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Enantioselective Synthesis of α -Methyl- β -Cyclopropyldihydrocinnamates

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ABSTRACT

 α - and β -substitution of dihydrocinnamates has been shown to increase the biological activity of various drug candidates. Recently, we identified enantio- and diastereopure α -methyl- β cyclopropyldihydrocinnamates to be important pharmacophores in one of our drug discovery programs and endeavored to devise an asymmetric hydrogenation strategy to improve access to this valuable framework. We used high throughput experimentation to define stereoconvergent Suzuki-Miyaura cross-coupling conditions affording (Z)- α -methyl- β -cyclopropylcinnamates and subsequent ruthenium-catalyzed asymmetric hydrogenation conditions affording the desired products in excellent enantio- and diastereoselectivities. These conditions were executed on α -methyl- β provide enantiopure multigram to kilogram scale to three key cyclopropyldihydrocinnamates with high selectivity.

INTRODUCTION

Dihydrocinnamate derivatives represent an important class of compounds in the field of drug discovery and development that are widely used as building blocks in the synthesis of drug candidates. In addition, dihydrocinnamate moieties have been observed in several compounds of biological interest. This observation may be explained by their unique structure, comprised of an aromatic ring and carboxylate group spaced by a two carbon aliphatic chain, which can lead to specific spatial interactions with biological targets.¹ Recent examples in the literature indicate that α - and β - substitution of dihydrocinnamate moieties can further increase biological activity in drug candidates.²

Recently, α -methyl- β -cyclopropyldihydrocinnamates were found to be important pharmacophores in one of our drug discovery programs. Their initial access route was fraught with long linear sequences, low yields, and requisite chiral chromatography – a bottleneck that quickly came to limit the discovery and development of new promising drug candidates. To overcome this challenge we embarked towards the discovery of a novel, efficient, enantio- and diastereoselective synthesis centered around asymmetric hydrogenation of tetra substituted cinnamate esters (Scheme 1).

Scheme 1. Asymmetric hydrogenation approach



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We immediately recognized that both the stereoselective synthesis of the tetra substituted cinnamate esters and the subsequent asymmetric hydrogenation³ would pose substantial challenges, particularly in the presence of the hydrogenation labile cyclopropyl substituents.⁴ Even though recent progress has been made in the asymmetric hydrogenation of tetra substituted enamides,⁵ α -dehydroamino acid derivatives,⁶ β -dehydroamino acid derivatives⁷ and unsaturated carboxylic acids;⁸ fewer examples can be found around the asymmetric hydrogenation of unsaturated esters,⁹ enones¹⁰ and unfunctionalized olefins¹¹ lacking strong coordinating functional groups. We therefore brought to bear the power of high throughput experimentation (HTE) to rapidly scan across reaction space and identify promising conditions for the development of these two key transformations.

Herein, we describe the utilization of HTE to define both a stereoselective Suzuki-Miyaura cross-coupling as well as an asymmetric hydrogenation affording the desired products in excellent enantio- and diastereoselectivities.

RESULTS & DISCUSSION

Preparation of (*Z*)- α -methyl- β -cyclopropylcinnamates. The initial strategy to access α methyl- β -cyclopropyldihydrocinnamates intercepted Meldrum's acid derivative **3**, installing the β -substituent via conjugate addition. The overall racemic synthesis was five linear steps followed by a challenging chiral separation, affording the desired products in less than 10% overall yield (Scheme 2). In addition, attempts to install the desired functionality using copper catalyzed conjugate addition to α , β -unsaturated esters failed to produce any of the desired product.

Scheme 2. Original route for the synthesis of α,β -disubstituted-dihydrocinnamates



Our first step towards accessing chiral α,β -disubstituted-dihydrocinnamates via asymmetric hydrogenation was to investigate the synthesis of geometrically pure (*Z*)- α,β -disubstitutedcinnamates, as we recognized that the olefin geometry would define the relative stereochemistry at the α - and β - positions. In addition, we aimed to design a synthesis that would allow for introduction of a variety of aryl substituents. Our strategy to obtain the (*Z*)-cinnamate centered on a cross-coupling reaction between an appropriate aryl nucleophile and a (*Z*)-vinyl halide or sulfonate, assuming the geometry could be preserved under the appropriate reaction conditions.^{6a,12} This modular route would allow for introduction of a high degree of diversity to support any future structure activity research (Scheme 3).

Scheme 3. Retrosynthetic analysis for preparation of α_{β} -disubstituted-dihydrocinnamates



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Execution of our planned synthesis began through alkylation of methyl 3-cyclopropyl-3oxopropanoate (6) with methyl iodide to afford α -substituted- β -ketoester 7, which, on treatment with KHMDS at -20 °C in the presence of tosyl anhydride provided enol tosylate 8 in good yield, albeit in a 1:1 E:Z ratio. Further optimization via screening of base and temperature combinations provided either stereoisomer with good selectivity. Deprotonation with NaHMDS at ambient temperature provided 95:5 selectivity for the desired (*Z*)-enol tosylate 8 (Table 1).

Table 1. Selective synthesis of the (Z)-enol tosylate



^aSignificant impurity generation observed. ^b58% isolated yield.

(Z)-enol tosylate **8** was then subjected to a series of conditions via HTE in order to develop the optimal Suzuki-Miyaura conditions. Upon evaluating 24 ligands in 8 base and solvent combinations, we found $Pd(OAc)_2$ / XPhos or SPhos with K_3PO_4 as base in a mixture of



acetonitrile and water afforded the highest yield of desired product (Figure 1).¹³ Crucially, cinnamate ester **10** was generated as a single observable stereoisomer.





^{*a*}Conditions: 1.0 equiv enol tosylate, 1.1 equiv boronic acid, 10 mol% Pd(OAc)₂, 20 mol% ligand, 3 equiv 1.0M aq base, 0.1M, 25 °C, 3 h. ^{*b*}Assay yields as determined by UPLC-MS at 210 nm using 1,2,3,5-tetramethoxybenzene as an internal standard.

To further study this key coupling reaction we subjected (*E*)-enol tosylate **8** to the optimized Suzuki conditions and were surprised to again isolate exclusively the (*Z*)-Suzuki product **10** (Scheme 4). This finding indicates an unexpected isomerization of either the reactant or product, most likely through a conjugate addition/elimination process.^{14,15} In order to test for a base catalyzed addition/elimination mechanism of the starting material, we treated the (*E*)- and (*Z*)enol tosylates independently with aqueous K_3PO_4 in acetonitrile, and observed no isomerization of either. In addition, the Suzuki reaction rates from both enol tosylate stereoisomers were similar. This leads us to suspect that palladium reinsertion and/or ligand effects may play a role in the isomerization. Two recent literature reports attribute the occurrence of isomerization under Suzuki-Miyaura conditions to palladium or ligand effects; further experiments are underway to confirm such effects in our system.^{6a,16}

Scheme 4. Formation of (Z)-Suzuki product from both (E)- and (Z)- enol tosylates



Development of Asymmetric Hydrogenation Conditions. With tetra substituted (*Z*)- α -methyl- β -cyclopropylcinnamate **10** in hand, we began HTE efforts to study the asymmetric hydrogenation to (*S*,*R*)- α -methyl- β -cyclopropyldihydrocinnamate **11**. To our knowledge, asymmetric hydrogenation of tetra substituted unsaturated esters bearing potentially hydrogenation-labile cyclopropyl moieties have not been previously reported.^{3,4,9} We focused

our initial evaluation on two transition metal precursors previously shown to catalyze the asymmetric hydrogenation of tetra substituted olefins, $(NBD)_2RhBF_4$ and $(Me-allyl)_2Ru(COD)/HBF_4$.^{6, 9} The screen design incorporated 24 chiral phosphine ligands and two solvents, 2MeTHF and MeOH. The permutations of these factors resulted in a 96-experiment array, which was placed in a 500 psi H₂ atmosphere at 60 °C overnight.

In general, rhodium catalysts gave low conversion to product due to significant substrate decomposition. Given that cyclopropylalkenes are known substrates for rhodium catalyzed cycloadditions, it is likely that rhodium catalyzed cyclopropane ring opening was responsible for the observed decomposition.¹⁷ While most ruthenium catalysts gave low conversion to the product, the combination of (Me-allyl)₂Ru(COD)/ HBF₄ and Josiphos J010-1¹⁸ in MeOH afforded 83% conversion and 94% ee for the (*R*,*S*)-enantiomer of dihydrocinnamate **11**, providing a promising hit for future investigation (Figure 2).



Figure 2. HTE results for asymmetric hydrogenation^{*a,b*}

^{*a*}Conditions: 20 mol% metal precursor, 21 mol% ligand, 40 mol% HBF₄-Et₂O, 0.02M, MeOH, 500 psi H₂, 60 °C, 20 h. ^{*b*}Scatter plot of % ee against % conversion as determined by chiral SFC at 210 nm. See supplemental information for list of ligands screened.

We then screened a broader collection of commercially available chiral phosphine ligands in combination with (Me-allyl)₂Ru(COD)/ HBF₄ in MeOH with the goal of improving on our initial lead and developing optimal conditions. Five high-performing catalyst systems were identified

that afforded excellent conversions and enantioselectivities for the (R,S)-enantiomer of dihydrocinnamate **11** (Table 2). Notably, all the ligands that furnished high-performing catalysts were members of the Josiphos and JoSPOphos ligand families.¹⁹ Three of these ligands displayed structural similarity in having biaryl phosphine substituents on the sterogenic center (Figure 3).





^{*a*}Conditions: 20 mol% (Me-allyl)₂Ru(COD), 21 mol% ligand, 40 mol% HBF₄-Et₂O, 0.02M, MeOH, 500 psi H₂, 60 °C, 20 h. ^{*b*}See Figure 3 for ligand structures. ^{*c*}As determined by chiral SFC at 210 nm.



Figure 3. Selected ligands from asymmetric hydrogenation screening

We subjected the most promising chiral ligands, Josiphos J502-1 and JoSPOphos J688-1, to comparative loading studies (Table 3). In order to achieve optimal catalyst loadings, we increased the substrate concentration from 0.02M to 0.2M and the reaction temperature from 60 °C to 80 °C. Each system catalyzed full conversion to product at 2 mol% loading, with the J502-1 bound catalyst giving slightly higher product enantioselectivity (Table 3, entry 3). Bearing in mind that a precious metal recovery step could potentially be implemented to offset the cost of high catalyst loading, enantiomeric ligand J502-2 was selected to synthesize desired (*S*,*R*)- α -methyl- β -cyclopropyldihydrocinnamate **11**.

Table 3. Loading study and comparison of J502-1 and J688-1.



^{*a*}Conditions: (Me-allyl)₂Ru(COD), ligand, HBF₄.Et₂O, 0.2M, MeOH, 500 psi H₂, 80 °C, 20 h. ^{*b*}A ratio of 1.05:1 Ligand/Ru and 2:1 HBF₄/Ru was used. ^{*c*}As determined by chiral HPLC at 210 nm.

The cationic ruthenium/ J502-2 complex proved proficient in catalyzing the asymmetric hydrogenation of three α -methyl- β -cyclopropylcinnamate analogs on multigram to kilogram scales, affording excellent enantioselectivities of products **11a-11c** (Scheme 5). Moreover, this improved route afforded **11a** in 36% overall yield from β -ketoester **6**, a four-fold improvement over the original route. This improvement in chemistry enabled rapid advancement of several candidates into toxicology studies.



Scheme 5. Kilogram and multigram syntheses of α -methyl- β -cyclopropyldihydrocinnamates

^{*a*}Conditions used for preparation of (**Z**)-10c: Pd(dppf)Cl₂·CH₂Cl₂, ag Cs₂CO₃, dioxane, 100 °C. ^bIsolated yields from Suzuki cross-couplings: (**Z**)-10a: 74%, (**Z**)-10b: 83%, (**Z**)-10c: 63%.

CONCLUSIONS

We have developed a facile route to enantiopure α -methyl- β -cyclopropyldihydrocinnamates bearing hydrogenation-labile cyclopropyl substituents. Upon identifying conditions for (Z)selective enol tosylate formation, we leveraged HTE to discover stereoconvergent (Z)-selective Suzuki-Miyaura cross-coupling as well as a cationic ruthenium-catalyzed asymmetric hydrogenation conditions. The developed conditions were mild enough to leave the cyclopropyl ring intact and general enough to be implemented in the multigram to kilogram scale syntheses of three enantiopure α -methyl- β -cyclopropyldihydrocinnamate intermediates.

EXPERIMENTAL

General Methods. Unless otherwise mentioned, all chemicals were purchased from commercial sources and used without further purification. Reactions were monitored by reversed-phase UPLC-MS. ¹H and ¹³C spectra were recorded on a 500 MHz NMR spectrometer. ¹H NMR chemical shifts were determined relative to CDCl₃ as the internal standard at δ 7.26 ppm. ¹³C NMR shifts were determined relative to CDCl₃ at δ 77.16 ppm. Mass spectra were recorded on a high-resolution mass spectrometer in the EI, FAB or ESI modes, Xevo G2-QTof. Enantiomeric excess (ee) values were determined by chiral SFC.

Methyl 3-cyclopropyl-2-methyl-3-oxopropanoate (7). To a clean dry vessel equipped with a mechanical stirrer, thermocouple probe and nitrogen inlet/outlet adapter was added solid K₂CO₃ (11.6 kg, 84 mol) followed by THF (50 L). The mixture was aged at room temperature for 30 min. Methyl 3-cyclopropyl-3-oxopropanoate (5.5 kg, 39 mol) was then added drop-wise over 30 min. The solution was aged for 30 min at room temperature. MeI (6.5 kg, 46 mol) was added drop-wise over 15 min keeping the internal temperature below 22 °C. The reaction was then aged at room temperature for 30 min then heated to 40 °C for 48 h. The reaction was cooled to room temperature and the batch concentrated under vacuum to 25 L. The resulting slurry was filtered and the wet cake was rinsed with THF (90 L). The solution was then concentrated under vacuum to 10 L, followed by addition of MTBE (40 L) and water (50 L). The organic layer was separated and washed with fresh water (50 L). The organic layer was separated and concentrated under reduced pressure to 25 L. The resulting 5.5 kg of methyl 3-cyclopropyl-2-methyl-3oxopropanoate was carried through to the next step as a 22.6 wt% solution in 94% assay yield. ¹H NMR (500 MHz, CDCl₃): δ 3.76 (s, 3 H), 3.68 (q, J = 7.1 Hz, 1 H), 2.10-2.03 (m, 1 H), 1.43 (d, J = 7.2 Hz, 3 H), 1.12-1.05 (m, 2 H), 0.98-0.92 (m, 2 H). ¹³C NMR (500 MHz, CDCl₃): δ

205.8, 171.1, 53.5, 52.3, 19.3, 12.8, 11.7, 11.6. HRMS (ESI) m/z calcd for $C_8H_{12}O_3$ (M + H) 157.0865, found 157.0863.

(Z)-Methyl 3-cyclopropyl-2-methyl-3-(tosyloxy)acrylate ((Z)-8). 1M NaHMDS (44 kg, 49 mol) was added slowly to the methyl 3-cyclopropyl-2-methyl-3-oxopropanoate solution (5.5 kg, 35 mol) over 2 h at room temperature. The mixture was aged for 3 h. Meanwhile tosyl anhydride (13 kg, 40 mol) was dissolved in THF (70 L). The tosyl anhydride solution was added slowly over 5 h at room temperature and the batch was aged for 1 h. AcOH was added to adjust the batch pH to 7. Water (60 L) was then added over 30 min and the batch aged for 30 min. EtOAc (111 L) was added to mixture. The layers were separated and the organic layer washed with brine twice. The organic solution was then concentrated to 10 L and the solvent switched to IPA, under vacuum, until the volume reached 10 L with no residual EtOAc. The solution was heated to 45 °C, seeded and aged for 3 h at 45 °C. The slurry was then cooled to 10 °C over 5 h and aged at 15 °C for 8 h. The slurry was filtered and the wet cake was washed with cold IPA (15 L). The wet cake was dried over vacuum to give 6.4 kg of (Z)-methyl 3-cyclopropyl-2-methyl-3-(tosyloxy)acrylate in 59% isolated yield. ¹H NMR (500 MHz, CDCl₃): δ 7.8 (d, J = 8.3 Hz, 2 H), 7.3 (d, J = 8.1 Hz, 2 H), 3.61 (s, 3 H), 2.49 (s, 3 H), 2.04 (s, 3 H), 1.65-1.57 (m, 1 H), 0.77-0.65 (m, 4 H). ¹³C NMR (500 MHz, CDCl₃): δ 167.1, 151.0, 144.9, 134.3, 129.6, 128.0, 121.4, 51.8, 21.6, 15.1, 12.9, 6.9. HRMS (ESI) m/z calcd for $C_{15}H_{18}O_5S$ (M + H) 311.0953, found 311.0950.

(*E*)-*Methyl 3-cyclopropyl-2-methyl-3-(tosyloxy)acrylate* ((*E*)-8). To a clean dry vessel equipped with a mechanical stirrer, thermocouple probe and nitrogen inlet/outlet adapter was added methyl 3-cyclopropyl-2-methyl-3-oxopropanoate (100 mg, 0.640 mmol) followed by THF. The solution was then cooled to -78 °C. A 1M solution of NaHMDS (0.700 mL, 0.700 mmol) was added drop-wise over 10 min keeping internal temperature below -70 °C. Once all the base was added,

the reaction was aged at -78 °C for 20 min. Meanwhile tosyl anhydride (209 mg, 0.640 mmol) was taken up in THF (2.0 mL) and added to the reaction solution over 5 min keeping the internal temperature below -70 °C. The reaction was then allowed to warm to room temperature overnight to give a 80:20 mixture of E:Z tosylate. The reaction was quenched by adding pH 7 buffer and EtOAc. The layers were separated and the organic layer was washed with pure water and then brine. The organic layer was concentrated and purified by silica gel chromatography to give 115 mg of (*E*)-methyl 3-cyclopropyl-2-methyl-3-(tosyloxy)acrylate in 57% yield. ¹H NMR (500 MHz, CDCl₃): δ 7.86 (d, J = 8.2 Hz, 2 H), 7.37 (d, J = 8.1 Hz, 2 H), 3.80 (s, 3 H), 2.49 (s, 3 H), 2.30-2.20 (m, 1 H), 1.75 (s, 3 H), 0.76-0.62 (m, 2 H), 0.69-0.63 (m, 2 H). ¹³C NMR (500 MHz, CDCl₃): δ 169.2, 157.6, 146.5, 134.5, 129.8, 127.9, 122.5, 51.9, 21.7, 14.8, 14.1, 7.1. HRMS (ESI) m/z calcd for C₁₅H₁₈O₅S (M + H) 311.0953, found 311.0956.

(Z)-Methyl 3-(3-(benzyloxy)phenyl)-3-cyclopropyl-2-methylacrylate ((Z)-10a). A mixture of acetonitrile (6.0 L) and water (1.2 L) was charged to a vessel equipped with a mechanical stirrer, thermocouple probe, nitrogen inlet/outlet adapter and a dual compression fitting adapter fitted with a fritted glass sparge tube and an outlet tube. The mixture was degassed by sparging with N₂ for 15min. K₃PO₄ (1.9 kg, 9.0 mol) followed by (3-(benzyloxy)phenyl)boronic acid (0.75 kg, 3.3 mol) were added as a solids as the sparging was continued (a slight exotherm was observed). Then 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (43 g, 0.090 mol), (Z)-methyl 3-cyclopropyl-2-methyl-3-(tosyloxy)acrylate (0.93 kg, 3.0 mol), and palladium(II) acetate (20 g, 0.090 mol) were charged as solids into the flask while the sparging was continued. The reaction mixture was stirred for 2 h at 30 °C at which point HPLC showed 80% conversion. The mixture was stirred for 30 min more at 30 °C. Then additional 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (21 g, 0.045 mol) and palladium(II) acetate (10 g, 0.045 mol) were added.

The mixture was stirred for 1 h at 25 °C at which point HPLC showed > 99% conversion. The mixture was evaporated under vacuum at 30 °C for 1 h. CPME (1.5 L) was added and the batch evaporated. Then CPME (1.5 L), heptane (1.5 L) and water (3.0 L) were added and the mixture was filtered. The organic phase was separated and washed with water (1.5 L), 0.5M aq NaOH (1.5 L) and water (1.5 L). The solution was dried over MgSO₄ (90 g), treated with Darco G60 (45 g) for 15min and filtered through a plug of silica (1.5 kg) and MgSO₄ (90 g). The cake was rinsed with 3:7 CPME/heptane (9.0 L). The filtrate was evaporated at 25 °C to ca 1L of an amber oil which was purified by silica gel chromatography to give 0.71 kg of (Z)-methyl 3-(3-(benzyloxy)phenyl)-3-cyclopropyl-2-methylacrylate in 74% isolated yield. ¹H NMR (500 MHz, CDCl₃): δ 7.47 (d, J = 7.5 Hz, 2 H), 7.41 (t, J = 7.5 Hz, 2 H), 7.35 (d, J = 7.2 Hz, 1 H), 7.25 (t, J = 7.7 Hz, 1 H), 6.89 (dd, J = 2.4, 5.8 Hz, 1 H), 6.68 (s, 1 H), 6.61 (d, J = 7.5 Hz, 1 H), 5.10 (s, 2 H), 3.48 (s, 3 H), 2.21 (s, 3 H) 1.93-1.84 (m, 1 H), 0.81-0.73 (m, 2 H), 0.39-0.34 (m, 2 H). ¹³C NMR (500 MHz, CDCl₃): δ 170.2, 158.0, 149.0, 140.3, 137.0, 128.5, 128.4, 127.9, 127.5, 121.3, 115.0, 113.4, 69.8, 51.2, 15.5, 14.6, 5.7. HRMS (ESI) m/z calcd for C₂₁H₂₂O₃ (M + H) 323.1647, found 323.1656.

(Z)-Methyl 3-(4-(benzyloxy)phenyl)-3-cyclopropyl-2-methylacrylate ((Z)-10b) To a clean dry vessel equipped with a mechanical stirrer, thermocouple probe and nitrogen inlet/outlet adapter were added (Z)-methyl 3-cyclopropyl-2-methyl-3-(tosyloxy)acrylate (151 g, 0.486 mol), (4-(benzyloxy)phenyl)boronic acid (126 g, 0.534 mol), palladium(II) acetate (5.45 g, 0.0243 mol) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (11.6 g, 0.0243 mol). Acetonitrile (1206 mL) was added and the slurry was sparged with N₂ for 10 min. Then degassed 2.0M aq K₃PO₄ (729 mL, 1.46 mol) was added via cannula over 10 min. The resulting black solution was stirred for 2 h at 25 °C. The reaction was quenched with sat NH₄Cl (600 mL) then diluted with

EtOAc (1500 mL) and water (300 mL). Upon 30 min agitation the resulting mixture was filtered and phases separated. The aqueous layer was back-extracted with EtOAc (450 mL). The organic layers were combined and washed with water, then dried over Na₂SO₄ and evaporated under vacuum. The crude compound was dissolved in MeOH and treated with 5 wt % charcoal. Upon agitation for 4 h, the slurry was filtered over solka floc and the solvent was removed. 500 mL of heptane was added and the solvent removed. The compound was dried under vacuum and purified by silica gel chromatography to give 108 g of (Z)-methyl 3-(4-(benzyloxy)phenyl)-3cyclopropyl-2-methylacrylate in 83% isolated yield. ¹H NMR (500 MHz, CDCl₃): δ 7.47 (d, J = 7.6 Hz, 2 H), 7.41 (t, J = 7.4 Hz, 2 H), 7.35 (d, J = 7.9 Hz, 1 H), 6.93 (q, J = 8.7, 4.3 Hz, 4 H), 5.10 (s, 2 H), 3.40 (s, 3 H), 2.19 (s, 3 H) 1.92-1.85 (m, 1 H), 0.81-0.75 (m, 2 H), 0.40-0.33 (m, 2 H). ¹³C NMR (500 MHz, CDCl₃): δ 170.5, 157.6, 148.7, 137.0, 131.3, 129.7, 128.5, 127.9, 127.6, 126.0, 113.8, 69.9, 51.2, 15.7, 14.6, 5.5. HRMS (ESI) m/z calcd for C₂₁H₂₂O₃ (M + H) 323.1643, found 323.1653. (Z)-methyl 3-cyclopropyl-3-(2-fluoro-3-hydroxyphenyl)-2-methylacrylate ((Z)-10c). To a clean

dry vessel equipped with a mechanical stirrer, thermocouple probe and nitrogen inlet/outlet adapter was added (*Z*)-methyl 3-cyclopropyl-2-methyl-3-(tosyloxy)acrylate (200 g, 0.644 mol), (2-fluoro-3-hydroxyphenyl)boronic acid (110 g, 0.705 mol) and Cs₂CO₃ (231 g, 0.709 mol) followed by degassed dioxane (2000 mL) and degassed H₂O (200 mL). Added Pd(dppf)Cl₂.CH₂Cl₂ (21 g, 0.026 mol) and agitated the mixture at 100 °C for 1h. TLC showed the reaction was completed. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated. The residue was purified by silica gel chromatography to obtain 102 g of (*Z*)-methyl 3-cyclopropyl-3-(2-fluoro-3hydroxyphenyl)-2-methylacrylate in 63% isolated yield. ¹H NMR (500 MHz, CDCl₃): δ 6.94-

6.85 (m, 2 H), 6.40 (dt, J = 2.5, 4.2, 1.7 Hz, 2 H), 5.59 (bs, 1 H), 3.45 (s, 3 H), 2.20 (s, 3 H) 1.96-1.88 (m, 1 H), 0.83-0.76 (m, 2 H), 0.37-0.30 (m, 2 H). ¹³C NMR (500 MHz, CDCl₃): δ 169.2, 148.8-147.0 (d, J = 234.1 Hz), 144.6, 143.3 (d, J = 14.1 Hz), 127.5, 126.9 (d, J = 15.0 Hz), 123.5 (d, J = 4.6 Hz), 121.3 (d, J = 2.8 Hz), 116.2 (d, J = 2.0 Hz), 51.4, 15.4, 14.6, 5.8. HRMS (ESI) m/z calcd for C₁₄H₁₅FO₃ (M + H) 251.1083, found 251.1091.

(2S,3R)-methyl 3-(3-(benzyloxy))phenyl)-3-cyclopropyl-2-methylpropanoate ((S,R)-11a). In a nitrogen-filled glove box with $O_2 < 5$ ppm, (COD)Ru(Me-allyl)₂ (17 g, 0.053 mol) and Josiphos SL-J502-2 (30 g, 0.056 mol) were charged to the precatalyst preparation vessel, followed by anhydrous degassed CH₂Cl₂ (500 mL). Upon 30 min agitation, HBF₄-Et₂O (17 g, 0.106 mol) was added drop wise over 20 min in order to control gas evolution and the precatalyst solution was aged for 30 min. Meanwhile, methyl (Z)-methyl 3-(3-(benzyloxy)phenyl)-3-cyclopropyl-2methylacrylate (1.0 kg, 3.1 mol) was dissolved in MeOH (5.0 L) and the solution was degassed for 2 h. The precatalyst solution was transferred to the reaction vessel, which was purged with argon three times. The headspace exchanged with H₂ six times. The reaction vessel was pressurized with 500 psi H_2 and agitated at 80 °C. The reaction was sampled after 40 h to give 100% conversion and cooled to room temperature. Three batches were combined for isolation (work-up basis 3.3 kg (Z)-methyl 3-(3-(benzyloxy)phenyl)-3-cyclopropyl-2-methylacrylate). The solvent was switched to MeOH at 50 °C under reduced pressure. MeOH (16 L) was added and the mixture heated to 50 °C. Upon a 60 min hold, the mixture was cooled to 45 °C, seeded and cooled to 25 °C over 4 h. Water (6.6 L) was added over 4 h and the slurry was aged at 25 °C for 10 h. The batch was filtered and the wet cake washed with a mixture of MeOH (4.0 L) and water (1.0 L). The wet cake was dried under vacuum at 45 °C for 30 h to obtain 2.9 kg (2S, 3R)-methyl 3-(3-(benzyloxy)phenyl)-3-cyclopropyl-2-methylpropanoate in 88.2% isolated yield with 98%

ee. ¹H NMR (500 MHz, CDCl₃): δ 7.49 (d, J = 7.4 Hz, 2 H), 7.41 (t, J = 7.3 Hz, 2 H), 7.35 (d, J = 7.1 Hz, 1 H), 7.25 (t, J = 8.0 Hz, 1 H), 6.89 (d, J = 8.2 Hz, 1 H), 6.81 (s, 1 H), 6.79 (d, J = 7.5 Hz, 1 H), 5.10 (s, 2 H), 3.78 (s, 3 H) 2.88-2.77 (m, 1 H), 1.98, (t, J = 9.8 Hz, 1 H), 1.13-1.02 (m, 1 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.64-0.55 (m, 1 H), 0.40-0.31 (m, 1 H), 0.31-0.22 (m, 1 H), 0.07-0.00 (m, 1 H). ¹³C NMR (500 MHz, CDCl₃): δ 176.6, 158.8, 144.8, 137.0, 129.3, 128.5, 127.9, 127.6, 120.7, 114.8, 112.4, 70.0, 54.6, 51.5, 45.9, 16.2, 16.0, 6.4, 3.3. [α]_D²⁰ +111 (c 1.3, MeOH). HRMS (ESI) m/z calcd for C₂₁H₂₄O₃ (M + H) 325.1804, found 325.1790.

(2S,3R)-methyl 3-(4-(benzyloxy)phenyl)-3-cyclopropyl-2-methylpropanoate ((S,R)-11b). In a nitrogen-filled glove box with $O_2 < 5$ ppm, (COD)Ru(Me-allyl)₂ (6.0 g, 0.019 mol) and Josiphos SL-J502-2 (10.4g, 0.019 mol) were charged to the precatalyst preparation vessel, followed by anhydrous degassed CH₂Cl₂ (100 mL). Upon 15 min agitation, HBF₄-Et₂O (6.0 g, 0.037 mol) was added drop wise in order to control gas evolution and the precatalyst solution was aged for 20 min. Meanwhile, (Z)-methyl 3-(4-(benzyloxy)phenyl)-3-cyclopropyl-2-methylacrylate (200 g, 0.620 mol) was dissolved in MeOH (2200 mL) and the solution was purged with N₂ (5 x 80 psi). The precatalyst solution was transferred to the reaction vessel and rinsed with MeOH (100 mL). The reactor was sealed and the headspace exchanged with H_2 (3 x 500 psi). The reaction vessel was pressurized with 500 psi H₂ and agitated at 80 °C. The reaction was sampled after 19 h to give 97% conversion, cooled to room temperature and dropped from the vessel. The vessel was rinsed with MeOH (800 mL), which was combined with the batch and concentrated under vacuum to 1000 mL total volume. The slurry was filtered the wet cake dried under vacuum at 45 °C for 16 h to obtain 139 g (2S,3R)-methyl 3-(4-(benzyloxy)phenyl)-3-cyclopropyl-2methylpropanoate in 80.1% isolated yield with 98% ee. ¹H NMR (500 MHz, CDCl₃): δ 7.48 (d, J = 8.7 Hz, 2 H), 7.42 (t, J = 7.4 Hz, 2 H), 7.3 (d, J = 1.5 Hz, 1 H), 7.11 (d, J = 4.5 Hz, 2 H), 6.98

(d, J = 4.5 Hz, 2H), 5.19 (s, 2 H), 3.78 (s, 3 H), 2.86-2.76 (m, 1 H), (t, J = 10 Hz, 1 H), 1.12-1.02 (m, 1 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.62-0.55 (m, 1 H), 0.39-0.32 (m, 1 H), 0.30-0.23 (m, 1 H), 0.06-0.00 (m, 1 H). ¹³C NMR (500 MHz, CDCl₃): δ 176.7, 157.4, 137.1, 135.5, 128.8, 128.5, 127.9, 127.5, 114.6, 114.3, 70.0, 53.7, 51.5, 46.1, 16.3, 15.8, 6.4, 3.3. [α]_D²⁰ +150 (c 0.54, MeOH). HRMS (ESI) m/z calcd for C₂₁H₂₄O₃ (M + H) 325.1804, found 325.1815.

(2S,3R)-methyl 3-cyclopropyl-3-(2-fluoro-3-hydroxyphenyl)-2-methylpropanoate ((S,R)-11c). In a nitrogen-filled glove box with $O_2 < 5$ ppm, (COD)Ru(Me-allyl)₂ (3.8 g, 0.012 mol) and Josiphos SL-J502-2 (6.7 g, 0.012 mol) were charged to the precatalyst preparation vessel, followed by anhydrous degassed MeOH (80 mL). Upon 10 min agitation, HBF₄-Et₂O (3.8 g, 0.024 mol) was added drop wise in order to control gas evolution and the precatalyst solution was aged for 30 min. Meanwhile, methyl (Z)-methyl 3-cyclopropyl-3-(2-fluoro-3hydroxyphenyl)-2-methylacrylate (295 g, 1.18 mol) was dissolved in MeOH (1910 mL) and the solution was purged with N_2 (5 x 80 psi). The precatalyst solution was transferred to the reaction vessel and rinsed with MeOH (80 mL). The reactor was sealed and the headspace exchanged with H_2 (3 x 500 psi). The reaction vessel was pressurized with 500 psi H_2 and agitated at 80 °C. The reaction was sampled after 20 h to give 100% conversion, cooled to room temperature and dropped from the vessel. The batch was concentrated down to an oil and purified by silica gel chromatography to obtain 222 g methyl (2S,3R)-methyl 3-cyclopropyl-3-(2-fluoro-3hydroxyphenyl)-2-methylpropanoate in 74.7% isolated yield with > 99% ee. ¹H NMR (500 MHz, CDCl₃): δ 7.00 (t, J = 8.3 Hz, 1 H), 6.90 (dt, J = 1.6, 6.6 Hz, 1 H), 6.74 (dt, J = 1.6, 6.3 Hz, 1 H), 6.74 (dt, J = 1.6, 1 H), 3.78 (s, 3 H), 2.99-2.91 (m, 1 H), 2.31, (t, J = 10 Hz, 1 H), 1.20-1.10 (m, 1 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.62-0.54 (m, 1 H), 0.38-0.32 (m, 1 H), 0.32-0.25 (m, 1 H), 0.07-0.00 (m, 1 H). ¹³C NMR (500 MHz, CDCl₃): δ 176.7, 150.5-148.6 (d, J = 236.4 Hz), 143.7 (d, J = 15.3 Hz), 130.5

(d, J = 12.8 Hz), 124.4 (d, J = 3.7 Hz), 120.2 (d, J = 4.3 Hz), 115.2 (d, J = 1.8 Hz), 51.7, 48.3, 45.02, 45.00, 16.0, 15.3, 6.5, 3.0. $[\alpha]_D^{20}$ +126 (c 1.10, MeOH). HRMS (ESI) m/z calcd for C₁₄H₁₇FO₃ (M + H) 253.1240, found 253.1242.

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

NMR spectra for all new compounds, chiral SFC traces of compounds 11a-11c, list of chiral

phosphine ligands screened in asymmetric hydrogenation.

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