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Catalytic Asymmetric Syntheses of α-Amino and α-Hydroxyl Acid Derivatives

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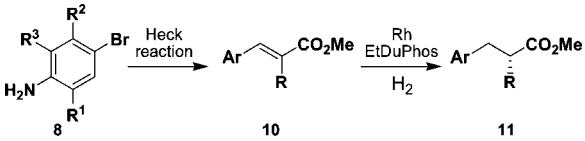


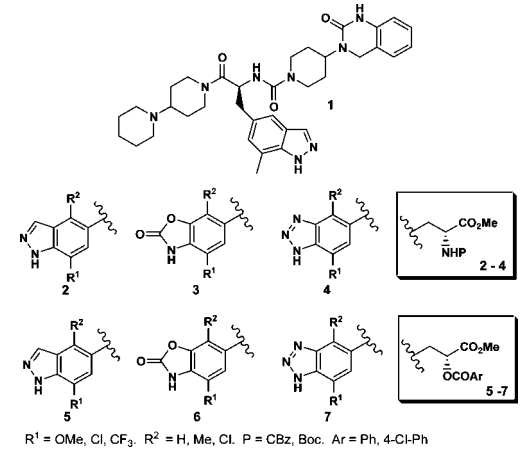
8 10 11

R = NHP; P = CBz , Boc. R = $OCOAr^1$; Ar^1 = Ph, 4-Cl-Ph

Herein we report the first room temperature Heck reaction of aryl bromides and CH_2═C(NHP)CO_2Me (P = Boc or CBz) to form ArCH═C(NHP)CO_2Me, which are then used for the asymmetric syntheses of α-amino acids. We also report the first syntheses of ArCH═C($OCOAr^1$)CO_2Me (Ar^1 = Ph, 4-Cl−Ph) from ArBr and CH_2═C($OCOAr^1$)CO_2Me by the Heck reaction and subsequent successful asymmetric hydrogenation to afford α-hydroxyl esters in excellent chemical yields and good-to-excellent enantioselectivities.

In the course of our synthesis of CGRP antagonists for the treatment of migraines, we found that the 7-methylindazole of **1** imparted excellent potency and an improved cytochrome P450 (CYP) profile in comparison with earlier program leads.[1] To expand our understanding of the SAR around the amino acid residue of the above-mentioned antagonists, we needed a practical asymmetric synthesis of orthogonally protected amino esters **2**−**4**. We were also interested in the preparation of the corresponding α-hydroxy esters **5**−**7** to form the corresponding carbamates. These might demonstrate better pharmacokinetic properties by virtue of their reduced hydrogen-bonding capacity.[2]

Previously, α-amino acid derivatives have been prepared by the coupling of aryl iodides or bromides **8** with enamides **9a**,**b** to form enamides **10**,[3] and the latter has been shown to undergo asymmetric hydrogenation to give **11** (Scheme 1).[4] Jeffery's ligandless conditions[5] [$Pd(OAc)_2$, TBAC, base ($NaHCO_3$ K_2CO_3, or Et_3N), solvent (THF, DMF, or MeCN), 80−120 °C, hours] are most commonly used for this Heck reaction in the literature. To increase functional group tolerance, we needed to develop milder reaction conditions that would tolerate more diverse functionality on the phenyl ring (R^1−R^3) to support our SAR studies. Moreover, it was desirable to develop conditions which were compatible with the use of aryl bromides (rather than aryl iodides) as these are more readily available, both synthetically and commercially.



R^1 = OMe, Cl, CF_3. R^2 = H, Me, Cl. P = CBz, Boc. Ar = Ph, 4-Cl-Ph

Enol esters (**10c**,**d**, Scheme 1) have been prepared by Horner−Wadsworth−Emmons olefination of aldehydes with α-benzoate phosphonate esters,[6] the synthesis of which often requires the use of diazomethane (vide infra). We believed that the Heck reaction of aryl bromides **8** with **9c**,**d**[7] could serve as a more practical route to **10c**,**d**, considering the commercial availability and ease of the syntheses of aryl bromides when compared with aryl aldehydes. Additionally, it would seem that the accessibility of **9c**,**d** would be preferable to the preparation of the α-benzoate phosphonate ester required for the Horner−Wadsworth−Emmons reaction[6,7] and would eliminate the need to use diazomethane.[8b] However, there were no literature reports on this approach (**8** + **9c**,**d** → **10c**,**d**). Also, there was very limited precedent for the asymmetric hydrogenation of **10c**,**d** forming chiral α-hydroxyl esters,[8] probably because of the weak

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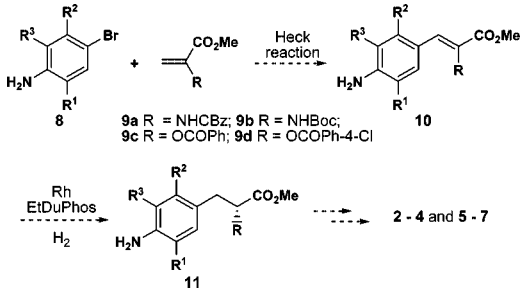
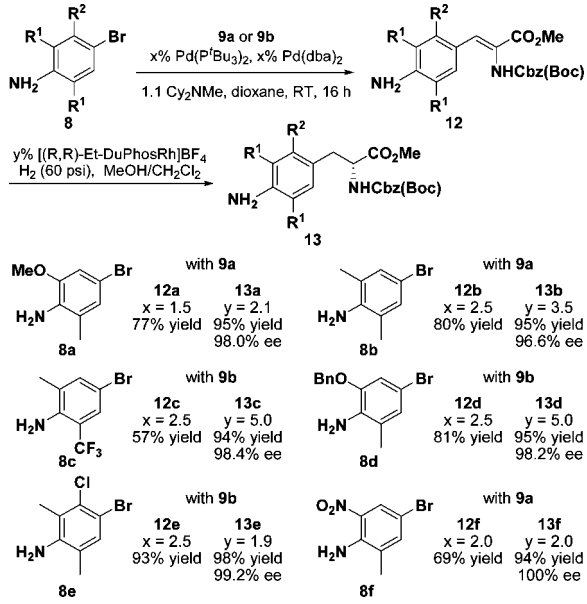
SCHEME 1. General Reaction Sequence of the Synthesis of 2−4 and 5−7



SCHEME 2. Asymmetric Syntheses of Aniline Substituted Alanines 13a−f

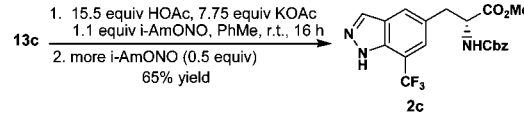


coordination power of the enol oxygen in **10c**,**d** to the transition metal, as well as the difficulties in accessing this class of substrates by earlier methods.

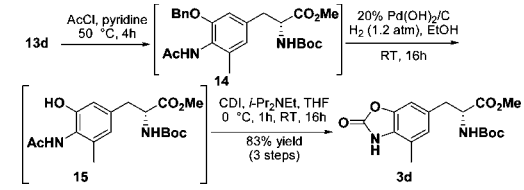
In this note, we report the first room temperature Heck reaction of aryl bromides **8** and enamides **9a**,**b** to make aryl enamides **10a**,**b**, the first Heck reaction of **8** and enol esters **9c**,**d** to make aryl enol esters **10c**,**d**, and the subsequent asymmetric hydrogenation to synthesize α-hydroxyl esters in good-to-excellent enantioselectivities.

The Heck reaction of **8a** and **9a,** under various Jeffery type conditions (bases, R_4NX, solvents, and temperatures) afforded **12a** in <20% isolated yield with only 40−60% conversion (Scheme 2). We were delighted to find that, under Fu and Littke's conditions[9] [1.5% Pd(P-*t*-Bu_3)$_2$, 1.5% Pd(dba)$_2$, 1.1 equiv Cy_2NMe, dioxane, rt, 16 h], the same reaction produced **12a** in 77% isolated yield with 100% conversion. To our knowledge, this is the first room temperature Heck reaction of aryl bromides **8** and enamides **9a**,**b**. These reaction conditions have been found to be quite general and have been successfully applied to a number of other aryl bromides (Scheme 2). The electronic nature of substituents on the aryl bromide did not significantly affect this reaction. Electron-rich (**8a** and **8d**), electron-deficient (**8c** and **8f**), and electron-neutral aryl bromides (**8b** and **8e**) all produced enamides **12** in good yields (77−93%) using only 3−5% palladium. Upon hydrogenation, employing

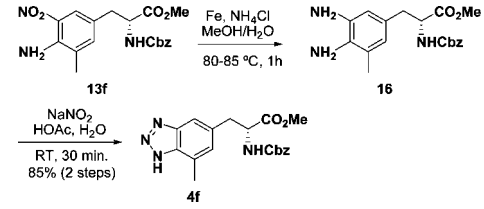
SCHEME 3. Synthesis of Indazole Amino Ester 2c



SCHEME 4. Synthesis of Oxazolidinone Amino Ester 3d



SCHEME 5. Synthesis of Benzotriazole Amino Ester 4f



Burk's rhodium complex of EtDuphos,[10] all aryl enamides **12a**−**f** produced amino esters **13a**−**f** in high chemical yields (90−95%) and excellent enantioselectivities (96.6−100% ee).

Treatment of aniline **13c** with *i*-AmONO in the presence of acetic acid and potassium acetate in toluene at room temperature afforded indazole amino ester **2c** in 65% yield (Scheme 3).[1] During optimization of this reaction, it was found that KOAc gave higher yields than NaOAc. Similarly, it was found that toluene was preferred to other solvents such as chloroform and dichloromethane. Presumably, the reaction proceeds via nucleophilic attack of the $-CH_2^-$ onto the diazonium ion. The balance between the basicity of the base and the stability of the diazonium salt was crucial for the reaction.

Acetylation of aniline **13d** with acetyl chloride, followed by removal of the benzyl protection group of **14** by hydrogenolysis, gave *o*-hydroxy anilide **15** (Scheme 4). Treatment of **15** with carbonyldiimidazole afforded oxazolidinone amino ester **3d** in 83% yield (three steps from **13d**, Scheme 4).[11] Benzotriazole amino ester **4f** was synthesized in 85% yield (two steps from **13f**) by reduction[12] of the nitro group in **13f** with iron and treatment of the resulting aniline (**16**) with sodium nitrite in acetic acid/water (Scheme 5).[13]

After much experimentation (vide supra), we found that the Heck coupling of aryl bromide **8a** with **9c** afforded enol ester

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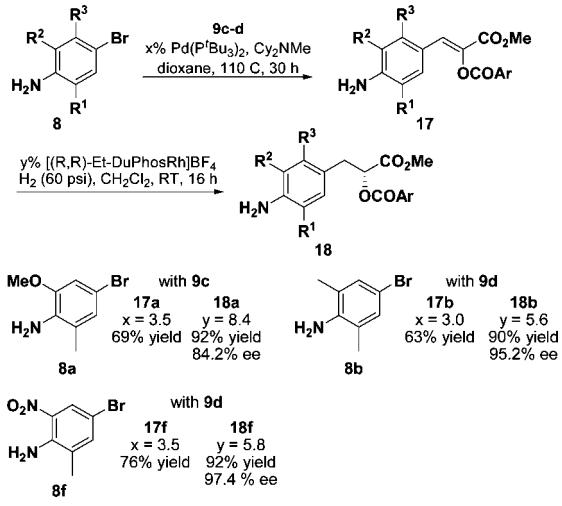
SCHEME 6. Asymmetric Syntheses of α-Hydroxyl Ester 18



17a in 69% yield using 5% Pd(P-*t*-Bu$_3$)$_2$ and Cy$_2$NMe in dioxane at 110 °C over 30 h (Scheme 6).[9] As we found with the enamides, introduction of electron-poor (**8f**) or electron-neutral (**8b**) aryl bromides had very little effect on the reaction, affording the corresponding enol esters **17f** and **17b** in good yields (Scheme 6). Hydrogenation of freshly prepared **17a**,**b** and **f** using Burk's conditions (5.6−8.4% of [(*R*,*R*)-Et-DuPhos(COD)]BF$_4$, H_2 (60 psi), CH_2Cl_2, rt, 16 h] afforded aryl α-hydroxyl esters **18a**,**b** and **f** in excellent chemical yields and with high levels of enantioselectivity (84.2%, 95.2%, and 97.4% ee, respectively). Dichloromethane alone gave better results than a 1:1 mixture of methanol and dichloromethane. The hydrogenation of enol esters required a higher catalyst loading in comparison with the corresponding enamides likely because of their reduced chemical stability. The aryl aniline esters **18a**,**b** and **f** were conveniently converted to the heteroaromatic α-hydroxyl esters **5**−**7**, employing the same methods used in the preparation of **2**−**4** from **13**.

In conclusion, we report the first room temperature Heck reaction of aryl bromides with CH_2═C(NHP)CO_2Me (P = Boc or CBz) to form ArCH═C(NHP)CO_2Me. The increased commercial availability of aryl bromides, the more facile preparation of aryl bromides in comparison with aryl iodides, and the use of these milder Heck reaction conditions significantly expands the range of enamides that can be prepared by our method. By coupling this method with Burk's well-established asymmetric hydrogenation of enamides, we have developed an efficient, mild, and practical route to unnatural α-amino acids. We also report the first Heck reaction route to the synthesis of ArCH═C(OCOAr^1)CO_2Me (Ar^1 = Ph, 4-Cl−Ph) from aryl bromides and CH_2═C(OCOAr^1)CO_2Me. Their subsequent asymmetric hydrogenation afforded novel α-hydroxyl esters in excellent chemical yields and good-to-excellent enantioselectivities.

Experimental Section

Representative Procedure for the Room Temperature Heck Reaction of ArBr (8) and CH_2═(NHP)CO_2Me (P = Boc or CBZ) (9): Enamide 12a. A flame-dried 500 mL Schlenk flask was charged with **8a** (10.0 g, 46.7 mmol), **9a** (12.1 g, 51.4 mmol), Pd(P-*t*-Bu$_3$)$_2$ (0.36 g, 0.70 mmol), and Pd(dba)$_2$ (0.40 g, 0.70 mmol). The flask was alternately evacuated and filled with N_2 five times. Dioxane (100 mL) and Cy$_2$NMe (10.9 mL, 51.4 mmol), both of which were degassed by bubbling N_2 through them for 30 min prior to use, were added. The resulting suspension was evacuated, filled with N_2 five times, and then stirred at rt for 16 h. The reaction mixture was diluted with EtOAc (500 mL) and filtered through a pad of Celite, washing with EtOAc (700 mL). The filtrate was concentrated and the residue subjected to flash chromatography, eluting with EtOAc/hexanes (1:5−1:2) containing 1% Et_3N to afford **12a** as an off-white solid (13.4 g, 77% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.11 (s, 3 H), 3.67 (br s, 3H), 3.78 (br s, 3H), 4.06 (br s, 2H), 5.14 (br s, 2H), 6.93 (s, 1H), 6.98 (s, 1H), 7.26−7.40 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 17.2, 52.4, 55.4, 67.4, 109.4, 120.1, 121.4, 122.6, 126.9, 128.3, 128.3, 128.4, 128.6, 135.3, 136.4, 137.0, 146.3, 166.5. HRMS (M + H)$^+$ calcd for $C_{20}H_{23}N_2O_5$ 371.1607, found 371.1613.

Representative Procedure for the Asymmetric Hydrogenation of Enamides 12: Amino Ester 13a. To a flame-dried Parr hydrogenation bottle were added **12a** (8.09 g, 21.9 mmol), CH_2Cl_2 (50 mL), and MeOH (50 mL). The resulting solution was degassed by bubbling N_2 through it for 20 min. After [(*R*,*R*)-EtDuPhos(COD)]BF$_4$ (0.30 g, 0.45 mmol) was added, the mixture was immediately transferred to a Parr hydrogenation apparatus and was agitated at rt under H_2 (60 psi) for 16 h. The reaction mixture was concentrated and the resulting residue subjected to flash chromatography eluting with EtOAc/hexanes (1:2) to afford **13a** as an off-white solid (7.72 g, 95% yield, and 98.0% ee). The ee was determined by HPLC analysis (Chiralcel OJ-H column, 4.6 × 250 mm, 5 μm; 10% MeOH in CO_2 at 2.0 mL/min for 15 min; λ = 220 nm; T = 35 °C; t_R = 9.15 min for the *R*- and 11.29 min for the *S*-enantiomer). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.11 (s, 3H), 2.99 (d, J = 5.49 Hz, 2H), 3.68 (br s, 2H), 3.72 (s, 3H), 3.76 (s, 3H), 4.54−4.63 (m, 1H), 5.04−5.14 (m, 2H), 5.14−5.20 (m, 1H), 6.40 (s, 1H), 6.42 (s, 1H), 7.28−7.38 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 17.3, 37.9, 52.3, 55.2, 55.7, 67.0, 109.1, 122.6, 123.6, 124.6, 128.2, 128.3, 128.6, 133.4, 136.4, 147.1, 155.8, 172.4. HRMS (M + H)$^+$ calcd for $C_{20}H_{25}N_2O_5$ 373.1763, found 373.1768.

α-Amino Ester 2c. *i*-AmONO (0.40 mL, 2.95 mmol) was added dropwise to a mixture of **13c** (1.0 g, 2.66 mmol), KOAc (2.02 g, 20.6 mmol), HOAc (2.35 mL, 41.2 mmol), and toluene (25 mL). The resulting suspension was stirred at rt for 16 h. Additional toluene (75 mL) and *i*-AmONO (0.18 mL, 1.33 mmol) were added to the resulting mixture. After stirring at rt for 20 h, H_2O (100 mL) and $NaHCO_3$ (5.0 g) were added, and stirring was continued at rt for 2 h. The mixture was partitioned between CH_2Cl_2 and H_2O. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated and the resulting residue subjected to flash chromatography, eluting with EtOAc/hexanes (1:1) to afford **2c** as an off-white solid (0.66 g, 64% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.42 (s, 9H), 3.20 (dd, J = 13.89, 5.65 Hz, 1H), 3.27−3.36 (m, 1H), 3.74 (s, 3 H), 4.66 (d, J = 7.02 Hz, 1H), 5.28 (d, J = 7.63 Hz, 1H), 7.40 (s, 1H), 7.68 (s, 1H), 8.06 (s, 1H), 10.67 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 28.4, 38.1, 52.5, 54.7, 80.3, 112.8 (q, J = 34.2 Hz), 124.2 (q, J = 272.6 Hz), 125.2, 125.4, 126.3, 128.8, 134.7, 135.0, 155.2, 172.2. HRMS (M + H)$^+$ calcd for $C_{17}H_{21}F_3N_3O_4$ 388.1484, found 388.1479.

α-Amino Ester 3d. To a mixture of **13d** (2.0 g, 4.83 mmol) and pyridine (50 mL) at 50 °C was added AcCl (0.52 mL, 7.25 mmol), and the mixture was heated at 50 °C for 1 h. A second portion of AcCl (0.52 mL) was added, and heating was continued at 50 °C. After 20 min, a final portion of AcCl (0.52 mL) was added, and heating was continued at 50 °C for 1.5 h. All volatiles were removed in vacuo, and the resulting residue was partitioned between EtOAc and 1:1 saturated $NaHCO_3$/brine. The organic layer was separated and the aqueous layer extracted with more EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The resulting solid was dissolved in 1:9 2 M NH_3−MeOH/CH_2Cl_2. All solvents were then removed and the solid dried under vacuum.

To a flame-dried Parr hydrogenation bottle was added the above crude solid in EtOH (120 mL). The resulting solution was degassed by bubbling N_2 through it for 20 min. Pearlman's catalyst (0.88 g) was added, and the mixture was agitated at rt under H_2 (1.2 atm) for 16 h. The reaction mixture was filtered through a pad of Celite and the filtrate concentrated to give a solid, which was dried under vacuum.

In a flame-dried round-bottom flask, the crude solid in THF (100 mL) and *i*-Pr_2NEt (1.7 mL, 9.64 mmol) were cooled to 0 °C. CDI (1.56 g, 9.64 mmol) was added, and the mixture was stirred at rt for 16 h. After all volatiles were removed in vacuo, the residue was subjected to flash chromatography eluting with EtOAc/hexanes (2:3) to afford **3d** (1.41 g, 4.01 mmol, 83% yield for three steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 1.42 (s, 9H), 2.29 (s, 3H), 3.02 (dd, J = 13.89, 5.65 Hz, 1H), 3.06−3.17 (m, 1H), 3.74 (s, 3H), 4.57 (d, J = 7.32 Hz, 1H), 5.11 (d, J = 7.93 Hz, 1H), 6.73 (s, 1 H), 6.82 (s, 1H), 9.70 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 16.2, 28.4, 38.4, 52.5, 54.8, 80.2, 108.4, 120.2, 126.4, 127.8, 130.7, 143.8, 155.3, 156.5, 172.6. HRMS $(M + H)^+$ calcd for $C_{17}H_{23}N_2O_6$ 351.1556, found 351.1564.

Amino Ester 4f. Immediately prior to use, both solvents (MeOH and H_2O) were degassed by bubbling N_2 through them for 30 min. A solution of **13f** (4.82 g, 12.4 mmol) in MeOH (90 mL) was added to a mixture of NH_4Cl (6.67 g, 124 mmol) and Fe powder (4.17 g, 74.7 mmol) in H_2O/MeOH (70 mL/50 mL). The mixture was heated at 85 °C for 1 h, and then, while still hot, it was filtered through a pad of Celite, rinsing the filter cake thoroughly with MeOH. The filtrate was concentrated and dried under high vacuum to afford an off-white solid.

To a suspension of the crude solid in HOAc/H_2O (97 mL/150 mL) was added a solution of $NaNO_2$ (0.86 g, 12.4 mmol) in H_2O (15 mL) at rt. The reaction mixture was stirred at rt for 35 min and then concentrated in vacuo. The resulting residue was partitioned between EtOAc and 1:1 saturated $NaHCO_3$/H_2O. The organic layer was separated, and the aqueous layer was extracted with additional EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to flash chromatography eluting with EtOAc/hexanes (2:3) to afford **4f** as a light tan solid (4.03 g, 85% yield for two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.66 (s, 3H), 3.10−3.23 (m, 1H), 3.24−3.36 (m, 1H), 3.74 (s, 3H), 4.66−4.82 (m, 1H), 4.96−5.19 (m, 2H), 5.37 (d, J = 7.63 Hz, 1H), 6.94 (s, 1H), 7.28−7.39 (m, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ ppm 16.7, 36.5, 51.8, 55.5, 65.3, 127.3, 127.6, 128.2, 136.8, 155.9, 172.1. HRMS $(M + H)^+$ calcd for $C_{19}H_{21}N_4O_4$ 369.1563, found 369.1570.

Representative Procedure for the Heck Reaction of ArBr 8 and Enol Esters 9c,d to Form Enol Esters 17: Enol Ester 17f. To a flame-dried three-neck flask equipped with a condenser were added **8f** (6.45 g, 28 mmol), **9d** (7.4 g, 30.8 mmol), and Pd(P-*t*-$Bu_3)_2$ (0.50 g, 0.98 mmol). After the system was purged with N_2 five times, degassed dioxane (65 mL) and Cy_2NMe (6.5 mL, 30.8 mmol) were added. Again, the system was purged with N_2 three times prior to heating the mixture at 110 °C for 24 h. The mixture was partitioned between CH_2Cl_2 and saturated $NaHCO_3$. The organic layer was separated and the aqueous layer extracted with additional CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was subjected to flash chromatography eluting with straight CH_2Cl_2 to afford **17f** as a light orange solid (8.3 g, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.17 (s, 3H), 3.84 (s, 3H), 6.37 (br s, 2H), 7.29 (s, 1H), 7.49 (s, 1H), 7.52 (d, J = 8.55 Hz, 2H), 8.17 (d, J = 8.55 Hz, 2H), 8.46 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 17.8, 52.8, 120.1, 125.6, 126.3, 126.8, 127.0, 129.3, 131.8, 132.1, 136.0, 137.3, 140.9, 144.2, 163.0, 163.5. HRMS $(M + H)^+$ calcd for $C_{18}H_{16}ClN_2O_6$ 391.0697, found 391.0704.

Representative Procedure for the Asymmetric Hydrogenation of Enol Esters 17 to Form α-Hydroxyl Esters 18: α-Hydroxyl Ester 18f. The title compound **18f** (3.67 g, 92% yield, and 97.4% ee) was prepared from **17f** (4.0 g, 10.2 mmol) according to the procedure described for the preparation of **13a**. The ee was determined by HPLC analysis (Chiralcel OD-H column, 4.6 × 250 mm, 5 μm; 15% MeOH in CO_2 at 2.0 mL/min for 12 min; λ = 220 nm; T = 35 °C; t_R = 7.51 min for the *S*- and 8.39 min for the *R*-enantiomer). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 2.21 (s, 3H), 3.12−3.24 (m, 2H), 3.76 (s, 3H), 5.39 (dd, J = 7.63, 4.88 Hz, 1H), 6.11 (br s, 2H), 7.21 (s, 1H), 7.42 (d, J = 8.55 Hz, 2H), 7.97 (d, J = 8.55 Hz, 2H), 8.00 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ ppm 17.7, 36.4, 52.7, 73.3, 123.4, 124.9, 125.8, 127.7, 129.0, 131.3, 132.1, 137.4, 140.2, 142.6, 165.0, 169.7. HRMS $(M + H)^+$ calcd for $C_{18}H_{18}ClN_2O_6$ 393.0853, found 393.0856.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds and HPLC traces for all ee determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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