Supporting Information

Aliphatic Ketone Claisen Rearrangement: Troubleshooting the Transetherification Step by Identifying a Stable Acid Catalyst

Veera Bruce[†], Kaveh Farshadfar[‡], Aino Rolig[†], Kari Laasonen[‡], Petri M. Pihko[†]*

†Department of Chemistry and NanoScience Center, University of Jyväskylä, P.O. Box 35, FI-40014, Jyväskylä, Finland

‡Department of Chemistry and Material Science, School of Chemical Engineering, Aalto University, 02150 Espoo, Finland

Petri.Pihko@jyu.fi

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1 General Information

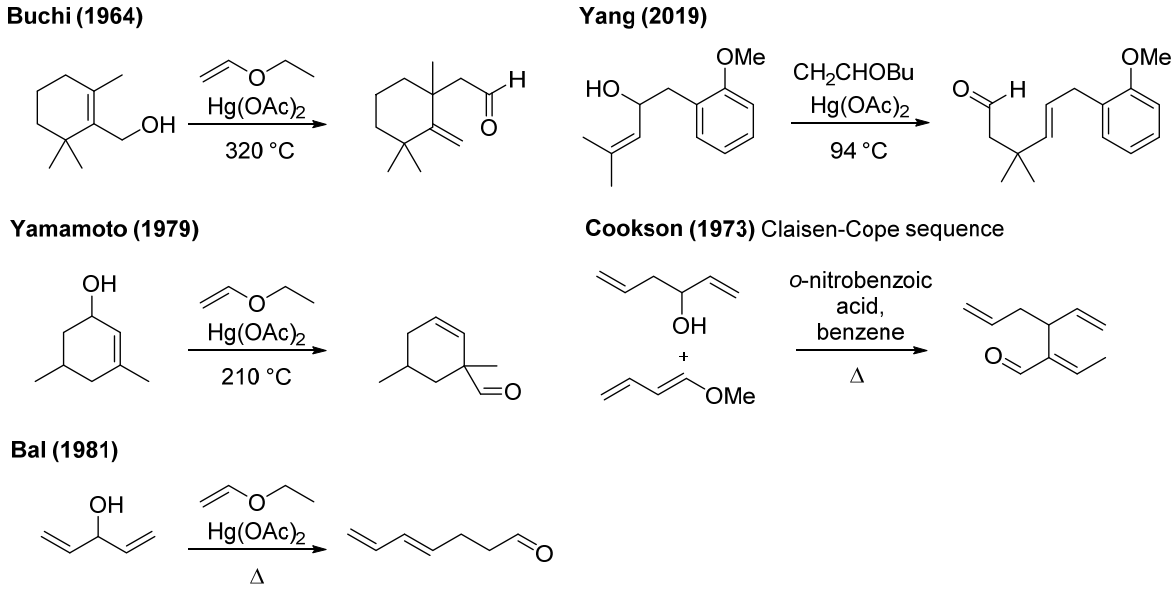
All reactions were carried out under an argon atmosphere in flame-dried glassware, unless otherwise noted. When needed, nonaqueous reagents were transferred under argon *via* syringe and dried prior to use. THF, Et_2O and DCM were obtained by passing deoxygenated solvents through activated alumina columns (MBraun SPS-800 Series solvent purification system). Other solvents and reagents were used as obtained from supplier, unless otherwise noted. The reactions were cooled with ice-water bath (nominally 0 °C, external temperature), ice-water-rock salt mixtures (external bath temperature –10 °C) or with acetone-liquid nitrogen mixture (external bath temperature –78 °C). The heating in reactions was done either with an oil bath or microwave oven.

Analytical TLC was performed using Merck silica gel F254 (230-400 mesh) plates and analyzed by UV light or by staining upon heating with anisaldehyde solution (2.8 mL anisaldehyde, 2 mL conc. H_2SO_4, 1.2 mL conc. CH_3COOH, 100 mL EtOH), vanillin solution (6 g vanillin, 5 mL conc. H_2SO_4, 3 mL glacial acetic acid, 250 mL EtOH) or $KMnO_4$ solution (1 g $KMnO_4$, 6.7 g K_2CO_3, 1.7 mL 1M NaOH, 100 mL H_2O). For silica gel chromatography, the flash chromatography technique with Merck silica gel 60 (230-400 mesh) and CombiFlash R_f 200 with RediSep Gold or Silver columns (20–40 µm spherical silica, 400–632 mesh) were used with p.a. grade solvents unless otherwise noted.

The ^{1}H NMR and $^{13}C\{^1H\}$ NMR spectra were recorded in either $CDCl_3$, CD_3CN, CD_2Cl_2 or $(CD_3)_2SO$ on Bruker Avance 500 or 300 spectrometers. The chemical shifts are reported in ppm relative to $CHCl_3$ (δ 7.26), CHD_2CN (δ 1.94), $CDHCl_2$ (δ 5.32) or DMSO-d_6 (2.50) for ^{1}H NMR. For the $^{13}C\{^1H\}$ NMR spectra, the residual $CDCl_3$ (δ 77.16), CD_3CN (δ 118.26), CD_2Cl_2 (δ 53.84) or $(CD_3)_2SO$ (39.52) were used as the internal standards. Melting points (mp) were determined in open capillaries using Bibby-Stuart Scientific SMP3 melting point apparatus. IR spectra were recorded on a Tensor27 FT-IR spectrometer. High resolution mass spectrometric data were measured using Agilent Technologies 6560 Ion Mobility ESI-Q-TOF mass spectrometer. For the microwave-assisted reactions, CEM Discovery-S –microwave oven was used.

2 Background of the aliphatic Claisen rearrangement to give aldehydes or ketones

Aliphatic Claisen rearrangement to produce γ,δ-unsaturated ketones or aldehydes from the corresponding allyl alcohols is less widely used in organic syntheses than the other Claisen variants (Johnson-Claisen, Ireland-Claisen and Eschenmoser-Claisen). While other variants proceed in mild conditions, the ketone and aldehyde variants require the use of corrosive/toxic catalysts such as Hg^{2+} salts[1–5] (Scheme 1) or/and harsh reaction conditions (100-200 °C, increased pressure).

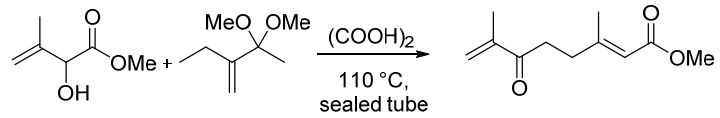


Scheme S1. Examples of aliphatic Claisen rearrangement with allyl alcohols to produce γ,δ-unsaturated aldehydes.[1–4,6]

Examples of aliphatic Claisen rearrangements to produce γ,δ-unsaturated ketones under acid catalysis have been described in the chemical literature, but typically the reactions have been carried out in sealed systems (Scheme 2).[7–13] In a series of papers from 1982 to 1986, Daub and coworkers investigated the ketone Claisen rearrangement with propionic or mesitoic acid catalysts (using 0.25 – 1 equiv of catalyst), but only a limited range of allylic alcohols were tested.[12–15] It is also worth noting that no systematic way has been described for predicting the optimal catalyst. Instead, in each case, the catalysts have been optimized for given allyl alcohol.[7,8] In addition to issues associated with the correct choice of catalyst, Baeckström and Li[8] also encountered problems while optimizing the reaction temperatures. With many allyl alcohol substrates, they reported

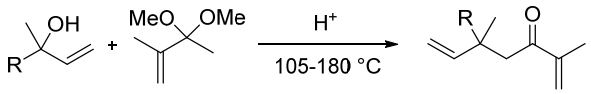
that the reactions stopped at the MOP ether stage, and temperatures up to 180 °C were required to obtain acceptable conversions.

Faulkner (1973)



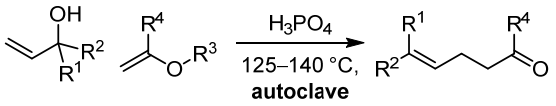
"It has been our experience that there is no certain way to predict the best acid catalyst for a given reaction."

Baeckstrom & Li (1991)

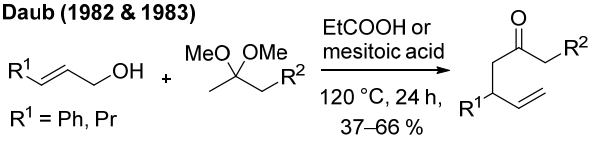


"In each case an effort had to be made to select an appropriate catalyst and vary the amounts to enable the reactions. The selection was made from the following catalysts: CH_2CH_2COOH, H_3PO_4/CH_3COOH, H_3PO_4/HCOOH, *o,p*-dinitrophenol and *o*-nitrobenzoic acid"

Saucy & Marbet (1967)

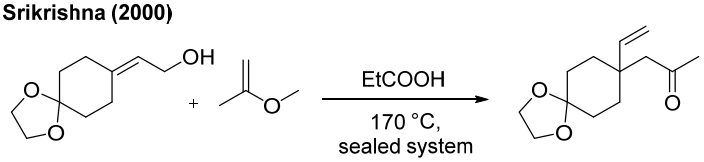


Daub (1982 & 1983)

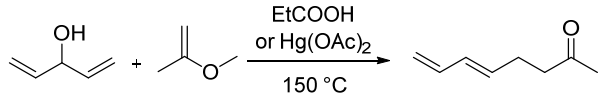


Limited range of allylic alcohols and 0.25-1 equiv of catalyst, but generally mild conditions

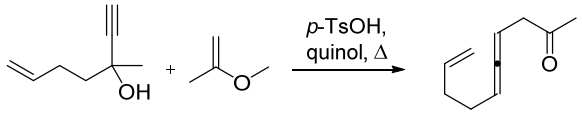
Srikrishna (2000)



Reddy (2004)



Cookson (1973) Claisen-Cope sequence



Scheme S2. Examples of ketone Claisen rearrangement starting from allyl alcohols.[5,7,8,10–13,15,16]

A comparison of published conditions for the ketone (ketal) Claisen rearrangement with different substrate classes is presented in Table S1. It is evident that while certain substrate combinations are amenable to the Johnson conditions (propionic acid catalyst), researchers have also opted for Hg^{2+} catalysis or autoclave conditions to obtain better yields with a range of allylic alcohol classes.

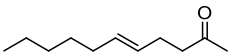
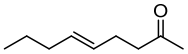
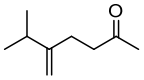
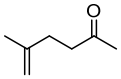
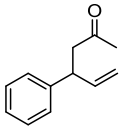
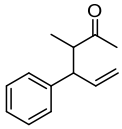
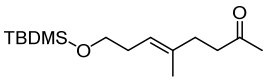
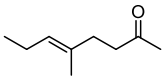
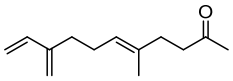
Allylic alcohol class	*Example from present study (Scheme 5)*	*Analogous literature examples prepared directly with Claisen rearrangement*	*References*
 *class 1a (2° OH)*	 **6a** quant.	 with cat. $Hg(TFA)_2$, 125 °C, sealed tube 72%	Snyder and coworkers *J. Am. Chem. Soc.* **2011**, *133*, 15898-15901
		with cat. propionic acid 56% (8 g scale)	Mulholland and Chamberlin *J. Org. Chem.* **1988**, *53*, 1082-1085.
 *class 2 (1° OH)*	 **6p** 90 %	 with formic acid and cat. H_3PO_4 sealed vessel, 150 °C 54 % (12 g scale)	Baeckström and coworkers *J. Org. Chem.* **1991**, *56*, 3358-3362 "caution: the reaction has to be performed in a metal autoclave, an explosion occurred when the reaction was performed in sealed glass tubes"
 *class 3a (1° OH)*	 **6t** 87 %	 cat. propionic acid, 120 °C (with 2,2-dimethoxybutane) 63%	Daub and coworkers *J. Org. Chem.* **1983**, *48*, 3876-3883
 *class 1,2 (2° OH)*	 **6y** 98 %	 oxalic acid, sealed tube, 110 °C 67% (after reduction)	Faulkner and Petersen *J. Am. Chem. Soc.* **1973**, *95*, 553-563
		 2,4-dinitrophenol, sealed tube, 150 °C 40% (after reduction)	Bäckström and Li *Tetrahedron* **1991**, *47*, 6521-6532

Table S1. Comparison of literature examples of the ketone Claisen rearrangement with the present study. [7–9,12,17,18]

3 Preliminary studies

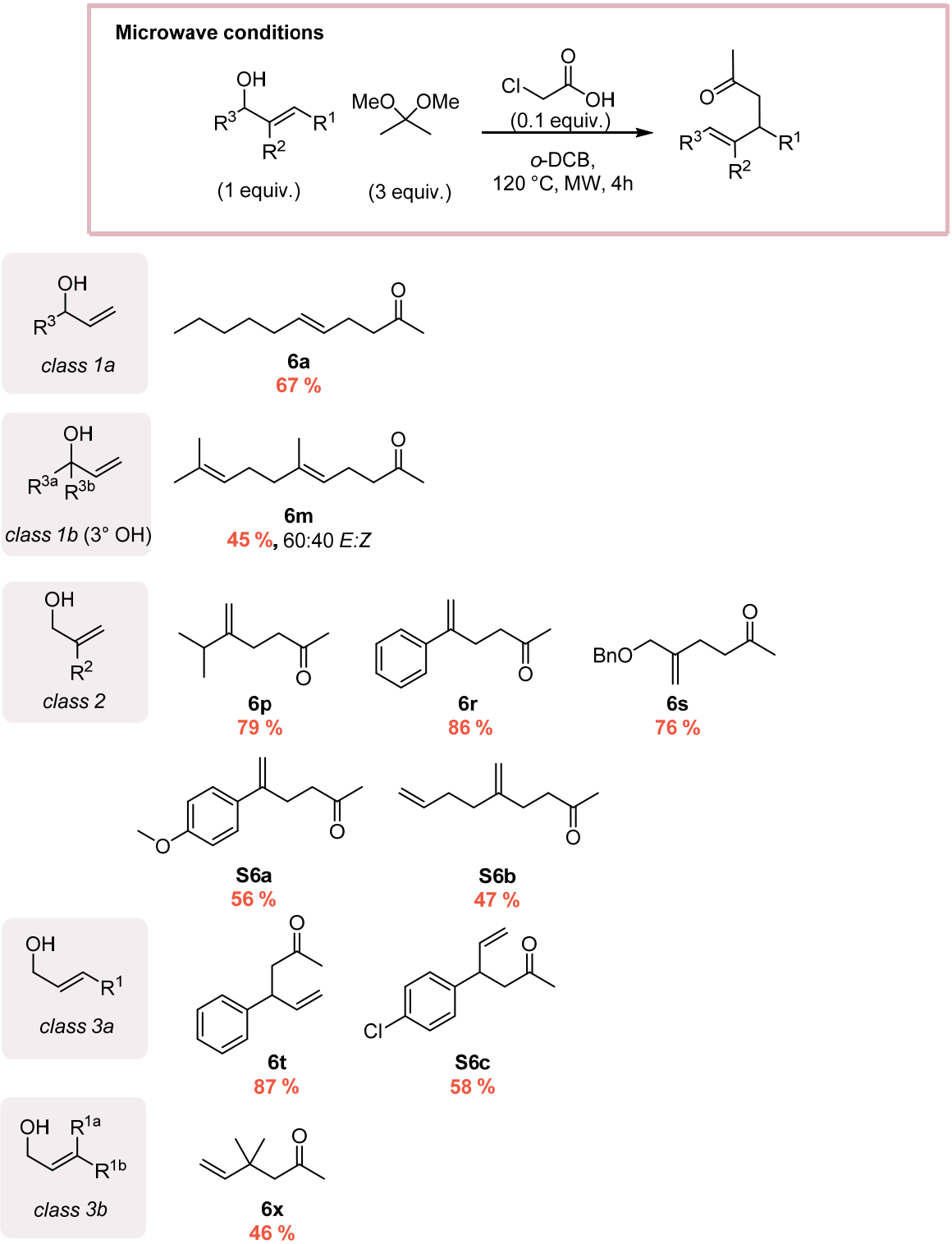
Initial screening of reaction conditions

Initial screening of reaction conditions for the aliphatic Claisen rearrangement was carried out in a microwave reactor. Three different carboxylic acids (citric acid: pK_a = 3.13, chloroacetic acid: pK_a = 2.87 and dichloroacetic acid: pK_a = 1.35) were chosen for the catalyst screening as their pK_a values corresponded closely to the previously reported acid catalysts H_3PO_4 (pK_a = 2.12) and HCOOH (pK_a = 3.75).[9,11] The reactions were run in sealed microwave tubes at 160 °C for 4 h with two different allyl alcohols, cinnamyl alcohol and 3-methyl-2-methylene-1-butanol.

These experiments revealed that citric acid was an inefficient catalyst, affording a complex mixture. Of the three acids screened, chloroacetic acid gave the best yields (69-70 %) and consequently further screens were carried out with this catalyst. After choosing the catalyst, screening the temperature between 90 to 160 °C were revealed that 120 °C was the optimal temperature. At higher temperatures, the starting materials and products started to degrade and at lower temperatures the reactions progressed too slowly. In these microwave experiments, the maximum pressure was set to 17 bar.

3.1 Substrate scope for preliminary Claisen rearrangement

Microwave assisted Claisen rearrangement reactions with different alcohol substrates were run with initial reaction conditions: allyl alcohol (1 equiv.), 2,2-dimethoxypropane (3 equiv.), catalyst (10 mol-%) in *o*-DCB at 160 °C for 4 h. The substrate scope for these reactions is shown in scheme S3. As the yields remained approximately at 60 % and the reaction monitoring in microwave was challenging further reaction optimization was chosen to be done using the same excess method for identification of optimal acid catalyst.



Scheme S3. Ketone Claisen rearrangement substrate scope (initial studies)

4 Optimization experiments

4.1 Same excess experiments for catalyst optimization

4.1.1 General considerations for the same excess experiments

The catalyst optimization study relied on the use of same excess experiment due to its ability to efficiently reveal catalyst decay via simple overlay of reaction progress plots. We hypothesized that the low conversions in our initial studies, and erratic results obtained in the literature, were at least partially caused by catalyst decay in the reaction conditions. Catalyst decay is not easy to assay in traditional reaction optimization procedures where typically only a single data point (conversion or yield at the end of the reaction) is collected from each experiment.

To enable periodic sampling of the reaction mixture, we used conventional heating (open flask with reflux condenser) instead of microwave reactor for the catalyst stability screens. We opted for gas chromatographic (GC) monitoring of the reaction progress due to high temperatures of the reaction which discouraged us from using NMR. Although the temporal resolution of the GC method is lower compared to NMR, the method is otherwise fast, automatable and quantitative. While the temporal resolution does not allow the determination of reaction rates by kinetic simulations, the visualized same excess plots enable a rapid qualitative enables a rapid visual evaluation of catalyst decay. As the samples were taken manually, there are gaps in the data which represents night times when no samples were collected, but it was found that these gaps did not prevent the assay of catalyst decay (see Sections 4.1.4 to 4.1.6 for examples of same excess plots).

Choice of substrates

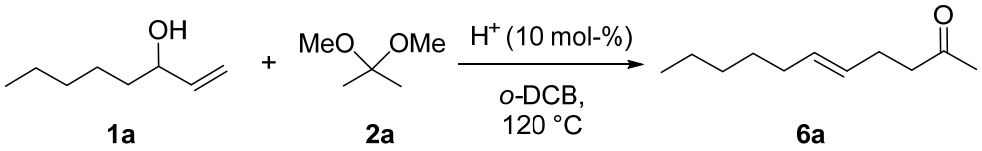
All same excess experiments of this study were performed tracking the consumption of 1-octen-3-ol **1a** as it showed good reactivity in the initial studies (see chapter 3.1). The conversion of the performed reactions were recorded with gas chromatography (GC) as all analytes were suitable for the method. Systematic acid screening was done with benzoic acids to avoid the risk of errors caused by the acid evaporation. Selected aliphatic carboxylic acids (formic acid, 2,2'-(Methylazanediyl)diacetic acid, 2,2-dichloroacetic acid, 2,2,2-trichloroacetic acid) were tested as well, but the conversions remained quite low with these acids. All the same excess experiment plots are presented in Sections 4.1.4-4.1.6.

Methodology

The consumption of **1a** was tracked with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic) and the peak area data obtained from each experiment was converted to concentration vs. time data using response factors (*RF*). Following the consumption of starting material and not the conversion to product, was considered sufficient as the reaction progress data indicates a clear correlation between the levels of catalyst decay and conversion to product **6a** (see Sections 4.1.4-4.1.6). Especially, with severely decaying catalysts (eq. 4-methoxybenzoic acid) the conversions remained low. Another observation was that the product began to decay in the reaction conditions if the heating was continued for too long (approx. 15-20 h). Therefore, following the consumption of **1a** was considered more reliable.

For each studied acid catalyst, two reactions were run with different starting concentrations of the starting materials **1a** and **2a** (but in same excess).

4.1.2 Representative procedure for same excess experiments



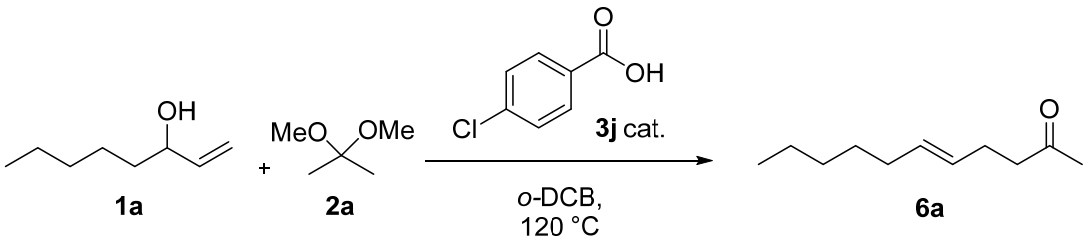
Scheme S4. Representative procedure for same excess experiment reactions

A representative procedure for same excess experiment reactions (Scheme S4): 1-octen-3-ol **1a**, 2,2-dimethoxypropane **2a**, acid catalyst **3** and cyclododecane (internal standard) was added in 2 mL of 1,2-dichlorobenzene (*o*-DCB) in a 25 mL two-neck round bottom flask equipped with a condenser. The reaction was heated at 120 °C and samples for GC analysis were taken periodically with the exception of night time. The starting concentrations for each reaction are mentioned in the Sections 4.1.4-4.1.6. Samples for GC reaction monitoring were prepared as follows: 100 µL of reaction mixture was quenched with 100 µL of $NaHCO_3$ in an Eppendorf vial. After addition of 0.9 mL of pentane and intensive mixing, small amount of $NaSO_4$ was added. The mixture was

centrifuged, and the pentane layer was separated with a syringe and injected through a syringe filter to a GC vial.

4.1.3 Conversion of peak areas to concentrations

The response factors (*RF*) and relative response factors (*RFF*) were determined with GC for alcohol **1a** and ketone product **6a** in the reaction solvent using cyclododecane as an internal standard. The reaction with 4-chlorobenzoic acid **3j** (Scheme S5) is used as an example for the calculations.



Scheme S5. Example reaction with 4-chlorobenzoic acid **3j** catalyst.

The *RF*s and *RFF*s were calculated using following equations (S1, S2). The calculated *RF*s, *RRF*s and retention times for **1a**, **6a** and IS are presented in the table S2.

$$RF_{1a} = \frac{\text{Peak Area of } \mathbf{1a}}{\text{Concentration of } \mathbf{1a}} \quad \text{(S1)}$$

$$RF_{IS} = \frac{\text{Peak Area of internal standard}}{\text{Concentration of internal standard}} \quad \text{(S2)}$$

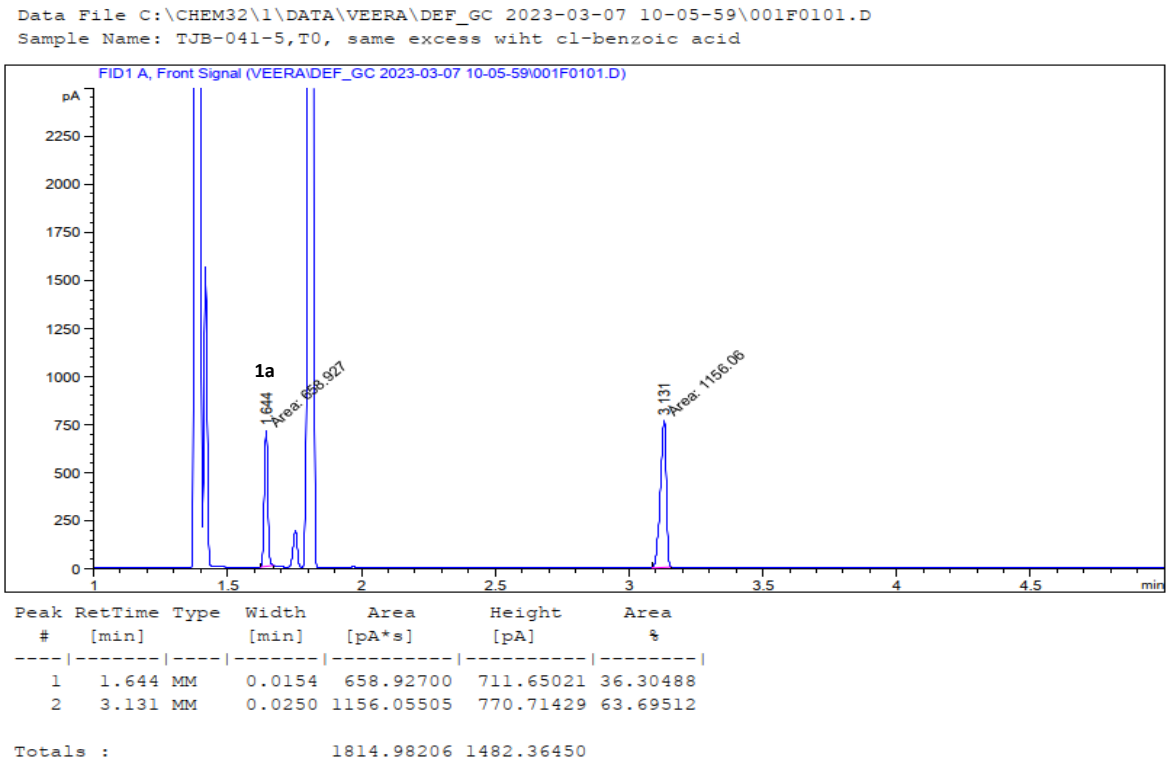
$$RRF_{1a} = \frac{RF_{1a}}{RF_{IS}} \quad \text{(S3)}$$

Table S2. Response factors, relative response factors and retention times

Compound	Area	c (M)	RF	RRF	retention times (min)
1a (1-octen-3-ol)	658.9	0.038995	16896.8	0.569933	1.64
6a	1066.7	0.038995	27354.4	0.922671	2.61
Internal standard	1156.1	0.038995	29647.0		3.13

(cyclododecane)

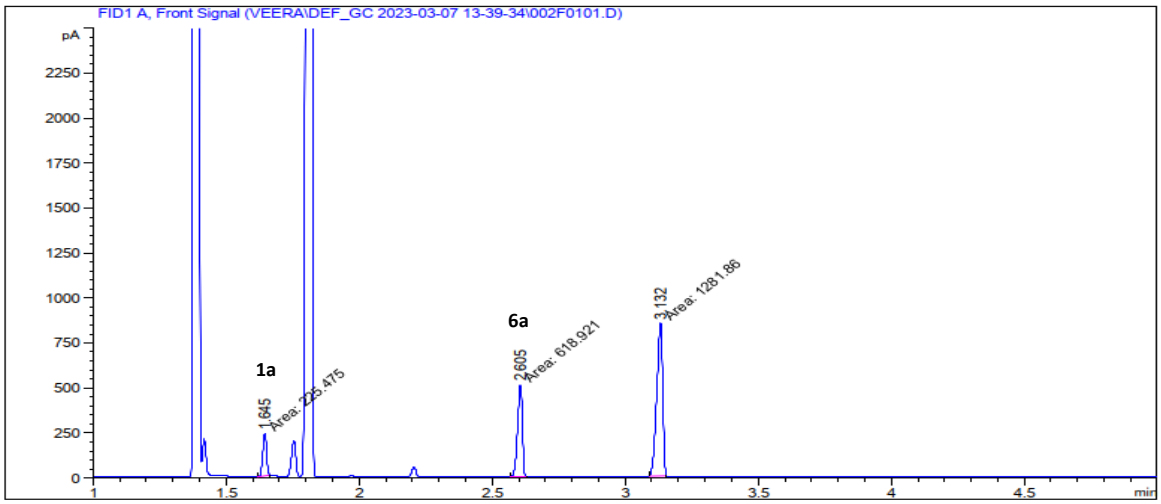
The data collection for the experiments was carried out with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic) and example chromatograms are presented in Figures S1-S3.



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	1.644	MM	0.0154	658.92700	711.65021	36.30488
2	3.131	MM	0.0250	1156.05505	770.71429	63.69512
Totals :				1814.98206	1482.36450	

Figure S1. Chromatogram recorded from reaction mixture of Scheme S5 at 0 h

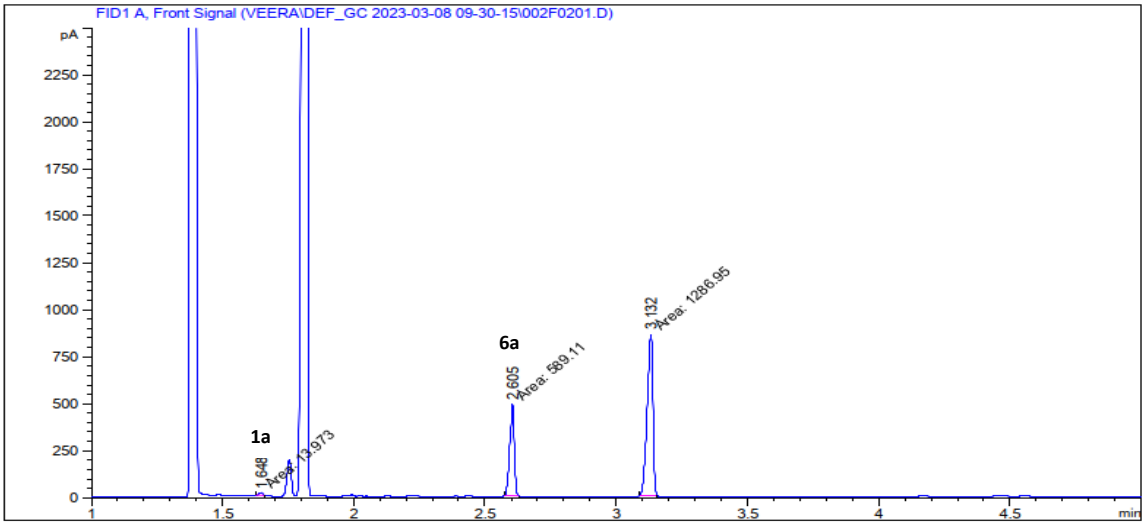
Data File C:\CHEM32\1\DATA\VEERA\DEF_GC 2023-03-07 13-39-34\002F0101.D
Sample Name: TJB-041-5,T5



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	1.645	MM	0.0159	225.47508	235.98726	10.60430
2	2.605	MM	0.0202	618.92108	510.78516	29.10843
3	3.132	MM	0.0251	1281.86475	849.96216	60.28727
Totals :				2126.26091	1596.73457	

Figure S2. Chromatogram recorded from reaction mixture of Scheme S5 at 4 h.

Data File C:\CHEM32\1\DATA\VEERA\DEF_GC 2023-03-08 09-30-15\002F0201.D
Sample Name: TJB-041-5,T9



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	1.648	MM	0.0152	13.97304	15.32526	0.73930
2	2.605	MM	0.0200	589.11035	491.73676	31.16932
3	3.132	MM	0.0249	1286.94910	862.23285	68.09137
Totals :				1890.03249	1369.29487	

Figure S3. Chromatogram recorded from reaction mixture of S5 at 23.7 h

The recorded areas from the reaction mixture over the course of the reaction are presented in the Table S3.

Table S3. Recorded areas

Time (h)	Area of **1a**	Area of **6a**	Area of internal standard
0	658.9	0	1156.1
0.5	518.1	35.0	1163.4
1	427.3	113.9	1179.0
2	342.5	337.8	1256.3
3	279.3	491.4	1295.2
4	225.5	618.9	1281.9
5	182.2	713.8	1312.2
6.33	145.0	800.0	1359.7
7.17	120.2	853.5	1398.3
23.67	14.0	589.1	1286.9
24.5	10.8	538.3	1250.4
25.5	9.6	520.6	1267.3

The peak areas were converted to concentrations using the following equation:

$$\text{Concentration of } \mathbf{1a} \text{ in GC sample} = \text{Area}_{1a} * \left(\frac{[\text{IS in GC sample}] * \frac{\text{Area}_{IS}(t_0)}{\text{Area}_{IS}}}{\text{Area}_{IS}} \right) * \left(\frac{1}{\text{RRF}_{1a}} \right) \quad \text{(S4)}$$

Due to fluctuation in the areas of IS over the course of the reaction the concentrations of IS are multiplied by a correction factor ($Area_{IS}(t_0)/Area_{IS}$) where $Area_{IS}(t_0)$ is the area of IS at 0 h. The GC sample concentrations were multiplied by 10 (dilution) to provide the corresponding reaction mixture concentrations (Table S4).

Table S4. Concentrations of **1a** and **6a** in diluted GC samples and reaction mixture

Concentrations of GC samples			**Reaction Concentrations**		
Time (h)	[**1a**] (M)	[**6a**] (M)	Time (h)	[**1a**] (M)	[**6a**] (M)
0	0.038995	0	0	0.389954765	0
0.5	0.030663	0.001279	0.5	0.306625533	0.012795
1	0.025289	0.004164	1	0.252887648	0.041639
2	0.02027	0.012349	2	0.202700724	0.12349
3	0.01653	0.017964	3	0.165297262	0.179642
4	0.013346	0.022625	4	0.133456973	0.226252
5	0.010783	0.026094	5	0.107830867	0.260945
6.33	0.008581	0.029246	6.33	0.085814905	0.292457
7.17	0.007114	0.031201	7.17	0.071137597	0.312015
23.67	0.000829	0.021536	23.67	0.008285577	0.215358
24.5	0.000639	0.019679	24.5	0.006391731	0.196787

The reaction progress data was treated using the methods for same excess experiment described previously by Bures[19] to provide the same excess plot (Figure S4).

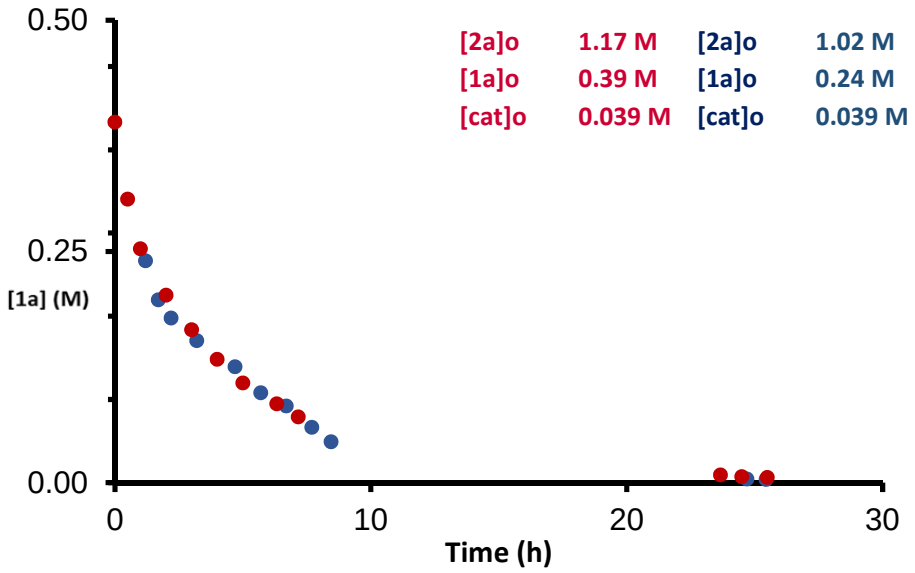


Figure S4. Same excess plot following the consumption of **1a**. The starting concentrations of **1a** and **2a** and catalyst **3j** are presented in the figure. See table S4 for more precise concentration data.

4.1.4 Catalysts displaying severe decay

Same excess plots from the reactions between **1a** and **2a** (Scheme S4) with severely decaying catalysts are presented below in figures S5-S8. The starting concentrations for given reactions are presented in the figures. To demonstrate the correlation between the degree of catalyst decay and the conversion to product the reaction progress plot for the reaction with 4-methoxybenzoic acid is presented in the figure S6.

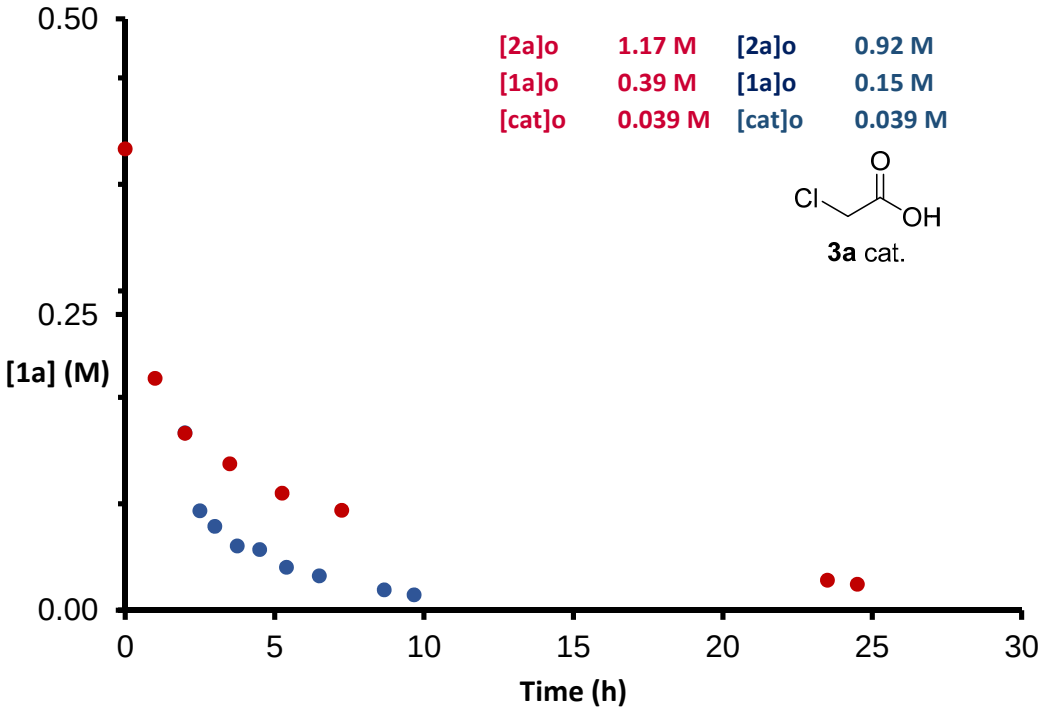


Figure S5. Same excess plot from the reaction with chloroacetic acid (**3a**).

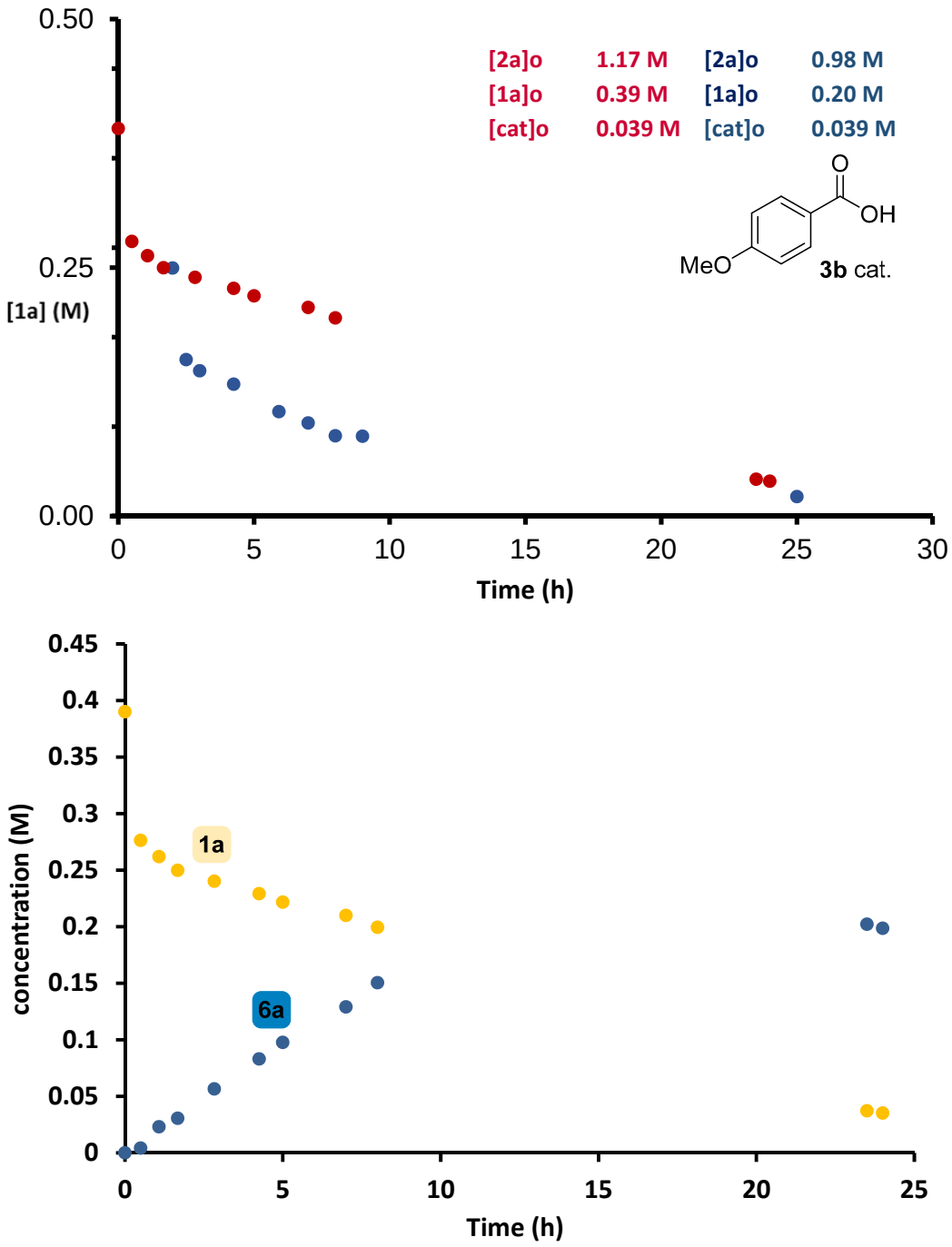


Figure S6. Same excess plot from the reaction with 4-methoxybenzoic acid (**3b**) and the reaction progress plot.

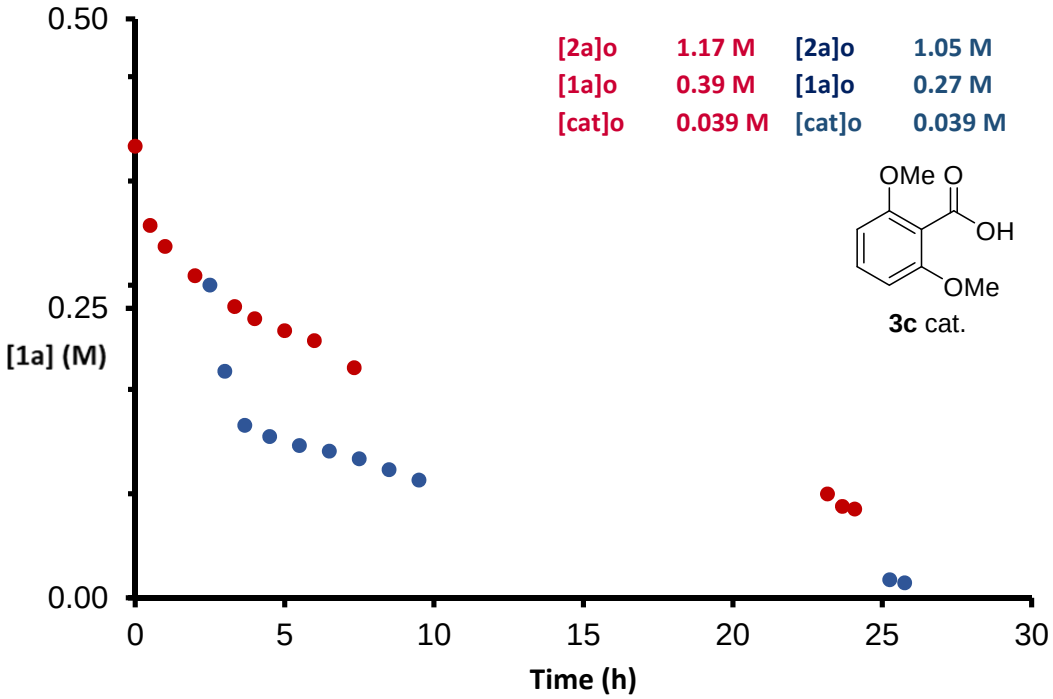


Figure S7. Same excess plot from the reaction with 2,6-dimethoxybenzoic acid (**3c**).

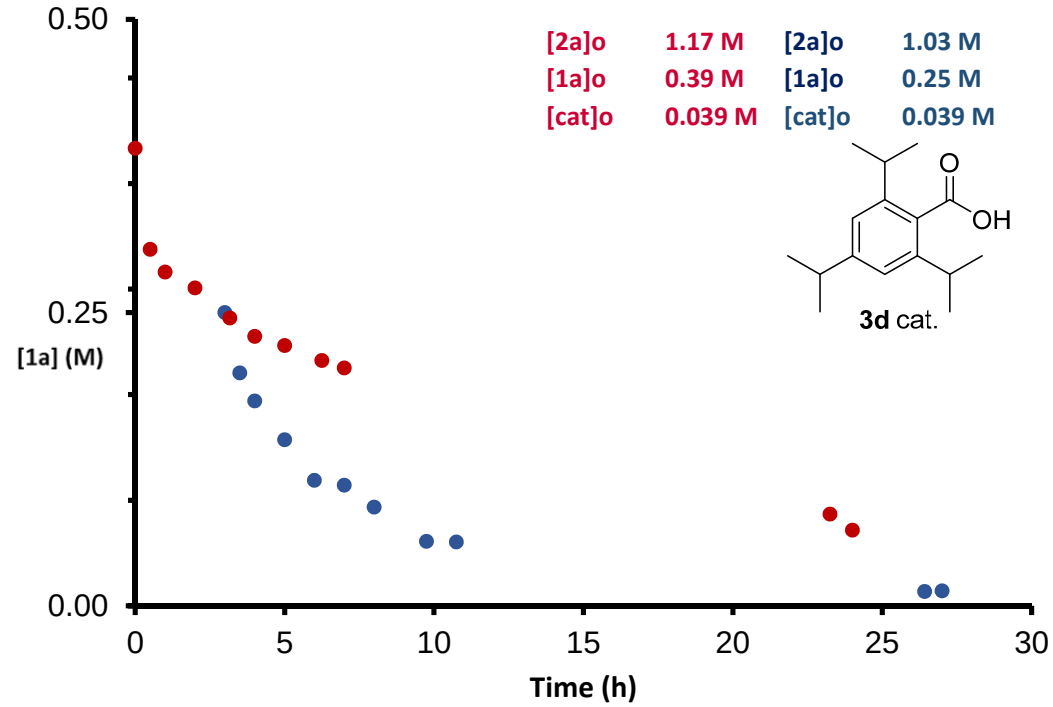


Figure S8. Same excess plot from the reaction with 2,4,6-tri-isopropylibenzoic acid (**3d**).

4.1.5 Catalysts displaying moderate decay

Same excess plots from the reactions between **1a** and **2a** (Scheme S4) with moderately decaying catalysts are presented below in Figures S9-S12. The starting concentrations for each experiment are also included. To demonstrate the correlation between the degree of catalyst decay and the conversion to product the reaction progress plot for the reaction with 2,6-dimethylbenzoic acid is presented in Figure S11.

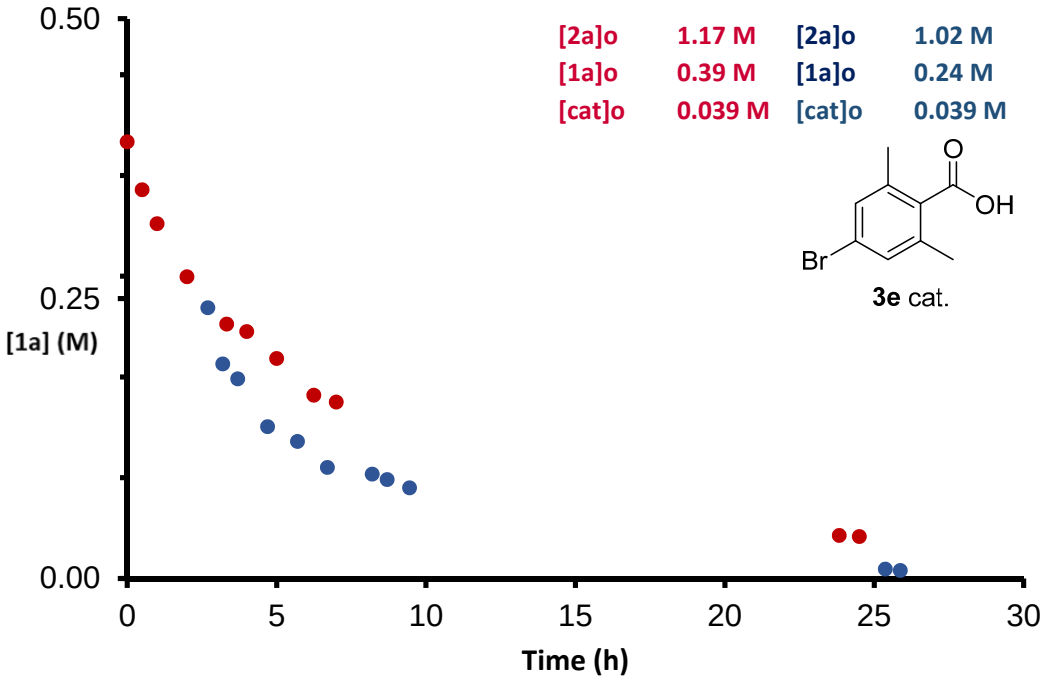


Figure S9. Same excess plot from the reaction with 2,6-dimethyl-4-bromobenzoic acid (**3e**).

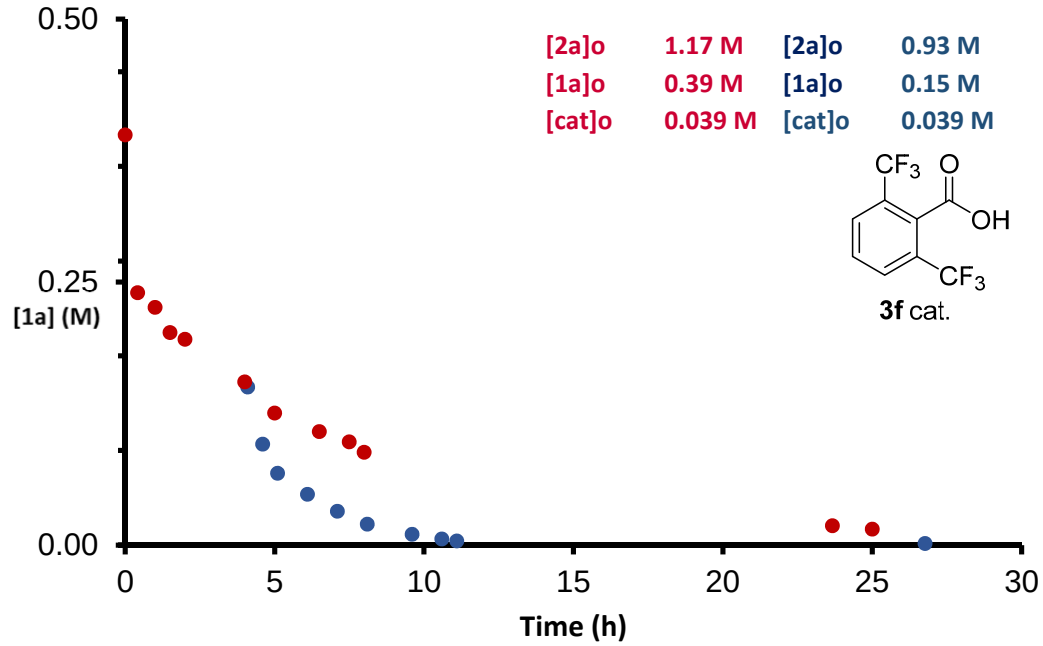
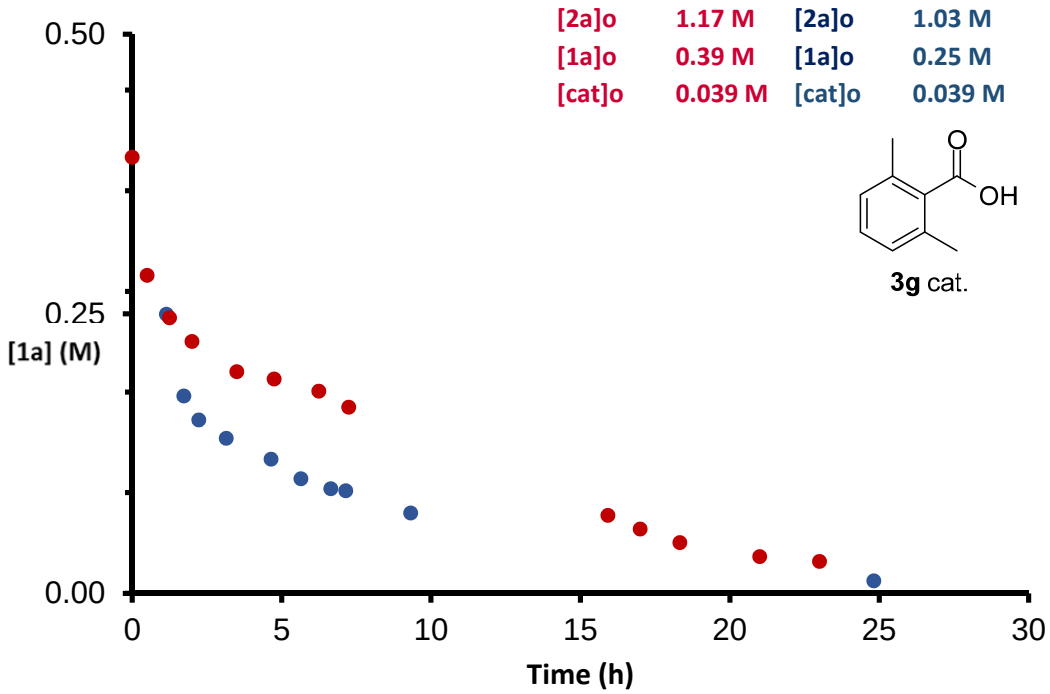


Figure S10. Same excess plot from the reaction with 2,6-trifluoromethylbenzoic acid (**3f**).



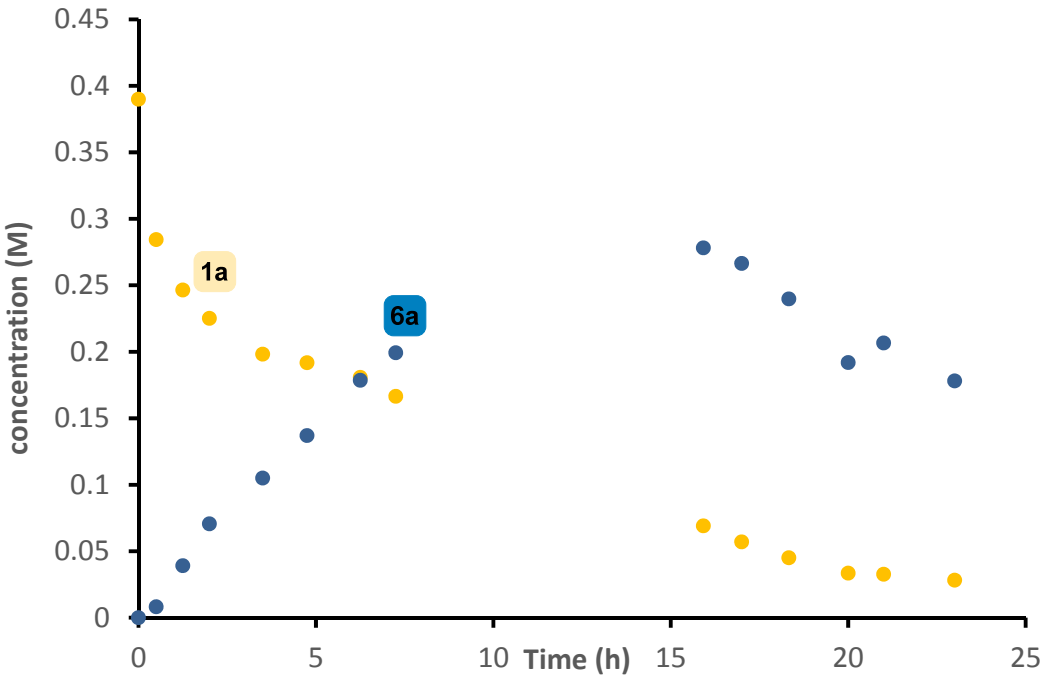


Figure S11. Same excess plot from the reaction with 2,6-dimethylbenzoic acid (**3g**) and the reaction progress plot.

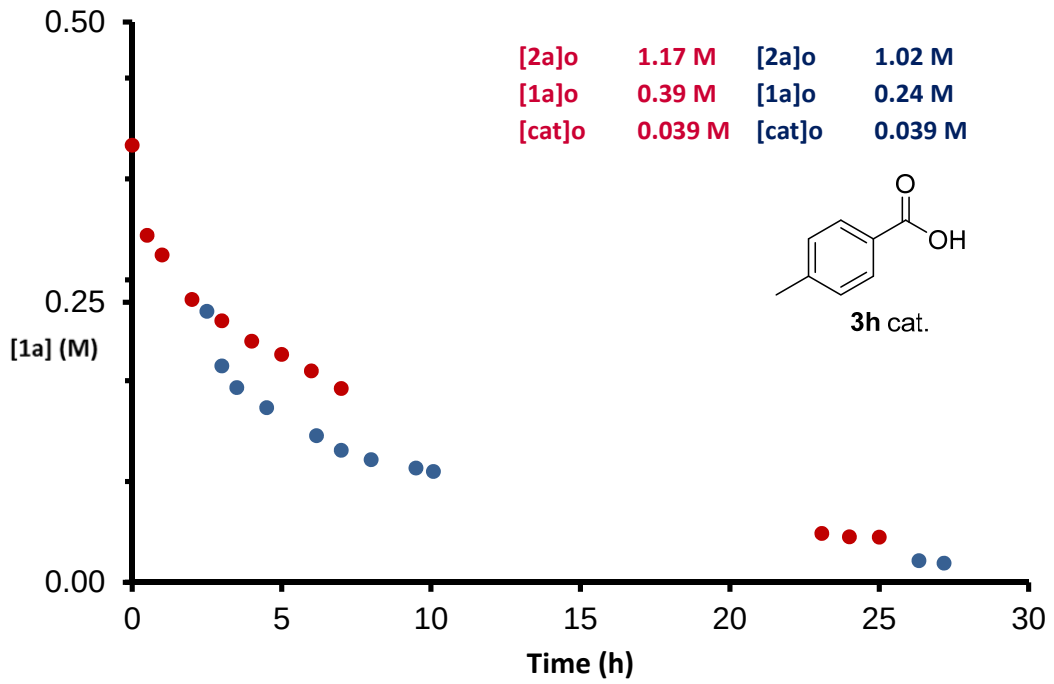


Figure S12. Same excess plot from the reaction with 4-methylbenzoic acid (**3h**).

4.1.6 Catalysts with little or no decay

Same excess plots from the reactions between **1a** and **2a** (Scheme S4) with moderately decaying catalysts are presented below in figures S13-S14. The starting concentrations for given reactions are presented in the figures. To demonstrate the correlation between the degree of catalyst decay and the conversion to product the reaction progress plot for the reaction with 4-chlorobenzoic acid is presented in the Figure S14.

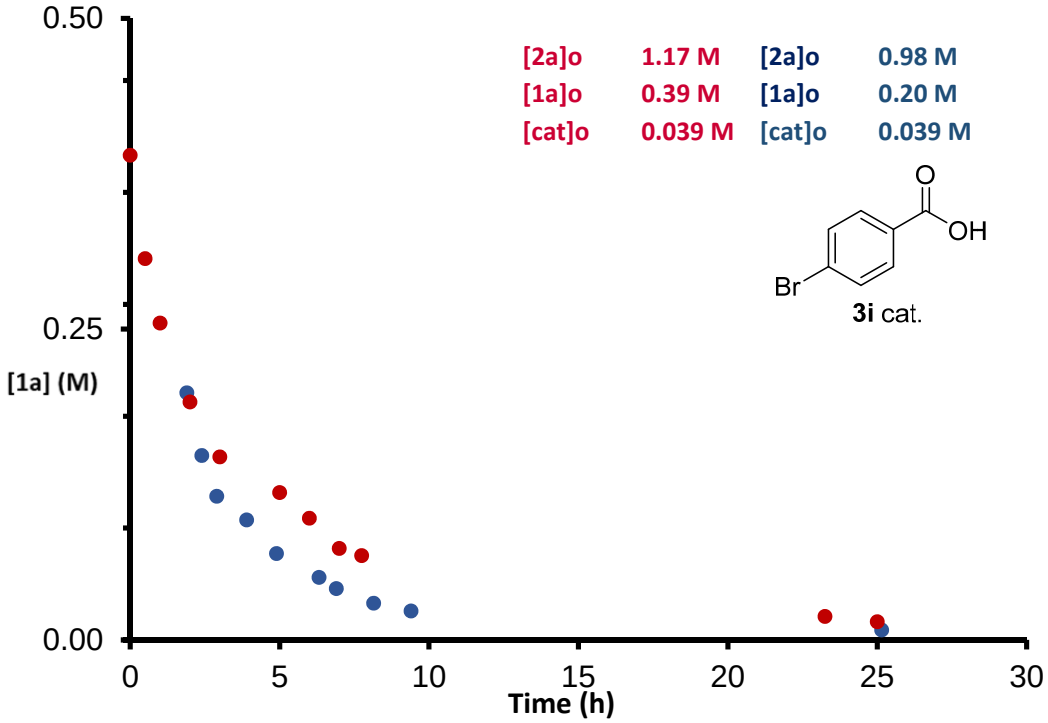


Figure S13. Same excess plot from the reaction with 4-bromobenzoic acid (**3i**).

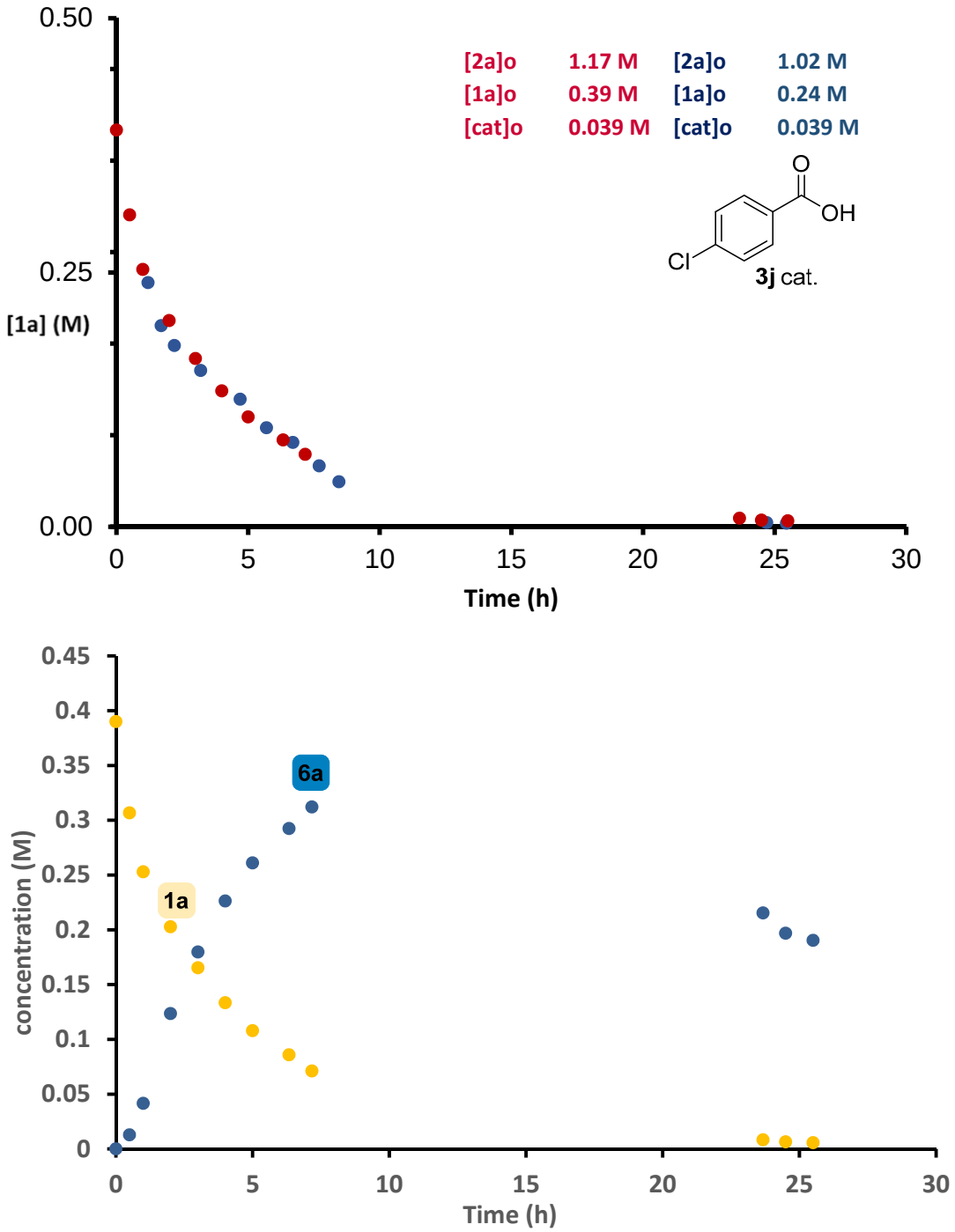


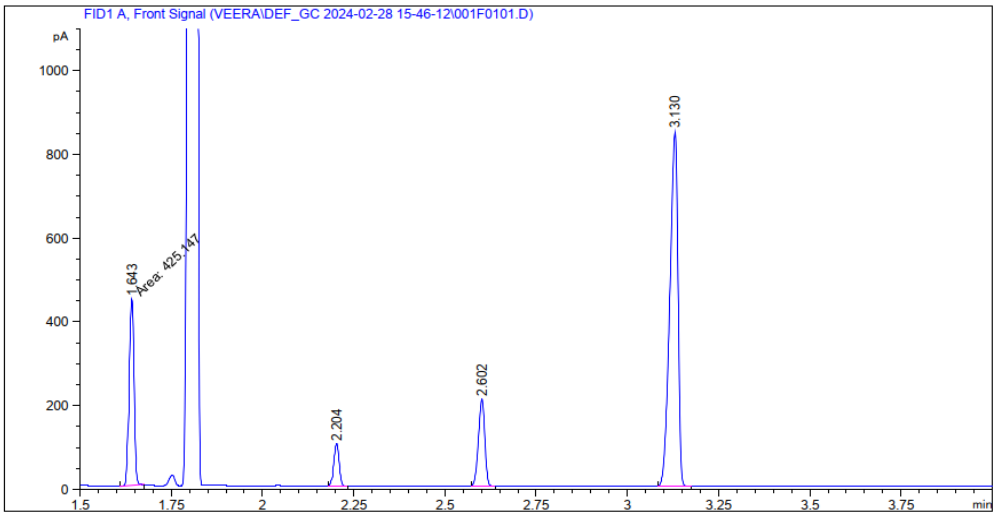
Figure S14. Same excess plot from the reaction with 4-chlorobenzoic acid (**3j**) and the reaction progress plot.

4.2 Control experiment to study potential catalyst esterification

We considered carboxylic acid esterification as one hypothetical cause for catalyst decay mechanism. In 1970, Johnson and co-workers.[20] reported (see ref 5 within the paper) esterification of carboxylic acids under their reaction conditions. To investigate whether a similar explanation applies to our catalyst decay, we conducted spiking experiments with catalyst **3b** which displayed significant decay in our same excess experiments. In these experiments, **3b** appeared to decay within 3-5 h from the start of the reaction under the standard conditions, as indicated by nearly complete halt in the consumption of the starting material **1a** (see Chapter 4.1.4, Figure S6).

In the control experiments the reaction with 4-methoxybenzoic acid **3b** was repeated using **1a** (1 equiv.) **2a** (3 equiv.) **3b** (10 mol-%), 120 °C in *o*-DCB and the reaction was monitored with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150°C isothermic) according to the representative procedure for same excess experiment reactions (Chapter 4.1.2). A stock solution (0.039 M) of methyl ester of **3b** was prepared by dissolving 13 mg (0.078 mmol) of the ester in 2 mL of pentane. After 4 h of reaction time, 4 identical samples from the reaction mixture were spiked with 0, 25, 50, and 100 microliters of the stock solution and the samples were diluted to 1 mL of pentane corresponding to 0, 2.5, 5 and 10 mol-% of the methyl ester. The methyl ester peak was not visible in the nonspiked sample (0 mol-%, Figure S15) but started to appear already at 2.5 mol-% (Figure S15-S18), demonstrating that the detection limit for the methyl ester corresponds to 2.5 mol-% of the ester in the reaction mixture. These experiments indicate that esterification does not appear to be the major mode of decay of the catalyst.

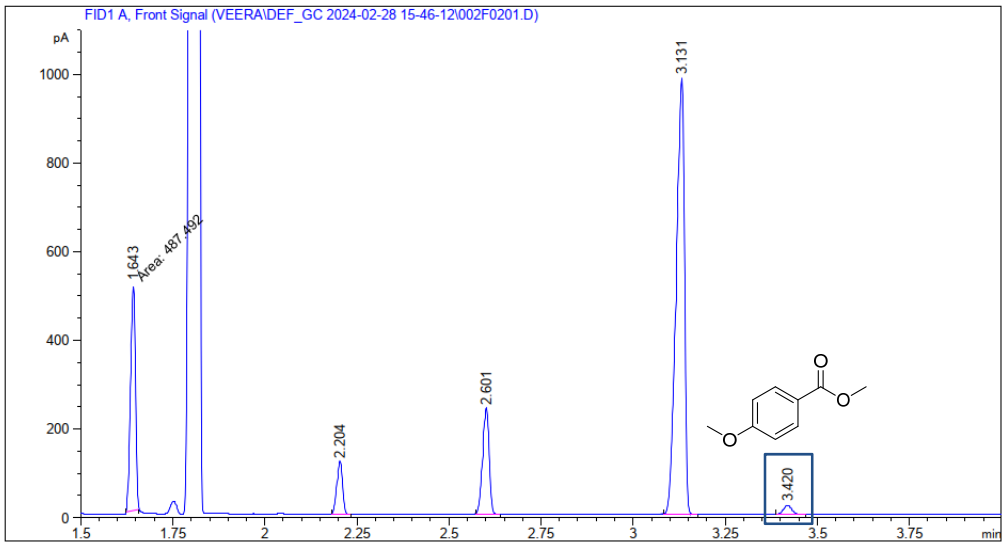
Data File C:\CHEM32\1\DATA\VEERA\DEF_GC 2024-02-28 15-46-12\001F0101.D
Sample Name: TJB-1-156,t5



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	1.643	MM	0.0159	425.14670	444.34738	20.40115
2	2.204	BB	0.0162	104.81585	100.03693	5.02971
3	2.602	BB	0.0191	250.61162	206.73300	12.02588
4	3.130	BB	0.0239	1303.36121	847.39722	62.54326

Figure S15. Reaction at 4 h without any added methyl ester of **3b**.

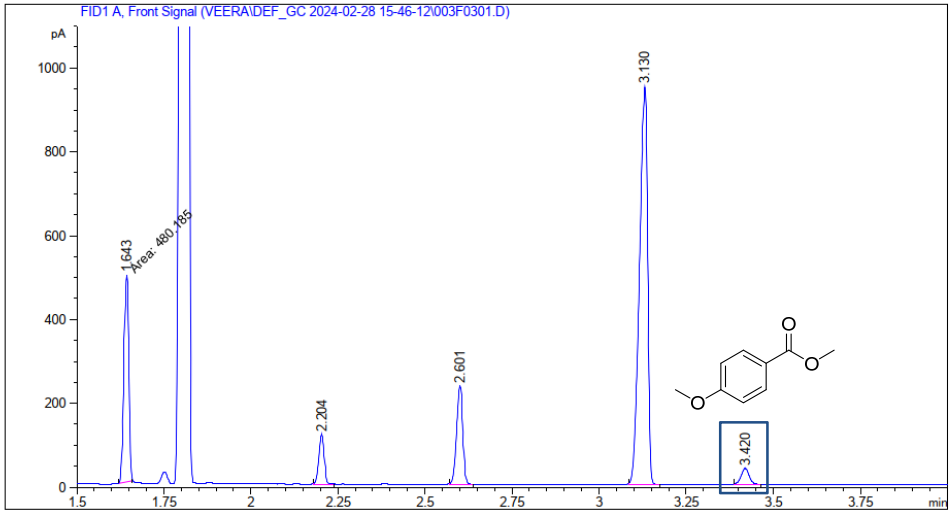
Data File C:\CHEM32\1\DATA\VEERA\DEF_GC 2024-02-28 15-46-12\002F0201.D
Sample Name: TJB-1-156,t5(2.5mol%ester)



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	1.643	MM	0.0159	487.49185	510.71045	19.68568
2	2.204	BB	0.0165	127.05153	118.91277	5.13054
3	2.601	BB	0.0194	294.10928	238.68686	11.87659
4	3.131	BB	0.0242	1535.30896	984.12915	61.99817
5	3.420	BB	0.0255	32.41609	20.46098	1.30901

Figure S16. Reaction at 4 h with 2.5 mol-% of added methyl ester of **3b**.

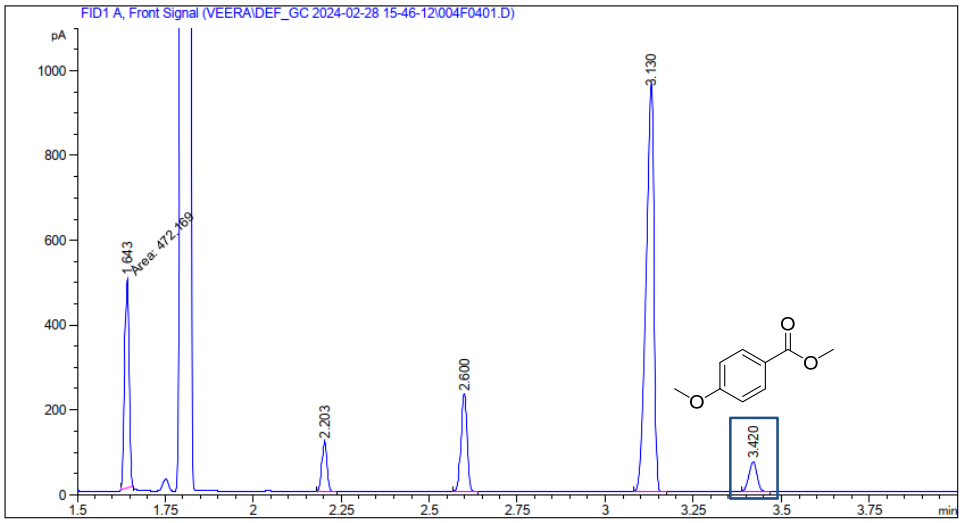
Data File C:\CHEM32\1\DATA\VEERA\DEF_GC 2024-02-28 15-46-12\003F0301.D
Sample Name: TJB-1-156,t5(5mol%ester)



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	1.643	MM	0.0162	480.18457	493.30975	19.70240
2	2.204	BB	0.0164	124.19125	116.58120	5.09568
3	2.601	BB	0.0192	284.62027	233.30040	11.67822
4	3.130	BB	0.0243	1488.93201	947.77716	61.09221
5	3.420	BB	0.0246	59.25972	37.21695	2.43148

Figure S17. Reaction at 4 h with 5 mol-% of added methyl ester of **3b**.

Data File C:\CHEM32\1\DATA\VEERA\DEF_GC 2024-02-28 15-46-12\004F0401.D
Sample Name: TJB-1-156,t5(10mol%ester)

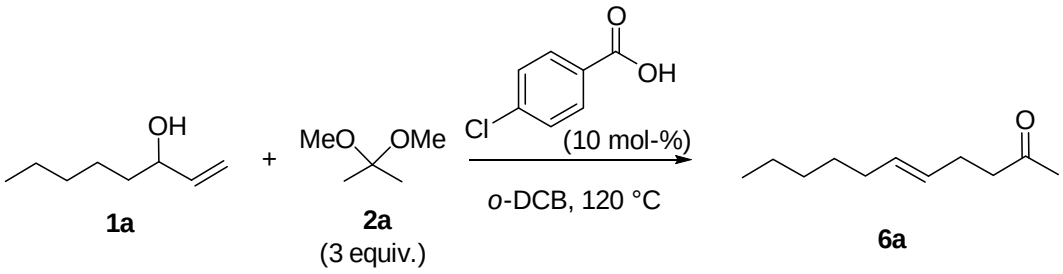


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	1.643	MM	0.0159	472.16876	494.95761	18.96504
2	2.203	BB	0.0175	125.68597	117.22015	5.04828
3	2.600	BB	0.0196	285.55380	228.82312	11.46950
4	3.130	BB	0.0244	1495.25122	947.98663	60.05797
5	3.420	BB	0.0246	111.02023	69.61372	4.45922

Figure S18. Reaction at 4 h with 10 mol-% of added methyl ester of **3b**.

4.3 Comparison of enol methyl ethers 2a and 2d

After discovering the optimal acid catalyst, we compared two enol methyl ethers to study their effect on the reaction rate. The same excess experiments with **3j** catalyst were run with two different enol methyl ether substrates, 2,2-dimethoxypropane **2a** (Figure S19) and 2-dimethoxypropene **2d** (Figure S20). From the same excess plots the half-lifes ($t_{1/2}$) were estimated. The consumption of the allylic alcohol **1a** in the reaction with **2a** ($t_{1/2}$ ≈ 2 h) was 4 times faster than in the reaction with **2d** ($t_{1/2}$ ≈ 0.5 h). As the reactions with **2d** were significantly faster, it was used in the further studies. However, **2a** was considered as a better choice for running the same excess experiments as the consumption of **1a** in the reaction with **2d** is even too fast to make reliable interpretations about the catalyst decay. Later on cyclic ketones were accessed using 1,1-dimethoxycyclopentane **2b** and 1,1-dimethoxycyclohexane **2c**, but their effect on the reaction rate was not studied.



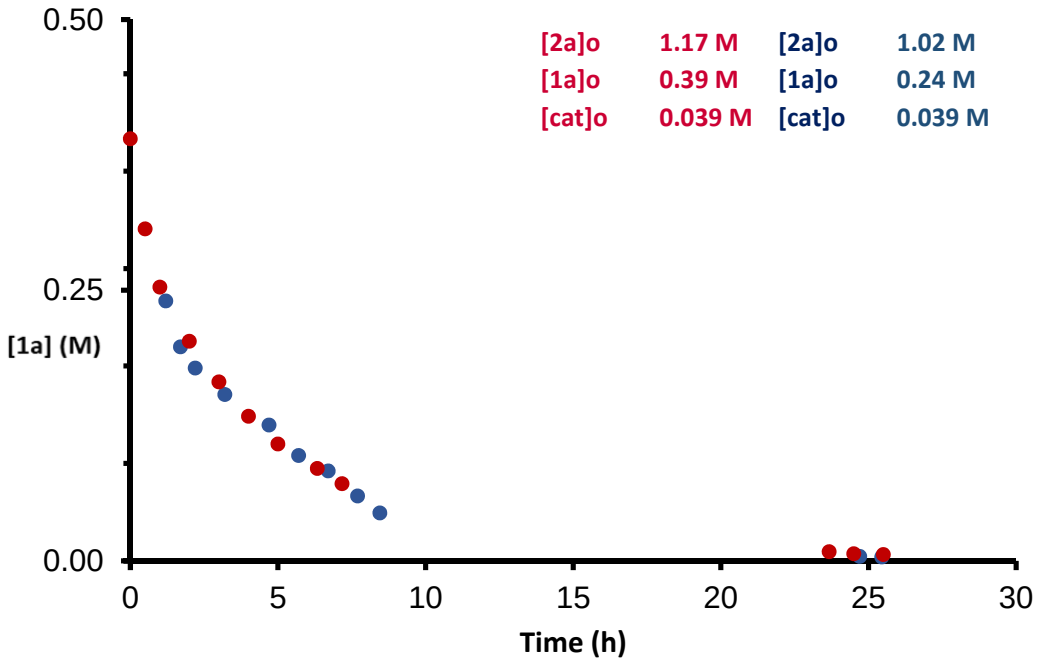


Figure S19. Same excess experiment from the reaction between **1a** and **2a**.

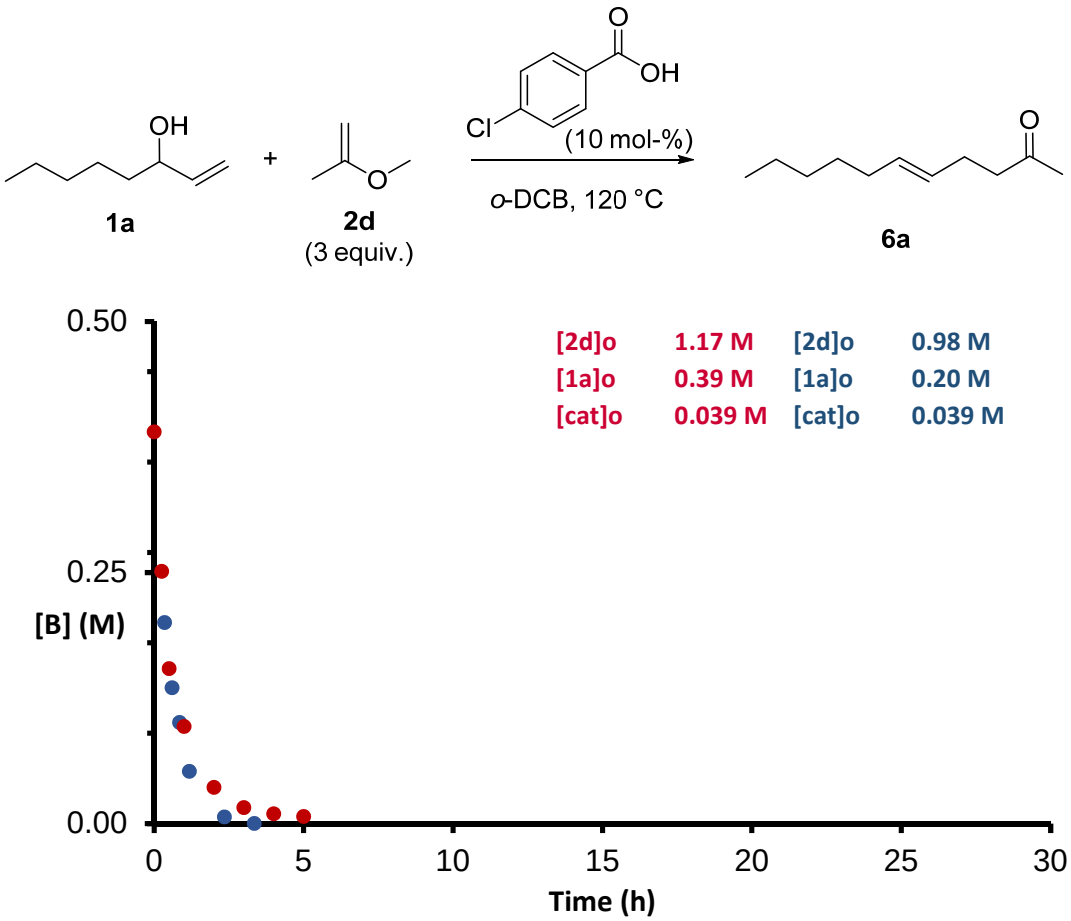
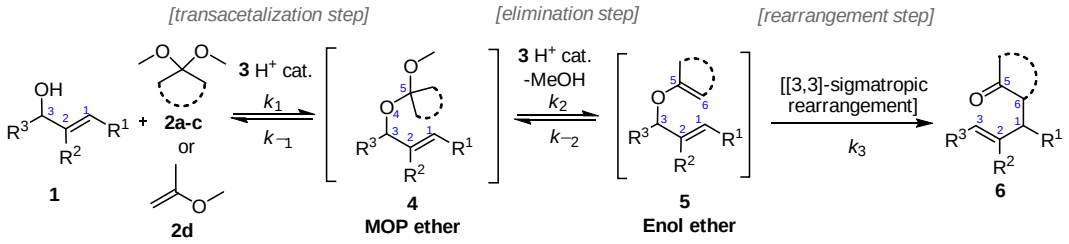


Figure S20. Same excess experiment from the reaction between **1a** and **2d**.

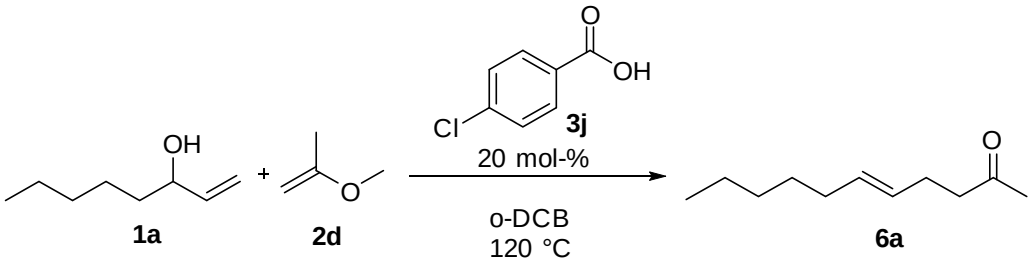
4.4 Reaction progress curves with intermediates: comparison of class 1a and class 2 substrates

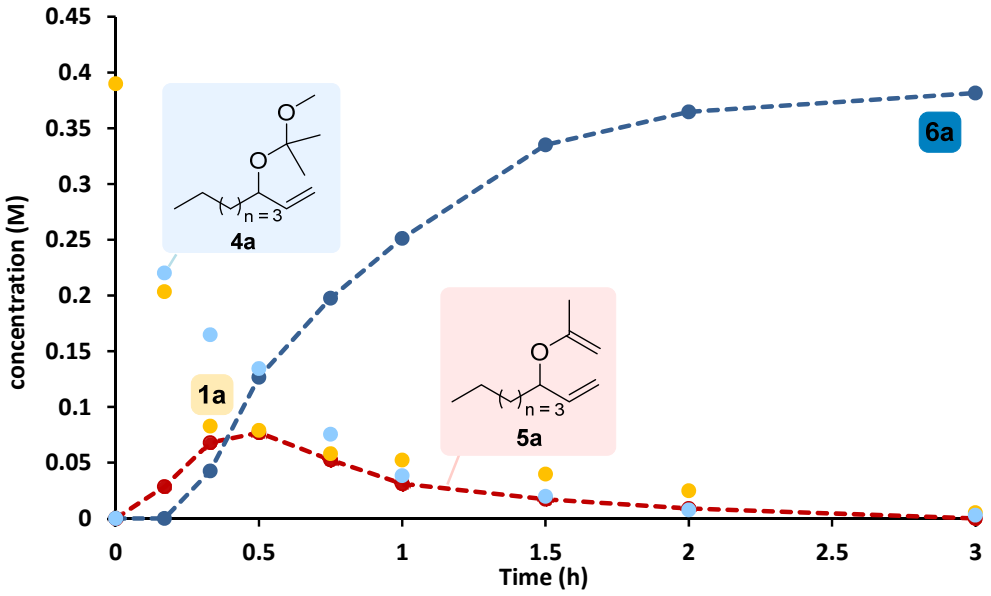
The aliphatic ketone Claisen rearrangement is believed to consist of three steps[11]: Transacetalization to produce the MOP-ether **4**, elimination of methanol to give rise the enol ether intermediate **5** and finally the [3,3]-sigmatropic rearrangement to the final ketone product **6** (Scheme S6). All of the intermediates are visible in the chromatograms from reaction mixture. The first two steps are considered to be acid catalysed equilibrium reactions. (For computational proof check section 5).



Scheme S6. Intermediates of the aliphatic ketone Claisen rearrangement.

The reaction progress curves from the reactions with 1-octen-3-ol **1a** (*class 1*) and 3-methyl-2-methylenebutan-1-ol **1p** (*class 2*) were compared to study the reaction limiting step. The reactions were monitored using GC (SUPELCO Astec CHIRALDEX B-DM column, isoflow He: 1.806 mL/min, 100 °C isothermic) and concentrations were calculated using response factors. The reaction with **1a** proceeded without any problems resulting in almost quantitative conversion to **6a** (Scheme S7).

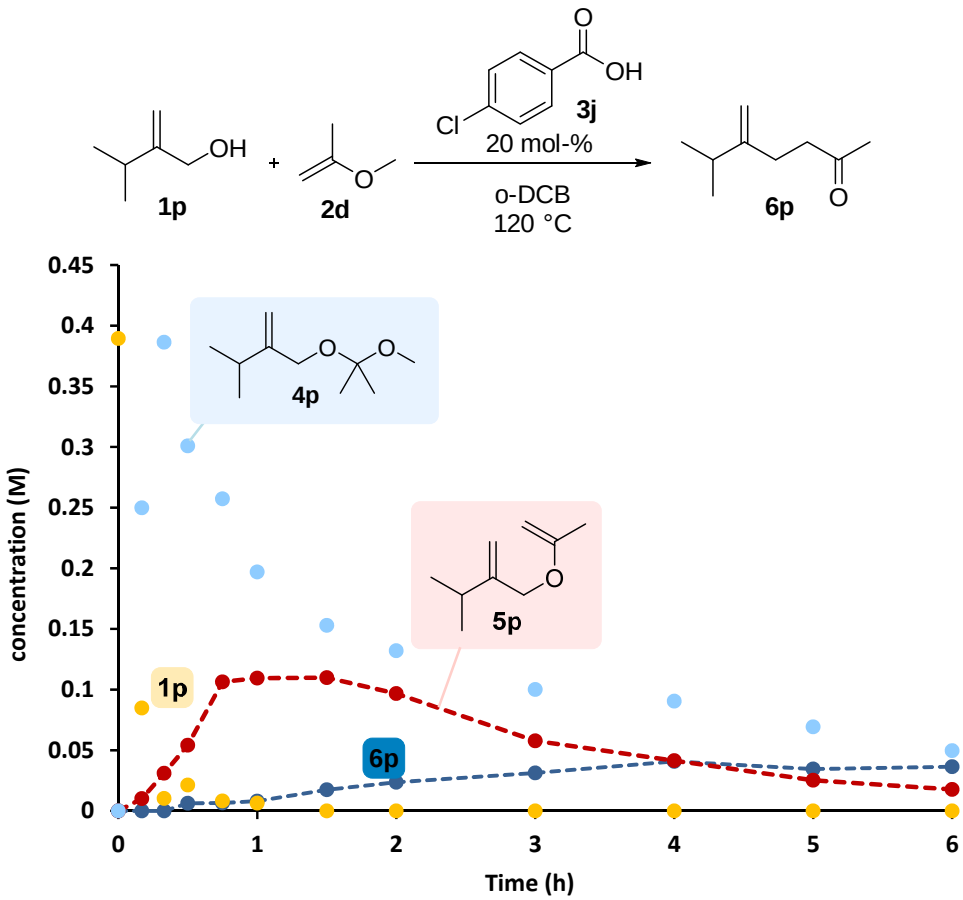




Scheme S7. Reaction progress curve from the reaction with **1a** in thermal conditions.

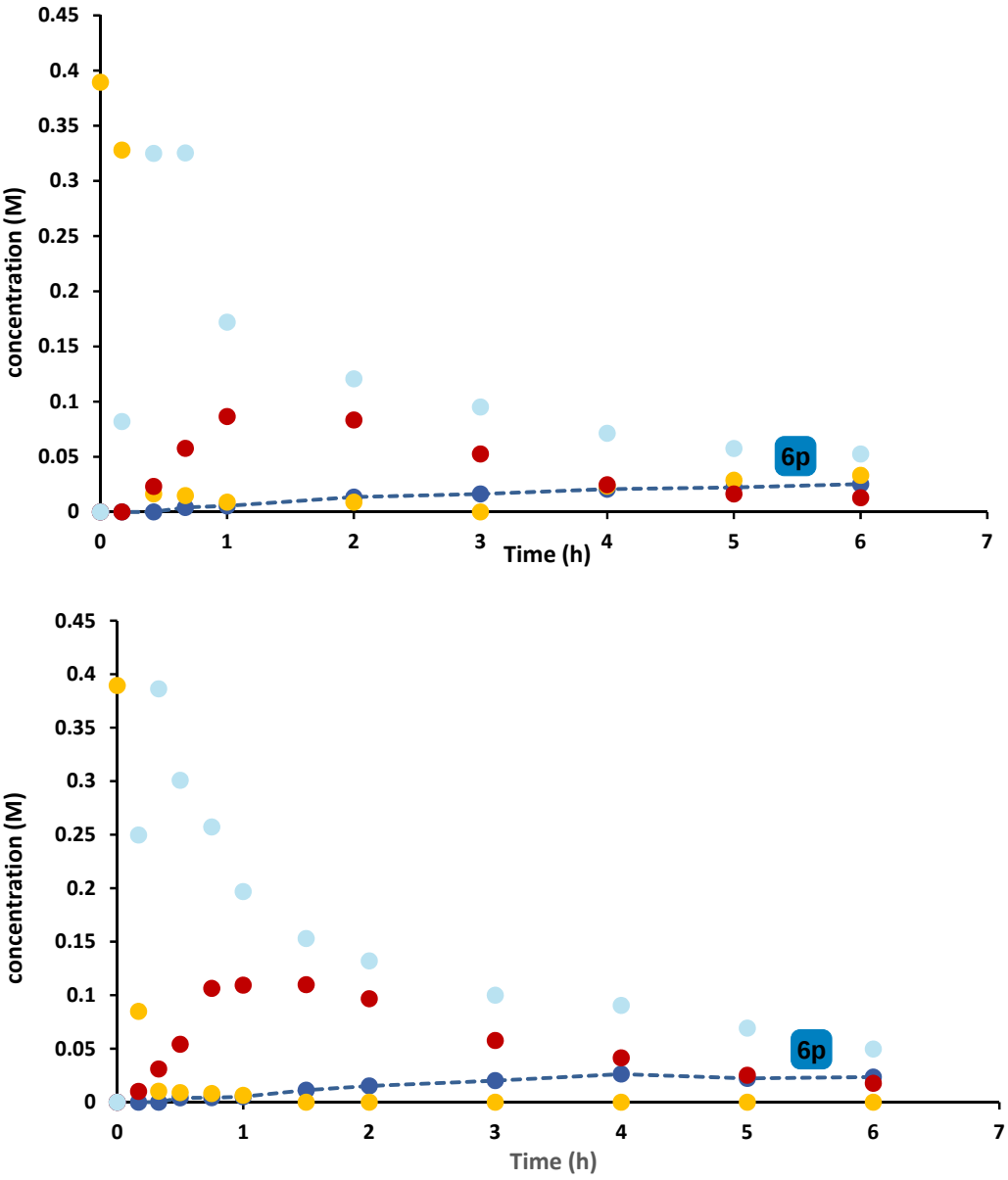
The reaction progress curves from the reaction with **1p** illustrates that both MOP-ether **4p** and the enol ether **5p** intermediates are formed uneventfully in succession, but they

decay before giving rise to the ketone product **6p** (Scheme S8). This result suggests that for *class 2* alcohols, the last rearrangement step has the highest activation barrier, but it is not the case for *class 1* alcohols. The results are in agreement with the computational studies (see Section 5).



Scheme S8. Reaction progress plot from the reaction with **1p** in thermal conditions

As an attempt to overcome the high activation barrier in the rearrangement step, the reaction with **1p** was run with increased catalyst loading (0.039, 0.078 and 0.117 M). This led to increasing amounts of intermediates **4p** and **5p**, but the product yield was not affected (Figure S21).


0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
concentration (M)
0
1
2
3
4
5
6
7
Time (h)
6p
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
concentration (M)
0
1
2
3
4
5
6
7
Time (h)
6p

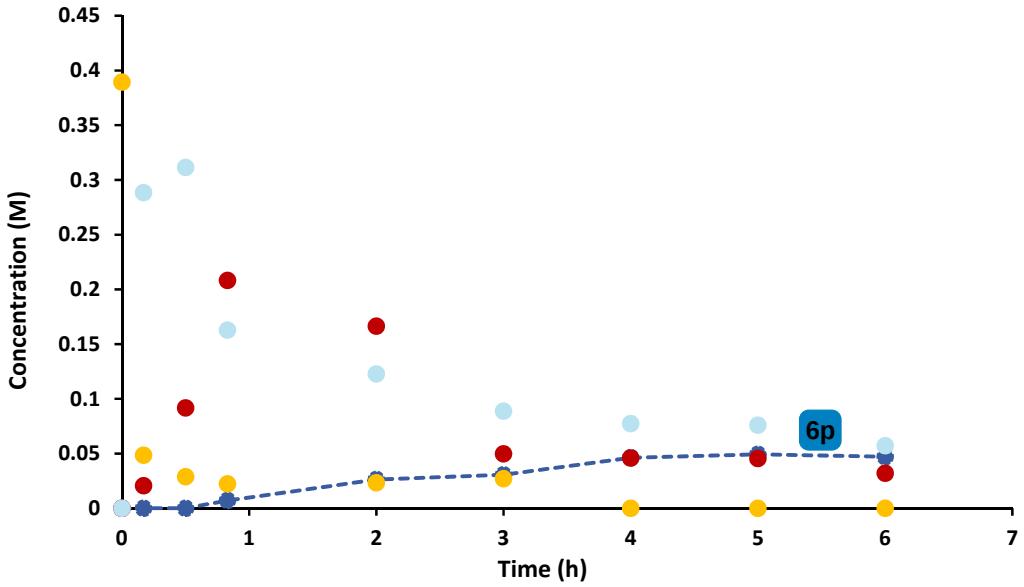


Figure S21. Reaction progress plot (**1p**) with 0.039 M, 0.078 M and 0.117 M catalyst loading respectively.

5 Computational studies

5.1 Computational details

Gaussian 16[21] was used to fully optimize the structures reported in this paper at the B3LYP level of theory.[22] For all the calculations, solvent effects were considered using the SMD solvation model[23] with ortho-dichlorobenzene as the solvent. The 6-31G(d) basis set was used for all atoms.[24] This basis set combination will be referred to as BS1. We also employed the D3 empirical dispersion correction for all the calculations. Frequency calculations were carried out at the same level of theory as those for the structural optimization. Transition structures were located using the Berny algorithm. IRC calculations were used to confirm the connectivity between transition structures and minima.[25,26] To further refine the energies obtained from the SMD/B3LYP-D3/SDD,6-31G(d) calculations, we carried out single-point energy calculations using the B3LYP-D3 functional method with the SMD solvation model in acetonitrile along with a larger basis set (BS2) for all the optimized structures. BS2 utilizes the def2-TZVP basis set[27] on all atoms. The tight convergence criterion and ultrafine integral grid were exploited to increase the accuracy of the calculations. The free energy for each species in solution was calculated using the following formula:

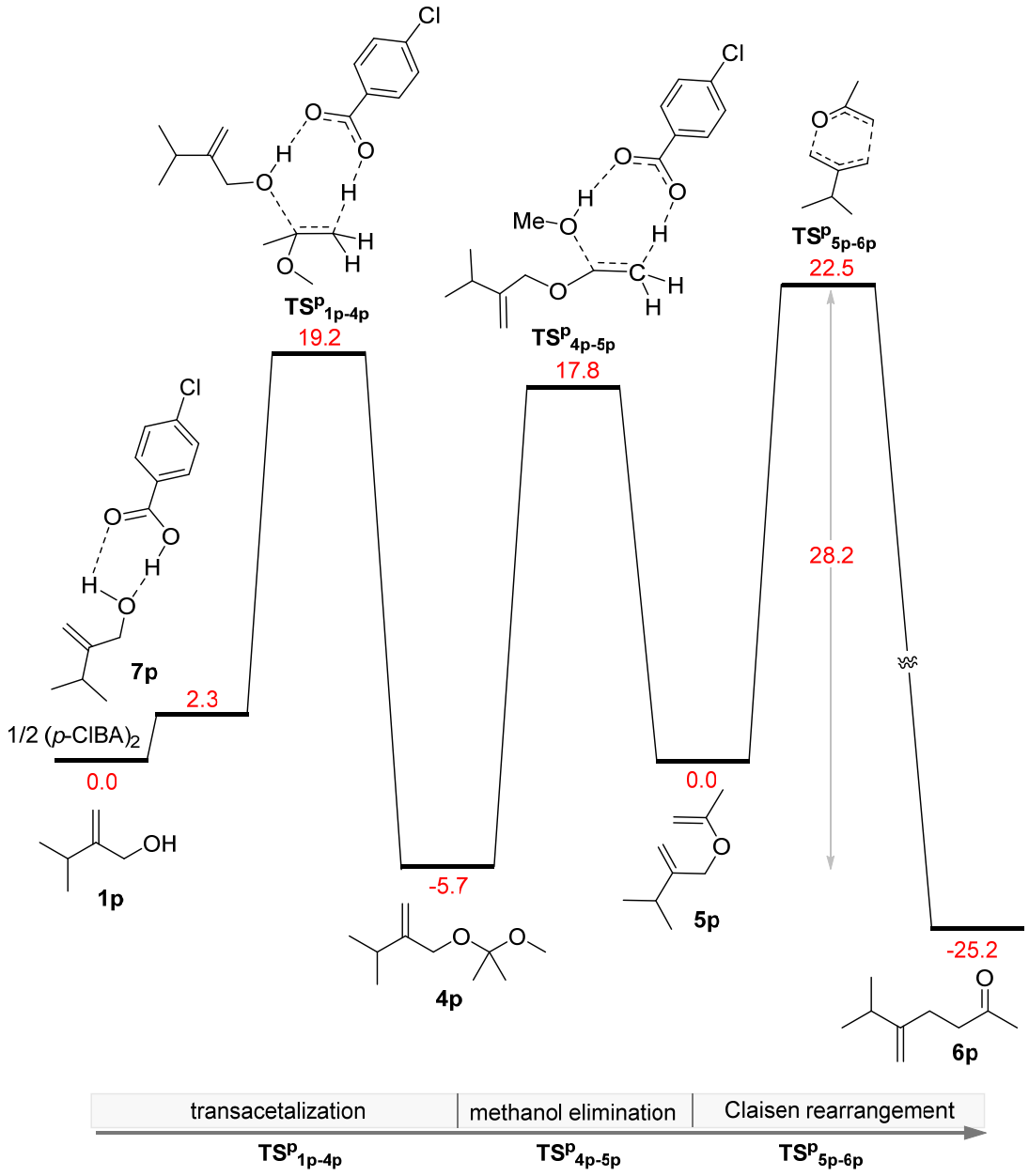
$$G = G(BS1) + E(BS2) - E(BS1) + \Delta G^{1atm \rightarrow 1M} \quad \text{(S5)}$$

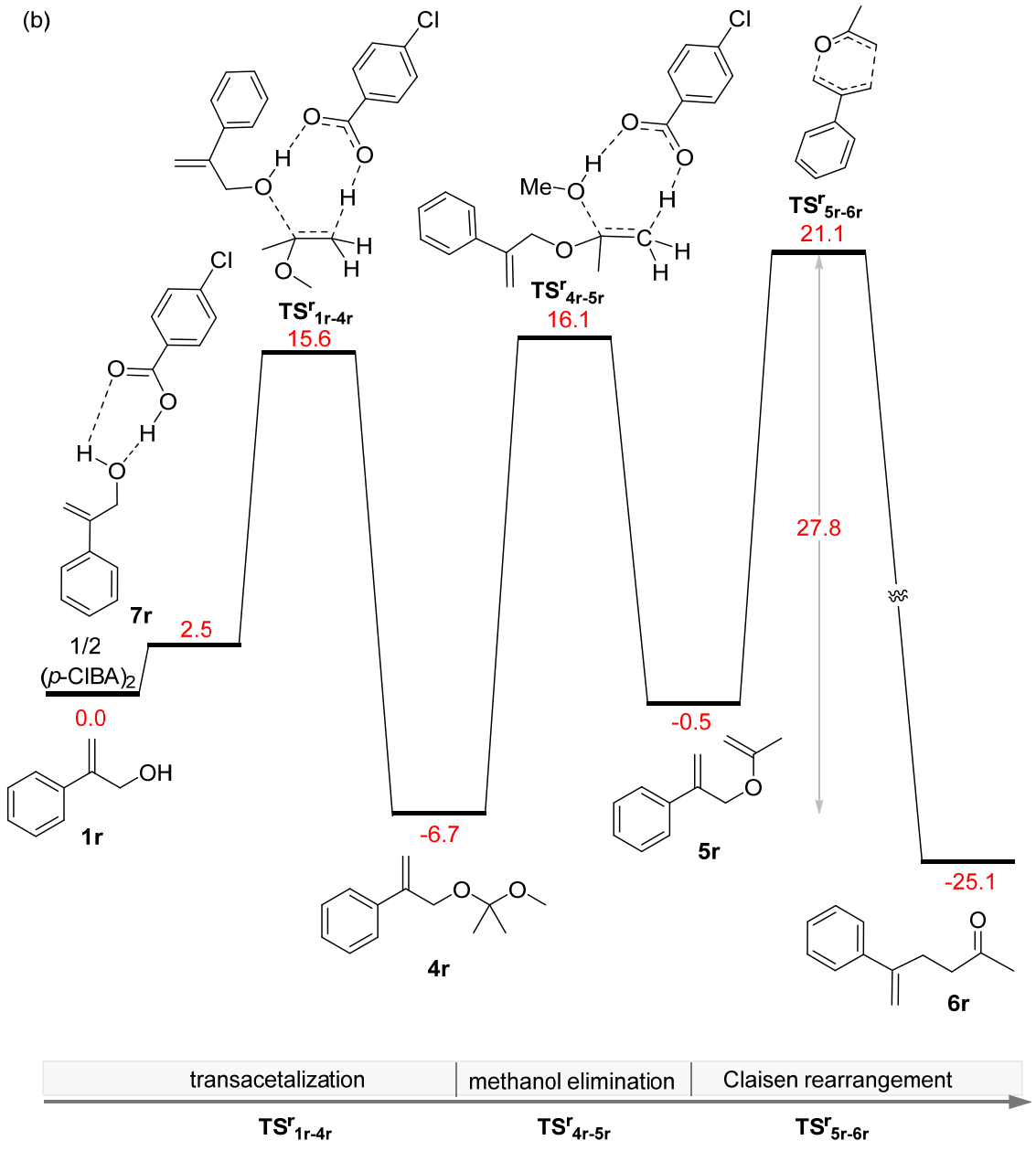
E1(BS1), E(BS2), and G(BS1) refer to the potential energies calculated based on BS1, BS2, and the Gibbs free energy calculated based on BS1, respectively. $\Delta G^{1\text{atm}\rightarrow 1\text{M}}$ represents the free energy change for compression of 1 mol of an ideal gas from 1 atm to the 1 M solution phase. This value is 1.89 kcal/mol at room temperature (rt, 298.15 K) and 2.50 kcal/mol at reaction temperature (120 °C, 393.15 K).

5.2 Calculated energy profiles at rt

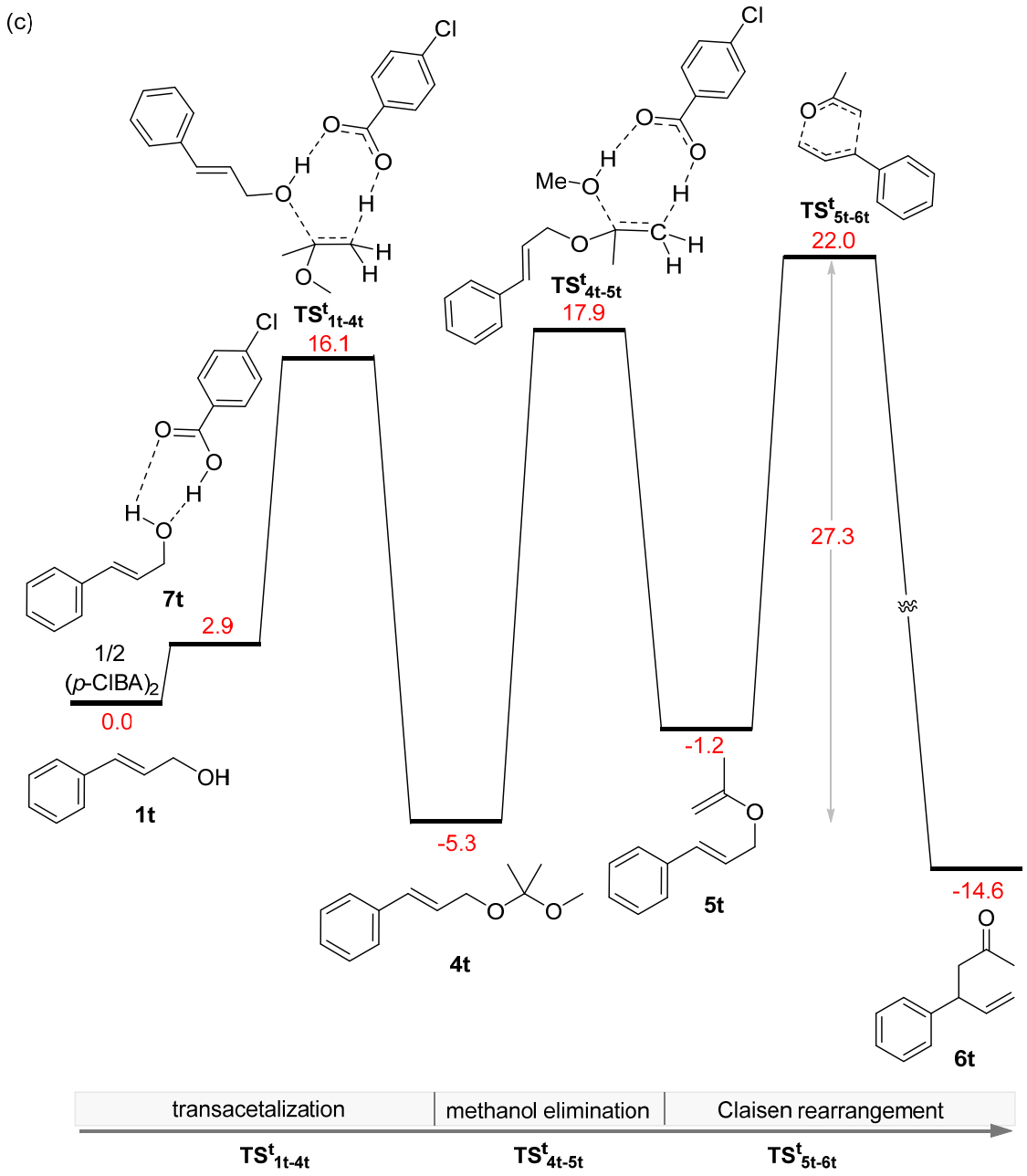
The results of DFT calculations using the SMD/B3LYP-D3/def2-TZVP//SMD/B3LYP-D3/6-31G(d) level of theory for substrates 3-methyl-2-methylenebutan-1-ol (**1p**), 2-phenylprop-2-en-1-ol (**1r**), (E)-3-phenylprop-2-en-1-ol (**1t**), 3-methylbut-2-en-1-ol (**1x**), tert-butyl (2-hydroxy-3-methylbut-3-en-1-yl) carbamate (**1z**), 1-octen-3-ol (**1a**) are shown in Figure S22a-e. The calculations (at rt) indicate that for all calculated compounds, the MOP-ether is the most stable species before reaching the final product. These results also suggest that the rate-determining step for this transformation is the Claisen rearrangement step at rt. However, this picture changes slightly when the free energies are evaluated at 120 °C (see Section 5.3.)

(a)

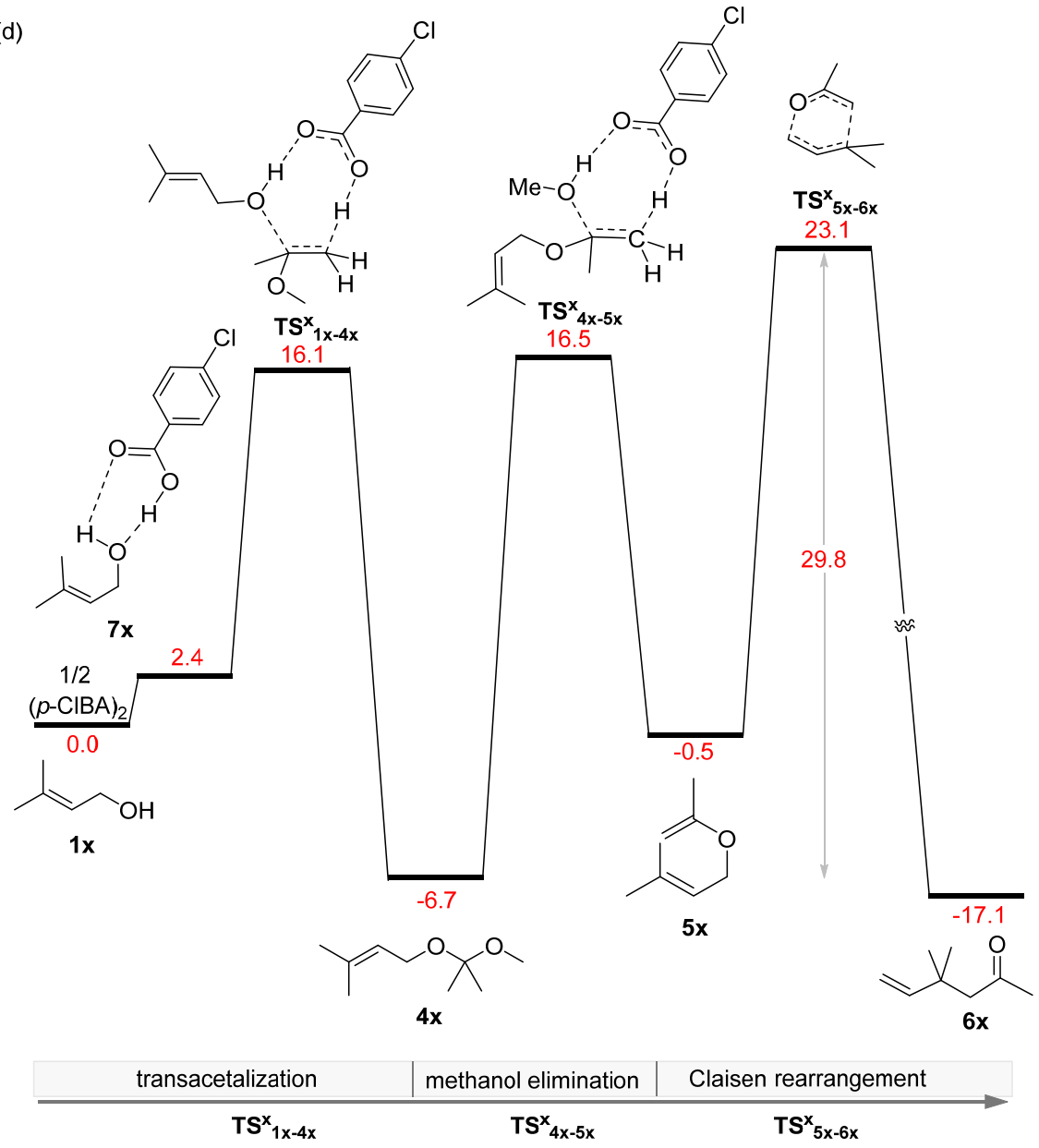

Cl
O
H
O
O
H
H
H
O
TS$^{p}_{1p-4p}$
19.2
Cl
O
H
Me
O
O
H
C
H
H
O
TS$^{p}_{4p-5p}$
17.8
O
TS$^{p}_{5p-6p}$
22.5
28.2
Cl
O
O
H
H
O
7p
2.3
1/2 (p-ClBA)$_2$
0.0
OH
1p
-5.7
O
O
4p
0.0
O
5p
-25.2
O
6p
transacetalization
methanol elimination
Claisen rearrangement
TS$^{p}_{1p-4p}$
TS$^{p}_{4p-5p}$
TS$^{p}_{5p-6p}$

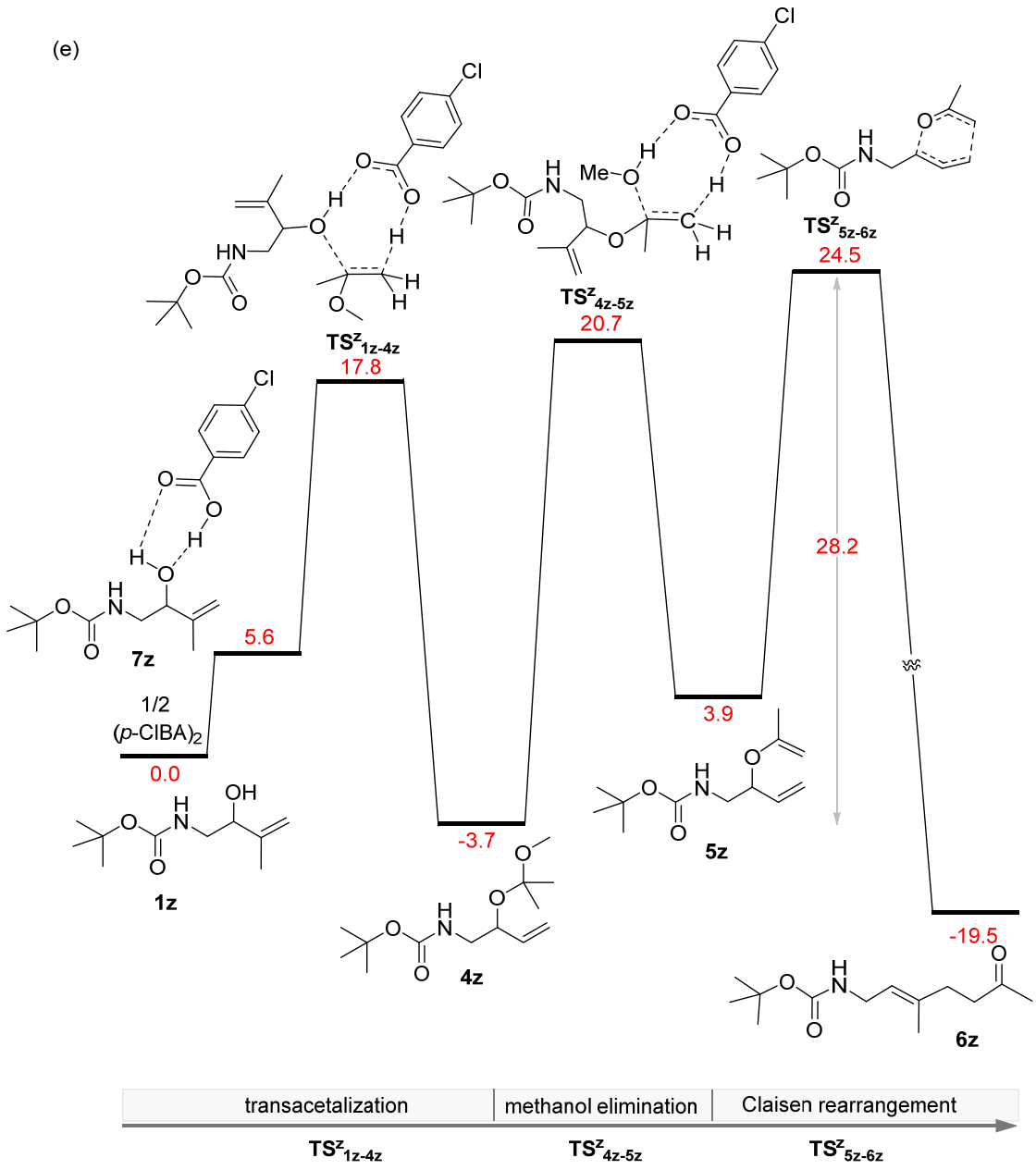

(b)
Cl
O
H
O
O
H
O
H
H
O
TS$^{r}_{1r-4r}$
15.6
Cl
O
O
H
H
O
7r
2.5
1/2
(p-ClBA)$_2$
0.0
OH
1r
-6.7
O
O
4r
Me
O
H
O
O
H
C
H
H
O
TS$^{r}_{4r-5r}$
16.1
-0.5
O
5r
O
TS$^{r}_{5r-6r}$
21.1
27.8
-25.1
O
6r
transacetalization
methanol elimination
Claisen rearrangement
TS$^{r}_{1r-4r}$
TS$^{r}_{4r-5r}$
TS$^{r}_{5r-6r}$

(c)


Cl
O
H
O
O
H
H
H
O
TS^t_{1t-4t}
16.1
Cl
O
O
H
H
O
7t
2.9
1/2
(*p*-ClBA)$_2$
0.0
OH
1t
-5.3
4t
Me
O
H
O
O
H
C
H
H
O
TS^t_{4t-5t}
17.9
-1.2
O
5t
O
TS^t_{5t-6t}
22.0
27.3
-14.6
O
6t
transacetalization
methanol elimination
Claisen rearrangement
TS^t_{1t-4t}
TS^t_{4t-5t}
TS^t_{5t-6t}

(d)


Cl
TS$^{x}_{1x-4x}$
16.1
TS$^{x}_{4x-5x}$
16.5
TS$^{x}_{5x-6x}$
23.1
29.8
7x
2.4
1/2
(p-ClBA)$_2$
0.0
1x
OH
-6.7
4x
-0.5
5x
-17.1
6x
transacetalization
methanol elimination
Claisen rearrangement
TS$^{x}_{1x-4x}$
TS$^{x}_{4x-5x}$
TS$^{x}_{5x-6x}$


(e)
7z
1/2 (p-ClBA)2
0.0
5.6
TSz1z-4z
17.8
1z
-3.7
4z
TSz4z-5z
20.7
3.9
5z
TSz5z-6z
24.5
28.2
-19.5
6z
transacetalization
methanol elimination
Claisen rearrangement
TSz1z-4z
TSz4z-5z
TSz5z-6z

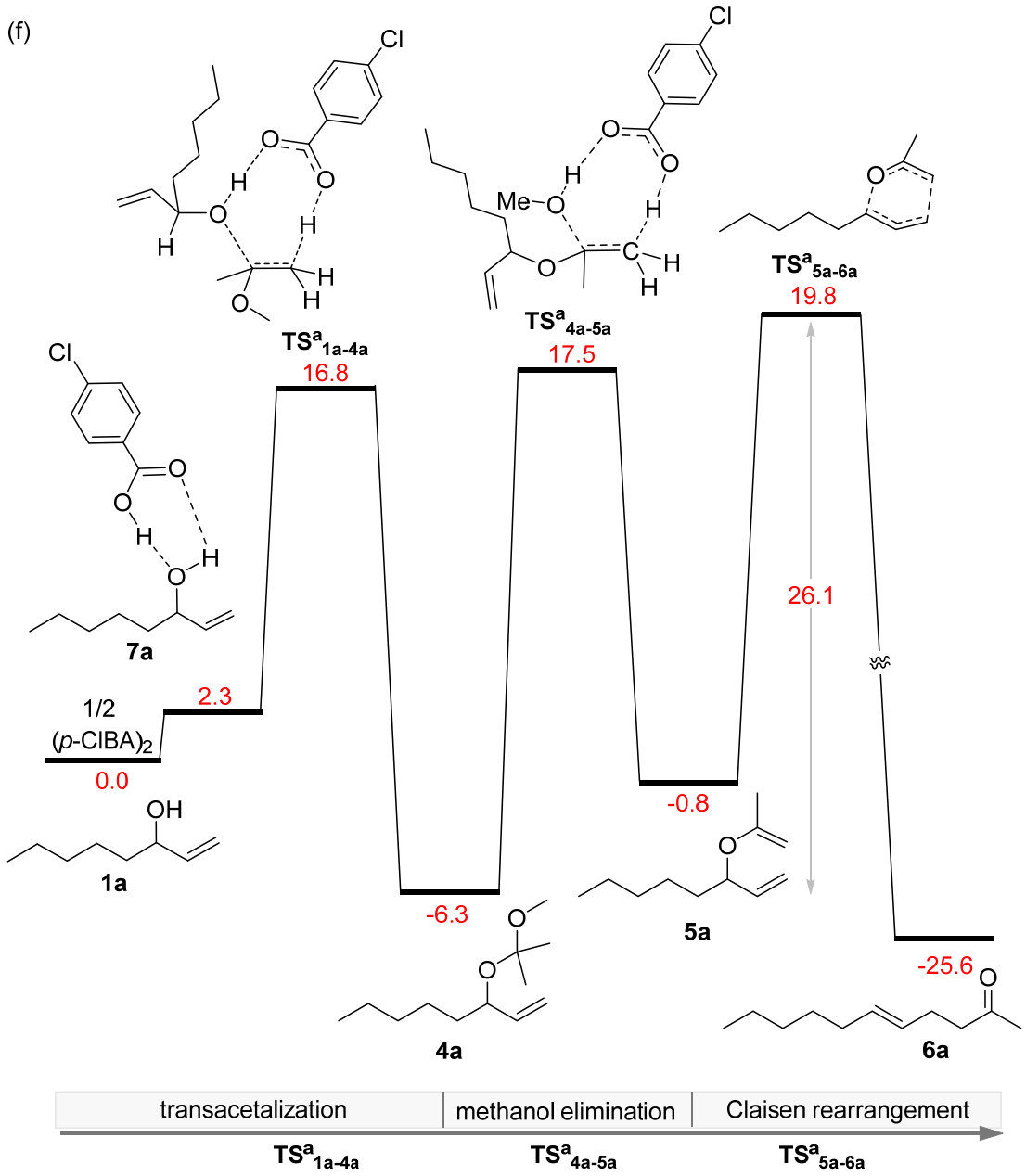


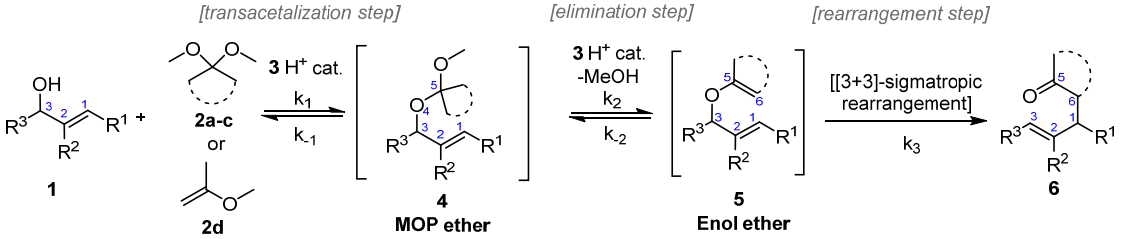
Figure S22 The calculated free energy profiles for the 4-chlorobenzoic acid-catalyzed transesterification followed by Claisen rearrangement for substrates: **1p**, **1r**, **1t**, **1x**, **1z**, and **1a** at rt. The second molecule from the acid dimer, 2-methoxypropene and the methanol side product are omitted for clarity but are included in the free energy calculations The relative free energies are given in kcal/mol (in red).

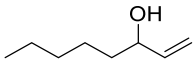
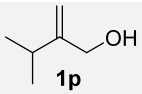
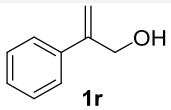
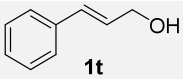
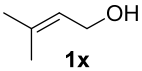
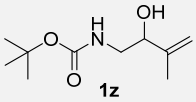
5.3 Calculated energy profiles at 120 ˚C

The calculated relative free energy profiles at 120 °C for substrate **1p**, **1r**, **1t**, **1x**, **1z** are shown in Figure S23. The calculated free energies are summarized in Table S5. The DFT results indicate that structures **7**, **4**, $\mathbf{TS}_{1\text{-}4}$, and $\mathbf{TS}_{4\text{-}5}$ exhibit a more pronounced enhancement in their relative free energy at 120 °C compared to 25 °C. This is attributed to the negative entropy change (ΔS) associated with these transition states and intermediates. Accordingly, as temperature increases, the entropy term (-TΔS) becomes less favorable for these structures.

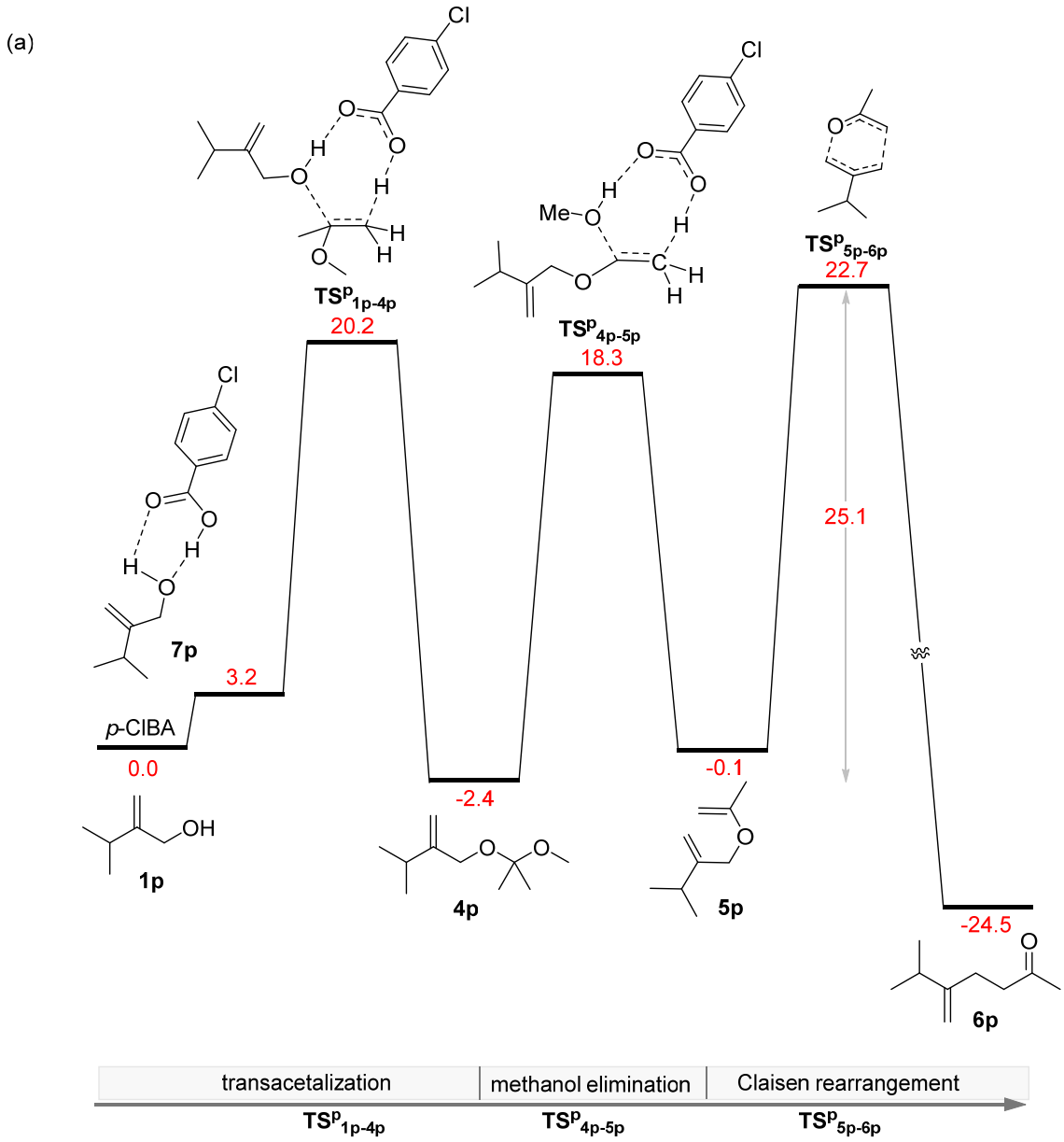
The higher observed concentration of **4p** compared to **4a** aligns with the computational results (Scheme S7, S8 and Figure S23). This is because the transition state $\mathbf{TS}^{\mathbf{p}}_{1\text{-}4}$ energy is lower than $\mathbf{TS}^{\mathbf{a}}_{1\text{-}4}$, facilitating the formation of **4p** over **4a**. However, the consumption of **4p** is slower than **4a** due to the requirement of higher activation energy to reach the final product. Additionally, DFT results at 120 °C indicate that for substrate **1a**, the methanol elimination step is the rate-determining step, whereas, for the other computed substrates (Figure S22), the Claisen rearrangement step exhibits the highest activation barrier.

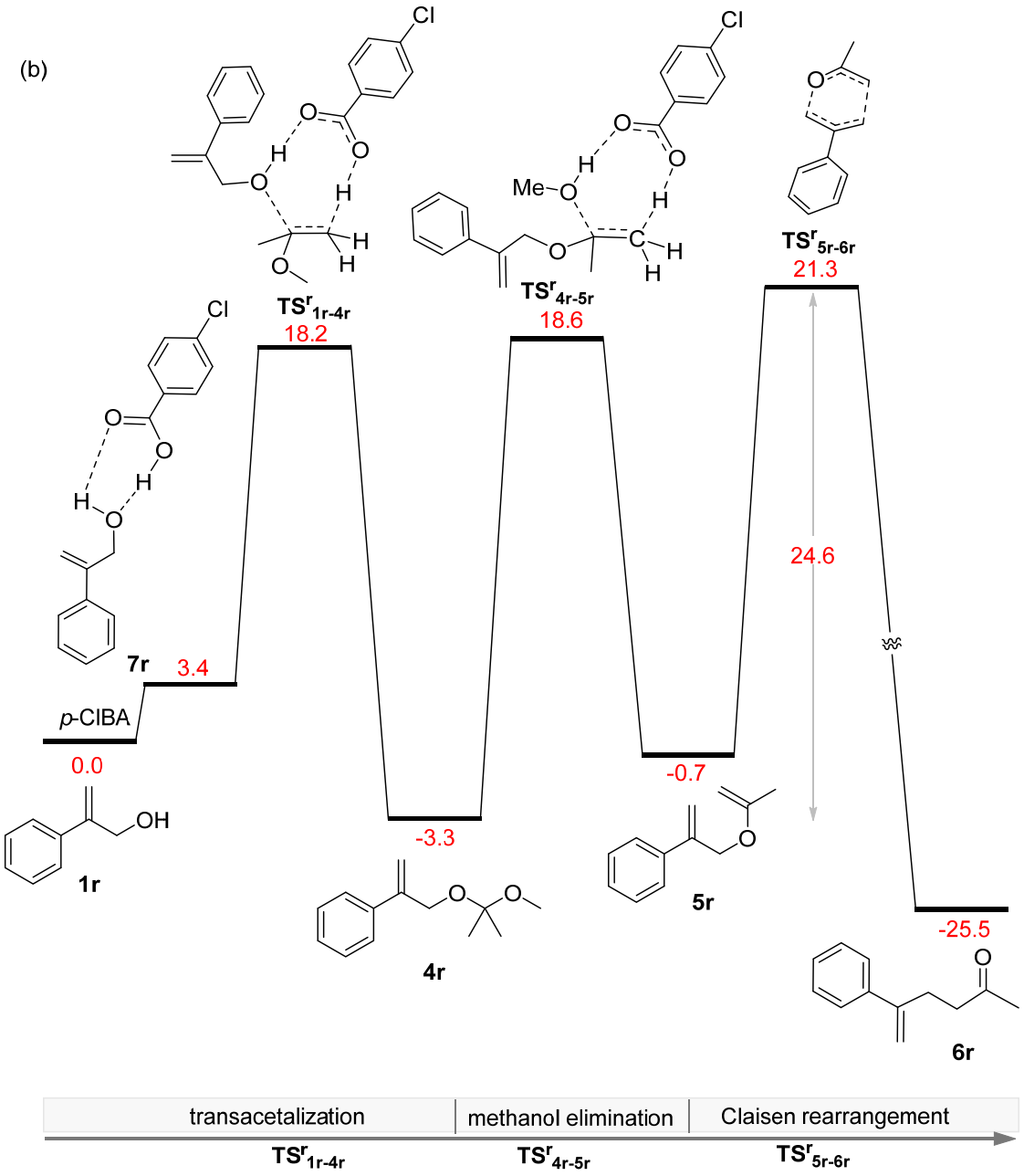
Table S5. The calculated free energies at 120 °C for the transition states (**TS$_{1_4}$**), (**TS$_{4_5}$**) and the final Claisen rearrangement step (**TS$_{5_6}$**), and stationary points including the intermediates **4**, **5** and the final product **6** of the 4-chlorobenzoic acid-catalyzed condensation – Claisen rearrangement sequence are shown. The following substrates are compared: 1-octen-3-ol (**1a**), 3-methyl-2-methylenebutan-1-ol (**1p**), 2-phenylprop-2-en-1-ol (**1r**), (E)-3-phenylprop-2-en-1-ol (**1t**), 3-methylbut-2-en-1-ol (**1x**), and tert-butyl (2-hydroxy-3-methylbut-3-en-1-yl) carbamate (**1z**) with 2-methoxypropene (**2d**).



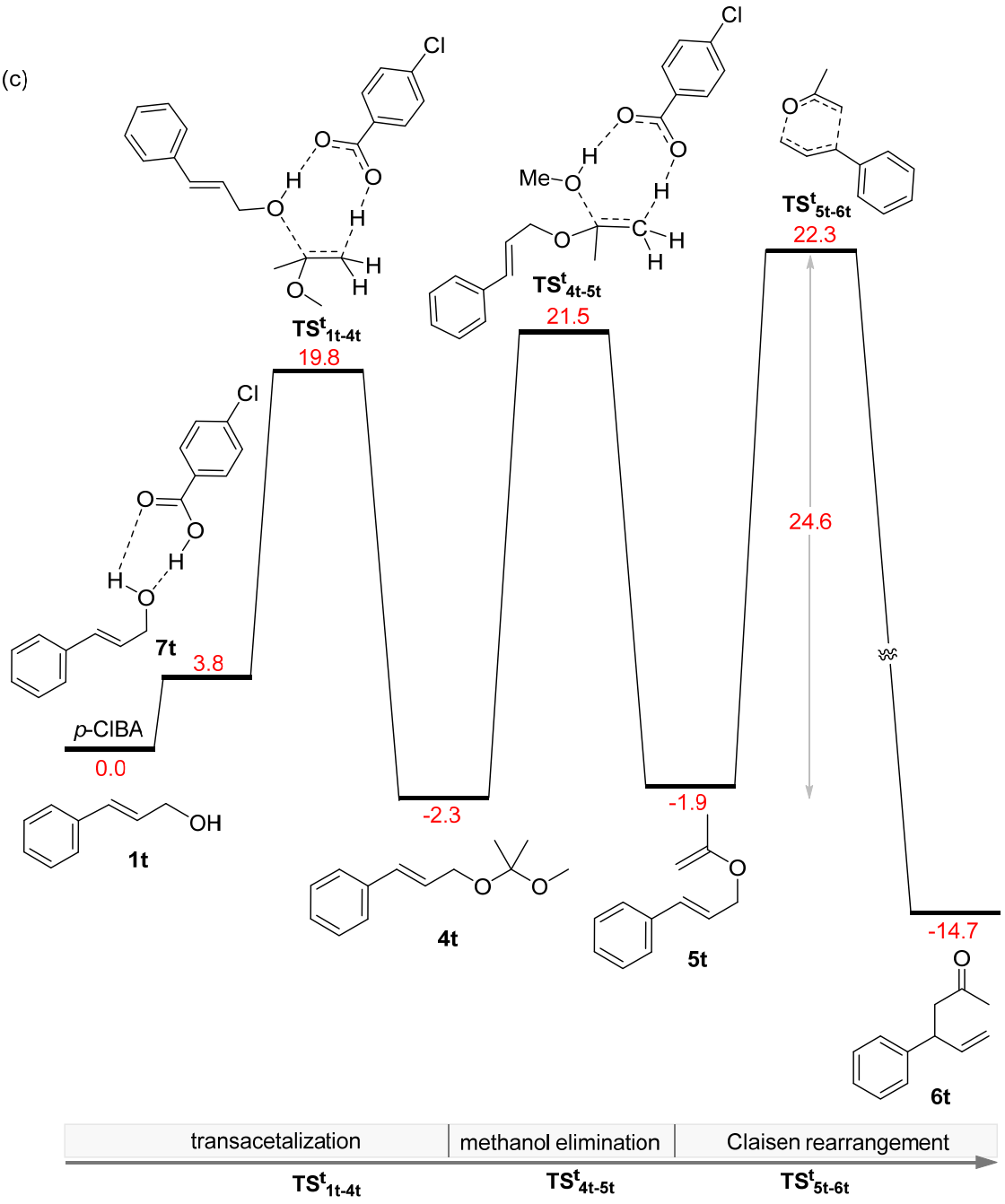
Class	Substrate	MW	TS$_{1-4}$	4	TS$_{4-5}$	5	TS$_{5-6}$	6
1	 **1a**	no	21.2	-2.9	21.0	-1.0	20.0	-26.3
2	 **1p**	yes	20.2	-2.4	18.3	-0.1	22.7	-24.5
2	 **1r**	yes	18.2	-3.3	18.6	-0.7	21.3	-25.5
3a	 **1t**	yes	19.8	-2.3	21.5	-1.9	22.3	-14.7
3b	 **1x**	yes	19.9	-3.5	20.1	-0.7	23.6	-17.2
1,2	 **1z**	yes	22.1	0.9	25.0	4.0	25.3	-20.0

(a)

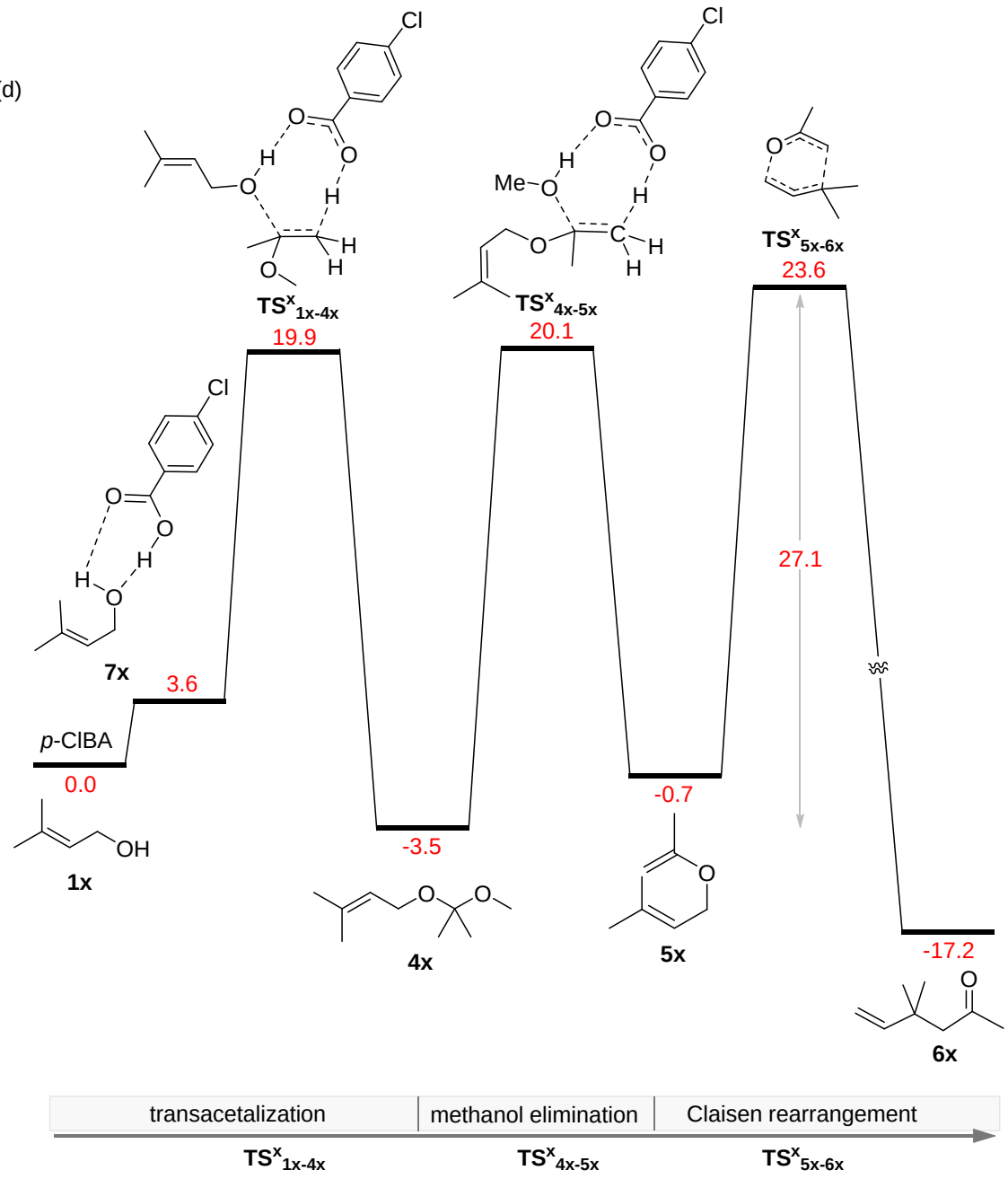

Cl
O
H
O
H
O
H
H
O
TS$^{p}_{1p-4p}$
20.2
Cl
O
H
O
Me
O
H
C
H
H
O
TS$^{p}_{4p-5p}$
18.3
Cl
O
O
H
H
O
7p
3.2
p-ClBA
0.0
OH
1p
-2.4
O
O
4p
-0.1
O
5p
TS$^{p}_{5p-6p}$
22.7
O
25.1
-24.5
O
6p
transacetalization
methanol elimination
Claisen rearrangement
TS$^{p}_{1p-4p}$
TS$^{p}_{4p-5p}$
TS$^{p}_{5p-6p}$


(b)
Cl
O
H
O
O
H
O
H
H
O
TS$^{r}_{1r-4r}$
18.2
Cl
O
O
H
H
O
7r
3.4
p-ClBA
0.0
OH
1r
-3.3
O
O
4r
Me
O
H
O
O
H
C
H
H
O
TS$^{r}_{4r-5r}$
18.6
-0.7
O
5r
O
TS$^{r}_{5r-6r}$
21.3
24.6
-25.5
O
6r
transacetalization
methanol elimination
Claisen rearrangement
TS$^{r}_{1r-4r}$
TS$^{r}_{4r-5r}$
TS$^{r}_{5r-6r}$

(c)


Cl
O
H
O
H
H
H
O
TS$^{t}_{1t-4t}$
19.8
Me
O
H
O
O
H
C
H
H
TS$^{t}_{4t-5t}$
21.5
O
TS$^{t}_{5t-6t}$
22.3
24.6
Cl
O
O
H
H
O
7t
3.8
p-ClBA
0.0
OH
1t
-2.3
4t
-1.9
O
5t
-14.7
O
6t
transacetalization
methanol elimination
Claisen rearrangement
TS$^{t}_{1t-4t}$
TS$^{t}_{4t-5t}$
TS$^{t}_{5t-6t}$

(d)


Cl
O
H
O
O
H
H
O
H
TS$^{x}_{1x-4x}$
19.9
Me
TS$^{x}_{4x-5x}$
20.1
TS$^{x}_{5x-6x}$
23.6
27.1
7x
3.6
p-ClBA
0.0
1x
OH
-3.5
4x
-0.7
5x
-17.2
6x
transacetalization
methanol elimination
Claisen rearrangement
TS$^{x}_{1x-4x}$
TS$^{x}_{4x-5x}$
TS$^{x}_{5x-6x}$

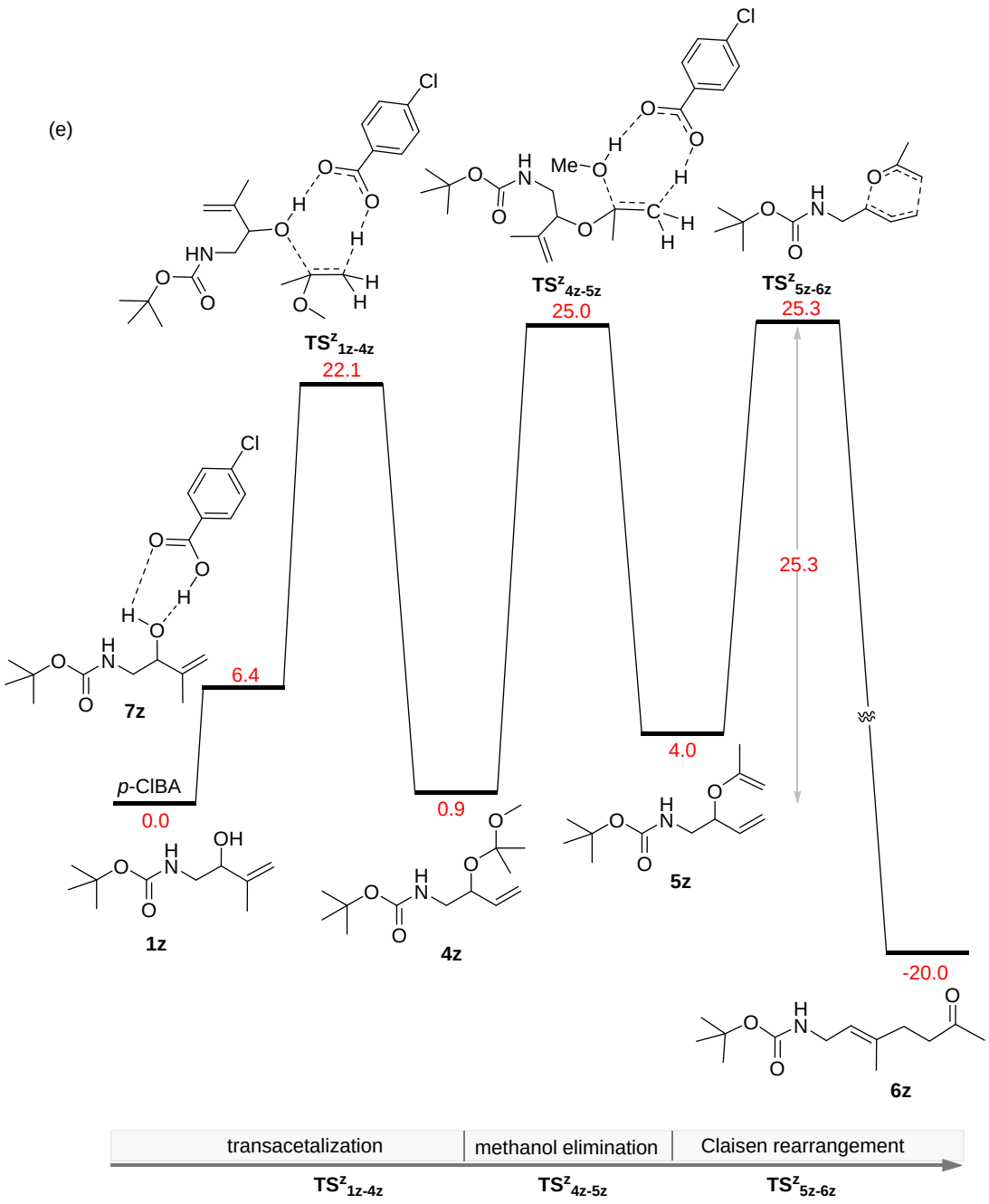


Figure S23. The calculated free energy profiles for the 4-Chlorobenzoic acid-catalyzed transetherification followed by Claisen rearrangement for substrates: **1p**, **1r**, **1t**, **1x**, and **1z** at 120 °C . 2-methoxypropene and the methanol side product are omitted for clarity but are included in the free energy calculations. The relative free energies are given in kcal/mol (in red).

5.4 The role of the acid catalyst in the rearrangement step

As it is unclear whether the acid catalyst participates in the last rearrangement step of the sequence, we performed a DFT study to investigate its effect of the activation energies. The DFT calculations on transition structures **TS**$^{a}_{5\text{-}6}$ and **TS**$^{p}_{5\text{-}6}$ revealed that the involvement of 4-chlorobenzoic acid (**3j**) does not lead to a decrease in the activation energy for the Claisen rearrangement (Figure S24).

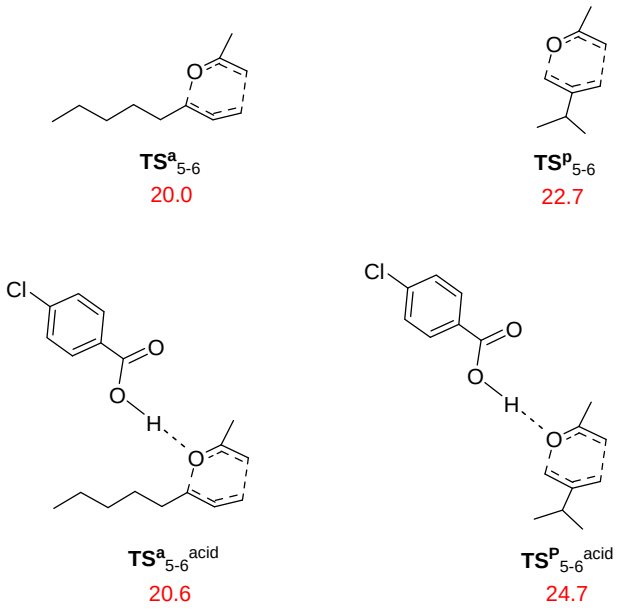
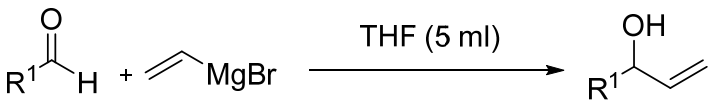


Figure S24. Comparison of the free energies for **TS**$^{a}_{5\text{-}6}$ and **TS**$^{p}_{5\text{-}6}$ with those involving 4-chlorobenzoic acid (**3j**) at 120 ˚C . The relative free energies are given in kcal/mol (in red).

6 Experimental details

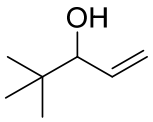
6.1 General procedure (GP1) for the preparation of R^3 substituted alcohols



*General procedure 1 (**GP1**):* A solution of vinylmagnesium bromide (1 M in THF, 1.20 equiv.) was dissolved in dry THF (10 mL) and cooled to 0 °C. After 15 min aldehyde (1

equiv.) in dry THF (5 mL) was added dropwise with stirring. Saturated aq. NH_4Cl (10 mL) was added, and the biphasic mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (30 mL), filtered and concentrated. The residue was purified by flash chromatography. The reaction times varied for each entry.

6.1.1 4,4-dimethylpent-1-en-3-ol (**1b**), TJB-1-066-2

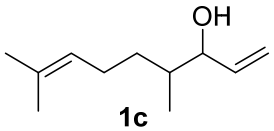


1b

Prepared according to **GP1**, using pivalaldehyde (2.00 g, 2.52 mL, 23.2 mmol). 4 h reaction time. The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 97:3) to give **1b** as a colourless oil (0.50 g, 4,18 mmol, 18 %). Spectral data corresponds to previously published data.[28]

R_f (EtOAc-Hex 10:90) = 0.32; IR (neat, ATR) ν_{max} 629, 777, 869, 920, 991, 1051, 1122, 1189, 1364, 1425, 1479, 1698, 2871, 2956, 3253; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (ddd, *J* = 17.2, 10.5, 6.7 Hz, 1H), 5.30 – 5.11 (m, 2H), 3.79 – 3.71 (m, 1H), 1.43 (d, *J* = 4.3 Hz, 1H), 0.92 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 138.2, 116.5, 81.3, 34.8, 25.8; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 130 °C isothermic): t_r = 1.29 min.

6.1.2 4,8-dimethylnona-1,7-dien-3-ol (**1c**), TJB-1-073



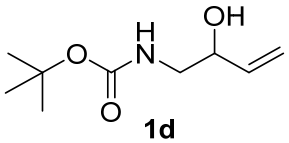
1c

Prepared according to **GP1**, using 2,6-dimethylhept-5-enal (2.00 g, 2.35 mL, 14.3 mmol). 6 h reaction time. The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 96:4) to give **1c** as a colourless oil (85:15 *E:Z*, 0.58 g, 3.43 mmol, 24 %). Spectral data corresponds to previously published data.[29]

R_f (EtOAc – Hex 10:90) = 0.40; IR (neat, ATR) ν_{max} 442, 920, 990, 1261, 1301, 1377, 1452, 1644, 2856, 2876, 1965, 3374; ^{1}H NMR (300 MHz, $CDCl_3$, *E*-isomer) δ 5.93 – 5.79 (m, 1H), 5.28 – 5.04 (m, 3H), 4.04 – 3.92 (m, 1H), 2.15 – 1.88 (m, 2H), 1.68 (s, 3H), 1.60 (d, *J* = 1.3

Hz, 3H), 1.58 – 1.48 (m, 1H), 1.43 (dd, *J* = 13.5, 4.4 Hz, 1H), 1.15 (dddd, *J* = 17.0, 14.1, 8.6, 5.4 Hz, 1H), 0.90 (d, *J* = 6.83 Hz, 3H, two overlapping dublets); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$, *E*-isomer) δf 139.3, 131.6, 124.7, 115.9, 115.3, 77.4, 38.3, 32.5, 25.8, 17.8, 14.9; In addition, the following diagnostic peaks were observed for the minor isomer: ^{1}H NMR (300 MHz, $CDCl_3$, *Z*-isomer) δ 4.68 (d, *J* = 7.9 H, 0.22H, corresponds to 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$, *Z*-isomer) δ 140.0, 115.3, 76.9, 38.2, 32.9, 25.7, 14.4 Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 2.39 min.

6.1.3 *tert*-Butyl (2-hydroxybut-3-en-1-yl)carbamate (**1d**) , TJB-074

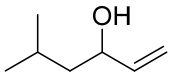


1d

Prepared according to **GP1**, using *N*-Boc-2-aminoacetaldehyde (0.50 g, 3.14 mmol). 6 h reaction time. The residue was purified by flash chromatography (gradient hex-EtOAc 100:0 to 82:18) to give **1d** as a colourless oil (0.30 g, 1.60 mmol, 51 %). Spectral data corresponds to previously published data.[30]

R_f (EtOAc – Hex 50:50) = 0.46; IR (neat, ATR) ν_{max} 438, 553, 658, 918, 948, 1167, 1249, 1528, 1679, 2933, 2979, 3011, 3331; ^{1}H NMR (300 MHz, d6-DMSO) δ 6.65 (s, 1H), 5.88 – 5.72 (m, 1H), 5.26 – 5.12 (m, 1H), 5.04 (d, *J* = 10.4 Hz, 1H), 4.91 (d, *J* = 5.1 Hz, 1H), 3.96 (t, *J* = 6.0 Hz, 1H), 3.32 (s, 1H), 3.03 – 2.81 (m, 2H), 1.37 (s, 9H); $^{13}C\{^{1}H\}$ NMR (75 MHz, d6-DMSO) δ 155.6, 140.0, 114.4, 77.5, 70.3, 46.1, 28.2.

6.1.4 5-methylhex-1-en-3-ol (**1e**) , TJB-1-072

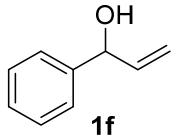


1e

Prepared according to **GP1**, using isobutyraldehyde (2.00 g, 2.55 mL, 23.2 mmol). 1.5 h reaction time. The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 93:7) to give **1e** as a colourless oil (2.30 g, 20.2 mmol, 87 %). Spectral data corresponds to previously published data.[31]

R_f (EtOAc – Hex 20:80) = 0.51; IR (neat, ATR) ν_{max} 549, 606, 841, 919, 988, 1093, 1152, 1384, 1468, 1644, 2870, 2923, 3341; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (ddd, *J* = 16.9, 10.4, 6.3 Hz, 1H), 5.23 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.09 (dt, *J* = 10.4, 1.4 Hz, 1H), 4.17 (p, *J* = 5.6 Hz, 1H), 1.85 – 1.66 (m, 1H), 1.58 – 1.27 (m, 3H), 0.93 (dd, *J* = 6.6, 1.7 Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 141.8, 114.5, 71.7, 46.4, 24.7, 23.2, 22.5; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 130 °C isothermic): t_r = 1.13 min.

6.1.5 1-phenylprop-2-en-1-ol (**1f**) , TJB-1-062

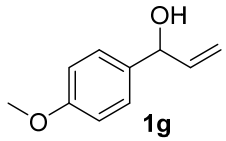


1f

Prepared according to **GP1**, using benzaldehyde (2.00 g, 1.91 mL, 18.9 mmol). 3 h reaction time. The residue was purified by flash chromatography (gradient hex-EtOAc 100:0 to 97:3) to give **1f** as a colourless oil (1.50 g, 11.3 mmol, 60 %). Spectral data corresponds to previously published data.[32]

R_f = (EtOAc-Hex 10:90) = 0.20; IR (neat, ATR) ν_{max} 522, 698, 760, 833, 925, 988, 1023, 1074, 1194, 1452, 1723, 2871, 3029, 3357; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.28 (m, 5H), 6.07 (ddd, *J* = 16.7, 10.5, 6.0 Hz, 1H), 5.36 (d, *J* = 17.4 Hz, 1H), 5.28 – 5.14 (m, 2H), 1.95 (d, *J* = 3.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, CDCl3) δ 142.7, 140.4, 128.7, 127.9, 126.5, 115.2, 75.5; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 2.07 min.

6.1.6 1-(4-methoxyphenyl)prop-2-en-1-ol (**1g**), TJB-1-067

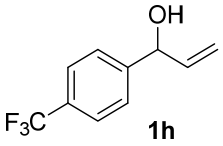


1g

Prepared according to **GP1**, using anisaldehyde (2.00 g, 1.79 mL, 14.7 mmol). 3 h reaction time. The residue was purified by flash chromatography (gradient hexanes-EtOAc 100:0 to 95.5:4.5) to give **1g** as a colourless oil (1.80 g, 1.36 mmol, 75 %). Spectral data corresponds to previously published data.[33]

R_f = (EtOAc-Hex 20:80) = 0.28; IR (neat, ATR) ν_{max} 540, 636, 777, 829, 923, 988, 1031, 1104, 1172, 1198, 1243, 1509, 2835, 2976, 3383; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.05 (ddd, *J* = 17.1, 10.3, 6.0 Hz, 1H), 5.40 – 5.28 (m, 1H), 5.18 (dt, *J* = 10.3, 1.4 Hz, 2H), 3.80 (s, 3H), 2.03 (d, *J* = 3.4 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.3, 140.5, 135.0, 127.8, 114.8, 114.1, 75.0, 55.4; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 3.70 min.

6.1.7 1-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (**1h**), TJB-089

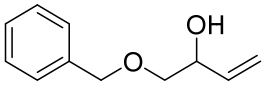


1h

Prepared according to **GP1**, using 4-(trifluoromethyl)benzaldehyde (1.00 g, 0.78 mL, 5.74 mmol). 4 h reaction time. No purification needed to give **1h** as a yellow oil (1.16 g, 5.74 mmol, 100 %). Spectral data corresponds to previously published data.[29]

R_f (EtOAc – Hex 20:80) = 0.68; IR (neat, ATR) ν_{max} 516, 825, 929, 988, 1039, 1066, 1119, 1162, 1322, 1418, 2885, 3333; ^{1}H NMR (500 MHz, DMSO) δ 7.68 (d, *J* = 8.1 Hz, 2H), 7.58 – 7.52 (m, 2H), 5.94 (ddd, *J* = 17.1, 10.3, 5.9 Hz, 1H), 5.71 (d, *J* = 4.5 Hz, 1H), 5.29 (dt, *J* = 17.1, 1.7 Hz, 1H), 5.17 (t, *J* = 5.2 Hz, 1H), 5.09 (dt, *J* = 10.3, 1.6 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, DMSO) δ 148.9, 141.3, 127.5 (q, $^2J_{C\text{-}F}$ = 31.9 Hz), 126.8, 124.9 (unresolved q), 124.2 (q, $^1J_{C\text{-}F}$ = 272.5 Hz) 114.1, 72.8; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 2.13 min.

6.1.8 1-(benzyloxy)but-3-en-2-ol (**1i**), TJB-1-075



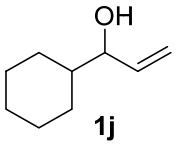
1i

Prepared according to **GP1**, using benzyloxyacetaldehyde (0.50 g, 0.47 mL, 3.33 mmol). 1.5 h reaction time The residue was purified by flash chromatography (gradient hex-

EtOAc 100:0 to 88:12) to give **1i as** a colourless oil (0.22 g, 1.23 mmol, 37 %). Spectral data corresponds to previously published data.[34]

R_f (EtOAc – Hex 20:80) = 0.37; IR (neat, ATR) ν_{max} 459, 697, 735, 990, 1027, 1101, 1206, 1453, 1736, 2859, 2982, 3030, 3064, 3419; ^{1}H NMR (300 MHz, d6-DMSO) δ 7.40 – 7.23 (m, 7H), 5.87 (ddd, *J* = 17.3, 10.5, 5.1 Hz, 1H), 5.25 (dt, *J* = 17.3, 1.9 Hz, 1H), 5.11 – 5.03 (m, 1H), 4.97 (d, *J* = 5.0 Hz, 1H), 4.50 (s, 3H), 4.16 (t, *J* = 5.5 Hz, 1H), 3.38 – 3.30 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, d6-DMSO) δ 177.0, 176.2, 165.8, 165.1, 165.0, 152.2, 111.9, 109.8, 107.7; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 3.80 min.

6.1.9 1-cyclohexylprop-2-en-1-ol **(1j**), TJB-1-080

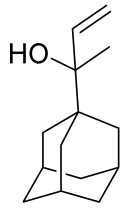


1j

Prepared according to **GP1**, using cyclohexanecarboxaldehyde (2.00 g, 2.16 mL, 17.8 mmol). 1 h reaction time. The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 98:2) to give **1j** as a colourless oil (0.72 g, 5.35mmol, 30 %). Spectral data corresponds to previously published data.[29]

R_f (EtOAc – Hex 10:90) = 0.40; IR (neat, ATR) ν_{max} 728, 892, 918, 991, 1018. 1051, 1424, 1449, 2852, 2921, 3371; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (ddd, *J* = 17.1, 10.4, 6.6 Hz, 1H), 5.26 – 5.10 (m, 2H), 3.85 (q, *J* = 5.8 Hz, 1H), 1.89 – 1.61 (m, 6H), 1.43 (dd, *J* = 12.8, 5.2 Hz, 2H), 1.28 – 1.14 (m, 3H), 1.01 (ddd, *J* = 12.2, 9.7, 5.9 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 140.0, 115.6, 77.9, 43.7, 28.9, 28.5, 26.7, 26.3, 26.2, Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 2.00 min.

6.1.10 2-((3r,5r,7r)-adamantan-1-yl)but-3-en-2-ol (**1n**), TJB-1-130

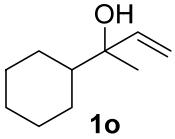


1n

Prepared according to **GP1**, using 1-adamantyl methyl ketone (1.00 g, 5.61 mmol). 24 h Reaction time. The residue was purified by flash chromatography (gradient hexane-EtOAc 100:0 to 90:10) to give **1n** as a colourless oil (0.90 g, 4.38 mmol, 78 %). Spectral data corresponds to previously published data.[35]

*R*f (EtOAc-hexane 20:80): 0.50; IR (neat, ATR) ν_{max} 501, 680, 703, 916, 999, 1102, 1119, 1344, 1360, 1450, 2848 2902, 2978, 3484; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (dd, *J* = 17.3, 10.9 Hz, 1H), 5.24 – 5.05 (m, 2H), 1.99 (s, 3H), 1.72 – 1.58 (m, 12H), 1.32 (s, 1H), 1.19 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 143.0, 112.4, 77.3, 38.8, 37.2, 36.5, 28.8, 22.3.

6.1.11 2-cyclohexylbut-3-en-2-ol (**1o**), TJB-1-132



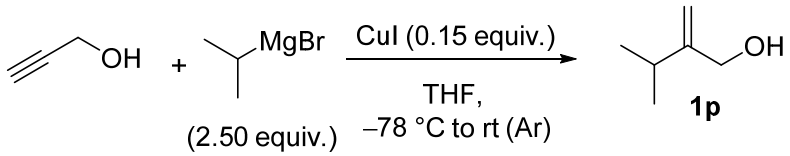
1o

Prepared according to **GP1**, using acetylcyclohexane (1.00 g, 1.09 mL, 7.92 mmol). 6h reaction time. The residue was purified by flash chromatography (gradient hexane-EtOAc 100:0 to 90:10) to give **1o** as a colourless oil (1.04 g, 6.73 mmol, 85 %). Spectral data corresponds to previously published data.[36]

*R*f (EtOAc-hexane 15:85): 0.41: IR (neat, ATR) ν_{max} 496, 694, 892, 917, 996, 1128, 1292, 1450, 2853, 2924, 3425; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.23 – 5.03 (m, 2H), 1.88 – 1.71 (m, 4H), 1.66 (d, *J* = 10.9 Hz, 1H), 1.39 – 1.27 (m, 2H), 1.23 (s, 3H), 1.21 – 0.88 (m, 4H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 144.6, 112.0, 75.4, 48.2, 27.6, 27.2, 26.8, 26.7, 26.6, 25.3.

6.2 Synthesis of R^1 and R^2 substituted alcohol substrates (classes 2 and 3)

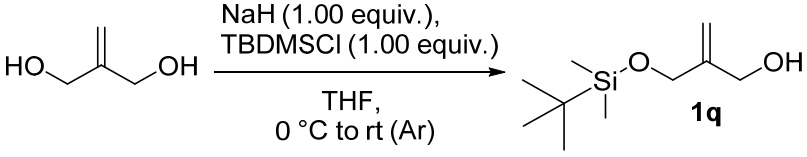
6.2.1 3-methyl-2-methylene-1-butanol (**1p**), class 2, TJB-1-100



To a cooled mixture (–78 °C) of propargyl alcohol (1.0 g, 17.8 mmol, 1.00 equiv.) and copper iodide (509 mg, 2.7 mmol, 0.15 equiv.) in THF (50 mL) was added isopropylmagnesium bromide (14.9 mL, 3.00 M in THF, 44.6 mmol, 2.50 equiv.) dropwise with stirring. The reaction mixture was allowed to warm to rt and stirred for 24 h. Saturated aq. NH_4Cl (20 mL) was then added at 0 °C and the biphasic mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated using argon flow. The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 80:20) to give **1p** as a colourless oil (663 mg, 6.60 mmol, 37 %). Spectral data corresponds to previously published data.[37]

*R*f (EtOAc-hexane 50:50): 0.7; I IR (neat, ATR) ν_{max} R (film, cm^{-1}): 696, 747, 895, 1026, 1462, 1650, 2872, 2961, 3318; ^{1}H NMR (300 MHz, d6-DMSO) δ 4.92 (s, 1H), 4.79 – 4.74 (m, 1H), 4.70 (t, *J* = 5.6 Hz, 1H), 3.91 (d, *J* = 5.6 Hz, 2H), 3.29 (s, 2H), 2.24 (p, *J* = 6.7 Hz, 1H), 1.00 (d, *J* = 6.9 Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, d6-DMSO) δ 155.6, 105.5, 62.7, 30.1, 21.6; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 130 °C isothermic): t_r = 2.06 min.

6.2.2 2-(((tert-butyldimethylsilyl)oxy)methyl)prop-2-en-1-ol (**1q**), class 2, TJB-1-121

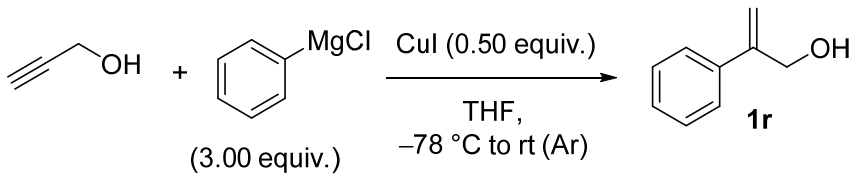


Sodium hydride (0.40 g, 60% dispersion in mineral oil, 10.0 mmol, 1.00 equiv.) and THF (30 mL) were added to 100 mL two-neck round bottom flask under argon atmosphere.

The reaction mixture was cooled to 0 °C and 2-methylenepropane-1,3-diol (0.88 g, 10.0 mmol, 1.00 equiv.) was added dropwise with stirring. The reaction mixture was allowed to warm to rt and stirred for 1 h. To this solution, tert-butyldimethylsilyl chloride (1.50 g, 10.0 mmol, 1.00 equiv.) was added in one portion and the mixture was stirred for additional 2 h. H_2O (10 mL) was added and the biphasic mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 90:10) to give **1q** as a colourless oil (1.25 g, 6.20 mmol, 62 %). Spectral data corresponds to previously published data.[37]

*R*f (EtOAc-hexane 20:80): 0.46; IR (neat, ATR) ν_{max} 562, 774, 833, 1080, 1253, 1389, 1472, 2856, 2929, 2955, 3339; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 (d, *J* = 4.7 Hz, 2H), 4.25 (s, 2H), 4.17 (d, *J* = 6.0 Hz, 2H), 1.92 (t, *J* = 6.0 Hz, 1H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 147.7, 111.2, 65.3, 64.9, 26.0, 18.4, –5.3; Retention time was measured with GC (SUPELCO Astec CHIRALDEX B-DM column, isoflow He: 1.806 mL/min, 130 °C isothermic): t_r = 4.17 min.

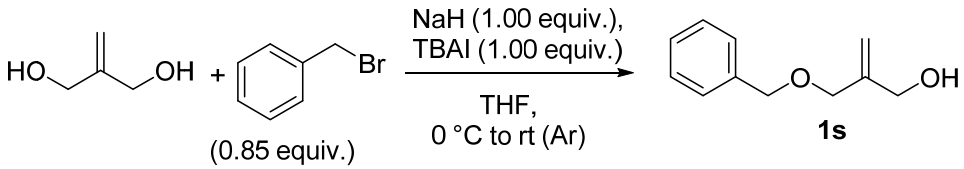
6.2.3 2-phenylprop-2-en-1-ol (**1r**), class 2, TJB-1-126



To a cooled mixture (–78 °C) of propargyl alcohol (1.00 g, 17.8 mmol, 1.00 equiv.) and copper iodide (1.70 g, 8.90 mmol, 0.50 equiv.) in toluene (50 mL) was added phenylmagnesium chloride (27.0 mL, 2.00 M in THF, 53.5 mmol, 3.00 equiv.) dropwise with stirring. The reaction mixture was allowed to warm to rt and stirred for 3.5 h. Saturated aq. NH_4Cl (20 mL) was then added at 0 °C and the biphasic mixture was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient hexane-EtOAc 100:0 to 85:15) to give **1r** as a colourless oil (1.71 g, 12.8 mmol, 72 %). Spectral data corresponds to previously published data. [38]

*R*f (EtOAc-hexane 30:70): 0.71; IR (neat, ATR) ν_{max} 536, 610, 705, 778, 901, 1024, 1111, 1242, 1495, 1736, 2871, 3056, 3334; ^{1}H NMR (300 MHz, DMSO) δ 7.49 – 7.41 (m, 2H), 7.39 – 7.24 (m, 3H), 5.44 (s, 1H), 5.33 (s, 1H), 5.03 (t, *J* = 5.5 Hz, 1H), 4.34 (d, *J* = 5.6 Hz, 2H), 1.61 (s, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 147.6, 138.7, 128.3, 127.5, 125.7, 111.0, 62.6; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 1.95 min.

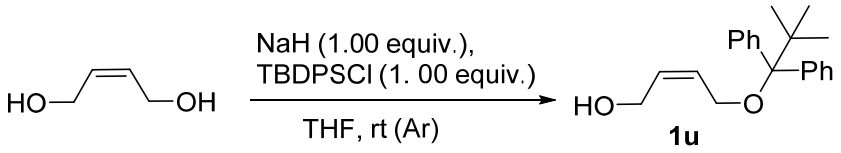
6.2.4 2-((benzyloxy)methyl)prop-2-en-1-ol (**1s**), class 2, TJB-1-006



NaH (90.8 mg, 60 % suspension in mineral oil, 2.27 mmol, 1.00 equiv.) in dry THF (8 mL) was cooled to 0 °C. The mixture of 2-methylenepropane-1,3-diol (0.20 g, 2.27 mmol, 1 equiv.) in THF (10 mL) was then added to dropwise over 15 min resulting in gas release. The mixture was stirred at 0 °C for 30 min and at rt for additional 15 min. TBAI (40.6 mg, 2.27 mmol, 1.00 equiv.) was then added followed by addition of benzyl bromide (0.23 mL, 1.93 mmol, 0.85 equiv.). Stirring was continued at rt for 3 h. The reaction was quenched by cautious addition of water (10 mL) and NH_4Cl (10 mL), extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient hexane-EtOAc 100:0 to 85:15) to give **1s** as a colourless oil (0.14 g, 0.77 mmol, 34 %). Spectral data corresponds to previously published data.[37]

*R*f (EtOAc-hexane 3:7): 0.54; IR (neat, ATR) ν_{max} 607, 697, 735, 909, 1026, 1063, 1205, 1363, 1496, 2857, 3030, 3374; ^{1}H NMR (300 MHz, CD_3CN) δ 7.42 – 7.25 (m, 5H), 5.15 (dq, *J* = 2.3, 0.8 Hz, 1H), 5.10 (dt, *J* = 2.2, 1.2 Hz, 1H), 4.48 (s, 2H), 4.09 – 4.01 (m, 4H), 2.81 (t, *J* = 5.8 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 186.3, 179.2, 169.7, 169.0, 154.7, 113.6, 113.0, 105.7. Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 3.94 min.

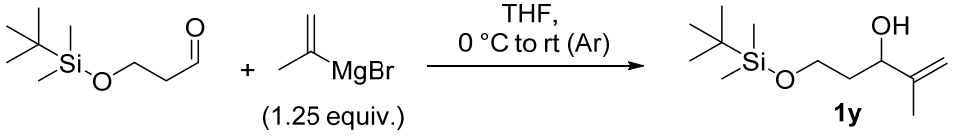
6.2.5 (Z)-4-((tert-butyldiphenylsilyl)oxy)but-2-en-1-ol (**1u**), class 3a, TJB-1-142



Sodium hydride (0.22 g, 60% dispersion in mineral oil, 5.67 mmol, 1.00 equiv.) and THF (12 mL) were added to 50 mL two-neck round bottom flask under argon atmosphere. cis-but-2-ene-1,4-diol (0.50 g, 5.67 mmol, 1.00 equiv.) was added dropwise with stirring. The reaction mixture was stirred for 1 h at rt. To this solution, TBDPSCl (1.48 mL, 5.67 mmol, 1.00 equiv.) was added dropwise and the mixture was stirred for additional 2 h. H_2O (10 mL) was then added and the biphasic mixture was extracted with EtOAc (4 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient hexane-EtOAc 100:0 to 92:8) to give **1u** as a colourless oil (1.74 g, 5.33 mmol, 94 %). Spectral data corresponds to previously published data.[39]

*R*f (EtOAc-hexane 30:70): 0.42; IR (neat, ATR) ν_{max} 488, 612, 699, 822, 1027, 1072, 1107, 1427, 2857, 2930, 2958, 3345; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 7.7, 1.8 Hz, 4H), 7.42 (dtt, *J* = 7.4, 6.0, 4.2 Hz, 6H), 5.80 – 5.57 (m, 2H), 4.27 (d, *J* = 5.2 Hz, 2H), 4.02 (t, *J* = 5.9 Hz, 2H), 1.52 (t, *J* = 5.9 Hz, 1H), 1.06 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 135.7, 133.6, 131.1, 130.1, 129.9, 127.9, 60.4, 58.9, 26.9, 19.2.

6.2.6 5-((tert-butyldimethylsilyl)oxy)-2-methylpent-1-en-3-ol (**1y**), class 1,2, TJB-1-138

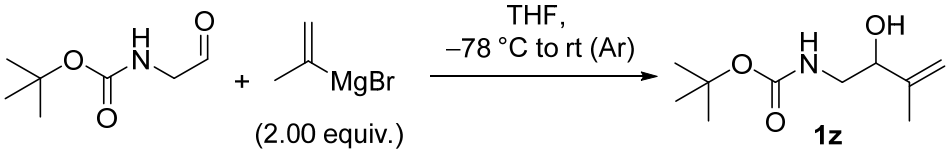


Isopropenylmagnesium bromide (9.29 mL, 4.65 mmol, 0.50 M in THF, 1.25 equiv.) was cooled to 0 °C. 3-((tert-butyldimethylsilyl)oxy)propanal (0.70 mg, 3,72 mmol, 1 equiv.) in dry THF (8 mL) was added dropwise with stirring through dropping funnel. Reaction was allowed to warm to rt and stirred for 3 h. Saturated aq. NH_4Cl (10 mL) was then added and the biphasic mixture was extracted with Et_2O (4 × 30 mL). The combined organic

layers were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography on alumina (gradient pentane/diethyl ether 100:0 to 97.7:2.5) to give **1y** as a colourless oil (0.46 g, 1.97 mmol, 53 %). Spectral data corresponds to previously published data.[40]

*R*f (EtOAc-hexane 20:80): 0.67; IR (neat, ATR) ν_{max} 540, 664, 731, 773, 831, 1005, 1083, 1253, 1361, 1389, 1462, 1471, 2857, 2885, 2929, 2953, 3369; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 – 5.00 (m, 1H), 4.85 (s, 1H), 4.30 – 4.22 (m, 1H), 3.92 – 3.74 (m, 2H), 3.26 (d, *J* = 3.3 Hz, 1H), 1.82 – 1.71 (m, 5H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 147.3, 110.5, 75.3, 62.3, 37.0, 26.0, 18.5, 18.3, -5.4, -5.4.

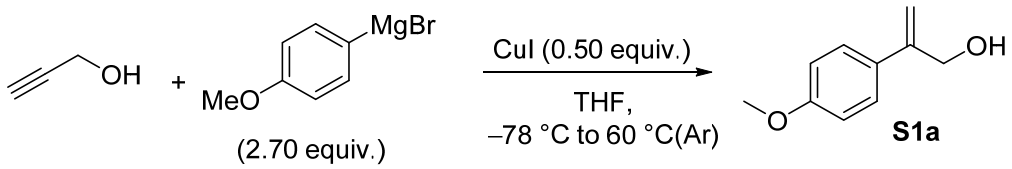
6.2.7 Tert-butyl (2-hydroxy-3-methylbut-3-en-1-yl)carbamate (**1z**), class 1,2, TJB-1-145



Isopropenylmagnesium bromide (12.6 mL, 0.50 M in THF, 6.25 mmol, 2.00 equiv.) was cooled to –78 °C. *tert*-butyl (2-oxoethyl)carbamate (0.50 g, 3.14 mmol, 1.00 equiv.) in dry THF (10 mL) was added dropwise through dropping funnel with stirring. The cooling bath was removed and the resulting mixture was allowed to warm to rt and stirred for 5 h. Saturated aq. NH_4Cl (10 mL) was added and the biphasic mixture was extracted with Et_2O (4 x 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient hex-EtOAc 100:0 to 75:25) to give **1z** as a colourless oil (0.56 g, 2.76 mmol, 88 %).

*R*f (EtOAc/*n*-hexane 50:50): 0.54; IR (neat, ATR) ν_{max} 519, 548, 780, 1045, 1101, 1167, 1242, 1366, 1452, 1509, 1691, 1740, 2870, 2933, 2977, 3400; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (d, *J* = 1.7 Hz, 1H), 4.92 (d, *J* = 2.0 Hz, 1H), 4.90 (s, 1H), 4.17 – 4.11 (m, 1H), 3.39 (ddd, *J* = 14.3, 6.8, 3.5 Hz, 1H), 3.16 – 3.08 (m, 1H), 2.59 (s, 1H), 1.74 (s, 3H), 1.44 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.0, 145.2, 111.8, 79.8, 75.1, 45.2, 28.5, 18.8; HRMS (ESI^+): m/z calcd for $[M+Na]^+$ = 224.1257 mDa, found 224.1251, Δ = – 2.63 ppm.

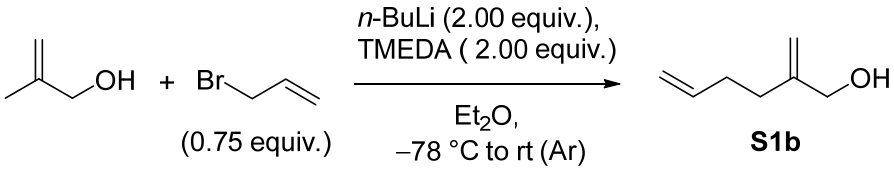
6.2.8 2-(4-methoxyphenyl)prop-2-en-1-ol (**S1a**), class 2, TJB-1-012



The mixture of propargyl alcohol (1.00 g, 17.8 mmol, 1.00 equiv.) and copper iodide (1.29 g, 8.90 mmol, 0.50 equiv.) in THF (40 mL) was stirred at 0 °C for 30 min. (4-methoxyphenyl)magnesium bromide (48.0 mL of 1 M solution, 48.2 mmol, 2.70 equiv.) was then added dropwise. The resulting mixture was heated to reflux (60 °C bath temperature) and maintained at that temperature for 3 h and then allowed to cool to rt. Saturated aq. NH_4Cl (20 mL) was added and the biphasic mixture was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient hexane-EtOAc 100:0 to 92:8) to give **S1a** as a yellow solid (1.70 g, 10.3 mmol, 58 %). Spectral data corresponds to previously published data.[41]

mp 66–68 °C; *R*f (EtOAc-hexane 50:50): 0.57; IR (neat, ATR) ν_{max} 476, 569, 836, 896, 1026, 1106, 1184, 1247, 1439, 1511, 1606, 2839, 2915, 3322; ^{1}H NMR (300 MHz, DMSO) δ 7.39 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 5.34 (m, 1H), 5.24 – 5.18 (m, 1H), 4.99 (t, *J* = 5.5 Hz, 1H), 4.29 (d, *J* = 5.5 Hz, 2H), 3.75 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO) δ 158.8, 146.9, 131.0, 126.8, 113.7, 109.2, 62.6, 55.1. Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 3.98 min.

6.2.9 2-methylenehex-5-en-1-ol (**S1b**), class 2, TJB-1-016

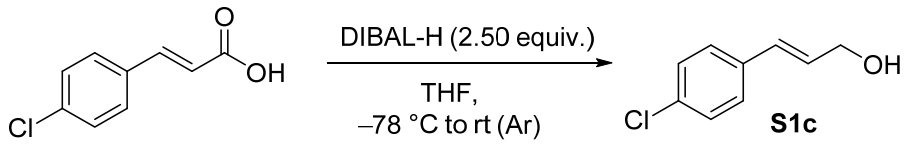


Dry diethyl ether (15 mL) was cooled to 0 °C followed by addition of *n*-BuLi (7.26 mL of 1.91 M solution, 13.9 mmol, 2.00 equiv.). After mixing for 10 min TMEDA (2.07 mL, 13.9 mmol, 2.00 equiv.) was added with stirring. After 15 min the mixture was cooled to –78

°C followed by addition of methallyl alcohol (0.58 mL, 6.93 mmol, 1.00 equiv.). The mixture was allowed to warm up to rt and stirred for 24 h. The yellow suspension was again cooled to –78 °C followed by dropwise addition of allyl bromide (0.45 mL, 5.20 mmol, 0.75 equiv.) with stirring. After stirring 1 h at –78 °C the cooling bath was removed, and the mixture was further stirred at rt for additional 21 h. Saturated aq. NH_4Cl (10 mL) was added and the biphasic mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with water (2 × 10 mL), saturated aq. $CuSO_4$ solution (2 × 20 mL) and brine (20 mL), dried (Na_2SO_4), filtered and concentrated under argon flow. The residue was purified by flash chromatography (gradient hexane-EtOAc 100:0 to 95:5) to give **S1b** as a colourless oil (0.20 g, 1.73 mmol, 25 %). Spectral data corresponds to previously published data.[42]

*R*f (EtOAc-hexane 30:70): 0.51; IR (neat, ATR) ν_{max} 560, 636, 698, 898, 1025, 1102, 1186, 1219, 1384, 1450, 1641, 2925, 3077, 3325; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 – 5.75 (m, 1H), 5.10 – 4.88 (m, 4H), 4.09 (d, *J* = 6.1 Hz, 2H), 2.31 – 2.11 (m, 4H), 1.35 (t, *J* = 6.2 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 148.5, 138.3, 115.0, 109.8, 66.1, 32.4, 32.1; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 1.30 min.

6.2.10 (*E*)-3-(4-chlorophenyl)prop-2-en-1-ol (**S1c**), class 3a, TJB-1-030

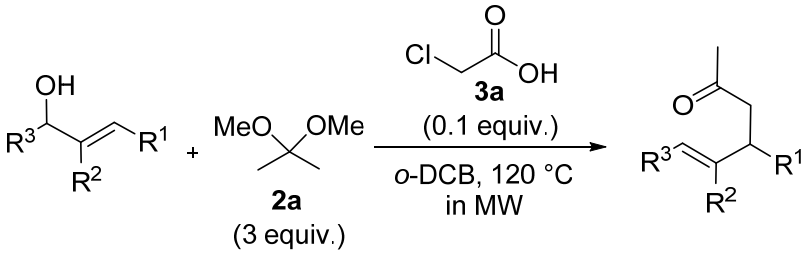


To a solution of (*E*)-3-(4-chlorophenyl)acrylic acid (913 mg, 5.00 mmol, 1.00 equiv.) in anhydrous THF (30 mL) under an atmosphere of argon at –78 °C was added dropwise, with stirring, a solution of DIBAL-H in hexanes (12.5 mL of 1 M solution, 12.5 mmol, 2.50 equiv.), and the resulting solution was stirred at this temperature for 5 h. The reaction was quenched at –78 °C by dropwise addition of ethyl acetate (15 mL) with vigorous strirring. The mixture was allowed to warm to rt. A solution of sat. NaK-tartate (20 mL) was added, and the resulting suspension was stirred for an additional 20 min to allow the suspension to resolve. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified

by flash chromatography (gradient hexane-EtOAc 100:0 to 80:20) to give **S1c** as a white solid (0.27 g, 1.60 mmol, 32 %). Spectral data corresponds to previously published data.[43]

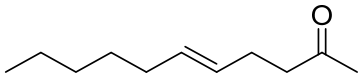
mp 56–58 °C (lit. 54–56 °C)[44]; *R*f (EtOAc-hexane 50:50): 0.41; IR (neat, ATR) ν_{max} 445, 504, 778, 798, 842, 972, 1009, 1087, 1403, 1454, 1487, 1591, 2873, 2927, 3238; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.39 – 7.25 (m, 4H), 6.64 – 6.52 (m, 1H), 6.35 (dt, *J* = 15.9, 5.4 Hz, 1H), 4.33 – 4.25 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2) δ 136.0, 133.5, 130.3, 129.5, 129.1, 128.1, 63.7; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 4.24 min.

6.3 General procedure (GP2) for the synthesis of ketones via Claisen rearrangement (initial studies)



*General procedure 2 (**GP2**):* Allylic alcohol (limiting reagent, 0.39 mmol, 1.00 equiv.), 2,2-dimethoxypropene **2a** (1.17 mmol, 3.00 equiv) and chloroacetic acid **3a** (0.039 mmol, 0.10 equiv.) in 1,2-dichlorobenzene (1 mL) was heated at 120 °C in microwave oven (CEM Discovery-S) for 4 h. The reactions were carried out in sealed reaction vessels and the temperature was monitored with an external sensor. The sensor temperature was maintained at 120 °C throughout the reaction. After 4 hours the reaction mixture was allowed to cool to rt, saturated aq. $NaHCO_3$ (2 mL) was added and the biphasic mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. *o*-dichlorobenzene was removed in the purification step.

6.3.1 undec-5-en-2-one (**6a**), TJB-1-019

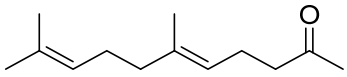


6a

Prepared with **GP2** using **1a** (50.0 mg, 0.39 mmol). The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 97:3) to give **6a** as a colourless oil (44.0 mg, 0.26 mmol, 67 %). Spectral data corresponds to previously published data.[45]

R_f (EtOAc-hexane 20:80) = 0.61; IR (neat, ATR) ν_{max} 536, 698, 968, 1046, 1160, 1226, 1358, 1411, 1439, 1456, 1717, 2855, 2924, 2957; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51 – 5.30 (m, 2H), 2.48 (t, *J* = 7.4 Hz, 2H), 2.32 – 2.19 (m, 2H), 2.13 (s, 3H), 1.95 (q, *J* = 6.5 Hz, 2H), 1.40 – 1.16 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 208.7, 131.8, 128.3, 43.8, 32.6, 31.5, 30.1, 29.3, 27.0, 22.7, 14.2; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 2.61 min.

6.3.2 (*E/Z*)-6,10-dimethylundeca-5,9-dien-2-one (**6m**), TJB-1-018

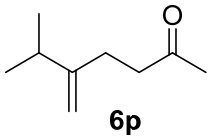


6m

Prepared with **GP2** using linalool (60.2 mg, 0.39 mmol). The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 95:5) to give **6m** as a colourless oil and a mixture of *E* and *Z*-isomers (40:60 *Z:E,* 35 mg, 0.17 mmol, 44 %). Spectral data corresponds to previously published data.[46]

R_f (EtOAc-hexane 20:80) = 0.61; IR (neat, ATR) ν_{max} 522, 581, 827, 984, 1158, 1357, 1440, 1716, 2856, 2916, 2966; ^{1}H NMR (300 MHz, $CDCl_3$, *E*-isomer) δ 5.14 – 5.03 (m, 2H), 2.45 (td, *J* = 7.5, 4.0 Hz, 2H), 2.32 – 2.21 (m, 2H), 2.13 (d, *J* = 0.7 Hz, 3H), 2.09 – 1.93 (m, 4H), 1.68-1.60 (four partially overlapping br s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, *E*-isomer) δ 208.9, 136.5, 131.5, 124.3, 122.7, 43.9. 39.8, 30.1, 26.8, 25.8, 22.6, 17.8, 16.1; In addition, following diagnostic peaks were observed for the *Z*-isomer: $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, *Z*-isomer) δ 208.9, 136.6, 131.8, 123.5, 44.2, 42.2, 32.0, 30.0, 26.7, 25.8, 23.5, 22.5, 17.8; GC: (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r (minor) = 3.22 min and t_r (major) = 3.43 min.

6.3.3 6-methyl-5-methyleneheptan-2-one (**6p**), TJB-1-017

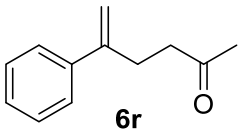


6p

Prepared with **GP2** using **1p** (39.1 mg, 0.39 mmol). The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 95:5) to give **6p** as a colourless oil (32 mg, 0.22 mmol, 57 %). Spectral data corresponds to previously published data.[47]

R_f (EtOAc-hexane 10:90) = 0.6; IR (neat, ATR) ν_{max} 540, 684, 888, 1161, 1280, 1322, 1716, 2873, 2962; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (d, *J* = 1.0 Hz, 1H), 4.63 (d, *J* = 1.4 Hz, 1H), 2.58 (dd, *J* = 9.1, 6.2 Hz, 2H), 2.35 – 2.19 (m, 3H), 2.16 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 208.6, 154.7, 106.7, 42.4, 34.4, 30.0, 28.0, 21.9; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 1.69 min.

6.3.4 5-phenylhex-5-en-2-one (**6r**) , TJB-1-005

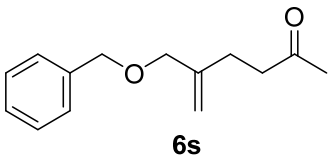


6r

Prepared with **GP2** using **1r** (52.3 mg, 0.39 mmol). The residue was purified by flash chromatography (gradient hexane-EtOAc 100:0 to 97.5:2.5) to give **6r** as a colourless oil (58.4 mg, 0.34 mmol, 86 %). Spectral data corresponds to previously published data.[48]

R_f (EtOAc-hexane 20:80) = 0.5; IR (neat, ATR) ν_{max} 525, 703, 778, 895, 1027, 1159, 1259, 1357, 1443, 1494, 1627, 1714, 2961, 3081; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H), 5.29 (dd, *J* = 1.2, 0.6 Hz, 1H), 5.07 (d, *J* = 1.3 Hz, 1H), 2.84 – 2.75 (m, 2H), 2.59 (dd, *J* = 8.7, 6.5 Hz, 2H), 2.12 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 208.2, 147.4, 140.8, 128.6, 127.7, 126.2, 112.9, 42.6, 30.2, 29.4; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 3.26 min.

6.3.5 5-((benzyloxy)methyl)hex-5-en-2-one (**6s**), TJB-1-015-2

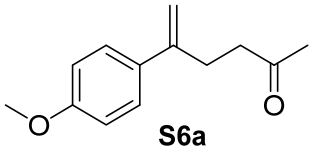


6s

Prepared with **GP2** using **1s** (69.5 mg, 0.39 mmol). The residue was purified by flash chromatography (gradient hex-EtOAc 100:0 to 90:10) to give **6s** as a colourless oil (64 mg, 0.29 mmol, 75 %). Spectral data corresponds to previously published data.[49]

R_f (EtOAc-hexane 20:80) = 0.45; IR (neat, ATR) ν_{max} 461, 541, 697, 736, 904, 1028, 1072, 1092, 1159, 1205, 1310, 1496, 1652, 1714, 2855, 2922, 3030, 3064; ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 5H), 5.06 (s, 1H), 4.90 (s, 1H), 4.47 (s, 2H), 3.95 (s, 2H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.36 (t, *J* = 7.6 Hz, 2H), 2.13 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 208.1, 144.9, 138.4, 128.5, 127.8, 127.7, 112.4, 73.4, 72.2, 41.9, 30.0, 27.3; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 8.76 min.

6.3.6 5-(4-methoxyphenyl)hex-5-en-2-one (**S6a**), TJB-1-013

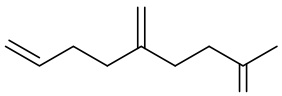


S6a

Prepared with **GP2** using **S1a** (21.1 mg, 0.39 mmol). The residue was purified by flash chromatography (gradient hex-EtOAc 100:0 to 95:5) to give **S6a** as a white solid (49 mg, 0.24 mmol, 62 %). Spectral data corresponds to previously published data.[50]

mp 34–37 °C; R_f (EtOAc-hexane 20:80) = 0.37; IR (neat, ATR) ν_{max} 468, 502, 552, 686, 839, 896, 1029, 1183, 1249, 1352, 1512, 1708, 2840, 2997, 3095; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 2H), 6.93 – 6.80 (m, 2H), 5.27 – 5.16 (m, 1H), 4.98 (d, *J* = 1.3 Hz, 1H), 3.82 (s, 3H), 2.76 (dd, *J* = 9.1, 6.0 Hz, 2H), 2.58 (dd, *J* = 8.7, 6.4 Hz, 2H), 2.12 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 208.3, 159.4, 146.6, 133.2, 127.3, 113.9, 111.3, 55.4, 42.7, 30.2, 29.5; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 8.38 min.

6.3.7 5-methylenenon-8-en-2-one (**S6b**), TJB-1-023

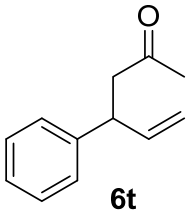


S6a

Prepared with **GP2** using **S1b** (43.8 g, 0.39 mmol). The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 97:3) to give **S6b** as a colourless oil (25.5 mg, 0.17 mmol, 43 %).

R_f (EtOAc-hexane 20:80) = 0.58; IR (neat, ATR) ν_{max} 542, 587, 635, 890, 908, 998, 1189, 1230, 1305, 1357, 1435, 1642, 1715, 2852, 2922, 2978, 3077; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (ddt, *J* = 16.8, 10.1, 6.2 Hz, 1H), 5.07 – 4.92 (m, 2H), 4.79 – 4.68 (m, 2H), 2.63 – 2.53 (m, 2H), 2.29 (t, *J* = 7.7 Hz, 2H), 2.23 – 2.07 (m, 7H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 208.4, 147.8, 138.3, 114.8, 109.6, 42.1, 35.8, 32.1, 30.0, 29.9, Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 1.65 min. HRMS (ESI+): m/z calcd for $[M+Na]^+$ = 175.1093, found 175.1091, Δ = –1.14 ppm.

6.3.8 4-phenylhex-5-en-2-one (**6t**), TJB-1-014

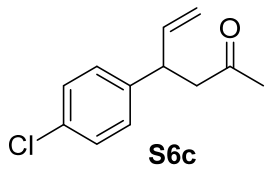


6t

Prepared with **GP2** using **1t** (52.3 mg, 0.39 mmol). The residue was purified by flash chromatography (gradient hex-EtOAc 100:0 to 94:6) to give **6t** as a colourless oil (42 mg, 0.24 mmol, 62 %). Spectral data corresponds to previously published data.[51]

R_f (EtOAc-hexane 10:90) = 0.39; IR (neat, ATR) ν_{max} 520, 699, 750, 916, 1160, 1357, 1712, 2926, 2979, 3003, 3028, 3062, 3082; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.17 (m, 5H), 5.97 (ddd, *J* = 17.1, 10.4, 6.8 Hz, 1H), 5.09 – 4.98 (m, 2H), 3.91 (q, *J* = 7.2 Hz, 1H), 2.94 – 2.77 (m, 2H), 2.09 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 207.1, 143.0, 140.7, 128.8, 127.8, 126.8, 114.8, 49.2, 44.7, 30.8; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 2.63 min.

6.3.9 4-(4-chlorophenyl)hex-5-en-2-one (**S6c**), TJB-1-032

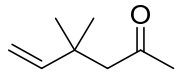


S6c

Prepared with **GP2** using S1c (65.8 mg, 0.39 mmol). The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 98:2) to give **S6c** as a colourless oil (46.2 mg, 0.22 mmol, 57 %). Spectral data corresponds to previously published data.[52]

R_f (EtOAc-hexane 10:90) = 0.39; IR (neat, ATR) ν_{max} 521, 588, 823, 862, 919, 993, 1013, 1090, 1160, 1246, 1358, 1408, 1490, 1637, 1714, 2923, 3082, 3369; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 5.93 (ddd, *J* = 17.1, 10.3, 6.7 Hz, 1H), 5.12 – 4.93 (m, 2H), 3.90 (q, *J* = 7.2 Hz, 1H), 2.91 – 2.74 (m, 2H), 2.09 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 206.6, 141.5, 140.3, 132.5, 129.2, 128.9, 115.1, 49.0, 43.9, 30.8; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic); t_r = 4.87 min.

6.3.10 4,4-dimethylhex-5-en-2-one (**6x**), TJB-1-031

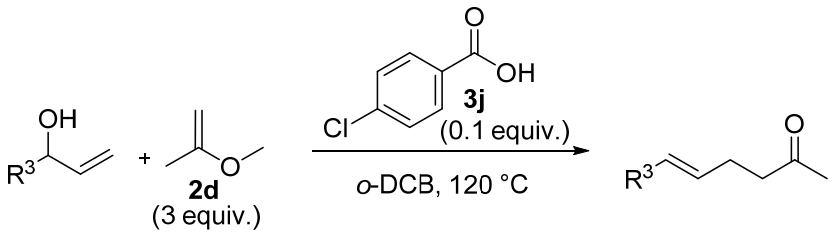


1x

Prepared with **GP2** using **1x** (33.6 g, 0.39 mmol). The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 97.4:2.6) to give **6x** as a colourless oil (22.5 mg, 0.18 mmol, 46 %). Spectral data corresponds to previously published data.[53]

R_f (EtOAc-hexane 10:90) = 0.44; IR (neat, ATR) ν_{max} 528, 595, 911, 1358, 1417, 1707, 2874, 2962, 3084; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (dd, *J* = 17.7, 10.5 Hz, 1H), 5.01 – 4.96 (m, 1H), 4.93 (q, *J* = 1.2 Hz, 1H), 2.42 (s, 2H), 2.10 (d, *J* = 0.5 Hz, 3H), 1.12 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 208.2, 147.3, 111.0, 55.3, 36.5, 32.4, 27.2; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 1.26 min.

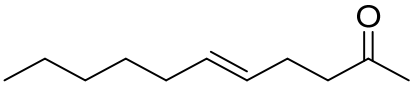
6.4 General procedure (GP3) for the synthesis of ketones via Claisen rearrangement under thermal conditions



*General procedure 3 (**GP3**):* A mixture of allylic alcohol **1** (limiting reagent, 0.78 mmol, 1 equiv.), 2-methoxypropene **2d** (2.34 mmol, 3 equiv) and 4-chlorobenzoic acid **3j** (0.078 mmol, 0.1 equiv.) in 1,2-dichlorobenzene (2 mL) was heated to 120 °C under reflux condenser in an open system. The reaction was monitored by taking small aliquots (100 μL) which were analyzed by GC. 1 equivalent of cyclododecane was used as an internal standard and the conversions were calculated using response factors. After complete conversion as indicated by GC, the reaction mixture was allowed to cool to rt, saturated aq. $NaHCO_3$ (2 mL) was added, and the resulting biphasic mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under air flow or vacuo to give a residue which was purified as described below for each entry.

Note: *o*-dichlorobenzene was remained after concentration and it was removed during the purification step.

6.4.1 Undec-5-en-2-one (**6a**), TJB-1-105

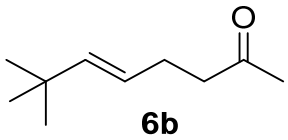


6a

Prepared with **GP3** using **1a** (0.10 g, 0.78 mmol). 3 h reaction time. The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 97:3) to give **6a** as a colourless oil (112 mg, 0.66 mmol, 85 %). Spectral data corresponds to previously published data.[45]

R_f (EtOAc-hexane 20:80) = 0.61; IR (neat, ATR) ν_{max} 536, 698, 968, 1046, 1160, 1226, 1358, 1411, 1439, 1456, 1717, 2855, 2924, 2957; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52 – 5.30 (m, 2H), 2.48 (t, *J* = 7.4 Hz, 2H), 2.26 (dd, *J* = 7.6, 5.7 Hz, 2H), 2.13 (s, 3H), 1.95 (q, *J* = 6.7 Hz, 2H), 1.39 – 1.19 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 208.7, 131.8, 128.3, 43.8, 32.6, 31.5, 30.1, 29.3, 27.0, 22.7, 14.2; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 2.61 min.

6.4.2 7,7-dimethyloct-5-en-2-one (**6b**), TJB-1-069

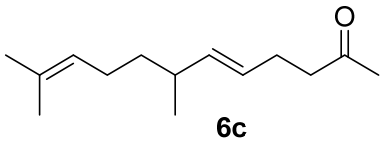


6b

Prepared with **GP3** using **1b** (89 mg, 0.78 mmol). 6h reaction time. The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 98:2) to give **6b** as a colourless oil (99.6 mg, 0.65 mmol, 83 %). Spectral data corresponds to previously published data.[54]

R_f (EtOAc-hexane 10:90) = 0.50; IR (neat, ATR) ν_{max} 540, 697, 972, 1158, 1361, 1476, 1717, 2866, 2956; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.47 (dt, *J* = 15.6, 1.3 Hz, 1H), 5.29 (dt, *J* = 15.6, 6.5 Hz, 1H), 2.48 (t, *J* = 7.4 Hz, 2H), 2.31 – 2.19 (m, 2H), 2.13 (s, 3H), 0.97 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, CDCl3) δ 208.7, 142.8, 122.9, 43.9, 32.9, 30.1, 29.8, 27.1; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 130 °C isothermic): t_r = 1.83 min.

6.4.3 7,11-dimethyldodeca-5,10-dien-2-one (**6c**), TJB-1-079

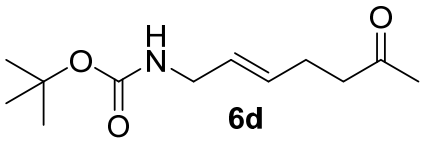


6c

Prepared with **GP3** using **1c** (0.13 g, 0.78 mmol). 3.5 h reaction time. The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 95.5:4.5) to give **6c** as a mixture of *E*- and *Z*-isomers a colourless oil (85:15 *E:Z*, 146.3 mg, 0.70 mmol, 90 %).

R_f (EtOAc-hexane 10:90) = 0.55; IR (neat, ATR) ν_{max} 969, 1160, 1358, 1441, 1717, 2854, 2914, 2962; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of *E*-isomers) δ 5.41 – 5.23 (m, 2H), 5.07 (ddt, *J* = 7.1, 5.7, 1.4 Hz, 1H), 2.48 (t, *J* = 7.4 Hz, 2H), 2.30 – 2.21 (m, 2H), 2.12 (s, 3H), 2.04 (p, *J* = 6.8 Hz, 1H), 1.99 – 1.86 (m, 2H), 1.67 (d, *J* = 1.3 Hz, 3H), 1.58 (s, 3H), 1.31 – 1.20 (m, 2H), 0.93 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, *E*-isomer): δ 208.7, 137.5, 131.3, 126.7, 124.8, 43.8, 37.3, 36.4, 30.1, 27.0, 25.9, 25.8, 20.9, 17.8; In addition, the following diagnostic peaks were observed for the *Z*-isomer: ^{1}H NMR (300 MHz, $CDCl_3$, mixture of *Z*-isomers) δ 4.65 (d, *J* = 9.8 Hz, 0.30H, corresponds to 2H); ^{13}C NMR (75 MHz, $CDCl_3$, *Z*-isomer): 137.6, 126.6, 109.8, 38.0, 36.7, 25.4, 22.5; Retention times for the two diastereomers were measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r(minor) = 4.82 min and t_r(major) = 5.11 min; HRMS (ESI+): m/z calcd for $[M+Na]^+$ = 231.1719, found 231.1719, Δ = – 0.17 ppm.

6.4.4 tert-butyl (6-oxohept-2-en-1-yl)carbamate (**6d**), TJB-076

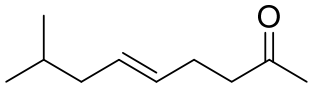


6d

Prepared with **GP3** using **1d** (0.15 g, 0.78 mmol). 4 h reaction time. The residue was purified by flash chromatography (gradient hex-EtOAc 100:0 to 83:17) to give **6d** as a colourless oil (111.5 mg, 0.49 mmol, 63 %).

R_f (EtOAc-hexane 60:40) = 0.50; IR (neat, ATR) ν_{max} 732, 864, 1161, 1245, 1365, 1511, 1701, 2930, 2977, 3359; ^{1}H NMR (300 MHz, DMSO) δ 6.88 (s, 1H), 5.53 – 5.31 (m, 2H), 3.45 (t, *J* = 5.6 Hz, 2H), 2.46 (d, *J* = 7.3 Hz, 2H), 2.15 (q, *J* = 7.0 Hz, 2H), 2.07 (s, 3H), 1.37 (s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO) δ 207.8, 155.4, 129.6, 127.8, 77.5, 42.1, 41.5, 29.7, 28.2, 25.8; HRMS (ESI+): m/z calcd for $[M+Na]^+$ = 250.1414, found 250.1414, Δ = 0.16 ppm.

6.4.5 8-methylnon-5-en-2-one (**6e**), TJB-1-077

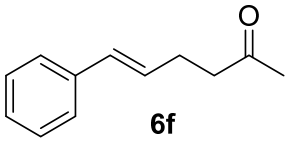


6e

Prepared with **GP3** using **1e** (89.1 mg, 0.78 mmol). 5 h reaction time. The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 95.5:4.5) to give **6e** as a colourless oil (120 mg, 0.78 mmol, quant.).

R_f (EtOAc-hexane 10:90) = 0.45; IR (neat, ATR) ν_{max} 969. 1161, 1365, 1465, 1716, 2869, 2955; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 – 5.29 (m, 2H), 2.48 (t, *J* = 7.4 Hz, 2H), 2.26 (qd, *J* = 6.4, 1.4 Hz, 2H), 2.13 (s, 3H), 1.89 – 1.80 (m, 2H), 1.65 – 1.49 (m, 1H), 0.85 (d, *J* = 6.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, CDCl3) δ 208.7, 130.4, 129.5, 43.8, 42.0, 30.1, 28.5, 27.1, 22.4. Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 130 °C isothermic): t_r = 2.11 min; HRMS (ESI+): m/z calcd for $[M+Na]^+$ = 177.1249, found 177.1244, Δ = –3.33 ppm.

6.4.6 6-Phenylhex-5-en-2-one (**6f**), TJB-1-064-2

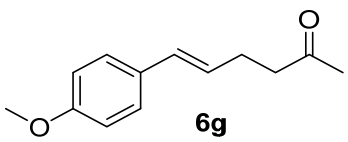


6f

Prepared with **GP3** using **1f** (0.10 g, 0.78 mmol). 5 h reaction time. The residue was purified by flash chromatography (gradient hex-EtOAc 100:0 to 94.7:5.3) to give **6f** as a pale yellow oil (54 mg, 0.31 mmol, 40 %). Spectral data corresponds to previously published data.[55]

R_f (EtOAc-hexane 20:80) = 0.5; IR (neat, ATR) ν_{max} 693, 965, 1158, 1364, 1713, 2924, 3026, 3059; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.16 (m, 6H), 6.41 (dt, *J* = 15.9, 1.4 Hz, 1H), 6.19 (dt, *J* = 15.8, 6.7 Hz, 1H), 2.62 (dd, *J* = 7.7, 6.0 Hz, 2H), 2.55 – 2.43 (m, 2H), 2.17 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, CDCl3) δ 208.1, 137.5, 130.9, 128.9, 128.6, 127.2, 126.1, 43.3, 30.2, 27.2; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 4.54 min.

6.4.7 6-(4-methoxyphenyl)hex-5-en-2-one (**6g**), TJB-1-068

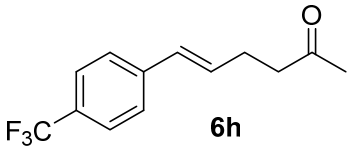


6g

Prepared with **GP3** using **1g** (0.13 g, 0.78 mmol). 4 h reaction time. The residue was purified by flash chromatography (gradient hex-EtOAc 100:0 to 95:5) to give **6g** as a colourless oil (68 mg, 0.34 mmol, 43 %). Spectral data corresponds to previously published data.[56]

R_f (EtOAc-hexane 20:80) = 0.44; IR (neat, ATR) ν_{max} 527, 727, 908, 1244, 1510, 1712, 2252, 2837, 2935, 3002; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.35 (d, *J* = 15.8 Hz, 1H), 6.04 (dt, *J* = 15.8, 6.7 Hz, 1H), 3.79 (s, 3H), 2.60 (t, *J* = 7.3 Hz, 2H), 2.46 (q, *J* = 6.9 Hz, 2H), 2.16 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 208.4, 159.0, 130.2, 127.2, 126.7, 114.1, 55.4, 43.5, 30.2, 27.3; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.806 mL/min, 150 °C isothermic): t_r = 6.49 min.

6.4.8 6-(4-(trifluoromethyl)phenyl)hex-5-en-2-one (**6h**), TJB-1-090

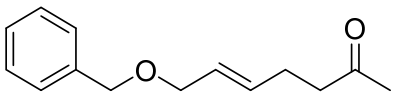


6h

Prepared with **GP3** using **1h** (0.16 g, 0.78 mmol). The residue was purified by flash chromatography (gradient hex-EtOAc 100:0 to 94.2:5.8) to give **6h** as a pale yellow oil (162,5 mg, 0.67 mmol, 86 %). Spectral data corresponds to previously published data.[55]

R_f (EtOAc-hexane 20:80) = 0.39; IR (neat, ATR) ν_{max} 595, 858. 1065, 1109, 1160, 1322, 1614, 1715, 2925; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 6.44 (d, *J* = 15.9 Hz, 1H), 6.30 (dt, *J* = 15.8, 6.5 Hz, 1H), 2.63 (dd, *J* = 7.6, 5.8 Hz, 2H), 2.52 (t, *J* = 6.8 Hz, 2H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, CDCl3) δ 207.7, 141.0, 131.9, 129.8, 126.3, 129.1 (q, $^2J_{C\text{-}F}$ = 31.5 Hz), 125.6 (q, $^3J_{C\text{-}F}$ = 3.8 Hz), 124.7 (q, $^1J_{C\text{-}F}$ = 231 Hz), 43.0, 30.1, 27.2; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 5.816 min.

6.4.9 7-(benzyloxy)hept-5-en-2-one (**6i**), TJB-1-078

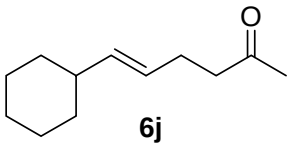


6j

Prepared with **GP3** using **1i** (0.14 g, 0.78 mmol). 7.5 h reaction time. The residue was purified by flash chromatography (gradient hex-EtOAc 100:0 to 92:8) to give **6i** as a colourless oil (129 mg, 0.59 mmol, 76 %).

R_f (EtOAc-hexane 20:80) = 0.47, IR (neat, ATR) ν_{max} 698, 737, 971, 1066, 1271, 1362, 1716, 2855, 2931, 2992; ^{1}H NMR (300 MHz, CDCl3) δ 7.40 – 7.23 (m, 6H), 5.79 – 5.54 (m, 2H), 4.49 (s, 2H), 3.96 (dd, *J* = 5.7, 1.0 Hz, 2H), 2.53 (t, *J* = 7.3 Hz, 2H), 2.33 (q, *J* = 7.0 Hz, 2H), 2.14 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, CDCl3) δ 208.1, 138.5, 132.7, 128.5, 127.9, 127.7, 127.4, 72.2, 70.8, 43.0, 30.1, 26.5; HRMS (ESI+): m/z calcd for $[M+Na]^+$ =241.1199, found 241.1200, Δ = 0.41 ppm.

6.4.10 6-cyclohexylhex-5-en-2-one (**6j**), TJB-1-083

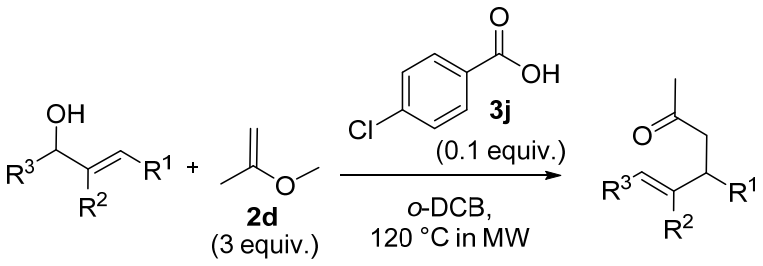


6j

Prepared with **GP3** using **1j** (0.11 g, 0.78 mmol). 2.5 h reaction time. The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 95.5:4.5) to give **6j** as a colourless oil (136 mg, 0.76 mmol, 97 %).

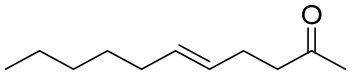
R_f (EtOAc-hexane 10:90) = 0.43; IR (neat, ATR) ν_{max} 967, 1120, 1359, 1447, 1715, 2850, 2922; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 – 5.27 (m, 2H), 2.47 (t, *J* = 7.4 Hz, 2H), 2.26 (dd, *J* = 7.6, 5.6 Hz, 2H), 2.13 (s, 3H), 1.88 (q, *J* = 8.8 Hz, 1H), 1.66 (d, *J* = 10.4 Hz, 5H), 1.32 – 0.94 (m, 5H); ^{13}C{^{1}H} NMR (75 MHz, CDCl3) δ 208.8, 137.7, 125.7, 43.9, 40.7, 33.2, 30.1, 27.1, 26.3, 26.2; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 4.06 min; HRMS (ESI+): m/z calcd for $[M+Na]^+$ = 203.1406, found 203.1407, Δ = 0.49 ppm.

6.5 General procedure (GP4) for the synthesis of ketones via Claisen rearrangement in microwave oven



*General procedure 4 (**GP4**):* A mixture of allylic alcohol **1** (0.79 mmol, 1.00 equiv.), 2-methoxypropene **2d** (2.37 mmol, 3.00 equiv) and 4-chlorobenzoic acid **3j** (0.079 mmol, 0.10 equiv.) in 1,2-dichlorobenzene (2 mL) was heated to 120 °C in microwave oven (CEM Discovery-S) for 6 h unless otherwise indicated. The reactions were performed in sealed reaction vessels and the temperature was monitored with an external sensor. The sensor temperature was maintained at 120 °C throughout the reaction. After 6 h if not otherwise mentioned the reaction mixture was allowed to cool to rt. Saturated aq. $NaHCO_3$ (2 mL) was added and the biphasic mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give a residue which was purified as described below for each entry.

6.5.1 Undec-5-en-2-one (**6a**), TJB-1-146

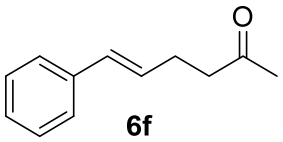


6a

Prepared with **GP4** using **1a** (0.10 g, 0.79 mmol). The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 97:3) to give **6a** as a colourless oil (131 mg, 0.79 mmol, quant.). Spectral data corresponds to previously published data.[45]

R_f (EtOAc-hexane 20:80) = 0.61; IR (neat, ATR) ν_{max} 536, 698, 968, 1046, 1160, 1226, 1358, 1411, 1439, 1456, 1717, 2855, 2924, 2957; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52 – 5.30 (m, 2H), 2.48 (t, *J* = 7.4 Hz, 2H), 2.26 (dd, *J* = 7.6, 5.7 Hz, 2H), 2.13 (s, 3H), 1.95 (q, *J* = 6.7 Hz, 2H), 1.39 – 1.19 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 208.7, 131.8, 128.3, 43.8, 32.6, 31.5, 30.1, 29.3, 27.0, 22.7, 14.2; Retention time was measured with GC (SUPELCO Astec CHIRALDEX B-DM column, isoflow He: 1.806 mL/min, 100 °C isothermic): t_r = 17.7 min.

6.5.2 6-phenylhex-5-en-2-one (**6f**), TJB-1-157

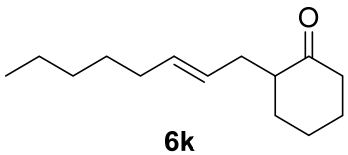


6f

Reaction carried out in **1 mmol** scale with **GP4** using **1f** (0.13 g, 1.00 mmol). The residue was purified by flash chromatography (gradient hex-EtOAc 100:0 to 95:5) to give **6f** as a colourless oil (171 mg, 0.98 mmol, 98 %). Spectral data corresponds to previously published data.

R_f (EtOAc-hexane 20:80) = 0.5; IR (neat, ATR) ν_{max} 693, 965, 1158, 1364, 1713, 2924, 3026, 3059; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.16 (m, 6H), 6.41 (dt, *J* = 15.9, 1.4 Hz, 1H), 6.19 (dt, *J* = 15.8, 6.7 Hz, 1H), 2.62 (dd, *J* = 7.7, 6.0 Hz, 2H), 2.55 – 2.43 (m, 2H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, CDCl3) δ 208.1, 137.5, 130.9, 128.9, 128.6, 127.2, 126.1, 43.3, 30.2, 27.2; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 4.54 min.

6.5.3 2-(oct-2-en-1-yl)cyclohexan-1-one (**6k**), TJB-1-148

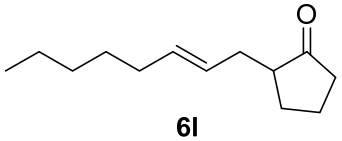


6k

Prepared with **GP4** using **1a** (0.10 g, 0.79 mmol) and 1,1-dimethoxycyclohexane **2c** (0.36 ml, 2.37 mmol) instead of 2-methoxypropene **2d**. The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 98.2:1.8) to give **6k** as a colourless oil (130 mg, 0.62 mmol, 79 %). Spectral data corresponds to previously published data.[57]

R_f (EtOAc-hexane 10:90) = 0.45; IR (neat, ATR) ν_{max} 519, 822, 847, 908, 970, 1053 1075, 1365, 1448, 1710, 2856, 2926; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 – 5.39 (m, 1H), 5.39 – 5.31 (m, 1H), 2.49 – 2.42 (m, 1H), 2.39 (dtd, *J* = 13.5, 4.0, 1.4 Hz, 1H), 2.33 – 2.25 (m, 2H), 2.15 – 2.08 (m, 1H), 2.03 (ddq, *J* = 10.3, 4.4, 3.0 Hz, 1H), 1.96 (q, *J* = 6.7 Hz, 2H), 1.91 (dd, *J* = 14.4, 7.4 Hz, 1H), 1.85 (ddd, *J* = 9.6, 3.9, 1.5 Hz, 1H), 1.72 – 1.59 (m, 2H), 1.38 – 1.22 (m, 7H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 213.1, 132.7, 127.6, 50.9, 42.2, 33.4, 32.7 (2C), 31.5, 29.4, 28.1, 25.0, 22.7, 14.2; HRMS (ESI+): m/z calcd for $[M+Na]^+$ = 231.1719, found 231.1718, Δ = –0.61 ppm.

6.5.4 2-(oct-2-en-1-yl)cyclopentan-1-one (**6l**), TJB-1-150

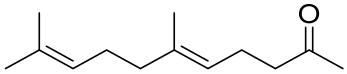


6l

Prepared with **GP4** using **1a** (0.10 g, 0.79 mmol) and 1,1-dimethoxycyclopentane **2c** (0.31 g, 2.37 mmol) instead of 2-methoxypropene **2d**. The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 96:4) to give **6l** as a colourless oil (130 mg, 0.67 mmol, 84 %).

R_f (EtOAc-hexane 10:90) = 0.49; IR (neat, ATR) ν_{max} 474, 450, 921, 969, 1053, 1114, 1152, 1270, 1406, 1437, 1453, 1738, 2855, 2872, 2957; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 – 5.42 (m, 1H), 5.33 (dtt, *J* = 15.2, 6.9, 1.3 Hz, 1H), 2.45 – 2.39 (m, 1H), 2.34 – 2.26 (m, 1H), 2.19 – 2.07 (m, 3H), 2.04 – 1.94 (m, 4H), 1.83 – 1.73 (m, 1H), 1.63 – 1.55 (m, 1H), 1.36 – 1.23 (m, 6H), 0.88 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 221.2, 133.0, 127.1, 49.2, 38.5, 32.8, 32.6, 31.5, 29.3, 29.0, 22.6, 20.8, 14.2; HRMS (ESI+): m/z calcd for $[M+Na]^+$ = 217.1562, found 217.1567, Δ = 1.84 ppm.

6.5.5 (E/Z)-6,10-dimethylundeca-5,9-dien-2-one (**6m**), TJB-1-118



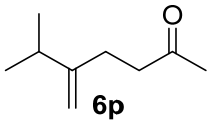
6m

Prepared with **GP4** using linalool (0.12 g, 0.79 mmol). The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 95:5) to give **6m** as a colourless oil and a mixture of *Z* and *E*-isomers (60:40 *E:Z*, 80 mg, 0.41 mmol, 52 %). Spectral data corresponds to previously published data.[46]

R_f (EtOAc-hexanes 20:80) = 0.61; IR (neat, ATR) ν_{max} 522, 581, 827, 984, 1158, 1357, 1440, 1716, 2856, 2916, 2966; ^{1}H NMR (300 MHz, $CDCl_3$, *E*-isomer) δ 5.14 – 5.03 (m, 2H), 2.45 (td, *J* = 7.5, 4.0 Hz, 2H), 2.32 – 2.21 (m, 2H), 2.13 (d, *J* = 0.7 Hz, 3H), 2.09 – 1.93 (m, 4H), 1.68-1.60 (four partially overlapping br s, 9H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, *E*-isomer) δ 208.9, 136.5, 131.5, 124.3, 122.7, 43.9. 39.8, 30.1, 26.8, 25.8, 22.6, 17.8, 16.1; In addition, the following diagnostic peaks were observed for the minor isomer: $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$, *Z*-isomer) δ 208.9, 136.6, 131.8, 123.5, 44.2, 42.2, 32.0, 30.0, 26.7, 25.8, 23.5, 22.5, 17.8. Retention time was measured with GC (SUPELCO Astec

CHIRALDEX B-DM column, isoflow He: 1.806 mL/min, 130 °C isothermic): t_r(minor) = 9.04 min and t_r(major) = 10.41 min.

6.5.6 6-methyl-5-methyleneheptan-2-one (**6p**), TJB-1-117

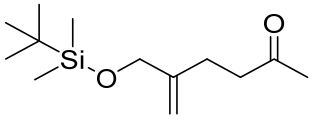


6p

Prepared with **GP4** using **1p** (79.1 mg, 0.79 mmol). Reaction time 2 h. The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 95:5) to give **6p** as a colourless oil (98 mg, 0.71 mmol, 90 %). Spectral data corresponds to previously published data.[47]

R_f (EtOAc-hexane 10:90) = 0.6; IR (neat, ATR) ν_{max} 540, 684, 888, 1161, 1280, 1322, 1716, 2873, 2962; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (d, *J* = 1.0 Hz, 1H), 4.63 (d, *J* = 1.4 Hz, 1H), 2.58 (dd, *J* = 9.1, 6.2 Hz, 2H), 2.35 – 2.19 (m, 3H), 2.16 (s, 3H), 1.04 (d, *J* = 6.8 Hz, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 208.6, 154.7, 106.7, 42.4, 34.4, 30.0, 28.0, 21.9; Retention time was measured with GC (SUPELCO Astec CHIRALDEX B-DM column, isoflow He: 1.806 mL/min, 100 °C isothermic): t_r = 4.33 min.

6.5.7 5-(((tert-butyldimethylsilyl)oxy)methyl)hex-5-en-2-one (**6q**), TJB-1-125



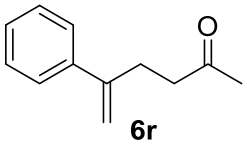
6q

Prepared with **GP4** using **1q** (0.16 g, 0.79 mmol). The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 93:7) to give **6q** as a colourless oil (177 mg, 0.73 mmol, 92%).

R_f (EtOAc-hexane 10:90) = 0.33; IR (neat, ATR) ν_{max} 774, 834, 896, 1081, 1109, 1252, 1360, 1718, 2856, 2929, 2955; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 – 5.00 (m, 1H), 4.82 – 4.75 (m, 1H), 4.07 (s, 2H), 2.61 (dd, *J* = 8.6, 6.6 Hz, 2H), 2.29 (t, *J* = 7.7 Hz, 2H), 2.15 (s,

3H), 0.91 (s, 9H), 0.07 (s, 6H); $^{13}C\{^{1}H\}$ NMR (75 MHz, CDCl3) δ 208.3, 147.5, 109.1, 66.2, 42.1, 30.0, 26.7, 26.1, 18.5, –5.2; Retention time was measured with GC (SUPELCO Astec CHIRALDEX B-DM column, isoflow He: 1.806 mL/min, 130 °C isothermic). t_r = 8.43 min; HRMS (ESI+): m/z calcd for $[M+Na]^+$ = 265.1594, found 265.1588, Δ = –2.42 ppm.

6.5.8 5-phenylhex-5-en-2-one (**6r**), TJB-1-127

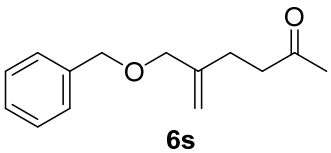


6r

Prepared with **GP4** using **1r** (0.11 g, 0.79 mmol). The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 96.5:6.5) to give **6r** as a colourless oil (108 mg, 0.62 mmol, 78%). Spectral data corresponds to previously published data.[48]

R_f (EtOAc-hexane 20:80) = 0.5; IR (neat, ATR) ν_{max} 525, 703, 778, 895, 1027, 1159, 1259, 1357, 1443, 1494, 1627, 1714, 2961, 3081; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.27 (m, 5H), 5.29 (dd, *J* = 1.2, 0.6 Hz, 1H), 5.07 (d, *J* = 1.3 Hz, 1H), 2.84 – 2.75 (m, 2H), 2.59 (dd, *J* = 8.7, 6.5 Hz, 2H), 2.12 (s, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): 29.4, 30.2, 42.6, 112.9, 126.2, 127.7, 128.6, 140.8, 147.4, 208.2; Retention time was measured with GC (SUPELCO Astec CHIRALDEX B-DM column, isoflow He: 1.806 mL/min, 130 °C isothermic): t_r = 10.51 min.

6.5.9 5-((benzyloxy)methyl)hex-5-en-2-one (**6s**), TJB-1-154



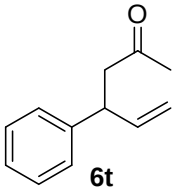
6s

Prepared with **GP4** using **1s** (0.14 g, 0.79 mmol). The residue was purified by flash chromatography (gradient hex-EtOAc 100:0 to 90:10) to give **6s** as a colourless oil (165 mg, 0.76 mmol, 96 %). Spectral data corresponds to previously published data.[49]

R_f (EtOAc-hexane 20:80) = 0.45; IR (neat, ATR) ν_{max} 461, 541, 697, 736, 904, 1028, 1072, 1092, 1159, 1205, 1310, 1496, 1652, 1714, 2855, 2922, 3030, 3064; ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.37 – 7.26 (m, 5H), 5.07 (s, 1H), 4.92 (s, 1H), 4.49 (s, 2H), 3.97 (s, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.39 (s, 2H), 2.14 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 208.1, 144.9, 138.4, 128.5, 127.8, 127.7, 112.4, 73.4, 72.2, 41.9, 30.0, 27.3; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 8.76 min.

6.5.10 4-phenylhex-5-en-2-one (**6t**), TJB-1-137

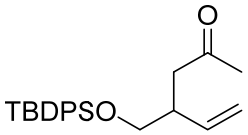


6t

Prepared with **GP4** using **1t** (0.11 g, 0.79 mmol). The residue was purified by flash chromatography (gradient hex-EtOAc 100:0 to 94:6) to give **6t** as a colourless oil (120 mg, 0.69 mmol, 87 %). Spectral data corresponds to previously published data.[51]

R_f (EtOAc-hexane 10:90) = 0.39; IR (neat, ATR) ν_{max} 520, 699, 750, 916, 1160, 1357, 1712, 2926, 2979, 3003, 3028, 3062, 3082; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.17 (m, 5H), 5.97 (ddd, *J* = 17.1, 10.4, 6.8 Hz, 1H), 5.09 – 4.98 (m, 2H), 3.91 (q, *J* = 7.2 Hz, 1H), 2.94 – 2.77 (m, 2H), 2.09 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 207.1, 143.0, 140.7, 128.8, 127.8, 126.8, 114.8, 49.2, 44.7, 30.8; Retention time was measured with GC (Agilent HP-5, isoflow He: 1.858 mL/min, 150 °C isothermic): t_r = 2.63 min.

6.5.11 4-(((*tert*-Butyldiphenylsilyl)oxy)methyl)hex-5-en-2-one (**6u**), TJB-1-143



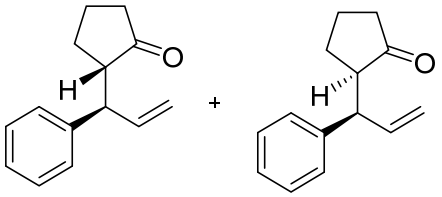
6u

Prepared with **GP4** using **1u** (0.26 g, 0.79 mmol). The residue was purified by flash chromatography (gradient hexane-EtOAc 100:0 to 95:5) to give **6u** as a colourless oil (0.19 g, 0.51 mmol, 64 %).

R_f (EtOAc-hexane 15:85) = 0.52; IR (neat, ATR) ν_{max} 488, 506, 613, 700, 739, 782, 823, 917, 1106, 1360, 1427, 1472, 1714, 2857, 2892, 2930, 3071; ^1H NMR (300 MHz, $CDCl_3$) δ

7.64 (dd, *J* = 7.7, 1.8 Hz, 4H), 7.48 – 7.31 (m, 6H), 5.72 (ddd, *J* = 17.7, 10.1, 7.6 Hz, 1H), 5.12 – 4.97 (m, 2H), 3.70 – 3.50 (m, 2H), 2.79 (ddd, *J* = 29.3, 14.7, 6.2 Hz, 2H), 2.45 (dd, *J* = 16.1, 8.0 Hz, 1H), 2.12 (s, 3H), 1.05 (s, 9H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 208.1, 138.4, 135.7, 133.7, 129.8, 127.8, 116.2, 66.6, 45.3, 41.8, 30.6, 27.0, 19.4; HRMS (ESI+): m/z calcd for $[M+Na]^+$ = 389.1907, found 389.1895, Δ = – 3.08 ppm.

6.5.12 2-(1-phenylallyl)cyclopentan-1-one (**6v**), TJB-1-151

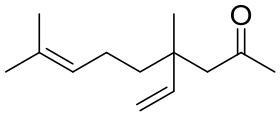


syn **6v** anti **6v**

Prepared with **GP4** using cinnamyl alcohol (0.10 g, 0.79 mmol) and 1,1-dimethoxycyclopentane **2c** (0.30 g, 2.37 mmol) instead of 2-methoxypropene **2d**. The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 97:3) to give **6v** as colourless oil as 4:1 mixture of diastereomers (110 mg, 0.57 mmol, 72 %). Spectral data and the diastereoselectivity corresponds to previously published data.[14,58]

R_f (EtOAc-hexane 10:90) = 0.34; IR (neat, ATR) ν_{max} 552, 612, 699, 834, 916, 1077, 1151, 1405, 1451, 1601, 1717, 1735, 2876, 2962, 3028, 3061; ^{1}H NMR (500 MHz, $CDCl_3$, syn diastereomer) δ 7.32 (d, *J* = 8.1 Hz, 3H), 7.20 (dd, *J* = 8.1, 1.4 Hz, 2H), 6.24 (ddd, *J* = 17.2, 10.4, 6.9 Hz, 1H), 5.21 – 5.12 (m, 2H), 3.92 (dd, *J* = 6.9, 5.4 Hz, 1H), 2.65 – 2.60 (m, 1H), 2.33 – 2.25 (m, 1H), 2.12 – 2.04 (m, 1H), 1.93 (ddd, *J* = 18.6, 10.2, 8.7 Hz, 1H), 1.84 – 1.72 (m, 2H), 1.60 (d, *J* = 0.5 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$, syn diastereomer) δ 219.6, 141.4, 139.9, 129.0, 128.5, 126.7, 115.3, 53.2, 48.5, 38.8, 26.6, 20.6; In addition, the following diagnostic peaks were observed for the minor diastereomer ^{1}H NMR (500 MHz, $CDCl_3$, anti-diastereomer) δ 6.06 (ddd, *J* = 17.0, 10.3, 8.3 Hz, 1H), 3.98 (dd, *J* = 8.3, 4.1 Hz, 1H), 2.58 – 2.51 (m, 1H), 2.23 – 2.14 (m, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 128.7, 126.7.

6.5.13 4,8-dimethyl-4-vinylnon-7-en-2-one (**6w**), TJB-129

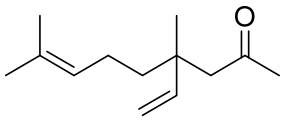


6w

Prepared with **GP4** using (*E*)-**1w** (0.12 g, 0.79 mmol). The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 97:3) to give **6w** as a colourless oil (116 mg, 0.59 mmol, 75%). Spectral data corresponds to previously published data.[53]

R_f (EtOAc-hexane 10:90) = 0.5; IR (neat, ATR) ν_{max} 608, 785, 837, 912, 1000, 1159, 1634, 1704, 2916, 2966, 3060; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.11 – 4.92 (m, 3H), 2.53 – 2.36 (m, 2H), 2.10 (s, 3H), 1.88 (q, *J* = 8.0 Hz, 2H), 1.67 (s, 3H), 1.58 (s, 3H), 1.42 (ddd, *J* = 11.8, 5.8, 3.9 Hz, 2H), 1.11 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 208.2, 146.0, 131.6, 124.6, 112.4, 53.7, 41.0, 39.6, 32.5, 25.8, 23.0, 23.0, 17.7. Retention times for the two enantiomers were measured with GC (SUPELCO Astec CHIRALDEX B-DM column, isoflow He: 1.806 mL/min, 120 °C isothermic): t_r = 8.61 min and t_r = 8.71 min.

6.5.14 4,8-dimethyl-4-vinylnon-7-en-2-one (**6w**), TJB-1-136

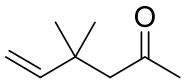


6w

Prepared with **GP4** using (*Z*)-**1w** (0.12 g, 0.79 mmol). The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 97:3) to give **6w** as a colourless oil (100 mg, 0.51 mmol, 65 %). Spectral data corresponds to previously published data.[53]

R_f (EtOAc-hexane 10:90) = 0.5; IR (neat, ATR) ν_{max} 608, 785, 837, 912, 1000, 1159, 1634, 1704, 2916, 2966, 3060; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.11 – 4.92 (m, 3H), 2.53 – 2.36 (m, 2H), 2.10 (s, 3H), 1.88 (q, *J* = 8.0 Hz, 2H), 1.67 (s, 3H), 1.58 (s, 3H), 1.42 (ddd, *J* = 11.8, 5.8, 3.9 Hz, 2H), 1.11 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 208.2, 146.0, 131.6, 124.6, 112.4, 53.7, 41.0, 39.6, 32.5, 25.8, 23.0, 23.0, 17.7; Retention times for the two enantiomers were measured with GC (SUPELCO Astec CHIRALDEX B-DM column, isoflow He: 1.806 mL/min, 120 °C isothermic): t_r = 8.61 min and t_r = 8.71 min.

6.5.15 4,4-dimethylhex-5-en-2-one (**6x**), TJB-1-120

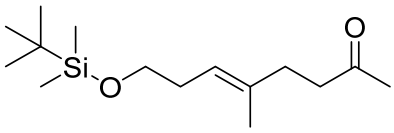


6x

Prepared with **GP4** using **1x** (68.1 mg, 0.79 mmol). The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 97.4:2.6) to give **6x** as a colourless oil (75 mg, 0.59 mmol, 75%). Spectral data corresponds to previously published data.[53]

R_f (EtOAc-hexane 10:90) = 0.44; IR (neat, ATR) ν_{max} 528, 595, 911, 1358, 1417, 1707, 2874, 2962, 3084; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (dd, *J* = 17.7, 10.5 Hz, 1H), 5.01 – 4.96 (m, 1H), 4.93 (q, *J* = 1.2 Hz, 1H), 2.42 (s, 2H), 2.10 (d, *J* = 0.5 Hz, 3H), 1.12 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 208.2, 147.3, 111.0, 55.3, 36.5, 32.4, 27.2; Retention time was measured with GC (SUPELCO Astec CHIRALDEX B-DM column, isoflow He: 1.806 mL/min, 100 °C isothermic): t_r = 2.53 min.

6.5.16 8-((tert-butyldimethylsilyl)oxy)-5-methyloct-5-en-2-one (**6y**), TJB-1-141

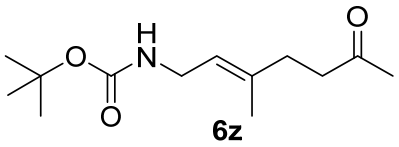


6y

Prepared with **GP4** using **1y** (0.18 g, 0.79 mmol). The residue was purified by flash chromatography on alumina (gradient pentane-Et_2O 100:0 to 98:2) to give **6y** as a colourless oil (213 mg, 0.79 mmol, quant.).

R_f (EtOAc-hexane 10:90) = 0.47; IR (neat, ATR) ν_{max} 661, 774, 833, 937, 1006, 1090, 1159, 1253, 1359, 1471, 1718, 2856, 2897, 2928, 2954; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (t, *J* = 7.2 Hz, 1H), 3.57 (t, *J* = 7.0 Hz, 2H), 2.52 (dd, *J* = 8.9, 6.6 Hz, 2H), 2.23 (dt, *J* = 14.7, 7.8 Hz, 4H), 2.14 (s, 3H), 1.62 (s, 3H), 0.89 (s, 10H), 0.05 (s, 6H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 208.8, 135.7, 121.3, 63.1, 42.5, 33.7, 32.0, 30.0, 26.1, 18.5, 16.4, –5.1; Retention time was measured with GC (SUPELCO Astec CHIRALDEX B-DM column, isoflow He: 1.806 mL/min, 100 °C isothermic): t_r = 10.03 min; HRMS (ESI+): m/z calcd for $[M+Na]^+$ = 293.1907, found 293.1915, Δ = 2.73 ppm.

6.5.17 *tert*-Butyl-(3-methyl-6-oxohept-2-en-1-yl)carbamate (**6z**), TJB-1-139

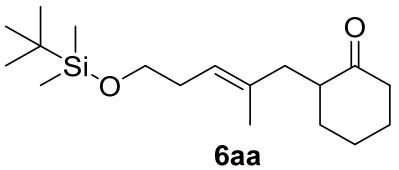


6z

Prepared with **GP4** using **1z** (0.16 g, 0.79 mmol). The residue was purified by flash chromatography on alumina (gradient hex-EtOAc 100:0 to 80:20) to give **6z** as a tan oil (99.1 mg, 0.41 mmol, 52 %).

R_f (EtOAc-hexane 50:50) = 0.56; IR (neat, ATR) ν_{max} 462, 524, 604, 780, 866, 1162, 1245, 1364, 1390, 1452, 1509, 2929, 2976, 3351; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.20 – 5.14 (m, 1H), 4.44 (s, 1H), 3.71 (d, *J* = 6.6 Hz, 2H), 2.53 (dd, *J* = 8.5, 6.8 Hz, 2H), 2.27 (s, 2H), 2.14 (s, 3H), 1.65 (d, *J* = 1.3 Hz, 3H), 1.44 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 208.4, 156.0, 137.7, 121.4, 79.4, 42.0, 38.5, 33.2, 30.1, 28.6, 16.5; HRMS (ESI+): m/z calcd for $[M+Na]^+$ = 264.1570 found 264.1566, Δ = –1.51 ppm.

6.5.18 (E)-2-(5-((tert-butyldimethylsilyl)oxy)-2-methylpent-2-en-1-yl)cyclohexan-1-one (**6aa**)



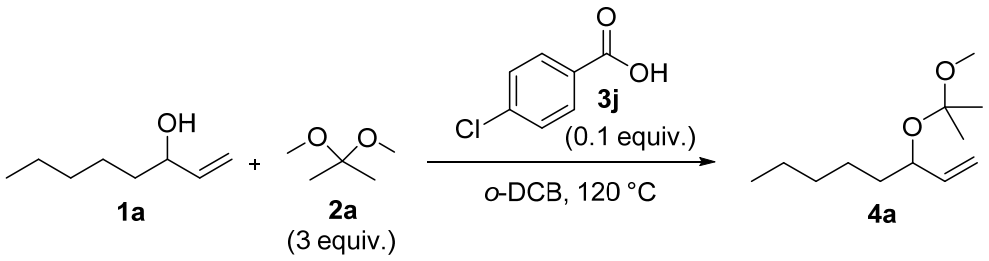
6aa

Prepared with **GP4** using **1y** (0.18 g, 0.78 mmol) and 1,1-dimethoxycyclohexane **2b** (0.36 ml, 2.34 mmol). The residue was purified by flash chromatography on alumina (gradient hex-EtOAc 100:0 to 98:2) to give **6aa** as a brown oil (169 mg, 0.55 mmol, 69 %).

R_f (EtOAc-hexane 10:90) = 0.33; IR (neat, ATR) ν_{max} 525, 558, 662, 774, 811, 833, 938, 1094, 1252, 1386, 1712, 2857, 2929, 3022, 3169; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.11 (ddd, *J* = 8.3, 5.9, 1.2 Hz, 1H), 3.57 (td, *J* = 7.0, 0.8 Hz, 2H), 2.54 (dd, *J* = 14.1, 4.5 Hz, 1H), 2.43 – 2.36 (m, 2H), 2.29 (dddd, *J* = 13.3, 11.9, 5.8, 1.2 Hz, 1H), 2.21 (q, *J* = 7.1 Hz, 2H), 2.03 (dddd, *J* = 13.2, 10.1, 5.2, 2.0 Hz, 2H), 1.89 – 1.81 (m, 2H), 1.71 – 1.58 (m, 2H), 1.57 – 1.55 (m, 3H), 1.31 – 1.22 (m, 1H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 213.3, 134.3, 122.9, 63.1, 48.4, 42.1, 39.4, 33.1, 32.0, 28.1, 26.1, 24.8, 18.5, 16.1, –5.1; HRMS (ESI+): m/z calcd for $[M+K]^+$ = 349.1960 found 349.1966, Δ = 1.72 ppm.

6.6 Synthesis of intermediates of the Claisen sequence

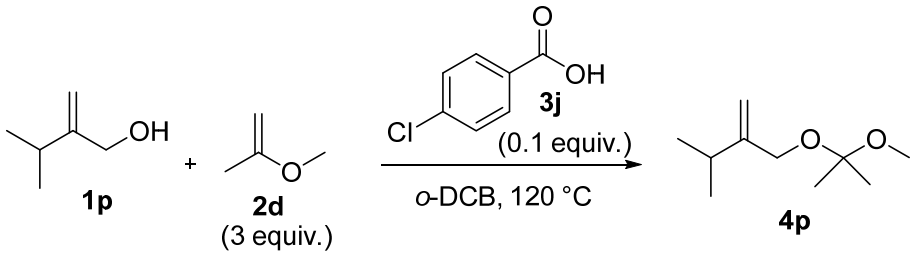
6.6.1 3-((2-methoxypropan-2-yl)oxy)oct-1-ene (**4a**), TJB-147/111



A mixture of 1-octen-3-ol **1a** (300 mg, 2.34 mmol, 1.00 equiv.), 2,2-dimethoxypropane **2a** (0.87 mL, 7.02 mmol, 3.00 equiv) and 4-chlorobenzoic acid **3j** (36.6 mg, 0.23 mmol, 0.10 equiv.) in 1,2-dichlorobenzene (6 mL) was heated to 120 °C under reflux condenser in an open system. After 1 h, the mixture was allowed to cool to rt. Saturated aq. $NaHCO_3$ (4 mL) was added, and the mixture was extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under air flow. (Note: Residual *o*-dichlorobenzene remained in the residue, and it was removed in the purification step.) The residue was purified by flash chromatography (gradient pentane-Et_2O 100:0 to 95:5) to give **4a** as a colourless oil (100 mg, 0.50 mmol, 21 %).

R_f (EtOAc-hexane 10:90) = 0.67; IR (neat, ATR) ν_{max} 586, 759, 856, 918, 1021, 1070, 1152, 1183, 1206, 1257, 1371, 1459, 1643, 2859, 2932, 2990, 3078, 3474; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 17.5, 10.4, 7.2 Hz, 1H), 5.16 – 4.99 (m, 2H), 4.11 (q, *J* = 6.8 Hz, 1H), 3.21 (s, 3H), 1.54 (s, 2H), 1.34 (d, *J* = 10.2 Hz, 12H), 0.91 – 0.84 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 141.4, 114.5, 100.9, 77.4, 72.7, 49.3, 36.6, 32.0, 26.0, 25.5, 24.9, 22.8, 14.2; Retention time was measured with GC (SUPELCO Astec CHIRALDEX B-DM column, isoflow He: 1.806 mL/min, 100 °C isothermic): t_r = 7.26 min; HRMS (ESI+): m/z calcd for $[M+Na]^+$ = 223.1669, found 223.1675, Δ = 2.69 ppm.

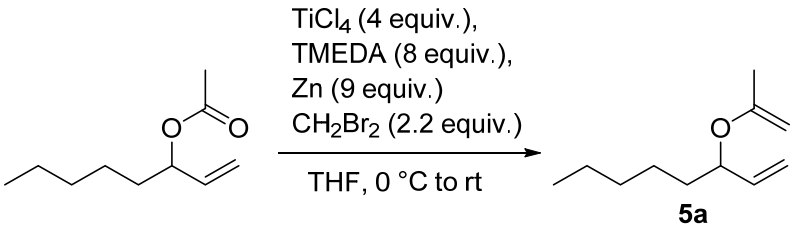
6.6.2 2-(((2-methoxypropan-2-yl)oxy)methyl)-3-methylbut-1-ene (**4p**), TJB-1-071



A mixture of 3-methyl-2-methylenebutan-1-ol **1p** (100 mg, 1.00 mmol, 1.00 equiv.), 2-methoxypropene **2d** (0.29 mL, 3.00 mmol, 3.00 equiv.) and 4-chlorobenzoic acid **3j** (15.6 mg, 0.10 mmol, 0.10 equiv.) in 1,2-dichlorobenzene (2.50 mL) was heated to 120 °C under reflux condenser in an open system. After 45 min, the mixture was allowed to cool to rt. Saturated aq. $NaHCO_3$ (2 mL) was added and the mixture was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under air flow. (Note: Residual *o*-dichlorobenzene remained in the residue, and it was removed in the purification step.) The residue was purified by flash chromatography (gradient hex-EtOAc 100:0 to 97.5:2.5) to give **4p** as a colourless oil (144 mg, 0.84 mmol, 84 %).

R_f (EtOAc-hexane 10:90) = 0.57; IR (neat, ATR) ν_{max} 750, 859, 898, 1039, 1151, 1211, 1376, 1462, 2961, 2991; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.09 – 5.01 (m, 1H), 4.92 – 4.83 (m, 1H), 3.92 (t, *J* = 1.3 Hz, 2H), 3.21 (s, 3H), 2.33 (dq, *J* = 13.8, 6.8 Hz, 1H), 1.38 (s, 6H), 1.07 (d, *J* = 6.8 Hz, 6H);^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 152.9, 107.6, 100.3, 62.7, 48.8, 31.4, 24.6, 21.9; Retention time was measured with GC (SUPELCO Astec CHIRALDEX B-DM column, isoflow He: 1.806 mL/min, 100 °C isothermic): t_r = 3.51 min; HRMS (ESI+): m/z calcd for $[M+Na]^+$ = 195.1356, found 195.1335, Δ = 10.8 ppm.

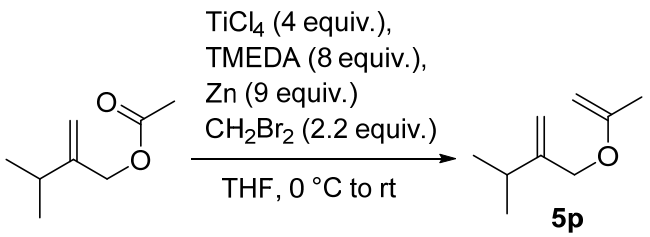
6.6.3 3-(prop-1-en-2-yloxy)oct-1-ene (**5a**), TJG-043



To dry THF (50 mL) was added $TiCl_4$ (20.0 mL, 20.0 mmol, 1M, 4.00 equiv.) in dry DCM at 0 °C resulting in a bright yellow mixture. Tetramethylethylenediamine (6.0 mL, 40.0 mmol, 8.00 equiv.) was added and the resulting brownish yellow mixture was allowed to stir for 10 min at rt. Zinc powder (2.94 g, 45.0 mmol, 9.00 equiv.) was added at rt and the resulting greenish blue mixture was allowed to stir for 30 min. A solution of oct-1-en-3-yl acetate (0.85 g, 5.00 mmol, 1.00 equiv.) and dibromomethane (0.77 mL, 11.0 mmol, 2.20 equiv.) in dry THF (10 mL) was added to the reaction mixture at rt and the resulting brown mixture was allowed to stir at rt for 22.5 h. (NOTE: Reaction did not go to completion during this time, but the decision was made to quench the reaction at this point to avoid decomposition of acid- and temperature-sensitive **5a**). The mixture was cooled to 0 °C and saturated aq. K_2CO_3 (7 mL) was added. The resulting biphasic mixture was stirred for 15 min. Et_2O (180 mL) was added, and the entire mixture was vacuum-filtered through a pad of alumina (2 cm, pH 7.5) with 500 mL of Et_2O/triethylamine (200:1). Solvent was evaporated under argon flow. During the evaporation process a significant amount of white solid emerged and the vacuum filtration was repeated with 200 mL of Et_2O:triethylamine (200:1). The residue was purified by flash chromatography with amino-functionalized silica (pentane 100 %) to give **5a** as a colourless oil (200 mg, 1.20 mmol, 24 %). Spectral data corresponds to previously published data.[59]

R_f (pentane 100 %, NH_2-modified silica TLC plate) = 1.00; IR (neat, ATR) ν_{max} 794, 920, 987, 1056, 1270, 1378, 1429, 1594, 1655, 2860, 2927, 2956; ^{1}H NMR (300 MHz, C_6D_6) δ 5.71 (ddd, *J* = 17.4, 10.6, 6.1 Hz, 1H), 5.16 – 4.98 (m, 2H), 4.32 (q, *J* = 6.2 Hz, 1H), 3.99 (s, 2H), 1.81 (s, 3H), 1.73 – 1.63 (m, 1H), 1.57 – 1.47 (m, 1H), 1.42 – 1.30 (m, 2H), 1.28 – 1.18 (m, 4H), 0.86 (t, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, C_6D_6) δ 158.6, 138.9, 115.2, 83.3, 77.8, 35.7, 32.1, 25.3, 23.0, 21.6, 14.2; Retention times for the two enantiomers of **5a** were measured with GC (SUPELCO Astec CHIRALDEX B-DM column, isoflow He: 1.806 mL/min, 100 °C isothermic): t_r = 4.00 min and 4.12 min.

6.6.4 3-methyl-2-((prop-1-en-2-yloxy)methyl)but-1-ene (**5p**), TJG-048



To dry THF (85 mL) was added $TiCl_4$ (35.4 mL, 35.4 mmol, 1M, 4.00 equiv.) in dry DCM at 0 □ resulting in a bright yellow mixture. Tetramethylethylenediamine (10.6 mL, 70.1 mmol, 8.00 equiv.) was added and the resulting brownish yellow mixture was allowed to stir for 10 min at rt Zinc powder (5.21 g, 79.6 mmol, 9.00 equiv.) was added at rt and the resulting greenish blue mixture was allowed to stir for 30 min. A solution of 3-methyl-2-methylenebutyl acetate (1.26 g, 8.90 mmol, 1.00 equiv.) and dibromomethane (1.35 mL, 19.5 mmol, 2.20 equiv.) in dry THF (17 mL) was added to the reaction mixture at rt and the resulting brown mixture was allowed to stir for 22 hours. (NOTE: Reaction did not go to completion during this time, but the decision was made to quench the reaction at this point to avoid decomposition of acid- and temperature-sensitive **5p**). The mixture was cooled to 0 °C and saturated aq. K_2CO_3 (12 mL) was added. The resulting biphasic mixture was stirred for 15 min. Et_2O (180 mL) was added, and the entire mixture was vacuum-filtered through a pad of alumina (2 cm, pH 7.5) with 800 mL of Et_2O/triethylamine (200:1). Solvent was evaporated under argon flow. During the evaporation process a significant amount of white solid emerged, and the vacuum filtration procedure was repeated with 300 mL of Et_2O/triethylamine (200:1). The residue was purified by flash chromatography with amino-functionalized silica (pentane 100 %) to give **5p** as a colourless oil (130 mg, 0.89 mmol, 10 %).

R_f (pentane 100, NH_2-modified Silica TLC plate) = 1.00; IR (neat, ATR) ν_{max} 509, 793, 87, 1068, 1158, 1276, 1367, 1449, 1595, 1655, 1729, 2873, 2926, 2961; ^{1}H NMR (300 MHz, C_6D_6) δ 5.11 – 5.06 (m, 1H), 4.92 (t, *J* = 1.2 Hz, 1H), 4.13 (s, 2H), 3.96 – 3.88 (m, 2H), 2.28 (p, *J* = 6.9 Hz, 1H), 1.80 (d, *J* = 0.8 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR (75 MHz, C_6D_6) δ 159.9, 151.2, 109.5, 82.0, 69.7, 31.4, 21.8, 21.1; Retention time was measured with GC (SUPELCO Astec CHIRALDEX B-DM column, isoflow He: 1.806 mL/min, 100 °C isothermic): t_r = 2.49 min.

7 References

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