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1. General materials and methods

Optical densities of *E. coli* cultures were determined with a DU 730 Life Sciences UV/Vis spectrophotometer (Beckman Coulter) by measuring absorbance at 600 nm. *E. coli* were routinely cultured at 37 ºC with shaking (175 rpm).

High-resolution mass spectral data for the synthetic compounds were obtained in the Magnetic Resonance Laboratory in CCB on Bruker MicroQTOF-QII fitted with a dual-spray electrospray ionization (ESI) source. The capillary voltage was set to 4.5 kV and the end plate offset to -500 V, the drying gas temperature was maintained at 190 ºC with a flow rate of 8 L/min and a nebulizer pressure of 21.8 psi. The liquid chromatography was performed using an Agilent Technologies 1100 series LC with 50% H_2O and 50% acetonitrile as solvent. Isopropanol, methanol, and water used for LC-ESI-MS were B & J Brand High Purity Solvents (Honeywell Burdick & Jackson). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using Varian INOVA 500 (500 MHz) or Varian INOVA 600 (600 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CDCl_3$, δ 7.26 ppm; $(CD_3)_2CO$, 2.05 ppm; $(CD_3)_2SO$, 2.50 ppm; CD_3OD, 3.31 ppm). Data are represented as: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, m = multiplet and/or multiple resonances), integration, coupling constant (*J*) in Hertz. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded using Varian INOVA 500 (125 MHz) NMR spectrometers at 23 °C. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.16 ppm; $(CD_3)_2CO$, 29.84 ppm; $(CD_3)_2SO$, 39.50 ppm; CD_3OD, 49.00 ppm). High-resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facility.

All chemicals were obtained from Sigma-Aldrich except for NaH_2PO_4 (AMRESCO) and KH_2PO_4 (BHD). Solvents were obtained from Sigma-Aldrich except hexanes (Macron Fine Chemicals), ethyl acetate and isopropanol (VWR), methanol and diethyl ether (EMD Millipore), and ethanol (KOPTEC). All water used was purified with a MilliQ purification system. All NMR solvents were purchased from Cambridge Isotope Laboratories. All catalysts used in the initial screen were from Strem Chemicals or Sigma-Aldrich.

All non-hydrogenation reactions were performed in round-bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air and moisture sensitive liquids were transferred by syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation (house vacuum, ca. 25−40 Torr) at ambient temperature, unless otherwise noted. Analytical thin layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore-size, 230−400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and then stained by submersion in aqueous ceric ammonium molybdate (CAM) or potassium permanganate solutions followed by brief heating with a heat gun. Flash-column chromatography was performed as described by Still *et al.* employing silica gel (60 Å, 60-200 μm, standard grade, BDH silica gel).[1] Tetrahydrofuran and dichloromethane were passed through two columns of

neutral alumina before use as a reaction solvent. All reagents were purchased from commercial sources and used without further purification. All solvents for work-up procedures were used without further purification.

Inductively coupled plasma optical emission spectroscopy (ICP-OES) analysis of the palladium content of commercial and synthetized catalysts was performed in the Microanalysis Laboratory at the University of Illinois at Urbana-Champaign. Samples were digested with a mixture of HNO_3, HCl, and HF in an Anton Parr Multiwave 3000 microwave digester, and the resulting solution was then analyzed with a PerkinElmer Optima 2000DvV ICP-OES.

2. Hydrogenation catalyst synthesis

Hydrogenation catalyst, 3% Pd on polyethylenimine/SiO_2 (40-200 mesh) (Royer Catalyst, CAS# 7440-05-3) was purchased from Strem Chemicals (product # 46-2089) as well as GFS Chemicals (product # 1068). ICP-OES analysis revealed that the actual Pd content of the catalyst was 2.44% (w/w), and this value was used to calculate catalyst loading. During the course of this work we observed variations in activity between different lots of catalyst from both companies. All experimental results described in the main text were carried out with active lots of commercial catalyst that contained 2.44 wt% Pd. Lot numbers of active catalysts were: Strem = 20246300, A0245109; GFS = P 999960. Lot numbers of less active catalysts were: Strem = 22102600, 21935800; GFS = C 256345, C 358679.

Attempts to understand the basis for this difference in reactivity revealed a simple procedure for activating less active commercial catalysts. We also developed and optimized our own synthesis of the Royer catalyst.

<u>Reactivation of Royer catalyst</u>

Catalyst was added to an open glass container (e.g. a 20 mL borosilicate scintillation vial) and then placed in a vacuum oven set at 110 ºC. After 24 hours, the catalyst was allowed to cool to room temperature in a desiccator, where it was stored until needed.

<u>Synthesis of Royer catalyst</u>

A $Pd(OAc)_2$ stock solution was prepared by dissolving $PdCl_2$ (Strem Chemicals, 200 mg) in concentrated hydrochloric acid (1 mL) using gentle heating with a heat gun. Addition of an aqueous solution of sodium acetate (49 mL, 15% w/v) yielded a stock solution containing 2.4 mg of palladium per mL. This solution (12.5 mL) was added to a 25 mL flask containing 970 mg of Royer® anion exchange resin PEI-100 (product # 1001, lot # C 257838). The resulting mixture was sonicated for 30 min, during which the supernatant turned nearly colorless. The supernatant was then decanted and the palladium-loaded resin was washed with DI water (2 x 5 mL). Additional DI water (1 mL) was added and the suspension was cooled to 0 ºC. A solution of sodium borohydride in water (1 mL,

1.32 M) was prepared, cooled to 0 ºC, and then added to the catalyst mixture. After being swirled rapidly for 1 min, the catalyst suspension was allowed to sit at 0 ºC for 30 min before the supernatant was decanted and the catalyst was washed with DI water (2 x 5 mL). This reduction step employing sodium borohydride was then repeated, followed by incubation with 30 % (v/v) formic acid solution (10 mL) for 15 hours. The catalyst was then washed with DI water (10 mL) and methanol (2 x 10 mL), dried briefly by being attached to a high-vacuum line, and finally dried in a vacuum oven set at 110 ºC for 48 hours. The palladium content of the resulting black catalyst was determined by ICP-OES analysis; the mean palladium content of four independent catalyst syntheses was 2.82 ± 0.18 w/w%.

Table S1. Comparison of catalyst performance in control experiments.

Reaction conditions	Conversion (%)[a] with active commercial catalyst	Conversion (%)[a] with inactive commercial catalyst	Conversion (%)[a] with reactivated commercial catalyst	Conversion (%)[a] with synthetic catalyst
full reaction	100	ND	97	96
full reaction (10 mM **1a**)	100	20	100	100
– *E. coli*	0	ND	0	0
– substrate **1a**	0	ND	0	0
– catalyst	0	ND	0	0
– substrate **1a**/ – catalyst	0	ND	0	0
– iron	93	ND	89	20
– IPTG	9	ND	10	5
Parental *E. coli* strain	14	ND	13	7

Reactions were run with 5 mM of substrate **1a** and 8 mol% Royer catalyst (based on palladium content) in 7 mL of growth medium under an atmosphere of nitrogen in 16 mL Hungate tubes shaken at 190 rpm. Conversions are the mean of three replicate experiments. [a] Determined by ^{1}H NMR. ND = not determined.

Table S2. ICP-OES analysis of catalyst Pd content.

Catalyst	Palladium content (% w/w)
Active commercial catalyst (GFS P999960)	2.44
Reactivated commercial catalyst (GFS C358679)	2.39
Synthetic catalyst	2.77

These catalysts were used for the reactions detailed in Table S1.

3. Strains, media, and culture conditions

Engineered hydrogen-producing strain *E. coli* DD-2 and the parental *E. coli* BL21(DE3) Δ*tonA* strain from which DD-2 was constructed have been described previously (*20*). In brief, the parental strain has had the following genes deleted to give a hydrogenase-free background: *hycE*, *hyaB*, and *hybC*. To construct strain DD-2, the parental strain was transformed with a modified pCDF-duet containing codon-optimized hydrogenase maturation factors HydEF (multiple cloning site 1) and HydG (multiple cloning site 2) from *Chlamydomonas reinhardtii*, a modified pACYC-duet vector containing pyruvate ferredoxin oxidoreductase from *Desulfovibrio africanus* (multiple cloning site 2), and a modified pET-duet vector encoding artificial fusion protein consisting of [Fe-Fe] hydrogenase and ferredoxin from *Clostridium acetylbutylicum* connected at the hydrogenase C-terminus via a $(Gly_4Ser)_2$ amino acid linker.

Both strains were obtained from Prof. Pam Silver and Dr. Daniel Ducat (Harvard Medical School, Boston, MA) and for routine cultivation were grown aerobically at 37 ºC on Luria-Burtani (LB) broth and agar. Strain DD-2 was always grown in the presence of ampicillin (50 µg/mL of media), spectinomycin (25 µg/mL of media), and chloramphenicol (12.5 µg/mL of media).

M9-glucose media was prepared according to the following procedure: 3 g of Na_2HPO_4, 1.5 g of KH_2PO_4, 500 mg of NH_4Cl, and 250 mg of NaCl were dissolved in 450 mL of Milli-Q (MQ) water and autoclaved at 121 ºC for 20 min. Upon cooling to room temperature, 1 mL of 1.0 M aqueous $MgSO_4$, 50 µL of 1.0 M aqueous $CaCl_2$, and 12.5 mL of aqueous 20% w/v glucose (0.5% w/v final concentration) were added and the total volume was brought up to 500 mL using sterile MQ water. M9CA-glucose media was prepared similarly: 3 g of Na_2HPO_4, 1.5 g of KH_2PO_4, 500 mg of NH_4Cl, 250 mg of NaCl,5 and 2.5 g of casamino acids (AMRESCO) were dissolved in 450 mL of water and autoclaved for 20 min. Upon cooling to room temperature, 50 µL of aqueous 10 mg/mL thiamine hydrochloride, 1 mL of 1.0 M aqueous MgSO4, 50 µL of 1.0 M aqueous CaCl2, 12.5 mL of aqueous 20% w/v solution of glucose (0.5% w/v final concentration) were added and the total volume was brought up to 500 mL using sterile MQ water. Both the M9-glucose media and the M9CA-glucose media were stored at 4 °C.

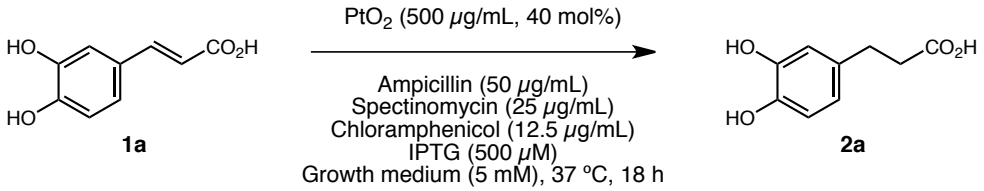
When iron supplementation of media was required, a freshly-prepared, filter sterilized aqueous solution of 50 mM $Fe(NH_4)_2(SO_4)_2$ (Sigma-Aldrich) was added to the reaction mixture to a final concentration of 50 µM as described in the general procedures for small and large scale hydrogenation reactions.

All small-scale reactions (3-10 mL) were performed in 16 mL Hungate tubes with butyl rubber septa and screw caps (Chemglass, # CLS-4208-01). Large-scale (90 mL) reactions were performed in serum bottles (Supelco, Sigma-Aldrich, # 33110-U) fitted with butyl septa (Chemglass, # CLS-4209-14) and aluminum crimp seals (Chemglass, # CLS-4209-12). The 0.9 L reaction was carried out in a 1.0 L media bottle (VWR catalog # 16157-191) capped with two two polytetrafluoroethylene flat septa (Belco Glass Inc., part # 5637-00030), Teflon tape, and an open top screw cap.

The growing *E. coli* cultures used for hydrogenations were inoculated from an overnight culture on the same day of the reaction. Overnight cultures (5 mL of M9CA-glucose media containing antibiotics) were inoculated the evening before from frozen glycerol stocks and were incubated aerobically at 37 ºC for 12-15 h. The overnight culture was then diluted 1:100 into an appropriate volume of M9CA-glucose containing antibiotics. This culture was incubated at 37 ºC with shaking (190 rpm) until the desired OD_{600} was reached.

4. Reaction discovery and optimization

Initial discovery



Reactions in growth media with added hydrogen:

To a 5 mL solution of the growth medium (LB or M9-glucose) in a Hungate tube were added caffeic acid (4.5 mg, 0.025 mmol), PtO_2 (2.5 mg, 0.010 mmol, 0.4 equiv) antibiotics (ampicillin (50 µg/mL of media), spectinomycin (20 µg/mL of media), and chloramphenicol (12.5 µg/mL of media), all final concentrations) and IPTG (5 µL of a 0.5 M solution, 500 µM). The Hungate tube was sealed with a septum and screw cap and was vortexed for 5 sec. The tube was placed under a hydrogen atmosphere by evacuating the headspace using a 22 gauge, 4 inch needle connected to house vacuum and backfilling with a balloon of hydrogen gas (4 cycles). The reaction mixture was placed on a rotating shaker (190 rpm) at 37 °C. After 18 hours, the reaction mixture was acidified with 4 drops of concentrated aqueous HCl (40 µL) and was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The reaction conversion was calculated based on the ratio of **2a** to **1a** in the crude ^{1}H NMR (MeOH-d_4).

For **2a** characterization data see page S19.

Reactions in growth media with *E. coli* DD-2 and added hydrogen:

To a 5 mL culture of *E. coli* DD-1 (OD_{600} = 0.4) in either LB or M9-glucose media with antibiotics (ampicillin (50 µg/mL of media), spectinomycin (25 µg/mL of media), and chloramphenicol (12.5 µg/mL of media) in a Hungate tube was added caffeic acid (4.5 mg, 0.025 mmol), PtO_2 (2.5 mg, 0.010 mmol, 0.4 equiv), and IPTG (5 µL of a 0.5 M solution, 500 µM) were then added and the mixture was vortexed for 5 sec. The reaction mixture was sparged with nitrogen gas for 30 min using a 22 gauge, 4 inch needle as the inlet and a 27 gauge, 0.5 inch needle as the outlet. The Hungate tube was then sealed with a septum and screw cap and was placed under a hydrogen atmosphere by evacuating the headspace using a 22 gauge, 4 inch needle connected to house vacuum and backfilling

with a balloon of hydrogen gas (4 cycles). The reaction mixture was placed on a rotating shaker (190 rpm) at 37 °C. After 18 hours, the reaction mixture was acidified with concentrated aqueous HCl (40 µL) and was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The reaction conversion was calculated based on the ratio of **2a** to **1a** in the crude ^{1}H NMR (MeOH-d_4).

Reactions in growth media with *E. coli* DD-2 and no added hydrogen:

To a 5 mL of a growing cultures of *E. coli* DD-2 (OD600 = 0.4) in either LB + 0.5% w/v glucose or M9-glucose media with antibiotics (5 µL each of ampicillin (50 µg/mL), spectinomycin (25 µg/mL), and chloramphenicol (12.5 µg/mL)) in Hungate tubes were added caffeic acid (4.5 mg, 0.025 mmol) and PtO_2 (2.5 mg, 0.010 mmol). The Hungate tube was capped tightly and then vortexed for 5 sec. The reaction mixture was sparged with nitrogen gas for 30 min using a 22 gauge, 4 inch needle as the inlet and a 27 gauge, 0.5 inch needle as the outlet, and then an aqueous solution of IPTG was added via gastight syringe (5 µL of a 0.5 M solution, 500 µM). The reaction mixture was placed on a rotating shaker (190 rpm) at 37 °C. After 18 hours, the reaction mixture was acidified with concentrated aqueous HCl (40 µL) and was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The reaction conversion was calculated based on the ratio of **2a** to **1a** in the crude ^{1}H NMR (MeOH-d_4).

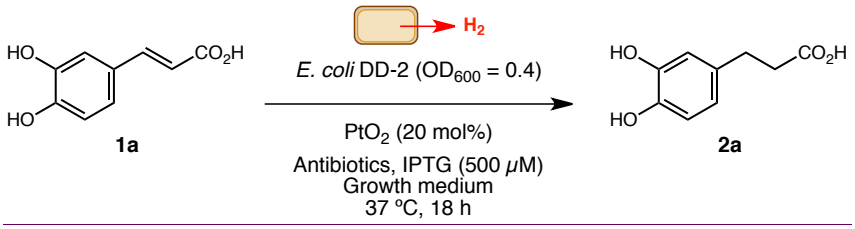
Optimization experiments – small scale:

General experimental procedure for optimization experiments – small scale:

A freshly grown *E. coli* DD-2 culture (in either M9-glucose or M9CA-glucose media with antibiotics), alkene substrate, and catalyst were added to a Hungate tube. The Hungate tube was capped tightly and then vortexed for 5 sec. The culture was sparged with nitrogen gas for 20 min, using 22 gauge, 4 inch needle as the inlet and a 27 gauge, 0.5 inch needle as the outlet. IPTG and $Fe(NH_4)_2(SO_4)_2$ (added to a final concentration of 50 µM for all Fe-containing media) were then added as aqueous stock solutions using a gastight syringe. The reaction mixture was placed on a rotating shaker (190 rpm) at 37 °C. At the desired time, the reaction mixture was acidified with concentrated aqueous HCl (40 µL) and was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The reaction conversion was calculated based on the ratio of **2a** to **1a** in the crude ^{1}H NMR (MeOH-d_4).

Figure S1. Experimental setup for small scale hydrogenation reactions.

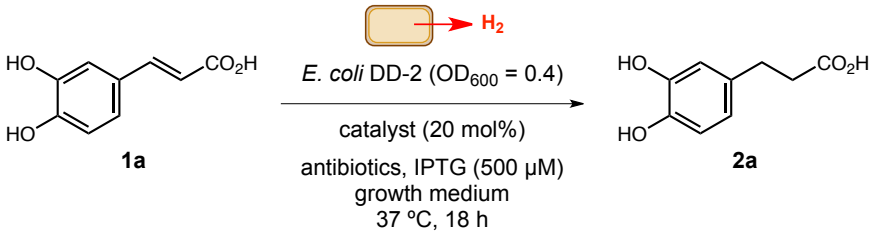
Table S3. Reaction media.



Entry	Growth medium	Conversion (%)[a]
1	M9 glucose	15[b]
2	M9 glucose + Fe[c]	45
3	M9CA glucose[d]	34
4	M9CA glucose + Fe	56

Reactions were performed at a 5 mM substrate concentration in 5 mL of growth medium under an atmosphere of nitrogen in 16 mL Hungate tubes with shaking at 190 rpm. [a] Determined by ^{1}H NMR. [b] This reaction was performed with 40 mol% Pt_2O [c] M9 glucose + Fe and M9CA-glucose + Fe medium contain 50 μM $Fe(NH_4)_2(SO_4)_2$ [d] M9CA-glucose and M9CA-glucose + Fe medium contain casamino acids (5 g/L).

Table S4. Catalyst screening during reaction optimization.



Entry	Growth medium	Catalyst	Conversion (%)[a]
1	M9CA glucose + Fe	Platinum (IV) oxide (Pt_2O)	56
2	M9CA glucose + Fe	Platinum, 5 wt% on calcium carbonate	12
3	M9CA glucose + Fe	Palladium, 5 wt% on barium sulfate	6
4	M9CA glucose + Fe	Palladium hydroxide, 20 wt% on carbon	47
5	M9CA glucose + Fe	Palladium, 5 wt% on silica powder	3
6	M9CA glucose + Fe	Palladium, 10 wt% on activated carbon	10
7	M9CA glucose + Fe	Palladium, 10 wt% on alumina	32
8	**M9CA glucose + Fe**	Royer catalyst[d]	**100 (100)[e]**
9	**M9CA glucose + Fe**	Royer catalyst	**100 (87% yield)[f]**

Reactions were performed at a 5 mM substrate concentration in 5 mL of growth medium under an atmosphere of nitrogen in 16 mL Hungate tubes with shaking at 190 rpm. [a] Determined by ^{1}H NMR. [b] M9 glucose + Fe and M9CA-glucose + Fe medium contain 50 μM $Fe(NH_4)_2(SO_4)_2$ [c] M9CA-glucose and M9CA-glucose + Fe medium contain casamino acids (5 g/L). [d] The Royer catalyst is palladium, 2.44 wt% on polyethyleneimine/silica gel. This reaction was performed with 16 mol% catalyst. [e] Reaction performed with 8 mol% Royer catalyst at a substrate concentration of 10 mM. [f] Isolated yield from reaction performed on a 9 mmol scale (1.7 g of **1a**) with 8 mol% Royer catalyst at a substrate concentration of 10 mM for 48 h.

Additional catalysts screened that gave no conversion: Platinum, 5% on alumina; Palladium powder (99.95%); Platinum sponge (99.95%); Platinum powder (99.9%); Platinum (97% (2-5 nanometers)); Palladium, 5 wt % on calcium carbonate poisoned with lead; Platinum black (minimum 98%); Palladium black (99.9%); Platinum, 5 % on silica powder, reduced, dry; Platinum, 5% on alumina powder, reduced, dry; Pt(0) EnCat™ 40 (0.06-0.14 mmol/g); Pd EnCat™ 40 (0.4 mmol/g).

Figure S2. Culture density (OD_{600}).

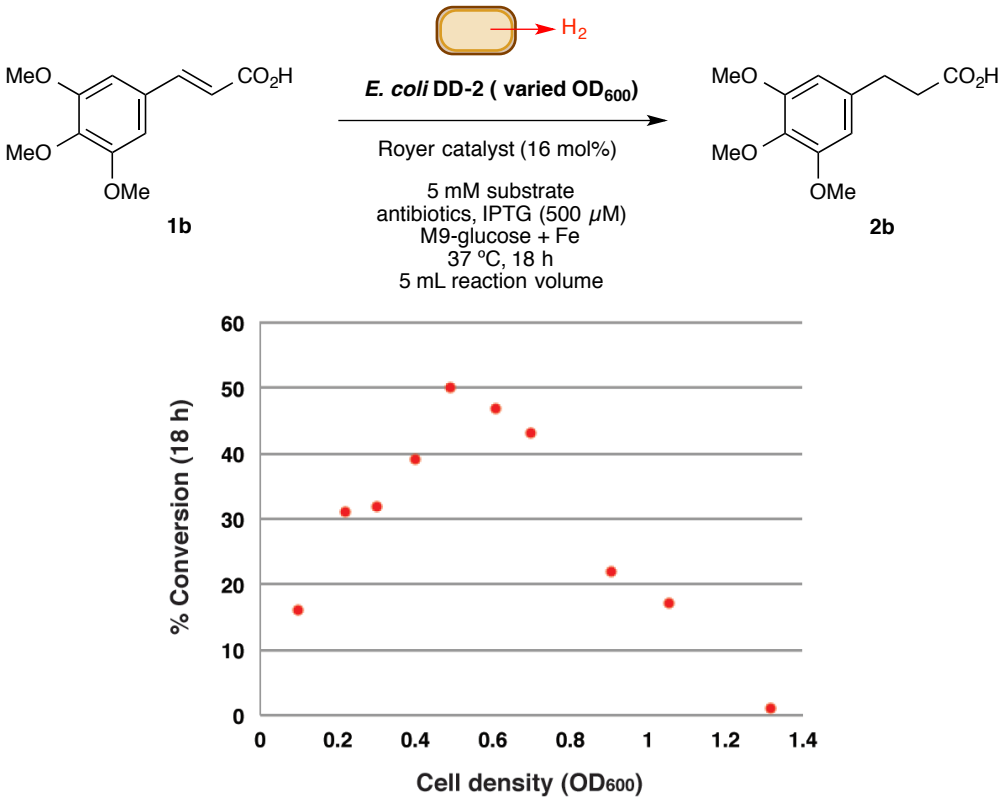
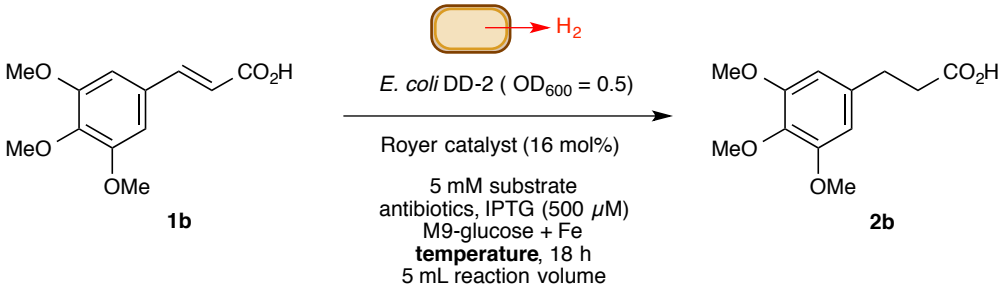
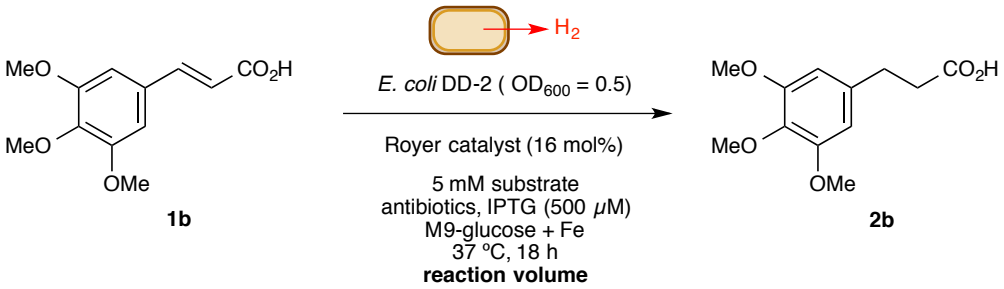


Table S5. Reaction temperature.



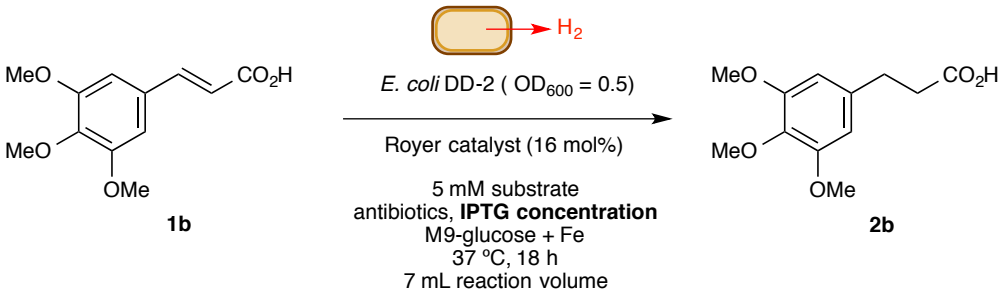
Temperature (°C)	Conversion (%)
37	49
30	29
room temperature (~25)	13
20	6
15	1

Table S6. Reaction headspace.



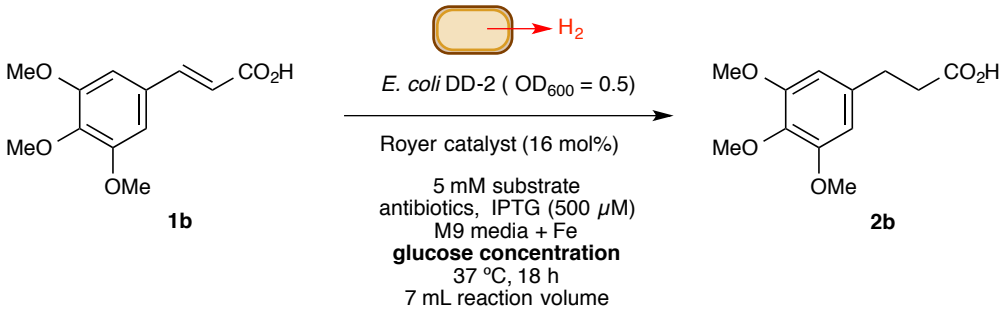
Reaction volume (mL)	Headspace volume (mL)	Conversion (%)
3	13	31
5	11	60
7	9	65
10	6	39

Table S7. IPTG concentration.



IPTG (mM)	Conversion (%)
0.01	19
0.05	43
0.1	55
0.25	54
0.50	52
0.75	52
1.0	49

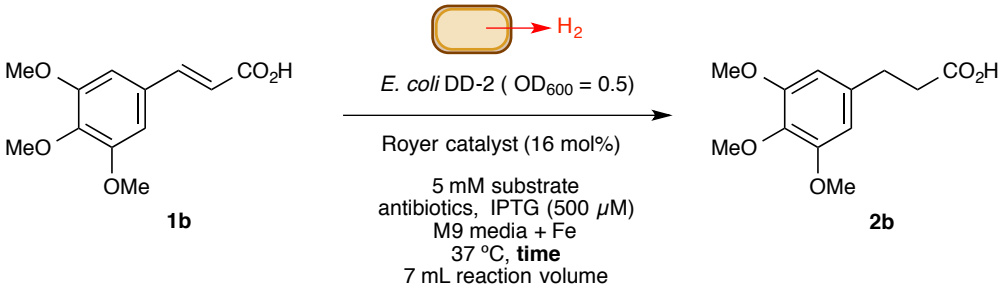
Table S8. Glucose concentration.



Amount of added glucose	Conversion (%)
0.1% w/v	6
0.3% w/v	50
0.5% w/v	51
0.7% w/v	63
0.9% w/v	56

E. coli starter cultures were grown in media containing 0.1% w/v glucose and additional glucose was added upon initiation of the reaction.

Table S9. Reaction time.



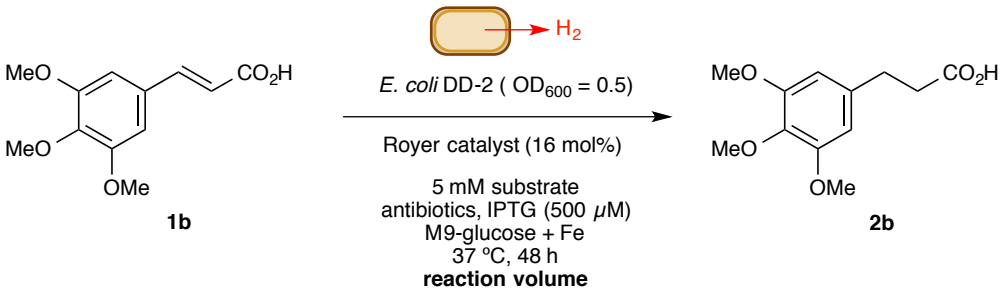
Time (h)	Conversion (%)
18	63
24	67
48	68
60	68

Optimization experiments – large scale:

General experimental procedure for optimization experiments – large scale:

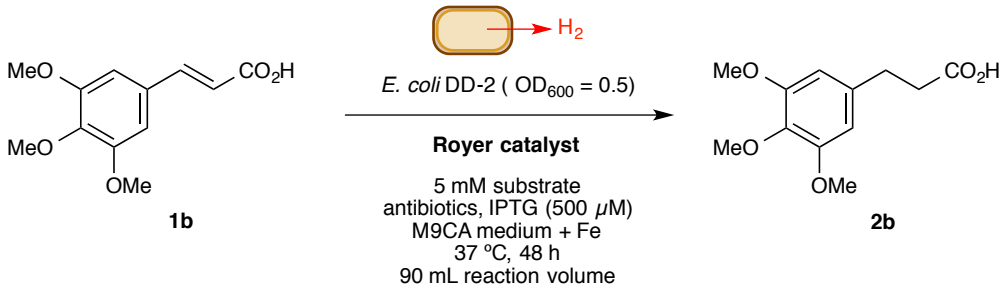
A freshly grown *E. coli* DD-2 culture was added to a serum bottle containing alkene substrate **1b**, Royer catalyst, and $Fe(NH_4)_2(SO_4)_2 \bullet 6H_2O$ (added to a final concentration of 50 µM). The serum bottle was capped with a septa and crimp seal and was agitated gently until the contents were well mixed. The culture was sparged with nitrogen gas for 30 min using a 22 gauge, 4 inch needle as the inlet and a 27 gauge, 0.5 inch needle as the outlet. IPTG was then added were then added as aqueous stock solution to a final concentration of 50 µM using a gastight syringe. The reaction mixture was placed on a rotating shaker (190 rpm) at 37 °C. After 48 hours, concentrated aqueous HCl (0.5 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The reaction conversion was calculated based on the ratio of **2a** to **1a** in the crude ^{1}H NMR (MeOH-d_4).

Table S10. Reaction headspace.



Reaction volume (mL)	Headspace volume (mL)	Conversion (%)
50	67	57
60	57	58
70	47	62
80	37	64
90	27	66
100	17	57

Table S11. Catalyst loading.



Catalyst loading (mol%)	Conversion (%)
16	68
20	65
24	93

5. General procedure for hydrogenation reactions (7 mL reaction volume)

7 mL of a growing culture of *E. coli* DD-2 (OD_{600} = 0.5) in M9CA-glucose media containing antibiotics was added to a Hungate tube containing alkene (0.035 mmol), and catalyst **3** (12.5 mg, 0.0028 mmol, 0.08 equiv or 25 mg, 0.0057 mmol, 0.16 equiv). The Hungate tube was capped tightly and then vortexed for 5 sec. The culture was sparged with nitrogen gas for 20 min using a 4-inch needle as the inlet and a small needle as the outlet, and then aqueous solutions of $Fe(NH_4)_2(SO_4)_2 \bullet 6H_2O$ (50 μM, 7 μL of a 0.05 M stock solution) and IPTG (500 μM, 7 μL of a 0.5 M stock solution) were added. The reaction mixture was placed on a platform shaker (190 rpm) and incubated at 37 °C. After 18 hours, the reaction mixture was acidified with concentrated aqueous HCl (40 μL) and was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The reaction conversion was calculated based on the ratio of **2a** to **1a** in the crude ^{1}H NMR (MeOH-d_4).

6. General procedure for hydrogenation reactions (90 mL reaction volume)

To a serum bottle containing alkene (0.453 mmol, 1.0 equiv), catalyst **3** (161 mg, 0.037 mmol, 0.08 equiv or 322 mg, 0.073 mmol, 0.16 equiv) and $Fe(NH_4)_2(SO_4)_2 \bullet 6H_2O$ (50 μM, 90 μL of a 0.05 M stock solution) was added a growing culture of *E. coli* DD-2 in M9CA-glucose containing antibiotics (90 mL, OD_{600} = 0.5). The serum bottle was capped with a septa and crimp seal and was agitated gently until the contents were well mixed. The culture was sparged with nitrogen gas for 30 min using a 22 gauge, 4 inch needle as the inlet and a 27 gauge, 0.5 inch needle as the outlet, and then an aqueous solution of IPTG (500 μM, 90 μL of a 0.5 M stock solution) was added via gastight syringe. The reaction mixture was placed on a platform shaker (190 rpm) and incubated at 37 °C. After 48 h, the reaction mixture was removed from the shaker, allowed to cool to room temperature, and worked up using one of the following three methods.

Method A:
Concentrated aqueous HCl (0.5 mL) was added to the reaction mixture, which was then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

Method B:
The reaction mixture was centrifuged (4000 rpm x 10 min) and then the supernatant was concentrated *in vacuo*. The remaining solid material was resuspended in water (20 mL) and the pH was adjusted to pH 3 using aqueous 1M HCl. This suspension was washed with ethyl acetate (2 x 15 mL) and then the pH was adjusted to pH 7 using aqueous 1M NaOH. The resulting solution was extracted with 20% ethanol in chloroform (4 x 50 mL). The combined organic layers were washed with brine (25 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

Method C:

The reaction mixture was extracted with ethyl acetate (3 x 50 mL; 10% methanol in ethyl acetate was used for amide substrates). The combined organic layers were washed with brine (25 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

7. Large-scale hydrogenation (877 mL reaction volume)

To a 1 L media bottle containing caffeic acid (1.580 g, 8.77 mmol, 1.0 equiv), catalyst **3** (3.111 g, 0.713 mmol, 8 mol%), and an aqueous ammonium iron(II) sulfate hexahydrate solution (50 mM, 877 µL, 0.044 mmol), was added a fresh culture of *E. coli* DD-2 in M9CA-glucose containing antibiotics (877 mL, OD_{600} = 0.5). The media bottle was capped with two polytetrafluoroethylene flat septa, wrapped with thread sealant Teflon tape, and sealed tightly with an open top screw cap. The culture was sparged with nitrogen gas for 30 min using a 20-gauge, 12-inch needle as the inlet and a 22-gauge, 4-inch needle as the outlet, and then an aqueous solution of IPTG (877 µL, 500 µM) was added via gastight syringe. The reaction mixture was rested horizontally on a rotating shaker (190 rpm) and incubated at 37 °C. After 48 h, the reaction mixture was removed from the shaker, allowed to cool to room temperature, and concentrated to a volume of 300 mL *in vacuo*. Concentrated HCl (2.0 mL) was added to this reaction mixture, which was then extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with brine (75 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (9:1 ethyl acetate–hexanes) to give 3-(3,4-dihydroxyphenyl)propanoic acid as a white solid (1.385 g, 87%).

8. Additional experiments

Control reactions and metabolite analyses

Details of control reactions:

All reactions (except –substrate and –substrate/–catalyst controls) were carried out with a 5 mM concentration of **1a** using the standard procedure for 7 mL hydrogenations. For each set of reaction conditions, three replicate experiments were run side by side for 18 h. Headspaces and reaction mixtures were sampled for hydrogen and formic acid analyses, and were then worked up using the standard procedure for 7 mL hydrogenations. Conversions were calculated based on the ratio of product **2a** to unreacted starting material **1a** in the crude ^{1}H NMR (MeOH-d_4).

Method for hydrogen quantitation:

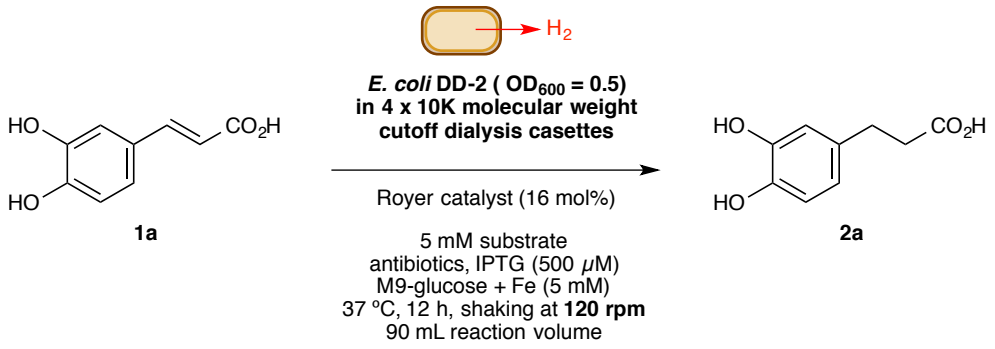
Immediately after completion of the 18 h incubation, the reaction mixtures were cooled to room temperature and 500 μL of each culture's headspace was removed using a gastight syringe with a twist valve closure (Hamilton SampleLock, # 81256) and immediately injected into a 7890A GC (Agilent) equipped with a 30 m HP-MOLESIEVES column (19095P-MSO, Agilent, Santa Clara, CA, USA). The GC inlet was maintained at 250 °C and the samples were injected in split 10:1 mode. The carrier gas was argon (5 mL/min). The samples were equilibrated for 4 min at 40 °C before being pressurized to 5.6 psi with nitrogen. The carrier gas was argon (5 mL/min). The samples were then heated to 150 °C at a rate of 40 °C/min for 6.5 min. The samples were detected using a thermal conductivity detector (TCD) with a heater temperature of 250 °C. The amount of hydrogen in each sample was quantified by comparing the peak area to a standard curve generated by analyzing samples containing known amounts of hydrogen gas (21, 16, 12, 8, 4, 2 μmoles).

Method for formic acid quantitation:

After removing samples of headspace for hydrogen analysis, 1 M aqueous NaOH (0.5 mL) was added to each reaction mixture. A 4.5 mL portion of the each mixture was transferred to a 10 mL headspace vial (Agilent, # 5182-0838) fitted with a butyl septum and crimp cap (Agilent, # 5183-4479). The samples were then acidified with aqueous phosphoric acid (0.5 mL, 85 wt %) and 1 mL of headspace was analyzed by GC-MS (7697A headspace autosampler coupled to a 7890A GC and a 5975C inert XL MSD, Agilent) on a 30 m HP-PLOT/U column (Agilent). The samples were equilibrated for 3 minutes at 95 °C before being pressurized with He to 20 psi. The samples were then vented to a 1 mL sample loop at 40 psi / minute until the sample headspace reached 10 psi. After a 9 second equilibration, the sample in the sample loop was transferred to the GC for 30 seconds. The GC inlet was maintained at 200 °C and the samples were injected in split 1:1 mode. The carrier gas was helium (1.8 mL / minute). The GC oven was maintained at 50 °C for 1.5 minutes, then increased to 160 °C at 10 °C / minute and remained at that temperature for 4.5 minutes. The mass spectrometer was scanned between 10 and 150 amu. The amount of formic acid in each sample was quantified by

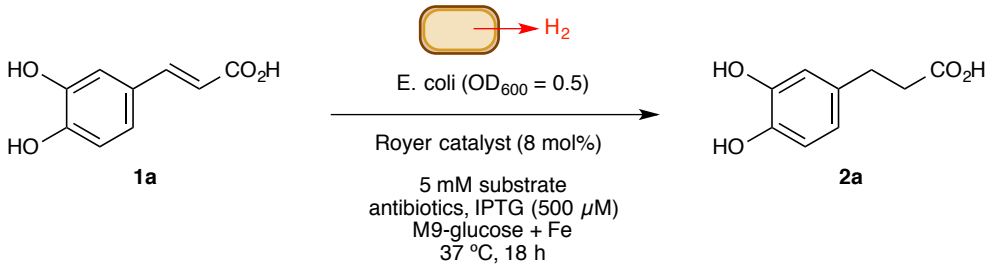
comparing the area of the m/z 46 peak against a standard curve made by analyzing samples containing known concentrations of formic acid (2, 5, 10, 15, 25 mM).

Physical separation between catalyst and cells:



A 90 mL culture of a culture of *E. coli* DD-2 in M9CA-glucose containing antibiotics was inoculated from an overnight culture grown to an OD_{600} of 0.45 at 37 ºC. The cultures were then centrifuged (4000 rpm x 10 min) and the cell pellets were resuspended in a total of 1.4 mL of M9CA-glucose. This cell suspension was distributed evenly among four 500 µL dialysis cassettes (Slide-A-Lyzer MINI Dialysis Devices, Thermo Scientific, # 69576). Substrate **1a** (162 mg, 0.34 mmol) and Royer catalyst (322 mg, 0.055 mmol, 16 mol%) were added to M9CA-glucose media containing antibiotics (90 mL) in a serum bottle. The dialysis cassettes were then suspended in this mixture and the bottle was capped with a septum and sealed. The culture was sparged with nitrogen gas for 20 min using a 22 gauge, 4 inch needle as the inlet and a 27 gauge, 0.5 inch needle as the outlet, and then aqueous solutions of iron $Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$ (50 µM, 90 µL of a 0.05 M stock solution) and IPTG (500 µM, 90 µL of a 0.5 M stock solution) were added. The reaction mixture was placed on a rotating shaker (120 rpm) at 37 °C for 24 h. The cassettes remained intact throughout the incubation. The reaction mixture was acidified with concentrated HCl (0.5 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Analysis of the crude ^{1}H NMR spectrum showed 67% conversion to **2a**.

Table S12. Control reactions and metabolite analyses.



Entry	Reaction conditions	Conversion (%)[a]	Hydrogen gas in headspace (μmol)	Formic acid in media (μmol)
1	full reaction	100	192 ± 11	52 ± 8
2	full reaction (10 mM substrate)	100	222 ± 18	Not measured
3	– *E. coli*	0	0	0
4	– substrate	0	158 ± 18	69 ± 9
5	– catalyst	0	143 ± 15	53 ± 2
6	– substrate/– catalyst	0	156 ± 16	77 ± 5
7	– iron	93	74 ± 17	63 ± 5
8	– IPTG	10	0	93 ± 1
9	Parental *E. coli* BL21(DE3) strain	14	0	102 ± 15
10	– *E. coli*, + 100 μmol formic acid	9	–	–
11	full reaction, *E. coli* in dialysis cassette	67	–	–

Reactions were run with 5 mM of substrate **1a** and 8 mol% Royer catalyst in 7 mL of growth medium under an atmosphere of nitrogen in 16 mL Hungate tubes shaken at 190 rpm. Hydrogen and formic acid were quantified in the reaction headspace and medium after 18 h using GC. For reactions that generated hydrogen and provided conversion, the amount of hydrogen incorporated into product **1b** was calculated and included in the value for total hydrogen produced; this calculation takes into account the estimated conversion due to formic acid. Conversion and metabolite analysis values are the mean of three replicate experiments, except for Entries 10 and 11. [a] Determined by ^{1}H NMR.

Assessing catalyst toxicity:

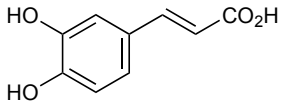
A series of 5 mL hydrogenation reactions with alkene substrate **1a** (5 mM substrate concentration) were carried out using the general procedure for small scale reactions. In addition to the full reaction, – catalyst, –substrate, and – catalyst/–substrate controls were also evaluated, with three replicate experiments set up for each set of conditions. All reaction mixtures were incubated at 37 ºC with shaking (190 rpm). After 18 h, 100 μL of each reaction mixture was removed and added to 900 μL of M9CA medium. The initial 10-fold dilutions were subjected to 10-fold serial dilution (10^2-10^8). Aliquots (100 μL) of three different dilutions (10^5, 10^6, 10^7) were plated onto separate LB agar plates containing ampicillin (50 μg/mL), spectinomycin (25 μg/mL), and chloramphenicol (12.5 μg/mL), and the plates were incubated at 37 °C overnight. The numbers of colonies observed on the 10^6-fold dilution plates were used to calculate the number of colony-forming units (CFUs) in each original reaction mixture.

After removing the aliquot for toxicity analysis, the remainder of each full reaction mixtures was worked up separately using the standard procedure for small scale reactions. Analysis of the crude ^{1}H NMR spectrum showed 100% conversion to **2a** in each replicate.

9. Characterization data

Hydrogenation reactions

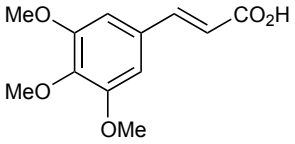
(*E*)-3-(3,4-Dihydroxyphenyl)acrylic acid (**1a**):



The reaction was performed with 10 mM substrate (0.899 mmol, 162 mg) and 8 mol% catalyst (319 mg, 0.073 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (100% ethyl acetate) to give 3-(3,4-dihydroxyphenyl)propanoic acid (**2a**) as a white solid (151 mg, 92%).

TLC: R_f = 0.20 (silica gel, ethyl acetate). HRMS (ESI): calcd for $C_9H_{10}NaO_4^+$ $[M+Na]^+$, 205.0471; found, 205.0476. ^{1}H NMR (500 MHz, CD_3OD) δ: 6.64 (d, 1H, *J* = 8.0 Hz, ArC**H**), 6.62 (d, 1H, *J* = 2.0 Hz, ArC**H**), 6.49 (dd, 1H, *J* = 8.3, 2.3 Hz, ArC**H**), 2.71 (t, 2H, *J* = 7.5 Hz, C$\mathbf{H_2}$), 2.48 (t, 2H, *J* = 7.8 Hz, C$\mathbf{H_2}$). ^{13}C NMR (125 MHz, CD_3OD) δ: 177.1, 146.1, 144.5, 133.7, 120.5, 116.4, 116.3, 37.1, 31.4.

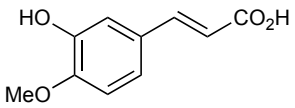
(*E*)-3-(3,4,5-trimethoxyphenyl)acrylic acid (**1b**):



The reaction was performed with 5 mM substrate (0.453 mmol, 108.0 mg) and 16 mol% catalyst (322 mg, 0.073 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to afford 99 mg of a 76:24 mixture of 3-(3,4,5-trimethoxyphenyl)propanoic acid and the starting material (*E*)-3-(3,4,5-trimethoxyphenyl)acrylic acid (91% total mass recovery, 69% yield of hydrogenated product).

TLC: R_f = 0.2 (ethyl acetate). HRMS (ESI): calcd for $C_{12}H_{16}NaO_5^+$ $[M+Na]^+$, 263.0890; found, 263.0894. ^{1}H and ^{13}C NMR data matched that reported previously.[2]

(*E*)-3-(3-hydroxy-4-methoxyphenyl)acrylic acid (**1c**):

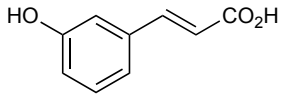


The reaction was performed with 5 mM substrate (0.453 mmol, 88.0 mg) and 16 mol% catalyst (322 mg, 0.073 mmol). Method A was used as the workup protocol. The crude

product was purified by flash chromatography on silica gel (ethyl acetate) to give 3-(3-hydroxy-4-methoxyphenyl)propanoic acid as a white solid (85 mg, 95%).

TLC: R_f = 0.2 (ethyl acetate). HRMS (ESI): calcd for $C_{10}H_{12}NaO_4^+$ $[M+Na]^+$, 219.0628; found, 219.0634. ^1H and ^{13}C NMR data matched that reported previously.[3]

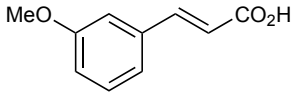
(*E*)-3-(3-hydroxyphenyl)acrylic acid (**1d**):



The reaction was performed with 5 mM substrate (0.453 mmol, 74.4 mg) and 8 mol% catalyst (161 mg, 0.037 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to give 3-(3-hydroxyphenyl)propanoic acid as a white solid (70 mg, 93%).

TLC: R_f = 0.25 (ethyl acetate). HRMS (ESI): calcd for $C_9H_{10}NaO_3^+$ $[M+Na]^+$, 189.0522; found, 189.0525. ^1H and ^{13}C NMR data matched that reported previously.[4,5]

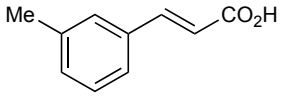
(*E*)-3-(3-methoxyphenyl)acrylic acid (**1e**):



The reaction was performed with 5 mM substrate (0.453 mmol, 80.7 mg) and 10 mol% catalyst (322 mg, 0.073 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to afford 69 mg of a 89:11 mixture of 3-(3-methoxyphenyl)propanoic acid and the starting material (*E*)-3-(3-methoxyphenyl)acrylic acid (85% total mass recovery, 75% yield of hydrogenated product).

TLC: R_f = 0.25 (ethyl acetate). HRMS (ESI): calcd for $C_{10}H_{12}NaO_3^+$ $[M+Na]^+$, 203.0679; found, 203.0685. ^1H and ^{13}C NMR data matched that reported previously.[6]

(*E*)-3-(*m*-tolyl)acrylic acid (**1f**):

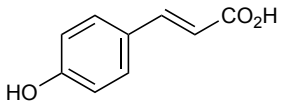


The reaction was performed with 5 mM substrate (0.453 mmol, 73.5 mg) and 16 mol% catalyst (322 mg, 0.073 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to afford 72

mg of a 80:20 mixture of 3-(*m*-tolyl)propanoic acid and the starting material (*E*)-3-(*m*-tolyl)acrylic acid (97% total mass recovery, 77% yield of hydrogenated product).

TLC: R_f = 0.25 (ethyl acetate). HRMS (ESI): calcd for $C_{10}H_{12}NaO_2^+$ $[M+Na]^+$, 187.0730; found, 187.0735. ^{1}H and ^{13}C NMR data matched that reported previously.[7]

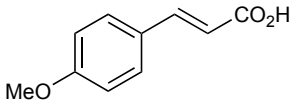
(*E*)-3-(4-Hydroxyphenyl)acrylic acid (**1g**):



The reaction was performed with 5 mM substrate (0.453 mmol, 74.4 mg) and 8 mol% catalyst (161 mg, 0.037 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to afford 73 mg of a 93:7 mixture of 3-(4-hydroxyphenyl)propanoic acid and the starting material (*E*)-3-(4-hydroxyphenyl)acrylic acid (97% total mass recovery, 90% yield of hydrogenated product).

TLC: R_f = 0.25 (ethyl acetate). HRMS (ESI): calcd for $C_9H_{10}NaO_3^+$ $[M+Na]^+$, 189.0522; found, 189.0528. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.01 (d, 2H, *J* = 8.5 Hz, 2 x Ar**CH**), 6.72 (dd, 2H, *J* = 6.5, 2.5 Hz 2 x Ar**CH**), 2.83 (t, 2H, *J* = 8.0 Hz, **CH$_2$**), 2.55 (t, 2H, *J* = 7.8 Hz, **CH$_2$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 176.3, 154.9, 131.8, 129.3, 115.3, 36.0, 30.1.

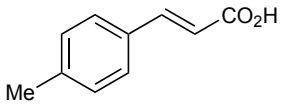
(*E*)-3-(4-methoxyphenyl)acrylic acid (**1h**):



The reaction was performed with 5 mM substrate (0.453 mmol, 80.7 mg) and 8 mol% catalyst (161 mg, 0.037 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (100% ethyl acetate) to afford 78 mg of a 87:13 mixture of 3-(4-methoxyphenyl)propanoic acid and the starting material (*E*)-3-(4-methoxyphenyl)acrylic acid (96% total mass recovery, 83% yield of hydrogenated product).

TLC: R_f = 0.25 (ethyl acetate). HRMS (ESI): calcd for $C_{10}H_{12}NaO_3^+$ $[M+Na]^+$, 203.0679; found, 203.0684. ^{1}H and ^{13}C NMR data matched that reported previously.[8]

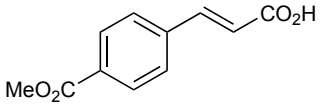
(*E*)-3-(*p*-tolyl)acrylic acid (**1i**):



The reaction was performed with 5 mM substrate (0.453 mmol, 73.5 mg) and 8 mol% catalyst (161 mg, 0.037 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to afford 74 mg of a 70:30 mixture of 3-(*p*-tolyl)propanoic acid and the starting material (*E*)-3-(*p*-tolyl)acrylic acid (99% total mass recovery, 70% yield of hydrogenated product).

TLC: R_f = 0.25 (ethyl acetate). HRMS (ESI): calcd for $C_{10}H_{12}NaO_2^+$ $[M+Na]^+$, 187.0730; found, 187.0735. ^{1}H and ^{13}C NMR data matched that reported previously.[8]

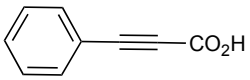
(*E*)-3-(4-(methoxycarbonyl)phenyl)acrylic acid (**1j**):



The reaction was performed with 5 mM substrate (0.453 mmol, 93.4 mg) and 8 mol% catalyst (161 mg, 0.037 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to afford 89 mg of a 92:8 mixture of 3-(4-(methoxycarbonyl)phenyl)propanoic acid and the starting material (*E*)-3-(4-(methoxycarbonyl)phenyl)acrylic acid (94% total mass recovery, 86% yield of hydrogenated product).

TLC: R_f = 0.25 (1:9 methanol–ethyl acetate). HRMS (ESI): calcd for $C_{11}H_{13}O_4^+$ $[M+H]^+$, 209.0808; found, 209.0807. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.99 (d, 2H, *J* = 8.5 Hz, 2 x Ar**CH**), 7.30 (d, 2H, *J* = 8.0 Hz 2 x Ar**CH**), 3.98 (s, 3H, O**CH$_3$**), 3.03 (t, 2H, *J* = 7.5 Hz, **CH$_2$**), 2.72 (t, 2H, *J* = 7.8 Hz, **CH$_2$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.6, 167.2, 145.7, 130.1, 128.5, 128.5, 52.2, 35.2, 30.6.

3-phenylpropiolic acid (**1k**):

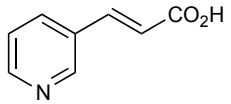


The reaction was performed with 5 mM substrate (0.453 mmol, 66.2 mg) and 8 mol% catalyst (161 mg, 0.037 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to give 3-phenylpropanoic acid as a white solid (62 mg, 92%).

TLC: R_f = 0.4 (ethyl acetate). HRMS (ESI): calcd for $C_9H_{10}NaO_2^+$ $[M+Na]^+$, 173.0573; found, 173.0590. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35 – 7.32 (m, 2H, 2 x Ar**CH**), 7.30 –

7.24 (m, 3H, 3 x ArC**H**), 3.04 (t, 2H, J = 7.8 Hz, C**H₂**), 2.78 – 2.75 (m, 2H, C**H₂**). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 179.5, 140.3, 128.7, 128.4, 126.5, 35.8, 30.7.

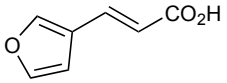
(*E*)-3-(pyridin-3-yl)acrylic acid (**1l**):



The reaction was performed with 5 mM substrate (0.453 mmol, 67.6 mg) and 8 mol% catalyst (161 mg, 0.037 mmol). Method B was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (1:4 ethanol–chloroform) to give 3-(pyridin-3-yl)propanoic acid as a white solid (57 mg, 83%).

TLC: R_f = 0.3 (1:4 ethanol–chloroform). HRMS (ESI): calcd for $C_8H_9NNaO_2^+$ $[M+Na]^+$, 174.0525; found, 174.0522. ^{1}H NMR (500 MHz, d_6-DMSO) δ: 8.46 (bs, 1H, ArC**H**), 8.40 (bs, 1H, ArC**H**), 7.67 – 7.65 (m, 1H, ArC**H**), 7.32 – 7.29 (m, 1H, ArC**H**), 2.83 (t, 2H, J = 7.5 Hz, C**H₂**), 2.58 (t, 2H, J = 7.3 Hz, C**H₂**). ^{13}C NMR (125 MHz, d_6-DMSO) δ: 174.3, 150.3, 148.0, 137.0, 136.5, 124.1, 35.5, 28.2.

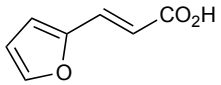
(*E*)-3-(furan-3-yl)acrylic acid (**1m**):



The reaction was performed with 5 mM substrate (0.453 mmol, 62.6 mg) and 8 mol% catalyst (161 mg, 0.037 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to afford 61 mg of a 90:10 mixture of 3-(furan-3-yl)propanoic acid and the starting material (*E*)-3-(furan-3-yl)acrylic acid (96% total mass recovery, 87% yield of hydrogenated product).

TLC: R_f = 0.3 (ethyl acetate). HRMS (ESI): calcd for $C_7H_8NaO_3^+$ $[M+Na]^+$, 163.0366; found, 163.0368. ^{1}H and ^{13}C NMR data matched that reported previously.[9]

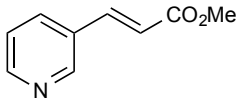
(*E*)-3-(furan-2-yl)acrylic acid (**1n**):



The reaction was performed with 5 mM substrate (0.453 mmol, 62.6 mg) and 8 mol% catalyst (161 mg, 0.037 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to afford 57 mg of a 87:13 mixture of 3-(furan-2-yl)propanoic acid and the starting material (*E*)-3-(furan-2-yl)acrylic acid (90% total mass recovery, 78% yield of hydrogenated product).

TLC: R_f = 0.3 (ethyl acetate). HRMS (ESI): calcd for $C_7H_8NaO_3^+$ $[M+Na]^+$, 163.0366; found, 163.0370. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.29 (d, 1H, *J* = 0.5 Hz, ArC**H**), 6.27 – 6.26 (m, 1H, ArC**H**), 6.03 – 6.02 (m, 1H, ArC**H**), 2.96 (t, 2H, *J* = 7.5 Hz, C$\mathbf{H_2}$), 2.70 (t, 2H, *J* = 7.8 Hz, C$\mathbf{H_2}$). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 178.9, 153.9, 141.5, 110.4, 105.6, 32.6, 23.3.

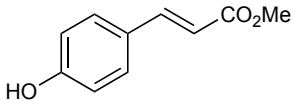
(*E*)-methyl 3-(pyridin-3-yl)acrylate (**1o**):



The reaction was performed with 5 mM substrate (0.453 mmol, 73.9 mg) and 8 mol% catalyst (161 mg, 0.037 mmol). Method C was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (1:1 ethyl acetate–hexanes) to afford 68 mg of a 92:8 mixture of methyl 3-(pyridin-4-yl)propanoate and the starting material (*E*)-methyl 3-(pyridin-4-yl)acrylate (91% total mass recovery, 83% yield of hydrogenated product).

TLC: R_f = 0.3 (1:1 ethyl acetate–hexanes). HRMS (ESI): calcd for $C_9H_{12}NO_2^+$ $[M+H]^+$, 166.0863; found, 166.0877. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.74 – 8.44 (m, 2H, 2 x ArC**H**), 7.52 (d, 1H, *J* = 8.0 Hz, ArC**H**), 7.20 (dd, 1H, *J* = 7.8, 4.8 Hz, ArC**H**), 3.65 (s, 3H, OC$\mathbf{H_3}$), 2.94 (t, 2H, *J* = 8.0 Hz, C$\mathbf{H_2}$), 2.63 (t, 2H, *J* = 7.8 Hz, C$\mathbf{H_2}$). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.6, 149.7, 147.7, 135.8 (2 x Ar**C**H), 123.3, 51.6, 35.0, 27.9.

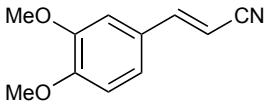
(*E*)-methyl 3-(4-hydroxyphenyl)acrylate (**1p**):



The reaction was performed with 5 mM substrate (0.453 mmol, 81.6 mg) and 8 mol% catalyst (161 mg, 0.037 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (1:1 ethyl acetate–hexanes) to afford 76 mg of a 75:25 mixture of methyl 3-(4-hydroxyphenyl)propanoate and the starting material (*E*)-methyl 3-(4-hydroxyphenyl)acrylate (93% total mass recovery, 71% yield of hydrogenated product).

TLC: R_f = 0.6 (1:1 ethyl acetate–hexanes). HRMS (ESI): calcd for $C_{10}H_{12}NaO_3^+$ $[M+Na]^+$, 203.0679; found, 203.0683. ^{1}H and ^{13}C NMR data matched that reported previously.[10]

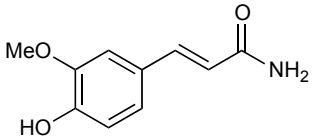
(*E*)-3-(3,4-dimethoxyphenyl)acrylonitrile (**1q**):



The reaction was performed with 5 mM substrate (0.453 mmol, 85.7 mg) and 8 mol% catalyst (161 mg, 0.037 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (1:1 ethyl acetate–hexanes) to afford 86 mg of a 80:20 mixture of 3-(3,4-dimethoxyphenyl)propanenitrile and the starting material (*E*)-3-(3,4-dimethoxyphenyl)acrylonitrile (99% total mass recovery, 79% yield of hydrogenated product).

TLC: R_f = 0.6 (1:1 ethyl acetate–hexanes). HRMS (ESI): calcd for $C_{11}H_{13}NNaO_2^+$ $[M+Na]^+$, 214.0838; found, 214.0851. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.78 – 6.75 (m, 3H, 3 x Ar**C**H), 3.87 (s, 3H, OC**H$_3$**), 3.85 (s, 3H, OC**H$_3$**), 2.89 (t, 2H, *J* = 7.3 Hz, C**H$_2$**), 2.59 (t, 2H, *J* = 7.3 Hz, C**H$_2$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 149.0, 148.0, 130.5, 120.2, 119.1, 111.4, 111.3, 55.8, 55.7, 31.0, 19.5.

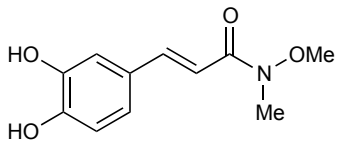
(*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylamide (**1r**):



The reaction was performed with 5 mM substrate (0.453 mmol, 87.5 mg) and 16 mol% catalyst (322 mg, 0.073 mmol). Method C was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (1:9 methanol–ethyl acetate) to afford 76 mg of a 99:1 mixture of 3-(4-hydroxy-3-methoxyphenyl)propanamide and the starting material (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylamide (86% total mass recovery, 85% yield of hydrogenated product).

TLC: R_f = 0.2 (1:9 methanol–ethyl acetate). HRMS (ESI): calcd for $C_{10}H_{13}NNaO_3^+$ $[M+Na]^+$, 218.0788; found, 218.0787. ^{1}H NMR (500 MHz, CD_3OD) δ: 6.77 (d, 1H, *J* = 2.0 Hz, Ar**C**H), 6.72 (d, 1H, *J* = 8.5 Hz, Ar**C**H), 6.65 (dd, 1H, *J* = 8.0, 2.0 Hz, Ar**C**H), 4.78 (s, 2H, CON**H$_2$**), 3.84 (s, 3H, OC**H$_3$**), 2.84 (t, 2H, *J* = 7.8 Hz, C**H$_2$**), 2.47 (t, 2H, *J* = 8.0 Hz, C**H$_2$**). ^{13}C NMR (125 MHz, CD_3OD) δ: 177.3, 147.7, 144.6, 132.6, 120.6, 115.1, 111.9, 55.5, 37.7, 31.4.

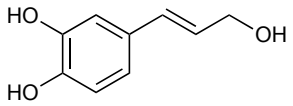
(*E*)-3-(3,4-dihydroxyphenyl)-*N*-methoxy-*N*-methylacrylamide (**1s**):



The reaction was performed with 5 mM substrate (0.453 mmol, 101.1 mg) and 16 mol% catalyst (322 mg, 0.073 mmol). Method C was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to afford 89 mg of a 89:11 mixture of 3-(3,4-dihydroxyphenyl)-*N*-methoxy-*N*-methylpropanamide and the starting material (*E*)-3-(3,4-dihydroxyphenyl)-*N*-methoxy-*N*-methylacrylamide (87% total mass recovery, 77% yield of hydrogenated product).

TLC: R_f = 0.3 (4:1 ethyl acetate–hexanes). HRMS (ESI): calcd for $C_{11}H_{16}NO_4^+$ $[M+H]^+$, 226.1074; found, 226.1080. ^{1}H NMR (500 MHz, CD_3COCD_3) δ: 6.76 (d, 1H, *J* = 2.0 Hz, ArC**H**), 6.74 (s, 1H, ArC**H**), 6.58 (dd, 1H, *J* = 7.8, 2.3 Hz, ArC**H**), 3.67 (s, 3H, NOC$\mathbf{H_3}$), 3.13 (s, 3H, NC$\mathbf{H_3}$), 2.76 (t, 2H, *J* = 8.0 Hz, C$\mathbf{H_2}$), 2.67 (t, 2H, *J* = 7.5 Hz, C$\mathbf{H_2}$). ^{13}C NMR (125 MHz, CD_3COCD_3) δ: 145.3, 143.6, 133.7, 120.0, 115.9, 115.6, 61.0, 34.2, 30.2, 28.9.

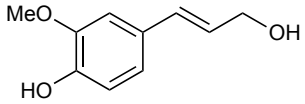
(*E*)-4-(3-hydroxyprop-1-en-1-yl)benzene-1,2-diol (**1t**):



The reaction was performed with 5 mM substrate (0.453 mmol, 75.3 mg) and 8 mol% catalyst (161 mg, 0.037 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (ethyl acetate) to give 4-(3-hydroxypropyl)benzene-1,2-diol as yellow solid (60 mg, 80%).

TLC: R_f = 0.4 (ethyl acetate). HRMS (ESI): calcd for $C_9H_{12}NaO_3^+$ $[M+Na]^+$, 191.0679; found, 191.0684. ^{1}H and ^{13}C NMR data matched that reported previously.[11]

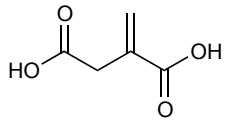
(*E*)-4-(3-hydroxyprop-1-en-1-yl)-2-methoxyphenol (**1u**):



The reaction was performed with 5 mM substrate (0.453 mmol, 81.6 mg) and 8 mol% catalyst (161 mg, 0.037 mmol). Method A was used as the workup protocol. The crude product was purified by flash chromatography on silica gel (1:1 ethyl acetate–hexanes) to give 4-(3-hydroxypropyl)-2-methoxyphenol as yellow solid (75 mg, 91%).

TLC: R_f = 0.4 (1:1 ethyl acetate–hexanes). HRMS (ESI): calcd for $C_{10}H_{14}NaO_3^+$ $[M+Na]^+$, 205.0835; found, 205.0845. ^{1}H and ^{13}C NMR data matched that reported previously.[12]

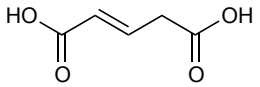
2-methylenesuccinic acid (**1v**):



The reaction was performed with 5 mM substrate (0.453 mmol, 59 mg) and 16 mol% catalyst (322 mg, 0.073 mmol). The reaction mixture was concentrated *in vacuo*, the remaining solid material was resuspended in water (10 mL), and the pH was adjusted to pH 10 using aqueous 1M NaOH. This suspension was washed with ethyl acetate (2 x 15 mL), and then the pH of the aqueous layer was adjusted to pH 3 using aqueous 1M HCl. The resulting solution was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by recrystallization using toluene and diethyl ether, and the resulting solid was collected and washed with dichloromethane to give 2-methylsuccinic acid, 2-methylmaleic acid, 2-methylfumaric acid and 2-methylsuccinic acid (17.5 : 0.2 : 1.0 : 1.0 product ratio; 38 mg of 2-methylsuccinic acid, 63% yield, 58% purity) along with lactic acid (9 mg) and succinic acid (13 mg) fermentation products.

HRMS (ESI): calcd for $C_5H_7O_4^-$ $[M-H]^-$, 131.03498; found, 131.03504. ^{1}H NMR (500 MHz, d_6-DMSO) δ: 2.68 – 2.61 (m, 1H, C**H**), 2.49 – 2.45 (m, 1H, C**H**), 2.28 (dd, 1H, J = 16.5, 5.5 Hz, C**H**), 1.08 (d, 3H, J = 7.0 Hz, C$\mathbf{H_3}$). ^{13}C NMR (125 MHz, d_6-DMSO) δ: 176.5, 173.6, 37.3, 35.3, 16.9.

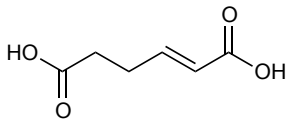
(*E*)-pent-2-enedioic acid (**1w**):



The reaction was performed with 5 mM substrate (0.453 mmol, 59 mg) and 16 mol% catalyst (322 mg, 0.073 mmol). The reaction mixture was concentrated *in vacuo*, the remaining solid material was resuspended in water (10 mL), and the pH was adjusted to pH 10 using aqueous 1M NaOH. This suspension was washed with ethyl acetate (2 x 15 mL), and then the pH of the aqueous layer was adjusted to pH 3 using aqueous 1M HCl. The resulting solution was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by recrystallization using dichloromethane and methanol, and the resulting solid was collected and washed with diethyl ether to give glutaric acid as a white solid (42 mg, 70% yield, 60% purity) along with lactic acid (8.3 mg) and succinic acid (20 mg) fermentation products.

HRMS (ESI): calcd for $C_5H_7O_4^-$ $[M-H]^-$, 131.03498; found, 131.0350. ^{1}H NMR (500 MHz, d_6-DMSO) δ: 2.23 (t, 4H, J = 7.3 Hz, 2 x C$\mathbf{H_2}$), 1.71 – 1.66 (m, 2H, C$\mathbf{H_2}$). ^{13}C NMR (125 MHz, d_6-DMSO) δ: 174.1, 32.8, 20.0.

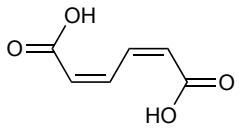
(*E*)-hex-2-enedioic acid (**1x**):



The reaction was performed with 5 mM substrate (0.450 mmol, 73 mg of 90% purity – remainder of the material was hex-3-enedoic acid) and 16 mol% catalyst (322 mg, 0.073 mmol). The reaction mixture was concentrated *in vacuo*, the remaining solid material was resuspended in water (10 mL), and the pH was adjusted to pH 10 using aqueous 1M NaOH. This suspension was washed with ethyl acetate (2 x 15 mL), and then the pH of the aqueous layer was adjusted to pH 3 using aqueous 1M HCl. The resulting solution was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by recrystallization using dichloromethane and methanol, and the resulting solid was collected and washed with diethyl ether to give adipic acid as a white solid (54 mg, 80% yield).

HRMS (ESI): calcd for $C_6H_{10}NaO_4^+$ $[M+Na]^+$, 169.04713; found, 169.04677. ^{1}H NMR (500 MHz, d_6-DMSO) δ: 11.99 (bs, 2H, 2 x CO_2**H**), 2.20 – 2.19 (m, 4H, 2 x C$\mathbf{H_2}$), 1.49 (t, 4H, J = 3.3 Hz, 2 x C$\mathbf{H_2}$).^{13}C NMR (125 MHz, d_6-DMSO) δ: 174.3, 33.4, 24.0.

(2*Z*,4*Z*)-hexa-2,4-dienedioic acid (**1y**):

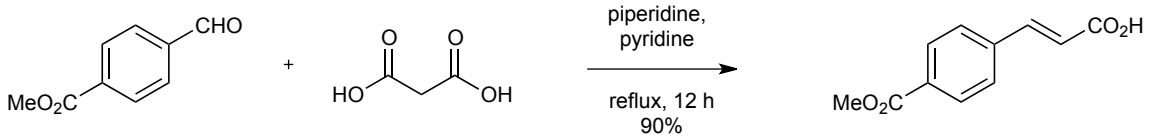


The reaction was performed with 2.5 mM substrate (0.225 mmol, 32 mg) and 16 mol% catalyst (161 mg, 0.037 mmol). The reaction mixture was concentrated *in vacuo*, the remaining solid material was resuspended in water (10 mL), and the pH was adjusted to pH 10 using aqueous 1M NaOH. This suspension was washed with ethyl acetate (2 x 15 mL), and then the pH of the aqueous layer was adjusted to pH 3 using aqueous 1M HCl. The resulting solution was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by recrystallization using dichloromethane and methanol, and the resulting solid was collected and washed with diethyl ether to give adipic acid and (*E*)-hex-2-enedioic acid (1.0 : 0.1 product ratio; 24 mg of adipic acid, 75% yield, 80% purity) along with lactic acid (3.0 mg) fermentation product.

All characterization data matched that obtained for the reduction of (*E*)-hex-2-enedioic acid **1x** (shown above).

Substrate syntheses

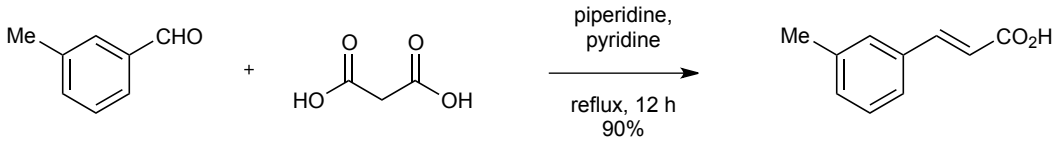
(*E*)-3-(4-(methoxycarbonyl)phenyl)acrylic acid:[13]



To a solution of malonic acid (82 mg, 0.792 mmol) in anhydrous pyridine (6 mL) were added methyl 4-formylbenzoate (100 mg, 0.609 mmol) and piperidine (26 mg, 0.305 mmol). The mixture was heated to reflux overnight. After cooling to room temperature, the reaction mixture was poured into cold concentrated hydrochloric acid (10 mL) and diluted with water (4 mL). The aqueous mixture was extracted with ethyl acetate (3 x 20 mL), and then the combined organic layers were washed with brine (10 mL), dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (1:9 methanol–ethyl acetate) to give (*E*)-3-(4-(methoxycarbonyl)phenyl)acrylic acid (113 mg, 90%) as a white solid.

TLC: R_f = 0.25 (1:9 methanol–ethyl acetate). HRMS (ESI): calcd for $C_{11}H_{11}O_4^+$ $[M+H]^+$, 207.0652; found, 207.0655. ^{1}H NMR (500 MHz, d_6-DMSO) δ: 12.60 (bs, 1H, CO_2**H**), 7.96 – 7.94 (m, 2H, 2 x ArC**H**), 7.83 – 7.81 (m, 2H, 2 x ArC**H**), 7.62 (d, 1H, *J* = 16.0 Hz, C**H**), 6.65 (dd, 1H, *J* = 16.0, 1.5 Hz, C**H**), 3.83 (s, 3H, $CO_2C\mathbf{H_3}$). ^{13}C NMR (125 MHz, d_6-DMSO) δ: 167.2, 165.7, 142.4, 138.8, 130.5, 129.6, 128.4, 121.9, 52.3.

(*E*)-3-(*m*-tolyl)acrylic acid:



This experiment was run on 500 mg (4.16 mmol) scale according to the procedure used for (*E*)-3-(4-(methoxycarbonyl)phenyl)acrylic acid to give 650 mg (96%) of (*E*)-3-(*m*-tolyl)acrylic acid.

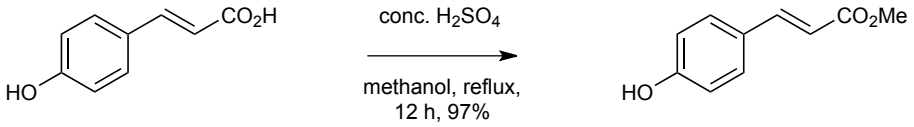
TLC: R_f = 0.25 (ethyl acetate). HRMS (ESI): calcd for $C_{10}H_{10}NaO_2^+$ $[M+Na]^+$, 185.0573; found, 185.0567. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.78 (d, 1H, *J* = 16.0 Hz, C**H**), 7.37 – 7.36 (m, 2H, 2 x ArC**H**), 7.30 (t, 1H, *J* = 7.8 Hz, ArC**H**), 7.24 (t, 1H, *J* = 8.8 Hz, ArC**H**), 6.45 (d, 1H, *J* = 16.0 Hz, C**H**), 2.39 (s, 3H, $C\mathbf{H_3}$). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.7, 147.4, 138.8, 134.1, 131.8, 129.2, 129.0, 125.7, 117.2, 21.5.

<u>General procedure for esterification:</u>

To a solution of the acid (1 mmol) in alcoholic solvent (methanol for methyl esters and ethanol for ethyl esters, 10 mL) was added concentrated sulfuric acid (0.05 mmol). The reaction mixture was refluxed overnight and then cooled to room temperature, concentrated *in vacuo*, diluted with water (10 mL), and extracted with ethyl acetate (3 x

20 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

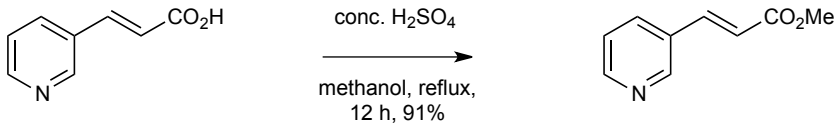
(*E*)-methyl 3-(4-hydroxyphenyl)acrylate:



This experiment was run on 200 mg (1.22 mmol) scale according to the general esterification procedure to give 210 mg (97%) of (*E*)-methyl 3-(4-hydroxyphenyl)acrylate.

TLC: R_f = 0.25 (ethyl acetate). HRMS (ESI): calcd for $C_{10}H_{10}NaO_3^+$ $[M+Na]^+$, 201.0522; found, 201.0524. ^{1}H NMR (500 MHz, CD_3OD) δ: 7.60 (d, 1H, *J* = 15.5 Hz, C**H**), 7.45 – 7.43 (m, 2H, 2 x ArC**H**), 6.80 – 6.78 (m, 2H, 2 x ArC**H**), 6.31 (d, 1H, *J* = 16.0 Hz, C**H**), 3.75 (s, 3H, $CO_2C\mathbf{H_3}$). ^{13}C NMR (125 MHz, CD_3OD) δ: 169.7, 161.3, 146.5, 131.1, 127.1, 116.8, 114.9, 52.0.

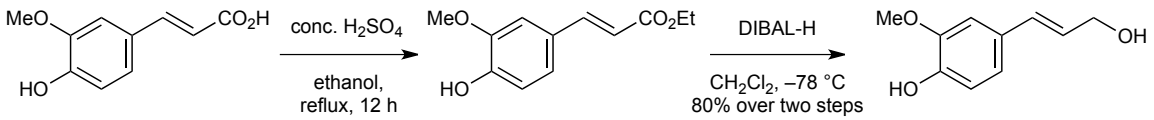
(*E*)-methyl 3-(pyridin-3-yl)acrylate:



This experiment was run on 500 mg (3.35 mmol) scale according to the general esterification procedure to give 500 mg (91%) of (*E*)-methyl 3-(pyridin-3-yl)acrylate.

TLC: R_f = 0.30 (1:1 ethyl acetate–hexanes). HRMS (ESI): calcd for $C_9H_{10}NO_2^+$ $[M+H]^+$, 164.0706; found, 164.0714. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.67 (s, 1H, ArC**H**), 8.53 (d, 1H, *J* = 4.5 Hz, ArC**H**), 7.76 (d, 1H, *J* = 7.5 Hz, ArC**H**), 7.61 (d, 1H, *J* = 16.0 Hz, C**H**), 7.27 – 7.24 (m, 1H, ArC**H**), 6.44 (dd, 1H, *J* = 16.3, 1.3 Hz, C**H**), 3.75 (s, 3H, $CO_2C\mathbf{H_3}$). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.8, 151.1, 149.8, 141.2, 134.3, 130.3, 123.9, 120.1, 52.0.

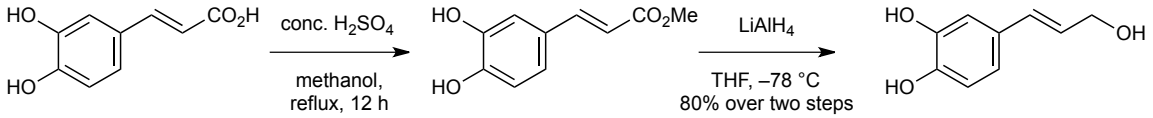
(*E*)-4-(3-hydroxyprop-1-en-1-yl)-2-methoxyphenol:



To a solution of (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylic acid (0.300 g, 1.55 mmol) in ethanol (15 mL) was added concentrated sulfuric acid (0.1 mL), and the reaction mixture was refluxed overnight. Upon cooling to room temperature, the solvent was evaporated *in vacuo*, and the resulting residue was diluted with water (10 mL) and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. To a solution of the crude ester in dichloromethane (15 mL) was added DIBAL-H (1.0 M solution in hexanes, 4.63 mL, 4.63 mmol) at –78 ° C. The reaction mixture was stirred at –78 °C for three hours and then a saturated aqueous solution of Rochelle's salt (5 mL) was added, followed by extraction of this mixture with ethyl acetate (2 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography on silica gel (1:1 ethyl acetate–hexanes) to give 220 mg (80% over two steps) of (*E*)-4-(3-hydroxyprop-1-en-1-yl)-2-methoxyphenol.

TLC: R_f = 0.40 (1:1 ethyl acetate–hexanes). HRMS (ESI): calcd for $C_{11}H_{13}O_3^+$ $[M+H]^+$, 181.0859; found, 181.0854. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.92 – 6.85 (m, 3H, 3 x Ar**C**H), 6.53 (d, 1H, *J* = 16.0 Hz, C**H**), 6.25 – 6.20 (m, 1H, C**H**), 5.64 (s, 1H, O**H**), 4.30 (d, 2H, *J* = 6.0 Hz, C**H$_2$**), 3.91 (s, 3H, CO_2C**H$_3$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 146.8, 145.7, 131.6, 129.4, 126.3, 120.5, 114.6, 108.5, 64.0, 56.0.

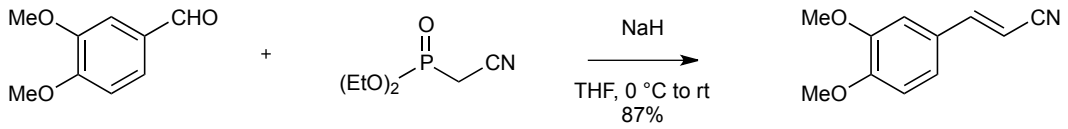
(*E*)-4-(3-hydroxyprop-1-en-1-yl)benzene-1,2-diol:



The route used to access (*E*)-4-(3-hydroxyprop-1-en-1-yl)-2-methoxyphenol was followed with these modifications: the acid was converted to the methyl ester and the ester intermediate was reduced using lithium aluminum hydride. This experiment was run on 450 mg (2.50 mmol) scale to give 353 mg (85%) of (*E*)-4-(3-hydroxyprop-1-en-1-yl)benzene-1,2-diol.

TLC: R_f = 0.40 (ethyl acetate). HRMS (ESI): calcd for $C_9H_{10}NaO_3^+$ $[M+Na]^+$, 189.0522; found, 189.0515. ^{1}H NMR (500 MHz, d_6-Acetone) δ: 6.96 (d, 1H, *J* = 1.5 Hz, Ar**C**H), 6.79 – 6.73 (m, 2H, 2 x Ar**C**H), 6.46 (d, 1H, *J* = 16.0 Hz, C**H**), 6.17 (dt, 1H, *J* = 11.5, 5.5 Hz, C**H**), 4.23 (dd, 2H, *J* = 5.0, 1.0 Hz, C**H$_2$**). ^{13}C NMR (125 MHz, d_6-Acetone) δ: 144.2, 144.0, 129.3, 128.7, 125.6, 117.9, 114.5, 112.1, 61.9.

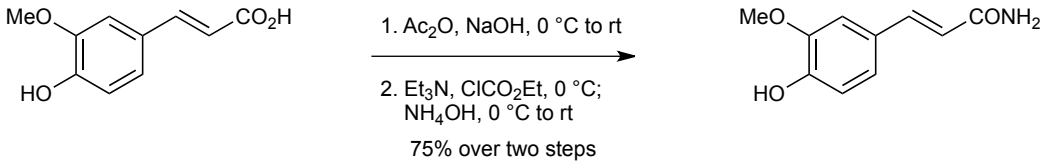
(*E*)-3-(3,4-dimethoxyphenyl)acrylonitrile:



To an ice-cold suspension of sodium hydride (0.313 g, 60 wt% in mineral oil, 7.82 mmol) in THF (50 mL) was added diethyl (cyanomethyl) phosphonate (1.28 g, 7.22 mmol). When the evolution of hydrogen gas had stopped (20 min), a solution of 3,4-dimethoxybenzaldehyde (1.00 g, 6.02 mmol) in THF (10 mL) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature overnight. The reaction mixture was then diluted with water (10 mL) and extracted with ethyl acetate (2 x 60 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (1:1 ethyl acetate–hexanes) to give 0.991 g (87%) of (*E*)-3-(3,4-dimethoxyphenyl)acrylonitrile.

TLC: R_f = 0.60 (1:1 ethyl acetate–hexanes). HRMS (ESI): calcd for $C_{11}H_{11}NaNO_2^+$ $[M+Na]^+$, 212.0682; found, 212.0684. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30 (d, 1H, *J* = 16.5 Hz, C**H**), 7.02 (dd, 1H, *J* = 8.3, 1.8 Hz, ArC**H**), 6.94 (d, 1H, *J* = 1.5 Hz, ArC**H**), 6.87 (d, 1H, *J* = 8 Hz, ArC**H**), 5.64 (d, 1H, *J* = 16.5 Hz, C**H**), 3.90 (s, 3H, OC$\mathbf{H_3}$), 3.89 (s, 3H, OC$\mathbf{H_3}$). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 151.7, 150.2, 149.3, 126.5, 122.0, 118.6, 111.0, 108.8, 93.4, 55.9, 55.9.

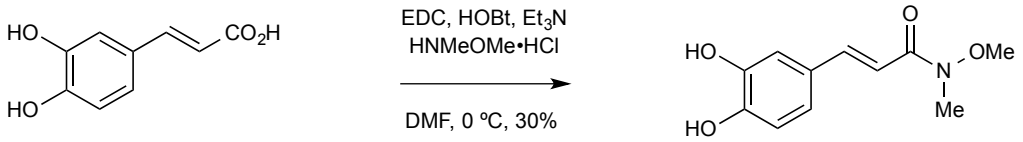
(*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylamide:



To a stirred solution of (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylic acid (1.00 g, 5.15 mmol) in 1M NaOH solution (13.3 mL) at 0 °C was added acetic anhydride (1.95 mL, 20.6 mmol) and the reaction was stirred at room temperature for 2 hours. The precipitate formed was filtered, washed with water (2 x 10 mL), and purified by flash column chromatography (1:1 ethyl acetate–hexanes) to afford 1.095 g (90%) of (*E*)-3-(4-acetoxy-3-methoxyphenyl)acrylic acid. To this product (1.00 g, 4.23 mmol) in THF (50 mL) at 0 °C was added triethylamine (3.60 mL, 9.74 mmol) and ethyl chloroformate (0.94 mL, 9.7 mmol) dropwise. The resulting solution was stirred for 30 min and then 30% aqueous ammonium hydroxide (3.8 mL, 97 mmol) was slowly added. The reaction mixture was warmed to room temperature, stirred overnight, concentrated to 20 mL volume *in vacuo*, and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water and brine (30 mL each), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (ethyl acetate) to afford 0.68 g (83%) of (*E*)-3-(4-hydroxy-3-methoxyphenyl)acrylamide.

TLC: R_f = 0.20 (1:9 methanol–ethyl acetate). HRMS (ESI): calcd for $C_{10}H_{12}NO_3^+$ $[M+H]^+$, 194.0812; found, 194.0816. ^{1}H NMR (500 MHz, d_6-DMSO) δ: 9.40 (bs, 1H, N**H**), 7.38 (bs, 1H, N**H**), 7.30 (d, 1H, *J* = 16.5 Hz, C**H**), 7.11 (d, 1H, *J* = 2.0 Hz, ArC**H**), 6.97 (dd, 1H, *J* = 7.8, 1.8 Hz, ArC**H**), 6.94 (bs, 1H, O**H**), 6.78 (d, 1H, *J* = 8.0 Hz, ArC**H**), 6.41 (d, 1H, *J* = 15.5 Hz, C**H**), 3.79 (s, 3H, OC**H$_3$**). ^{13}C NMR (125 MHz, d_6-DMSO) δ: 167.1, 148.3, 147.8, 139.6, 126.3, 121.6, 119.0, 115.6, 110.7, 55.5.

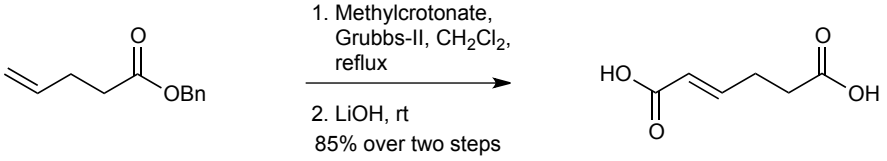
(*E*)-3-(3,4-dihydroxyphenyl)-*N*-methoxy-*N*-methylacrylamide:



This experiment was run on 500 mg (2.78 mmol) scale according to a previously reported procedure to give 186 mg (30%) of (*E*)-3-(3,4-dihydroxyphenyl)-*N*-methoxy-*N*-methylacrylamide.

TLC: R_f = 0.30 (4:1 ethyl acetate–hexanes). HRMS (ESI): calcd for $C_{11}H_{14}NO_4^+$ $[M+H]^+$, 224.0917; found, 224.0925. ^{1}H and ^{13}C NMR data matched that reported previously.[14]

(*E*)-hex-2-enedioic acid:[15]



To a solution of benzyl 4-pentenoate (0.300 g, 1.58 mmol) and methyl crotonate (0.474 g, 4.73 mmol) in dichloromethane (15 mL) was added the Grubbs–II catalyst (0.054 g, 0.063 mmol). The reaction mixture was sparged with argon for 15 min and then refluxed for 12 h. Upon cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The crude product was purified by flash column chromatography (1:9 ethyl acetate–hexanes) to give 0.360 g (92%) of (*E*)-6-benzyl 1-methyl hex-2-enedioate as the major product (>20:1 *E* to *Z* isomer ratio).

TLC: R_f = 0.30 (1:9 ethyl acetate–hexanes). HRMS (ESI): calcd for $C_{14}H_{17}O_4^+$ $[M+H]^+$, 249.1121; found, 249.1116. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.29 – 7.22 (m, 5H, 5 x ArC**H**), 6.90 – 6.84 (m, 1H, C**H**), 5.77 (d, 1H, *J* = 15.5 Hz, C**H**), 5.04 (s, 2H, OC**H$_2$**) 2.45 – 2.40 (m, 4H, 2 x C**H$_2$**). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.6, 166.3, 146.5, 135.5, 128.3 (2 x Ar**C**H), 128.0 (3 x Ar**C**H), 121.6, 66.1, 51.1, 32.1, 26.9.

To a solution of (*E*)-6-benzyl 1-methyl hex-2-enedioate (0.250 g, 1.01 mmol) in a mixture of THF:methanol:water (3:2:2, 7 mL) was added lithium hydroxide (0.145 g,

6.04 mmol). After 16 hours, the pH of the mixture was adjusted to pH 10 using aqueous 1M sodium hydroxide and the mixture was then washed with 15 mL of ethyl acetate. The aqueous phase was adjusted to pH 3 using aqueous 2M hydrochloric acid and then extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with water and brine (10 mL each), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (8:2:0.05 ethyl acetate–methanol–acetic acid) to give of (*E*)-hex-2-enedioic acid (0.133 g, 92%) in greater than 90% purity (product mixture contained ~3% isomerized product, (*E*)-hex-3-enedioic acid).

TLC: R_f = 0.20 (1:9 methanol–ethyl acetate). ^{1}H NMR (500 MHz, d_6-DMSO) δ: 12.18 (bs, 2H, 2 x CO_2**H**), 6.82 – 6.76 (m, 1H, C**H**), 5.77 (d, 1H, *J* = 15.5 Hz, C**H**), 2.37 (bs, 4H, 2 x C$\mathbf{H_2}$). ^{13}C NMR (125 MHz, d_6-DMSO) δ: 174.0, 167.6, 147.0, 122.9, 32.5, 27.0.

10. References

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