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Enantioselective Synthesis of α-Methyl-β-cyclopropyldihydrocinnamates

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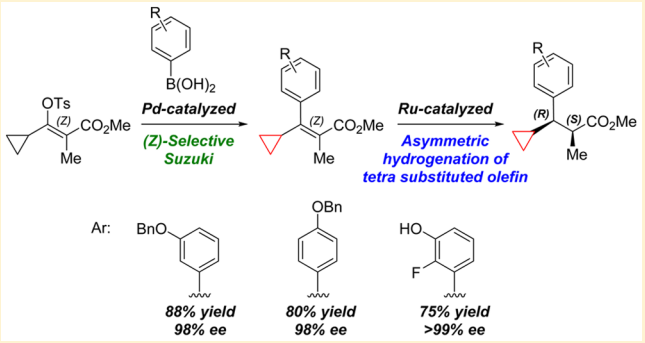
Supporting Information

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 multigram to kilogram scale to provide three key enantiopure α-methyl-β-cyclopropyldihydrocinnamates with high selectivity.



INTRODUCTION

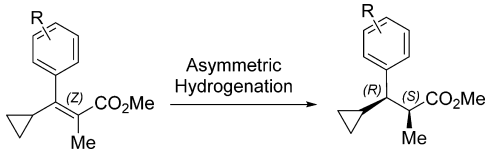
Dihydrocinnamate derivatives represent an important class of compounds in the field of drug discovery and development that are widely used as building blocks in the synthesis of drug candidates. In addition, dihydrocinnamate moieties have been observed in several compounds of biological interest. This 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 toward the discovery of a novel, efficient, enantio- and diastereoselective synthesis centered around asymmetric hydrogenation of tetra substituted cinnamate esters (Scheme 1).

We immediately recognized that both the stereoselective synthesis of the tetra substituted cinnamate esters and the subsequent asymmetric hydrogenation[3] 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 derivatives,[7] and unsaturated carboxylic acids;[8] fewer examples can be found around the asymmetric hydrogenation of unsaturated esters,[9] enones[10] and unfunctionalized olefins[11] 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.

Scheme 1. Asymmetric Hydrogenation Approach



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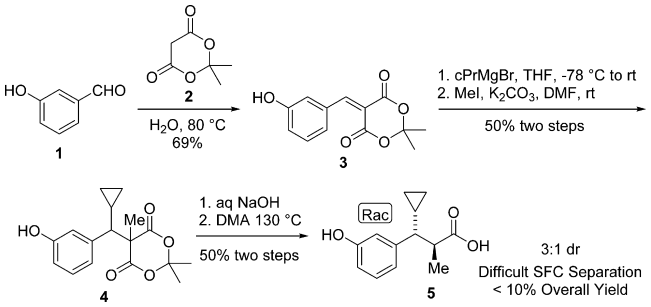
RESULTS AND DISCUSSION

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

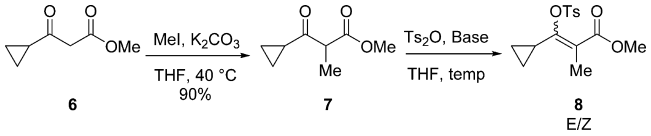


Our first step toward accessing chiral α,β-disubstituted-dihydrocinnamates via asymmetric hydrogenation was to investigate the synthesis of geometrically pure (*Z*)-α,β-disubstituted-cinnamates, as we recognized that the olefin geometry would define the relative stereochemistry at the α- and β- positions. 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).

Execution of our planned synthesis began through alkylation of methyl 3-cyclopropyl-3-oxopropanoate (**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).

(*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

Table 1. Selective Synthesis of the (*Z*)-Enol Tosylate



Entry	Base	Temperature	E/Z
1	KHMDS	-20 °C	50/50
2	LiHMDS	-20 °C	70/30
3	LiHMDS	rt	5/95[a]
4	NaH	rt	20/80
5	NaHMDS	-78 °C	80/20
6	NaHMDS	rt	5/95[b]
7	NaOtBu	-20 °C	30/70

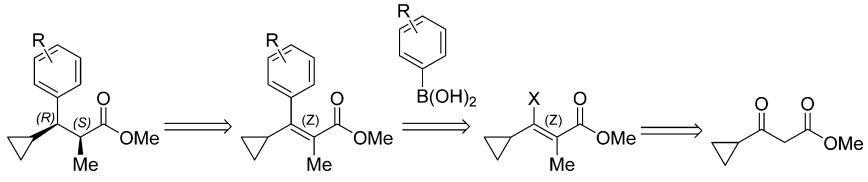
[a]Significant impurity generation observed. [b]58% isolated yield.

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.

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]

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 $(Me\text{-}allyl)_2Ru(COD)/HBF_4$.[6,9] The screen design incorporated 24 chiral phosphine ligands and two

Scheme 3. Retrosynthetic Analysis for Preparation of α,β-Disubstituted-Dihydrocinnamates



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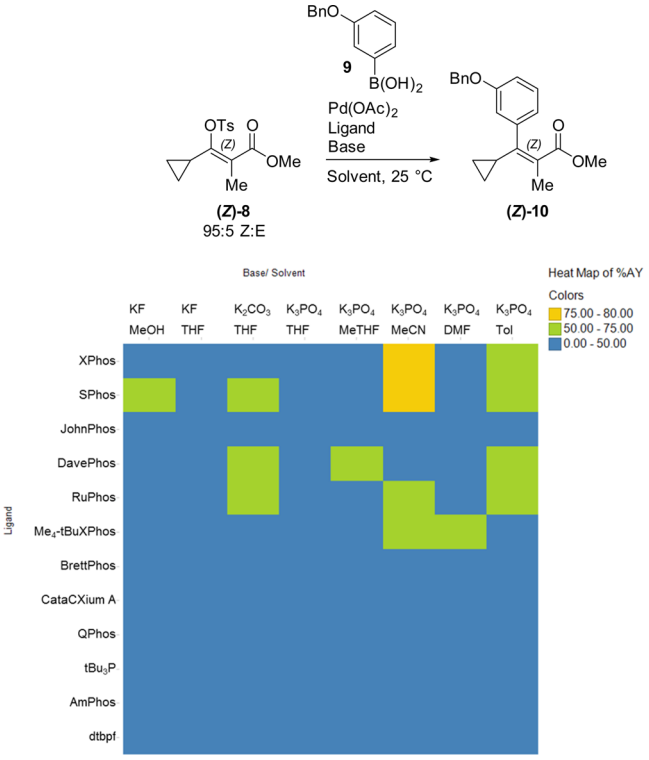


Figure 1. HTE results for Suzuki–Miyaura coupling. Conditions: 1.0 equiv enol tosylate, 1.1 equiv boronic acid, 10 mol % $Pd(OAc)_2$, 20 mol % ligand, 3 equiv 1.0 M aq base, 0.1M, 25 °C, 3 h. Assay yields as determined by UPLC-MS at 210 nm using 1,2,3,5-tetramethoxybenzene as an internal standard.

solvents, 2MeTHF and MeOH. The permutations of these factors resulted in a 96-experiment array, which was placed in a 500 psi H_2 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 $(Me\text{-}allyl)_2Ru(COD)$/ HBF_4 and Josiphos J010-1[18] 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).

We then screened a broader collection of commercially available chiral phosphine ligands in combination with $(Me\text{-}allyl)_2Ru(COD)$/ HBF_4 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

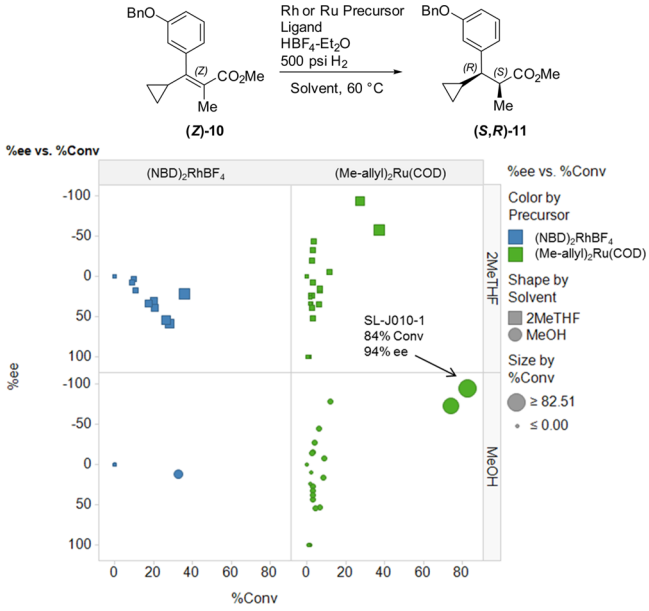
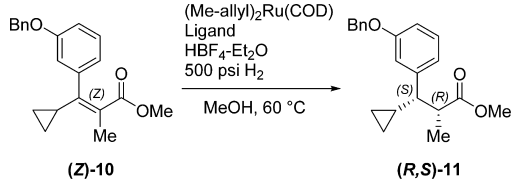


Figure 2. HTE results for asymmetric hydrogenation. Conditions: 20 mol % metal precursor, 21 mol % ligand, 40 mol % HBF_4-Et_2O, 0.02M, MeOH, 500 psi H_2, 60 °C, 20 h. Scatter plot of % ee against % conversion as determined by chiral SFC at 210 nm. See Supporting Information for list of ligands screened.

Table 2. Best Results from Chiral Phosphine Ligand Screen

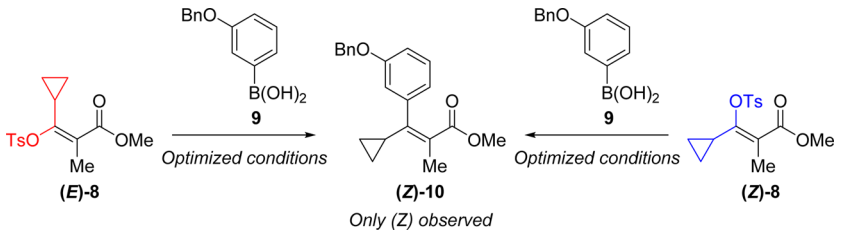


entry[a]	ligand[b]	conv[c]	%ee[c]
1	J010-1	84	94
2	J506-1	100	96
3	J502-1	100	94
4	J688-1	99	94
5	J301-1	100	94
6	J212-1	100	90

[a]Conditions: 20 mol % $(Me\text{-}allyl)_2Ru(COD)$, 21 mol % ligand, 40 mol % HBF_4-Et_2O, 0.02M, MeOH, 500 psi H_2, 60 °C, 20 h. [b]See Figure 3 for ligand structures. [c]As determined by chiral SFC at 210 nm.

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).

Scheme 4. Formation of (*Z*)-Suzuki Product from both (*E*)- and (*Z*)-Enol Tosylates



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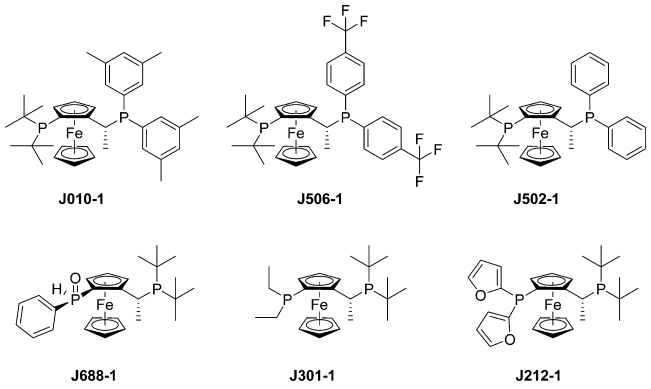
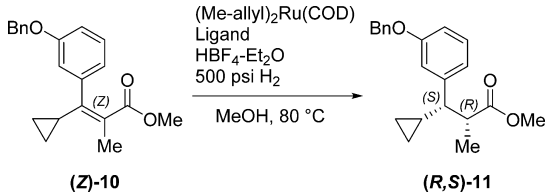


Figure 3. Selected ligands from asymmetric hydrogenation screening.

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

Table 3. Loading Study and Comparison of J502-1 and J688-1



		J502-1		J688-1	
entry[a]	% Ru[b]	conv[c]	%ee[c]	conv[c]	%ee[c]
1	10	100	98	100	96
2	5	100	98	100	97
3	2	100	98	100	97
4	1	91	98	97	97
5	0.5	58	98	67	97

[a]Conditions: (Me-allyl)$_2$Ru(COD), ligand, HBF$_4$.Et$_2$O, 0.2M, MeOH, 500 psi H$_2$, 80 °C, 20 h. [b]A ratio of 1.05:1 Ligand/Ru and 2:1 HBF$_4$/Ru was used. [c]As determined by chiral HPLC at 210 nm.

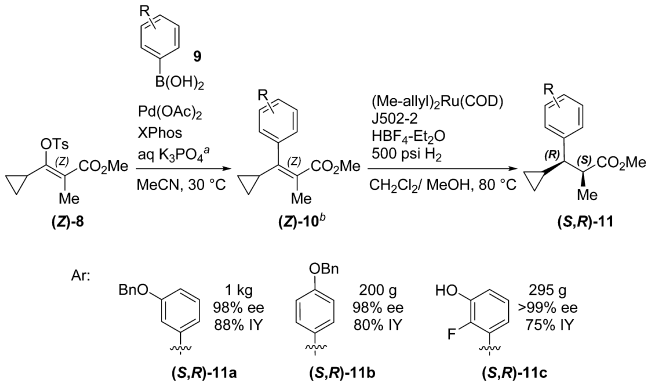
increased the substrate concentration from 0.02 to 0.2 M and the reaction temperature from 60 to 80 °C. Each system catalyzed full conversion to product at 2 mol % loading, with the J502-1 bound catalyst giving slightly higher product enantioselectivity (Table 3, entry 3). Bearing in mind that a precious 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**.

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 4-fold improvement over the original route. This improvement in chemistry enabled rapid advancement of several candidates into toxicology studies.

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.

Scheme 5. Kilogram and Multigram Syntheses of α-Methyl-β-cyclopropyldihydrocinnamates[a,b]



[a]Conditions used for preparation of (*Z*)-**10c**: Pd(dppf)Cl$_2$.CH$_2$Cl$_2$, aq Cs$_2$CO$_3$, dioxane, 100 °C. [b]Isolated yields from Suzuki cross-couplings: (*Z*)-**10a**: 74%, (*Z*)-**10b**: 83%, (*Z*)-**10c**: 63%.

EXPERIMENTAL SECTION

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. ^{1}H and ^{13}C spectra were recorded on a 500 MHz NMR spectrometer. ^{1}H NMR chemical shifts were determined relative to CDCl$_3$ as the internal standard at δ 7.26 ppm. ^{13}C NMR shifts were determined relative to CDCl$_3$ 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 K$_2$CO$_3$ (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 dropwise over 30 min. The solution was aged for 30 min at room temperature. MeI (6.5 kg, 46 mol) was added dropwise 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-3-oxopropanoate was carried through to the next step as a 22.6 wt % solution in 94% assay yield. ^{1}H NMR (500 MHz, CDCl$_3$): 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). ^{13}C NMR (500 MHz, CDCl$_3$): δ 205.8, 171.1, 53.5, 52.3, 19.3, 12.8, 11.7, 11.6. HRMS (ESI) *m*/*z* calcd. for C$_8$H$_{12}$O$_3$ (M + H) 157.0865, found 157.0863.

*(Z)-Methyl 3-cyclopropyl-2-methyl-3-(tosyloxy)acrylate (**(Z)-8**).* 1 M NaHMDS (44 kg, 49 mol) was added slowly to the methyl 3-cyclopropyl-2-methyl-3-oxopropanoate solution (5.5 kg, 35 mol) over

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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. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (500 MHz, $CDCl_3$): 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 1 M solution of NaHMDS (0.700 mL, 0.700 mmol) was added dropwise 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. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (500 MHz, $CDCl_3$): 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 $C_{15}H_{18}O_5S$ (M + H) 311.0953, found 311.0956.

(Z)-Methyl 3-(3-(benzyloxy)phenyl)-3-cyclopropyl-2-methyl Acrylate ***((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 N_2 for 15 min. K_3PO_4 (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), 0.5 M aq NaOH (1.5 L) and water (1.5 L). The solution was dried over $MgSO_4$ (90 g), treated with Darco G60 (45 g) for 15 min and filtered through a plug of silica (1.5 kg) and $MgSO_4$ (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-methyl acrylate in 74% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (500 MHz, $CDCl_3$): 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 $C_{21}H_{22}O_3$ (M + H) 323.1647, found 323.1656.

(Z)-Methyl 3-(4-(benzyloxy)phenyl)-3-cyclopropyl-2-methyl Acrylate ***((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 N_2 for 10 min. Then degassed 2.0 M aq K_3PO_4 (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 NH_4Cl (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 Na_2SO_4 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)-3-cyclopropyl-2-methyl acrylate in 83% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (500 MHz, $CDCl_3$): 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 $C_{21}H_{22}O_3$ (M + H) 323.1643, found 323.1653.

(Z)-Methyl 3-cyclopropyl-3-(2-fluoro-3-hydroxyphenyl)-2-methyl acrylate ***((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 Cs_2CO_3 (231 g, 0.709 mol) followed by degassed dioxane (2000 mL) and degassed H_2O (200 mL). Added $Pd(dppf)Cl_2.CH_2Cl_2$ (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 Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography to obtain 102 g of (*Z*)-methyl 3-cyclopropyl-3-(2-fluoro-3-hydroxyphenyl)-2-methyl acrylate in 63% isolated yield. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (500 MHz, $CDCl_3$): 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 $C_{14}H_{15}FO_3$ (M + H) 251.1083, found 251.1091.

(2S,3R)-Methyl 3-(3-(benzyloxy)phenyl)-3-cyclopropyl-2-methyl-propanoate ***((S,R)-11a)***. In a nitrogen-filled glovebox 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 CH_2Cl_2 (500 mL). Upon 30 min agitation, HBF_4-Et_2O (17 g, 0.106 mol) was added dropwise 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-2-methyl acrylate (1.0 kg, 3.1 mol) was dissolved in MeOH (5.0 L) and the solution was degassed for 2 h.

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The precatalyst solution was transferred to the reaction vessel, which was purged with argon three times. The headspace exchanged with H_2 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 (workup basis 3.3 kg (*Z*)-methyl 3-(3-(benzyloxy)phenyl)-3-cyclopropyl-2-methyl acrylate). 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. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (500 MHz, $CDCl_3$): 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. $[\alpha]_D^{20}$ + 111 (c 1.3, MeOH). HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{24}O_3$ (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 glovebox with O_2 < 5 ppm, (COD)Ru(Me-allyl)$_2$ (6.0 g, 0.019 mol) and Josiphos SL-J502−2 (10.4 g, 0.019 mol) were charged to the precatalyst preparation vessel, followed by anhydrous degassed CH_2Cl_2 (100 mL). Upon 15 min agitation, HBF_4-Et_2O (6.0 g, 0.037 mol) was added dropwise 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-methyl acrylate (200 g, 0.620 mol) was dissolved in MeOH (2200 mL) and the solution was purged with N_2 (5 × 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 × 500 psi). The reaction vessel was pressurized with 500 psi H_2 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-2-methylpropanoate in 80.1% isolated yield with 98% ee. ^{1}H NMR (500 MHz, $CDCl_3$): 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). ^{13}C NMR (500 MHz, $CDCl_3$): 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. $[\alpha]_D^{20}$ + 150 (c 0.54, MeOH). HRMS (ESI) *m*/*z* calcd. for $C_{21}H_{24}O_3$ (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 glovebox 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, HBF_4-Et_2O (3.8 g, 0.024 mol) was added dropwise in order to control gas evolution and the precatalyst solution was aged for 30 min. Meanwhile, methyl (*Z*)-methyl 3-cyclopropyl-3-(2-fluoro-3-hydroxyphenyl)-2-methyl acrylate (295 g, 1.18 mol) was dissolved in MeOH (1910 mL) and the solution was purged with N_2 (5 × 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 × 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-3-hydroxyphenyl)-2-methylpropanoate in 74.7% isolated yield with >99% ee. ^{1}H NMR (500 MHz, $CDCl_3$): 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), 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). ^{13}C NMR (500 MHz, $CDCl_3$): 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 $C_{14}H_{17}FO_3$ (M + H) 253.1240, found 253.1242.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02296.

NMR spectra for all new compounds, chiral SFC traces of compounds **11a−11c**, list of chiral phosphine ligands screened in asymmetric hydrogenation (PDF)

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Notes

The authors declare no competing financial interest.

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