Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting information

From trials on Rosuvastatin production waste valorization to development of new catalytic method for $Z \rightarrow E$ isomerization of alkenes

Agata Tyszka-Gumkowska,[a] Błażej Peta,[a] Kamil Kosik,[a,b] Emil Szepiński,[b] Anna Kajetanowicz,[a,*] and Karol Grela[a,*]

[a] Biological and Chemical Research Centre, Faculty of Chemistry, University of Warsaw Żwirki i Wigury 101, 02-089 Warsaw, Poland

[b] Polpharma SA Pharmaceutical Works, Pelplińska 19, 83-200 Starogard Gdański, Poland

Email address: a.kajetanowicz@uw.edu.pl, klgre@uw.edu.pl

Table of contents

1. General remarks

All reactions required the exclusion of oxygen and moisture were carried out in dry glassware (kept overnight in an oven at 120 °C) with dry anhydrous solvents (purified using mBraun's SPS) under a dry and oxygen-free argon atmosphere using the Schlenk technique. The addition of dry solvents or reagents was carried out using argon flushed stainless steel cannulas and plastic syringes.

For spectroscopic and analytic characterizations, the following devices were used:

Analytical thin layer chromatography (TLC) was performed on Merck Silica gel 60 F254 precoated aluminum sheets. Components were visualized by observation under UV light (254 or 365 nm) or dyed by aqueous $KMnO_4$ or anisaldehyde reagent.

Flash column chromatography was performed using silica gel 60 (230–400 mesh), purchased from Merck.

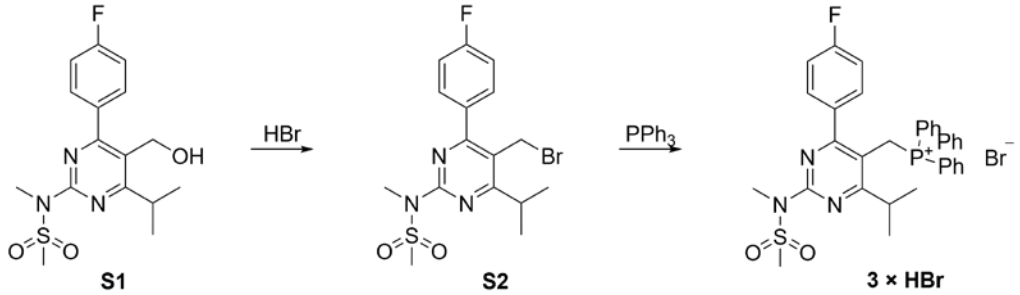
^1H NMR spectra were recorded in $CDCl_3$ at room temperature on Agilent Mercury spectrometer (400 MHz). The data were interpreted in first-order spectra. Chemical shifts δ are reported in parts per million (ppm) downfield from trimethylsilane as a reference to the residual solvent signal: chloroform (δ_H = 7.26 ppm). The following abbreviations are used to indicate the signal multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), dd (doublet of doublet), dt (doublet of triplet), ddd (doublet of doublet of doublet), etc., bs (broad signal), m (multiplet). Coupling constants (J) are given in Hz and refer to H,H-couplings.

^{13}C NMR spectra were recorded in $CDCl_3$ at room temperature on Agilent Mercury spectrometer (400 MHz). Chemical shifts δ are reported in parts per million (ppm) as a reference to the residual solvent signal: chloroform (δ_C = 77.16 ppm, central line of the triplet). If no coupling constants are given, the multiplicity refers to ^1H-decoupled spectra; otherwise, the coupling constants belong to heteroatoms.

2. Research on Rosuvastatin waste valorization

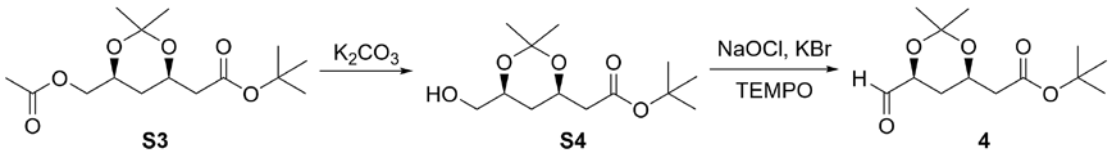
2.1. Synthesis of Rosuvastatin Calcium

*2.1.1. Preparation of N-[5-bromomethyl-4-(4-fluorophenyl)-6-isopropylpyrimidin-2-yl]-N-methylmethanesulfonamide triphenyl phosphine (**3×HBr**)*



100 g (0.283 mol) **S1** and toluene (600 mL) were charged to reactor. Upon stirring 48% aqueous hydrogen bromide (47.5 mL) was charged and reaction was refluxed at 90-110 °C with azeotropic removal of water for 3-8 h. After water was distilled from the reaction mixture reaction was refluxed for additional 2 h. After reaction competition mixture was cooled to 50-60 °C and quenched with 5% sodium thiosulfate (200 mL). After phase separation organic phase was washed twice with 10% brine (200 mL) at 50-60 °C. Acetone (75 mL) was added to organic phase and reaction mixture was heated to 70-80 °C. Triphenylphosphine (82 g, 0.313 mol) was dissolved in toluene (50 mL) and acetone (290 mL) and solution was added dropwise to reaction mixture. After addition reaction was stirred at reflux and maintained for 4 h at this temperature. Reaction mixture was cooled to 20-25 °C and maintained for 4 h at this temperature. The suspension was then filtered and solid was washed with toluene/acetone mixture (150 mL:83 mL). Product was dried at 60-70 °C for 8 hours to give **3 × HBr** as a solid (182 g, 95% yield).

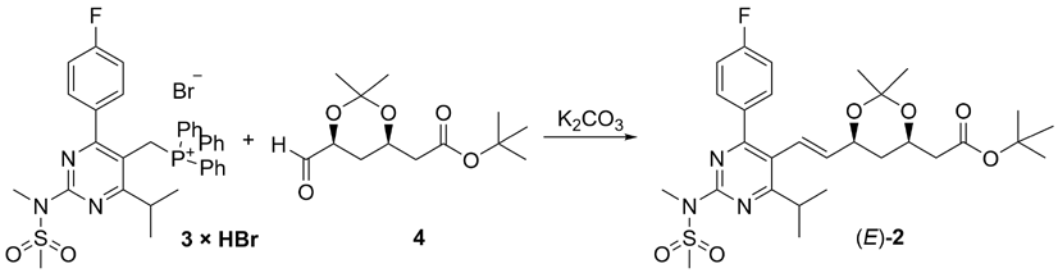
*2.1.2. Preparation of tert-butyl [(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate (**4**)*



Potassium carbonate (0.367 g, 0.00265 mol) was added to a solution of **S3** (100 g, 0.33 mol) in methanol (600 mL). Reaction was stirred at 20-25 °C for 4 h. Reaction progress was checked and reaction mixture was concentrated under reduced pressure till dryness. DCM (200 mL) was charged to residue and solvent was once again distilled under reduced pressure. To residue DCM (300 mL) and water (350 mL) was charged. After vigorous stirring phases were separated and water phase was extracted with DCM (300 mL). Combined organic phases were washed with water (225 mL). To organic phase potassium bromide (6 g, 0.05 mol), sodium bicarbonate (33 g, 0.393 mol), and water (100 mL) were added. Reaction mixture was cooled to -5-0 °C and TEMPO (0.5 g, 0.003 mol) was charged. Sodium hypochlorite solution (8% solution, 29.6 g NaOCl, 0.4 mol) was charged at -5-5 °C. Reaction was stirred for 1 h at -5-5 °C and after that time water (225 mL) was charged. Reaction mixture was heated to 10-20 °C and stirred for 30 minutes. After separation of phases water phase was extracted twice with DCM (2 × 225 mL). Combined organic phases were washed with 10% brine (200 mL). After extractions

organic layer was separated and concentrated under vacuum till dryness. **4** as oily residue was unloaded and directed to next synthesis step (71 g, 83% yield).

*2.1.3. Synthesis of 1,1-dimethyl[(4R,6S)-6-[(E)-2-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]ethenyl]-2,2-dimethyl-1,3-dioxan-4-yl]acetate (E)-**2**)*



Smaller scale: To **4** (15.3 g, 0.059 mol) dissolved in DMSO (230 mL) **3×HBr** (38.2 g, 0.056 mol) and potassium carbonate (9.5 g, 0.069 mol) were added. Reaction mixture was heated to 65-70 °C and maintained in this temperature for 4 h. After that time reaction progress was checked and isopropanol (245 mL) was added. Reaction mixture was heated to 80-85 °C and water (162 mL) was added. Reaction mass was stirred for 1 h at 80-8 5°C, cooled to 20-25 °C and stirred for 4 h. Product was obtained as a mixture of (*E*) and (*Z*) isomers. To remove (*Z*) isomer the mixture was filtered and washed with isopropanol:water mixture (35 mL of each solvent) and isopropanol (30 mL). Wet product was heated with isopropanol (200 mL) and water to 70-85 °C for 1 h and filtered. Filtrate was cooled to 20-25 °C, obtained suspension was filtered, washed with isopropanol:water mixture (20 mL each solvent) and then *n*-heptane (20 mL). Product was dried at 45-55 °C for 8 hours to give (*E*)-**2** as a solid (18.3 g, 56% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J = 8.9, 5.4 Hz, 2H), 7.08 (t, J = 8.7 Hz, 2H), 6.51 (dd, J = 16.2, 1.4 Hz, 1H), 5.46 (dd, J = 16.2, 5.4 Hz, 1H), 4.42 (dd, J = 10.6, 5.3 Hz, 1H), 4.34 – 4.19 (m, 1H), 3.57 (s, 3H), 3.51 (s, 3H), 3.37 (dt, J = 13.5, 6.7 Hz, 1H), 2.44 (dd, J = 15.3, 6.9 Hz, 1H), 2.29 (dd, J = 15.3, 6.3 Hz, 1H), 1.48 (s, 3H), 1.45 (s, 9H), 1.40 (s, 3H), 1.26 (dd, J = 6.7, 3.2 Hz, 6H).

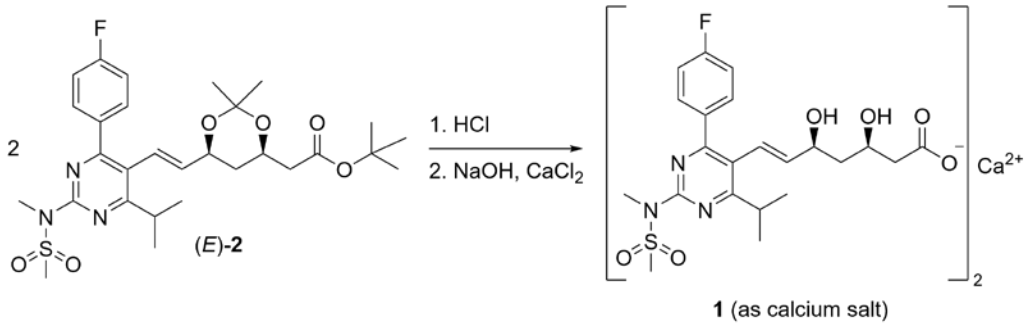
Larger scale: To **4** (61.08 g, 0.236 mol) dissolved in DMSO (690 mL) **3×HBr** (138 g, 0.203 mol) and potassium carbonate (37.05 g, 0.268 mol) were added. Reaction mixture was heated to 65-70 °C and maintained in this temperature for 4 h. After that time reaction progress was checked and isopropanol (942 mL) was added. Reaction mixture was heated to 80-85 °C and water (628 mL) was added. Reaction mass was stirred for 1 h at 80-85°C, cooled to 20-25 °C and stirred for 4 h. Product was obtained as a mixture of (*E*) and (*Z*) isomers. To remove (*Z*) isomer the mixture was filtered and washed with isopropanol:water mixture (135 mL of each solvent) and isopropanol (180 mL). Wet product was heated with isopropanol (616 mL) and water (409 mL) to 70-85 °C for 1 h and filtered. Filtrate was cooled to 20-25 °C, obtained suspension was filtered, washed with isopropanol:water mixture (90 mL each solvent) and then *n*-heptane (90 mL). Product was dried at 45-55 °C for 8 hours to give (*E*)-**2** as a solid (70 g, 59.6% yield).

2.1.4 Sample of pure (Z)-2 isolation for R&D studies

Liquors from crystallization were distilled under reduced pressure. Residue was dissolved in cyclohexane (100 mL). The solution was cooled to 5-10 °C. Obtained suspension was filtered and the solid was discarded. Filtrate was taken and concentrated under vacuum. Residue was purified on silica gel (starting mobile phase heptane: ethyl acetate 85:15). Fraction with (*Z*)-isomer were combined and

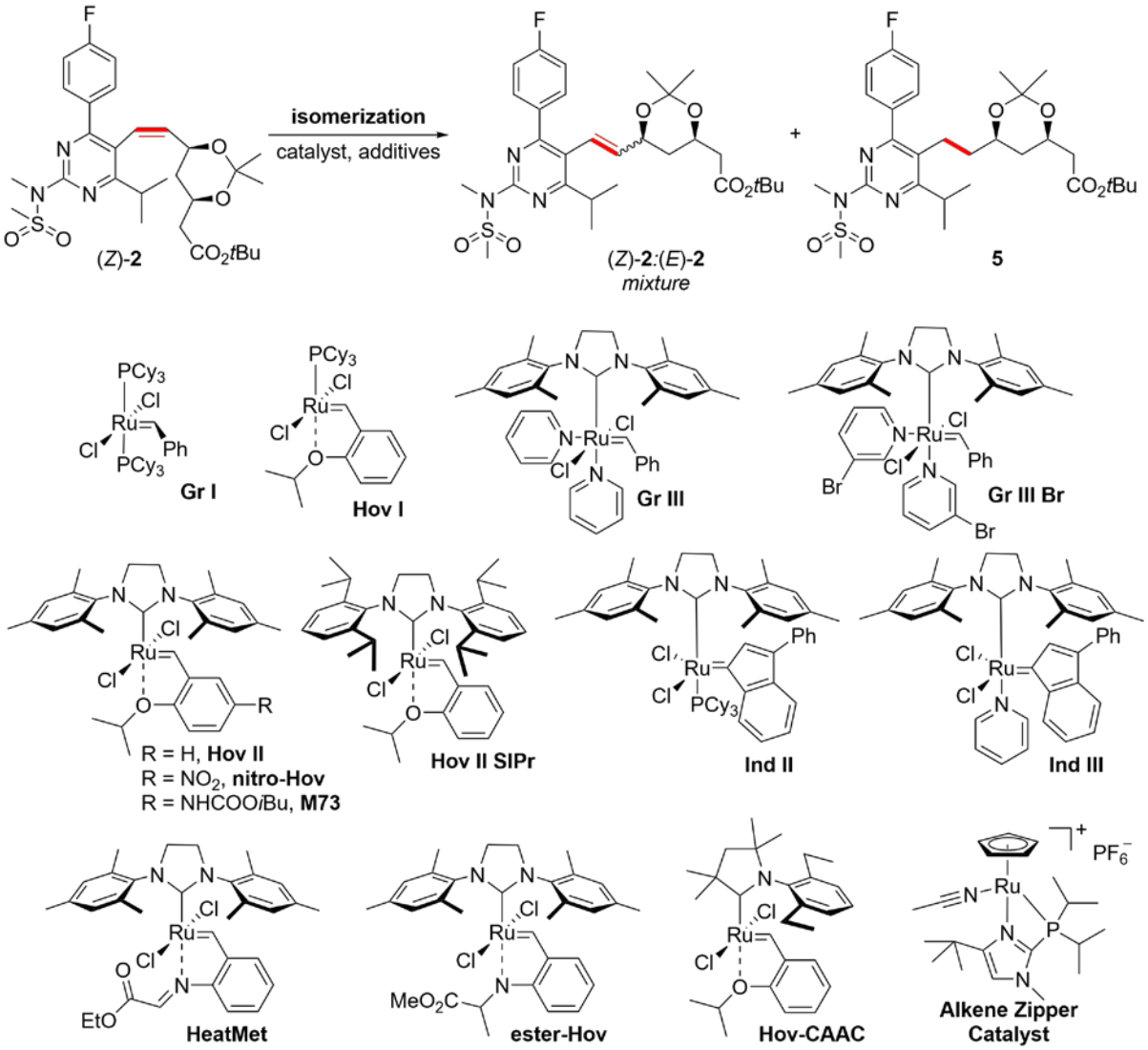
solvents were removed under reduced pressure. Residue was dissolved in methanol (40 mL) at 40-50 °C and cooled to 0-5 °C. Suspension was filtered and washed with cooled methanol (10 mL). After drying at 40 °C under vacuum pure (*Z*)-**2** was isolated.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 2H), 7.16 – 7.02 (m, 2H), 6.52 (d, J = 11.4 Hz, 1H), 5.61 (dd, J =11.4, 8.1 Hz, 1H), 4.12 – 3.86 (m, 2H), 3.60 (s, 3H), 3.53 (s, 3H), 3.39 – 3.10 (m, 1H), 2.41 – 2.21 (m, 1H), 2.19 – 1.96 (m, 1H), 1.40 (s, 9H), 1.23 (dd, J = 6.6, 2.6 Hz, 9H), 1.10 (s, 3H).

2.1.5. Synthesis of Rosuvastatin Calcium



(*E*)-**2** (47.5 g, 0.082 mol), toluene (72 mL) and methanol (190 mL) were charged into reactor. Upon stirring mixture was heated to 28-32 °C and 0.8 N HCl (9 mL) was added. Reaction was stirred for 1 h 45 min at 28-32 °C and after completion 5% NaOH solution (15 g) was added dropwise. Mixture was cooled to 10-20 °C and remaining 5% NaOH solution (65 g) was added dropwise. Reaction was continued for 4 h at 10-20 °C and after completion 0.2 N HCl solution was added dropwise to pH = 11-12. Then water (105 mL) was added and mixture was stirred for 30 min. After phase separation organic phase was discarded and water phase was distilled under reduced pressure at 40-45 °C to 1/2 volume left. After cooling to 20-25 °C water phase was washed with MTBE (2 x 100 mL). Organic phases were discarded. To water phase 50 mL of water was added and water phase was distilled under reduced pressure at 40-45 °C to 1/2 volume left in reactor. Water (105 mL) was added and pH was adjusted with 0.2 N HCl to pH = 8.2-9.0. Reaction mixture was filtered and filter was washed with water (35 mL) and heated to 23-27 °C. Dropwise was added a solution of calcium chloride (7.7 g, 0.07 mol) in water (130 mL). Obtained suspension was heated to 36-38 °C and stirred for 30 min in this temperature, then cooled to 15-25 °C and stirred for 30 minutes in this temperature. Product was filtered and washed with cold water (3 x 100 mL). Product was dried under reduced pressure at 40-45 °C to obtain **1** as calcium salt (34.2 g, 83% yield).

2.2. Isomerization of Rosuvastatin precursor



2.2.1. General protocol for isomerization reaction

5 mL vial was charged with *(Z)*-Rosuvastatin precursor (0.025 mmol, 1 equiv.), additive (according to data in Table) and stirring element. Vials were transferred to glovebox. In an additional vial, a stock solution of the catalyst in anhydrous toluene was prepared. Using a Hamilton syringe, an appropriate volume (depending on the tested conditions) of stock solution of the catalyst was added. Then indicated volume of toluene and carboxylic acids (depending on conditions) was added. Reaction mixtures were intensively stirred and heated using a heating mantle at 120 °C. After 16 hours, stirring elements were removed, internal standard (1,3,5-trimethoxybenzene) was added and solvent was evaporated in vacuo. The residue was dissolved in deuterated chloroform and a ^{1}H NMR experiment was conducted to calculate the yields and selectivity.

Table S1. *(Z)*-Rosuvastatin precursor isomerization results.

Entry	Catalyst	Conditions	(*Z*)-2 to (*E*)-2 ratio	Over reduction by-product 5 yield
1	**Hov II**	**10 equiv. HCOONa** 5 mol% catalyst 0.6 mL toluene reflux, 24 h	50:50	26%
2	**Hov II SIPr**		88:12	1%
3	**Gr III**		95:5	3%
4	**Gr III Br**		46:54	35%
5	**Ind III**		44:56	36%
6	**M73**		73:27	9%
7	**Hov II**	10 equiv. HCOONa 5 mol% catalyst 0.6 mL toluene **100°C**, 24 h	85:15	5%
8	**Hov II**	10 equiv. HCOONa 5 mol% catalyst 0.6 mL **THF** 100°C, 24 h	No isomerization or reduction	
9	**Hov II**	10 equiv. HCOONa **10 mol% catalyst** 0.6 mL toluene reflux, 24 h	34:66	53%
10	**Hov II SIPr**		23:77	38%
11	**Gr III Br**		34:66	50%
12	**Ind III**		30:70	58%
13	**Hov II**	**10 equiv. $HCOONH_4$** 5 mol% catalyst 0.6 mL toluene reflux, 24 h	No isomerization or reduction	
14	**Hov II**	**10 equiv. HCOOH** 5 mol% catalyst 0.6 mL toluene reflux, 24 h	55:45	28%
15	**Hov II SIPr**		89:12	8%
16	**Gr III**		91:9	3%
17	**Gr III Br**		37:63	42%
18	**Ind III**		40:60	57%
19	**HeatMet**		88:12	4%
20	**Nitro-Hov**		62:38	21%
21	**Ester-Hov**		64:36	36%
22	**Hov-CAAC**		Decomposition	
23	**Gr I**		No isomerization or reduction	
24	**Hov I**		No isomerization or reduction	
25	**Ind II**		No isomerization or reduction	
26	**$Ru(PPh_3)_3(CO)(H)Cl$**		No isomerization or reduction	
27	**Hov II**	10 equiv. HCOOH 5 mol% catalyst **0.8 mL toluene** reflux, 24 h	63:37	52%
28	**Hov II**	10 equiv. HCOOH 5 mol% catalyst **0.3 mL toluene** reflux, 24 h	79:21	5%
29	**Ind III**		62:38	12%
30	**Hov II**	**15 equiv. HCOOH** 5 mol% catalyst 0.6 mL toluene reflux, 24 h	36:74	73%
31	**Gr III Br**		29:71	65%
32	**Hov II**	**5 equiv. HCOOH** 5 mol% catalyst	85:15	6%
33	**Gr III Br**		46:54	33%

		0.6 mL toluene reflux, 24 h		
34	**Hov II**	5 equiv. HCOOH **2.5 mol% catalyst** 0.6 mL toluene reflux, 24 h	90:10	2%
35	**Hov II**	**20 equiv. HCOOH** 5 mol% catalyst 0.6 mL toluene reflux, 24 h	27:73	76%
36	**Hov II**	**15 equiv. HCOOH** 5 mol% catalyst 0.6 mL toluene 80°C, 24 h	No isomerization or reduction	
37	**Hov II**	**5 equiv. AcOH** **5 equiv. HCOOH** 5 mol% catalyst 0.6 mL toluene reflux, 24 h	**75:25**	**1%**
38	**Hov II SIPr**		71:29	11%
39	**Gr III Br**		38:62	41%
40	**Ind III**		30:70	56%
41	**Hov II**	**5 equiv. AcOH** **5x2 equiv. HCOOH** 5 mol% catalyst 0.6 mL toluene reflux, 24 h	84:16	7%
42	**Hov II SIPr**		88:12	5%
43	**Gr III Br**		27:76	67%
44	**Ind III**		54:46	21%
45	**Hov II**	**5 equiv. AcOH** **10 equiv. HCOOH** 5 mol% catalyst 0.6 mL toluene reflux, 24 h	60:40	20%
46	**Hov II SIPr**		88:12	7%
47	5 mol% **$Ru(PPh_3)_3(CO)(H)Cl$**	toluene, reflux 24 h	Traces of *E*-isomer	
48	5 mol% **$Ru(PPh_3)_3(H)Cl$** toluene adduct		No isomerization	
49	20 mol% **$PdCl_2(MeCN)_2$**		No isomerization	
50	20 mol% **$PdCl_2(PhCN)_2$**		No isomerization	
51	5 mol% **Alkene Zipper Catalyst**		No isomerization	
52	8.5 mol% **$Ru(PPh_3)_3(CO)(H)Cl$**	DCM, 60 °C, 24 h, close vial	No isomerization	
53	8.5 mol% **$Ru(PPh_3)_3(CO)(H)Cl$**	THF, 60 °C, 24 h, close vial	No isomerization	
54	8.5 mol% **$Ru(PPh_3)_3(CO)(H)Cl$**	Et_2O, 60 °C, 24 h, close vial	No isomerization	
55	2 mol% **$(Ir(cod)Cl)_2$** 8 mol% **tbppf**	**50 equiv. HCOOH** THF 2 mL, 80 °C, 24 h	Decomposition	
56	I_2	10 mol% **I_2**, toluene, reflux, 24 h	Decomposition	
57	AIBN/NBS	10 mol% **AIBN**, **NBS** 1.1 equiv.	Decomposition	
58	Bz_2O_2/ NBS	10 mol% **benzoyl**	Decomposition	

		peroxide, **NBS** 2 equiv.	
58	I_2	10 mol% $\mathbf{I_2}$, $CHCl_3$, 80 °C, 24 h	Decomposition
60	AIBN/NBS	10 mol% **AIBN**, **NBS** 1.1 equiv. CCl_4, 80 °C, 24 h	Decomposition
61	Bz_2O_2/ NBS	10 mol% **benzoyl peroxide**, **NBS** 2 equiv. CCl_4, 80 °C, 24 h	Decomposition

Other additives checked with Ru-catalysts Hov II: **NaH** (no isomerization or decomposition), $\mathbf{NaBH_4}$ or $\mathbf{NaCNBH_3}$ (no isomerization), **trimethylortoformate** (no isomerization), $\mathbf{HSiMe_3}$ (no isomerization), $\mathbf{B(OH)_3}$ (no isomerization), $\mathbf{BH_3NH_3}$ (decomposition). Yield = combined yield of (*Z*)-**2** and (*E*)-**2** after reaction, while the rest of mass balance was the over-reduced product **5**. (*Z*):(*E*) ratio and yield were calculated based on ^{1}H NMR spectra.

2.3 E-factor calculations for (*E*)-2 synthesis and comparison with (theoretical) process involving one recycle of waste (*Z*)-2

Table S2. E-factor calculations.

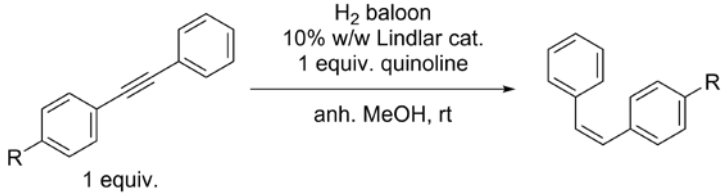
Reaction route:			**Classical**	**Once recycled***
Product		**[Unit]**		
(*E*)-**2**		g	70,0	75,2
Waste	**Note**	**[Unit]**		
4	unreacted substrate	g	8,5	8,5
DMSO	solvent	g	759,0	759,0
K_2CO_3	unreacted substrate	g	9,0	9,0
i-PrOH	work-up	g	1 719,6	1 719,6
H_2O	work-up	g	1 262,0	1 262,0
n-Hepane	work-up	g	61,6	61,6
KBr	by-product	g	24,2	24,2
$Ph_3P{=}O$	by-product	g	56,5	56,5
(*Z*)-**2**	by-product	g	20,9	15,7
Toluene	solvent	g		42,2
HovII	catalyst	g		0,6
Σ waste		g	**3921,2**	**3958,9**
E-factor			***56***	***53***

*E-factor calculation for reaction at 0,203 mol scale, with theoretical 25% recycle of (*Z*)-**2**. Separation step of (Z)-2 and (E)-2 not included in calculations, because is the same in both cases.

3. Research on *Z*→*E* isomerization method

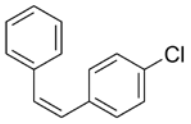
3.1. Substrate synthesis–general protocols for semihydrogenation of alkynes

3.1.1. Method A



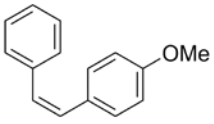
In a round bottom two-neck flask, the solution of the diphenylacetylene derivative (1.0 equiv.) in dry MeOH (c = 0.2 M) was degassed for 15 minutes. Then the Lindlar cat. (10% w/w) and quinoline (4 equiv.) were added. After that, a balloon filled with H_2 was installed and the reaction mixture was stirred at room temperature until full substrate consumption. Reaction progress was monitored using TLC (SiO_2, 1% EtOAc/*n*-hexane) and ^{1}H NMR. After completion, the reaction mixture was filtered through a Celite pad and concentrated in vacuo. The residue was dissolved in hexane and placed on a SiO_2 pad, washed with hexane to separate the quinoline. The fractions were collected and concentrated in vacuo. The crude product was purified by combi flash chromatography (SiO_2, EtOAc/*n*-hexane) to obtain the desired product.

Synthesis of (*Z*)-1-chloro-4-styrylbenzene (*Z*)-6a



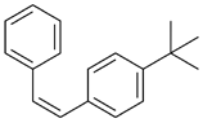
Following the general procedure **method A**, using 1-chloro-4-(phenylethynyl)benzene (200 mg) as substrate. The desired product was obtained as colorless oil (159.9 mg, 79%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–6.95 (m, 9H), 6.62 (dd, J = 12.1, 9.7 Hz, 1H), 6.52 (dd, J = 12.2, 9.5 Hz, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8, 135.6, 132.7, 130.9, 130.2, 128.9, 128.8, 128.4, 128.3, 127.3.
^{1}H and ^{13}C NMR spectra are in agreement with those previously reported.[1]

Synthesis of *(Z)*-1-methoxy-4-styrylbenzene (*Z*)-6e



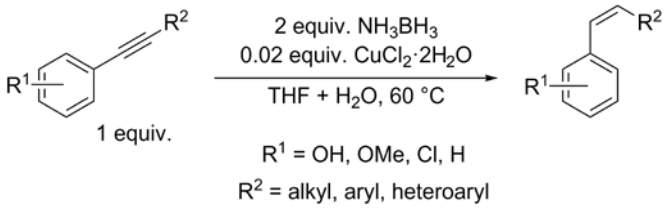
Following the general procedure **method A**, using 1-methoxy-4-(phenylethynyl)benzene (200 mg) as substrate. The desired product was obtained as colorless oil (103,9 mg, 51%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–6.97 (m, 9H), 6.86–6.64 (m, 1H), 6.49 (d, J = 15.0 Hz, 1H), 3.77 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 137.6, 130.1, 129.7, 129.6, 128.8, 128.7, 128.2, 126.9, 113.6, 55.2.
^{1}H and ^{13}C NMR spectra are in agreement with those previously reported.[1]

Synthesis of *(Z)*-1-(*tert*-butyl)-4-styrylbenzene (*Z*)-6f



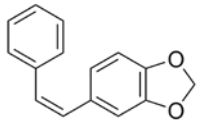
Following the general procedure **method A**, using 1-(*tert*-butyl)-4-(phenylethynyl)benzene (200 mg) as substrate. The desired product was obtained as colorless oil (129,0 mg, 64%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.13 (m, 9H), 6.54 (s, J = 12.6 Hz, 2H), 1.29 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1, 137.6, 134.2, 130.1, 129.5, 128.8, 128.6, 128.2, 126.9, 125.1, 34.5, 31.3.^{1}H and ^{13}C NMR spectra are in agreement with those previously reported.[1]

3.1.2. Method B



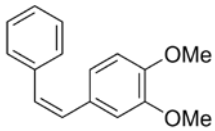
A vial was charged with alkyne (1 equiv.), THF (c = 1 M) and $CuCl_2 \cdot 2H_2O$ (0.02 equiv.). Subsequently, ammonia-borane (2 equiv.), THF (c = 0.33 M) and water (c = 0.25 M) were added to the solution. The mixture was stirred at 60 °C. After completion of the reaction, which was indicated by TLC, the mixture was quenched with water and the aqueous phase was extracted with DCM (3×15 mL). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by combi flash chromatography (SiO_2, EtOAc/n-hexane) to obtain the desired product.

Synthesis of *(Z)*-5-styrylbenzo[d][1,3]dioxole (*Z*)-6c



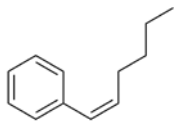
Following the general procedure **method B**, using 5-(phenylethynyl)benzo[*d*][1,3]dioxole (279 mg) as substrate. The desired product was obtained as colorless oil (208 mg, 74%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.16 (m, 5H), 6.78 – 6.65 (m, 3H), 6.57 – 6.44 (m, 2H), 5.92 (s, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 147.3, 147.0, 137.3, 131.1, 129.8, 129.2, 128.8, 128.3, 127.0, 123.0, 109.0, 108.2, 101.0.
^{1}H and ^{13}C NMR spectra are in agreement with those previously reported.[1]

Synthesis of *(Z)*-1,2-dimethoxy-4-styrylbenzene (*Z*)-6d



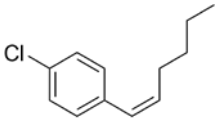
Following the general procedure **method B**, using 1,2-dimethoxy-4-(phenylethynyl)benzene (200 mg) as substrate. The desired product was obtained as colorless oil (88 mg, 40%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.15 (m, 5H), 6.84 – 6.71 (m, 3H), 6.57 – 6.48 (m, 2H), 3.86 (s, 3H), 3.59 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 148.2, 137.7, 129.9, 129.8, 128.9, 128.2, 127.0, 121.9, 111.7, 110.7, 55.8, 55.4.
^{1}H and ^{13}C NMR spectra are in agreement with those previously reported.[1]

Synthesis of *(Z)*-hex-1-en-1-ylbenzene (*Z*)-6b



Following the general procedure **method B**, using hex-1-yn-1-ylbenzene (158 mg) as substrate. The desired product was obtained as colorless oil (147 mg, 92%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.16 (m, 5H), 6.41 (dt, J = 11.7, 1.8 Hz, 1H), 5.67 (dt, J = 11.7, 7.3 Hz, 1H), 2.37 – 2.30 (m, 2H), 1.49 – 1.27 (m, 4H), 0.90 (t, J = 7.28 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 131.5, 128.2, 127.4, 124.1, 90.4, 80.5, 30.8, 22.0, 19.1, 13.7.
^{1}H and ^{13}C NMR spectra are in agreement with those previously reported.[1]

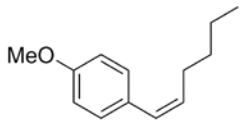
Synthesis of *(Z)*-1-chloro-4-(hex-1-en-1-yl)benzene (*Z*)-6i



Following the general procedure **method B**, using 1-chloro-4-(hex-1-yn-1-yl)benzene (225 mg) as substrate. The desired product was obtained as colorless oil (80 mg, 36%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.06 (m, 4H), 6.37 (d, J = 11.6 Hz, 1H), 5.62 (dt, J = 11.7, 7.3 Hz, 1H), 2.34 (t, J = 7.0 Hz, 2H), 1.49 – 1.21 (m, 4H), 0.89 (t, J = 7.2 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 136.2, 133.9, 130.4, 130.0, 128.2, 127.5, 32.0,

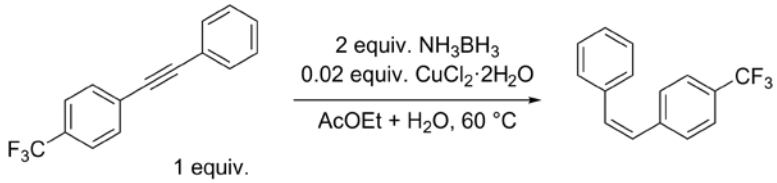
28.3, 22.4, 13.9.
^{1}H and ^{13}C NMR spectra are in agreement with those previously reported.[2]

Synthesis of *(Z)*-1-(hex-1-en-1-yl)-4-methoxybenzene (*Z*)-6h



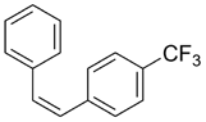
Following the general procedure **method B**, using 1-(hex-1-yn-1-yl)-4-methoxybenzene (210 mg) as substrate. The desired product was obtained as colorless oil (149 mg, 64%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 2H), 6.90 – 6.84 (m, 2H), 6.33 (dt, J = 13.4, 1.8 Hz, 1H), 5.57 (dt, J = 11.6 Hz, 1H), 3.81 (s, 3H), 2.32 (qd, J = 7.5, 1.8 Hz, 2H), 1.48 – 1.27 (m, 4H), 0.90 (t, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 131.7, 130.5, 129.9, 128.4, 113.5, 55.2, 32.2, 28.4, 22.4, 14.0.
^{1}H and ^{13}C NMR spectra are in agreement with those previously reported.[1]

3.1.3. Method C



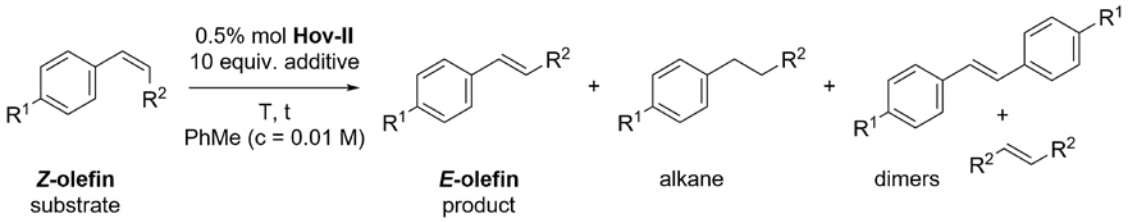
A vial was charged with 1-(phenylethynyl)-4-(trifluoromethyl)benzene (143 mg, 1 equiv.), EtOAc (c = 1 M) and $CuCl_2{\cdot}2H_2O$ (0.02 equiv.). Subsequently, ammonia-borane (2 equiv.), EtOAc (c = 0.33 M) and water (c = 0.25 M) were added to the solution. The mixture was stirred at 60 °C. After completion of the reaction, which was indicated by TLC, the mixture was quenched with water and the aqueous phase was extracted with DCM (3×15 ml). The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by combi flash chromatography (SiO_2, EtOAc/n-hexane) to obtain the desired product.

Synthesis of *(Z)*-1-styryl-4-(trifluoromethyl)benzene (*Z*)-6g



Following the general procedure **method C**, using 1-(phenylethynyl)-4-(trifluoromethyl)benzene (143 mg) as substrate. The desired product was obtained as colorless oil (80 mg, 56%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.2 Hz, 2H), 7.37 – 7.31 (m, 2H), 7.29 – 7.17 (m, 5H), 6.72 (d, J = 12.2 Hz, 1H), 6.60 (d, J = 12.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 136.6, 132.3, 129.8, 129.1, 128.8, 128.7, 128.4, 127.5, 125.1 (q, J = 3.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.56 (s).
^{1}H, ^{19}F, and ^{13}C NMR spectra are in agreement with those previously reported.[1]

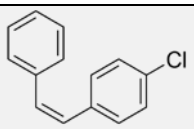
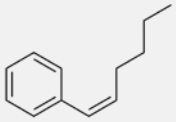
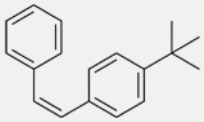
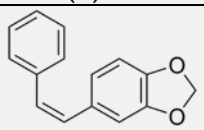
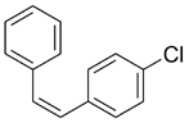
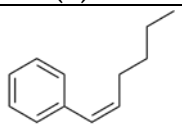
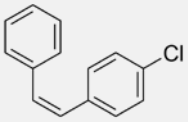
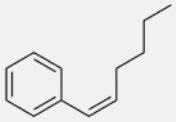
3.2. Optimization of isomerization conditions



3.2.1. General protocol for setting up isomerization reaction

5 mL vial was charged with *(Z)*-alkene (0.05 mmol, 1 equiv.), additive (according to data in Tables 2-4) and stirring element. Vials were transferred to glovebox. In an additional vial, a stock solution of the Hoveyda-Grubbs II generation catalyst in anhydrous toluene (c = 0.0025 M) was prepared. Using a Hamilton syringe, an appropriate volume (depending on the tested conditions) of stock solution was added to vials charged with (*Z*)-alkenes. Then 0.5 mL of toluene was added and when necessary carboxylic acid (depending on conditions). Reaction mixtures were intensively stirred and heated using a heating mantle (at a temperature depending on the conditions). After a certain time, stirring elements were removed, internal standard (durene or 1,3,5-trimethoxybenzene) was added and solvent was evaporated in vacuo. The residue was dissolved in deuterated chloroform and a ^{1}H NMR experiment was conducted to calculate the yields and selectivity.

Table S3. Initial optimization of isomerization conditions.

Entry	Substrate	Conditions	Composition of reaction mixture[a]			
			unreacted substrate (*Z*)-alkene	Product (*E*)-alkene	alkane	dimers
1	 **(*Z*)-6a**	T = 120°C, t = 12 h	-	67%	-	29%
2	 **(*Z*)-6b**		16%	29%	14%	41%
3	 **(*Z*)-6f**		-	59%	-	41%
4	 **(*Z*)-6c**		-	41%	-	48%
5	 **(*Z*)-6a**	T = 120°C, t = 3 h	-	62%	-	23%
6	 **(*Z*)-6b**		16%	29%	7%	48%
7	 **(*Z*)-6a**	T = 90°C, t = 12 h	-	55%	3%	43%
8	 **(*Z*)-6b**		15%	29%	15%	41%

[a]calculated based on ^{1}H NMR experiments

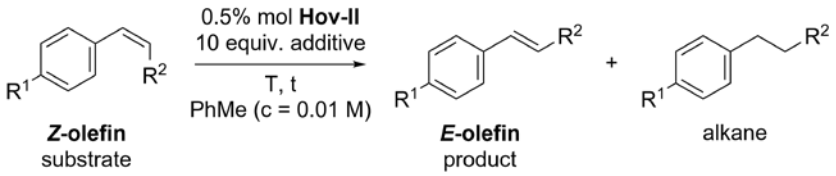
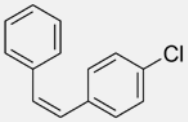
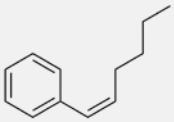
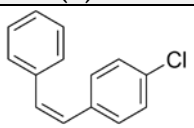
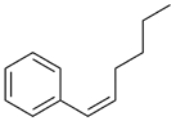
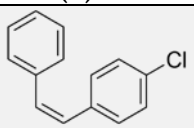
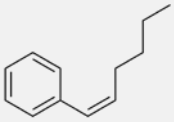
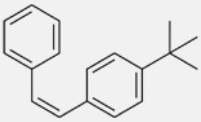
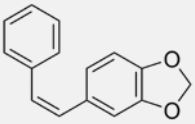
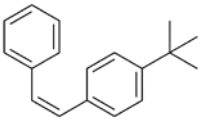
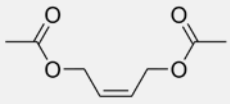
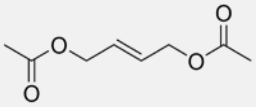
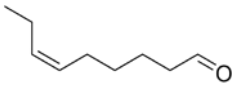
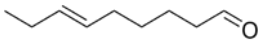


Table S4. Further optimization of isomerization conditions.

Entry	Substrate	Conditions	Composition of reaction mixture[a]		
			unreacted substrate:	product (*E*)-alkene	alkane
1	 (*Z*)-6a	T = 120°C, t = 12 h, 10 equiv. HCOOH	-	90%	10%
2	 (*Z*)-6b		-	-	100%
3	 (*Z*)-6a	T = 120°C t = 12 h 10 equiv. $HCOONH_4$	35%	65%	-
4	 (*Z*)-6b		27%	73%	-
5	 (*Z*)-6a	T = 120°C t = 12 h 10 equiv. HCOONa	-	96%	4%
6	 (*Z*)-6b		-	99%	1%
7	 (*Z*)-6f		2%	85%	13%
8	 (*Z*)-6c		-	99%	0%
9	 (*Z*)-6f	T = 120°C t = 3 h 10 equiv. HCOONa	20%	66%	14%

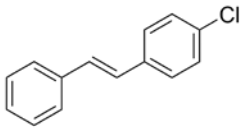
[a] calculated based on ^{1}H NMR experiments using internal standard

Table S5. Testing of aliphatic compounds.[a]

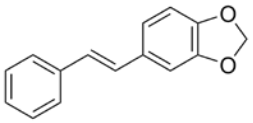
Entry	Substrate: (*Z*)-alkene	Product: (*E*)-alkene	Yield[b]
1	 **(*Z*)-6j**		77% (83%)[c]
2	 **(*Z*)-6k**		35% (66%)[c]

[a] conditions: 0.5 mol% cat., T = 120 °C, t = 12 h, 10 equiv. HCOONa
[b] calculated based on ^{1}H NMR experiments
[c] 1 mol% of catalyst was used

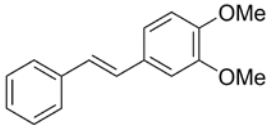
4. Analytical data for isomerized products



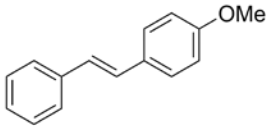
***(E)*-1-chloro-4-styrylbenzene (*E*)-6a**
Isomerization yield 99%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.50 (m, 2H), 7.50 – 7.42 (m, 2H), 7.37 (ddt, J = 16.3, 9.1, 2.1 Hz, 5H), 7.12 – 7.03 (m, 2H).
^{1}H NMR spectrum is in agreement with this previously reported.[4]



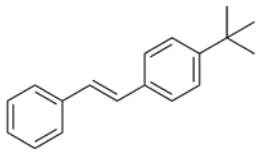
***(E)*-5-styrylbenzo[d][1,3]dioksole (*E*)-6c**
Isomerization yield 99%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, J = 9.0, 7.7 Hz, 2H), 7.35 (dd, J = 10.4, 4.8 Hz, 2H), 7.26 (dd, J = 6.1, 2.2 Hz, 2H), 7.06 – 6.96 (m, 2H), 6.94 (dd, J = 8.0, 6.3 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 5.98 (s, 2H).
^{1}H NMR spectrum is in agreement with this previously reported.[6]



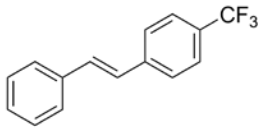
***(E)*-1,2-dimethoxy-4-styrylbenzene (*E*)-6d**
Isomerization yield 93%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 2H), 7.41 – 7.33 (m, 2H), 7.27 – 7.23 (m, 1H), 7.07 (dd, J = 13.3, 1.8 Hz, 3H), 7.01 (s, 1H), 6.87 (d, J = 8.2 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H).
^{1}H NMR spectrum is in agreement with this previously reported.[3]



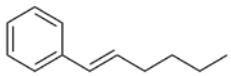
***(E)*-1-methoxy-4-styrylbenzene (*E*)-6e**
Isomerization yield 99%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.42 (m, 5H), 7.36 (t, J = 7.6 Hz, 2H), 7.03 (dd, J = 38.2, 16.3 Hz, 2H), 6.95 – 6.86 (m, 2H), 3.84 (s, 3H).
^{1}H NMR spectrum is in agreement with this previously reported.[3]



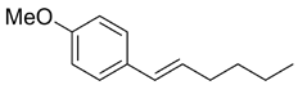
***(E)*-1-(*tert*-butyl)-4-styrylbenzene (*E*)-6f**
Isomerization yield 85%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 8.2, 1.0 Hz, 2H), 7.50 – 7.38 (m, 5H), 7.38 – 7.31 (m, 2H), 7.16 – 7.05 (m, 2H), 1.35 (s, 9H).
^{1}H NMR spectrum is in agreement with this previously reported.[5]



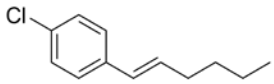
***(E)*-1-styryl-4-(trifluoromethyl)benzene (*E*)-6g**
Isomerization yield 99%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 5H), 7.59 – 7.50 (m, 2H), 7.40 (t, J = 7.4 Hz, 2H), 6.92 (s, 2H).
^{1}H NMR spectrum is in agreement with this previously reported.[7]



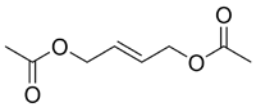
***(E)*-hex-1-en-1-ylbenzene (*E*)-6b**
Isomerization yield 99%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 5H), 6.92 (m, 2H), 2.42 (t, J = 7.0 Hz, 2H), 1.67 – 1.42 (m, 4H), 0.96 (t, J = 7.3 Hz, 3H).
^{1}H NMR spectrum is in agreement with this previously reported.[3]



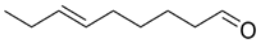
***(E)*-1-(hex-1-en-1-yl)-4-methoxybenzene (*E*)-6h**
Isomerization yield 65%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 2H), 6.92 – 6.88 (m, 2H), 6.30 (d, J = 5.9 Hz, 1H), 6.09 – 6.04 (m, 1H), 3.80 (d, J = 2.7 Hz, 3H), 2.24 – 2.12 (m, 2H), 1.50 – 1.24 (m, 4H), 0.96 – 0.89 (t, J = 7.2 Hz, 3H).
^{1}H NMR spectrum is in agreement with this previously reported.[3]



***(E)*-1-chloro-4-(hex-1-en-1-yl)benzene (*E*)-6i**
Isomerization yield 85%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 4H), 6.33 (d, J = 16.7 Hz, 1H), 6.21 (dt, 1H), 2.24 – 2.14 (m, 2H), 1.51 – 1.34 (m, 4H), 0.93 (t, J = 7.05 Hz, 3H).
^{1}H NMR spectrum is in agreement with this previously reported.[8]



(*E*)-but-2-ene-1,4-diyl diacetate (*E*)-6j
Isomerization yield 83%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (tt, J = 3.0, 1.4 Hz, 2H), 4.58 (dd, J = 3.0, 1.3 Hz, 4H), 2.08 (s, 6H)
^{1}H NMR spectrum is in agreement with this previously reported.[9]



(*E*)-non-6-enal (*E*)-6k
Isomerization yield 66%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, J = 1.9 Hz, 1H), 5.50–5.33 (m, 2H), 2.42 (dt, J = 7.2, 1.9 Hz, 2H), 2.03–1.96 (m, 4H), 1.68–1.60 (m, 2H), 1.43–1.36 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H)
^{1}H NMR spectrum is in agreement with this previously reported.[10]

5. NMR Spectra

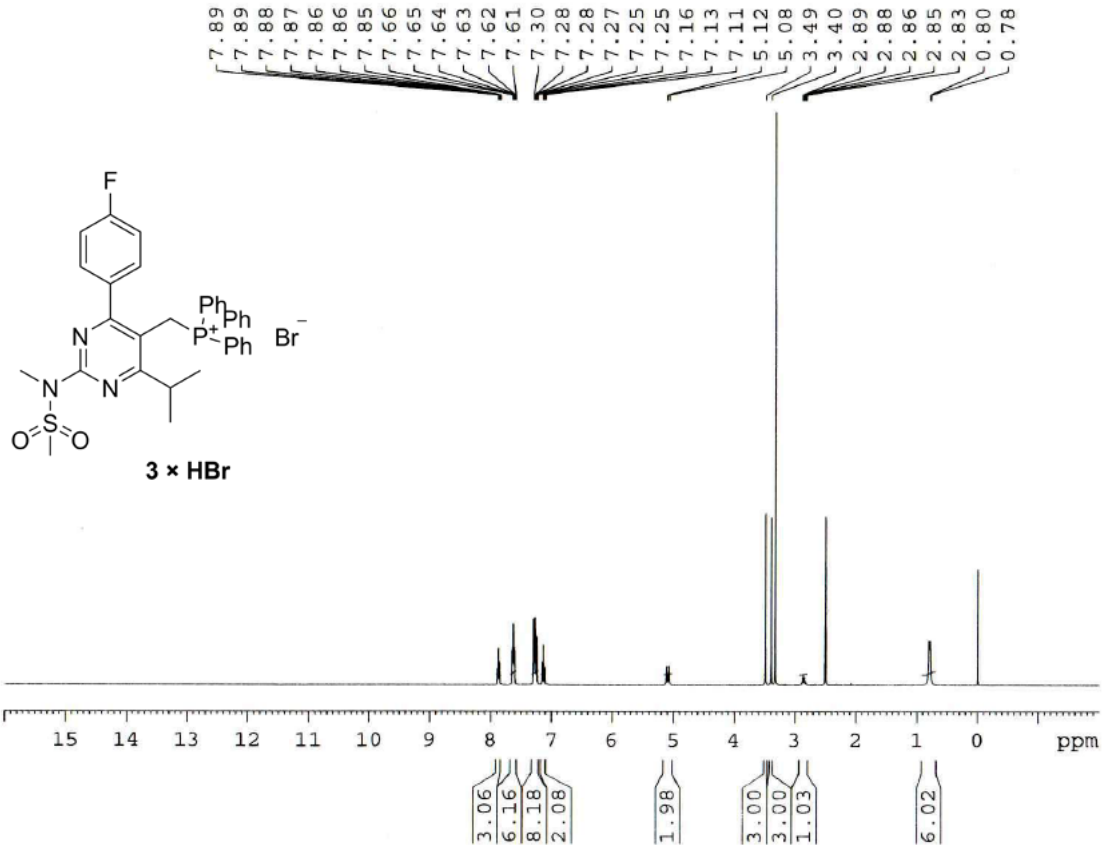


Figure S1. ^{1}H NMR spectrum of **3 × HBr**.

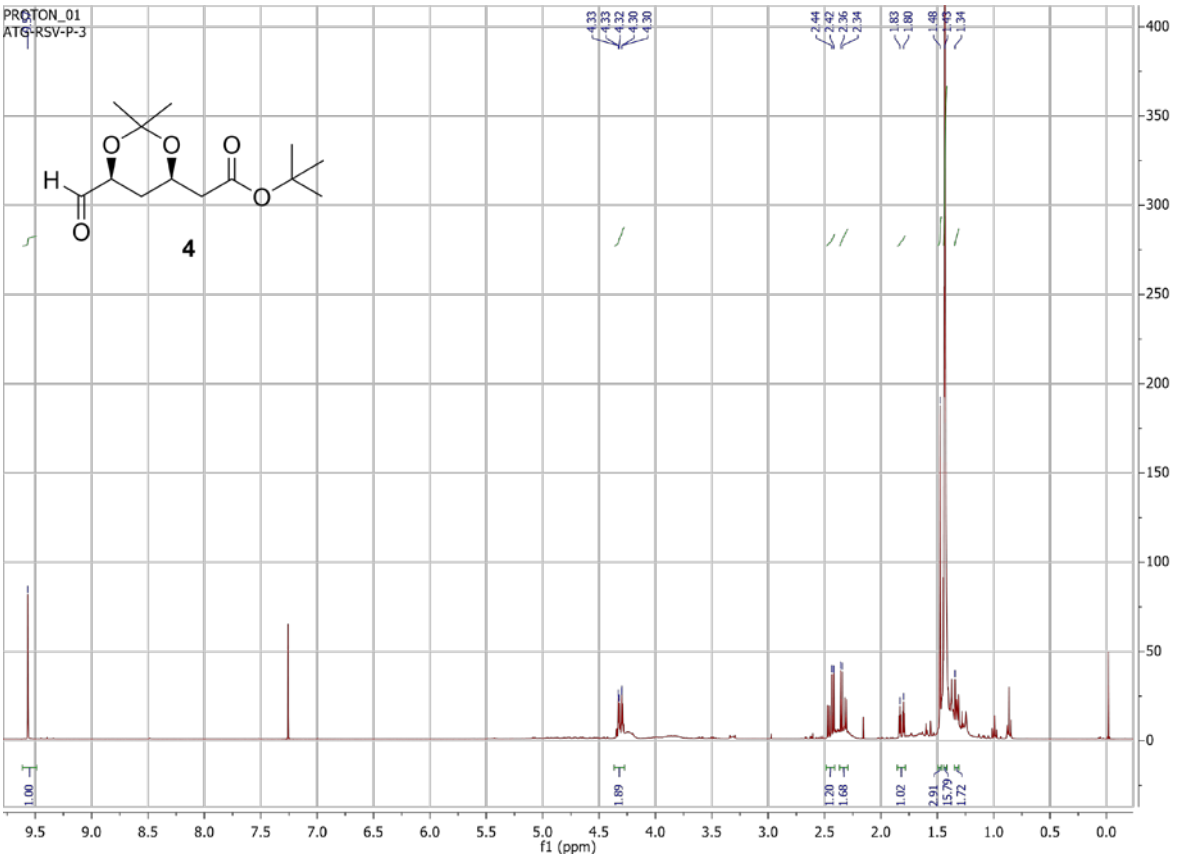


Figure S2. ^{1}H NMR spectrum of **4**.

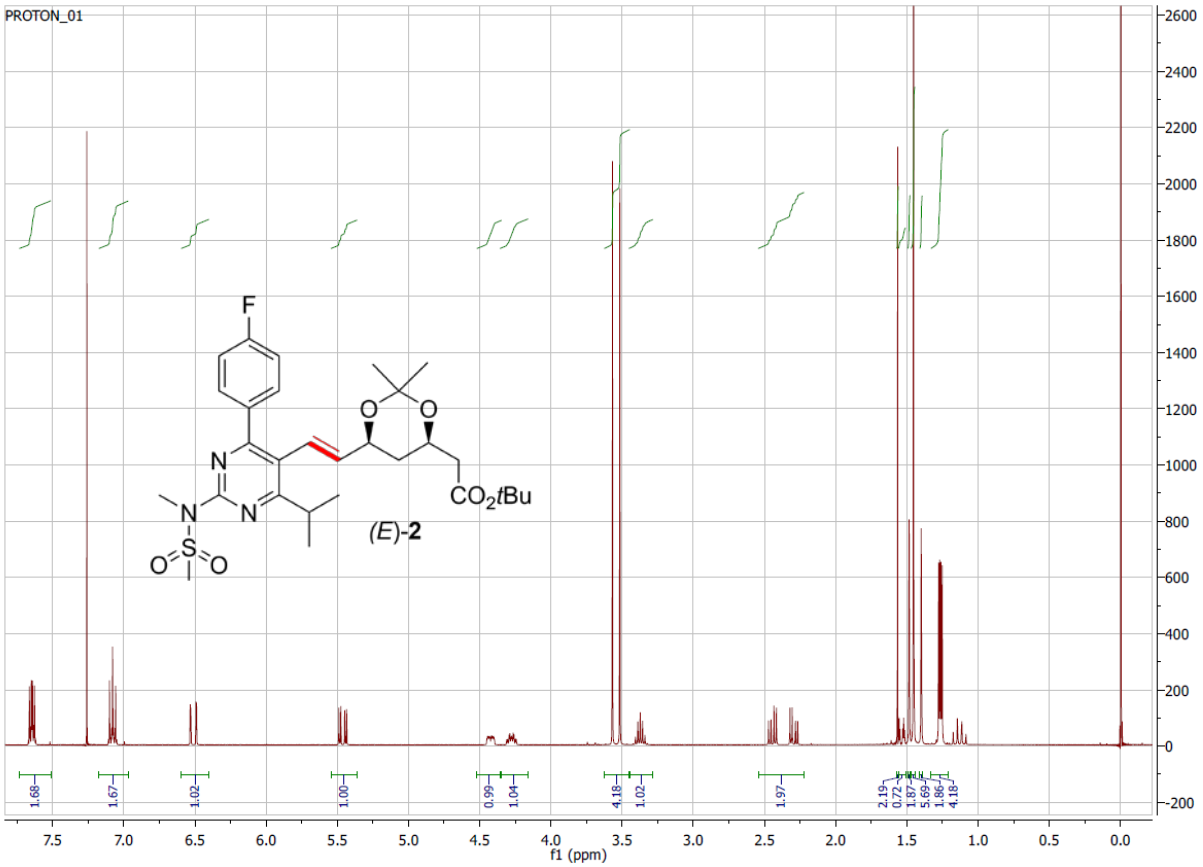


Figure S3. ^{1}H NMR spectrum of (*E*)-**2**.

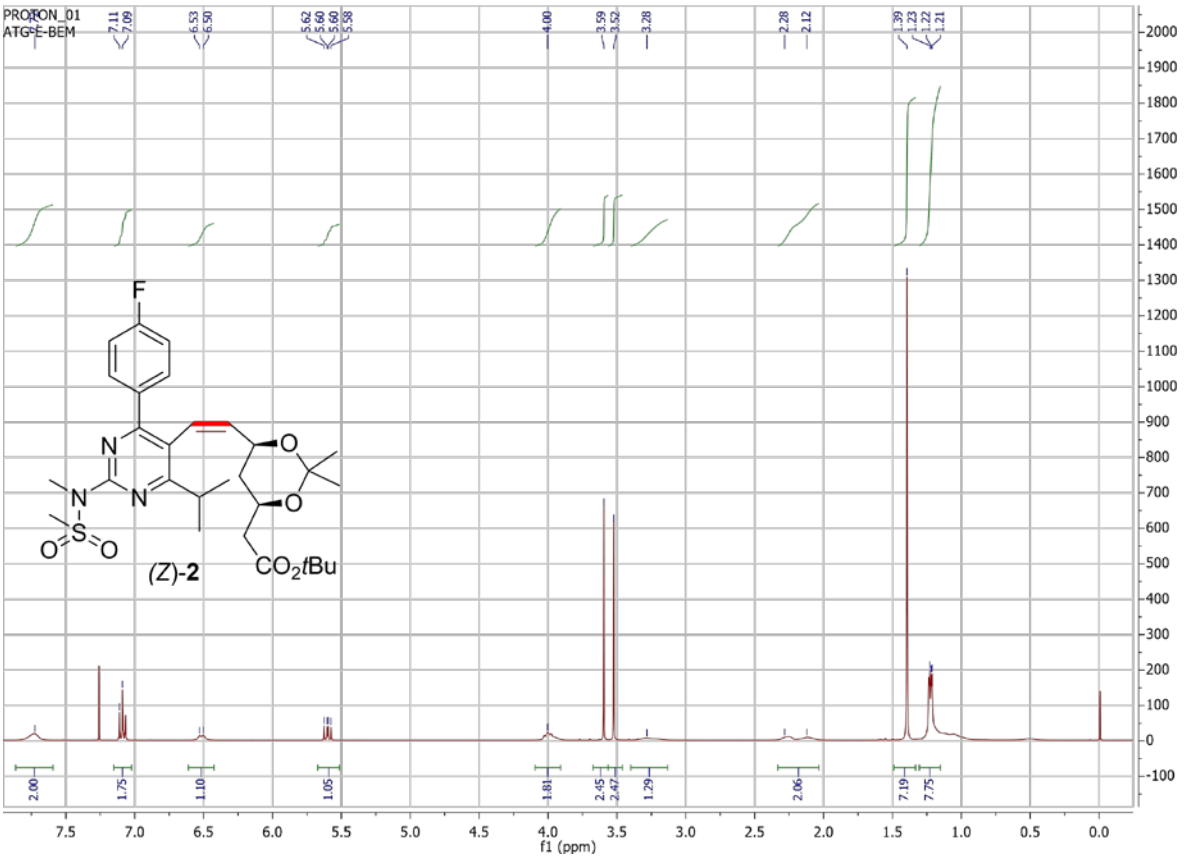


Figure S4. ^{1}H NMR spectrum of (*Z*)-**2**.

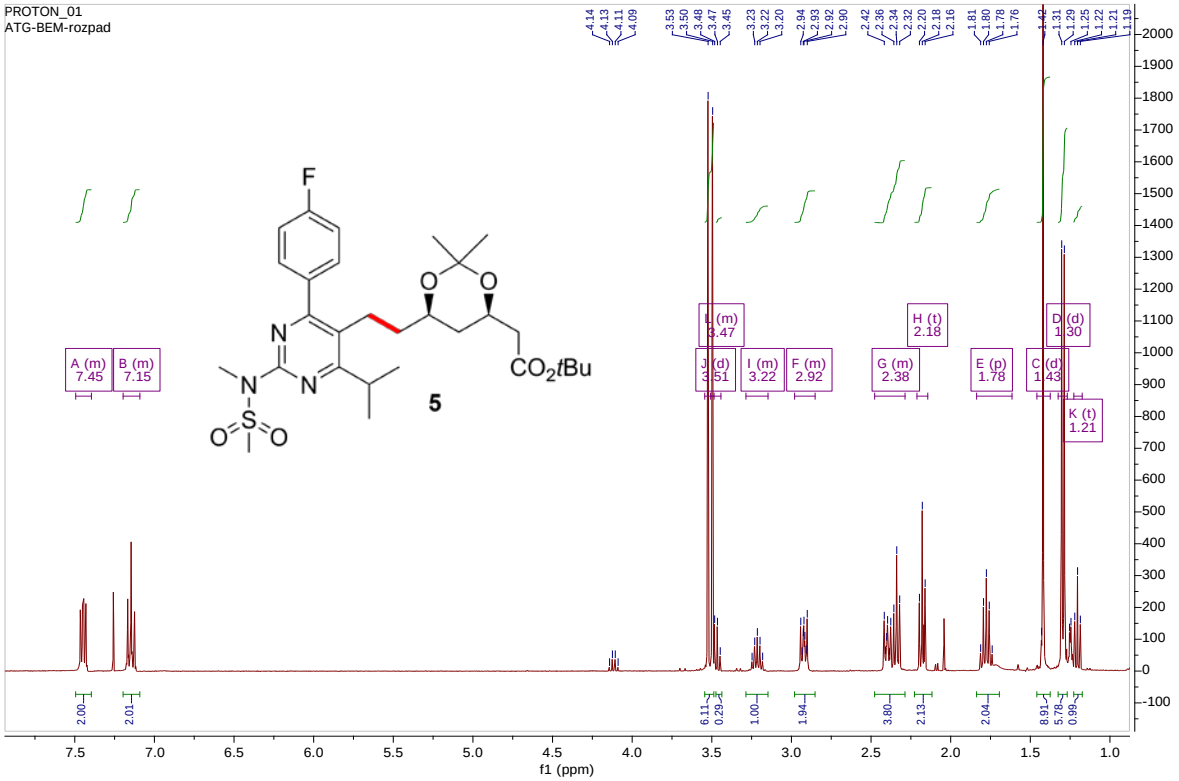


Figure S4. ^{1}H NMR spectrum of **5**.

6. References

(1) Grela, K.; Kusy, R. Ligand-Free (*Z*)-Selective Transfer Semihydrogenation of Alkynes Catalyzed by in Situ Generated Oxidizable Copper Nanoparticles. *Green Chem.* **2021**, *23*, 5494-5502.

(2) Tucci, F. C.; Chieffi, A.; Comasseto, J. V; Marino, J. P. Tellurium in Organic Synthesis. Preparation of *Z*-Vinylic Cuprates from *Z*-Vinylic Tellurides and Their Reaction with Enones and Epoxides. *J. Org. Chem.* **1996**, *61*, 4975–4989.

(3) Kusy, R.; Grela, K. *E*- and *Z*-Selective Transfer Semihydrogenation of Alkynes Catalyzed by Standard Ruthenium Olefin Metathesis Catalysts. *Org. Lett.* **2016**, *18*, 6196–6199.

(4) Aryanasab, F. Mizoroki–Heck Coupling Reaction on the Surface of Sepiolite Clay-Supported Pd/Cu Nanoalloy. *Synth. Commun.* **2022**, *52*, 521–534.

(5) Lerch, S.; Fritsch, S.; Strassner, T. The Mizoroki-Heck Reaction in Tunable Aryl Alkyl Ionic Liquids. *Eur. J. Org. Chem.* **2022**, *2022*, e202200008.

(6) Chen, P.; Wang, Z.-Y.; Peng, X.-S.; Wong, H. N. C. Stereospecific Iron-Catalyzed Carbon (Sp2)–Carbon (Sp2) Cross-Coupling of Aryllithium with Vinyl Halides. *Org. Lett.* **2021**, *23*, 4385–4390.

(7) Zhang, J.; Tang, Y. Iron-Catalyzed Regioselective Oxo- and Hydroxy-Phthalimidation of Styrenes: Access to α-Hydroxyphthalimide Ketones. *Adv. Synth. Catal.* **2016**, *358*, 752–764.

(8) Shi, H.; Dai, W.; Wang, B.; Cao, S. Copper- and Nickel-Catalyzed Cross-Coupling Reaction of Monofluoroalkenes with Tertiary, Secondary, and Primary Alkyl and Aryl Grignard Reagents. *Organometallics* **2018**, *37*, 459–463.

(9) Diethelm, S.; Schoenebeck, F.; Carreira, E. M., Mechanistic Insight into the Spirocyclopropane Isoxazolidine Ring Contraction. *Org. Lett.* **2014**, *16*, 960-963.

(10) Frerot, E.; Bagnoud, A., Easy Access to Aroma Active Unsaturated γ-Lactones by Addition of Modified Titanium Homoenolate to Aldehydes. *J. Agric. Food Chem.* **2011**, *59*, 4057-4061.