these reactions stall before reaching 100% conversion, consistent with the active catalyst decomposing during the reaction. The exchange data show that the ligands bound to electron-deficient aniline derivatives are

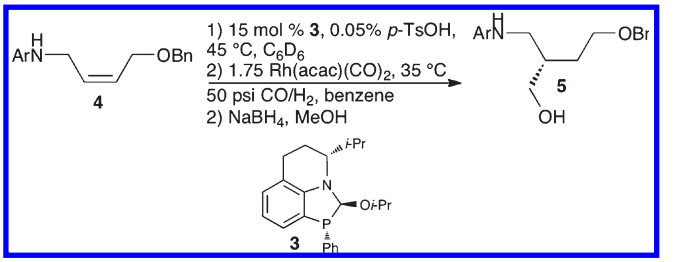
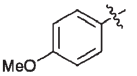
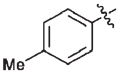
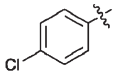
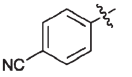
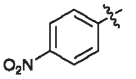
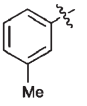
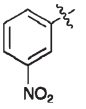
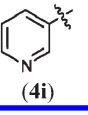


Table 2. Electronic Effects on Hydroformylation of Aniline Substrates

entry	Ar	product	yield (%)[b]	ee (%)[c]
1[d]	 (4a)	5a	70	92
2	 (4b)	5b	79	92
3	 (4c)	5c	77	91
4	 (4d)	5d	72	88
5	 (4e)	5e	49	65
6	 (4f)	5f	41	52
7	 (4g)	5g	60	89
8	 (4h)	5h	61	84
9	 (4i)	5i	64	87

[a] Unless otherwise noted, the following reaction conditions were used: (1) 15 mol % **3**, 0.05 mol % *p*-TsOH, 45 °C, C_6D_6; (2) 1.75 mol % $Rh(acac)(CO)_2$, 35 °C, 50 psi of H_2/CO, benzene; (3) $NaBH_4$, MeOH. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis. [d] Standard conditions, except 0.03 mol % *p*-TsOH was used for the pre-exchange.

thermodynamically less stable, which may be leading to a more rapid decomposition of the ligand. Analysis of the pre-exchange reaction prior to hydroformylation by ^{31}P NMR indicates considerable decomposition of ligand **3** to a variety of unidentifiable

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phosphorus compounds in the presence of compounds **4e**,**f**. The Hammett data suggest that electron-withdrawing groups not directly in conjugation with the aniline lone pair would be thermodynamically more stable. Using a substrate with a *m*-NO_2 group gives the alcohol product in improved enantioselectivity and yield (Table 2, entry 8), consistent with this prediction. Similarly, a substrate with an electron-deficient pyridine ring affords the desired product in moderate yield (64%) and good enantioselectivity (87% ee). We also attempted to perform hydroformylations with substitution, such as Cl and CH_3, at the ortho position of the aromatic ring. These provided low conversion to product; we believe this is a result of difficulties in binding sterically large substrates to the ligand.

CONCLUSIONS

The asymmetric hydroformylation of aniline derivatives has been achieved using a chiral scaffolding ligand. By studying the substrate/ligand exchange and hydroformylation reactions, we found a correlation between binding affinity and the yield and enantioselectivity of the hydroformylation reaction. Substrates with high affinity for the ligand generally afford improved enantioselectivity. Substrates with a low affinity for ligand give lower enantioselecitvity and yield, which is potentially a result of decomposition of the ligand during the reaction. With this information, we are currently developing ligands with improved stability, with the aim of improving yields and selectivities.

EXPERIMENTAL SECTION

All general considerations are the same as those previously reported.[35] The following compounds were made according to literature procedures and matched reported spectra: ligand **1**,[26] ligand **3**(OMe),[35] and ligand **3**(O*i*Pr),[35] *N*-(but-2-yn-1-yl)-4-methoxyaniline,[35] (*Z*)-*N*-(but-2-en-1-yl)-4-methoxyaniline (**2a**),[35] 2-(but-2-yn-1-yl)isoindoline-1,3-dione,[40] but-2-yn-1-amine,[41] (*Z*)-4-(benzyloxy)but-2-en-1-ol, (*Z*)-*N*-(4-(benzyloxy)but-2-en-1-yl)-4-methoxyaniline (**4a**),[35] (*Z*)-(7((4-chlorobut-2-en-1-yl)oxy)methyl)benzene,[35] 2-isobutyrylcyclohexanone,[42] 1-iodo-3-nitrobenzene,[43] 3-iodopyridine,[44] (*S*)-4-(benzyloxy)-2-(((4-methoxyphenyl)amino)methyl)butan-1-ol (**5a**).[35]

Equilibrium Substrates. *General Procedure 1.* To a flame-dried flask was added *p*-toluidine (3.36 g, 31.4 mmol), CH_3CN (30 mL), and 1-bromo-2-butyne (0.55 mL, 6.3 mmol). The reaction mixture was stirred overnight, diluted with Et_2O (100 mL), and washed with water (2 × 40 mL) and saturated NH_4Cl (3 × 25 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated.

General Procedure 2. A flame-dried flask was charged with Lindlar's catalyst (172 mg) and purged with nitrogen. *N*-(But-2-yn-1-yl)-4-methylaniline (1.23 g, 7.74 mmol) in EtOH (15 mL) was added, followed by quinoline (82 μL, 0.70 mmol). The flask was purged with H_2 (4×), fitted with a H_2 balloon, and stirred at room temperature for 40 min. The reaction mixture was filtered through a plug of silica and concentrated. Column chromatography (10% EtOAc/Hex) afforded the title compound.

N-(But-2-yn-1-yl)-4-methylaniline. General Procedure 1 was used. Column chromatography (5% EtOAc/Hex) gave an orange oil (781 mg, 78%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.01−7.04 (m, 2H), 6.60−6.62 (m, 2H), 3.85 (s, 2H), 3.71 (br s, 1H), 2.26 (app d, 3H, J = 4.2), 1.80−1.81 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.2, 129.9, 127.7, 113.8, 79.1, 76.5, 34.5, 20.6, 3.5. IR: 1616, 1517, 1249, 806, 502 cm^{-1}. HRMS (DART-TOF): calcd for $C_{11}H_{14}N$ $[M + H]^+$ 160.1126, found 160.1119.

*(Z)-N-(But-2-en-1-yl)-4-methylaniline (**2b**).* General Procedure 2 was used, giving an orange oil (1.02 g, 82%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.99 (d, 2H, J = 7.8), 6.55−6.58 (m, 2H), 5.63−5.67 (m, 1H), 5.55−5.59 (m, 1H), 3.74 (d, 2H, J = 6.6), 3.50 (br s, 1H), 2.23 (s, 3H), 1.71−1.73 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.3, 129.9, 128.1, 127.2, 127.0, 113.3, 41.4, 20.6, 13.3; IR: 1616, 1517, 1313, 1256, 805 cm^{-1}. HRMS (DART-TOF): calcd for $C_{11}H_{16}N$ $[M + H]^+$ 162.1283, found 162.1277.

N-(But-2-yn-1-yl)aniline. General Procedure 1 with aniline (7.73 mL, 84.8 mmol) was used. Column chromatography (5% EtOAc/Hex) gave a yellow oil (1.9 g, 78%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.20−7.24 (m, 2H), 6.77−6.80 (m, 1H), 6.67−6.70 (m, 2H), 3.88 (s, 2H), 3.85 (br s, 1H), 1.81−1.82 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.5, 129.4, 118.4, 113.6, 79.2, 76.3, 34.2, 3.7. IR: 1601, 1502, 1313, 747, 690 cm^{-1}. HRMS (DART-TOF): calcd for $C_{10}H_{12}N$ $[M + H]^+$ 146.0970, found 146.0967.

*(Z)-N-(But-2-en-1-yl)aniline (**2c**, 7% E Isomer).* General Procedure 2 with *N*-(but-2-yn-1-yl)aniline (1.01 g, 7.02 mmol) was used, affording an orange oil (720 mg, 73%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.17−7.21 (m, 2H), 6.71−6.74 (t, 1H, J = 7.3), 6.62−6.64 (m, 2H), 5.65−5.68 (m, 1H), 5.54−5.59 (m, 1H), 3.78 (d, 2H, J = 6.6), 3.69 (d, 2H$_{E\,\text{isomer}}$, J = 6.1), 3.63 (br s, 1H), 1.71−1.72 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.5, 129.4, 127.8, 127.4, 117.6, 113.1, 41.0, 13.3. IR: 1601, 1503, 1312, 1260, 747, 690, 507 cm^{-1}. HRMS (DART-TOF): calcd for $C_{10}H_{14}N$ $[M + H]^+$ 148.1126, found 148.1119.

N-(But-2-yn-1-yl)-4-chloroaniline. General Procedure 1 with 4-chloroaniline (1.88 g, 14.7 mmol) was used. Column chromatography (20% EtOAc/Hex) yielded a light red oil (331 mg, 66%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.15−7.17 (m, 2H), 6.59−6.61 (m, 2H), 3.86 (s, 2H), 1.81 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.0, 129.2, 123.1, 114.7, 79.5, 75.9, 34.3, 3.7. IR: 1599, 1496, 1312, 814, 500 cm^{-1}. HRMS (DART-TOF): calcd for $C_{10}H_{11}ClN$ $[M + H]^+$ 180.0580, found 180.0581.

*(Z)-N-(But-2-en-1-yl)-4-chloroaniline (**2d**).* General Procedure 2 with *N*-(but-2-yn-1-yl)-4-chloroaniline (1.02 g, 5.68 mmol) was used, affording an orange oil (814 mg, 81%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.11−7.13 (m, 2H), 6.52−6.55 (app dd, 2H, J = 6.6, 2.2), 5.65−5.68 (m, 1H), 5.51−5.54 (m, 1H), 3.73 (d, 2H, J = 6.6), 3.64 (br s, 1H), 1.70−1.72 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.0, 129.2, 127.7, 127.4, 122.1, 114.1, 41.1, 13.3. IR: 1599, 1496, 1311, 1176, 812, 503 cm^{-1}. HRMS (DART-TOF): calcd for $C_{10}H_{13}ClN$ $[M + H]^+$ 182.0737, found 182.0739.

4-(But-2-yn-1-ylamino)benzonitrile. A flame-dried flask was charged with K_2CO_3 (6.00 g, 45.4 mmol), 4-aminobenzonitrile (7.00 g, 56.7 mmol), DMF (140 mL), and 1-bromo-2-butyne (2.51 g, 18.9 mmol). The reaction mixture was stirred overnight at 80 °C. The reaction mixture was diluted with EtOAc (200 mL) and washed with water (2 × 100 mL). The aqueous layer was washed with EtOAc (200 mL), and the organics were dried over $MgSO_4$, filtered, and concentrated. Column chromatography (20% EtOAc/Hex) afforded an orange oil (1.32 g, 16%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42−7.44 (m, 2H), 6.60−6.62 (m, 2H), 4.47 (br s, 1H), 3.87−3.90 (m, 2H), 1.78−1.79 (app t, 3H, J = 2.4). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.6, 133.7, 120.4, 112.9, 99.7, 80.0, 74.8, 33.4, 3.6. IR: 3371, 2212, 1604, 1522, 1324, 1174, 824, 543 cm^{-1}. HRMS (DART-TOF): calcd for $C_{11}H_{11}N_2$ $[M + H]^+$ 171.0922, found 171.0923.

*(Z)-4-(But-2-en-1-ylamino)benzonitrile (**2e**, 5% E Isomer).* General Procedure 2 with 4-(but-2-yn-1-ylamino)benzonitrile (800 mg, 4.70 mmol) was used, affording an orange oil (622 mg, 77%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38−7.42 (m, 2H), 6.54−6.56 (m, 2H), 5.67−5.74 (m, 1H), 5.47−5.53 (m, 1H), 4.27 (br s, 1H) 3.78−3.81 (t, 2H, J = 5.6), 3.70−3.72 (m, 2H$_{E\,\text{isomer}}$), 1.71−1.73 (m, 3H), 1.69−1.70 (m, 2H$_{E\,\text{isomer}}$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 151.4, 133.8, 128.5, 126.3, 120.7, 112.4, 98.8, 40.2, 13.3. IR: 3367, 2209, 1602, 1521, 1171,

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820, 542 cm^{-1}. HRMS (DART-TOF): calcd for $C_{11}H_{13}N_2$ $[M + H]^+$ 173.1079, found 173.1080.

N-(But-2-yn-1-yl)-4-nitroaniline. In a flame-dried flask were added KF (426 mg, 6.17 mmol), K_2CO_3 (853 mg, 6.17 mmol), and 1-fluoro-4-nitrobenzene (871 mg, 6.17 mmol). But-2-yn-1-amine (426 mg, 6.17 mmol) was added to the flask as a solution in DMSO (20 mL). The reaction mixture was stirred at room temperature overnight. Water (5 mL) was added, and the mixture was extracted with Et_2O (150 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Column chromatography (15% EtOAc/Hex) afforded a yellow oil (660 mg, 56%). ^1H NMR ($CDCl_3$, 500 MHz): δ 8.11 (d, 2H, J = 9.3), 6.59−6.62 (m, 2H), 4.69 (br s, 1H), 3.93−3.95 (m, 2H), 1.79−1.80 (m, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 152.5, 138.9, 126.4, 111.9, 80.5, 74.4, 33.7, 3.7. IR: 1616, 1515, 1231, 805, 512 cm^{-1}. HRMS (DART-TOF): calcd for $C_{10}H_{11}N_2O_2$ $[M + H]^+$ 191.0821, found 191.0819.

*(Z)-N-(But-2-en-1-yl)-4-nitroaniline (**2f**, 14% E Isomer).* General Procedure 2 with *N*-(but-2-yn-1-yl)-4-nitroaniline (66 mg, 0.35 mmol) was used, affording a yellow oil (60 mg, 90%). ^1H NMR ($CDCl_3$, 500 MHz): δ 8.07−8.11 (m, 2H), 6.52−6.55 (m, 2H), 5.71−5.77 (m, 1H), 5.46−5.49 (m, 1H), 3.85−3.87 (m, 2H), 3.77−3.79 (m, $2H_{E\,isomer}$), 1.73−1.75 (m, 3H), 1.71−1.72 (m, $3H_{E\,isomer}$). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.4, 138.3, 129.0, 126.6, 125.9, 111.4, 40.5, 13.4. IR: 3378, 1600, 1503, 1471, 1318, 1302, 1283, 1111 cm^{-1}. HRMS (DART-TOF): calcd for $C_{10}H_{13}N_2O_2$ $[M + H]^+$ 193.0977, found 193.0985.

Equilibrium Experiments. In a drybox, a solution of isopropyl alcohol (100 μL, 1.31 mmol) in benzene-d_6 (1.63 M) was prepared. The solution was dispensed into three NMR tubes. A second solution of (*Z*)-*N*-(but-2-enyl)-4-methoxyaniline (70 mg, 0.43 mmol), ligand (25 mg, 0.086 mmol), and *p*-TsOH (298 μL, 7.2 × 10^{-4} M in C_6H_6; note that C_6H_6 was removed prior to mixing with substrate and ligand) in C_6D_6 (1.5 mL) was made. The solution was dispensed into three NMR tubes. The total volume of each tube was brought to 0.7 mL. Each reaction was allowed to equilibrate overnight at 45 °C.

Hydroformylation Substrates. *General Procedure 3.*[45] To a flame-dried flask was added L-proline (325 mg, 2.82 mmol), CuI (537 mg, 2.82 mmol), and K_2CO_3 (1.17 g, 8.46 mmol). (*Z*)-4-(Benzyloxy)-but-2-en-1-amine (500 mg, 2.82 mmol) was added to the flask as a solution in DMSO (5 mL), followed by iodobenzene (314 μL, 2.82 mmol). The reaction mixture was heated to 60 °C for 8 h. The mixture was diluted with EtOAc (100 mL) and washed with water (70 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated.

General Procedure 4. To a flame-dried flask was added K_2CO_3 (420 mg, 3.04 mmol), 4-fluorobenzonitrile (368 mg, 3.04 mmol), (*Z*)-4-(benzyloxy)but-2-en-1-amine (700 mg, 3.94 mmol), and DMSO (10 mL), which was heated to 90 °C overnight. The reaction was quenched by the addition of water (25 mL) and was diluted with Et_2O (70 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated.

General Procedure 5.[42] To an oven-dried flask was added CuI (232 mg, 1.22 mmol) and Cs_2CO_3 (2.00 g, 6.10 mmol). (*Z*)-4-(Benzyloxy)-but-2-en-1-amine (600 mg, 3.05 mmol), 1-iodo-3-methylbenzene (392 μL, 3.05 mmol), DMF (1.5 mL), and 2-isobutyrylcyclohexanone (410 mg, 2.44 mmol) were added. The reaction mixture was stirred for 12 h. The mixture was filtered through a pad of Celite, washed with EtOAc (100 mL), and extracted with water (2 × 25 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated.

*(Z)-N-(4-(Benzyloxy)but-2-en-1-yl)-4-methylaniline (**4b**).* To a flame-dried flask was added *p*-toluidine (3.26 g, 30.5 mmol), (*Z*)-(((4-chlorobut-2-en-1-yl)oxy)methyl)benzene (1.20 g, 6.10 mmol), and acetonitrile (30 mL). The reaction mixture was stirred for 12 h. The mixture was diluted with Et_2O (100 mL) and was washed with H_2O (3 × 50 mL) and saturated aqueous NH_4Cl (3 × 50 mL). The organics were dried over anhydrous $MgSO_4$, filtered, and concentrated. Column chromatography (15% EtOAc/Hex) afforded an orange oil (748 mg, 46%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.28−7.36 (m, 5H), 7.00 (d, 2H, J = 8.1), 6.54 (d, 2H, J = 8.6), 5.74−5.82 (m, 2H), 4.54 (s, 2H), 4.15 (d, 2H, J = 4.9), 3.75 (d, 2H, J = 4.5), 3.55 (br s, 1H), 2.25 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.9, 138.3, 131.0, 129.9, 129.0, 128.6, 128.0, 127.9, 127.2, 113.4, 72.7, 65.9, 41.9, 20.6. IR: 1616, 1518, 1252, 1070, 806, 734, 696 cm^{-1}. HRMS (DART-TOF): calcd for $C_{18}H_{22}NO$ $[M + H]^+$ 268.1701, found 268.1698.

(Z)-2-(4-(Benzyloxy)but-2-en-1-yl)isoindoline-1,3-dione. A flame-dried flask was charged with (*Z*)-4-(benzyloxy)but-2-en-1-ol (3.74 g, 21.0 mmol), triphenylphosphine (3.74 g, 21.0 mmol), phthalimide (3.09 g, 21.0 mmol), tetrahydrofuran (105 mL), and diisopropyl azodicarboxylate (4.13 mL, 21.0 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was concentrated. Column chromatography (20% EtOAc/Hex) gave a colorless oil (4.23 g, 65%). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.81−7.85 (m, 2H), 7.69−7.72 (m, 2H), 7.28−7.39 (m, 5H), 5.78−5.84 (m, 1H), 5.62−5.68 (m, 1H), 4.58 (s, 2H), 4.32−4.34 (m, 2H), 4.30−4.32 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.1, 138.4, 134.2, 132.4, 131.0, 128.6, 128.1, 127.9, 126.4, 123.5, 72.7, 65.9, 35.2. IR: 1709, 1390, 1088, 1072, 735, 715, 698 cm^{-1}. HRMS (DART-TOF): calcd for $C_{19}H_{18}NO_3$ $[M + H]^+$ 308.1287, found 308.1284.

(Z)-4-(Benzyloxy)but-2-en-1-amine. A 100 mL flask was charged with (*Z*)-2-(4-(benzyloxy)but-2-en-1-yl)isoindoline-1,3-dione (4.23 g, 13.7 mmol), hydrazine hydrate (1.6 mL, 25.7 mmol), and ethanol (10 mL). The mixture was heated to 70 °C overnight. The solid was filtered and washed with water (100 mL). The aqueous solution was acidified to pH ∼2 with concentrated HCl and was washed with Et_2O (120 mL). The aqueous layer was then basified to pH ∼13 by solid KOH pellets. The solution was washed with Et_2O (200 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated to obtain the title compound as a pale yellow oil (1.92 g, 79%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.27−7.36 (m, 5H), 5.61−5.71 (m, 2H), 4.51 (s, 2H), 4.07 (d, 2H, J = 6.0), 3.31 (d, 2H, J = 6.1), 1.13 (br s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.3, 134.9, 128.6, 128.0, 127.8, 126.7, 72.5, 65.7, 39.3. IR: 3067, 2854, 1453, 1088, 734, 696 cm^{-1}. HRMS (DART-TOF): calcd for $C_{11}H_{16}NO$ $[M + H]^+$ 178.1232, found 178.1240.

*(Z)-N-(4-(Benzyloxy)but-2-en-1-yl)aniline (**4c**).* General Procedure 3 was used. Column chromatography (20% EtOAc/Hex) gave a pale orange oil (301 mg, 42%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.28−7.37 (m, 5H), 7.16−7.21 (m, 2H), 6.75 (app t, 1H, J = 7.3), 6.61 (d, 2H, J = 7.6), 5.74−5.83 (m, 2H), 4.55 (s, 2H), 4.15 (d, 2H, J = 5.4), 3.78 (d, 2H, J = 5.6), 3.68 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.2, 138.3, 130.8, 129.5, 129.1, 128.6, 128.0, 127.9, 117.9, 113.2, 72.7, 65.9, 41.6. IR: 3027, 2856, 1603, 1504, 1094, 1071, 749, 695 cm^{-1}. HRMS (DART-TOF): calcd for $C_{17}H_{20}NO$ $[M + H]^+$ 254.1545, found 254.1555.

*(Z)-N-(4-(Benzyloxy)but-2-en-1-yl)-4-chloroaniline (**4d**).* General Procedure 3 with 1-bromo-4-chlorobenzene (540 mg, 2.82 mmol) was used. Column chromatography (20% EtOAc/Hex) gave an orange oil (358 mg, 44%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.28−7.37 (m, 5H), 7.10−7.13 (m, 2H), 6.49−6.51 (m, 2H), 5.79−5.84 (m, 1H), 5.70−5.75 (m, 1H), 4.54 (s, 2H), 4.14 (d, 2H, J = 6.4), 3.74 (d, 2H, J = 6.6), 3.71 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.7, 138.2, 130.4, 129.4, 129.3, 128.7, 128.0, 127.9, 122.5, 114.2, 72.8, 65.8, 41.7. IR: 2854, 1598, 1496, 1357, 1070, 814, 735, 696, 504 cm^{-1}. HRMS (DART-TOF): calcd for $C_{17}H_{19}ClNO$ $[M + H]^+$ 288.1155, found 288.1145.

*(Z)-4-((4-(Benzyloxy)but-2-en-1-yl)amino)benzonitrile (**4e**).* General Procedure 4 was used. Column chromatography (20% EtOAc/Hex) afforded an orange oil (201 mg, 37%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.39−7.42 (m, 2H), 7.29−7.37 (m, 5H), 6.51−6.53 (m, 2H), 5.82−5.87 (m, 1H), 5.67−5.71 (m, 1H), 4.55 (s, 2H), 4.26 (br s, 1H), 4.12−4.13 (m, 2H), 3.81 (br m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz):

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δ 151.2, 138.0, 133.9, 130.0, 129.4, 128.7, 128.1, 128.0, 120.6, 112.5, 99.2, 72.9, 65.8, 40.8; IR: 3367, 1606, 1525, 1207 cm^{-1}. HRMS (DART-TOF): calcd for $C_{18}H_{19}N_2O$ $[M + H]^+$ 279.1497, found 279.1498.

*(Z)-N-(4-(Benzyloxy)but-2-en-1-yl)-4-nitroaniline (**4f**).* General Procedure 4 with 1-fluoro-4-nitrobenzene (429 mg, 3.04 mmol) was used. Column chromatography (20% EtOAc/Hex) gave a bright yellow oil (457 mg, 50%). ^1H NMR ($CDCl_3$, 500 MHz): δ 8.07 (d, 2H, *J* = 9.3), 7.31−7.37 (m, 5H), 6.49 (d, 2H, *J* = 9.3), 5.86−5.90 (m, 1H), 5.69−5.74 (m, 1H), 4.63 (br s, 1H), 4.56 (s, 2H), 4.15 (d, 2H, *J* = 6.4), 3.86−3.89 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.2, 138.4, 138.0, 130.3, 128.9, 128.7, 128.1, 128.0, 126.5, 111.4, 72.9, 65.8, 40.9. IR: 3372, 1595, 1299, 1278, 1107, 830, 694 cm^{-1}. HRMS (DART-TOF): calcd for $C_{17}H_{19}N_2O_3$ $[M + H]^+$ 299.1396, found 299.1407.

*(Z)-N-(4-(Benzyloxy)but-2-en-1-yl)-3-methylaniline (**4g**).* General Procedure 5 was used. Column chromatography (10% EtOAc/Hex) afforded an orange oil (653 mg, 80%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.30−7.37 (m, 5H), 7.08 (t, 1H, *J* = 7.3), 6.56 (d, 1H, *J* = 7.1), 6.43−6.42 (m, 2H), 5.76−5.81 (m, 2H), 4.55 (s, 2H), 4.16 (d, 2H, *J* = 5.4), 3.76 (d, 2H, *J* = 5.6), 3.63 (br s, 1H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.2, 139.2, 138.3, 130.9, 129.3, 129.0, 128.6, 128.0, 127.9, 118.8, 114.0, 110.4, 72.7, 65.9, 41.6, 21.8. IR: 1604, 1491, 1089, 1070, 769, 735, 692 cm^{-1}. HRMS (DART-TOF): calcd for $C_{18}H_{22}NO$ $[M + H]^+$ 268.1701, found 268.1702.

*(Z)-N-(4-(Benzyloxy)but-2-en-1-yl)-3-nitroaniline (**4h**).* General Procedure 3 with 1-iodo-3-nitrobenzene (886 mg, 3.56 mmol) was used. Column chromatography (15% EtOAc/Hex) afforded a bright orange oil (561 mg, 53%). ^1H NMR (DMSO, 500 MHz): δ 7.31−7.36 (m, 5H), 7.27−7.29 (m, 2H), 6.95−6.97 (m, 1H), 6.52−6.55 (m, 1H), 5.69−5.74 (m, 1H), 5.58−5.62 (m, 1H), 4.50 (s, 2H), 4.16−4.17 (m, 2H), 3.76−3.78 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.6, 148.9, 138.1, 130.1, 129.9, 129.5, 128.7, 128.1, 128.0, 119.1, 112.4, 106.6, 72.9, 65.9, 41.3. IR: 2857, 1621, 1581, 1344, 1089, 1070, 734, 689, 672 cm^{-1}. HRMS (DART-TOF): calcd for $C_{17}H_{19}N_2O_3$ $[M + H]^+$ 299.1396, found 299.1400.

*(Z)-N-(4-(Benzyloxy)but-2-en-1-yl)pyridin-3-amine (**4i**).* General Procedure 5 with 3-iodopyridine (833 mg, 4.06 mmol) was used. Column chromatography (50% EtOAc/Hex) afforded an orange oil (366 mg, 37%). ^1H NMR ($CDCl_3$, 500 MHz): δ 8.00−8.01 (d, 1H, *J* = 3.0), 7.97−7.99 (dd, 1H, *J* = 4.6, 1.0), 7.29−7.35 (m, 5H), 7.06−7.08 (m, 1H), 6.83−6.86 (m, 1H), 5.81−5.86 (m, 1H), 5.72 −5.76 (m, 1H), 4.54 (s, 2H), 4.13 (d, 2H, *J* = 6.1), 3.78 (d, 2H, *J* = 5.1), 3.78 (br s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.1, 139.3, 128.1, 136.5, 130.0, 129.7, 128.7, 128.1, 128.0, 123.8, 118.8, 72.8, 65.8, 41.1. IR: 2861, 1519, 1092, 808, 736, 697 cm^{-1}. HRMS (DART-TOF): calcd for $C_{16}H_{19}N_2O$ $[M + H]^+$ 255.1497, found 255.1484.

Hydroformylation Products. *General Hydroformylation Procedure.* (*Z*)-*N*-(4-(Benzyloxy)but-2-en-1-yl)-4-methylaniline (53.4 mg, 0.200 mmol), (*i*PrO)-**2** (205 μL, 0.146 M solution in C_6D_6), 0.05% *p*-toluenesulfonic acid in benzene (175 μL, 1 × 10^{-4} mmol), and C_6D_6 (0.4 mL) were mixed and heated to 45 °C in a sealed NMR tube. The solution was concentrated in a dry glovebox and then was redissolved in C_6D_6. The solution was heated to 45 °C for 4 h before being concentrated again in a glovebox. The resulting residue was dissolved in benzene (1.5 mL), mixed with 1.75% $Rh(acac)(CO)_2$ (0.9 mg, 0.0035 mmol), and injected into the Endeavor, followed by 0.5 mL of benzene to wash the injection port. The Endeavor was purged with nitrogen (4 × 100 psi). The temperature was held at 35 °C for 10 min, and the Endeavor was pressurized to 50 psi with H_2/CO. The hydroformylation was carried out at 35 °C and 50 psi H_2/CO for 14 h with stirring at 700 rpm. The Endeavor was depressurized and cooled to ambient temperature. A solution of 1,3,5-trimethoxybenzene in $CHCl_3$ (100 μL, 0.1863 M) was added, and the sample was concentrated. The resulting residue was added, as a solution in MeOH (3 mL), to a flame-dried flask containing $NaBH_4$ (23.0 mg, 0.600 mmol). The reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organics were dried over Na_2SO_4, filtered, and concentrated. The crude reaction mixture was chromatographed (1% MeOH/DCM) to yield the title compound.

*(S)-4-(Benzyloxy)-2-((p-tolylamino)methyl)butan-1-ol (**5b**).* Yellow oil (47.4 mg, 79%). HPLC (OD-H, 1.0 mL/min, 23% *i*PrOH/77% Hexanes, 240 nm): t_r(major) = 11.9 min and t_r(minor) = 20.6 min, 92% ee. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.29−7.37 (m, 5H), 6.98 (d, 2H, *J* = 8.6), 6.54 (d, 2H, *J* = 8.3), 4.54 (s, 2H), 3.69 (d, 2H, *J* = 5.1), 3.55−3.64 (m, 2H), 3.11−3.18 (m, 2H), 2.24 (s, 3H), 2.00−2.02 (m, 1H), 1.72−1.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.1, 138.1, 129.9, 128.7, 128.0, 127.9, 127.1, 113.6, 73.5, 68.7, 65.4, 47.5, 38.8, 30.3, 20.6. IR: 3380, 2923, 2854, 1521, 1260, 1095, 807 cm^{-1}. HRMS (DART-TOF): calcd for $C_{19}H_{26}NO_2$ $[M + H]^+$ 300.1964, found 300.1977. $[\alpha]_D^{20}$ = +21.8° (*c* = 0.330, $CHCl_3$, *l* = 50 mm).

*(S)-4-(Benzyloxy)-2-((phenylamino)methyl)butan-1-ol (**5c**).* Yellow oil (43.9 mg, 77%). HPLC (OD-H, 1.0 mL/min, 15% *i*PrOH/85% Hexanes, 240 nm): t_r(major) = 15.5 min and t_r(minor) = 20.4 min, 91% ee. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.29−7.38 (m, 5H), 7.15−7.18 (m, 2H), 6.69−6.72 (app t, 1H, *J* = 7.3), 6.60 (d, 2H, *J* = 7.8), 4.54 (s, 2H), 3.70 (d, 2H, *J* = 5.1), 3.55−3.65 (m, 2H), 3.13−3.21 (m, 2H), 1.99−2.02 (m, 1H), 1.74−1.78 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.6, 138.0, 129.4, 128.7, 128.0, 117.6, 113.2, 73.5, 68.8, 65.2, 46.8 38.9, 30.3. IR: 2924, 2862, 1602, 1092, 1025, 748, 610 cm^{-1}. HRMS (DART-TOF): calcd for $C_{18}H_{24}NO_2$ $[M + H]^+$ 286.1807, found 286.1806. $[\alpha]_D^{20}$ = +19.6° (*c* = 0.310, $CHCl_3$, *l* = 50 mm).

*(S)-4-(Benzyloxy)-2-(((4-chlorophenyl)amino)methyl)butan-1-ol (**5d**).* Orange oil (45.9 mg, 72%). HPLC (OD-H, 1.0 mL/min, 15% *i*PrOH/85% Hexanes, 240 nm): t_r(major) = 13.5 min and t_r(minor) = 18.5 min, 88% ee. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.29−7.38 (m, 5H), 7.07−7.10 (m, 2H), 6.47−6.50 (m, 2H), 4.53 (s, 2H), 3.68 (d, 2H, *J* = 4.9), 3.55−3.62 (m, 2H), 3.07−3.17 (m, 2H), 1.96−2.01 (m, 1H), 1.72−1.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.2, 138.0, 129.2, 128.7, 128.1, 128.0, 122.0, 114.1, 73.5, 68.7, 65.0, 46.8, 38.8, 30.2. IR: 3378, 2924, 2860, 1600, 1500, 1093, 816 cm^{-1}. HRMS (DART-TOF): calcd for $C_{18}H_{23}ClNO_2$ $[M + H]$ 320.1417, found 320.1425. $[\alpha]_D^{20}$ = +20.3° (*c* = 0.325, $CHCl_3$, *l* = 50 mm).

*(S)-4-((4-(Benzyloxy)-2-(hydroxymethyl)butyl)amino)benzonitrile (**5e**).* Orange oil (30.3 mg, 49%). HPLC (OD-H, 1.0 mL/min, 15% *i*PrOH/85% Hexanes, 220 nm): t_r(major) = 17.3 min and t_r(minor) = 20.3 min, 65% ee. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.30−7.38 (m, 7H), 6.44−6.47 (m, 2H), 4.90 (br s, 1H), 4.53 (s, 2H), 3.70 (d, 2H, *J* = 4.7), 3.56−3.63 (m, 2H), 3.12−3.25 (m, 2H), 2.25 (br s, 1H), 1.98−2.02 (m, 1H), 1.70−1.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 151.8, 137.9, 133.7, 128.8, 128.2, 128.1, 120.8, 112.3, 98.5, 73.7, 68.7, 64.8, 45.9, 38.8, 30.1. IR: 3373, 2922, 2867, 2211, 1606, 1528, 1173 cm^{-1}. HRMS (DART-TOF): calcd for $C_{19}H_{23}N_2O_2$ $[M + H]$ 311.1760, found 311.1756. $[\alpha]_D^{20}$ = +34.2° (*c* = 0.090, $CHCl_3$, *l* = 50 mm).

*(S)-4-(Benzyloxy)-2-(((4-nitrophenyl)amino)methyl)butan-1-ol (**5f**).* Yellow oil (27.2 mg, 41%). HPLC (AS-H, 1.0 mL/min, 15% *i*PrOH/85% Hexanes, 220 nm): t_r(major) = 53.9 min and t_r(minor) = 46.6 min, 52% ee. ^1H NMR ($CDCl_3$, 500 MHz): δ 8.01−8.04 (m, 2H), 7.32−7.38 (5H, m), 6.37−6.39 (m, 2H), 5.36 (br s, 1H), 4.54 (s, 2H), 3.71 (br s, 2H), 3.60−3.62 (t, 2H, *J* = 5.5), 3.17−3.31 (m, 2H), 2.28 (br s, 1H), 2.00−2.05 (m, 1H), 1.71−1.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.9, 137.8, 137.7, 128.8, 128.3, 128.2, 126.6, 111.0, 73.7, 68.8, 64.9, 46.2, 38.8, 30.0. IR: 3370, 2922, 2855, 1598, 1308, 1279, 1108, 697 cm^{-1}. HRMS (DART-TOF): calcd for $C_{18}H_{23}N_2O_4$ $[M + H]$ 331.1658, found 331.1657. $[\alpha]_D^{20}$ = +28.7° (*c* = 0.060, $CHCl_3$, *l* = 50 mm).

*(S)-4-(Benzyloxy)-2-((m-tolylamino)methyl)butan-1-ol (**5g**).* Yellow oil (35.8 mg, 60%). HPLC (OD-H, 1.0 mL/min, 23% *i*PrOH/77% Hexanes, 240 nm): t_r(major) = 10.3 min and t_r(minor) = 12.3 min, 89% ee. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.29−7.38 (m, 5H), 7.04−7.07

(m, 1H), 6.53 (d, 1H, J = 7.3), 6.41−6.42 (m, 2H), 4.54 (s, 2H), 3.69 (d, 2H, J = 5.3), 3.55−3.63 (m, 2H), 3.11−3.19 (m, 2H), 2.27 (s, 3H), 2.00−2.02 (m, 1H), 1.73−1.77 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.6, 139.2, 138.1, 129.3, 128.7, 128.0, 127.8, 118.6, 114.0, 110.3, 73.5, 68.8, 65.3, 46.9, 39.0, 30.3, 21.8. IR: 3378, 2919, 2858, 1604, 1092, 1028, 769, 737, 695 cm^{-1}. HRMS (DART-TOF): calcd for $C_{19}H_{26}NO_2$ [M + H] 300.1964, found 300.1958. $[\alpha]_D^{20}$ = +28.2° (c = 0.160, $CHCl_3$, l = 50 mm).

*(S)-4-(Benzyloxy)-2-(((3-nitrophenyl)amino)methyl)butan-1-ol (**5h**).* Orange oil (40.4 mg, 61%). HPLC (OD-H, 1.0 mL/min, 7% *i*PrOH/93% Hexanes, 240 nm): t_r(major) = 55.9 min and t_r(minor) = 37.8 min, 84% ee. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45−7.47 (app dd, 1H, J = 8.1, 1.5), 7.28−7.37 (m, 6H), 7.19−7.22 (t, 1H, J = 8.1), 6.75−6.77 (m, 1H), 4.65 (br s, 1H), 4.53 (s, 2H), 3.70 (d, 2H, J = 4.4), 3.56−3.64 (m, 2H), 3.14−3.24 (m, 2H), 2.48 (br s, 1H), 1.99−2.04 (m, 1H), 1.71−1.82 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.7, 149.5, 137.9, 129.8, 128.8, 128.2, 128.1, 119.0, 111.8, 106.2, 73.6, 68.7, 65.0, 46.5, 38.8, 30.1. IR: 3386, 2923, 2859, 1527, 1454, 1092, 733, 698 cm^{-1}. HRMS (DART-TOF): calcd for $C_{18}H_{23}N_2O_4$ [M + H] 331.1658, found 331.1662. $[\alpha]_D^{20}$ = +19.8° (c = 0.200, $CHCl_3$, l = 50 mm).

*(S)-4-(Benzyloxy)-2-((pyridin-3-ylamino)methyl)butan-1-ol (**5i**).* Orange oil (36.5 mg, 64%). HPLC (OD-H, 1.0 mL/min, 21% *i*PrOH/79% Hexanes, 240 nm): t_r(major) = 17.2 min and t_r(minor) = 27.6 min, 87% ee. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.93 (br s, 2H), 7.28−7.36 (m, 5H), 7.05 (br s, 1H), 6.82 (d, 1H, J = 5.0), 4.52 (s, 2H), 4.26 (br s, 1H), 3.70 (d, 2H, J = 4.7), 3.55−3.63 (m, 2H), 3.11−3.21 (m, 2H), 1.98−2.02 (m, 1H), 1.73−1.77 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.8, 138.4, 138.0, 136.0, 128.7, 128.1, 128.0, 123.9, 118.7, 73.5, 68.7, 64.8, 46.3, 38.7, 30.1. IR: 2858, 1589, 1091, 794, 734, 632 cm^{-1}. HRMS (DART-TOF): calcd for $C_{17}H_{23}N_2O_2$ [M + H] 287.1760, found 287.1759. $[\alpha]_D^{20}$ = +3.5° (c = 0.465, $CHCl_3$, l = 50 mm).

■ ASSOCIATED CONTENT

Supporting Information. Figures and tables giving NMR spectra for all compounds, HPLC traces, and equilibrium data. This material is available free of charge via the Internet at http://pubs.acs.org.

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